

## Osteoporosis in Men: An Endocrine Society Clinical Practice Guideline

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**Objective:** The aim was to formulate practice guidelines for management of osteoporosis in men.

**Evidence:** We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe the strength of recommendations and evidence quality.

**Consensus Process:** Consensus was guided by systematic evidence reviews, one in-person meeting, and multiple conference calls and e-mails. Task Force drafts were reviewed successively by The Endocrine Society's Clinical Guidelines Subcommittee and Clinical Affairs Core Committee; representatives of ASBMR, ECTS, ESE, ISCD; and members at large. At each stage, the Task Force received written comments and incorporated needed changes. The reviewed document was approved by The Endocrine Society Council before submission for peer review.

**Conclusions:** Osteoporosis in men causes significant morbidity and mortality. We recommend testing higher risk men [aged  $\geq 70$  and men aged 50–69 who have risk factors (e.g. low body weight, prior fracture as an adult, smoking, etc.)] using central dual-energy x-ray absorptiometry. Laboratory testing should be done to detect contributing causes. Adequate calcium and vitamin D and weight-bearing exercise should be encouraged; smoking and excessive alcohol should be avoided. Pharmacological treatment is recommended for men aged 50 or older who have had spine or hip fractures, those with T-scores of  $-2.5$  or below, and men at high risk of fracture based on low bone mineral density and/or clinical risk factors. Treatment should be monitored with serial dual-energy x-ray absorptiometry testing. (*J Clin Endocrinol Metab* 97: 1802–1822, 2012)

### Summary of Recommendations

#### 1.0. Evaluation

1.1. We suggest testing men at increased risk for osteoporosis by measurement of bone mineral density (BMD). Age 70 is a sufficient risk factor. Younger men (aged 50–69) should be tested if additional risk factors are present. A history of fracture after age 50 is a particularly important indication for evaluation. Other rea-

sons for testing men aged 50–69 include diseases/conditions such as delayed puberty, hypogonadism, hyperparathyroidism, hyperthyroidism, or chronic obstructive pulmonary disease; drugs such as glucocorticoids or GnRH agonists; life choices such as alcohol abuse or smoking; or other causes of secondary osteoporosis. FRAX, Garvan, or other fracture risk calculators can improve the assessment of fracture risk and the selection of patients for treatment. (2|⊕⊕○○)

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Abbreviations: ADT, Androgen-deprivation therapy; b-ALP, bone alkaline phosphatase; BMD, bone mineral density; BMI, body mass index; BTM, bone turnover marker; CI, confidence interval; CTX, C-telopeptide of type I collagen; DXA, dual-energy x-ray absorptiometry; NTX, N-telopeptide of type I collagen; 25(OH)D, 25-hydroxyvitamin D; PINP, procollagen I N-propeptide; VFA, vertebral fracture assessment.

1.2. We recommend dual-energy x-ray absorptiometry (DXA) of the spine and hip in men at risk for osteoporosis. (1|⊕⊕○○)

1.3. We suggest measuring forearm DXA (1/3 or 33% radius) when spine or hip BMD cannot be interpreted and for men with hyperparathyroidism or receiving androgen-deprivation therapy (ADT) for prostate cancer. (2|⊕⊕○○)

1.4. We suggest a complete history and physical examination for men being evaluated for osteoporosis or considered for pharmacological treatment (*e.g.* those with low BMD and/or high fracture risk). Important information includes medications used, chronic diseases, alcohol or tobacco abuse, falls and/or fractures as an adult, and family history of osteoporosis. Physical examination should assess patient height in comparison with maximum height, kyphosis, balance, mobility, overall frailty, and evidence of causes of secondary osteoporosis, including testicular atrophy, signs of hyperthyroidism, and evidence of chronic obstructive pulmonary disease. Men for whom bisphosphonate therapy is considered should have an examination of the teeth. (2|⊕⊕○○)

1.4.1. We suggest measuring serum calcium, phosphate, creatinine (with estimated glomerular filtration rate), alkaline phosphatase, liver function, 25-hydroxyvitamin D [25(OH)D], total testosterone, complete blood count, and 24-h urinary calcium (creatinine and sodium) excretion in men being evaluated for osteoporosis or considered for pharmacological treatment with bone-active agents. (2|⊕⊕○○)

1.4.2. If history or physical examination suggest a specific cause of osteoporosis, further testing should be done. Depending on the findings of the history and physical examination, such testing may include (but is not limited to) calculated free or bioavailable testosterone (using measurements of SHBG), serum protein electrophoresis with free  $\kappa$  and  $\lambda$  light chains and/or urine protein electrophoresis, tissue transglutaminase antibodies (for celiac disease), thyroid function tests, and PTH levels. (2|⊕⊕○○)

1.4.3. In men with low bone mass (osteopenia) or osteoporosis who might have previously undiagnosed vertebral fractures, we recommend vertebral fracture assessment (VFA) using DXA equipment. If VFA is not available or is technically limited, lateral spine radiographs should be considered. (1|⊕⊕○○)

## 2.0. Lifestyle

2.1. We recommend that men with or at risk for osteoporosis consume 1000–1200 mg calcium daily, ideally from dietary sources, with calcium supplements added if dietary calcium is insufficient. (1|⊕⊕○○)

2.2. We suggest that men with low vitamin D levels [ $<30$  ng/ml (75 nmol/liter)] receive vitamin D supplementa-

tion to achieve blood 25(OH)D levels of at least 30 ng/ml (75 nmol/liter). (2|⊕⊕○○)

2.3. We suggest that men at risk of osteoporosis participate in weight-bearing activities for 30–40 min per session, three to four sessions per week. (2|⊕○○○)

2.4. We suggest that men at risk of osteoporosis who consume three or more units of alcohol per day reduce their alcohol intake. (2|⊕○○○)

2.5. We recommend that men at risk of osteoporosis who smoke cease smoking. (1|⊕⊕○○)

## 3.0. Treatment

### 3.1. Selection of men for treatment

#### All men

3.1. We recommend pharmacological therapy for men at high risk for fracture including, but not limited to:

- Men who have had a hip or vertebral fracture without major trauma. (1|⊕⊕○○)
- Men who have not experienced a spine or hip fracture but whose BMD of the spine, femoral neck, and/or total hip is 2.5 SD or more below the mean of normal young white males. (1|⊕⊕○○)
- In the United States, men who have a T-score between  $-1.0$  and  $-2.5$  in the spine, femoral neck, or total hip plus a 10-yr risk of experiencing any fracture  $\geq 20\%$  or 10-yr risk of hip fracture  $\geq 3\%$  using FRAX; further studies will be needed to determine appropriate intervention levels using other fracture risk assessment algorithms. For men outside the US, region-specific guidelines should be consulted. (1|⊕⊕○○)
- Men who are receiving long-term glucocorticoid therapy in pharmacological doses (*e.g.* prednisone or equivalent  $>7.5$  mg/d, according to the 2010 guidelines of the American Society of Rheumatology). (1|⊕⊕○○)

### 3.2. Selection of therapeutic agent

3.2. We recommend that men at high risk of fracture be treated with medication approved by regulatory agencies such as the U.S. Food and Drug Administration (FDA) or the European Union (EU) European Medicines Agency (EMA) (at the time of this writing, alendronate, risedronate, zoledronic acid, and teriparatide; also denosumab for men receiving ADT for prostate cancer) and that the selection of therapeutic agent be individualized based on factors including fracture history, severity of osteoporosis (T-scores), the risk for hip fracture, patterns of BMD [*i.e.* whether BMD is worse at sites where cortical bone (*e.g.* 1/3 radius) or trabecular bone (*e.g.* spine) predominate], comorbid conditions (*e.g.* peptic ulcer disease, gastroesophageal reflux, malabsorption syndromes, malignancy, *etc.*), cost, and other factors. In men with a recent

hip fracture, we suggest treatment with zoledronic acid. When teriparatide is administered, we suggest that it not be given with concomitant antiresorptive therapy. Agents that have not been approved by regulatory agencies for treatment of osteoporosis in men (calcitonin, ibandronate, strontium ranelate, *etc.*) should be used only if the approved agents for male osteoporosis cannot be administered. (1|⊕⊕○○)

### Management of hypogonadal men at high risk of fracture

3.3. For men at high risk of fracture who are receiving testosterone therapy, we suggest adding an agent with proven antifracture efficacy (*e.g.* a bisphosphonate or teriparatide). (2|⊕○○○)

3.4. We suggest testosterone therapy in lieu of a “bone drug” for men at borderline high risk for fracture who have serum testosterone levels below 200 ng/dl (6.9 nmol/liter) on more than one determination, if accompanied by signs or symptoms of androgen deficiency (*e.g.* low libido, unexplained chronic fatigue, loss of body hair, hot flushes, *etc.*) or “organic” hypogonadism (*e.g.* due to hypothalamic, pituitary, or specific testicular disorder). If testosterone treatment does not alleviate symptoms of androgen deficiency after 3–6 months, it should be discontinued and other therapy considered. (2|⊕⊕○○)

3.5. We suggest testosterone therapy for men at high risk for fracture with testosterone levels below 200 ng/dl (6.9 nmol/liter) who lack standard indications for testosterone therapy but who have contraindications to approved pharmacological agents for osteoporosis. (2|⊕⊕○○)

### Men with prostate cancer receiving ADT

3.6. We recommend pharmacological treatment for osteoporosis for men with prostate cancer receiving ADT who have a high risk of fracture (see *Section 3.1*). (1|⊕⊕⊕○)

## 4.0. Monitoring therapy

4.1. We suggest that clinicians monitor BMD by DXA at the spine and hip every 1–2 yr to assess the response to treatment. If BMD appears to reach a plateau, the frequency of BMD measurements may be reduced. (2|⊕⊕⊕○)

4.2. We suggest that clinicians consider measuring a bone turnover marker (BTM) at 3–6 months after initiation of treatment using a bone resorption marker [such as serum C-telopeptide of type I collagen (CTX) or serum or urine N-telopeptide of type I collagen (NTX)] for antiresorptive therapy and a bone formation

marker [such as serum procollagen I N-propeptide (PINP)] for anabolic therapy. (2|⊕⊕⊕○)

## Method of Development of Evidence-Based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee of The Endocrine Society deemed the subject of osteoporosis in men a priority and appointed this Task Force to formulate evidence-based recommendations. Consensus was guided by systematic reviews of evidence and discussions through a series of conference calls, e-mails, and one in-person meeting. An initial draft was prepared by the chair of the Task Force and was reviewed successively by The Endocrine Society’s Clinical Guidelines Subcommittee and Clinical Affairs Core Committee; representatives of the American Society for Bone and Mineral Research (ASBMR), European Calcified Tissue Society (ECTS), European Society of Endocrinology (ESE), and International Society for Clinical Densitometry (ISCD); and members at large. At each stage, the Task Force received written comments and incorporated needed changes. The reviewed document was approved by The Endocrine Society Council before submission for peer review.

Evidence was rated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system. The GRADE group has expertise in development and implementation of evidence-based guidelines (1); a detailed description has been published elsewhere (2). The Task Force used the best available evidence and two commissioned systematic reviews and meta-analyses (3, 4). The Task Force also used consistent language and graphical descriptions of the strength of a recommendation and the quality of evidence. Strong recommendations use the phrase “we recommend” and the number 1; weak recommendations use the phrase “we suggest” and the number 2. *Cross-filled circles* indicate the quality of the evidence: ⊕○○○ denotes very low quality; ⊕⊕○○, low quality; ⊕⊕⊕○, moderate quality; and ⊕⊕⊕⊕, high quality. The Task Force has confidence that persons who receive care according to strong recommendations will derive, on average, more good than harm. Weak recommendations require more careful consideration of the person’s circumstances, values, and preferences to determine the best course of action. Linked to each *recommendation* is a description of the *evidence* and the *values* that panelists considered; in some instances, there are *remarks*, a section in which panelists offer technical suggestions for testing conditions, dosing, and monitoring. These

comments reflect the best available evidence applied to most men being treated. Often this evidence comes from the unsystematic observations of the panelists and their values and preferences; therefore, these remarks should be considered suggestions.

The Endocrine Society maintains a rigorous conflict of interest review process for the development of clinical practice guidelines. All Task Force members must declare any potential conflicts of interest, which are reviewed before they are approved to serve on the Task Force and periodically during the development of the guideline. The conflict of interest forms are vetted by the Clinical Guidelines Subcommittee (CGS) before the members are approved by the Society's Council to participate on the guideline Task Force. Participants in the guideline development must include a majority of individuals without conflict of interest in the matter under study. Participants with conflicts of interest may participate in the development of the guideline but they have disclosed all conflicts. The CGS and the Task Force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined by remuneration in any amount from the commercial interest(s) in the form of grants; research support; consulting fees; salary; ownership interest (*e.g.*, stocks, stock options, or ownership interest excluding diversified mutual funds); honoraria or other payments for participation in speakers' bureaus, advisory boards, or boards of directors; or other financial benefits. Completed forms are available through The Endocrine Society office.

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### **Epidemiology and pathophysiology**

Osteoporosis is a silent disorder characterized by reduced bone strength predisposing to increased fracture risk (5). Although osteoporosis affects women more often than men, approximately 20% of the 44 million Americans who have osteoporosis or low BMD are men (6). Between 30 and 40% of fractures due to osteoporosis occur in men; the lifetime risk of fracture for men aged 50 or older is between 13 and 30% (7).

Men with hip fractures have a mortality rate two to three times higher than women (8, 9, 202). Fractures in childhood and teenage years are more common in males, probably due to differences in lifestyle and trauma; most are at peripheral sites (10–15). Past middle age, fractures due to osteoporosis are more common in women. In later years, fracture risk rises exponentially in both sexes, but the increase occurs about a decade later in

men than in women. Of the 3.5 million fractures in men worldwide in 2000, 14% were at the hip, 10% at the forearm, 16% at the vertebrae, 5% at the humerus, and 55% elsewhere (16).

