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# Osteoporosis in men: Suspect secondary disease first

## ABSTRACT

Since osteoporosis in men is more often secondary rather than primary (idiopathic), we need to seek the underlying cause through the history and laboratory testing. Treatment options are similar to those for women, although data are limited about their efficacy in men.

## KEY POINTS

Prevention is the best approach to treatment of osteoporosis in men, given the limited options at the moment.

Glucocorticoids top the list of drugs that can cause osteoporosis. Prescribe a bisphosphonate prophylactically when starting long-term glucocorticoid therapy.

Bone densitometry can be problematic in men, as the T score is often indexed to a reference database in young women. Men are currently not covered for reimbursement under the Bone Mass Measurement Act, but they should undergo densitometry as women do.

The biochemical evaluation tends to be more extensive in men with osteoporosis because the bone loss is usually secondary to another condition. The younger the male patient, the more important the laboratory evaluation.

Alendronate has been shown to increase skeletal density in men comparably to levels seen in women. It is now approved for use in men. Teriparatide, a parathyroid hormone preparation, is now approved to increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture.

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**C**ONTRARY TO POPULAR NOTIONS, osteoporosis is a disease not only of women. In fact, men account for about 20% of cases of osteoporosis and 25% of hip fractures.

But there are differences. The consequences are worse for men than for women. Compared with women, men with hip fractures have higher rates of mortality and morbidity.<sup>1,2</sup> More are institutionalized, and 30% to 50% die within a year of fracture vs about 20% of women.

Another difference of note: from 50% to 70% of cases of osteoporosis in men are secondary to another condition, whereas osteoporosis in women is usually primary (idiopathic). Hence, in assessing a man, we should think of secondary osteoporosis first and primary second.

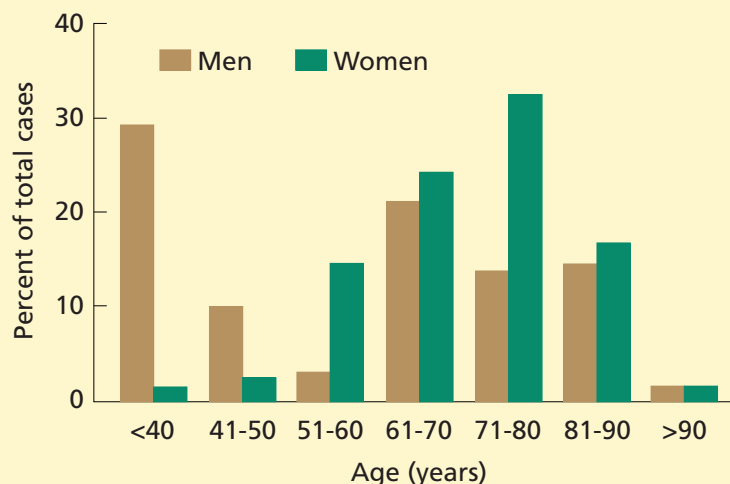
Many advances have occurred in the past decade, including increased awareness of osteoporosis, the technology to diagnose it in its early, asymptomatic stage, and many new treatments. Osteoporosis is now viewed as a treatable disease, rather than as an inevitable consequence of aging. Unfortunately, awareness of osteoporosis in men lags behind that in women, as do research and rates of detection and treatment.

This article outlines the unique features of osteoporosis in men, including its pathophysiology, causes, diagnosis, and treatment.

## BIMODAL PREVALENCE BY AGE

The prevalence of osteoporosis by age in men and in women is quite different (**FIGURE 1**). Whereas in women the distribution of osteoporosis with age is skewed toward the later years, in men many cases occur before age 50,

### Distribution of osteoporosis cases by age in men and women



**FIGURE 1.** In women most cases of osteoporosis occur in the later years; in men the distribution is bimodal. The early peak is mostly due to secondary osteoporosis, while the later peak mostly represents primary osteoporosis.

