Osteoporosis in Men

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Case

A 58-year-old Caucasian man with a past history of degenerative disc disease, osteoarthritis, severe gastroesophageal reflux disease (GERD), alcohol dependence, hepatic steatosis, and prior heavy smoking was initially referred for evaluation for osteoporosis after presenting to the emergency department with complaints of back pain. He was found to have compression deformities of T4–T7 with evidence of an acute compression fracture of T7. He reported significant loss of height but no history of trauma. Upon further interview, it was noted he had a T4 compression fracture at age 53 that was evident on an X-ray, which led to bone mineral density testing but no treatment. He underwent a kyphoplasty at T7 before our evaluation.

The patient had no family history of osteoporosis or prior use of glucocorticoids or androgen deprivation therapy. He did not consume dairy products or eat other calcium rich foods but reported taking cholecalciferol 2000 international units (50 μg)

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daily. His physical activity was limited by back pain. On exam, he was in a wheelchair because of the distance from the parking lot to the clinic. Vital signs were normal, and his BMI was 32.5 kg/m^2. Height measurements had not been taken previously; the patient had provided his estimated height. He had a few teeth in poor condition, and his back was diffusely tender to palpation.

Assessment and Diagnosis

Basic laboratory tests were normal: calcium, phosphate, albumin, renal function, and alkaline phosphatase. His 25-hydroxyvitamin D level was 25.4 ng/mL. A spot urine calcium to creatinine ratio was low. Given the patient's young age, additional laboratories were obtained to exclude secondary causes such as hypogonadism and hyperthyroidism. Malabsorption and celiac disease were not assessed. One year prior to presentation, a bone mineral density demonstrated borderline osteopenia with T-scores of -1 at both the lumbar spine and hip. His atraumatic fractures of the spine were enough to justify the diagnosis of osteoporosis and to require treatment.

Osteoporosis is a musculoskeletal disease characterized by decreased bone quantity as measured by bone mineral density and decreased bone quality, resulting in increased risk of fragility fractures. For a long time, men were not screened for osteoporosis until further investigation revealed the impact of fractures in men on morbidity, mortality, and societal cost.

According to the WHO diagnostic classification, osteoporosis is defined by BMD at the hip or lumbar spine that is less than or equal to 2.5 standard deviations below the mean BMD of a young-adult reference population. This is expressed as a T-score of −2.5. Most organizations believe that the young adult white female database should be used for the calculation of the T-score for all adults. Low bone mass or osteopenia is defined as a T-score between −1 and −2.5, and the great majority of fractures occur in such people because there are so many more people in this category. However, it is instructive to note that fragility fractures can occur in some patients with normal bone density, suggesting that poor bone quality is the reason for their fracture risk, as illustrated

by this case. The Endocrine Society Male Osteoporosis Guideline [1] suggests that men should be screened for osteoporosis with BMD at age 70. A recent observational study [2] reported that performing BMD testing at age 80 led to fewer fractures.

Trabecular bone score (TBS) is a recently developed tool that performs novel gray-level texture analysis on lumbar spine DXA images and thereby captures information relating to trabecular microarchitecture, a possible indicator of bone quality. For TBS to usefully add to BMD and clinical risk factors in osteoporosis risk stratification, it must be independently associated with fracture risk, readily obtainable, and, ideally, present a risk which is amenable to osteoporosis treatment [3].

There are two main types of osteoporosis in men: primary and secondary. In cases of primary osteoporosis, either the condition is caused by age-related bone loss (sometimes called *senile osteoporosis*) or the cause is unknown (*idiopathic osteoporosis*). The term idiopathic osteoporosis is typically used only for men younger than 70 years old; in older men, age-related bone loss is assumed to be the cause, although there may be many risk factors present [4–6]. There are multiple theories as to the etiology of idiopathic male osteoporosis, such as genetic factors or a family history. Several epidemiological and clinical observations have shown that osteoporosis in both men and women has an important genetic component. Multiple genes may have effects on bone development, strength, and density [7]. In many studies, most men with osteoporosis have at least one (sometimes more than one) secondary cause. In cases of secondary osteoporosis, low bone mass is due to certain lifestyle behaviors, diseases, or medications [4–6].

Secondary causes in men include the use of glucocorticoids, immunosuppressive drugs, hypogonadism, excessive alcohol consumption, smoking, chronic obstructive pulmonary disease (COPD) or asthma, cystic fibrosis, malabsorption, hypercalciuria, anticonvulsant medications, thyrotoxicosis, hyperparathyroidism, immobilization, bariatric surgery, ankylosing spondylitis, rheumatoid arthritis, and systemic mastocytosis. There is overlap between what could be called a risk factor for osteoporosis and a secondary cause [5, 6]. Of the listed secondary causes, medica-

tions (especially glucocorticoids, androgen deprivation therapy for prostate cancer, and anti-seizure medications), COPD, hyperparathyroidism, alcohol abuse, hypercalciuria, and hypogonadism are probably the most common causes of secondary osteoporosis in men.