The incidence of fractures due to osteoporosis varies with race/ethnicity and geography. The highest rates in men are in Northern Europe and North America (17, 18). Lowest rates are in blacks and Asians (17, 18) as well as in some parts of South America (19, 20). The ratio of hip fractures between women and men also varies by geography. Although the female-to-male ratio among Caucasians is about 3–4:1, the ratio is much closer to 1:1 or even higher in Asia (18, 21, 22).

Before puberty, BMD measured with DXA is similar in boys and girls and increases slowly but progressively. At puberty, bone turnover increases dramatically, followed by a rapid increase in BMD (23). Androgens increase periosteal bone apposition, increasing the cross-sectional diameter of bone (24). Because BMD measured by DXA is directly related to bone size, part of the apparent pubertal BMD increase is due to a projection artifact from increasing bone size. Peak spine BMD as measured by DXA is generally reached by age 18 in males. Peak trabecular volumetric BMD as measured by quantitative computed tomography, and peak BMD of the hip, as measured by DXA, are reached several years later (25). As men and women age, bone resorption exceeds formation, leading to bone loss (26–30). BMD may begin to decline in men as early as age 30 to 40, decreasing slowly (about 0.5–1.0% annually), without the acceleration that is seen in women at menopause. In elderly men, however, degenerative change often increases DXA-measured BMD in the spine.

### **Bone quality**

Microarchitectural deterioration with advancing age is an important feature of osteoporosis (31). Because of differences in bone remodeling with age, trabeculae become thinner in men, whereas in women, trabeculae lose their connectivity (32).

### **Sex steroids**

There are many studies on the roles of gonadal steroids in bone development and adult bone homeostasis, but there are also many unanswered questions. Fully androgenized men are believed to benefit from anabolic properties of endogenous androgens with regard to bone mass and bone geometry (33). However, it is clear that estrogen is at least as important in men, particularly for skeletal accrual (34). Men with inactivating mutations of the aromatase or estrogen receptor genes (35) have markedly reduced bone mass despite normal or increased levels of testosterone (34–37). Whereas tes-

**TABLE 1.** Summary of risk factors for fractures in males (4)

Risk factor	No. of studies	OR	95% CI		P value	I <sup>2a</sup>
			LL	UL		
Age						
Age (continuous variable) <sup>b</sup>	11	1.12	1.07	1.18	0.00	87
Age (every 5–10 yr) <sup>c</sup>	6	1.29	1.17	1.43	0.00	52
Age >70 <sup>d</sup>	5	1.52	1.11	2.08	0.01	69
Race (vs. White)						
Black	3	0.69	0.57	0.85	0.00	91
Hispanic	2	1.05	0.62	1.78	0.84	60
BMI						
BMI (all studies)	23	0.89	0.83	0.96	0.00	71
BMI (quintile or 1 sd increase)	18	0.77	0.68	0.87	0.00	62
BMI (1 kg/m <sup>2</sup> )	5	1.01	0.95	1.08	0.76	66
Alcohol (daily or >10 drinks/week)	22	1.28	1.08	1.53	0.01	81
Smoking (current)	27	1.49	1.29	1.72	0.00	54
Chronic corticosteroid use (various definitions)	8	1.29	1.03	1.61	0.03	38
Prior fracture	9	2.08	1.57	2.77	0.00	75
Parental fractures						
Fracture, father	2	1.18	0.70	1.98	0.54	NA
Fracture, mother	2	1.32	0.97	1.81	0.08	NA
Fracture, parents	1	1.30	1.00	1.69	0.05	NA
History of falls within the last year	7	2.11	1.44	3.10	0.00	83
Hypogonadism (all studies)	8	1.76	1.37	2.26	0.00	85
Hypogonadism (nonpharmacological)	4	2.77	1.30	5.87	0.01	51
Hypogonadism (drug-induced)	4	1.53	1.19	1.96	0.00	91
Kidney stones	2	0.53	0.35	0.80	0.00	NA
History of stroke	4	3.73	1.75	7.92	0.00	73
DM	8	1.57	1.14	2.15	0.01	77
Asthma	2	1.01	0.56	1.84	0.96	56
Cardiovascular disease (CHF/MI)	6	1.07	0.86	1.33	0.55	86
Dementia	2	2.84	0.93	8.64	0.07	97
Osteoarthritis	4	1.03	0.57	1.88	0.91	87
Rheumatoid arthritis	5	1.46	0.97	2.19	0.07	60

NA, Not applicable (I<sup>2</sup> is not meaningful if the number of studies is less than three); CHF, congestive heart failure; DM, diabetes mellitus; LL, lower limit; MI, myocardial infarction; OR, odds ratio; UL, upper limit.

<sup>a</sup> I<sup>2</sup> statistic is defined as the proportion of heterogeneity not attributable to chance or random error.

<sup>b</sup> Age as a continuous variable reflects that the OR represents increases in odds per year of age.

<sup>c</sup> OR (95% CI) for studies: 5 yr = 1.41 (1.12–1.78); 7.7 yr = 1.16 (1.03–1.31); 10 yr = 1.39 (1.15–1.67).

<sup>d</sup> Age >70 is compared vs. age ≤70 in studies with mean age of 40–80.

tosterone administration had no effect on bone turnover in a man with an inactivating mutation in the estrogen receptor  $\alpha$  gene, estrogen increased BMD in a man with a null mutation of his aromatase gene (38). In older men, stronger associations have been reported between blood levels of estradiol and BMD than between levels of testosterone and BMD, although the differences are small and the associations weak (27, 39–43). Controlled physiological studies in which androgens, estrogens, or both are selectively suppressed have demonstrated that both androgens and estrogens are important regulators of bone turnover in adult men (41, 44).

### Hormonal abnormalities

25(OH)D levels are higher in men than in women at all ages but decline with age in both sexes (45, 46) due to decreased sun exposure, skin production, and dietary intake (47–51).

PTH levels increase with age (52–54), to a large extent due to declining kidney function and reduced synthesis of 25(OH)D.

Many factors may contribute to differences in the incidence and prevalence of osteoporosis and fractures between men and women (24, 55, 56). Men's larger bones contribute to greater bone strength (57). Risk factors that may be more common in men include delayed puberty (58) and hypercalciuria. Men fall less often than women (59, 60); higher androgen levels have been associated with reduced fall risk (39). Finally, men have a shorter life expectancy.

## 1.0. Evaluation

### Recommendation

1.1. We suggest testing men at increased risk for osteoporosis by measurement of BMD. Age 70 is a sufficient

risk factor. Younger men (aged 50–69 yr) should be tested if additional risk factors are present. A history of fracture after age 50 is a particularly important indication for evaluation. Other reasons for testing men ages 50–69 include diseases/conditions such as delayed puberty, hypogonadism, hyperparathyroidism, hyperthyroidism, or chronic obstructive pulmonary disease; drugs such as glucocorticoids or GnRH agonists; life choices such as alcohol abuse or smoking; or other causes of secondary osteoporosis. FRAX, Garvan, or other fracture risk calculators can improve the assessment of fracture risk and the selection of patients for treatment. (2|⊕⊕○○)

### 1.1. Evidence

In addition to low BMD, age is an independent risk factor for osteoporosis and for fracture (61–65). Table 1 lists other risk factors for low BMD or fractures in men (27, 42, 66–74). These were assessed in a systematic review and meta-analysis (4). Most of the associations were weak (*i.e.* adjusted odds ratios were in general <2), and the level of evidence was low; therefore, the strength of this recommendation is low.

### 1.1. Remarks

The FRAX calculator ([www.shef.ac.uk/FRAX/](http://www.shef.ac.uk/FRAX/)) and the Garvan nomogram ([www.fractureriskcalculator.com](http://www.fractureriskcalculator.com)) are commonly-used algorithms for predicting fracture risk. Both use age, weight, history of fracture, and femoral neck BMD, although other variables differ (75, 76). In a validation study from Australia, FRAX underestimated fracture risk in men (77). A simple score using BMD, prior fracture, and corticosteroid use developed for Canadian women (78) has been applied to men (79). Simple risk calculators such as the Osteoporosis Self-Assessment Tool (OST) and Male Osteoporosis Screening Tool (MOST) (80, 81) may be useful to identify men likely to have osteoporosis by DXA. Age has been shown to be an important predictor of fracture risk (63, 71, 74).

### Recommendation

1.2. We recommend DXA of the spine and hip in men at risk for osteoporosis. (1|⊕⊕○○)

### 1.2. Evidence

In men as in women, BMD correlates strongly with fracture risk (64). In a large study of men and women over age 65, BMD (total hip and femoral neck) was strongly associated with hip fracture risk, with a stronger association in men (82). Spine BMD was also significantly associated with hip fracture risk, although less strongly than hip DXA. Spine and hip BMD predict nonvertebral frac-

ture risk similarly (82). Femoral neck BMD identifies fewer men than women who suffered a hip fracture (83). Using only hip BMD would identify a small proportion of the men who will experience a fracture. Although spine BMD is useful in younger men, a high frequency of artifacts and degenerative change reduce its utility in older men.

DXA is helpful in choosing men for therapy because men with DXA-proven osteoporosis or “osteopenia” plus a previous fracture respond to currently available therapy (84–88).

### 1.2. Remarks

Third-party payers, including Medicare, vary in their coverage of DXA testing in men. For example, Medicare covers initial DXA only in men who have vertebral fractures, radiographic osteopenia, hyperparathyroidism or are on oral glucocorticoid therapy (89).

### Recommendation

1.3 We suggest measuring forearm DXA (1/3 or 33% radius) when spine or hip BMD cannot be interpreted and for men with hyperparathyroidism or receiving ADT for prostate cancer. (2|⊕⊕○○)

### 1.3. Evidence

Radius BMD predicts fractures in men (90, 91). BMD measurement at skeletal sites where osteoarthritis is uncommon, such as the 1/3 (33%) radius, may be more sensitive for detecting bone loss in elderly men (91, 92). A large study found osteoporosis (T-scores of  $-2.5$  or below) at the 1/3 radius in about 15% of men aged 70 or older who had T-scores better than  $-2.5$  in the spine and hip (92). In the Geelong Study, mean spine BMD was about the same in men aged 20–85 yr; however, after age 47, there was a considerable, progressive decrease in the midforearm BMD (93).

Radius BMD declines to a greater extent than hip or spine BMD in men with prostate cancer receiving ADT (94–96). Moreover, radius BMD measurements performed as well as spine or hip BMD for distinguishing between effects of denosumab and placebo (97).

Because artifacts and localized degenerative change in the spine and hip are common in men, particularly those older than 60 (98), radius BMD may provide a more realistic measure of skeletal status. In some subjects, such as patients with hyperthyroidism or hyperparathyroidism, T-scores for radius BMD are often lower than T-scores for the spine or hip (99). The ISCD recommends only considering the T-score from the 1/3 (33%) radius site (100).

### 1.3. Remarks

Medicare and other payers may not cover forearm BMD testing (89). Although radius BMD predicts fractures in men (91) and appears to be particularly important in men on ADT (94), there are no studies showing that men with osteoporosis in the radius and not at other sites respond to current treatments.

### Recommendations

1.4. We suggest a complete history and physical examination for men being evaluated for osteoporosis or considered for pharmacological treatment (*e.g.* those with low BMD and/or high fracture risk). Important information includes medications used, chronic diseases, alcohol or tobacco abuse, falls and/or fractures as an adult, and family history of osteoporosis. Physical examination should assess patient height in comparison with maximum height, kyphosis, balance, mobility, overall frailty, and evidence of causes of secondary osteoporosis, including testicular atrophy, signs of hyperthyroidism, and evidence of chronic obstructive pulmonary disease. Men for whom bisphosphonate therapy is considered should have an examination of the teeth. (2|⊕⊕○○)

1.4.1. We suggest measuring serum calcium, phosphate, creatinine (with estimated glomerular filtration rate), alkaline phosphatase, liver function, 25(OH)D, total testosterone, complete blood count, and 24-h urinary calcium (creatinine and sodium) excretion in men being evaluated for osteoporosis or considered for pharmacological treatment with bone-active agents. (2|⊕⊕○○)

1.4.2. If history or physical examination suggest a specific cause of osteoporosis, further testing should be done. Depending on the findings of the history and physical examination, such testing may include (but is not limited to) calculated free or bioavailable testosterone (using measurements of SHBG), serum protein electrophoresis with free  $\kappa$  and  $\lambda$  light chains and/or urine protein electrophoresis, tissue transglutaminase antibodies (for celiac disease), thyroid function tests, and PTH levels. (2|⊕⊕○○)

1.4.3. In men with low bone mass (osteopenia) or osteoporosis who might have previously undiagnosed vertebral fractures, we recommend VFA using DXA equipment. If VFA is not available or is technically limited, lateral spine radiographs should be considered. (1|⊕⊕○○)

### 1.4. Evidence

Potentially important information can come from the history and physical examination. An oral exam is important; clinicians should assess whether additional dental evaluation or care may be needed before starting bisphosphonate therapy. The yield and cost-effectiveness of laboratory studies in men with low BMD are not

well established. Nevertheless, in men at increased risk of fracture, laboratory tests may be useful to determine factors that contribute to low BMD or fracture risk and to design appropriate therapy. History and physical examination may provide important information. Osteomalacia, usually due to severe vitamin D deficiency, is common in men with hip fractures. Other causes of bone loss, such as hyperparathyroidism, kidney and liver disease, hypogonadism, and hypercalciuria, are sufficiently common in high-risk men to warrant evaluation (101). A 24-h urine calcium measurement is useful to identify idiopathic hypercalciuria or calcium malabsorption. Hypercalciuria can be managed with thiazide diuretics (102). Moderate vitamin D deficiency is common in men and is associated with low bone mass and increased fracture risk. Other laboratory tests may be appropriate, depending on the clinical context.

