



# Clinical manifestations, diagnosis, and evaluation of osteoporosis in men

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Literature review current through: **Nov 2025**.

This topic last updated: **Mar 10, 2025**.

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## INTRODUCTION

Osteoporosis is a common disorder that is characterized by low bone mass with microarchitectural disruption and skeletal fragility, resulting in an increased risk of fracture. The World Health Organization (WHO) has defined diagnostic thresholds for low bone mass and osteoporosis based upon bone mineral density (BMD) measurements compared with a young adult reference population (T-score) ( [table 1](#)).

Early diagnosis and quantification of bone loss and fracture risk have become more important because of the availability of therapies that can slow or even reverse the progression of osteoporosis.

The clinical manifestations, diagnosis, and evaluation of osteoporosis in men will be reviewed here. The treatment and the epidemiology and etiology of osteoporosis in men are discussed separately. (See "[Treatment of osteoporosis in men](#)" and "[Etiology of osteoporosis in men](#)".)

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## CLINICAL MANIFESTATIONS

Osteoporosis has no clinical manifestations until a fracture occurs.

- **Vertebral fractures** – Many vertebral fractures are asymptomatic and are discovered as an incidental finding on chest or abdominal radiographs. Asymptomatic vertebral fractures are sentinel events that are strong predictors of future clinically symptomatic fractures. The clinical

manifestations of symptomatic vertebral fractures include variable degrees of pain and muscle spasms. The clinical manifestations of vertebral fractures are reviewed in detail separately. (See ["Osteoporotic thoracolumbar vertebral compression fractures: Clinical manifestations and treatment"](#), section on 'Clinical manifestations'.)

- **Hip fractures** – Hip fractures are the most devastating consequence of osteoporosis in men as they frequently lead to chronic pain, loss of mobility, and increased mortality. Men experience higher mortality than women after sustaining a fragility fracture [1]. (See ["Hip fracture in older adults: Epidemiology and medical management"](#), section on 'Morbidity and mortality'.)

## DIAGNOSIS OF OSTEOPOROSIS

**Diagnostic criteria by age** — Osteoporosis is characterized by low bone mass and microarchitectural disruption, which reduces bone strength and increases the risk of fracture.

- **<50 years of age** – In men <50 years of age, bone mineral density (BMD) measurements alone are not sufficient to establish a diagnosis of osteoporosis [2]. Instead, osteoporosis is defined by lower than expected BMD for age (Z-score  $\leq -2.0$ ) plus a history of a fragility fracture and/or a major risk factor for osteoporosis (eg, hypogonadism, glucocorticoid therapy, hyperparathyroidism) ( [table 2](#) ) [3].
- **$\geq 50$  years of age** – In men  $\geq 50$  years, a diagnosis of osteoporosis can be made when there is a history of low trauma (fragility) fracture or in men whose BMD is at least 2.5 standard deviations below the young adult reference mean (ie, T-score of  $\leq -2.5$ ) ( [table 1](#) ). Male and female reference means are variably used across centers to calculate T-scores. (See ["Use of a male or female reference database"](#) below.)

Causes of osteoporosis in men			
Endocrine disorders		Connective tissue disorders	
<ul style="list-style-type: none"><li>• Hypogonadism<ul style="list-style-type: none"><li>• Primary</li><li>• Secondary</li></ul></li><li>• Delayed puberty</li><li>• Estrogen deficiency</li><li>• Hyperparathyroidism</li><li>• Hyperthyroidism</li><li>• Hypoparathyroidism</li><li>• Infantile D deficiency</li><li>• Growth hormone deficiency</li><li>• Diabetes mellitus (type 1 and 2)</li></ul>		<ul style="list-style-type: none"><li>• Osteogenesis imperfecta</li><li>• Ehlers-Danlos syndrome</li><li>• Marfan syndrome</li><li>• Homocystinuria</li></ul>	
Gastrointestinal disorders		Drugs	
<ul style="list-style-type: none"><li>• Malabsorption syndromes (eg, celiac disease, bariatric surgery, intestinal resection)</li><li>• Inflammatory bowel disease</li><li>• Cirrhosis</li></ul>		<ul style="list-style-type: none"><li>• Alcohol</li><li>• Heroin</li><li>• Glucocorticoids</li><li>• Thyroxine suppressive therapy</li><li>• Antidiabetic medications</li><li>• Gonadotropin-releasing hormone analogs</li><li>• Chemotherapy</li><li>• Chemotherapy (eg, tenofovir)</li><li>• HIV medications (eg, zidovudine)</li></ul>	
Hematologic disorders		Miscellaneous causes	
<ul style="list-style-type: none"><li>• Multiple myeloma</li><li>• Chronic hemolytic anemia</li><li>• Systemic mastocytosis</li></ul>		<ul style="list-style-type: none"><li>• Eating disorders (eg, anorexia nervosa)</li><li>• Hyperparathyroidism</li><li>• Immobilization</li><li>• Rheumatoid arthritis</li><li>• Kidney disease</li><li>• Hepatic disease</li><li>• Tobacco</li></ul>	

