The Endocrine Society's
CLINICAL GUIDELINES

Osteoporosis in Men:

An Endocrine Society Clinical Practice Guideline

THE ENDOCRINE SOCIETY®

JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

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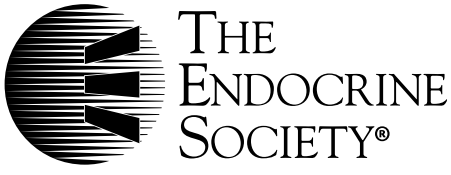

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Table of Contents

Abstract

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

Participants: The Task Force was composed of a chair, selected by the Clinical Guidelines Subcommittee of The Endocrine Society, five additional experts, and a methodologist.

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 to JCEM.

Conclusions: Osteoporosis in men causes significant morbidity and mortality. We recommend testing higher risk men [aged ≥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.

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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.

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 reasons 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 | ⊕⊕◯◯)

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 κ and λ 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 supplementation 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 ≥20% or 10-yr risk of hip fracture ≥3% using FRAX; further studies will be needed to determine appropriate intervention levels using other fracture risk assessment algorithms. For men outside the U.S., 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.

Funding for this guideline was derived solely from The Endocrine Society and thus the Task Force received no funding or remuneration from commercial or other entities.

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 testosterone administration had no effect on bone turnover in a man with an inactivating mutation in the estrogen receptor a 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/) and the Garvan nomogram (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 fracture risk similarly (82).

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

Risk Factor	No. of studies	OR	95% CI		*P-value*	I^{2a}
			LL	UL		
Age						
Age (continuous variable)[b]	11	1.12	1.07	1.18	0.00	87
Age (every 5–10 yrs)[c]	6	1.29	1.17	1.43	0.00	52
Age >70[d]	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^2)	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 (nonpharmacologic)	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^2 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.

a I^2 statistic is defined as the proportion of heterogeneity not attributable to chance or random error.

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

c 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).

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

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, or 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 κ and λ 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 μg/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 | ⊕⊕◯◯)

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 ≤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 μg) 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 intraand 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 (≥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 ≥20% or 10-yr risk of hip fracture ≥3% using FRAX; further studies will be needed to determine appropriate intervention levels using other fracture risk assessment algorithms. For men outside the U.S., 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 experience 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, 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 | ⊕⊕◯◯)

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 post-menopausal 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 ≤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 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 | ⊕⊕◯◯)

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 ± SE baseline level of 399 ± 10 ng/dl (13.8 ± 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 advance 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 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 therapy. 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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❍ Nurse/Healthcare Professional
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❍ Teacher/Educator
❍ Fellow (Clinical)
❍ Fellow (Postdoctoral/Research)
❍ Student
❍ Other _____

Race or Ethnic Affiliation (voluntary)

❍ African American, Black
❍ Asian
❍ Hispanic
❍ Native American, Eskimo, Aleut
❍ Pacific Islander
❍ White, Caucasian
❍ Other _____

What goes into our

Clinical Guidelines

is a *story worth telling*

The *Osteoporosis in Men* clinical practice guideline was developed independently by a team of experts, evidence-based, and vetted through a rigorous, multi-step peer review process.

To complement this guideline, the Society hosted a 60-minute webinar on June 5, 7:30 pm ET.

Access this and other archived webinars here: **www.endo-society.org/education/webinars/**.

Other Endocrine Society Guidelines COMING SOON

- *Acromegaly*
- *Diabetes & Pregnancy*
- *Hypertriglyceridemia*
- *Hyponatremia*
- *Hypothalamic Amenorrhea*
- *Medical, Nutritional, & Pharmacologic Management of Obesity*
- *Medical Therapies of Hypothyrodism*
- *Paget's Disease of the Bone*
- *Pheochromocytoma/Paraganglioma*
- *PCOS*

Endocrine Society Clinical Guidelines ALSO AVAILABLE

- *Management of Hyperglycemia in Hospitalized Patients in Non-Critical Care Setting* NEW
- *Continuous Glucose Monitoring*
- *Vitamin D*
- *Adult Growth Hormone Deficiency*
- *Pituitary Incidentaloma*
- *Hyperprolactinemia*
- *Post-Bariatric Surgery Patient*
- *Congenital Adrenal Hyperplasia*
- *Testosterone Therapy in Adult Men*
- *Endocrine Treatment of Transsexual Persons*
- *Adult Hypoglycemic Disorders*
- *Pediatric Obesity*
- *CVD and Type 2 Diabetes in Patients at Metabolic Risk*
- *Patients with Primary Aldosteronism*
- *The Diagnosis of Cushing's Syndrome*
- *Hirsutism in Premenopausal Women*
- *Thyroid Dysfunction during Pregnancy & Postpartum*
- *Androgen Therapy in Women*




To purchase available guidelines visit: **www.endo-society.org/guidelines/Current-Clinical-Practice-Guidelines.cfm**.

To view patient guides (companion pieces to the clinical guidelines), visit The Hormone Health Network's Web site at **http://www.hormone.org/Resources/patientguides.cfm**.

Visit **http://www.guidelinecentral.com** to purchase pocket cards developed from select Endocrine Society guidelines.

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For more information on The Endocrine Society's Clinical Practice Guidelines, visit: http://www.endo-society.org/guidelines/index.cfm

To view patient guides (companion pieces to the clinical practice guidelines) visit The Hormone Health Network's website at: http://www.hormone.org/Resources/patientguides.cfm.

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