VFA is a low-cost, low-risk method for detecting vertebral fractures using standard DXA devices. The ISCD recommends VFA for men over age 80 with osteopenia or younger men with historical height loss greater than 6 cm (103). Additionally, younger men (aged 70–79) are candidates for VFA if they have a chronic disease such as rheumatoid arthritis, Crohn's disease, or chronic obstructive pulmonary disease. Although VFA detects many vertebral fractures, imaging quality may be limited, particularly in the midthoracic spine and higher, where radiographs may be needed. Still, VFA can provide useful clinical information, particularly if there is clinical suspicion of occult vertebral fractures.

## 2.0. Lifestyle

### Recommendation

2.1. We recommend that men with or at risk for osteoporosis consume 1000–1200 mg calcium daily, ideally from dietary sources, with calcium supplements added if dietary calcium is insufficient. (1|⊕⊕⊕○)

### 2.1. Evidence

Several studies have addressed the effects of calcium on BMD and fracture risk in men, with inconsistent findings. No benefit for BMD was observed from calcium/vitamin D supplementation in well-nourished men (mean dietary calcium intake >1000 mg/d) (104). However, an increase in BMD was seen in healthy older men given calcium and vitamin D supplements (105). Calcium- and vitamin D-fortified milk increased BMD (106) and improved femoral bone structure in older men (107). Dietary calcium was not related to fractures in men in the Health Professionals Follow-Up Study (108), but low dietary calcium intake was associated with higher fracture risk in a cohort of Australian men (109). Calcium supplementation alone

has not been demonstrated to reduce fracture risk in men with prior fractures (110). In clinical trials of alendronate (84), risedronate (86), and teriparatide (87) for osteoporosis in men, calcium (500–1000 mg/d) and vitamin D [400–1200 IU/d (10–30  $\mu$ g/d)] supplementation was provided for all subjects.

In women, calcium supplementation is more beneficial in those with low calcium intake (111) and, together with vitamin D, reduces hip fracture risk in compliant subjects (112). There are no similar studies in men.

The Institute of Medicine (IOM) recommends a calcium intake of 1000 mg/d for men aged 51–70 and 1200 mg/d for men (and women) older than 70 (113).

A meta-analysis showed that calcium supplements may be associated with an increased risk of myocardial infarction but no other cardiovascular end points or death in women (114). This finding has not been confirmed in men (115).

In older women, calcium supplementation increases the risk of kidney stones (112). The prevalence of kidney stones is higher in men than in women, but no increase in kidney stones has been demonstrated in men at the level of calcium intake recommended for optimal bone health. An observational study suggested that the risk of metastatic prostate cancer was higher in men who received high doses of supplemental calcium (1500–2000 mg/d) (116), but this has not been substantiated in clinical trials (117).

## Recommendation

2.2. We suggest that men with low vitamin D levels [ $<30$  ng/ml (75 nmol/liter)] receive vitamin D supplementation to achieve blood 25(OH)D levels of at least 30 ng/ml (75 nmol/liter). (2| $\oplus\oplus\oplus\oplus$ )

## 2.2. Evidence

Vitamin D deficiency is common in older men (118) and has been associated with an increased risk of hip and non-vertebral fractures (119).

Severe vitamin D deficiency [25(OH)D levels  $\leq 10$  ng/ml (25 nmol/liter)] may lead to osteomalacia, which should be treated with calcium and vitamin D; treatment results in symptomatic and biochemical improvement and sometimes large increases in BMD. This degree of vitamin D deficiency should be at least partially corrected before considering treatment for osteoporosis.

Vitamin D status can be assessed by measuring serum 25(OH)D. Because vitamin D is a threshold nutrient, the usual approach to defining normality in a “healthy” population is inappropriate. Insufficiency needs to be defined with reference to changes in calcium homeostasis, BMD, or fracture risk.

Serum 25(OH)D measurement is recommended in men at high risk for vitamin D deficiency (120). This includes men with osteomalacia, osteoporosis, malabsorption (*e.g.* celiac disease, bariatric surgery, *etc.*), and liver disease, as well as older men with a history of falls and those taking medications that alter vitamin D status, such as some anticonvulsants (121).

International consensus is lacking on a reference range for 25(OH)D levels, partly due to assay variability. Many experts support a minimum desirable 25(OH)D level of 30 ng/ml (75 nmol/liter) for bone health (122), although a committee of the IOM concluded that 20 ng/ml (50 nmol/liter) was adequate for bone health (113); it should be noted that the IOM recommendations are for healthy individuals and may not be appropriate for patients with osteoporosis. For men at high risk of fracture, we are recommending a target 25(OH)D level of 30 ng/ml, consistent with The Endocrine Society 2011 Clinical Practice Guidelines on Evaluation, Treatment, and Prevention of Vitamin D Deficiency (123).

For most people, optimal vitamin D levels can be achieved with 1000–2000 IU (25–50  $\mu$ g) of vitamin D daily. Larger doses [*e.g.* 50,000 IU (1.25 mg) orally weekly for 8 wk or 300,000 IU (7.5 mg) by im injection every 3 months] may be required for patients with more severe vitamin D deficiency.

Vitamin D at high doses may result in toxicity (hypercalcemia or hypercalciuria), but this is rarely seen unless 25(OH)D levels exceed 150 ng/ml (375 nmol/liter) (121), and such levels are unlikely with the doses of vitamin D recommended here. In a recent report of high-dose vitamin D [500,000 IU (12.5 mg) orally once a year] given to women older than 70 yr, there was an increased risk of fracture and falling, especially in the first 3 months after administration, when 25(OH)D levels were on average 50 ng/ml (125 nmol/liter) (124). This finding needs to be confirmed in women and has not been documented in men, but it raises caution about giving high doses of vitamin D intermittently.

## 2.2. Remarks

Measurement of serum 25(OH)D is challenging because assay variability is high and between-assay calibration is poor. Not unexpectedly, the intra- and interassay variability is much greater at lower 25(OH)D levels (125). Although mean serum 25(OH)D differs depending on the assay method (RIA, chemiluminescence, or liquid chromatography-tandem mass spectrometry), the relative ranking is similar between assays (125). The International Vitamin D External Quality Assessment Scheme is an effort to harmonize 25(OH)D assays (126). Still, the latitude between “reference” and “toxic” levels is quite wide.



**Recommendation**

2.3. We suggest that men at risk of osteoporosis participate in weight-bearing activities for 30–40 min per session, three to four sessions per week. (2|⊕○○○)

**2.3. Evidence**

Low physical activity in older men is associated with poor health (127). Studies of exercise interventions in men and in postmenopausal women at risk for osteoporosis have generally been of poor quality (128). However, weight-bearing activities, such as walking 30–40 min for three to four sessions per week, is a logical recommendation (129), supported by small studies showing improvement in BMD (130) and decreased fall risk (131).

**Recommendation**

2.4. We suggest that men at risk of osteoporosis who consume three or more units of alcohol per day reduce their alcohol intake. (2|⊕○○○)

**2.4. Evidence**

High alcohol intake is associated with increased bone loss, falling, and fractures in older men (132), although the mechanism is unclear. There may be a threshold effect (133–135), with no excess risk 2 U/d of alcohol [one unit of alcohol is defined as 10 ml in the United Kingdom and as 10 g (12.7 ml) in Australia—approximately half a pint of beer, one small glass of wine, or a single measure of spirits]. The relative hazard for alcohol consumption of at least 3 U/d was 1.33 for all fractures [95% confidence interval (CI), 1.10 to 1.60] and 1.92 for hip fractures (95% CI, 1.28 to 2.88), with no contribution from BMD, body mass index (BMI), or age. If the association with alcohol intake is causal, then it accounts for approximately 7% of hip fractures in men (133). The risk of fractures remains elevated even when alcohol consumption is reduced (134).

Self-reported alcohol intake may be underestimated, and the intakes in populations studied (Dutch, Canadian, Australian) appeared lower than reported for the United Kingdom (133). This may indicate that the threshold observed in U.S. and Danish studies may be more accurate ( $\geq 4$  U/d).

**2.4. Remarks**

A strategy should be in place to support men who wish to reduce their alcohol intake.

**Recommendation**

2.5. We recommend that men at risk of osteoporosis who smoke cease smoking. (1|⊕○○○)

**2.5. Evidence**

A meta-analysis of more than 15,000 men suggested that the association of smoking with fracture risk was higher in men than in women (136). The relative hazard for a current male smoker was 1.5 for all fractures (95% CI, 1.3 to 1.8), 1.5 for osteoporosis-related fractures (95% CI, 1.3 to 1.8), and 1.8 for hip fractures (95% CI, 1.3 to 2.5); the increase in risk was independent of age. The contribution of low BMD to increased fracture risk was 40%. BMD contributed more than BMI to the effect of smoking on fracture risk. As with alcohol, the mechanisms by which smoking may increase fracture risk have not been determined. The offset of effects in men is not known, but in women, the benefits of stopping smoking on hip fracture risk were not apparent until after 10 yr (137). This observation is in keeping with the Framingham Study; men who were current smokers had greater bone loss from the proximal femur (but not spine or forearm) than former smokers or men who never smoked (138).

**2.5. Values and preferences**

Smoking is harmful to health, and smoking cessation reduces risk not only of fractures but also of other diseases. Smoking cessation should be recommended as a general health measure for current smokers. Panel members placed higher value on preventing other smoking-related complications because data showing that smoking cessation reduces fracture risk are limited.

**2.5. Remarks**

Medical support may be required to assist with smoking cessation (139).

**3.0. Treatment****3.1. Selection of men for treatment****Recommendation****All men**

3.1. We recommend pharmacological therapy for men at high risk for fracture including, but not limited to:

- Men who have had a hip or vertebral fracture without major trauma. (1|⊕⊕⊕○)
- Men who have not experienced a spine or hip fracture but whose BMD of the spine, femoral neck, and/or total hip is 2.5 SD or more below the mean of normal young white males. (1|⊕⊕○○)
- In the United States, men who have a T-score between  $-1.0$  and  $-2.5$  in the spine, femoral neck, or total hip plus a 10-yr risk of experiencing any fracture  $\geq 20\%$  or 10-yr risk of hip fracture  $\geq 3\%$  using FRAX; further studies will be needed to determine appropriate intervention levels using other fracture risk assessment al-

gorithms. For men outside the US, region-specific guidelines should be consulted. (1|⊕⊕○○)

- Men who are receiving long-term glucocorticoid therapy in pharmacological doses (*e.g.* prednisone or equivalent >7.5 mg/d) according to the 2010 guidelines of the American Society of Rheumatology. (1|⊕⊕○○)

### 3.1. Evidence

In contrast to the large fracture-end point trials of osteoporosis therapies in women, studies in men have generally been small, with change in BMD as the primary end point. Thus, recommendations regarding treatment efficacy in men are provided with lesser confidence. Nevertheless, treatment trials in men have yielded effects on BMD, biochemical markers of bone remodeling, and trends in fracture reduction that closely mirror those seen in larger trials in postmenopausal women with osteoporosis. A systematic review and meta-analysis came to this conclusion (3). Therefore, we conclude that available therapies are likely to be effective in men and that it is appropriate to recommend pharmacological therapy in men with increased fracture risk. Alendronate increased BMD and reduced the incidence of radiographic vertebral fractures (by quantitative morphometry but not by semiquantitative assessment) in men with low femoral neck or spine T-scores or whose femoral neck BMD T-score was at least  $-1$  with at least one vertebral deformity or a history of nonvertebral fracture (84). Risedronate increased BMD and reduced the incidence of vertebral fractures in men with T-scores in the spine of  $-2.0$  or below and femoral neck  $-1.0$  or below (85, 86). Teriparatide increased BMD in men with osteoporosis (87) and appeared to reduce the risk of vertebral fractures in men whose T-score for spine, femoral neck, and/or total hip was  $-2.0$  or below (87). Similarly, zoledronic acid has been shown to have positive effects in men with low BMD (140). Based on a cost-effectiveness analysis specific to the United States, the National Osteoporosis Foundation (NOF) concluded that a 10-yr risk of hip fracture of at least 3% or 10-yr risk of major fracture of at least 20% was sufficient to justify treatment of women (141). Cost-effectiveness has not been studied adequately in men. Because FRAX may underestimate fracture in men (77) and because the NOF study assumed a treatment cost higher than present costs, we believe that it is conservative to use the NOF treatment thresholds in men.

The evidence available to provide guidance about who is at sufficient risk to warrant pharmacological therapy is inadequate and controversial. Criteria based only on BMD T-scores (T-score  $-2.5$  or below in the spine or hip) are too restrictive because they identify too few men for therapy (<10%), whereas approximately 25% of men ex-

perience a fracture after age 60 (142), and a majority of men who fracture have T-scores that are better than  $-2.5$  (83). T-score-only criteria ignore important, independent contributions to fracture risk from factors other than BMD, such as age, previous fractures, and comorbidities. This along with other factors can now more accurately predict risk fractures. The use of FRAX identifies a larger proportion of older men in whom therapy appears to be cost-effective (141) than use of T-scores alone. However, these algorithms may not be sufficiently sensitive because they do not incorporate risk factors that also are likely to affect fracture risk (*e.g.* malabsorption, renal insufficiency, fall risk, some medications) and because they consider only hip BMD.

Acknowledging the shortcomings of the available data, we recognize the need to be sufficiently inclusive to identify both an adequate number of the men at risk and to incorporate multivariable risk models. Therefore, we recommend that several criteria be considered in making treatment choices.

