Treatment of Male Osteoporosis: A Review

Authors

Chaim Vanek, MD

Oregon Health & Science University; Portland, OR

vanekc@ohsu.edu

Eric S. Orwoll, MD

Oregon Health & Science University; Portland, OR

orwoll@ohsu.edu

Abstract

Pope John Paul II fell in the bathroom and broke his hip in May 1994. Since that time, it has become evident that osteoporosis in men is a significant public health issue. Aging men can benefit from osteoporosis diagnoses and treatment in a manner similar to post-menopausal women. We will review current therapeutic options for male osteoporosis (calcium, vitamin D, bisphosphonates, RANK ligand inhibitors, anabolic agents). Bone loss due to androgen deprivation therapy for prostate cancer is a unique scenario for men that requires special attention for oncologists and primary care physicians.

Main Text

The third National Health and Nutrition Examination Survey (NHANES III, 1988-1994) identified that between 9-15 million older men in the United States have low bone mass.[1] Men account for 30% of all fractures in individuals over the age 50 and have a higher post-fracture mortality rate than women. The revelation that a substantial number are at risk for fragility fractures provides a strong rationale for the diagnoses and treatment of osteoporosis in men.

Calcium and Vitamin D

The Institute of Medicine recommends a total daily calcium intake of 1000 mg for men over age 50, 1200 mg for those over age 70, and a vitamin D intake of 400 – 800 international units daily to achieve a serum vitamin D (25-OH) level of at least 20 ng/ml.[2] The Endocrine Society recommends a goal vitamin D (25-OH) level of 30 ng/ml with a suggested intake of 2000 – 4000 international units daily.[3] Malabsorption syndromes increase the requirement for vitamin D, and those affected may require 10,000 or more units per day.[4] In those patients, serum vitamin D (25-OH) levels can be used to determine the amount of supplemental vitamin D required. Vitamin D (25-OH) levels above 80 ng/ml can result in toxicity (hypercalcemia, hypercalciuria, hyperphosphatemia).

Bisphosphonates

Bisphosphonates are the most commonly prescribed osteoporosis drugs. Their mechanism of action is chemical mimicry of the bone pyrophosphate structure (phosphorus-oxygen-phosphorus) with the bisphosphonate structure (phosphorus-carbon-phosphorus) allowing binding of the drug into the bone matrix. Bisphosphonates reduce osteoclast formation, induce osteoclast apoptosis, reduce remodeling rate, and increase bone mineral density (BMD); leading to an increase in bone strength and fracture prevention.[5]

A pivotal study of the effectiveness of alendronate led to Food and Drug Administration (FDA) approval of the first drug for the treatment of osteoporosis in men. 241 men (mean age: 63 years) with low bone mass (femoral neck bone density T-score less than -2.0) were randomized to 10 mg of daily oral alendronate versus placebo for two years.[6] All participants

received calcium and vitamin D supplementation. Compared to the placebo-treated group there were significant increases in spine, hip, and femoral neck BMD in the group treated with alendronate. Moreover, the incidence of radiographic vertebral fractures was significantly reduced in the alendronate-treated group. A number of subsequent small studies have revealed similar results, and meta-analyses support the likely effectiveness of alendronate in the treatment of men with osteoporosis.[7] Moreover, alendronate has also been shown to be cost effective in this situation.[8]

Once weekly preparations (alendronate 70 mg, Fosamax ™ or risedronate 35 mg, Actonel™) are the current treatment standard. Oral bisphosphonates have poor bioavailability and must be taken on an empty stomach, with water only, and without reclining for 30-60 minutes after ingestion. Patients with gastrointestinal acid reflux, dysphagia, Barrett's esophagitis, or those who cannot adhere to the above directions can be treated with intravenous formulations. Zoledronic acid 5 mg (Reclast™) is a once yearly intravenous bisphosphonate infusion given over thirty minutes. A 2012 study of 1200 men over age 50 with osteoporosis treated with yearly zoledronic acid showed a 67 % reduction in the rate of new radiographic vertebral fractures versus placebo after 24 months.[9]

For both oral and intravenous bisphosphonate therapy, renal function as assessed by glomerular filtration rate (GFR via the Cockcroft-Gault formula) should be greater than 35 ml/min. Hypocalcemia and serum vitamin D (25-OH) levels less than 20 ng/ml are contraindications to bisphosphonate therapy

Rank-Ligand Inhibition

Osteoclast differentiation, maturation, and activation are stimulated via the RANK (Receptor Activator of Nuclear Factor B)/RANK-ligand system. RANK-ligand produced by osteoblasts and osteocytes binds to RANK on the osteoclast cell surface to increase osteoclast formation, osteoclast activity, and bone resorption. Osteoblasts can also modulate osteoclast activity with the production of osteoprotegerin (OPG) that acts as a decoy receptor for RANK, therefore preventing RANK-ligand binding.[10] Denosumab (Prolia™) is a fully human monoclonal antibody that binds to RANK-ligand, preventing its activation of osteoclast