### Glucocorticoids attack the skeleton on two fronts

with a second peak in the later years. The cases early in life in men tend to be secondary osteoporosis and the later cases tend to be primary, although this is not always true.

#### ■ WHY FEWER MEN GET OSTEOPOROSIS

Although men do get osteoporosis, they have a lower prevalence than women, for several reasons:

**Men accumulate more bone mass** during the peak growth years, making the adult male skeleton generally stronger. They also accumulate more muscle mass during puberty, which contributes to skeletal strength.

**Men do not go through menopause.** Male hormone production does not abruptly cease. Instead, testosterone levels decline slowly throughout life unless there is an abrupt change (eg, due to surgical or chemical orchiectomy).

**Life expectancy for men has been shorter** than for women, so that primary osteoporosis had less time to develop and cause fragility fractures. However, more men are now living long enough to develop primary osteoporosis.

**Ascertainment bias.** Fewer men than women undergo bone density measurement, leading to the incorrect conclusion that men do not get osteoporosis. However, the third National Health and Nutrition Examination Survey,<sup>3</sup> using T-score criteria, found that 28% to 47% of men over age 50 have osteopenia at the femoral neck, and 36% have osteoporosis. For a 50-year-old man, the lifetime risk for any fracture of the femur, vertebrae, or distal forearm ranges from 13% to 50%.<sup>3</sup>

#### ■ PRIMARY OSTEOPOROSIS MAY BE DIFFERENT IN MEN

Primary osteoporosis is often ascribed to aging. Some believe that in men it results from trabecular thinning rather than from trabecular destruction, as seen in women.<sup>4</sup>

With age, a variety of metabolic and endocrine changes combine to weaken the skeleton.<sup>5-10</sup> Production of testosterone and growth hormone decreases, and muscles deteriorate. Calcium absorption becomes inefficient. Secondary hyperparathyroidism arises. Ambient parathyroid hormone levels are higher in older than in younger patients. Varying degrees of vitamin D dysfunction may be seen, from ineffective function to deficiency.

#### ■ CAUSES OF SECONDARY OSTEOPOROSIS

Many diseases and drugs can cause secondary osteoporosis (TABLE 1).

#### Drug-induced bone loss

**Glucocorticoids** top the list of drugs that can cause osteoporosis. Although oral glucocorticoids are the major culprits, potent inhaled glucocorticoids may also have systemic effects on the skeleton.<sup>11</sup>

Excessive doses of glucocorticoids have many bad effects on calcium and bone metabolism.<sup>12</sup> They blunt intestinal calcium absorption directly, even with adequate serum levels of vitamin D, and secondary hyperparathyroidism develops. Osteoclasts increase their activity, and skeletal turnover increases. The drugs also directly blunt osteoblastic activity, thus attacking skeletal integrity on two fronts.



Renal tubulopathy and calciuria develop (a direct effect of the steroids), drawing calcium from the body and exaggerating the hyperparathyroid state. Sex steroid production declines by suppression of gonadal function and pituitary gonadotropin secretion.

However, many other drugs can cause osteopenia, osteoporosis, and osteomalacia,<sup>13</sup> including:

- **Anticonvulsants**, which enhance vitamin D metabolism and cause calcium malabsorption and secondary hyperparathyroidism
- **Antigonadotropic drugs** used in treating prostate cancer are known to cause osteopenia, but the true incidence of clinical osteoporosis and fracture rates is not known.

**Tobacco and alcohol** are both directly toxic to the skeleton. Alcohol use is an independent risk factor for osteoporosis.<sup>14</sup> It suppresses osteoblast activity: intake of as little as 50 g (four standard drinks) per day causes a dose-dependent decrease in osteocalcin, a marker of osteoblastic activity. Higher intakes (>100 g/day) used for years cause decreased skeletal mass.<sup>15</sup> However, moderate drinking is not deleterious.

