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*The authors reported no  
potential conflict of interest  
relevant to this article.*

# Osteoporosis: What about men?

Men sustain up to 40% of osteoporotic fractures, with potentially fatal results. But because osteoporosis is largely viewed as a women's disease, its presence in men is often missed.

## PRACTICE RECOMMENDATIONS

- › Order dual-energy x-ray absorptiometry of the spine and hip for men who are at increased risk for osteoporosis and candidates for pharmacotherapy. **C**
- › Prescribe bisphosphonates for men with osteoporosis to reduce the risk of vertebral fractures. **A**
- › Advise men who have, or are at risk for, osteoporosis to consume 1000 to 1200 mg of calcium and 600 to 800 IU of vitamin D daily. **B**

### Strength of recommendation (SOR)

- A** Good-quality patient-oriented evidence
- B** Inconsistent or limited-quality patient-oriented evidence
- C** Consensus, usual practice, opinion, disease-oriented evidence, case series

**W**ith older women in the United States about 4 times more likely than their male counterparts to develop osteoporosis,<sup>1,2</sup> physicians often fail to screen for—or to treat—low bone mass in men. There are plenty of reasons why they should.

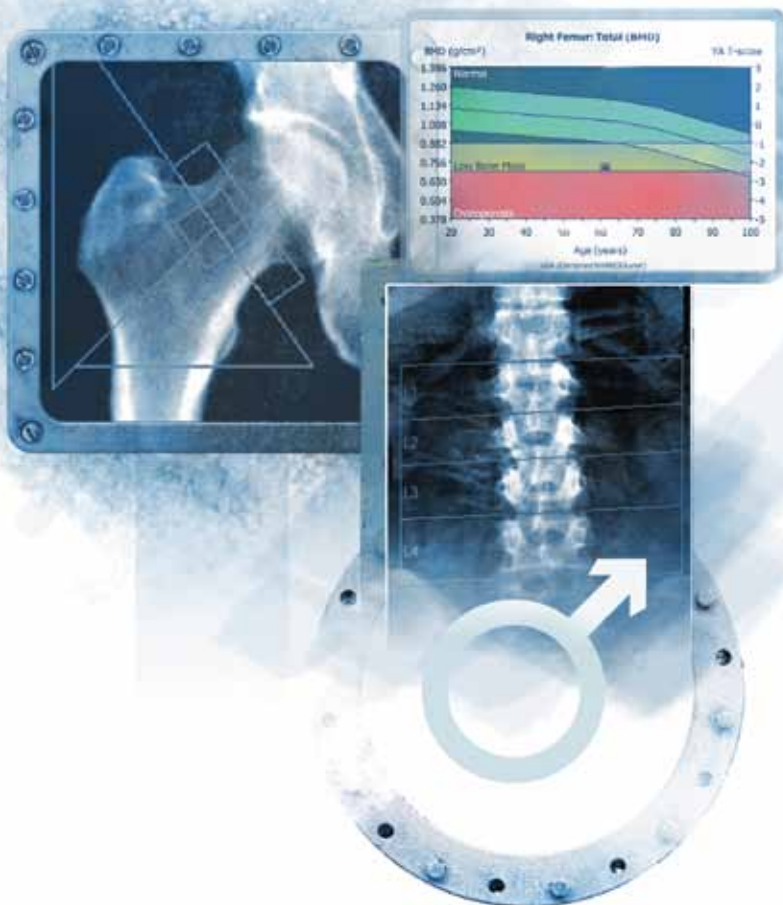
First and foremost: Osteoporosis is a leading cause of morbidity and mortality in the elderly.<sup>3</sup> An estimated 8.8 million American men suffer from osteoporosis or osteopenia.<sup>3</sup> And, although only about 20% of osteoporosis patients are male, men sustain between 30% and 40% of osteoporotic fractures.<sup>1,2</sup> What's more, hip fracture in men has a mortality rate of up to 37.5%—2 to 3 times higher than that of women with hip fracture.<sup>4,5</sup>

Clearly, then, it is crucial to be aware of the risks of osteoporosis faced by both men and women as they age. Here's a look at what to consider, when to screen, and how to treat male patients who have, or are at risk for, osteoporosis.

