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OSTEOPOROSIS: MANAGEMENT AND TREATMENT
STRATEGIES FOR ORTHOPAEDIC SURGEONS

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Osteoporosis: Management and Treatment Strategies for Orthopaedic Surgeons

By Laura Gehrig, MD, Joseph Lane, MD, and Mary I. O'Connor, MD

An Instructional Course Lecture, American Academy of Orthopaedic Surgeons

The purpose of this lecture is to provide orthopaedic surgeons with a guide for osteoporosis management and treatment that may be used in the practice setting. Fracture prevention is the key efficacy end point in the medical management of osteoporosis for any patient. Enhancement of bone mass and improvement of bone quality are achieved by a combination of lifestyle modification, dietary supplementation with calcium and vitamin D, and pharmacologic treatment. This strategy has proved effective for the prevention and treatment of osteoporosis.

The orthopaedic surgeon is in a unique position to identify patients with osteoporosis. As the orthopaedic surgeon is often the only physician to see a patient who has sustained a fracture, he or she must make every effort to determine if the injury is a fragility fracture so that the patient can be treated to prevent future fractures.

Treatment

Nonpharmacologic Treatment

A multidisciplinary approach is essential in the treatment of osteoporosis. Nonpharmacologic treatments are used to complement pharmacologic therapy and thus optimize fracture risk reduction. Commonly used nonpharmacologic interventions include calcium and vitamin-D supplementation, fall prevention, hip protectors, and balance and exercise programs.

Calcium Supplementation

Optimal bone health depends on adequate calcium. A normal calcium status is defined as a corrected serum calcium level of 9.5 to 10.5 mg/dL (2.4 to 2.6 mmol/L). The National Osteoporosis Foundation recommends a daily calcium intake of 1000 mg/day for men and women under the age of fifty years and 1200 mg/day for men and women over the age of fifty years[1]. Since a typical American woman consumes approximately 600 mg of calcium through diet alone, supplementation is indicated for the majority of patients. Supplementary calcium is available in two forms, calcium carbonate and calcium citrate. Calcium citrate is the preferred form. The use of calcium carbonate by individuals with a physiologic or pharmacologically induced reduction in acid production results in suboptimal calcium absorption, as calcium carbonate requires a low pH for salt dissociation[2]. The incidence of kidney stones is decreased in patients taking supplemental calcium citrate instead of calcium carbonate as citrate binds to oxalate, reducing its intestinal absorption. In an effort to optimize absorption, total daily calcium supplementation should be divided throughout the day with individual doses limited to ≤500 mg[3].

Vitamin D

Orthopaedic surgeons know that vitamin D plays a critical role in promoting absorption of calcium from the gut and that insufficient absorption results in lower serum calcium levels. These lower

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levels trigger the release of parathyroid hormone, which mobilizes calcium from bone (secondary hyperparathyroidism), ultimately resulting in osteopenia and eventually osteoporosis. Recent studies have also indicated that patients with osteoarthritis can have osteoporosis as well as vitamin-D deficiency[4].

Vitamin-D deficiency has been shown to increase the risk of falls by the elderly[5-7]. In a recent randomized controlled trial, the impact of a high dose of vitamin D on nursing home residents' risk of falling was compared with that of a placebo over a five-month period[6]. The researchers found a 72% reduction in the risk of falls for individuals given 800 IU of vitamin D2 plus calcium compared with those who received a placebo. Moreover, severe vitamin-D deficiency is associated with persistent, nonspecific musculoskeletal pain[8].

Beyond the musculoskeletal system, vitamin D influences many other organ systems (the brain, heart, gut, skin, pancreas, and immune system). These organs have cells with vitamin-D receptors and may even express the enzyme to convert vitamin D to its active form[9]. Furthermore, insufficient vitamin D has been associated with type-1 diabetes, multiple sclerosis, Crohn disease, hypertension, cardiovascular disease, schizophrenia, depression, rheumatoid arthritis, and osteoarthritis[10]. With insufficient vitamin D, the serum level of calcium is also at risk of being insufficient. This couples the physiologic state of low calcium and vitamin D to these diseases and to the skeleton of those who have these diseases. The skeletons of those with these diseases are at risk for low bone density, osteoporosis, and fracture.

Sources of Vitamin D

Vitamin D can be obtained from three sources: exposure of skin to sunlight of adequate ultraviolet strength, diet (such as salmon, tuna, sardines, and cod liver oil) including fortified foods (breakfast cereals, milk, some orange juices, and yogurts), and dietary supplements. Synthesis of vitamin D from the skin occurs with exposure of 7-dehydrocholesterol, a lipid in the dermis, to pre-vitamin D3. Approximately one to fifteen minutes of sun exposure to the hands and arms two or three days per week is thought to be adequate. However, the intensity of the sunlight is critical. In northern latitudes such as Boston and Seattle, there is no vitamin production from November through February regardless of the length of sun exposure[11]. In Los Angeles and Atlanta, vitamin-D3 synthesis is adequate throughout the year. Use of sunscreen dramatically reduces vitamin-D3 synthesis, with 99% eliminated with the use of a sunscreen with a sun protection factor (SPF) of 15 and 92.5% eliminated with use of a SPF-8 sunscreen[9,12]. Synthesis is decreased, potentially by as much as 99%[12], in individuals with dark skin pigmentation. Furthermore, the epidermis thins with aging. Lipid content is lost with a resultant estimated 75% reduction in vitamin-D synthesis in a person who is seventy years old[9].