### Gastrointestinal diseases

Gastrointestinal diseases such as primary liver disease (with or without cirrhosis), ulcers requiring gastrectomy, inflammatory bowel disease, pancreatic insufficiency, and malabsorptive problems cause osteoporosis and, at times, osteomalacia.<sup>16-19</sup> Alcoholic cirrhosis, primary biliary cirrhosis, and steroid-treated autoimmune hepatitis lead more to osteoporosis than to osteomalacia.

### Hypercalciuria:

#### Hyperabsorptive or renal tubular?

Hypercalciuria, with or without stone disease, is found in 20% of men with osteoporosis evaluated in our clinic. Often, it is occult and is not associated with overt stone disease. In my experience, patients with latent calciuria may have normal calcium excretion because their calcium intake is low, but if you give them a calcium supplement for a week and remeasure their calcium excretion, it will be high.

Both hyperabsorptive hypercalciuria and renal tubular hypercalciuria (renal leak) are associated with osteopenia and osteoporosis.

**TABLE 1**

## Causes of secondary osteoporosis

### Drugs

Alcohol  
Anticonvulsants  
Antigonadotropins  
Glucocorticoids (oral, inhaled)  
Nonsteroidal anti-inflammatory drugs  
Thyroxine  
Tobacco

### Endocrine

Acromegaly  
Hypocortisolism  
Hyperparathyroidism  
Hyperprolactinemia  
Hyperthyroidism  
Hypogonadism

### Gastrointestinal

Cirrhosis  
Inflammatory bowel disease  
Malabsorption

### Genetic and metabolic

Homocystinuria  
Hypophosphatasia  
Marfan syndrome  
Osteogenesis imperfecta

### Neoplastic

Anemia (vitamin B<sub>12</sub> deficiency, thalassemia)  
Leukemia  
Myeloma, benign gammopathies

### Neurologic

Disuse syndrome  
Glucocorticoid, adrenocorticotropin therapy for myasthenia gravis, multiple sclerosis  
Immobilization  
Muscle atrophy  
Paralysis

### Pulmonary

Cystic fibrosis  
Drug therapy for asthma, chronic obstructive pulmonary disease  
Idiopathic pulmonary fibrosis

### Renal

Chronic renal failure, dialysis  
Mineral-losing tubulopathies  
Stone disease

### Transplantation bone disease

Lung, liver, heart, kidney

The hyperabsorptive problem is associated with increased or high-normal levels of 1,25 dihydroxyvitamin D. This above-normal level increases bone metabolism and, consequently, skeletal loss.<sup>20-24</sup>

In renal tubular hypercalciuria, initially there is a failure to reclaim urinary calcium, and serum levels decline. A sustained compensatory rise in serum parathyroid hormone corrects this drop in calcium at the expense of increased bone turnover.

Renal tubular acidosis is another entity to be mindful of.<sup>25</sup>

### Endocrine disorders

Several endocrine disorders are well-known causes of osteoporosis. The clinical challenge is when they occur in an atypical or occult fashion.

**Hypogonadism** during puberty is an established cause of adult skeletal deficiency, primarily as it inhibits the development of peak bone mass.<sup>26–28</sup> In a young patient, replacement of sex steroids may reverse the problem.

Abrupt hypogonadism in adult men following chemical or surgical orchiectomy (eg, for the treatment of prostate cancer)<sup>29</sup> is comparable to menopause in women and is equally destructive to the skeleton. On the other hand, the milder forms of hypogonadism of aging have not been shown to cause bone loss.

**Hyperparathyroidism** causes bone destruction, although skeletal problems such as osteitis fibrosis cystica are rare nowadays because this disorder is usually discovered early in routine health care evaluations and laboratory testing. More than 80% of patients with hyperparathyroidism have no symptoms, however. Secondary and tertiary hyperparathyroidism of renal disease is not a diagnostic challenge, but it is often overlooked, even in patients on renal dialysis.

**Endogenous hypercortisolism** can present atypically. About 5% of patients present with osteoporosis and never show the typical features of cortisol excess, such as centripetal obesity, aberrant deposition of fat, diabetes mellitus, or hypertension. Fractures may be the only presenting characteristic.