## Which men are at risk?

The incidence of fractures secondary to osteoporosis varies with race/ethnicity and geography. The highest rates worldwide occur in Scandinavia and among Caucasians in the United States; black, Asian, and Hispanic populations have the lowest rates.<sup>6,7</sup> As with women, the risk of osteoporotic fracture in men increases with age. However, the peak incidence of fracture occurs about 10 years later in men than in women, starting at about age 70.<sup>8</sup> Approximately 13% of white men older than 50 years will experience at least one osteoporotic fracture.<sup>9</sup>

There are 2 main types of osteoporosis: primary and secondary. Up to 40% of osteoporosis in men is primary,<sup>4</sup> with bone loss due either to age (senile osteoporosis) or to an unknown cause (idiopathic osteoporosis).<sup>10</sup> For men 70 years or



The most common causes of secondary osteoporosis in men include exposure to glucocorticoids, primary or secondary hypogonadism, diabetes, alcohol abuse, and smoking.

older, osteoporosis is assumed to be age related. Idiopathic osteoporosis is diagnosed only in men younger than 70 who have no obvious secondary cause.<sup>10</sup> There are numerous secondary causes, however, and most men with bone loss have at least one.<sup>4</sup>

**Common secondary causes:  
Lifestyle, medical conditions, and meds**

The most common causes of secondary osteoporosis in men are exposure to glucocorticoids, primary or secondary hypogonadism (low testosterone), diabetes, alcohol abuse, smoking, gastrointestinal (GI) disease, hypercalciuria, low body weight (body mass index <20 kg/m<sup>2</sup>), and immobility (TABLE 1).<sup>4,5,8,10</sup>

Chronic use of corticosteroids, often used to treat chronic obstructive pulmonary disease (COPD), asthma, and rheumatoid arthritis, directly affects the bone, decreasing skeletal muscle, increasing immobility, and reducing intestinal absorption of calcium as well as serum testosterone levels.<sup>10</sup> Men with androgen deficiency (which may be due to androgen deprivation therapy to treat pros-

tate cancer) or chronic use of opioids are also at increased risk.<sup>4,5,10-12</sup>

**Diagnostic criteria and screening**

The World Health Organization has established diagnostic criteria for osteoporosis using bone mineral density (BMD), reported as both T-scores and Z-scores as measured on dual-energy x-ray absorptiometry (DEXA) scan.<sup>13</sup> The T-score represents the number of standard deviations above or below the mean BMD for young adults, matched for sex and race, but not age. It classifies individuals into 3 categories: normal; low (osteopenia), with a T-score between -1 and -2.5; and osteoporosis (T-score ≤ -2.5).<sup>4,14</sup> The Z-score indicates the number of standard deviations above or below the mean for age, as well as sex and race. A Z-score of ≤ -2.0 is below the expected range, indicating an increased likelihood of a secondary form of osteoporosis.<sup>14</sup>

**Which men to screen?**

The US Preventive Services Task Force has concluded that evidence is insufficient to

IMAGE: © JOE GORMAN

➤ Several organizations recommend screening men ages ≥70 years and those ages 50 to 69 who have risk factors for fractures or who sustained a fracture after age 50.

**TABLE 1**  
**Secondary causes of low BMD<sup>4,5,8,10</sup>**

Cause	Comments
Alcohol use/abuse	>2 drinks/d
Ankylosing spondylitis or RA	Elevated rheumatoid factor, cyclic citrullinated peptide
Antiepileptic drugs	Carbamazepine, phenobarbital, phenytoin, primidone
Calcium and vitamin D deficiency	Low 24-hour urinary Ca; serum 25(OH)D <30 ng/mL
Chronic corticosteroid use	Varies; prednisone >5 mg/d for >3 mo
Chronic kidney or liver disease	Low GFR; elevated LFT
Cushing's syndrome	Elevated 24-hour urinary free cortisol
Diabetes mellitus	Types 1 and 2
Family history	History of fracture with minimal trauma
HIV	Treatment with protease inhibitors
Hypercalciuria	Urinary calcium >250 mg/d
Hypogonadism	Low testosterone levels
Immobility	Lack of weight-bearing exercise and comorbidities preventing activity
Low BMI	<20 kg/m <sup>2</sup>
Malabsorption	Including celiac disease
Mastocytosis	Bone pain, fractures
Monoclonal gammopathies	Multiple myeloma; abnormal immunoglobulin protein
Organ transplantation	Immunosuppressive drugs
Osteogenesis imperfecta	Positive collagen type I genetic test
Primary hyperparathyroidism	Hypercalcemia; elevated parathyroid hormone
Tobacco use	Current smoker

BMD, bone mineral density; BMI, body mass index; Ca, calcium; GFR, glomerular filtration rate; HIV, human immunodeficiency virus; LFT, liver function tests; RA, rheumatoid arthritis.

assess the balance of benefits and harms of screening for osteoporosis in men. It therefore makes no recommendation to screen men who don't have evidence of previous fractures or secondary causes of osteoporosis.<sup>15</sup>

Other organizations agree that there is insufficient evidence to recommend routine screening for men without known osteoporotic fractures or secondary causes for osteoporosis. There are, however, some guidelines that are useful in clinical practice.