RANK receptor and thus modeling the OPG system. Denosumab is the first and only anti-osteoporosis agent with this mechanism of action. Treatment with denosumab reduces bone resorption and the rate of bone turnover. Moreover, some degree of bone formation appears to be preserved during denosumab therapy, and may underlie the recent finding (in women) that increases in BMD are sustained over at least 10 years of therapy.[11]

ADAMO was a two-year multinational, placebo controlled, randomized trial of 242 males (mean age 65 years) with osteoporosis. Subjects received denosumab 60 mg subcutaneously every six months or placebo. All study participants received calcium/vitamin D supplementation. Significant increases in spine, hip, and femoral neck BMD were observed in the active group versus placebo.[12] Denosumab is highly efficacious in both increasing BMD and reducing fracture risk in women. Although similar anti-fracture effects are likely in men, the effectiveness of denosumab in reducing fracture risk in men has not been evaluated in well-powered trials.

Denosumab may have advantages compared to bisphosphonates in regards to patient treatment adherence since the twice a year subcutaneous denosumab injection can be given and monitored in a primary care/office setting. Oral bisphosphonates are known to have poor treatment persistence, and intravenous zoledronic acid requires special infusion facilities. Although denosumab is more costly than oral alendronate, if one considers the advantage in adherence with denosumab it appears to be cost effective in men.[13]

Denosumab can be used in patients with reduced renal function, but not those on hemodialysis. However, there is an increased risk of hypocalcemia with denosumab in patients with GFRs less than 35 ml/min. Increased susceptibility to infections (skin, bladder, heart) have been reported to be a side effect of denosumab in older women, possibly due to the role of the RANK system in immunological function. Denosumab should be used with caution in immunocompromised patients or those on immune-suppressing medications.

Long term denosumab use in postmenopausal women has a reassuring safety profile. Rates of adverse effects

declined from 165.3 per 100 patient-years in the first year of the trial to 95.9 per 100 patients-years in year seven of a ten year extension trial.[11] Cessation of denosumab therapy is associated with a rapid increase in bone resorption and bone loss, and there is some concern that this period of accelerated bone turnover may be associated with increased fracture risk.[14] At present, the ideal duration of therapy with denosumab and how to handle drug cessation are uncertain.

American Society of Bone and Mineral Research suggests cessation of oral bisphosphonates after five years and cessation of intravenous therapy after three years in women. Treatment is often resumed after a 1-2 year hiatus or 'drug holiday'. Those who remain at high risk for fracture (i.e hip T-score less than -2.5) can potentially remain on therapy for continued fracture prevention.[16] These recommendations are applicable to men even though specific data concerning the optimal duration of therapy are lacking.

Atypical Femur Fractures (AFF) and Osteonecrosis of the Jaw (ONJ) with antiresorptive therapies

AFF are a rare side effect of long term therapy with bisphosphonates and denosumab. These fractures occur in the femoral diaphysis and are marked by four of five major features: minimal trauma, localized periosteal/endosteal thickening of the lateral cortex, transverse orientation of fracture line across the cortex, involves both the medial and lateral cortices, and non-comminuted.[15] The pathophysiology of these fractures is unclear but may be due to prolonged suppression of bone turnover from potent anti-osteoclast therapy. The

ONJ is also a rare side effect of bisphosphonate and denosumab therapy (estimates suggest between 1 in 10,000 to 100,000 patient-years) and is more common following a major dental procedure such as an extraction.[17] During antiresorptive therapy, patients should have good oral hygiene, regular dental visits, and inform their dental care provider of bisphosphonate or denosumab therapy.

Anabolic Therapy

Anabolic agents differ from anti-resorptives (bisphosphonates, RANK-ligand inhibitors

(denosumab)) in that they target the osteoblast, the bone-forming cell. Teriparatide (Forteo™) and abaloparatide (Tymlos™) are analogs of human parathyroid hormone (PTH) that stimulate osteoblast maturation and activity, and the rate of bone remodeling, when provided in daily, subcutaneous bolus dosing. These effects of intermittent administration of PTH-related drugs is strikingly different from the increased bone resorption and bone loss seen during chronic elevations of PTH, as in primary hyperparathyroidism. Teriparatide has been shown to significantly increase BMD in men but the effects of teriparatide on fracture risk reduction have not been studied in adequately powered trials.[18] Abaloparatide has not yet been studied in men. The anabolic agents are very efficacious in increasing spinal (trabecular) bone mass compared to anti-resorptive therapies but are more expensive. Teriparatide is FDA approved for the treatment of men and post-menopausal women at high risk for fracture (i.e. previous spinal compression fracture) or failure/intolerance of a prior anti-resorptive agent. Adverse events are usually not severe and rarely result in cessation of the drug. They can include headache, nausea or leg discomfort. Occasionally mild hypercalcemia can occur. Teriparatide and abaloparatide are not associated with atypical femur fractures nor osteonecrosis of the jaw.

