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Male Osteoporosis

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Over the past few years, our understanding of osteoporosis has shifted. We no longer consider it a disease exclusively in postmenopausal women, but have come to realize that it can affect men as well. Despite the increased prevalence of male osteoporosis, there are very little data to guide clinicians on how to diagnose, investigate, and/or treat men with the disease. The case and discussion points in this issue of *Endocrinology Rounds* provide an evidence-based approach to the management of male osteoporosis.

The Case

Mr. R. is a 53-year-old man who is seen annually for routine medical assessment. Over the past year, he has been generally well; however, during the last month, he slipped on ice and fractured his wrist. Mr. R. has smoked one package of cigarettes a day for the past 30 years. He drank 4 to 6 glasses of vodka a day for the past 20 years, but stopped drinking 6 months ago. He has never used steroids or other medications. He has no complaints of sexual dysfunction, height loss, or other low trauma fractures. His mother and sister have been diagnosed with osteoporosis. His physical examination is normal.

What is meant by “osteoporosis” in a man?

There is no consensus on the definition of osteoporosis in a man. However, it has been suggested that osteoporosis be defined as “the presence of a low trauma fracture by age 40.” Clinically, a low trauma fracture is defined as one that occurs as a result of minimal trauma such as a fall from a standing height or less or no identifiable trauma.^{1,2} Osteoporosis can also be defined by the bone mineral density (BMD) T-score. The World Health Organization defines osteoporosis as a BMD T-score that is lower than -2.5 at the hip or the spine.¹ The T-score is the number of standard deviations above or below the mean BMD in a reference population of young healthy adults of the same sex and race. It is important to note that this definition applies to postmenopausal women and, currently, there is no standard definition of osteoporosis in men.

Choosing a T-score that defines osteoporosis in men is somewhat controversial. For example, should we use the same T-score in men that we use in women (ie, less than or equal to -2.5)? In women, there is a consistent relationship between low BMD and increased fracture risk that is quantified by the “relative risk per standard deviation decrease in BMD.” A relative risk/standard deviation (RR/SD) of 1.5 indicates that a BMD score of 1 SD below the mean for a young adult (ie, a T-score of -1) is associated with a 50% increase in fracture risk.³⁻⁸ Among postmenopausal Caucasian women, the RR/SD between hip BMD and hip fracture is 2.6.⁶ In men, however, there is a paucity of data on the relationship between fracture risk and BMD and, as such, it is not clear if we should use the same T-score.

Another area of controversy is which gender should serve as the reference range – young men or young women? Some suggest a comparison to young women, but one reason



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Table 1: Average 10-year probability (%) of an osteoporotic fracture by sex, age, and BMD expressed as a T-score.

Age (years)	Overall average probability	T-score				
		1	0	-1	-2.0	Below -2.5
Men						
50	3.3	1.8	2.7	4.2	6.3	9.2
55	3.9	1.9	3.0	4.6	7.0	10.4
60	4.9	2.5	3.6	5.4	7.9	11.6
65	5.9	3.0	4.3	6.2	8.8	13.0
70	7.6	3.4	5.1	7.4	10.9	16.2
75	10.4	4.1	6.3	9.6	14.4	21.5
80	13.1	5.3	7.7	11.1	15.8	23.2
85	13.1	5.3	7.5	10.4	14.3	21.4
Women						
50	6.0	2.4	3.8	5.9	9.2	13.9
55	7.8	2.6	4.1	6.7	10.7	16.8
60	10.6	3.2	5.1	8.2	13.0	20.5
65	14.3	4.0	6.3	10.0	15.6	24.9
70	18.9	4.3	7.1	11.5	18.3	29.8
75	22.9	4.2	7.0	11.8	19.4	32.6
80	26.5	4.6	7.7	12.7	20.5	34.4
85	27.0	4.5	7.4	12.0	19.1	33.1

to refrain is that men have bigger bones than women, which leads to an increase in areal bone density. Areal BMD (ie, bone mineral content/bone area) is the factor that is measured by BMD machines; thus, dual-energy x-ray absorptiometry (DEXA) overestimates BMD in men relative to women. What we do know is that correction for skeletal size eliminates differences in BMD among men and women. Men with fractures have lower BMD than men without fractures, and men and women have the same risk of fractures at equivalent BMDs.⁹⁻¹² Based on these data, we recommend that osteoporosis in men be defined as “a T-score of less than or equal to -2.5 compared to healthy young men. Most, but not all, manufacturers use male reference ranges to report T-scores for men.

It is important to note that, similar to women, fracture risk increases in men, both with increasing age and decreasing BMD (Table 1).¹³ For example, the 10-year probability of fracture in a 50-year-old man with a T-score of -2.0 is 6.3%. This increases to 14.3% in an 83-year-old man with the same T-score. The interaction between age and BMD and its effect on fracture risk highlights the importance of considering absolute fracture risk and not just BMD values when making treatment decisions for both men and women.