**Hyperprolactinemia** in men is insidious. Unrecognized, it decreases testosterone production and libido and in theory can cause osteoporosis. Whether fractures develop, however, depends on other issues, such as chronicity of the disorder, initial peak bone mass, and traumatic events.

**Primary hyperthyroidism** is an unlikely cause of osteoporosis because it is usually diagnosed long before it can destroy the skeleton. The real concern is exogenous hyperthyroidism caused by thyroxine supplementation that suppresses thyroid-stimulating hormone. However, this should not be a clinically significant issue now that we have sensitive assays for thyroid-stimulating hormone, bone densitometry, and therapy to counteract bone loss.

**Acromegaly** can lead to osteoporosis paradoxically, apparently when a growing pituitary tumor produces less gonadotropin, thus suppressing testosterone synthesis.

### Other causes

**Plasma cell dyscrasias** cause osteoporosis or osteopenia.

**Multiple myeloma** and even benign monoclonal gammopathy increase bone turnover.<sup>30</sup> This skeletal effect arises from increased osteoclastic activity due to the elaboration of cytokines within the bone marrow. The degree to which these disorders are occult and go undiagnosed determines the extent of skeletal destruction.

**Leukemia** may also be associated with bone destruction if sufficiently occult and chronic.<sup>31</sup>

**Benign hematologic disorders** such as thalassemia and vitamin B<sub>12</sub> deficiency also contribute to bone loss.<sup>32,33</sup>

**Focal metastatic disease** causes local bone destruction, not systemic osteoporosis.

**Humoral hypercalcemia of malignancy** is not a clinically significant cause of osteoporosis, since it portends a short prognosis.

**Genetic or metabolic disorders** known to cause osteoporosis or osteopenia include homocystinuria, Marfan syndrome, hypophosphatasia, and osteogenesis imperfecta.<sup>34–37</sup> A family history of any skeletal disorder should raise our suspicion, although the rarity of many of these disorders makes them less likely considerations in general medical practice.

### ■ BONE DENSITOMETRY AND T SCORES

Bone densitometry is the greatest single advance that has made possible the awareness, diagnosis, and early treatment of osteoporosis. Dual energy x-ray absorptiometry of the spine

Fracture may be the only presenting feature in some men with occult endocrine disorders



and hip can detect osteoporosis in women and men quite early in its course.

I believe that bone density evaluation should be mandatory for men after age 60 or 65 if there is no specific history of unexplained fracture, and certainly before this age in any man with a history of low trauma fracture. Guidelines for its use are likely to be the same for men as for women, although this has not been clearly delineated.

Unfortunately, although the federal Bone Mass Measurement Act requires Medicare to pay for bone density measurements for women within certain guidelines, men have not yet been included. One hopes that Congress will rectify this omission.

### Caveats about T scores

The T score, used to determine the risk for fracture in women, is also used in men, but with a caveat: a male data base must be used for deriving the score.

Recall that the T score is the number of standard deviations (SD) below or above the mean value in a reference population. If a female data base is used, only 3% to 5% of men have osteoporosis, whereas 30% of men over age 50 have osteopenia or osteoporosis when a male data base is used. Hence, a male data base is mandatory for accurate diagnosis of osteoporosis in men.

The definitions of disease by T scores are the same for men as for women. A T score of 2.5 or more standard deviations (SD) below the mean (ie,  $< -2.5$  SD) is classified as osteoporosis. (Remember that these are negative numbers, so  $-3.5$  is less than  $-2.5$ .) A T score of  $-1.5$  to  $-2.5$  is classified as osteopenia, and a T score of  $-1.5$  or higher is normal.

But T scores should only be considered as guidelines for detection of osteoporosis. Treatment should not be withheld until a patient's T score reaches a specific level. Rather, the diagnosis and decision to treat should be based on clinical criteria. Sometimes, treatment should be started before the T score declines to  $-2.5$ , for example, in patients taking glucocorticosteroids.