Men who have suffered fragility hip or clinical vertebral fractures are at high risk of additional fractures and should be considered for pharmacological treatment. A T-score of  $-2.5$  or below in the spine, femoral neck, or total hip (using the young male reference range) should also be a factor in the decision to treat. Finally, we recommend the use of FRAX or Garvan or another risk assessment tool in men who have not sustained a fragility fracture and in whom the T-score is between  $-1.0$  and  $-2.5$ , and, at least in the United States, to recommend pharmacological therapy for men who have a 10-yr risk of greater than 3% for hip fracture or at least 20% for major osteoporosis-related fracture using FRAX.

We endorse the 2010 guidelines of the American College of Rheumatology (143) for selecting men who require long-term systemic glucocorticoid therapy for pharmacological treatment with bone-active agents.

## Recommendation

### 3.2. Selection of therapeutic agent

We recommend that men at high risk of fracture be treated with medication approved by regulatory agencies such as the U.S. FDA or EU EMA (at the time of this writing, alendronate, risedronate, zoledronic acid, and teriparatide; also denosumab for men receiving ADT for prostate cancer) and that the selection of therapeutic agent be individualized based on factors including fracture history, severity of osteoporosis (T-scores), the risk for hip fracture, patterns of BMD [*i.e.* whether BMD is worse at sites where cortical bone (*e.g.* 1/3 radius) or trabecular bone (*e.g.* spine) predominates], comorbid conditions (*e.g.* peptic ulcer disease, gastroesophageal reflux, malabsorp-

tion syndromes, malignancy, *etc.*), cost, and other factors. In men with a recent hip fracture, we suggest treatment with zoledronic acid. When teriparatide is administered, we suggest that it not be given with concomitant antiresorptive therapy. Agents that have not been approved by regulatory agencies for treatment of osteoporosis in men (calcitonin, ibandronate, strontium ranelate, *etc.*) should be used only if the approved agents for male osteoporosis cannot be administered. (1|⊕⊕○○)

### 3.2. Evidence

The effects of bisphosphonates and teriparatide on BMD and BTM appear to be similar in men and women (144). Of the FDA-approved agents used to treat osteoporosis in men, alendronate, risedronate, and zoledronic acid have been shown to reduce the risk of hip fractures in women with postmenopausal osteoporosis (145–147). Denosumab has been shown to increase BMD and reduce the incidence of vertebral fractures in men receiving ADT for non-metastatic prostate cancer. Once-yearly treatment with iv zoledronic acid reduced risk of recurrent fractures in more than 2100 subjects (~25% were men) who had undergone repair of a hip fracture within 90 d of treatment initiation (148). Teriparatide increases spine BMD more than alendronate; combining teriparatide with alendronate seems to attenuate the anabolic effect of teriparatide on BMD in both the spine and the hip (149, 150). The effects of combining teriparatide with an antiresorptive agent on fracture risk have not been examined.

### 3.2. Remarks

For most men who are candidates for pharmacological therapy, generic alendronate will often be preferred because of: 1) extensive experience with its use; 2) lack of evidence that other agents are more effective or better tolerated; and 3) low cost. For men with upper or lower gastrointestinal problems, a nonoral therapy (*e.g.* zoledronic acid or teriparatide) may be preferred. In postmenopausal women, risedronate has been shown to reduce hip fracture risk and is a reasonable alternative for men at risk for hip fractures. For men at high risk of vertebral fracture, teriparatide may be preferred because it increases spine BMD more than alendronate, although it is more expensive (149). Teriparatide could also be considered for men who fail to tolerate or respond adequately to other agents. Because concomitant antiresorptive therapy seems to reduce the efficacy of teriparatide, increase costs, and expose patients to additional potential side effects, it should be discontinued when teriparatide is administered. Clinical and social context should be considered in selecting therapeutic agents, as well as side effects and safety concerns. Bisphosphonate therapy should not

be used in men with impaired kidney function (estimated glomerular filtration rate  $\leq 30$ – $35$  ml/min). Potential safety concerns with bisphosphonates include osteonecrosis of the jaw (151) and atypical femur fractures (152). The optimal duration of bisphosphonate therapy has not been determined (153). Teriparatide should not be used in men with prior irradiation. Full prescribing information should be consulted.

## Recommendations

### Management of hypogonadal men at high risk of fracture

3.3. For men at high risk of fracture who are receiving testosterone therapy, we suggest adding an agent with proven antifracture efficacy (*e.g.* a bisphosphonate or teriparatide). (2|⊕○○○)

3.4. We suggest testosterone therapy in lieu of a “bone drug” for men at borderline high risk for fracture who have serum testosterone levels below 200 ng/dl (6.9 nmol/liter) on more than one determination, if accompanied by signs or symptoms of androgen deficiency (*e.g.* low libido, unexplained chronic fatigue, loss of body hair, hot flashes, *etc.*) or “organic” hypogonadism (*e.g.* due to hypothalamic, pituitary, or specific testicular disorder). If testosterone treatment does not alleviate symptoms of androgen deficiency after 3–6 months, it should be discontinued and other therapy considered. (2|⊕⊕○○)

3.5. We suggest testosterone therapy for men at high risk for fracture with testosterone levels below 200 ng/dl (6.9 nmol/liter) who lack standard indications for testosterone therapy but who have contraindications to approved pharmacological agents for osteoporosis. (2|⊕⊕○○)

### 3.3.–3.5. Evidence

In men with congenital hypogonadal disorders, such as Kallmann’s or Klinefelter syndromes, BMD is thought to be reduced because of inadequate pubertal bone accretion leading to a lower peak bone mass (154, 155). In men with acquired disorders that reduce testosterone levels, such as primary gonadal failure, pituitary or hypothalamic tumors, or hemochromatosis, BMD declines because of accelerated bone resorption (156–160).

Normalization of testosterone levels increases BMD in men with hypogonadism due to GnRH deficiency, particularly in subjects who have not yet reached skeletal maturity (161). Even with prolonged androgen replacement, however, BMD fails to normalize in these men (161). Normalization of testosterone increases BMD in men with acquired hypogonadism due to prolactin-secreting adenomas (162), other pituitary-hypothalamic disorders, or primary testicular disorders (159, 160). In men with acquired

hypogonadism, testosterone therapy reduces BTM, suggesting that the testosterone-induced increases in BMD are due to antiresorptive effects (159, 163) possibly mediated through conversion of testosterone to estradiol.

Our recommendation to treat men with testosterone if they have hypogonadism due to organic disease or symptoms of androgen deficiency is consistent with the current standard of care in these men (164). Our suggestion to add a pharmacological agent to treat osteoporosis if fracture risk is high reflects the convincing fracture-prevention data in women treated with bisphosphonates or teriparatide and the lack of fracture-prevention data in men treated with testosterone. Our suggestion that testosterone alone be considered if such men have a modest or borderline risk of fracture reflects our desire to manage both the hypogonadism and the low BMD with a single agent, thus reducing costs and the risk of medication side effects, as well as our belief that it is likely that the beneficial effects of testosterone on BMD in hypogonadal men indicate that it will also reduce fracture risk.

Because testosterone and estradiol levels decline as men age, it has been suggested that this decline may be responsible, at least in part, for the decrease in BMD that occurs in aging men. The effects of testosterone therapy on BMD in aging men with low or borderline low testosterone levels and no known disorders of the hypothalamic-pituitary-gonadal axis have been examined in several small ( $n = 13$ – $108$ ) placebo-controlled studies of varying durations (6–36 months). The effect of testosterone on BMD appears to be related to baseline levels; testosterone therapy fails to increase BMD in men whose testosterone levels are within the reference range, whereas it increases BMD in men whose levels are below the reference range. For example, in men aged 65 yr or older with serum testosterone levels below 470 ng/dl (16.3 nmol/liter) [mean  $\pm$  SE baseline level of  $399 \pm 10$  ng/dl ( $13.8 \pm 0.3$  nmol/liter)], testosterone for 6 months had no significant effect on BMD (165). Similarly, in 108 men more than 65 yr of age with serum testosterone levels below 475 ng/dl (16.5 nmol/liter), spine BMD increased to the same extent in men treated with testosterone compared with those receiving with placebo for 3 yr (166). A *post hoc* analysis, however, suggested that testosterone therapy increased BMD more than placebo in men with baseline testosterone levels below 200 ng/dl (6.9 nmol/liter). Three placebo-controlled trials have examined the effect of testosterone administration on BMD in older men with low baseline testosterone levels. Spine, trochanter, and total hip BMD increased with testosterone compared to placebo over 36 months in men more than 65 yr of age with baseline testosterone levels below 350 ng/dl (12.1 nmol/liter) (163). In men age 60 or older with baseline testosterone levels below 320

ng/dl, 12 months of testosterone increased spine and total hip BMD, but there was no significant change at the femoral neck (167). Twelve months of testosterone prevented a decline in femoral neck BMD in men age 65 or older with baseline bioavailable testosterone levels below normal (168).

Measurements of serum testosterone levels are useful to identify men who have androgen deficiency and who may be candidates for testosterone replacement. Low levels of both testosterone and estradiol are associated with bone loss and fractures in men, although the associations are weak (43, 169, 170). Low estradiol levels are more strongly associated with increased fracture risk and accelerated bone loss in older men (27, 171, 172). Measurement of estradiol levels in clinical situations in men is not recommended because of the lack of easily available, accurate assay methods (mass spectrometry) and the absence of validated clinical algorithms that incorporate estradiol measurements into treatment decisions. High SHBG levels are associated with increased fracture incidence and bone loss in older men.

Skeletal health may be compromised when serum testosterone levels fall below 200–250 ng/dl (6.9–8.7 nmol/liter). As noted above, testosterone administration increased BMD in elderly men whose baseline testosterone levels were 200–300 ng/dl (6.9–10.4 nmol/liter) but not in men with higher baseline levels (166). Second, in the Osteoporotic Fractures in Men study, the odds of having osteoporosis at the hip tripled, as did the odds of experiencing rapid hip bone loss in men with baseline testosterone levels below 200 ng/dl (6.9 nmol/liter) *vs.* men with testosterone levels above 200 ng/dl (6.9 nmol/liter) (42). Additionally, in the Dubbo Osteoporosis Epidemiology Study, the risk of low-trauma fracture was higher in men with baseline testosterone levels in the lowest quartile [median level of 227 ng/dl (7.9 nmol/liter)] (142). Finally, in healthy men given a GnRH agonist with testosterone gel for 16 wk, bone resorption increased when serum testosterone levels fell below 200 ng/dl (6.9 nmol/liter), although there did not appear to be a distinct threshold (173). Thus, men whose serum testosterone level is 200–300 ng/dl (6.9–10.4 nmol/liter) or below appear to be at higher risk for bone loss and fracture and are more likely to have a favorable response to testosterone therapy. Because the benefits of testosterone therapy are not well established and the risks of therapy are not clear, we feel that a more conservative level [*i.e.* 200 ng/dl (6.9 nmol/liter)] should be used for intervention until further data are available.

No studies have assessed the effects of combining testosterone with bisphosphonates or other osteoporosis drugs in hypogonadal men. The available data from both

controlled and uncontrolled trials, together with data from animal studies, suggest that testosterone is an effective therapy for hypogonadal men with osteoporosis. For men with hypogonadism due to organic disease and/or symptomatic hypogonadism who have a marginal increase in fracture risk, testosterone therapy may be adequate. However, in men who need testosterone therapy for hypogonadism and who have a high fracture risk, we recommend adding an approved pharmacological agent.

## Recommendation

### Men with prostate cancer receiving ADT

3.6. We recommend pharmacological treatment for osteoporosis for men with prostate cancer receiving ADT who have a high risk of fracture (see *Section 3.1*). (1|⊕⊕⊕⊕)

### 3.6. Evidence

Orchiectomy or administration of long-acting GnRH agonists to men with prostate cancer lowers serum testosterone and estradiol levels to the prepubertal range, increasing bone resorption and inducing rapid bone loss. Several small studies have examined rates of bone loss during the first year of GnRH agonist therapy in men with prostate cancer. In general, spine BMD declines by 3–4% in the first year (95, 174–178). Decreases in hip BMD are more modest (95, 174–178). Interestingly, BMD declined more rapidly in the radius than in the spine or hip (95, 97). Fracture risk is increased in men receiving ADT (179–181).

Randomized controlled trials have been performed to determine whether antiresorptive agents prevent bone loss in men receiving ADT for prostate cancer. Intravenous pamidronate every 12 wk prevented bone loss in men with locally advanced or recurrent prostate cancer initiating GnRH agonist therapy (175, 177). Similar results have been reported with other bisphosphonates, including iv zoledronic acid (177, 182) and oral alendronate (183, 184). Two randomized controlled trials have examined the effects of selective estrogen receptor modulators on bone health in men with prostate cancer receiving chronic GnRH agonist therapy. Administration of raloxifene for 12 months increased BMD of the hip and tended to increase BMD of the spine compared with placebo (183). In a study of men with prostate cancer and low BMD of the spine and/or hip receiving GnRH agonist therapy for at least 6 months, toremifene reduced the risk of new or worsening morphometric vertebral fractures, clinical fragility fractures, or significant bone loss after 24 months (184).

A placebo-controlled trial showed the benefits of denosumab in men with early prostate cancer receiving

ADT; after 36 months of treatment, denosumab increased spine, hip, and distal radius BMD and decreased the incidence of vertebral fractures by 62% (97, 185); denosumab is now approved by the FDA and EU EMA for treatment of men with non-metastatic prostate cancer receiving ADT. Denosumab in higher doses than used to treat osteoporosis has been shown to improve the outcome of men with advanced prostate cancer metastatic to bone (denosumab 60 mg SQ every 6 months is the dose for treatment of osteoporosis; 120 SQ monthly is the dose for treatment of bone metastases) (203).