The Endocrine Society, American College of Physicians (ACP), and National Osteoporosis Foundation (NOF) recommend screening men ages 70 years or older, and men ages 50 to 69 who have risk factors for fracture and/or a history of fracture sustained after age 50.<sup>5,16,17</sup> (See "Did you know?" on

page 550.)<sup>1,2,4,5,9-12,16,17</sup> Prior to screening, it is important to do a complete medical history and physical examination.

■ **Screening considerations.** The Endocrine Society, ACP, and NOF recommend a DEXA scan of the spine and hip for men who are at increased risk for osteoporosis and have no contraindications to drug therapy.<sup>5,16,17</sup> In patients who have degenerative changes of the spine and hip that would likely obscure DEXA outcomes, a scan of the radius may provide a more accurate assessment of bone status. Men receiving androgen deprivation therapy for prostate cancer will have a greater decline of bone density in the radius than in the hip or spine and are therefore ideal candidates for DEXA of the forearm, as well.<sup>5,11</sup> Keep in mind, however, that no stud-

TABLE 2

## Male Osteoporosis Risk Estimation Score (MORES)

Risk factor	Points
<b>Age (years)</b>	
≤55	0
56-74	3
≥75	4
<b>Weight</b>	
≤70 kg (≤154 lb)	6
>70-80 kg (>154-176 lb)	4
>80 kg (>176 lb)	0
<b>History of COPD</b>	3
<b>TOTAL:</b>	<b>≥6=positive score</b>

COPD, chronic obstructive pulmonary disease.

Adapted from: Shepherd AJ, et al. *Ann Fam Med*. 2007.<sup>18</sup>

ies have looked at how well, or whether, men with osteoporosis measured only in the radius respond to treatment.<sup>5</sup>

A DEXA scan is not always widely available, nor is it a perfect predictor of fracture risk. In addition, it is not always cost effective. For some patients, the use of a validated clinical predictive tool is preferable as an initial option.

■ **The Male Osteoporosis Risk Estimation Score (MORES)** uses age, weight, and history of COPD to identify men 60 years or older who are at risk for osteoporosis (TABLE 2).<sup>18</sup> The score can be easily calculated during a clinical encounter and is beneficial for identifying men who should be referred for DEXA scan. A score of ≥6 has been found to yield an overall sensitivity of 0.93 (95% confidence interval [CI], 0.85-0.97) and a specificity of 0.59 (95% CI, 0.56-0.62), with a number needed to screen to prevent one additional hip fracture of 279.<sup>18</sup>

■ **The Osteoporosis Self-assessment Tool (OST)** (<http://depts.washington.edu/osteoed/tools.php?type=ost>) is a calculated value that uses age and weight to determine an individual's risk for osteoporosis (risk score=weight [in kg] - age [in years]/5).<sup>16,19</sup> Although there is not a defined value to determine a positive OST risk score, scores of -1 to 3 have been used in a variety of studies.<sup>16</sup> In a study of 181 American men, the OST predicted osteoporosis with a sensitivity of 93%

and a specificity of 66% when using a cutoff score of 3.<sup>20</sup>

### Treating men at risk

Pharmacologic therapy is recommended for men at an increased risk for fracture. This includes men who have had a hip or vertebral fracture without major trauma, as well as those who have not had such a fracture but have a BMD of the spine, femoral neck, and/or total hip of ≤-2.5.<sup>5,17</sup> This standard also applies to the radius when used as an alternative site.

The International Society for Clinical Densitometry and International Osteoporosis Foundation endorse the use of the Fracture Risk Assessment Tool (FRAX). Available at <http://shef.ac.uk/FRAX/tool.aspx?country=9>, FRAX is a computer-based calculator that uses risk factors and BMD of the femoral neck to estimate an individual's 10-year fracture probability.<sup>21</sup> Men who are 50 years or older, have a T-score between -1.0 and -2.5 in the spine, femoral neck, or total hip, and a 10-year risk of ≥20% of developing any fracture or ≥3% of developing a hip fracture based on FRAX, should be offered pharmacotherapy.<sup>5,17</sup>

### Bisphosphonates are first-line therapy

Although oral bisphosphonates are first-line therapy for men who meet these criteria,<sup>4</sup>



Because a DEXA scan is not always available or cost effective, a validated clinical predictive tool is preferred as an initial screening option.