Management

Risks and benefits of osteoporosis treatment were discussed with the patient after which he elected to start therapy with intravenous zoledronic acid. He was not a good candidate for daily injections of the anabolic agent teriparatide because of his alcohol abuse, and he had severe gastroesophageal reflux disease, which made oral bisphosphonates not a good choice. The patient subsequently received three doses of zoledronic acid over 4 years. In addition, he was counseled on fall prevention strategies, advised to perform weight-bearing exercises, and recommended to consume 1200 mg of calcium and 2000 IU of vitamin D daily.

The patient was seen annually in the metabolic bone clinic, and his vitamin D supplementation was adjusted to a target of 25-hydroxyvitmain D >30 ng/mL. He was ambulating with a cane and had incorporated dairy into his diet (yogurt and cheese). Physical exam during follow-up visits was notable for obesity, mild kyphosis, and poor dentition (but no osteonecrosis of the jaw). A follow-up BMD demonstrated increased density in the spine and total hip, 4.9% and 2.3%, respectively (see Table 7.1). However, the spine trabecular bone score (TBS) T-score was

Table 7.1 Comparison between pretreatment (initial) and posttreatment (after 3.5 years) BMD

BMD	T-score spine L1–4	T-score right hip	T-score femoral neck	T-score distal 1/3 radius
Pretreatment (08/2014)	−1	+0.7	−1	+1.5
Posttreatment (02/2019)	−0.2	1.8	−0.8	+2.7

−2.3; it had not been available previously. A full-length image of his left femur did not show any early evidence of atypical fracture.

Age-appropriate intake of calcium and vitamin D is advised for all patients. The National Academy of Medicine (formerly the Institute of Medicine) recommends men ages 50–70 consume 1000 mg/day of elemental calcium [8]. If an adequate dietary intake cannot be achieved, calcium supplements should be used. For adults age 50 and older, a vitamin D intake of 800–1000 IU daily is recommended by the National Osteoporosis Foundation [9].

As with our patient, and with any patient at risk of deficiency or with osteoporosis, 25-hydroxyvitamin D levels should be measured. Supplements should be recommended with the goal of achieving a serum 25-hydroxyvitamin D level of approximately 30 ng/mL [10]. While vitamin D deficiency can be treated with weekly doses of ergocalciferol at 50,000 IU/week for 8–12 weeks, many experts prefer cholecalciferol in daily doses of up to 4000 IU (100 μg) daily with lower doses as maintenance.

Regular weight-bearing and muscle-strengthening exercises are recommended with the intention of improving agility, strength, and balance. Some examples are Tai Chi, walking, jogging, tennis, and weight training. Fall risk assessment should be individualized and will be impacted by all the above. Other potentially modifiable factors include vision impairment, polypharmacy, and home safety. Tobacco use cessation and avoidance of excessive alcohol consumption are also crucial parts of this comprehensive approach to osteoporosis management.

The US FDA-approved pharmacotherapy for osteoporosis treatment in men includes bisphosphonates (alendronate, risedronate, ibandronate, and zoledronic acid), teriparatide, and denosumab. Among bisphosphonates, zoledronic acid increased bone density to a greater extent in men on oral glucocorticoids than did risedronate [11]. In an international trial with vertebral fracture as the primary outcome, intravenous zoledronic acid was found to provide a 67% relative fracture risk reduction, compared to placebo infusion [12]. This is similar to the drug's impact in women.

Denosumab was initially approved in 2011 to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. The following

year, it was approved to increase bone mass in men with osteoporosis at high risk for fracture or those who have failed or are intolerant to other therapies [13].

The anabolic agent teriparatide is indicated for treatment of male osteoporosis with high fracture risk and for glucocorticoid-induced osteoporosis. It has shown equivalent increases in BMD in men and women; interestingly, the described bone loss after discontinuation of therapy was greater in women than men [14].

Abaloparatide is a modification of parathyroid hormone-related peptide approved for treatment of osteoporosis in postmenopausal women. Recent studies [15, 16] have shown that in osteopenic orchiectomized rats, abaloparatide can increase endocortical bone formation and improve trabecular bone volume and microarchitecture by augmenting osteoblast numbers without increasing osteoclast numbers. Based on the above, it may be warranted to consider off-label use of this drug for male osteoporosis. There is an ongoing study of abaloparatide in men with osteoporosis. The newest anabolic agent, romosozumab, is FDA approved for postmenopausal women, but there is evidence [17] that it works similarly in men.