The use of anabolic agents (teriparatide/abaloparatide) is limited to two years because of an increased incidence of osteosarcoma in laboratory rats treated with these agents. They should not be used in patients who may be at risk for osteosarcoma such as Pagets disease of bone, history of external beam radiation, or have unexplained elevation of serum alkaline phosphatase. Seven years of postmarketing surveillance in the United States found no link between teriparatide and osteosarcoma in humans.[19] Teriparatide should not be used in patients with abnormal renal function and who are at risk of secondary hyperparathyroidism.

Androgen Deprivation Therapy and Glucocorticoid Induced Osteoporosis

Androgen-deprivation therapy (ADT), with orchiectomy or gonadotropin releasing hormone agonists such as leuprolide acetate (Lupron™), is a standard therapy for prostate cancer. Because of reductions in androgen and estrogen levels, ADT increases bone

resorption, reduces BMD, and increases fracture risk.[20] Denosumab has been shown to be highly effective in preventing these effects. 1500 men with prostate cancer on ADT were randomized to denosumab 60 mg subcutaneous injection every six months or placebo, all participants received calcium/vitamin D supplementation. Men on denosumab had significant increases in spine, hip, and femoral neck BMD versus placebo.[21] There was also a significant 62% relative risk reduction in vertebral fractures in the denosumab treated group. Bisphosphonates have also been shown to prevent BMD loss or increase BMD in men on ADT but only denosumab has a specific FDA indication for this usage. A higher dose formulation of denosumb (Xgeva™) is used to treat metastatic prostate cancer to the bone and should not be used in combination with Prolia™.[22]

Glucocorticoid induced osteoporosis (GIO) is a distinct metabolic bone disease. Glucocorticoids (e.g. prednisone, hydrocortisone, dexamethasone) increase osteoclast activity and inhibit osteoblast function. Bone density is reduced and the relative risk of fracture is increased in patients on chronic systemic steroids at doses more than 7.5 mg of prednisone equivalent (7.5 mg of prednisone equals 30 mg of hydrocortisone or 0.5 mg of dexamethasone). Moreover, glucocorticoids further increase the risk of fractures independent of BMD.[23] Alendronate, risedronate, zoledronic acid, and teriparatide are FDA approved for the treatment/prevention of GIO in men and women. The American College of Rheumatology recommends teriparatide for those glucocorticoid-treated patients at highest risk of fracture (i.e. known spinal fracture).[24]

Testosterone

Low sex steroid levels in older men are associated with an increased risk of fragility fractures.[25] Low estradiol levels have a more detrimental effect than low testosterone. The effects of transdermal testosterone supplements were studied in a double-blind manner in 210 older men with testosterone levels less than 275 ng/dl in the Bone Trial of the Testosterone Trials.[26] The treatment arm had significant increases in total testosterone, free testosterone, and estradiol levels compared to placebo. Lumbar spine trabecular BMD increased 6.8% compared with placebo after one year. Estimated spinal bone strength assessed by finite

element analysis increased by 8.5%. However, testosterone replacement therapy has not been shown to prevent fractures in men with osteoporosis, and the long-term safety of testosterone therapy remains uncertain.[27] Therefore, anti-osteoporosis agents should be preferentially used in men with osteoporosis, even if they are concurrently receiving androgen replacement therapy for hypogonadal symptoms.[28]

Summary

Male osteoporosis has been recognized in the past 20 years as a major health issue.[29] Anti-resorptive agents (bisphosphonates, denosumab) increase bone density in men with osteoporosis. Teriparatide, an anabolic agent, also increases bone density in men. Although the available clinical trials have not been adequately powered to definitively demonstrate a reduction in the risk of clinical fractures, the available data strongly suggest that these therapies are effective in reducing fracture rates in men. These agents can also prevent bone loss and fractures due to special circumstances, as in androgen deprivation for prostate cancer and steroid induced osteoporosis. Adequate calcium and vitamin D supplementation should be ensured in the treatment of male osteoporosis. Hypogonadism and age-related declines in sex steroid levels contribute to bone loss and fragility fractures, but testosterone replacement therapy has yet to be shown to be safe and effective for long term fracture prevention.

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