Clinical trials of zoledronic acid on BMD have shown benefits in men with prostate cancer receiving ADT and men with prostate cancer metastatic to bone (186). If treatment with zoledronic acid is not feasible due to prior side effects, cost, or other logistical issues, oral alendronate therapy is a reasonable alternative, based on a single randomized controlled trial in men with prostate cancer receiving ADT and on the more extensive data in men with primary osteoporosis and women with postmenopausal osteoporosis.

## 4.0. Monitoring therapy

### Recommendation

4.1. We suggest that clinicians monitor BMD by DXA at the spine and hip every 1 to 2 yr to assess the response to treatment. If BMD appears to reach a plateau, the frequency of BMD measurements may be reduced. (2|⊕⊕⊕⊕)

### 4.1. Evidence

Treatments for osteoporosis increase BMD but only modestly. Alendronate increased BMD of the spine and femoral neck by about 7 and 2.5%, respectively, after 2 yr (84). Similarly, risedronate increased BMD of the spine and femoral neck by about 6 and 1.5%, respectively, after 2 yr (86). Teriparatide (20 µg/d) increased BMD of the spine and femoral neck by about 6 and 1.5%, respectively, after 9 months (87). In hypogonadal men, testosterone enanthate therapy (200 mg every 2 wk) increased spine, trochanter, and total hip BMD by about 8, 5, and 3.5%, respectively, after 2 yr (163). Evidence to support the use of BMD for monitoring treatment response is weak but suggests that it can be used for this purpose (187).

It has been suggested that serial BMD measurements in treated subjects may identify patients who are not adhering to treatment or patients who have an overlooked cause for bone loss. Although there is evidence that total hip BMD changes reflect medication compliance (185), use of serial BMD to identify subjects with secondary osteoporosis is anecdotal. It has also been suggested that serial BMD measurements may identify subjects who fail ther-

apy. A retrospective study in men showed that BMD monitoring was associated with good compliance (188).

#### 4.1. Remarks

There is uncertainty over what constitutes an adequate BMD response to treatment. Stable or increasing BMD appears to indicate a good response (187). One approach is to consider whether any BMD change exceeds that expected due to normal variation (the least significant change approach); this requires information about normal BMD variability. There are no formal reports of variability in men. In women with osteopenia, estimates of least significant change at the spine and hip made in research settings are between 3 and 5% in the short term (189). In all of the studies above, changes in spine BMD were greater than least significant change in most men treated for 2 yr, whereas changes in hip BMD were generally within the expected reproducibility error.

Whether change in BMD is a suitable surrogate for fracture risk reduction in men is unclear. In women, it has been estimated that BMD response to treatment accounts for 4–41% of the fracture risk reduction with treatments for osteoporosis (190, 191). The least significant change approach can also be used to identify significant bone loss in men who are untreated or to identify offset of effect after stopping treatment for osteoporosis. Because the expected rate of bone loss is slower in these situations than the rate of gain during treatment, it may be better to wait longer between measurements (e.g. 2–3 yr) in untreated men.

Assessing change in BMD on serial measurements requires careful attention to detail. Using the same machine and a trained technologist aware of the pitfalls of bone densitometry can mitigate these problems. The provider responsible for reporting the results also needs to be aware of these limitations. Degenerative change in the spine is particularly common in older men and may falsely give the impression of a gain in BMD.

#### Recommendation

4.2. We suggest that clinicians consider measuring a BTM at 3–6 months after initiation of treatment using a bone resorption marker (such as serum CTX or serum or urine NTX) for antiresorptive therapy and a bone formation marker (such as serum PINP) for anabolic therapy. (2|⊕⊕⊕⊕)

#### 4.2. Evidence

Treatments for osteoporosis in men produce significant changes in BTMs. As in women, alendronate reduces BTMs by about 40–50% (84). Reductions in BTMs become maximal within several months and remain stable

throughout therapy. Bone formation and resorption markers increase dramatically during the first 6–12 months of teriparatide therapy in men, after which they gradually decline toward baseline levels (150). BTM decline consistently when hypogonadal men receive physiological doses of testosterone, indicating that testosterone in physiological doses acts as an antiresorptive agent (159), perhaps through conversion to estradiol.

There is uncertainty over what constitutes an optimal BTM response to treatment. Decreasing bone resorption markers (for antiresorptive agents) or increasing bone formation markers (for anabolic agents) indicates a good response to treatment. Clinical experience suggests that inadequate response may be due to secondary osteoporosis or noncompliance with treatment. Extrapolating data from women to men, we assume that change in BTM relates to fracture risk reduction with treatments.

#### 4.2. Remarks

Monitoring treatment with BTMs requires attention to detail. Because of diurnal variation (higher turnover in the morning) and effect of food (bone resorption markers decrease after eating), samples for bone resorption markers (urinary NTX, and serum CTX) should be collected with the patient in the fasting state, in the morning. Because manual and automated assays give different results for the same analysis, changes can be compared only if the lab continues to use the same assay.

As with changes in BMD, changes in BTMs can be compared with the least significant change to determine whether observed changes exceed those likely to occur as a result of normal variation. This requires information about normal variability in BTMs, but for men, little is known. Variability appears similar for bone resorption markers (such as urinary deoxypyridinoline, NTX, and CTX) for men and women (192). In women with osteopenia, estimates of least significant change for bone alkaline phosphatase (b-ALP) activity and urinary NTX made in research settings are between 14% (for b-ALP) and 37% (for urinary NTX) in the short term (192). Thus, in all of the studies above, in more than half of men receiving standard treatments for 1–2 yr, changes in BTMs would appear to exceed the least significant change, and patients would be considered to be “responders” using these markers. The response of BTMs could be identified as early as within 3 months of starting treatment. Newer markers have been developed and evaluated for treatment response in women, including serum PINP and CTX (193). They have performed well in studies of drugs such as alendronate (194) and teriparatide (195).

Evidence that change in BTM is a suitable surrogate for fracture risk reduction in men is lacking. In women, it has

been estimated that BTM response to treatment may account for 30–75% of the fracture risk reduction with standard treatments for osteoporosis (196–200). Also, the magnitude of the BTM response has been shown to be associated with the level of compliance (201).

Some experts recommend measuring a BTM before and 3–6 months after starting treatment. Because there have only been publications on the association of BTMs and fracture risk reduction in women (and not in men), there is some disagreement among experts regarding this issue. Urine NTX or serum CTX can be used to monitor anti-resorptive treatment; PINP or b-ALP can be used to monitor anabolic treatment. If the change in markers exceeds the least significant change (~40%; see 4.2. *Remarks*), then one goal has been met. With women, a low risk of fractures on treatment is associated with BTMs that are below the median of the reference interval for young women (196); this could be a target for men, but it has not yet been studied. If markers do not change, there are several options, including questioning the patient about compliance with medication, considering causes of secondary osteoporosis, or changing the medication or its route of administration.

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## References

1. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schünemann HJ, Edejer TT, Varonen H, Vist GE, Williams Jr JW, Zaza S 2004

- Grading quality of evidence and strength of recommendations. *BMJ* 328:1490
2. Swiglo BA, Murad MH, Schünemann HJ, Kunz R, Vigersky RA, Guyatt GH, Montori VM 2008 A case for clarity, consistency, and helpfulness: state-of-the-art clinical practice guidelines in endocrinology using the grading of recommendations, assessment, development, and evaluation system. *J Clin Endocrinol Metab* 93:666–673
  3. Murad MH, Mullan R, Drake M, Mauck K, Lane MA, Stuart L, Abo Alnour N, Hazem A, Li T, Puhon M, Erwin PJ, Montori VM 2012 Comparative effectiveness of drug treatments to prevent fragility fractures: a systematic review and network meta-analysis. *J Clin Endocrinol Metab* 97:1861–1870
  4. Drake M, Murad MH, Lane MA, Mullan R, Mauck K, Stuart L, Hazem A, Undavalli C, Berima T, Prasad C, Erwin PJ, Montori VM 30 March 2012 Risk factors of osteoporosis related fractures in men: a systematic review and meta-analysis. *J Clin Endocrinol Metab* doi: 10.1210/jc.2011–3058
  5. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy 2001 Osteoporosis prevention, diagnosis, and therapy. *JAMA* 285:785–795
  6. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson AN 2007 Incidence and economic burden of osteoporosis-related fractures in the United States. *J Bone Miner Res* 22:465–475
  7. Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR 2009 Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. *JAMA* 301: 513–521
  8. Forsén L, Sogaard AJ, Meyer HE, Edna T, Kopjar B 1999 Survival after hip fracture: short- and long-term excess mortality according to age and gender. *Osteoporos Int* 10:73–78
  9. Haentjens P, Magaziner J, Colón-Emeric CS, Vanderschueren D, Milisen K, Velkeniers B, Boonen S 2010 Meta-analysis: excess mortality after hip fracture among older women and men. *Ann Intern Med* 152:380–390
  10. Amin S 2010 Epidemiology of fractures. In: Orwoll ES, Bilezikian JP, Vanderschueren D, eds. *Osteoporosis in men*. San Diego: Academic Press; 351–360
  11. Kanis JA, Pitt FA 1992 Epidemiology of osteoporosis. *Bone* 13(Suppl 1):S7–S15
  12. Singer BR, McLauchlan GJ, Robinson CM, Christie J 1998 Epidemiology of fractures in 15,000: the influence of age and gender. *J Bone Joint Surg Br* 80:243–248
  13. van Staa TP, Dennison EM, Leufkens HG, Cooper C 2001 Epidemiology of fractures in England and Wales. *Bone* 29:517–522
  14. Court-Brown CM, Caesar B 2006 Epidemiology of adult fractures: a review. *Injury* 37:691–697
  15. Donaldson LJ, Reckless IP, Scholes S, Mindell JS, Shelton NJ 2008 The epidemiology of fractures in England. *J Epidemiol Community Health* 62:174–180
  16. Johnell O, Kanis JA 2006 An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int* 17:1726–1733
  17. Memon A, Pospula WM, Tantawy AY, Abdul-Ghaffar S, Suresh A, Al-Rowaih A 1998 Incidence of hip fracture in Kuwait. *Int J Epidemiol* 27:860–865
  18. Maggi S, Kelsey JL, Litvak J, Heyse SP 1991 Incidence of hip fractures in the elderly: a cross-national analysis. *Osteoporos Int* 1:232–241
  19. Castro da Rocha FA, Ribeiro AR 2003 Low incidence of hip fractures in an equatorial area. *Osteoporos Int* 14:496–499
  20. Kanis JA, Johnell O, De Laet C, Jonsson B, Oden A, Ogelsby AK 2002 International variations in hip fracture probabilities: implications for risk assessment. *J Bone Miner Res* 17:1237–1244
  21. Xu L, Lu A, Zhao X, Chen X, Cummings SR 1996 Very low rates of hip fracture in Beijing, People's Republic of China: the Beijing Osteoporosis Project. *Am J Epidemiol* 144:901–907
  22. Solomon L 1968 Osteoporosis and fracture of the femoral neck in the South African Bantu. *J Bone Joint Surg Br* 50:2–13
  23. Krabbe S, Christiansen C, Rødbro P, Transbøl I 1980 Pubertal growth as reflected by simultaneous changes in bone mineral content and serum alkaline phosphatase. *Acta Paediatr Scand* 69: 49–52
  24. Seeman E 1995 The dilemma of osteoporosis in men. *Am J Med* 98:76S–88S
  25. Bonjour JP, Theintz G, Law F, Slosman D, Rizzoli R 1994 Peak bone mass. *Osteoporos Int* 4(Suppl 1):7–13
  26. Fatayerji D, Eastell R 1999 Age-related changes in bone turnover in men. *J Bone Miner Res* 14:1203–1210
  27. Khosla S, Melton 3rd LJ, Atkinson EJ, O'Fallon WM, Klee GG, Riggs BL 1998 Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men and women: a key role for bioavailable estrogens. *J Clin Endocrinol Metab* 83: 2266–2274
  28. Gallagher JC, Kinyamu HK, Fowler SE, Dawson-Hughes B, Dalsky GP, Sherman SS 1998 Calcitropic hormones and bone markers in the elderly. *J Bone Miner Res* 13:475–482
  29. Clarke BL, Ebeling PR, Jones JD, Wahner HW, O'Fallon WM, Riggs BL, Fitzpatrick LA 2002 Predictors of bone mineral density in aging healthy men varies by skeletal site. *Calcif Tissue Int* 70: 137–145
  30. Binkley N, Adler RA 2010 Dual-energy x-ray absorptiometry (DXA) in men. In: Orwoll ES, Bilezikian JP, Vanderschueren D, eds. *Osteoporosis in men*. San Diego: Academic Press; 525–540
  31. Zebaze R, Seeman E 2010 Age-related changes in bone remodeling and microarchitecture. In: Orwoll ES, Bilezikian JP, Vanderschueren D, eds. *Osteoporosis in men*. San Diego: Academic Press; 167–178
  32. Riggs BL, Melton Iii 3rd LJ, Robb RA, Camp JJ, Atkinson EJ, Peterson JM, Rouleau PA, McCollough CH, Bouxsein ML, Khosla S 2004 Population-based study of age and sex differences in bone volumetric density, size, geometry, and structure at different skeletal sites. *J Bone Miner Res* 19:1945–1954
  33. Szulc P 2010 Changes in bone size and geometry with aging. In: Orwoll ES, Bilezikian JP, Vanderschueren D, eds. *Osteoporosis in men*. San Diego: Academic Press; 193–206
  34. Gennari L, Khosla S, Bilezikian JP 2008 Estrogen and fracture risk in men. *J Bone Miner Res* 23:1548–1551
  35. Smith EP, Boyd J, Frank GR, Takahashi H, Cohen RM, Specker B, Williams TC, Lubahn DB, Korach KS 1994 Estrogen resistance caused by a mutation in the estrogen receptor gene in a man. *N Engl J Med* 331:1056–1061
  36. Carani C, Qin K, Simoni M, Faustini-Fustini M, Serpente S, Boyd J, Korach KS, Simpson ER 1997 Effect of testosterone and estradiol in a man with aromatase deficiency. *N Engl J Med* 337:91–95
  37. Morishima A, Grumbach MM, Simpson ER, Fisher C, Qin K 1995 Aromatase deficiency in male and female siblings caused by a novel mutation and the physiological role of estrogens. *J Clin Endocrinol Metab* 80:3689–3698
  38. Bilezikian JP, Morishima A, Bell J, Grumbach MM 1998 Increased bone mass as a result of estrogen therapy in a man with aromatase deficiency. *N Engl J Med* 339:599–603
  39. Orwoll E, Lambert LC, Marshall LM, Blank J, Barrett-Connor E, Cauley J, Ensrud K, Cummings SR 2006 Endogenous testosterone levels, physical performance, and fall risk in older men. *Arch Intern Med* 166:2124–2131
  40. Greendale GA, Edelstein S, Barrett-Connor E 1997 Endogenous sex steroids and bone mineral density in older women and men: the Rancho Bernardo study. *J Bone Miner Res* 12:1833–1843
  41. Falahati-Nini A, Riggs BL, Atkinson EJ, O'Fallon WM, Eastell R, Khosla S 2000 Relative contributions of testosterone and estrogen in regulating bone resorption and formation in normal elderly men. *J Clin Invest* 106:1553–1560
  42. Fink HA, Ewing SK, Ensrud KE, Barrett-Connor E, Taylor BC, Cauley JA, Orwoll ES 2006 Association of testosterone and estro-