Table 2 - larger image below

**Bone mineral density measurement** — The use of bone densitometry to diagnose osteoporosis is less well standardized in men than in postmenopausal women [4]. However, because the relationship between BMD and fracture is similar in men age  $\geq 50$  years and postmenopausal women, the World Health Organization (WHO) diagnostic thresholds for osteoporosis are similar for both groups ( [table 1](#) ). In fact, for every standard deviation that BMD is reduced in men, the relative risk of fracture is similar to, or even greater than, the relative risk in women. However, the age-specific prevalence of osteoporosis and fracture is lower in men

than in women, so that men nonetheless tend to have a lower absolute risk for fracture than women [5]. (See ["Fracture risk assessment", section on 'Dual-energy x-ray absorptiometry \(DXA\)'](#).)

## Controversies in the diagnosis of osteoporosis in men

**Patient selection for BMD measurement** — BMD always should be measured in men with a history of fragility fracture(s), height loss of 1.5 inches or more, radiographic osteopenia, or kyphosis, as well as in men with disorders that increase the risk of developing osteoporosis (eg, glucocorticoid use, hypogonadism, malabsorption, primary hyperparathyroidism, rheumatoid arthritis, frailty) ( [table 2](#)). (See ["Screening for osteoporosis in men aged ≥50 years and postmenopausal women", section on 'Candidates for BMD testing'](#).)

**Use of a male or female reference database** — The decision whether to use a young adult male or female reference database for dual-energy x-ray absorptiometry (DXA) in men is controversial. The ISCD and the WHO both endorse the use of a female reference database to calculate T-scores in men. However, many centers use sex-specific reference databases [3]. With use of sex-specific reference databases, osteoporosis in men is defined by a BMD value at the spine, hip, or forearm at least 2.5 standard deviations below the young, healthy male reference mean. We prefer this approach to diagnose osteoporosis in men because all osteoporosis treatment trials in men recruited participants based on T-scores calculated using healthy male controls [3]. (See ["Overview of dual-energy x-ray absorptiometry", section on 'Reference databases'](#).)

**Skeletal site selection for BMD measurement** — We recommend measuring BMD of both the hip and spine. The proximal femur is the best site for evaluating men for osteoporosis. Although lumbar spine BMD is highly useful in the evaluation of osteoporosis in postmenopausal women, men are more likely to have degenerative changes in the lumbar spine, the presence of which increases the measured BMD and limits the utility of spine DXA in men. If pharmacologic therapy is planned, measurement of spine BMD is useful as it shows less inter-measurement variability and can detect responses to therapy earlier than hip BMD.

If degenerative changes or other factors limit interpretation of BMD measurements of the spine and/or the hip, then some centers routinely measure forearm BMD. Forearm BMD may also be more sensitive than spine or hip DXA for detecting bone loss in men undergoing androgen deprivation therapy for prostate cancer [6].

Cumulative fracture risk can be predicted by measuring BMD at a variety of sites including the lumbar spine, proximal femur, or the distal radius. Selection of skeletal sites for BMD

measurement is discussed in greater detail elsewhere. (See ["Fracture risk assessment", section on 'Skeletal site to measure'.](#))

## EVALUATION

**Initial evaluation** — The initial osteoporosis evaluation includes a history to assess for clinical risk factors for fracture and to evaluate for other conditions that contribute to bone loss, a physical examination, and basic laboratory tests.