Is osteoporosis in men a cause for concern?

The estimated lifetime risk of any fracture is almost 40% in white women and 13% in white men aged ≥50 years.^{2,14,15} Furthermore, data from the Canadian Multi-centre Osteoporosis Study (CaMos) demonstrated that

the prevalence of radiographic vertebral fractures is similar in men (21.5%) and women (23.5%).¹⁶ CaMos also demonstrated that both men and women have a decrease in their quality of life following osteoporotic fractures.¹⁷ As in women, the incidence of fractures in men increases with increasing age so that, as our population ages, the prevalence of osteoporosis in men increases. What is particularly concerning about osteoporosis in men is that, compared with women, they have greater morbidity and mortality after hip and spine fractures. For example, after a spine fracture, men have an approximate 2.4-fold increase in mortality compared with a 2.0-fold increase in women. After a hip fracture, men have an approximate 3.2-fold increase in mortality, compared to a 2.0-fold increase in women.¹⁸ Furthermore, after a hip or spine fracture, 5-year survival is decreased to a greater degree in men than in women (ie, 0.72 in men versus 0.84 in women).¹⁹ The increased morbidity and mortality following fractures, together with the fact that once a person has had one fracture, the risk of having a second within one year increases by 20%, highlights the importance of preventing and treating osteoporosis in men.²⁰

What are the risk factors for osteoporosis in men?

As is the case for women, the two primary risk factors for osteoporotic fractures in men are likely low BMD and falls (or diseases that increase the risk of injurious falls).²¹ The major causes of low BMD are failure to attain peak bone mass and risk factors for ongoing bone loss. In men, peak bone mass is typically achieved by age 20 at the latest. Several factors influence the amount of bone attained at peak.

- Genetics accounts for 70% of bone mass and likely explains why boys have greater peak bone mass than girls and why blacks have greater peak bone mass than whites.
- Hormonal factors also influence peak bone mass; therefore, boys with delayed puberty (no physical manifestations of sexual maturation by age 14 years) have lower peak bone mass than those without delayed puberty.
- Intake of calcium and vitamin D and physical activity are other factors that may influence peak bone mass. However, there are less data about how these factors influence peak bone mass in boys compared to the data available in girls.⁴

Causes of ongoing bone loss include age, which accounts for a 5% to 10% decrease in BMD per decade. Glucocorticoid excess (endogenous or exogenous) and chronic illnesses (eg, rheumatoid arthritis and inflammatory bowel disease) are also associated with bone loss. In addition, sex steroid deficiency (eg, androgen-deprivation therapy for prostate cancer) is known to cause bone loss and has recently been demonstrated to increase fracture

Table 2: Risk factors for male osteoporosis	
Risk factors for failure to attain peak bone mass	Risk factors for ongoing bone loss
<ul style="list-style-type: none"> Genetic predisposition (accounts for 70% of peak bone mass) Dietary factors (low intake of calcium or vitamin D during childhood or malnutrition) Lifestyle factors (decreased physical activity during childhood) 	<ul style="list-style-type: none"> Age-related bone loss (approximately 5% to 10% per decade) Sex steroid deficiencies Glucocorticoid excess Chronic illnesses Dietary factors (decreased intake of calcium or vitamin D) Lifestyle factors (decreased physical activity)

risk.²² Other factors that may play a role in ongoing bone loss include inadequate intake of calcium, vitamin D, and lack of exercise, although there are far fewer data concerning these factors and their effects on bone in men compared with women. Table 2 lists the factors that influence peak bone mass and others that may cause ongoing bone loss.

In contrast to the data on BMD, very few studies have examined risk factors for fracture in men. Table 3 lists the risk factors in the history and physical examination (based on a case-controlled study of about 500 men) that should be considered associated with hip fractures in men.^{23,24} Note that while many other factors have been purported to be associated with an increased risk of hip fracture in the medical literature (eg, hypogonadism, hyperthyroidism, chronic use of anticonvulsants, and

multiple myeloma), they appear to have relatively little influence on the occurrence of hip fractures in the community.

When assessing men (and women) with low trauma fractures, it is important to inquire about falls and assess risk factors for falls. Approximately 90% of hip fractures are due to falls and 5% to 10% of falls result in hip fractures. Of the men and women who have hip fractures due to falls, over half have normal BMD. This highlights the importance of considering absolute fracture risk and not just BMD when making treatment decisions. Not only does falling lead to fractures, it also leads to a fear of future falls, which decreases independence and mobility. Furthermore, it has been shown that multiple falls lead to nursing home admissions. Risk factors for falls include impaired vision, physical inactivity (which decreases muscle strength and coordination and may have a direct effect on BMD), use of sedatives, impaired mental status, and environmental home hazards (eg, area rugs and dim lighting).²⁵⁻²⁸ Assessing risk factors for falls can be done very quickly in the office and these factors are often reversible.²⁹ As such, it is worthwhile to inquire about risk factors for falls in men who have had low trauma fractures.