- diol deficiency with osteoporosis and rapid bone loss in older men. *J Clin Endocrinol Metab* 91:3908–3915
43. LeBlanc ES, Nielson CM, Marshall LM, Lapidus JA, Barrett-Connor E, Ensrud KE, Hoffman AR, Laughlin G, Ohlsson C, Orwoll ES 2009 The effects of serum testosterone, estradiol, and sex hormone binding globulin levels on fracture risk in men. *J Clin Endocrinol Metab* 94:3337–3346
  44. Leder BZ, LeBlanc KM, Schoenfeld DA, Eastell R, Finkelstein JS 2003 Differential effects of androgens and estrogens on bone turnover in normal men. *J Clin Endocrinol Metab* 88:204–210
  45. Rao DS, Honasoge M 1996 Metabolic bone disease in gastrointestinal, hepatobiliary, and pancreatic disorders. In: Favus MJ, ed. *Primer on the metabolic bone diseases and disorders of mineral metabolism*. 3rd ed. New York: Lippincott-Raven; 306–310
  46. Siegel LM, Bilezikian JP 1995 Metabolic bone diseases and disorders of the gastrointestinal tract. In: Singer MV, Ziegler R, eds. *Gastrointestinal tract and endocrine system (Falk Symposium)*. Dordrecht, The Netherlands: Kluwer Academic Publishers; 113–129
  47. Looker AC, Pfeiffer CM, Lacher DA, Schleicher RL, Picciano MF, Yetley EA 2008 Serum 25-hydroxyvitamin D status of the US population: 1988–1994 compared with 2003–2004. *Am J Clin Nutr* 88:1519–1527
  48. MacLaughlin J, Holick MF 1985 Aging decreases the capacity of the human skin to produce vitamin D<sub>3</sub>. *J Clin Invest* 76:1536–1538
  49. Clemens TL, Zhou XY, Myles M, Endres D, Lindsay R 1986 Serum vitamin D<sub>3</sub> and vitamin D<sub>2</sub> concentrations and absorption of vitamin D<sub>2</sub> in elderly subjects. *J Clin Endocrinol Metab* 63:656–660
  50. Ebeling PR, Sandgren ME, DiMaggio EP, Lane AW, DeLuca HF, Riggs BL 1992 Evidence of an age-related decrease in intestinal responsiveness to vitamin D: relationship between serum 1,25-dihydroxyvitamin D<sub>3</sub> and intestinal vitamin D receptor concentrations in normal women. *J Clin Endocrinol Metab* 75:176–182
  51. Barragry JM, France MW, Corless D, Gupta SP, Switala S, Boucher BJ, Cohen RD 1978 Intestinal cholecalciferol absorption in the elderly and in young subjects. *Clin Sci Mol Med* 55:213–220
  52. Epstein S, Bryce G, Hinman JW, Miller ON, Riggs BL, Hui SL, Johnston Jr CC 1986 The influence of age on bone mineral regulating hormones. *Bone* 7:421–425
  53. Sherman SS, Hollis BW, Tobin JD 1990 Vitamin D status and related parameters in a healthy population: the effects of age, sex, and season. *J Clin Endocrinol Metab* 71:405–413
  54. Khosla S, Melton III LJ, Riggs BL 2001 Parathyroid function in the normal aging process. In: Bilezikian JP, Marcus R, Levine MA, eds. *The parathyroids*. San Diego: Academic Press; 835–842
  55. Ebeling PR 2008 Clinical practice. Osteoporosis in men. *N Engl J Med* 358:1474–1482
  56. Diamond TH, Thornley SW, Sekel R, Smerdely P 1997 Hip fracture in elderly men: prognostic factors and outcomes. *Med J Aust* 167:412–415
  57. Wang XF, Duan Y, Beck TJ, Seeman E 2005 Varying contributions of growth and ageing to racial and sex differences in femoral neck structure and strength in old age. *Bone* 36:978–986
  58. Finkelstein JS, Klibanski A, Neer RM 1999 Evaluation of lumbar spine bone mineral density (BMD) using dual energy x-ray absorptiometry (DXA) in 21 young men with histories of constitutionally delayed puberty. *J Clin Endocrinol Metab* 84:3400–3401
  59. Sattin RW, Lambert Huber DA, DeVito CA, Rodriguez JG, Ros A, Bacchelli S, Stevens JA, Waxweiler RJ 1990 The incidence of fall injury events among the elderly in a defined population. *Am J Epidemiol* 131:1028–1037
  60. Stevens JA, Sogolow ED 2005 Gender differences for non-fatal unintentional fall related injuries among older adults. *Inj Prev* 11:115–119
  61. Liu H, Paige NM, Goldzweig CL, Wong E, Zhou A, Suttorp MJ, Munjas B, Orwoll E, Shekelle P 2008 Screening for osteoporosis in men: a systematic review for an American College of Physicians guideline. *Ann Intern Med* 148:685–701
  62. Papaioannou A, Kennedy CC, Cranney A, Hawker G, Brown JP, Kaiser SM, Leslie WD, O'Brien CJ, Sawka AM, Khan A, Siminoski K, Tarulli G, Webster D, McGowan J, Adachi JD 2009 Risk factors for low BMD in healthy men age 50 years or older: a systematic review. *Osteoporos Int* 20:507–518
  63. Kanis JA, Johnell O, Oden A, De Laet C, Mellstrom D 2004 Epidemiology of osteoporosis and fracture in men. *Calcif Tissue Int* 75:90–99
  64. Lewis CE, Ewing SK, Taylor BC, Shikany JM, Fink HA, Ensrud KE, Barrett-Connor E, Cummings SR, Orwoll E: Osteoporotic Fractures in Men (MrOS) Study Research Group 2007 Predictors of non-spine fracture in elderly men: the MrOS Study. *J Bone Miner Res* 22:211–219
  65. Cawthon PM, Ewing SK, McCulloch CE, Ensrud KE, Cauley JA, Cummings SR, Orwoll ES: Osteoporotic Fractures in Men (MrOS) Research Group 2009 Loss of hip BMD in older men: the osteoporotic fractures in men (MrOS) study. *J Bone Miner Res* 24:1728–1735
  66. Cauley JA, Fullman RL, Stone KL, Zmuda JM, Bauer DC, Barrett-Connor E, Ensrud K, Lau EM, Orwoll ES 2005 Factors associated with the lumbar spine and proximal femur bone mineral density in older men. *Osteoporos Int* 16:1525–1537
  67. Mackey DC, Lui LY, Cawthon PM, Bauer DC, Nevitt MC, Cauley JA, Hillier TA, Lewis CE, Barrett-Connor E, Cummings SR 2007 High-trauma fractures and low bone mineral density in older women and men. *JAMA* 298:2381–2388
  68. Finkelstein JS, Klibanski A, Neer RM 1996 A longitudinal evaluation of bone mineral density in adult men with histories of delayed puberty. *J Clin Endocrinol Metab* 81:1152–1155
  69. Szulc P, Munoz F, Duboeuf F, Marchand F, Delmas PD 2005 Bone mineral density predicts osteoporotic fractures in elderly men: the MINOS study. *Osteoporos Int* 16:1184–1192
  70. Orwoll ES, Bevan L, Phipps KR 2000 Determinants of bone mineral density in older men. *Osteoporos Int* 11:815–821
  71. Trimpou P, Landin-Wilhelmsen K, Odén A, Rosengren A, Wilhelmsen L 2010 Male risk factors for hip fracture—a 30-year follow-up study in 7,495 men. *Osteoporos Int* 21:409–416
  72. Chiu GR, Araujo AB, Travison TG, Hall SA, McKinlay JB 2009 Relative contributions of multiple determinants to bone mineral density in men. *Osteoporos Int* 20:2035–2047
  73. Heilberg IP, Weisinger JR 2006 Bone disease in idiopathic hypercalciuria. *Curr Opin Nephrol Hypertens* 15:394–402
  74. Thomas-John M, Codd MB, Manne S, Watts NB, Mongey AB 2009 Risk factors for the development of osteoporosis and osteoporotic fractures among older men. *J Rheumatol* 36:1947–1952
  75. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E 2008 FRAX and the assessment of fracture probability in men and women from the UK. *Osteoporos Int* 19:385–397
  76. Kanis JA, McCloskey EV, Johansson H, Oden A 2010 Diagnostic thresholds for osteoporosis in men. In: Orwoll ES, Bilezikian JP, Vanderscheren D, eds. *Osteoporosis in men*. San Diego: Academic Press; 605–611
  77. Sandhu SK, Nguyen ND, Center JR, Pocock NA, Eisman JA, Nguyen TV 2010 Prognosis of fracture: evaluation of predictive accuracy of the FRAX algorithm and Garvan nomogram. *Osteoporos Int* 21:863–871
  78. Leslie WD, Tsang JF, Lix LM 2009 Manitoba Bone Density Program. Simplified system for absolute fracture risk assessment: clinical validation in Canadian women. *J Bone Miner Res* 24:353–360
  79. Leslie WD, Lix LM 2010 Simplified 10-year absolute fracture risk assessment: a comparison of men and women. *J Clin Densitom* 13:141–146
  80. Adler RA, Tran MT, Petkov VI 2003 Performance of the osteoporosis self-assessment screening tool for osteoporosis in American men. *Mayo Clin Proc* 78:723–727
  81. Lynn HS, Woo J, Leung PC, Barrett-Connor EL, Nevitt MC, Cau-