Dietary supplements, therefore, are a very important source of vitamin D. Both vitamin D2 (usually labeled as calciferol or ergocalciferol) and vitamin D3 (usually labeled as cholecalciferol) are used in over-the-counter supplements, but the form available by prescription in the United States is vitamin D2[10]. Vitamin D3 is the preferred form, as vitamin D2 is only approximately 30% as effective in maintaining serum 25-hydroxyvitamin-D levels[13,14]. If vitamin D2 is used, up to three times as much of the vitamin may be required[10].

Vitamin-D Supplements and Risk of Fracture

It is well established that many patients with osteoporosis or a history of a fragility fracture have suboptimal levels of vitamin D. Furthermore, the prevalence of low vitamin-D levels is greater in individuals in nursing homes than in those living in the community. A meta-analysis of studies in which individuals were given 400 IU of vitamin D3 per day showed little benefit in terms of reduction of hip or vertebral fractures. However, higher doses of vitamin D have been found to have benefits. In individuals with inadequate vitamin-D levels of 17 ng/mL (42.4 nmol/L), 700 to 800 IU of vitamin D per day resulted in a mean increase in vitamin-D levels of approximately 40 ng/mL (99.8 nmol/L) and a reduction in the prevalence of both nonvertebral and vertebral fractures[5].

Ethnic differences have also been observed relative to vitamin D and fragility fractures. In a series of eighty-five patients with acute fragility fractures, black and Hispanic patients were significantly younger than whites ($p < 0.001$) and more likely to have serious comorbidities such as diabetes or hypertension. Perhaps of even greater interest is the fact that, despite significantly higher bone mineral density values ($p < 0.01$), blacks had the highest rate of vitamin-D deficiency and secondary hyperparathyroidism[15].

Recommendations for Vitamin-D Supplementation

The current recommendations from the Institute of Medicine are 200 IU daily from birth to the age of fifty years, 400 IU daily for adults fifty-one to seventy years of age, and 600 IU daily for those seventy-one years of age and older[16]. Many experts in the field consider these recommendations to be too low and believe that the minimum adult intake should be 800 to 1000 IU daily.

Higher doses of vitamin D are required to replenish depleted total body stores. Fifty thousand international units of ergocalciferol (vitamin D2) can be taken orally twice a week for six to eight weeks, followed by a maintenance dose of 1000 IU per day. Toxicity, even with these higher doses, is very rare. Doses of up to 10,000 IU per day for up to five months have not caused toxicity[17].

Evaluation of the vitamin-D level followed by treatment if a deficiency is found is now part of the management of osteoporosis. This is essential as vitamin-D deficiency is completely preventable and reversible.

Lifestyle

Lifestyle evaluation is an important component of the comprehensive treatment for osteoporosis. In addition to encouraging smoking cessation and

moderation of alcohol consumption, physicians should also counsel patients about fall prevention and appropriate exercise training to further reduce the risk of fracture.

Fall Prevention and Hip Protectors

The evaluation of osteoporotic patients' risk of falling and the initiation of appropriate intervention are important for fracture prevention. Fracture prevention is most effective when both intrinsic and environmental risk factors for a fall are taken into consideration. Physicians should limit sedative medications when possible, recommend regular weight-bearing exercise, consider physical and occupational therapy for fall prevention, and facilitate environment modification such as the installation of assistive devices in the home. In addition, clinicians may encourage their patients to wear hip protectors, which effectively attenuate force from a fall and are associated with >50% reductions in the risk of hip fracture as well as improvement in the patient's self-confidence that they can avoid a fracture if they fall[2,18]. However, compliance is low as many patients find hip protectors difficult to manipulate when they dress and undress[2].

Balance, Posture, and Exercise Training

Osteoporotic patients are likely to benefit from programs that target balance, posture, and strength. Balance training programs are ass-ociated with an approximate 50% reduction in the incidence of falls. Postural exercise programs have been shown to increase back extensor strength. Activities such as tai chi may be particularly helpful, with intense training programs reducing the risk of falls in elderly populations by as much as 47%[19]. Careful attention must be paid to identifying appropriate weight-bearing activities, as fragile patients with severe osteoporosis are known to sustain new fractures during routine activities such as bending over and turning in bed[18].

Pharmacologic Treatment

The pharmacologic agents currently available are commonly divided into two classes, antiresorptive and anabolic. Antiresorptive agents such as the bisphosphonates limit bone resorption through inhibition of osteoclast activity. The anabolic agent parathyroid hormone promotes active building of bone mass. Both antiresorptive and anabolic agents have demonstrated antifracture efficacy in randomized clinical trials[18].