**History and physical examination** — Many coexisting medical conditions may contribute to bone loss ( [table 2](#)). Thus, evaluation for alternative causes of bone loss to detect potentially reversible causes should be performed if suggested by history and/or physical examination. Lifestyle factors that contribute to bone loss (including smoking, excessive alcohol, physical inactivity, and poor nutrition) should be addressed. Height and weight should be measured. For all patients, family history of osteoporosis and personal history of fracture should be obtained.

**Laboratory testing** — The initial evaluation should include routine biochemical tests to evaluate for kidney disease and a complete blood count, calcium, phosphate, alkaline phosphatase, and 25-hydroxyvitamin D ( [table 3](#)).

**Additional evaluation** — Men who have abnormalities on the initial laboratory testing, have suspicious findings on history and physical examination, or who have unexplained low bone mass after the initial evaluation may also require additional laboratory tests ( [table 3](#)), such as:

- **24-hour urine calcium and creatinine** – We measure this in men with hypercalcemia or history of kidney stones. High urine calcium may suggest primary hyperparathyroidism or idiopathic hypercalciuria. (See ["Primary hyperparathyroidism: Diagnosis, differential diagnosis, and evaluation"](#).)
- **Parathyroid hormone to screen for primary hyperparathyroidism** – We typically measure this in men with hypercalcemia, hypercalciuria, or history of kidney stones. Some clinicians prefer to measure parathyroid hormone in all men with osteoporosis as part of the initial

Laboratory evaluation for men osteoporosis	
Initial laboratory tests	
25-Hydroxyvitamin D	
Calcium, phosphorus	
Complete blood count	
Complete chemistry profile (including alkaline phosphatase)	
Additional laboratory tests if indicated	
1,25-dihydroxyvitamin D	
24-hour urine for calcium and creatinine	
24-hour urine for free cortisol	
Celiac screen	
COX-14 genetic testing for osteogenesis imperfecta	
Erythrocyte sedimentation rate	
Estrogen	
Parathyroid hormone	
PTHrP	
Thyroid-stimulating hormone	
Intact PTH	
Iron and total iron binding capacity	
Magnesium	
Prostate	
Rheumatoid factor	
Serum and urine markers of bone turnover	
Serum protein electrophoresis/urine protein electrophoresis	
Serum triphosphate and testosterone levels	
Skin biopsy for connective tissue disorders	
Testosterone	
TSH	

Laboratory evaluation for men osteoporosis

Table 3 - larger image below

evaluation. (See ["Primary hyperparathyroidism: Diagnosis, differential diagnosis, and evaluation"](#).)

- **Serum testosterone to screen for hypogonadism** – We measure this in men with signs or symptoms of hypogonadism. In adult men with acquired hypogonadism, additional evaluation may also include serum **estradiol**, as estrogen deficiency may contribute more to bone loss than androgen deficiency, particularly when estradiol levels are below 10 to 15 pg/mL [7]. Accurate measurement of such low levels of estradiol is best performed using mass spectroscopy. (See ["Clinical features and diagnosis of male hypogonadism"](#).)
- **Tissue transglutaminase antibodies to screen for celiac disease** – We typically measure this in men who have a low 25-hydroxyvitamin D level and/or low urinary calcium. Some experts recommend these tests in all men with idiopathic osteoporosis. (See ["Diagnosis of celiac disease in adults"](#).)
- **Thyroid-stimulating hormone (TSH)** – We measure TSH in men who are taking [levothyroxine](#), or if there are clinical findings suspicious for hyperthyroidism (eg, palpitations, heat intolerance, tremor). (See ["Bone disease with hyperthyroidism and thyroid hormone therapy"](#).)

Additional testing for other, rare conditions associated with osteoporosis should be performed in selected clinical settings:

- Serum and urine protein electrophoresis to uncover a hematological or myeloproliferative disorder – We typically recommend these measurements in men with anemia and/or vertebral compression fractures.
- Urinary cortisol excretion – We measure 24-hour urinary free cortisol if clinical manifestations of Cushing syndrome are present. Some experts recommend measurement of 24-hour urine free cortisol in men with unexplained low bone density or vertebral fractures, even in the absence of traditional clinical manifestations of Cushing syndrome. (See ["Establishing the diagnosis of Cushing syndrome"](#) and ["Epidemiology and clinical manifestations of Cushing syndrome"](#), section on 'Impact of subclinical hypercortisolism'.)
- Serum tryptase to screen for systemic mastocytosis – We consider performing this measurement in men with fractures, unexplained osteoporosis, or bone pain. (See ["Mastocytosis \(cutaneous and systemic\) in adults: Epidemiology, pathogenesis, clinical manifestations, and diagnosis"](#).)
- In rare cases, iliac crest bone biopsy after double [tetracycline](#) labeling may be useful, particularly for distinguishing osteoporosis from osteomalacia or in the setting of advanced chronic kidney disease (CKD; stage 4+). The clinical availability of bone biopsy is limited.

## SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See ["Society guideline links: Osteoporosis"](#).)

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## INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5<sup>th</sup> to 6<sup>th</sup> grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10<sup>th</sup> to 12<sup>th</sup> grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see ["Patient education: Osteoporosis and osteopenia \(low bone mass\) \(The Basics\)"](#) and ["Patient education: Medicines for osteoporosis \(The Basics\)"](#))
  - Beyond the Basics topics (see ["Patient education: Osteoporosis prevention and treatment \(Beyond the Basics\)"](#))
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## SUMMARY AND RECOMMENDATIONS

- **Clinical manifestations** – Osteoporosis is a silent disorder until a fracture occurs. Complications of fractures include pain, deformity, disability, loss of height, and increased mortality. (See ["Clinical manifestations"](#) above.)
- **Diagnosis of osteoporosis**
  - **Men aged <50 years** – In men <50 years of age, bone mineral density (BMD) measurements alone are not sufficient to establish a diagnosis of osteoporosis. Instead, osteoporosis is defined by lower than expected BMD for age (Z-score  $\leq -2.0$ ) plus a history of a fragility

fracture and/or a major risk factor for osteoporosis (eg, hypogonadism, glucocorticoid therapy, hyperparathyroidism) ( [table 2](#)). (See '[Diagnosis of osteoporosis](#)' above.)

- **Men aged  $\geq 50$  years** – In men  $\geq 50$  years, a diagnosis of osteoporosis can be made when there is a history of low trauma (fragility) fracture or in men whose BMD is at least 2.5 standard deviations below the young adult reference mean (ie, T-score of  $\leq -2.5$ ) ( [table 1](#)). (See '[Diagnosis of osteoporosis](#)' above.)
- **Selection of men for BMD measurement** – BMD should be measured in men with clinical manifestations of low bone mass, such as radiographic osteopenia, history of low trauma fractures, loss of more than 1.5 inches in height, as well as in those with risk factors for fracture, such as long-term glucocorticoid therapy, hypogonadism, primary hyperparathyroidism, intestinal disorders, and increased frailty ( [table 2](#)). Some expert groups recommend BMD measurement in men based on age alone (eg, 70 years or above). (See '[Patient selection for BMD measurement](#)' above and "[Screening for osteoporosis in men aged  \$\geq 50\$  years and postmenopausal women](#)", section on '[Candidates for BMD testing](#)'.)

We use a male reference database for calculating T-scores in men. (See '[Use of a male or female reference database](#)' above.)

- **Evaluation** – The goal of the evaluation of men with osteoporosis is to rule out secondary causes ( [table 2](#)). Many secondary etiologies of osteoporosis can be determined from history and physical examination. (See '[Initial evaluation](#)' above.)

Most men with low bone mass or fragility fracture should have basic laboratory testing. Initial laboratory studies should include a complete blood count, biochemistry profile, and 25-hydroxyvitamin D ( [table 3](#)), particularly if no clear explanation for low BMD is present. (See '[Initial evaluation](#)' above.)

Based on the results of the history, physical examination, and basic laboratory testing, more extensive testing may be indicated. Additional testing may include measurement of serum testosterone and/or urinary calcium excretion. (See '[Additional evaluation](#)' above.)

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Topic 2052 Version 22.0

GRAPHICS

Table 1: Diagnostic categories for osteoporosis and low bone mass based upon BMD measurement by DXA

Category	BMD
Normal	A value for BMD within 1.0 SD of the young adult female reference mean (T-score greater than or equal to −1.0).
Low bone mass (osteopenia)	A value for BMD more than 1.0 but less than 2.5 SD below the young adult female reference mean (T-score less than −1.0 and greater than −2.5).
Osteoporosis	A value for BMD 2.5 or more SD below the young adult female reference mean (T-score less than or equal to −2.5).
Severe (established) osteoporosis	A value for BMD more than 2.5 SD below the young adult female reference mean in the presence of one or more fragility fractures.