- ley JA, Adler RA, Orwoll ES, Osteoporotic Fractures in Men (MrOS) Study 2008 An evaluation of osteoporosis screening tools for the osteoporotic fractures in men (MrOS) study. *Osteoporos Int* 19:1087–1092
82. Cummings SR, Cawthon PM, Ensrud KE, Cauley JA, Fink HA, Orwoll ES: Osteoporotic Fractures in Men (MrOS) Research Groups; Study of Osteoporotic Fractures Research Groups 2006 BMD and risk of hip and nonvertebral fracture in older men: a prospective study and comparison with older women. *J Bone Miner Res* 21:1550–1556
  83. Schuit SC, van der Klift M, Weel AE, de Laet CE, Burger H, Seeman E, Hofman A, Uitterlinden AG, van Leeuwen JP, Pols HA 2004 Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam study. *Bone* 34:195–202
  84. Orwoll E, Ettinger M, Weiss S, Miller P, Kendler D, Graham J, Adami S, Weber K, Lorenc R, Pietschmann P, Vandormael K, Lombardi A 2000 Alendronate for the treatment of osteoporosis in men. *N Engl J Med* 343:604–610
  85. Ringe JD, Faber H, Farahmand P, Dorst A 2006 Efficacy of risendronate in men with primary and secondary osteoporosis: results of a 1-year study. *Rheumatol Int* 26:427–431
  86. Boonen S, Orwoll ES, Wenderoth D, Stoner KJ, Eusebio R, Delmas PD 2009 Once-weekly risendronate in men with osteoporosis: results of a 2-year, placebo-controlled, double-blind, multicenter study. *J Bone Miner Res* 24:719–725
  87. Orwoll ES, Scheele WH, Paul S, Adami S, Syversen U, Diez-Perez A, Kaufman JM, Clancy AD, Gaich GA 2003 The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis. *J Bone Miner Res* 18:9–17
  88. Schousboe JT, Taylor BC, Fink HA, Kane RL, Cummings SR, Orwoll ES, Melton 3rd LJ, Bauer DC, Ensrud KE 2007 Cost effectiveness of bone densitometry followed by treatment of osteoporosis in older men. *JAMA* 298:629–637
  89. Watts NB 1999 Understanding the Bone Mass Measurement Act. *J Clin Densitom* 2:211–217
  90. Gärdsell P, Johnell O, Nilsson BE 1990 The predictive value of forearm bone mineral content measurements in men. *Bone* 11:229–232
  91. Melton 3rd LJ, Atkinson EJ, O'Connor MK, O'Fallon WM, Riggs BL 1998 Bone density and fracture risk in men. *J Bone Miner Res* 13:1915–1923
  92. Wiemann LM, Vallarta-Ast N, Krueger D, Binkley N 2007 Effect of female database use for T-score derivation in men. *J Clin Densitom* 10:244–248
  93. Henry MJ, Pasco JA, Korn S, Gibson JE, Kotowicz MA, Nicholson GC 2010 Bone mineral density reference ranges for Australian men: Geelong Osteoporosis Study. *Osteoporos Int* 21:909–917
  94. Bruder JM, Ma JZ, Basler JW, Welch MD 2006 Prevalence of osteopenia and osteoporosis by central and peripheral bone mineral density in men with prostate cancer during androgen-deprivation therapy. *Urology* 67:152–155
  95. Mittan D, Lee S, Miller E, Perez RC, Basler JW, Bruder JM 2002 Bone loss following hypogonadism in men with prostate cancer treated with GnRH analogs. *J Clin Endocrinol Metab* 87:3656–3661
  96. Adler RA, Hastings FW, Petkov VI 2010 Treatment thresholds for osteoporosis in men on androgen deprivation therapy: T-score versus FRAX. *Osteoporos Int* 21:647–653
  97. Smith MR, Egerdie B, Hernández Toriz N, Feldman R, Tammela TL, Saad F, Heracek J, Szwedowski M, Ke C, Kupic A, Leder BZ, Goessl C 2009 Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med* 361:745–755
  98. Watts NB 2004 Fundamentals and pitfalls of bone densitometry using dual-energy x-ray absorptiometry (DXA). *Osteoporos Int* 15:847–854
  99. Silverberg SJ, Shane E, de la Cruz L, Segre GV, Clemens TL, Bilezikian JP 1989 Abnormalities in PTH secretion and 1,25-dihydroxyvitamin D<sub>3</sub> formation in women with osteoporosis. *N Engl J Med* 320:277–281
  100. Simonelli C, Adler RA, Blake GM, Caudill JP, Khan A, Leib E, Maricic M, Prior JC, Eis SR, Rosen C, Kendler DL 2008 Dual-energy x-ray absorptiometry technical issues: the 2007 ISCD official positions. *J Clin Densitom* 11:109–122
  101. Ryan CS, Petkov VI, Adler RA 2011 Osteoporosis in men: the value of laboratory testing. *Osteoporos Int* 22:1845–1853
  102. Legroux-Gerot I, Catanzariti L, Marchandise X, Duquesnoy B, Cortet B 2004 Bone mineral density changes in hypercalciuric osteoporotic men treated with thiazide diuretics. *Joint Bone Spine* 71:51–55
  103. Schousboe JT, Vokes T, Broy SB, Ferrar L, McKiernan F, Roux C, Binkley N 2008 Vertebral fracture assessment: the 2007 ISCD official positions. *J Clin Densitom* 11:92–108
  104. Orwoll ES, Oviatt SK, McClung MR, Deftos LJ, Sexton G 1990 The rate of bone mineral loss in normal men and the effects of calcium and cholecalciferol supplementation. *Ann Intern Med* 112:29–34
  105. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE 1997 Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med* 337:670–676
  106. Daly RM, Brown M, Bass S, Kukuljan S, Nowson C 2006 Calcium- and vitamin D<sub>3</sub>-fortified milk reduces bone loss at clinically relevant skeletal sites in older men: a 2-year randomized controlled trial. *J Bone Miner Res* 21:397–405
  107. Daly RM, Bass S, Nowson C 2006 Long-term effects of calcium-vitamin-D<sub>3</sub>-fortified milk on bone geometry and strength in older men. *Bone* 39:946–953
  108. Owusu W, Willett WC, Feskanich D, Ascherio A, Spiegelman D, Colditz GA 1997 Calcium intake and the incidence of forearm and hip fractures among men. *J Nutr* 127:1782–1787
  109. Center JR, Bliuc D, Nguyen TV, Eisman JA 2007 Risk of subsequent fracture after low-trauma fracture in men and women. *JAMA* 297:387–394
  110. Grant AM, Avenell A, Campbell MK, McDonald AM, MacLennan GS, McPherson GC, Anderson FH, Cooper C, Francis RM, Donaldson C, Gillespie WJ, Robinson CM, Torgerson DJ, Wallace WA 2005 Oral vitamin D<sub>3</sub> and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or Vitamin D, RECORD): a randomised placebo-controlled trial. *Lancet* 365:1621–1628
  111. Fardellone P, Brazier M, Kamel S, Guéris J, Graulet AM, Liénard J, Sebert JL 1998 Biochemical effects of calcium supplementation in postmenopausal women: influence of dietary calcium intake. *Am J Clin Nutr* 67:1273–1278
  112. Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, Bassford T, Beresford SA, Black HR, Blanchette P, Bonds DE, Brunner RL, Brzyski RG, Caan B, Cauley JA, Chlebowski RT, Cummings SR, Granek I, Hays J, Heiss G, Hendrix SL, Howard BV, Hsia J, Hubbell FA, Johnson KC, Judd H, Kotchen JM, Kuller LH, Langer RD, Lasser NL, Limacher MC, Ludlam S, Manson JE, Margolis KL, McGowan J, Ockene JK, O'Sullivan MJ, Phillips L, Prentice RL, Sarto GE, Stefanick ML, Van Horn L, Wactawski-Wende J, Whitlock E, Anderson GL, Assaf AR, Barad D 2006 Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med* 354:669–683
  113. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G, Kovacs CS, Mayne ST, Rosen CJ, Shapses SA 2011 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* 96:53–58
  114. Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD, Reid IR 2010 Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ* 341:c3691
  115. Wang L, Manson JE, Song Y, Sesso HD 2010 Systematic review:

- vitamin D and calcium supplementation in prevention of cardiovascular events. *Ann Intern Med* 152:315–323
116. Giovannucci E, Liu Y, Stampfer MJ, Willett WC 2006 A prospective study of calcium intake and incident and fatal prostate cancer. *Cancer Epidemiol Biomarkers Prev* 15:203–210
  117. Baron JA, Beach M, Wallace K, Grau MV, Sandler RS, Mandel JS, Heber D, Greenberg ER 2005 Risk of prostate cancer in a randomized clinical trial of calcium supplementation. *Cancer Epidemiol Biomarkers Prev* 14:586–589
  118. Orwoll E, Nielson CM, Marshall LM, Lambert L, Holton KF, Hoffman AR, Barrett-Connor E, Shikany JM, Dam T, Cauley JA; Osteoporotic Fractures in Men (MrOS) Study Group 2009 Vitamin D deficiency in older men. *J Clin Endocrinol Metab* 94:1214–1222
  119. Cauley JA, Parimi N, Ensrud KE, Bauer DC, Cawthon PM, Cummings SR, Hoffman AR, Shikany JM, Barrett-Connor E, Orwoll E; Osteoporotic Fractures in Men (MrOS) Research Group 2010 Serum 25-hydroxyvitamin D and the risk of hip and nonspine fractures in older men. *J Bone Miner Res* 25:545–553
  120. Dawson-Hughes B, Mithal A, Bonjour JP, Boonen S, Burckhardt P, Fuleihan GE, Josse RG, Lips P, Morales-Torres J, Yoshimura N 2010 IOF position statement: vitamin D recommendations for older adults. *Osteoporos Int* 21:1151–1154
  121. Holick MF, Chen TC 2008 Vitamin D deficiency: a worldwide problem with health consequences. *Am J Clin Nutr* 87:1080S–1086S
  122. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B 2006 Estimation of optimal serum concentration of 25-hydroxyvitamin D for multiple health outcomes. *Am J Clin Nutr* 84:18–28
  123. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM 2011 Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 96:1911–1930
  124. Sanders KM, Stuart AL, Williamson EJ, Simpson JA, Kotowicz MA, Young D, Nicholson GC 2010 Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *JAMA* 303:1815–1822
  125. Binkley N, Krueger D, Gemar D, Drezner MK 2008 Correlation among 25-hydroxy-vitamin D assays. *J Clin Endocrinol Metab* 93:1804–1808
  126. Carter GD, Carter R, Jones J, Berry J 2004 How accurate are assays for 25-hydroxyvitamin D? Data from the international vitamin D external quality assessment scheme. *Clin Chem* 50:2195–2197
  127. Janney CA, Cauley JA, Cawthon PM, Kriska AM 2010 Longitudinal physical activity changes in older men in the Osteoporotic Fractures in Men Study. *J Am Geriatr Soc* 58:1128–1133
  128. de Kam D, Smulders E, Weerdesteyn V, Smits-Engelsman BC 2009 Exercise interventions to reduce fall-related fractures and their risk factors in individuals with low bone density: a systematic review of randomized controlled trials. *Osteoporos Int* 20:2111–2125
  129. Sinaki M, Pfeifer M, Preisinger E, Itoi E, Rizzoli R, Boonen S, Geusens P, Minne HW 2010 The role of exercise in the treatment of osteoporosis. *Curr Osteoporos Rep* 8:138–144
  130. Kukuljan S, Nowson CA, Sanders KM, Nicholson GC, Seibel MJ, Salmon J, Daly RM 2011 Independent and combined effects of calcium-vitamin D3 and exercise on bone structure and strength in older men: an 18-month factorial design randomized controlled trial. *J Clin Endocrinol Metab* 96:955–963
  131. Smulders E, Weerdesteyn V, Groen BE, Duysens J, Eijssbouts A, Laan R, van Lankveld W 2010 Efficacy of a short multidisciplinary falls prevention program for elderly persons with osteoporosis and a fall history: a randomized controlled trial. *Arch Phys Med Rehabil* 91:1705–1711
  132. Cawthon PM, Harrison SL, Barrett-Connor E, Fink HA, Cauley JA, Lewis CE, Orwoll ES, Cummings SR 2006 Alcohol intake and its relationship with bone mineral density, falls, and fracture risk in older men. *J Am Geriatr Soc* 54:1649–1657
  133. Kanis JA, Johansson H, Johnell O, Oden A, De Laet C, Eisman JA, Pols H, Tenenhouse A 2005 Alcohol intake as a risk factor for fracture. *Osteoporos Int* 16:737–742
  134. Felson DT, Kiel DP, Anderson JJ, Kannel WB 1988 Alcohol consumption and hip fractures: the Framingham Study. *Am J Epidemiol* 128:1102–1110
  135. Høidrup S, Grønbaek M, Gottschau A, Lauritzen JB, Schroll M 1999 Alcohol intake, beverage preference, and risk of hip fracture in men and women. Copenhagen Centre for Prospective Population Studies. *Am J Epidemiol* 149:993–1001
  136. Kanis JA, Johnell O, Oden A, Johansson H, De Laet C, Eisman JA, Fujiwara S, Kroger H, McCloskey EV, Mellstrom D, Melton LJ, Pols H, Reeve J, Silman A, Tenenhouse A 2005 Smoking and fracture risk: a meta-analysis. *Osteoporos Int* 16:155–162
  137. Cornuz J, Feskanich D, Willett WC, Colditz GA 1999 Smoking, smoking cessation, and risk of hip fracture in women. *Am J Med* 106:311–314
  138. Hannan MT, Felson DT, Dawson-Hughes B, Tucker KL, Cupples LA, Wilson PW, Kiel DP 2000 Risk factors for longitudinal bone loss in elderly men and women: the Framingham Osteoporosis Study. *J Bone Miner Res* 15:710–720
  139. Lemmens V, Oenema A, Knut IK, Brug J 2008 Effectiveness of smoking cessation interventions among adults: a systematic review of reviews. *Eur J Cancer Prev* 17:535–544
  140. Orwoll ES, Miller PD, Adachi JD, Brown J, Adler RA, Kendler D, Bucci-Rechtweg C, Readie A, Mesenbrink P, Weinstein RS 2010 Efficacy and safety of a once-yearly i.v. infusion of zoledronic acid 5 mg versus a once-weekly 70-mg oral alendronate in the treatment of male osteoporosis: a randomized, multicenter, double-blind, active-controlled study. *J Bone Miner Res* 25:2239–2250
  141. Tosteson AN, Melton 3rd LJ, Dawson-Hughes B, Baim S, Favus MJ, Khosla S, Lindsay RL; National Osteoporosis Foundation Guide Committee 2008 Cost-effective osteoporosis treatment thresholds: the United States perspective. *Osteoporos Int* 19:437–447
  142. Nguyen ND, Ahlborg HG, Center JR, Eisman JA, Nguyen TV 2007 Residual lifetime risk of fractures in men and women. *J Bone Miner Res* 22:781–788
  143. Grossman JM, Gordon R, Ranganath VK, Deal C, Caplan L, Chen W, Curtis JR, Furst DE, McMahon M, Patkar NM, Volkman E, Saag KG 2010 American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Care Res (Hoboken)* 62:1515–1526
  144. MacLean C, Newberry S, Maglione M, McMahon M, Ranganath V, Suttrop M, Mojica W, Timmer M, Alexander A, McNamara M, Desai SB, Zhou A, Chen S, Carter J, Tringale C, Valentine D, Johnsen B, Grossman J 2008 Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. *Ann Intern Med* 148:197–213
  145. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE 1996 Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. *Lancet* 348:1535–1541
  146. McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, Adami S, Fogelman I, Diamond T, Eastell R, Meunier PJ, Reginster JY 2001 Effect of risedronate on the risk of hip fracture in elderly women. *N Engl J Med* 344:333–340
  147. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, Cosman F, Lakatos P, Leung PC, Man Z, Mautalen C, Mesenbrink P, Hu H, Caminis J, Tong K, Rosario-Jansen T, Krasnow J, Hue TF, Sellmeyer D, Eriksen EF, Cummings SR, HORIZON Pivotal