Antiresorptive Agents

The antiresorptive agents currently approved for use in patients with osteoporosis include calcitonin, hormone replacement therapy, selective estrogen receptor modulators, and bisphosphonates.

Calcitonin

Calcitonin effectively inhibits bone resorption by decreasing osteoclast formation and activity[20,21]. Calcitonin acts quickly. Its effects are reversible and transient. This is likely due to its rapid clearance from the body and desensitization and internalization of the calcitonin receptor with prolonged exposure[21,22]. Calcitonin has been approved by the U.S. Food and Drug Administration for treatment of established osteoporosis but not for prevention of postmenopausal osteoporosis. It is available as both a parenteral injection and nasal spray. The intranasal formulation of calcitonin is the most widely prescribed because of its ease of use and superior tolerability[21].

Nasal calcitonin has proven to decrease bone turnover and modestly increase bone mineral density over one to five years[20,21]. Despite this increase, gains in bone mineral density are not maintained after discontinuation of treatment[21]. The efficacy of calcitonin in reducing the risk of vertebral fractures was best examined in the PROOF (Prevent Recurrence of Osteoporotic Fractures) study[20]. This five-year, double-blind, randomized, placebo-controlled study of 1255 postmenopausal osteoporotic women showed that treatment with 200 IU of nasal calcitonin daily reduced the risk of new vertebral fractures by 33% as compared with the risk in individuals taking a placebo. The effects of calcitonin treatment on the risks of hip and other nonvertebral fractures remain uncertain[20,21]. The fact that calcitonin substantially reduces the risk of vertebral fracture with only modest increases in bone mineral density suggests that yet to be elucidated calcitonin-mediated enhancement of bone quality may contribute to fracture risk reduction[22]. In addition to its antiresorptive action, patients with painful new vertebral compression fractures who were treated with calcitonin had, by two weeks, reduced pain, consumed fewer traditional analgesic medications, and regained mobility sooner, which may reduce bone loss secondary to prolonged bed rest[21,23]. Calcitonin-induced analgesia may be mediated by increases in plasma β-endorphins. This implicates involvement of the endogenous opiate system, while animal studies demonstrating calcitonin-binding sites in brain areas involved in pain perception suggest that calcitonin may directly modulate nociception in the central nervous system[23].

Hormone Replacement Therapy

Estrogen formulations were approved by the U.S. Food and Drug Administration for use in prevention of osteoporosis, but not for treatment of osteoporosis. Estrogen, both with and without progestin, has consistently been shown to not only maintain, but also increase, bone mineral density[24,25]. The Women's Health Initiative (WHI) clinical trials of hormone replacement therapy showed that long-term therapy with estrogen alone reduced the rate of hip, clinical vertebral, and total osteoporotic fractures by 30% to 39% as compared with the rates in patients taking a placebo[26]. Fracture reduction rates of a similar magnitude were found among participants randomized to receive long-term treatment with estrogen plus progestin. Hip and clinical vertebral fracture rates were reduced by 34%. Total osteoporotic fracture rates were reduced by 24% when compared with the rates in patients taking a placebo[25-27]. While the majority of studies and meta-analyses support the bone health benefits of hormone replacement therapy,

some studies, most notably the Heart and Estrogen/Progestin Replacement Study (HERS), have not demonstrated evidence of fracture risk reduction in women similarly treated with hormone replacement therapy[25,28,29]. However, HERS had limited power to detect fracture risk reduction; it was able to detect only large reductions of at least 80%[25].

While improvements in bone mineral density and reductions in the rate of fracture occur, the associated risks of treatment preclude the use of estrogen formulations as primary agents in the treatment of osteoporosis. Women treated with estrogen alone have no change in the incidence of coronary heart disease; however, they have been found to have increased rates of stroke and deep vein thrombosis[27,29,30]. In addition, estrogen plus progestin increases the risk of breast cancer, dementia, and gallbladder disease[27,29,31]. The risks for cardiovascular disease, breast cancer, and dementia far exceed the benefits of estrogen and estrogen plus progestin therapy with respect to osteoporosis. This is true even for women at greatest risk for osteoporotic fracture[26]. This unfavorable safety profile restricts use of hormone replacement therapy for osteoporotic patients. However, women receiving short-term hormone replacement therapy for menopausal symptoms are likely to reap additional benefits with regard to bone health. Referral to a primary care physician or a gynecologist is the safest approach if hormone replacement therapy is planned.

Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators are a class of compounds that bind estrogen receptors. They act as estrogen receptor agonists in some tissues and as estrogen receptor antagonists in others. Of the selective estrogen receptor modulators currently approved for clinical use, only raloxifene has been approved for the prevention and treatment of osteoporosis[32]. The effects of raloxifene on bone are known. Raloxifene has consistently proven to increase bone mineral density in the lumbar spine and femoral neck by 2% to 3% and to moderately decrease levels of bone-turnover markers by 30% to 40% (levels comparable with mean levels found in premenopausal women), suggesting an antiresorptive effect on bone tissue[33-35]. More importantly, raloxifene has also been shown to reduce the risk of vertebral fracture[34,35]. However, reductions in the overall risk of nonvertebral fractures did not reach significance[34-36]. The effect of raloxifene on fracture reduction is greater than what would be expected in light of the modest increases in bone mineral density. This suggests that raloxifene may also contribute to improvements in other components of bone quality[34].