Moreover, there is no "safe" T score, ie, no discrete cutoff for "osteoporosis" or "no osteoporosis." The scores are a continuum of fracture risk. People with lower scores (more stan-

**TABLE 2**

## Diagnostic evaluation of osteoporosis in men

### History

- Family history
- Past medical history (secondary causes identifiable)
- Health habits (use of alcohol or tobacco, lack of exercise)
- Drug use (bone-toxic agents)

### Physical examination

- Signs of specific diseases

### Initial laboratory evaluation

- Complete blood cell count
- Complete chemical profile
- Parathyroid hormone
- 25 vitamin D
- 24-hour urinary calcium

### Follow-up laboratory evaluation

- Urine cortisol
- Serum testosterone
- Protein electrophoresis of serum
- Serum growth hormone
- Insulin-like growth factor 1
- Prolactin

dard deviations below the mean) are at greater risk than people with higher scores, but the score alone does not diagnose osteoporosis: the clinician diagnoses osteoporosis on the basis of the personal and family history, physical examination, laboratory values, and bone densitometry.

### CLINICAL AND LABORATORY DIAGNOSIS OF OSTEOPOROSIS IN MEN

In men, we should consider primary osteoporosis only after ruling out a specific cause. In women, too, we should never assume that osteoporosis is primary: the high incidence of primary disease in women often obscures consideration of secondary causes, but secondary causes do exist and need to be considered.

### History and physical examination

In most men with osteoporosis, the history raises the suspicion of a possible cause, which is then pursued with appropriate laboratory and radiologic testing (TABLE 2).

**Do not withhold treatment until the T score reaches an arbitrary number**

A family history of osteoporosis is as important a consideration in men as it is in women. Osteoporosis in family members is a risk factor, especially in families with a tendency toward small, thin stature. In addition, pediatric data show similarities in bone density of parents and their children.<sup>38,39</sup>

The physical examination may reveal cushingoid features, acromegaly, or hypogonadism, or evidence of blood dyscrasias or cancer, liver disease, or pathognomonic skeletal abnormalities.

#### Laboratory testing more extensive in men

The biochemical evaluation tends to be more extensive in men with osteoporosis because the bone loss is usually secondary to another condition. The younger the male patient, the more important the laboratory evaluation.

A tiered evaluation is recommended, proceeding from routine to more exotic metabolic and endocrine tests.

Routine biochemical profiles and a complete blood cell count may reveal suspicious findings that should be evaluated further, such as abnormalities in calcium, phosphorus, other electrolytes, alkaline phosphatase, liver or kidney function, and blood counts.

Routine urine testing for 24-hour excretion of calcium is suggested initially in all men because hypercalciuria is common. Levels of urinary phosphorus and other substances, such as amino acids or sugars, may be evaluated later if there is suspicion of renal tubulopathy and associated bone disease.

Measurement of parathyroid hormone and 25-hydroxyvitamin D may uncover subtle secondary hyperparathyroidism or vitamin D deficiency.

In rare cases, evaluation for hypophosphatasia, homocystinuria, or osteogenesis imperfecta might be needed. Evaluate for hypophosphatasia in patients with fracture and low serum alkaline phosphatase. Evaluate for homocystinuria in those with physical features and a history of fracture. Evaluate for osteogenesis imperfecta in those with a family history, fracture as a child, and physical features.

#### Skeletal biopsy

If no abnormality is found on laboratory test-

ing, tetracycline-labeled biopsy of the skeleton might be helpful. Histologic study may show unexpected findings, such as hematologic disease or osteomalacia. In our clinical experience, however, biopsy has not proven as helpful as laboratory or clinical data. Nonetheless, it should be kept in mind, such as in a patient with a continuing history of fractures or bone pain and no obviously abnormal laboratory tests.