- Fracture Trial 2007 Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 356:1809–1822
148. Lyles KW, Colón-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, Hyldstrup L, Recknor C, Nordsletten L, Moore KA, Lavecchia C, Zhang J, Mesenbrink P, Hodgson PK, Abrams K, Orloff JJ, Horowitz Z, Eriksen EF, Boonen S 2007 Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med* 357:1799–1809
  149. Finkelstein JS, Hayes A, Hunzelman JL, Wyland JJ, Lee H, Neer RM 2003 The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. *N Engl J Med* 349:1216–1226
  150. Finkelstein JS, Leder BZ, Burnett SM, Wyland JJ, Lee H, de la Paz AV, Gibson K, Neer RM 2006 Effects of teriparatide, alendronate, or both on bone turnover in osteoporotic men. *J Clin Endocrinol Metab* 91:2882–2887
  151. Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, Gagel RF, Gilsanz V, Guise T, Koka S, McCauley LK, McGowan J, McKee MD, Mohla S, Pendrys DG, Raisz LG, Ruggiero SL, Shafer DM, Shum L, Silverman SL, Van Poznak CH, Watts N, Woo SB, Shane E 2007 Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 22:1479–1491
  152. Shane E, Burr D, Ebeling PR, Abrahamsen B, Adler RA, Brown TD, Cheung AM, Cosman F, Curtis JR, Dell R, Dempster D, Einhorn TA, Genant HK, Geusens P, Klaushofer K, Koval K, Lane JM, McKiernan F, McKinney R, Ng A, Nieves J, O'Keefe R, Papapoulos S, Sen HT, van der Meulen MC, Weinstein RS, Whyte M 2010 Atypical subtrochanteric and diaphyseal femoral fractures: report of a Task Force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 25:2267–2294
  153. Watts NB, Diab DL 2010 Long-term use of bisphosphonates in osteoporosis. *J Clin Endocrinol Metab* 95:1555–1565
  154. Foresta C, Ruzza G, Mioni R, Meneghello A, Baccichetti C 1983 Testosterone and bone loss in Klinefelter syndrome. *Horm Metab Res* 15:56–57
  155. Finkelstein JS, Klibanski A, Neer RM, Greenspan SL, Rosenthal DI, Crowley Jr WF 1987 Osteoporosis in men with idiopathic hypogonadotropic hypogonadism. *Ann Intern Med* 106:354–461
  156. Stépán JJ, Lachman M, Zvěřina J, Pacovský V, Baylink DJ 1989 Castrated men exhibit bone loss: effect of calcitonin treatment on biochemical indices of bone remodeling. *J Clin Endocrinol Metab* 69:523–527
  157. Greenspan SL, Neer RM, Ridgway EC, Klibanski A 1986 Osteoporosis in men with hyperprolactinemic hypogonadism. *Ann Intern Med* 104:777–782
  158. Diamond T, Stiel D, Posen S 1989 Osteoporosis in hemochromatosis: iron excess, gonadal deficiency, or other factors? *Ann Intern Med* 110:430–436
  159. Katznelson L, Finkelstein JS, Schoenfeld DA, Rosenthal DI, Anderson EJ, Klibanski A 1996 Increase in bone density and lean body mass during testosterone administration in men with acquired hypogonadism. *J Clin Endocrinol Metab* 81:4358–4365
  160. Behre HM, Kliesch S, Leifke E, Link TM, Nieschlag E 1997 Long term effect of testosterone therapy on bone mineral density in hypogonadal men. *J Clin Endocrinol Metab* 82:2386–2390
  161. Finkelstein JS, Klibanski A, Neer RM, Doppelt SH, Rosenthal DI, Segre GV, Crowley Jr WF 1989 Increases in bone density during treatment of men with idiopathic hypogonadotropic hypogonadism. *J Clin Endocrinol Metab* 69:776–783
  162. Greenspan SL, Oppenheim DS, Klibanski A 1989 Importance of gonadal steroids to bone mass in men with hyperprolactinemic hypogonadism. *Ann Intern Med* 110:526–531
  163. Amory JK, Watts NB, Easley KA, Sutton PR, Anawalt BD, Matsumoto AM, Bremner WJ, Tenover JL 2004 Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. *J Clin Endocrinol Metab* 89:503–510
  164. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM; Task Force, Endocrine Society 2010 Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 95:2536–2559
  165. Christmas C, O'Connor KG, Harman SM, Tobin JD, Münzer T, Bellantoni MF, Clair CS, Pabst KM, Sorkin JD, Blackman MR 2002 Growth hormone and sex steroid effects on bone metabolism and bone mineral density in healthy aged women and men. *J Gerontol A Biol Sci Med Sci* 57:M12–M18
  166. Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Holmes JH, Dlewati A, Staley J, Santanna J, Kapoor SC, Attie MF, Haddad Jr JG, Strom BL 1999 Effect of testosterone treatment on bone mineral density in men over 65 years of age. *J Clin Endocrinol Metab* 84:1966–1972
  167. Basurto L, Zarate A, Gomez R, Vargas C, Saucedo R, Galván R 2008 Effect of testosterone therapy on lumbar spine and hip mineral density in elderly men. *Aging Male* 11:140–145
  168. Kenny AM, Prestwood KM, Gruman CA, Marcello KM, Raisz LG 2001 Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels. *J Gerontol A Biol Sci Med Sci* 56:M266–M272
  169. Mellström D, Johnell O, Ljunggren O, Eriksson AL, Lorentzon M, Mallmin H, Holmberg A, Redlund-Johnell I, Orwoll E, Ohlsson C 2006 Free testosterone is an independent predictor of BMD and prevalent fractures in elderly men: MrOS Sweden. *J Bone Miner Res* 21:529–535
  170. Cauley JA, Ewing SK, Taylor BC, Fink HA, Ensrud KE, Bauer DC, Barrett-Connor E, Marshall L, Orwoll ES; Osteoporotic Fractures in Men Study (MrOS) Research Group 2010 Sex steroid hormones in older men: longitudinal associations with 4.5 year change in hip bone mineral density—the Osteoporotic Fractures in Men Study. *J Clin Endocrinol Metab* 95:4314–4323
  171. Khosla S, Melton 3rd LJ, Atkinson EJ, O'Fallon WM 2001 Relationship of serum sex steroid levels to longitudinal changes in bone density in young versus elderly men. *J Clin Endocrinol Metab* 86:3555–3561
  172. Mellström D, Vandenput L, Mallmin H, Holmberg AH, Lorentzon M, Odén A, Johansson H, Orwoll ES, Labrie F, Karlsson MK, Ljunggren O, Ohlsson C 2008 Older men with low serum estradiol and high serum SHBG have an increased risk of fractures. *J Bone Miner Res* 23:1552–1560
  173. Finkelstein JS, Burnett-Bowie SM, Moore AF, Jones BF, Borges LF, Youngner JM, Hahn CW, Barry CV, Leder BZ 2008 Toward a physiologically-based definition of hypogonadism in men: dose-response relationship between testosterone and bone resorption (Abstract 1102). *ASBMR 30th Annual Meeting* 1001–1300. *J Bone Miner Res* 23:S2–S85
  174. Maillefert JF, Sibilia J, Michel F, Saussine C, Javier RM, Tavernier C 1999 Bone mineral density in men treated with synthetic gonadotropin-releasing hormone agonists for prostatic carcinoma. *J Urol* 161:1219–1222
  175. Smith MR, McGovern FJ, Zietman AL, Fallon MA, Hayden DL, Schoenfeld DA, Kantoff PW, Finkelstein JS 2001 Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. *N Engl J Med* 345:948–955
  176. Stoch SA, Parker RA, Chen L, Bublely G, Ko YJ, Vincelette A, Greenspan SL 2001 Bone loss in men with prostate cancer treated with gonadotropin-releasing hormone agonists. *J Clin Endocrinol Metab* 86:2787–2791
  177. Smith MR, Eastham J, Gleason DM, Shasha D, Tchekmedyan S, Zinner N 2003 Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. *J Urol* 169:2008–2012
  178. Greenspan SL, Coates P, Sereika SM, Nelson JB, Trump DL, Resnick NM 2005 Bone loss after initiation of androgen deprivation therapy in patients with prostate cancer. *J Clin Endocrinol Metab* 90:6410–6417

179. Daniell HW 1997 Osteoporosis after orchiectomy for prostate cancer. *J Urol* 157:439–444
180. Dickman PW, Adolfsson J, Aström K, Steineck G 2004 Hip fractures in men with prostate cancer treated with orchiectomy. *J Urol* 172:2208–2212
181. Shahinian VB, Kuo YF, Freeman JL, Goodwin JS 2005 Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med* 352:154–164
182. Greenspan SL, Nelson JB, Trump DL, Resnick NM 2007 Effect of once-weekly oral alendronate on bone loss in men receiving androgen deprivation therapy for prostate cancer: a randomized trial. *Ann Intern Med* 146:416–424
183. Smith MR, Fallon MA, Lee H, Finkelstein JS 2004 Raloxifene to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer: a randomized controlled trial. *J Clin Endocrinol Metab* 89:3841–3846
184. Lin DW, Marks LS, Morton RA, Rodriguez D 2009 Positive fracture reduction trial of toremifene 80 mg in men on ADT demonstrates significant fracture risk in untreated placebo group (Abstract 639). *J Urol* 181:229
185. Clowes JA, Peel NF, Eastell R 2004 The impact of monitoring on adherence and persistence with antiresorptive treatment for postmenopausal osteoporosis: a randomized controlled trial. *J Clin Endocrinol Metab* 89:1117–1123
186. Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, Chin JL, Vinholes JJ, Goas JA, Chen B 2002 A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst* 94:1458–1468
187. Watts NB, Lewiecki EM, Bonnick SL, Laster AJ, Binkley N, Blank RD, Geusens PP, Miller PD, Petak SM, Recker RR, Saag KG, Schousboe J, Siris ES, Bilezikian JP 2009 Clinical value of monitoring BMD in patients treated with bisphosphonates for osteoporosis. *J Bone Miner Res* 24:1643–1646
188. Hansen KE, Swenson ED, Baltz B, Schuna AA, Jones AN, Elliott ME 2008 Adherence to alendronate in male veterans. *Osteoporos Int* 19:349–356
189. Rogers A, Glover SJ, Eastell R 2009 A randomised, double-blinded, placebo-controlled, trial to determine the individual response in bone turnover markers to lasofoxifene therapy. *Bone* 45:1044–1052
190. Watts NB, Cooper C, Lindsay R, Eastell R, Manhart MD, Barton IP, van Staa TP, Adachi JD 2004 Relationship between changes in bone mineral density and vertebral fracture risk associated with risedronate: greater increases in bone mineral density do not relate to greater decreases in fracture risk. *J Clin Densitom* 7:255–261
191. Watts NB, Geusens P, Barton IP, Felsenberg D 2005 Relationship between changes in BMD and nonvertebral fracture incidence associated with risedronate: reduction in risk of nonvertebral fracture is not related to change in BMD. *J Bone Miner Res* 20:2097–2104
192. Ju HS, Leung S, Brown B, Stringer MA, Leigh S, Scherrer C, Shepard K, Jenkins D, Knudsen J, Cannon R 1997 Comparison of analytical performance and biological variability of three bone resorption assays. *Clin Chem* 43:1570–1576
193. Vasikaran S, Eastell R, Bruyère O, Foldes AJ, Garnero P, Griesmacher A, McClung M, Morris HA, Silverman S, Trenti T, Wahl DA, Cooper C, Kanis JA 2011 Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. *Osteoporos Int* 22:391–420
194. Rosen CJ, Hochberg MC, Bonnick SL, McClung M, Miller P, Brody S, Kagan R, Chen E, Petruschke RA, Thompson DE, de Papp AE 2005 Treatment with once-weekly alendronate 70 mg compared with once-weekly risedronate 35 mg in women with postmenopausal osteoporosis: a randomized double-blind study. *J Bone Miner Res* 20:141–151
195. Eastell R, Krege JH, Chen P, Glass EV, Reginster JY 2006 Development of an algorithm for using PINP to monitor treatment of patients with teriparatide. *Curr Med Res Opin* 22:61–66
196. Eastell R, Barton I, Hannon RA, Chines A, Garnero P, Delmas PD 2003 Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate. *J Bone Miner Res* 18:1051–1056
197. Sarkar S, Reginster JY, Crans GG, Diez-Perez A, Pinette KV, Delmas PD 2004 Relationship between changes in biochemical markers of bone turnover and BMD to predict vertebral fracture. *J Bone Miner Res* 19:394–401
198. Reginster JY, Sarkar S, Zegels B, Henrotin Y, Bruyere O, Agnusdei D, Collette J 2004 Reduction in PINP, a marker of bone metabolism, with raloxifene treatment and its relationship with vertebral fracture risk. *Bone* 34:344–351
199. Bauer DC, Black DM, Garnero P, Hochberg M, Ott S, Orloff J, Thompson DE, Ewing SK, Delmas PD 2004 Change in bone turnover and hip, non-spine, and vertebral fracture in alendronate-treated women: the fracture intervention trial. *J Bone Miner Res* 19:1250–1258
200. Delmas PD, Munoz F, Black DM, Cosman F, Boonen S, Watts NB, Kendler D, Eriksen EF, Mesenbrink PG, Eastell R 2009 Effects of yearly zoledronic acid 5 mg on bone turnover markers and relation of PINP with fracture reduction in postmenopausal women with osteoporosis. *J Bone Miner Res* 24:1544–1551
201. Eastell R, Vrijens B, Cahall DL, Ringe JD, Garnero P, Watts NB 2011 Bone turnover markers and bone mineral density response with risedronate therapy relationship with fracture risk and patient adherence. *J Bone Miner Res* 26:1662–1669
202. Holt G, Smith R, Duncan K, Hutchison JD, Gregori A 2008 Gender differences in epidemiology and outcome after hip fracture: evidence from the Scottish Hip Fracture Audit. *J Bone Joint Surg* 90B:480–483
203. Smith MR, Saad F, Coleman R, Shore N, Fizazi K, Tombal B, Miller K, Sieber P, Karsh L, Damiao R, Tammela TL, Egerdie B, Van Poppel H, Chin J, Morote J, Gomez-Veiga F, Borkowski T, Ye Z, Kupic A, Dansey R, Goessl C 2012 Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. *Lancet* 379:39–46



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