BMD: bone mineral density; DXA: dual-energy x-ray absorptiometry; SD: standard deviation.

*Data from: WHO scientific group on the assessment of osteoporosis at the primary health care level: Summary meeting report, 2004. Geneva: World Health Organization, 2007.*

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Table 2: Causes of osteoporosis in men

Endocrine diseases	Connective tissue diseases
<ul style="list-style-type: none"> <li>▪ Hypogonadism <ul style="list-style-type: none"> <li>• Primary</li> <li>• Secondary</li> </ul> </li> <li>▪ Delayed puberty</li> <li>▪ Estrogen deficiency</li> <li>▪ Hypercortisolism</li> <li>▪ Hyperthyroidism</li> <li>▪ Hyperparathyroidism</li> <li>▪ Vitamin D deficiency</li> <li>▪ Growth hormone deficiency</li> <li>▪ Diabetes mellitus (type 1 and 2)</li> </ul>	<ul style="list-style-type: none"> <li>▪ Osteogenesis imperfecta</li> <li>▪ Ehlers-Danlos syndrome</li> <li>▪ Marfan syndrome</li> <li>▪ Homocystinuria</li> </ul>
Gastrointestinal diseases	Drugs
<ul style="list-style-type: none"> <li>▪ Malabsorption syndromes (eg, celiac disease, bariatric surgery, intestinal resection)</li> <li>▪ Inflammatory bowel disease</li> <li>▪ Cirrhosis</li> </ul>	<ul style="list-style-type: none"> <li>▪ Alcohol</li> <li>▪ Heparin</li> <li>▪ Glucocorticoids</li> <li>▪ Thyroxine suppressive therapy</li> <li>▪ Antiseizure medications</li> <li>▪ Gonadotropin-releasing hormone analogs</li> <li>▪ Cyclosporine</li> <li>▪ Chemotherapy</li> <li>▪ HIV medications (eg, tenofovir)</li> </ul>
Hematologic disorders	Miscellaneous causes
<ul style="list-style-type: none"> <li>▪ Multiple myeloma</li> <li>▪ Chronic hemolytic anemia</li> <li>▪ Systemic mastocytosis</li> </ul>	<ul style="list-style-type: none"> <li>▪ Eating disorders (eg, anorexia nervosa)</li> <li>▪ Hypercalciuria</li> <li>▪ Immobilization</li> <li>▪ Rheumatoid arthritis</li> <li>▪ Kidney disease</li> <li>▪ Hepatic disease</li> <li>▪ Tobacco</li> </ul>

HIV: human immunodeficiency virus.

Table 3: Laboratory evaluation for men osteoporosis

<b>Initial laboratory tests</b>
25-hydroxyvitamin D
Calcium, phosphorus
Complete blood count
Complete chemistry profile (including alkaline phosphatase)
<b>Additional laboratory tests if indicated</b>
1,25-dihydroxyvitamin D
24-hour urine for calcium and creatinine
24-hour urine for free cortisol
Celiac screen
<i>COL1A</i> genetic testing for osteogenesis imperfecta
Erythrocyte sedimentation rate
Estradiol
Ferritin
FSH, LH
Homocysteine
Intact PTH
Iron and total iron binding capacity
Magnesium
Prolactin
Rheumatoid factor
Serum and urine markers of bone turnover
Serum protein electrophoresis/urine protein electrophoresis
Serum tryptase and histamine levels
Skin biopsy for connective tissue disorders
Testosterone
TSH

FSH: follicle-stimulating hormone; LH: luteinizing hormone; PTH: parathyroid hormone; TSH: thyroid-stimulating hormone.

Graphic 51140 Version 7.0

## Contributor Disclosures

**Joel S Finkelstein, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Elaine W Yu, MD** Equity Ownership/Stock Options: Opko [Pharmaceutical company]. Grant/Research/Clinical Trial Support: Amgen Inc [Osteoporosis therapies]. All of the relevant financial relationships listed have been mitigated. **Clifford J Rosen, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Katya Rubinow, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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