As a result of raloxifene's selective estrogen receptor antagonist properties in breast tissue, women treated with raloxifene also benefit from a 62% reduction in the incidence of all types of breast cancer, with a 72% reduction in the risk of invasive breast cancer and an 84% reduction in the risk of invasive estrogen receptor-positive breast cancer[28]. Additionally, raloxifene is not associated with an increased risk of endometrial cancer[28]. The risk of venous thromboembolic events is increased threefold, which is comparable with the elevated risk seen with hormone replacement therapy. Use of raloxifene also increases the incidence of vasomotor symptoms and may increase the risk of fatal stroke[34,37]. Clinicians must weigh the benefits of the reduced risks of vertebral fracture and invasive breast cancer against the increased risks of venous thromboembolism and fatal stroke when considering osteoporosis management.

Tamoxifen, a selective estrogen receptor modulator approved for use for the prevention and treatment of breast cancer, has been associated with reductions in the risk of vertebral fracture of a magnitude similar to those seen with raloxifene[38-40]. However, the greater risk of venous thromboembolism imparted by tamoxifen, as compared with that associated with raloxifene, and its association with an increased risk of endometrial cancer preclude its use in the treatment of postmenopausal osteoporosis[32,38-40].

Bisphosphonates

The bisphosphonates, a class of antiresorptive agents, are the current cornerstone of osteoporosis treatment and prevention. These nitrogen-containing compounds bind to the bone surface. There they exert their effect on the bone reabsorbing osteoclasts, decreasing osteoclastic activity and reducing cellular life span. Treatment with bisphosphonates reduces the rate of bone resorption, increases bone mineral density, and improves trabecular connectivity. These resultant effects serve to improve bone strength and reduce fracture risk. Both oral and intravenous forms of the treatment exist.

Currently, four bisphosphonates have been approved by the U.S. Food and Drug Administration for the treatment of postmenopausal osteoporosis: alendronate (Fosamax), risedronate (Actonel), ibandronate (Boniva), and zoledronic acid (Reclast). These drugs differ in their potency, dosing schedules, and mode of administration. All have been shown to possess antifracture efficacy. Placebo-controlled trials involving postmenopausal women treated with one of these agents have demonstrated reductions in the risk of vertebral fractures, ranging from 45% to 70%, relative to the risks for patients taking a placebo.

Alendronate, an oral bisphosphonate currently given in doses of 70 mg/wk for the treatment of osteoporosis, has been shown to increase bone mineral density in the spine, hip, and femur as well as to reduce the risk of fracture by an average of 50%[41]. Women with low bone mineral density and a history of vertebral fracture treated with daily alendronate for three years had a 47% reduction in the risk of vertebral fracture compared with the risk for those treated with a placebo[41]. Participants without a prior vertebral fracture had a reduction in the risk of a future vertebral fracture of 44%[42]. A meta-analysis of studies involving the effect of alendronate on the risk of hip fracture demonstrated an overall risk reduction of 45%[43]. Alendronate therapy has proven efficacious in the treatment of osteoporosis in men. Bone mineral

density in the hip, spine, and total body is increased. The risk of vertebral fracture is decreased[44]. These antifracture effects of alendronate have been observed as early as one year after the initiation of therapy and have persisted ten years into the treatment period. Concerns regarding prolonged treatment are beginning to arise, as described below[45]. In a twelve-month head-to-head trial comparing two bisphosphonates, alendronate and risedronate (discussed below), patients in the alendronate group were found to have greater gains in bone mineral density and reductions in bone-turnover markers[46]. However, another study comparing the two agents failed to show any significant difference[47,48].

Risedronate, an oral bisphosphonate given in doses of 35 mg/wk, has also been shown to increase bone mineral density and reduce the risk of vertebral, nonvertebral, and hip fractures in osteoporotic women. In the placebo-controlled Vertebral Efficacy with Risedronate Therapy (VERT) study, daily treatment of postmenopausal women with osteoporosis (as defined by the previous occurrence of a vertebral insufficiency fracture) with 5 mg of risedronate decreased the cumulative incidence of new vertebral fractures by 41% and reduced the incidence of nonvertebral fractures by 39%[49]. A reduction of vertebral fracture risk of up to 61% has been found after only one year of treatment[50]. In another study, specifically assessing the effect of risedronate on the risk of hip fracture, that risk was found to be reduced by 30% compared with that associated with a placebo[51].

Ibandronate, one of the newer bisphosphonates made popular by its monthly (150-mg) oral dosing schedule and monthly intravenous (3-mg) formulation option, confers similar antiosteoporotic effects. As with alendronate and risedronate, patients treated with ibandronate have substantial increases in bone mineral density at all sites. In addition, they have decreases in vertebral fracture risk. However, ibandronate's anti-hip-fracture efficacy is still to be shown[52,53]. If compliance is an issue, ibandronate may be a useful option in certain patient groups. Patient compliance with weekly dosing regimens remains suboptimal, with rates ranging from 58% to 76% at one year[54]. If patient compliance is increased, treatment with ibandronate may improve therapeutic outcome.