TABLE 3

Pharmacotherapy for men at risk for osteoporotic fracture<sup>22,23</sup>

Medication (drug class)	Dosage/frequency	Adverse effects	Approximate cost
Alendronate (Bisphosphonate)	70 mg oral/wk	Esophagitis, abdominal pain	\$55/mo
Risedronate (Bisphosphonate)	35 mg oral/wk	Esophagitis, abdominal pain	\$170/mo
Zoledronic acid (Bisphosphonate)	5 mg IV/yr	Flu-like symptoms, arthralgia/myalgia	\$1355/y
Teriparatide (Recombinant human PTH)	20 mcg SC/d	Transient hypercalcemia, arthralgia	\$1505/mo
Denosumab (Monoclonal antibody)	60 mg SC/6 mo	Hypocalcemia, back pain	\$2050/y

IV, intravenous; PTH, parathyroid hormone; SC, subcutaneous.

pharmacotherapy should be individualized based on factors such as fracture history, severity of osteoporosis, comorbidities (eg, peptic ulcer disease, malignancy, renal disease, or malabsorption), and cost (TABLE 3).<sup>22,23</sup>

■ **Alendronate once weekly** has been proven to increase BMD and to reduce the risk of fracture in men.<sup>24,25</sup> A randomized, placebo-controlled trial of 241 men with osteoporosis found that alendronate increased BMD by 7.1% ( $\pm 0.3$ ) at the lumbar spine, 2.5% ( $\pm 0.4$ ) at the femoral neck, and 2% ( $\pm 0.2$ ) for the total body. Those in the placebo group had a 1.8% ( $\pm 0.5$ ) increase in BMD of the lumbar spine, with no significant change in femoral neck or total-body BMD—and a higher incidence of vertebral fractures (7.1% vs. 0.8% for those on alendronate;  $P=.02$ ).<sup>24</sup>

■ **Risedronate once daily** has also been proven to increase BMD in the lumbar spine and hip, with a reduction in vertebral fractures.<sup>26</sup> Another investigation—a 2-year, multicenter double-blind placebo-controlled study of 284 men with osteoporosis—found that risedronate given once a week increased BMD in the spine and hip, but did not reduce the incidence of either vertebral or non-vertebral fractures.<sup>27</sup>

Both alendronate and risedronate are effective for secondary causes of bone loss, such as corticosteroid use, androgen depriva-

tion therapy/hypogonadism, and rheumatologic conditions.<sup>28</sup> Oral bisphosphonates may cause GI irritation, however. Abdominal pain associated with alendronate use is between 1% and 7%, vs 2% to 12% for risedronate.<sup>23</sup> Neither medication is recommended for use in patients with an estimated glomerular filtration rate  $<35$  mL/min.<sup>23</sup> There is no clearly established duration of therapy for men.

■ **Zoledronic acid infusions**, given intravenously (IV) once a year, are available for men who cannot tolerate oral bisphosphonates. In a multicenter double-blind, placebo-controlled trial, zoledronic acid was found to reduce the risk of vertebral fractures in men with primary or hypogonadism-associated osteoporosis by 67% (1.6% vertebral fractures in the treatment group after 24 months vs 4.9% with placebo).<sup>29</sup> Given within 90 days of a hip fracture repair, zoledronic acid was associated with both a reduction in the rate of new fractures and an increased survival rate.<sup>30</sup>

Adverse effects of zoledronic acid include diffuse bone pain (3%-9%), fever (9%-22%) and flu-like symptoms (1%-11%). Osteonecrosis of the jaw has been reported in  $<1\%$  of patients.<sup>23</sup>

#### Recombinant human parathyroid hormone stimulates bone growth

Teriparatide, administered subcutaneously (SC) once a day, directly stimulates bone for-



Pharmacotherapy should be individualized based on factors such as fracture history, severity of osteoporosis, comorbidities (eg, peptic ulcer disease, malignancy), and cost.



**Supplementation of testosterone to restore correct physiologic levels in men with low testosterone will decrease bone turnover and increase bone density.**

mation. In a randomized placebo-controlled trial of 437 men with a T-score of -2, teriparatide was found to increase BMD at the spine and femoral neck. Participants were randomized to receive teriparatide (20 or 40 mcg/d) or placebo. Those who received teriparatide had a dose-related increase in BMD from baseline at the spine (5.9% with 20 mcg and 9% with 40 mcg) and femoral neck (1.5% and 2.9%, respectively) compared with the placebo group.<sup>31</sup> Teriparatide was shown to reduce vertebral fractures by 51% compared with placebo in a randomized study of 355 men with osteoporosis.<sup>32</sup>