How should osteoporosis in men be evaluated (Table 3)?

Few data are available concerning the management of osteoporosis in men. Men suspected of having osteoporosis (eg, those with medical conditions or using medications associated with an increased risk of fracture) and all men who have had a low trauma fracture since age 40 should have BMD testing.^{4,30} In addition, the recently published Canadian guidelines suggest measuring bone density in men aged >65 years since, after this age, frac-

Table 3: Clinical approach to the evaluation of male osteoporosis	
History	Physical examination
<p>Inquire about:</p> <ul style="list-style-type: none"> History of low trauma fractures, back pain, height loss Family history of osteoporotic fracture in first degree relative (particularly maternal hip fracture) Gastric surgery, pernicious anemia, diarrhea, weight loss (may be indicative of malabsorption syndrome) Physical activity History of falls Neurologic conditions (Parkinson's, hemiplegia) that increase propensity to fall Presence of vertigo/dizziness Current and past use of alcohol (and amount) Current smoking Current and past use of oral glucocorticoids (at least 7.5 mg of prednisone or equivalent for at least 3 months) Changes in shaving habits, hair growth, sexual function, problems with fertility, galactorrhea (may be indicative of hypogonadism) 	<p>Inspect for</p> <ul style="list-style-type: none"> Stigmata of chronic alcohol abuse Cushingoid appearance Thoracic kyphosis <p>Measure</p> <ul style="list-style-type: none"> Height Weight <p>Assess</p> <ul style="list-style-type: none"> Visual acuity Balance

ture risk increases independently of other risk factors.²

Men who have osteoporosis (confirmed by either BMD testing or the presence of a low trauma fracture) should undergo a history and physical examination to identify any underlying cause of the osteoporosis. Laboratory testing can also be done to rule-out more common causes of secondary osteoporosis. It is often suggested that men with osteoporosis are more likely to have secondary causes of their disease, compared with women. This common misconception is based on the fact that, until recently, most men diagnosed with osteoporosis had severe symptomatic disease and were often referred to specialists for investigation (so-called “selection bias”). This misconception is likely to change as our awareness of male osteoporosis increases since more and more otherwise healthy men will be diagnosed with osteoporosis and they will be diagnosed earlier.

While few studies have addressed the clinical utility of laboratory testing for secondary osteoporosis, a reasonable evaluation might include a complete blood count, serum calcium, alkaline phosphatase, serum creatinine, free testosterone, and a 24-hour urine for calcium and creatinine. Other tests that could be ordered, based on clinical suspicion of disease, include serum prolactin (hypogonadism), serum protein electrophoresis (multiple myeloma), serum parathyroid hormone (hyperparathyroidism), tissue transglutaminase antibodies, and serum IgA for celiac disease.

Several studies have demonstrated that serum estradiol is more strongly correlated with BMD than testosterone in men.^{31,32} Further, low serum estradiol may be a risk factor for future hip fractures in elderly men.³³ However, there is no evidence that estrogen replacement therapy is an effective treatment for men with osteoporosis and low estradiol levels. Thus, measuring estradiol is not currently advised.

If the history, physical examination, and laboratory testing fail to reveal the cause of the osteoporosis – and this may not be unusual – empiric therapy (see below) and close follow-up (office visits every 6 months and yearly BMD testing) should be considered. Men with substantial bone loss (cumulative loss of 5% of BMD at one or more sites during two separate measures) or those with ongoing fractures during treatment should be referred to a specialist in bone disease.

How should osteoporosis in men be treated?

All men should be advised to take calcium and vitamin D. For men aged ≥ 50 years, the Canadian Guidelines recommend 1500 mg of calcium and 800

IU of vitamin D daily. In addition, treatment with either alendronate or risedronate can be considered. A 2-year, placebo-controlled, randomized trial in men with osteoporosis, some of whom had low testosterone levels, demonstrated that, compared with placebo, alendronate at 10 mg daily increased BMD and decreased the incidence of vertebral fractures.³⁴ Similarly, data (published only in abstract form) from an open-label trial of risedronate at 5 mg daily demonstrated that this bisphosphonate also increased BMD and decreased the incidence of vertebral fractures in men.³⁵