The side effects of the oral bisphosphonates are similar and are due to their inherent toxicity to epithelial cells lining the gastrointestinal tract. The result may be gastrointestinal irritation and ulceration. Therefore, it is recommended that patients take the medication first thing in the morning on an empty stomach along with 8 oz (0.2 L) of water and then remain upright for thirty minutes. Osteonecrosis of the jaw, defined as exposed bone in the maxillofacial region that fails to heal within eight weeks after identification by a health-care provider, is a troubling potential complication of bisphosphonate use[55]. It has been reported that the patients who are at greatest risk are those with multiple myeloma or metastatic carcinoma of the skeleton who are being treated with relatively high doses of the intravenous bisphosphonates zoledronic acid and pamidronate. This patient population has included 94% of the reported cases[56]. In a recent report, the American Society for Bone and Mineral Research estimated the risk of osteonecrosis of the jaw in patients taking oral bisphosphonates for the treatment of osteoporosis to be between one in 10,000 and less than one in 100,000 patient-treatment years[55]. This is lower than the estimated incidence of one to ten cases per 100 patients with cancer receiving intravenous treatment[55]. Sixty percent of the cases of osteonecrosis that do occur are preceded by a surgical dental procedure. Theories regarding potential mechanisms for the development of osteonecrosis of the jaw include oversuppression of bone turnover and bisphosphonate toxicity of the soft tissues overlying the jaw[56-58]. Limited data exist regarding prevention and management of the condition. It is recommended that patients in need of a dental procedure establish meticulous oral hygiene and consider completing dental work prior to starting bisphosphonate treatment[58,59]. No evidence supports the discontinuation of established bisphosphonate therapy prior to a dental procedure[60].

Zoledronic acid is available in an intravenous formulation given once yearly as an infusion. It has demonstrated efficacy in increasing bone mineral density and reducing fracture risk[61,62]. In the multinational, multicenter, placebo-controlled HORIZON (Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly) Pivotal Fracture Trial, women who received an infusion of 5 mg of zoledronic acid once yearly had a 70% reduction in the risk of new spine fractures ($p < 0.0001$) and a 41% reduction in the risk of hip fractures ($p = 0.0032$) over three years compared with the risks for women taking a placebo[62]. In a group of osteoporotic patients who had received an infusion of zoledronic acid within ninety days after a hip fracture repair, the risk of any fracture decreased by 35% and mortality from any cause decreased by 28% compared with the rates for patients given a placebo[63]. Patients being treated with weekly oral alendronate can switch to zoledronic acid and maintain the beneficial bone effects for twelve months after a single infusion. The most common side effects associated with use of zoledronic acid include influenza-like post-infusion symptoms of fever, muscle pain, headache, and bone pain. The majority of symptoms resolve within three days. Osteonecrosis of the jaw was not seen in any of the trials investigating the use of zoledronic acid in postmenopausal women with osteoporosis[61-63]. Atrial fibrillation has also been seen. This association is yet to be defined[62,63]. Given the convenience of a yearly dosing schedule, zoledronic acid may be a suitable option for osteoporotic patients in need of bisphosphonate treatment for whom gastrointestinal toxicity is a problem.

Once a decision has been made to begin treatment with bisphosphonates, optimization of the mineral environment and monitoring of the bone turnover state ensure that the best

possible result is achieved. The importance of adequate vitamin-D and calcium status is highlighted by case reports of bisphosphonate-induced hypocalcemia in patients with unrecognized vitamin-D deficiency. Animal studies have also demonstrated a blunting of the bisphosphonate response in the setting of vitamin-D deficiency[64,65]. All patients should receive 1500 mg of calcium citrate and 800 IU of vitamin D3. Those found to have deficiencies (a serum calcium level of <9.5 mg/dL [<2.4 mmol/L] and/or a serum 25-hydroxyvitamin-D level of <32 ng/mL [<79.9 nmol/L]) may require greater doses for a short time until they are considered calcium and/or vitamin-D-replete.

Measures of bone mineral density may clinically diagnose osteoporosis but are of limited value for assessing a patient's response to bisphosphonate treatment[66]. Fractures are a key efficacy end point in bisphosphonate trials. Studies have demonstrated an inconsistent relationship between changes in bone density and fracture risk[67]. Data relating changes in bone turnover to subsequent fracture outcomes suggest that high turnover itself may be an independent risk factor for fracture[68]. Thus, markers of bone turnover may be useful for assessing a patient's response to treatment. The markers most commonly used in clinical practice include the markers of bone formation, bone-specific alkaline phosphatase and osteocalcin; and the markers of bone resorption, urine N-telopeptide of collagen cross links (NTx) and serum C-telopeptide of collagen cross links. In the Fracture Intervention Trial (FIT), greater reductions in bone turnover with alendronate therapy were associated with fewer hip, non-spine, and vertebral fractures[68]. Despite these results, controversy remains regarding the use of bone turnover markers in monitoring response to treatment. For patients taking bisphosphonates, the ideal therapeutic range of urine levels of NTx is 20 to 40 nmol BCE (bone collagen equivalents)/mmol of creatinine.