#### ■ TREATING SECONDARY OSTEOPOROSIS IN MEN

Treating osteoporosis in men usually implies treating the underlying cause. The reversibility of osteoporosis after the underlying cause is controlled or eliminated depends on the degree of bone damage. Treatment of hypercortisolism, hyperparathyroidism, acromegaly, or hyperprolactinemia can reverse bone loss to varying degrees. Resolution of a deficiency, such as hypogonadism or vitamin D deficiency, may be all that is needed.

Skeletal disease due to intestinal or drug-induced malabsorption often responds well to calcium and vitamin D supplementation.

Drug-related bone loss should, in theory, respond to stopping the drug, but this may not be easy. For example, the therapeutic need for glucocorticoids may preclude stopping them. Fortunately, the bisphosphonates alendronate (Fosamax) and risedronate (Actonel) are available for patients using glucocorticoids, and these two drugs should be prescribed prophylactically when chronic steroid treatment is started.

Thiazide diuretics can stop renal calcium loss and reverse skeletal deficiency to varying degrees.

Treatment of various neoplastic diseases may control the skeletal disease and fractures attending these illnesses, but additional bone-specific therapies are often needed.

#### ■ TREATING IDIOPATHIC OSTEOPOROSIS IN MEN

Idiopathic osteoporosis in men was not satisfactorily treated until the recent approval of alendronate for use in men.

**Measure 24-hour calcium excretion in all men with osteoporosis**



## Nonpharmacologic measures

Nonpharmacologic measures alone are not sufficient. Nevertheless, calcium and vitamin D supplementation and exercise should be part of any treatment program for men. A healthy lifestyle with smoking cessation and limited use of alcohol is as important in men as it is in women.

## Hormonal therapy

**Testosterone therapy** is marginally effective in the hypogonadism of aging but is more effective in hypogonadism of younger men.<sup>40,41</sup>

**Estradiol** has been found, in a few rare cases, to have a positive effect on the male skeleton, although the true clinical significance of this is not yet known.<sup>42,43</sup>

**Calcitonin** has not undergone any large studies in men with primary osteoporosis, although small increases in bone density and a reduction in vertebral fractures were seen in major studies in women.<sup>44</sup>

**Parathyroid hormone** increases skeletal density in men,<sup>45</sup> but its full potential has not been explored. A commercial product, teriparatide (Forteo), has received FDA approval for use in men and women.<sup>46</sup>

**Growth hormone** increases bone density in patients with adult growth hormone deficiency.<sup>47</sup> Since growth hormone secretion decreases with aging, its use has theoretical merit in the treatment of osteoporosis.<sup>48,49</sup> Its

high cost and parenteral route of administration are limitations to its widespread use, however.

## Sodium fluoride

Sodium fluoride has long been used in women as an osteoblastic stimulator, and most studies of its efficacy have been in women. Its use in men has not been fully evaluated, but there are limited studies.<sup>50</sup> Unfortunately, the safety margin is narrow.<sup>51</sup> In women, excessive doses produce dense but poor-quality bone that is prone to fracture.

## Bisphosphonates

**Alendronate** is the first drug to show efficacy in men in a well-controlled trial, increasing skeletal density comparably to levels seen in women. Its effects do not appear to depend on testosterone levels. The study was not statistically powered to evaluate the efficacy of fracture reduction, but a tendency in that direction was noted.<sup>52</sup>

**Etidronate** in cyclical regimens is used in women and, theoretically, should help men. Risedronate should also be beneficial.<sup>53–55</sup>

## ■ PREVENTION IS BEST TREATMENT

The take-home message is essentially the same as that for women: prevention is better than treatment, given the limited treatment options at the moment. ■

**Calcium, vitamin D, exercise are part of any treatment plan in men**

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## INTERNAL MEDICINE BOARD REVIEW

Clinical vignettes and questions on the differential diagnosis and treatment of medical conditions likely to be encountered on the Qualifying Examination in Medicine — as well as in practice. Take the challenge.

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