Teriparatide is indicated for men with severe osteoporosis and those for whom bisphosphonate treatment has been unsuccessful. Its use is limited to 2 years due to a dose-dependent risk of osteosarcoma. Teriparatide is contraindicated in patients with skeletal metastasis and has been associated with transient hypercalcemia 4 to 6 hours after administration.<sup>23</sup> Its use in combination with bisphosphonates is not recommended due to the lack of proven benefit, risk of adverse effects, and associated cost.<sup>5</sup>

**Testosterone boosts bone density**

Testosterone therapy is recommended for men with low levels of testosterone (<200 ng/dL), high risk for fracture, and contraindications to pharmacologic agents approved for the treatment of osteoporosis.<sup>5</sup> Supplementation of testosterone to restore correct physiologic levels will decrease bone turnover and increase bone density.<sup>33</sup> In a meta-analysis of 8 trials with a total of 365 participants, testosterone administered intramuscularly was found to increase lumbar BMD by 8% compared with placebo. The effect on fractures is not known.<sup>12</sup>

**Monoclonal antibody reduces fracture risk**

Denosumab, a monoclonal antibody that prevents osteoclast formation leading to decreased bone resorption, is administered SC every 6 months.<sup>23</sup> In a placebo-controlled trial of 242 men with low bone mass, denosumab increased BMD at the lumbar spine (5.7%), total hip (2.4%), femoral neck (2.1%), trochanter (3.1%), and one-third radius (0.6%) compared with placebo after one year.<sup>34</sup> In

**Did you know?**<sup>1,2,4,5,9-12,16,17</sup>

- Although US women are 4 times more likely than men to suffer from osteoporosis, men incur between 30% and 40% of osteoporotic fractures.
- Men who sustain hip fractures have a mortality rate of up to 37.5%—2 to 3 times that of women with hip fractures.
- Men treated with androgen deprivation therapy face an increased risk of osteoporosis.
- About 13% of white men older than 50 years will experience at least one osteoporotic fracture in their lifetime.
- The Endocrine Society, American College of Physicians, and National Osteoporosis Foundation recommend screening all men ages 70 years or older—and younger men with risk factors for fracture and/or a history of fracture after age 50—for osteoporosis.

men receiving androgen deprivation therapy for nonmetastatic prostate cancer, denosumab has been shown to increase BMD and reduce the incidence of vertebral fractures.<sup>35</sup>

Adverse effects include hypocalcemia, hypophosphatemia, fatigue, and back pain.<sup>23</sup> No data exist on the ability of denosumab to reduce fracture risk in men without androgen deprivation.

**Calcium and vitamin D for men at risk**

Men who are at risk for or have osteoporosis should consume 1000 mg to 1200 mg of calcium per day. Ideally, this should come through dietary sources, but calcium supplementation may be added when diet is inadequate.<sup>5</sup> The Institute of Medicine recommends a calcium intake of 1000 mg/d for men ages 51 to 70 years and 1200 mg/d for men ages 70 and older.<sup>36</sup>

Men with vitamin D levels below 30 ng/mL should receive vitamin D supplementation to attain blood 25(OH) D levels of at least 30 ng/mL.<sup>5</sup> The Institute of Medicine recommends a daily intake of 600 international units (IU) of vitamin D for men ages 51 to 70 and 800 IU for men 70 and older.<sup>36</sup> A recent

Cochrane review on vitamin D and vitamin D analogues concluded that vitamin D alone was unlikely to prevent fractures in older people; when taken with calcium, however, it may have a preventive effect.<sup>37</sup>

## Counseling and follow-up

Lifestyle modification is an important means of primary prevention for osteoporosis. Advise men at risk for osteoporosis to limit alcohol consumption to 2 drinks daily.<sup>4,5,8,10</sup> Tell those who smoke that doing so increases their risk for osteoporotic fracture and refer them for smoking cessation counseling. Emphasize that weight-bearing exercise can improve BMD and should be done at least 3 days per week.<sup>4,5,8,10</sup> It is important, too, to do a medi-

ation review to look for drug-drug interactions and to discuss fall prevention strategies, such as gait training and an environmental assessment and removal of fall hazards.

The evidence for monitoring treatment using BMD is not very strong.<sup>5,14</sup> However, the Endocrine Society recommends that response to treatment be monitored using DEXA scans every one to 2 years, with reduced frequency once the BMD has stabilized.<sup>5</sup> Any patient found to have a decrease in BMD after treatment is initiated should undergo further evaluation to determine the cause of the decline.

JFP

### CORRESPONDENCE

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**A Cochrane review concluded that vitamin D alone was unlikely to prevent fractures in older people; when taken with calcium, however, it may have a preventive effect.**

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