Long-term use of bisphosphonates may suppress bone turnover to such an extent that a paradoxical decrease in bone strength and resilience develops; this is referred to as *adynamic bone*. In this state of oversuppression, microfractures generated through the wear and tear of normal daily life begin to accumulate and coalesce, leading to spontaneous nonspinal fractures[69]. Accumulation of microdamage is associated with a reduction in bone toughness, defined in animal studies as the ability of the bone to sustain deformation before breaking[70]. In another study, this decrease in toughness was found to be offset by an increase in bone volume and mineralization, the combination of which resulted in no significant impairment in bone mechanical properties[71]. Odvina et al. reported on nine women treated with high-dose alendronate who presented with a spontaneous fracture of a long bone[72]. Six of these women also displayed evidence of delayed or absent fracture-healing during alendronate therapy. Histomorphometric analysis of bone biopsy specimens from these patients revealed marked suppression of bone turnover, demonstrated by a reduced or absent osteoblastic surface, a diminished osteoclastic surface, and minimal matrix synthesis. For these patients, changes in therapy such as a rest period from bisphosphonates or the use of an anabolic agent such as teriparatide (as discussed below) should be considered. In a study comparing women who stopped taking alendronate after an average of five years of use with those who continued to use the drug, those who stopped did not have accelerated bone loss or a marked increase in bone turnover[73]. These results indicate a persistence of alendronate's effect on bone after therapy is stopped[73]. Currently, it is unknown whether long-term treatment with bisphosphonates beyond five years is indicated. More studies are needed to investigate the potential positive and negative impact that prolonged bone suppression can have on fracture risk.

Anabolic Agents

Parathyroid Hormone

Approved by the U.S. Food and Drug Administration in 2002, teriparatide (parathyroid hormone [PTH1-34]) is the only anabolic agent available for the treatment of postmenopausal osteoporosis. Self-administered subcutaneously with use of a pen-like device, daily teriparatide injection is the most effective therapy for restoring bone quality[74,75]. The effects of parathyroid hormone are mediated by enhancement of bone turnover. When administered intermittently, the anabolic effects predominate, increasing bone mass up to 13% over two years of therapy. This increase is greater than that achieved with bisphosphonate therapy[76]. The antifracture efficacy of teriparatide is similar to that seen with bisphosphonates. After treatment of postmenopausal women with osteoporosis (as defined by bone mineral density) with daily 20-μg injections of parathyroid hormone, the risk of vertebral fracture and nonvertebral fracture was reduced by 65% and 53%, respectively[76]. The antifracture efficacy of parathyroid hormone may be related to more than just increases in bone mineral density. Microcomputer tomographic analysis has demonstrated an increase in trabecular number as well as trabecular thickness[77].

Although it has been proven to be efficacious across the spectrum of osteoporosis disease severity, the use of parathyroid hormone has been limited[78], most likely as a result of the combination of high cost, relative inconvenience, and potential adverse reactions associated with use of the drug. Evidence of osteosarcoma in rodents exposed to prolonged high doses of teriparatide led the U.S. Food and Drug Administration to prohibit its use in patients at high risk for skeletal cancer[79,80]. The use of teriparatide is contraindicated in patients with active Paget disease of bone, metastatic cancer in the skeleton, or a history of skeletal irradiation, and in children with open epiphyses. In an estimated more than 300,000 exposures to teriparatide for the treatment of postmenopausal osteoporosis, a single case of osteosarcoma was recently reported[81], and the existence of a causal relationship between teriparatide use and osteosarcoma in

humans remains uncertain. Additional adverse reactions associated with teriparatide include nausea, swelling, pain, weakness, erythema around the injection site, and elevation in plasma calcium levels. Plasma calcium may be adjusted, and vitamin-D supplementation may be needed[82,83]. Hypercalcemia may be monitored by measuring serum calcium levels at one month following the initiation of treatment[84].

Antiresorptive therapies have long been, and continue to be, the mainstay of osteoporosis treatment. Patients who have been previously treated with antiresorptive therapy constitute a large group in whom parathyroid hormone treatment may be indicated. Data suggest that previous treatment with potent inhibitors of bone turnover, such as alendronate, appears to diminish the initial response to teriparatide[85]. It also appears that the degree of the initial teriparatide effect depends on the potency of the previously used antiresorptive agent, and this effect has not been demonstrated in association with less potent agents such as raloxifene[86]. Many practitioners advocate a brief (six-month) rest period between the discontinuation of the antiresorptive agent and the start of teriparatide treatment.