It is worth mentioning that treatment decisions are made according to the patient's comorbidities, preferences, and cost. In clinical practice, it is common to have patients start on antiresorptive therapy (usually oral bisphosphonates) and later transition to anabolic agents after intolerance, unsatisfactory response, or drug failure. However, prior use of bisphosphonates may blunt or delay the impact of anabolic agents on bone density [18, 19]. For this reason, many experts now suggest using anabolic drugs first in patients at highest risk for fracture. There are no studies of drug holidays or even long-term treatment of osteoporosis in men. Hence, general recommendations for women (e.g., [20]) are used to guide long-term treatment.

Outcome

At the most recent visit, which was by telephone because of the pandemic, the patient had been sober for 2 years, had stayed off tobacco, and had improved his diet and exercise. A follow-up in

person assessment and repeat BMD were planned to consider whether anabolic treatment or other anti-resorptive therapy would be helpful at this time. He has had no further clinical fractures.

Clinical Pearls

- Osteoporosis needs to be evaluated and treated in men.
- Fractures can occur in patients with normal bone density. A clinical fracture is a sentinel event.
- Evaluation and treatment of men are similar to that in women.
- Very high fracture risk patients should be considered for anabolic treatment first.

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References

1. Watts NB, et al. Osteoporosis in men: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2012;97(6):1802–22.
2. Colon-Emeric CS, et al. Limited osteoporosis screening effectiveness due to low treatment rates in a national sample of older men. Mayo Clin Proc. 2018;93:1749–59.
3. Harvey NC, et al. Trabecular bone score (TBS) as a new complementary approach for osteoporosis evaluation in clinical practice. Bone. 2015;78:216–24.
4. Willson T, et al. The clinical epidemiology of male osteoporosis: a review of the recent literature. Clin Epidemiol. 2015;7:65–76.
5. Adler RA. Update on osteoporosis in men. Best Pract Res Clin Endocrinol Metab. 2018;32:758–72.
6. Ryan CS, et al. Osteoporosis in men: the value of laboratory testing. Osteoporos Int. 2011;22:1845–53.
7. Chen S, et al. Genetic burden contributing to extremely high or low bone mineral density in a senior male population from the osteoporotic fractures in men study (MrOS). JBMR Plus. 2020;4(3):e10335.

8. Ross AC, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab. 2011;96(1):53–8.
9. Cosman F, et al. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int. 2014;25(10):2359–81.
10. El-Hajj Fuleihan G, et al. Serum 25-hydroxyvitamin D levels: variability, knowledge gaps, and the concept of a desirable range. J Bone Miner Res. 2015;30:1119–33.
11. Reid DM, et al. Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): a multicentre, double-blind, double-dummy, randomized controlled trial. Lancet. 2009;373:1253–63.
12. Boonen S, et al. Fracture risk and zoledronic acid therapy in men with osteoporosis. N Engl J Med. 2012;367:1714–23.
13. Sidlauskas KM, et al. Osteoporosis in men: epidemiology and treatment with denosumab. Clin Interv Aging. 2014;9:593–601.
14. Leder BZ, et al. Effects of teriparatide treatment and discontinuation in postmenopausal women and eugonadal men with osteoporosis. J Clin Endocrinol Metab. 2009;94(8):2915–21.
15. Besschetnova T, et al. Abaloparatide improves cortical geometry and trabecular microarchitecture and increases vertebral and femoral neck strength in a rat model of male osteoporosis. Bone. 2019;124:148–57.
16. Chandler H, Lanske B, Aurore Varela A, et al. Abaloparatide, a novel osteoanabolic PTHrP analog, increases cortical and trabecular bone mass and architecture in orchiectomized rats by increasing bone formation without increasing bone resorption. Bone. 2019;120:148–55.
17. Lewiecki EM, et al. A phase III randomized placebo-controlled trial to evaluate efficacy and safety of romosozumab in men with osteoporosis. J Clin Endocrinol Metab. 2018;103:3183–93.
18. Leder BZ. Optimizing sequential and combined anabolic and antiresorptive osteoporosis therapy. JBMR Plus. 2018;2(2):62–8.
19. Cosman F. Anabolic therapy and optimal treatment sequences for patients with osteoporosis at high risk for fracture. Endocr Pract. 2020;26(7):777–86.
20. Adler RA, et al. Managing osteoporosis in patients on long-term bisphosphonate treatment: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2016;31(1):16–35.