The anabolic agent, human parathyroid hormone (PTH), 1 to 34, has also been studied in men. Data from two randomized controlled trials demonstrated that PTH increases BMD at the hip and spine (approximately 25% at the spine and 6% at the hip) compared to baseline in one study after 24 months of treatment with PTH at 40 μg day.^{36,37} There are no published data on fractures. One should consider PTH treatment in men with severe osteoporosis (T-score below -2.5 and an osteoporotic fracture) or in those who fracture while taking alendronate or risedronate. It would be reasonable to refer patients being considered for PTH therapy to a bone specialist. PTH is prescribed as 20 μg a day subcutaneously for 18 months and, after the treatment is completed, patients should be started on alendronate or risedronate to maintain BMD. Other agents that could be used include:

- Etidronate: several small studies have demonstrated increases in spine BMD, but not hip BMD, in men taking etidronate,^{38,39} however, there are no fracture data.
- Calcitonin can also be used; a small (n=5) non-randomized study demonstrated that 100 IU of subcutaneous calcitonin 3 times a week increased BMD by 3% at the hip and spine.⁴⁰

If a cause of osteoporosis is identified, specific treatments should be directed towards the cause. For example, men with steroid-induced osteoporosis should be treated with a bisphosphonate, while those with alcoholism should be advised to abstain from alcohol.

The use of testosterone therapy should be limited to men with symptoms of low testosterone (eg, decreased libido or decreased sexual function) who have no contraindications to its use (eg, prostatic hypertrophy or prostate cancer). Note that data to support the use of testosterone in men with hypogonadism are limited; there are only a few small studies with short follow-up and BMD assessment.⁴¹⁻⁴³ Thus, there are no data on the reduction of fracture risk or the long-term side effects.

Case summary

BMD testing in Mr. R. revealed a T-score of -2.6 at the lumbar spine (L1 to L4) and -3.4 at the total hip. All laboratory tests were normal. It is highly likely that Mr. R.'s low BMD is attributable to his excessive alcohol intake, smoking, and family history of osteoporosis. Mr. R. was advised to stop smoking and counseled to continue his abstinence from alcohol. In addition, given his prior low trauma fracture and low BMD, he was advised (to his surprise) that he had osteoporosis. He was prescribed risedronate 35 mg on a weekly basis, as well as calcium and vitamin D. He will be seen again in 4 weeks to monitor his progress.

Take home points

This case and the discussion following it highlight 5 points concerning male osteoporosis:

- Osteoporosis is common in men.
- Men with low trauma fractures should be considered to have osteoporosis.
- Osteoporosis can be diagnosed by BMD testing. A T-score of less than or equal to -2.5, compared to young healthy men, should be the basis of the diagnosis.
- The etiology of osteoporosis in men has not been extensively studied, but there are likely to be a large number of men with so-called "idiopathic osteoporosis."
- Treatment for osteoporosis in men is the same as for women, namely antiresorptive (alendronate and risedronate) or anabolic agents (PTH).

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Abstract of interest

The Near Absence of Osteoporosis in Older Men with Fractures

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BACKGROUND: The burden of osteoporotic fractures in older men is significant, and treatment rates for secondary prevention are low. The study objectives were to 1) Characterize older men with fractures associated with osteoporosis, 2) Determine if treatment rates for osteoporosis are improving, and 3) Identify patient, healthcare benefit and utilization, and clinician characteristics that are significantly associated with treatment.

METHODS: Design. Retrospective cohort study used multiple logistic regression to evaluate pre-fracture factors for their association with osteoporosis treatment in the 6-month post-fracture period.

Setting. A non-profit health maintenance organization in the United States.

Participants. 1,171 men aged 65 or older with any new fracture associated with osteoporosis between January 1, 1998, and June 20, 2001.

Main Outcome Measure. Pharmacologic treatment for osteoporosis in the 6 months after the index fracture.

RESULTS: Average age was 76.7 years; 3.3% had a diagnosis of osteoporosis and 15.2% a diagnosis or medication associated with secondary osteoporosis. Only 7.1% of the study population received a medication for osteoporosis following the index fracture, and treatment rates did not improve over time. In the multivariate model, a higher value on the Charlson Comorbidity Index (odds ratio 1.26, 95% confidence interval 1.05-1.51), having an osteoporosis diagnosis (odds ratio 8.11, 95% confidence interval 3.08-21.3), chronic steroid use (odds ratio 5.37, 95%

confidence interval 2.37-12.2), and a vertebral fracture (odds ratio 16.6, 95% confidence interval 7.8-31.4) were significantly associated with drug treatment. Bone mineral density measurement was rare (n=13, 1.1%).

CONCLUSIONS: There is under-ascertainment of osteoporosis and modifiable secondary causes in older men with fractures. Fracture does not prompt sufficient bone mineral density measurement or treatment. Information systems merging diagnostic and treatment information can help delineate gaps in patient management. Interventions showing promise in other conditions should be evaluated to improve care for osteoporosis.

Abstract #1113 presented at the 26th Annual Meeting of the American Society for Bone and Mineral Research.

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