Combination Therapy

Despite an initial attractiveness of the combined use of anabolic and anticatabolic therapy, a synergistic effect between teriparatide and the bisphosphonates has not been seen. On the contrary, concurrent use of a bisphosphonate has been shown to blunt the bone-building potential of parathyroid hormone[87,88]. However, in a recent trial by Deal et al., concurrent administration of raloxifene was found to enhance the bone-forming effects of teriparatide[89]. Postmenopausal women who received a combination of teriparatide and raloxifene over a period of six months had a greater increase in bone mineral density in the hip compared with groups that received raloxifene or teriparatide alone. A similar synergistic effect has been seen following coadministration of teriparatide and hormone replacement therapy[90]. Additional studies that include the assessment of fracture outcome as well are needed.

The bisphosphonates, while not recommended during teriparatide treatment, can play a valuable role after completion of teriparatide therapy. Soon after discontinuation of teriparatide treatment, gains in bone mineral density begin to regress rapidly. Declines in bone mineral density begin as early as eighteen months after the last dose of teriparatide is given[91]. The immediate use of bisphosphonates or other antiresorptive therapy has been shown to optimize valuable gains in bone mineral density. The use of bisphosphonates not only prevents a decline in bone mineral density but also enhances additional densitometric gains[92,93]. Subsequent treatment with bisphosphonates facilitates the mineralization of osteoid laid down during the previous period of increased metabolic activity. In an effort to "lock in" and "protect" the valuable gains in bone mineral density achieved during the two years of teriparatide treatment, many practitioners advocate starting or restarting antiresorptive therapy on completion of the anabolic therapy.

Tables I and II present the pharmacologic agents recommended to treat osteoporosis and reduce fracture risk[18].

Future Directions

The treatment of osteoporosis is currently associated with numerous problems ranging from adverse drug reactions to suboptimal patient compliance[94-98]. Better drugs with more specific targets will reduce the adverse effects and improve the outcome of therapy. The understanding of cellular mechanisms regulating bone formation and remodeling has improved substantially in the last few years. In the arena of antiresorptive agents, denosumab, a human monoclonal antibody against receptor activator of nuclear factor-κB ligand (RANKL), has been shown in preclinical trials to increase bone min-

TABLE I Recommended Pharmacologic Agents to Treat Osteoporosis and Reduce Fracture Risk[18]*†

Antiresorptive Agent	Vertebral Fracture‡	Hip Fracture‡	Nonvertebral Fracture‡‡
Bisphosphonates			
Alendronate	A§	A	A
Risedronate	A	A	A
Etidronate	A	C	C
Estrogen replacement therapy/hormone replacement therapy	A	A	A
Selective estrogen receptor modulators (raloxifene)	A	C	C
Calcitonin, intranasal	A	C	C
Teriparatide (parathyroid hormone [1-34])	A	—	A
Calcium and vitamin-D preparations			
Vitamin-D monotherapy and analogs (calcitriol, alfacalcidol, etc.)	C	C	C
Calcium monotherapy	B	C	C
Vitamin D plus calcium	C	A	A

*From randomized, placebo-controlled clinical trials of women with prior vertebral fractures or with osteoporosis. †A = convincing evidence of antifracture efficacy, B = inconsistent results, and C = ineffective or insufficient evidence of efficacy. ‡Osteoporosis fractures exclusive of those of the spine. §Also seen in men.

TABLE II Recommended Pharmacologic Agents to Treat Osteoporosis and Reduce the Risk of Future Fracture in Patients with a Fragility Fracture[18]*

Generic Name	Trade Name	Approved Indication	Recommended Dose	Dosing Instructions and Contraindications
Alendronate	Fosamax	Osteoporosis in postmenopausal women and in men	10 mg orally once per day or 70 mg orally weekly	With full glass of water, >30 min before food in morning. Contraindications: severe renal insufficiency, esophageal motility problem, hypocalcemia, or inability to stand or sit upright for 30 min
Risedronate	Actonel	Osteoporosis in postmenopausal women and in men	5 mg orally once per day or 35 mg orally weekly	With full glass of water, >30 min before food in morning. Contraindications: severe renal insufficiency, hypocalcemia, or inability to stand or sit upright for 30 min
Raloxifene	Evista	Osteoporosis in postmenopausal women	60 mg orally once per day	With meals at any time of the day. Contraindications: premenopausal women and those with history of or active venous thromboembolic events
Teriparatide (parathyroid hormone [PTH1-34])	Forteo	Postmenopausal women with osteoporosis who are at severe risk for fracture	20-μg subcutaneous injection once per day	Injection into thigh or abdominal wall. Contraindications: Paget disease, prior radiation therapy, bone metastases, history of skeletal malignant tumors, or hypercalcemia

*See prescribing information for each drug for additional recommendations and guidelines.

eral density and decrease bone resorption in postmenopausal women with osteoporosis. Used commonly in patients with multiple myeloma and metastatic disease of the skeleton, denosumab exerts its action through inhibition of RANKL, a key mediator in osteoclast activation[99,100]. Denosumab is now awaiting approval for entry into the market. Cathepsin-K inhibitors are another group of novel antiresorptive agents. It is hoped that these drugs, which were designed to reduce the activity of cathepsin K (a powerful osteoclast protease), can limit the enzymatic degradation of bone matrix proteins[101]. The efficacy of cathepsin-K inhibitors in the treatment of postmenopausal osteoporosis is still under investigation in clinical trials.

New anabolic agents are currently on the treatment horizon. Strontium ranelate, used routinely in Europe but unavailable in the United States, is considered to be the only agent to have a dual mechanism of action, acting as both an antiresorptive and an anabolic agent. Treatment of postmenopausal osteoporotic women with strontium ranelate has been shown to decrease fracture risk and increase bone mineral density. While the long-term effects remain unknown, strontium may prove to be an attractive option for patients unwilling or unable to use parathyroid hormone[102,103]. The development of alternative forms of parathyroid hormone, including noninjectable forms (oral, nasal, sublingual, and transdermal modes), is also under way. These new analogs of parathyroid hormone appear to possess longer half-lives, allowing sustained exposure in the setting of less frequent dosing[94,96-98,104-106].

Osteoporosis Therapy in Common Orthopaedic Situations

Calcium and Vitamin-D Supplementation for Patients with a Fracture

Calcium and vitamin-D supplementation is a baseline critical component of any fracture treatment therapy. The increased bone turnover stimulated by fracture repair and remodeling leads to an increased metabolism and demand for calcium and vitamin D. The estimated daily intake required for fracture-healing is 1500 to 2500 mg of calcium and 1000 to 2000 IU of vitamin D.

Use of Bisphosphonates for Patients with a Fracture

Healing of both stabilized and unstabilized fractures involves stages of osteoclastic activity[107]. The limited data currently available indicate that the use of bisphosphonates does not impair, and may actually enhance, fracture-healing[108]. Studies have shown that, while development and remodeling of the fracture callus is delayed in the setting of bisphosphonate use, the overall mechanical strength of the callus is either unchanged or increased[109,110]. Concern regarding a bisphosphonate-driven increase in the rate of nonunion also continues to be unsupported in the

literature[108-110]. Timing may play a role in the effect of bisphosphonates on fracture-healing. The administration of zoledronic acid to rats two weeks after creation of a fracture resulted in a greater increase in the mechanical strength of callus compared with what was seen with administration prior to the fracture[111]. Given the development of the primary callus during the first two weeks of fracture-healing, some studies support initiation or continuation of bisphosphonate treatment after this time[108]. Animal fracture data combined with the known efficacy of bisphosphonates in preventing future fractures are compelling enough to support initiation of treatment in a "timely fashion" for all patients with an osteoporotic fragility fracture[112].

Since bisphosphonates inhibit osteoclastic resorption and osteoclastic activity is involved in fracture repair, a patient who is already being treated with bisphosphonates may have an initial delay in the early stages of the fracture repair process. Some animal studies have shown interference with fracture repair and the mechanical strength of the fracture site dependent on the chemical structure, dosage potency, and duration of the treatment with the bisphosphonate. Additional studies of humans are needed to determine the ultimate effect on union and on the restoration of mechanical strength and anatomic architecture after fracture-healing. Physicians may choose to stop the bisphosphonate treatment for two weeks—i.e., until the initial fracture-repair period has passed.

Use of Teriparatide for Patients with a Fracture

Recent animal studies have suggested that teriparatide may also play a valuable role in the treatment of fractures. An acceleration of fracture-healing has been demonstrated in animals treated with intermittent doses of parathyroid hormone[113-116]. Stimulation of proliferation and differentiation of chondrocytes and osteoprogenitor cells, leading to an increase in the production of bone matrix proteins, is believed to be the mechanism[113,117]. The fracture callus in parathyroid-hormone-treated animals forms more rapidly, remodels more quickly, and possesses superior biomechanical properties when compared with that of controls[114,115]. Parathyroid hormone (PTH1-34) may prove to be an attractive agent to enhance healing and limit the risk of nonunion of poorly healing or high-risk fractures when human trials on fracture-healing have been performed.

Use of Bisphosphonates for Patients Who Have Undergone Arthroplasty

Aseptic loosening and osteolysis are the most common causes of failure of total joint arthroplasty. Osteolysis is caused by wear-debris-mediated stimulation of the osteoclast. This leads to subsequent bone resorption. Drugs used to treat osteoporosis inhibit the osteoclast and also increase endosteal bone formation[118]. They have therefore been used experimentally[119-126] as possible therapies to improve the life of prostheses; however, additional animal and human studies are needed.

Most studies have shown that patients being treated with bisphosphonates maintain more periprosthetic bone mineral density and have less periprosthetic bone loss[127-131]. Bisphosphonates have a larger effect on bone loss following arthroplasties with cement, and especially knee arthroplasties with cement[132]. With anabolic bone therapy, uncemented prostheses may have the potential for better ingrowth and survival. However, future human studies may demonstrate better prosthetic survival in patients using drugs for reduced bone mass. Nevertheless, patients undergoing total joint replacement should be evaluated and treated for decreased bone mass if they have a number of risk factors for osteoporosis.

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