OSTEOPOROSIS IN MEN

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ABSTRACT

While progress has been made, osteoporosis in men is still under-diagnosed and under-treated. In general, men fracture about 10 years later than women, with large increases in fracture risk after about age 75, although a small number of men may present with vertebral fractures in middle age. There is overlap between secondary causes of osteoporosis and risk factors for primary osteoporosis, but men with fragility fractures or low bone density require evaluation by history and physical examination as well as a short list of laboratory tests. Bone mineral density by dual-energy x-ray absorptiometry remains the best test for diagnosing osteoporosis in men, although opportunistic bone density measurements from CT scans are promising. Clinicians should recommend a comprehensive program of treatment with fall risk reduction, attention to diet and vitamin D status, and pharmacologic treatment. In general, medications that work in women should lead to fewer fractures in men, although there are few studies in men with fracture risk reduction as the primary outcome. Most men with osteoporosis should be treated with oral or intravenous bisphosphonates, but men at very high fracture risk should be considered for initial anabolic treatment. Compared to women, men are more likely to die after hip fracture. The long-term management of men with osteoporosis is based solely on a few studies in women.

INTRODUCTION

Despite new information and even some attention in popular publications, osteoporosis in men remains under-appreciated, under-diagnosed, and under-treated. While the evidence base for evaluation and management of male osteoporosis will always be less than that of female osteoporosis, there is enough information available to identify those men at highest risk, evaluate them thoroughly, and treat them with a program that will reduce osteoporotic fractures. Nonetheless, there are many impediments to quality care at all stages: recognition, diagnosis, assessment, and management (both short- and long-term). In this chapter, the challenges for the primary care and specialty clinician will be addressed with the purpose of providing an approach to reducing osteoporotic fracture in men.

DEFINITION, CLASSIFICATION, AND EPIDEMIOLOGY OF MALE OSTEOPOROSIS

Definitions of Osteoporosis in Men

In an older adult, regardless of gender, a fall from a standing position should not result in a fracture. Hence, one definition of osteoporosis is just such a fracture. By consensus, some fractures are considered osteoporotic; and others may or may not be, even if they occur with minimal trauma. For the most commonly used fracture risk calculator FRAX (see below), low trauma fractures of the spine, hip, forearm (radius and ulna), and humerus are considered osteoporotic. Pelvic, rib, and sternal fractures may also be osteoporotic. Most authorities do not count skull or digital fractures, and ankle fractures are the most controversial. Interestingly, in a study (1) of older men (MrOS, see below), any fracture after age 50 increased the risk of osteoporotic hip fracture, when combined with bone mineral density (BMD) measured by dual energy x-ray absorptiometry (DXA). The above is compatible with the standard definition of osteoporosis as compromised bone strength leading to increased risk of low trauma fracture (2). A more operational diagnosis relies on DXA measurements, with a BMD T-score of -2.5 or worse in the spine or hip serving as the diagnosis of osteoporosis (3). This means that the patient's BMD is at least 2.5 standard deviations below the normal young mean. As the BMD decreases, the fracture risk rises markedly. In men there has been great controversy about the normative database that should be used for the calculation of T-scores. Based on the fact that men and women fracture at similar (overlapping but not quite identical) absolute bone density measurements (in g/cm^2),

several major osteoporosis organizations, including the International Society for Clinical Densitometry (ISCD), recommend use of the young, white female normative database for all T-score calculations (4). The reader is directed to a discussion of this subject (5), and more details about DXA are discussed below. While the man with a T-score of -2.5 or less is clearly at the highest risk for fracture, more fractures occur in men with T-scores between -1 and -2.5, what is called osteopenia or low bone mass. The reason for this is that there are many more men in this category. For example, baseline DXA testing was done in the Rotterdam study (6), a large, long-term observational study. In men, 29% of hip fractures were in those with osteoporosis by DXA, 64% had osteopenia, and 7% had normal bone density. DXA measures bone quantity, and fracture risk is also determined by bone quality, which is impossible to measure definitively with current clinical tools. Thus, fracture risk calculators have been established, based on epidemiological data, to reflect bone quality and add to the predictive power of DXA. The most commonly used fracture risk calculator is FRAX (7), available online as www.sheffield.ac.uk/FRAX/. FRAX calculates the 10-year risk of hip fracture and of major osteoporotic fracture (MOF) based on the femoral neck BMD in g/cm^2 plus a series of risk factors: age, sex, previous fracture, parental hip fracture, current smoking, having more than 3 alcoholic drinks daily, rheumatoid arthritis, exposure to systemic glucocorticoid drugs, and secondary osteoporosis. It also can be calculated using the body mass index (BMI) as a surrogate for femoral neck BMD. While some studies (e.g. 8) suggest that FRAX works better in women than men, the calculator has been adopted internationally.

There are other risk calculators, such as the Garvan nomogram (9), which unlike FRAX includes falls as a risk factor for determining fracture risk. It is interesting to note that at age 50, a man has a risk of experiencing an osteoporotic fracture of 13 to 25%, depending on the population studied. A much smaller percentage of men over age 50 have T-scores of -2.5 or worse, although the proportion increases with age. In a study of NHANES data, osteoporosis was defined from FRAX calculations: a 10-year hip fracture risk of $\geq$ 3% or MOF of $\geq$ 20% (10,11,12). Using this definition 16% of American men at age 50 and 46% at age 80 met criteria for osteoporosis, much more similar to actual incidences of osteoporotic fracture (12). There is some evidence (e.g. 13) that treating women who meet this fracture risk criterion respond to current osteoporosis treatment. There are, to my knowledge, no studies in men that show that diagnosing osteoporosis in a man by this method and treating him with standard medication leads to fewer fractures. Indeed Ensrud (14) has reported that men with osteoporosis by DXA have the best response to osteoporosis treatment, compared to those with better BMD. However, as will be described below, studies of osteoporosis medications in men have almost always used the more liberal male normative database for the calculation of the T-score and accepted men with osteopenia plus a history of an osteoporotic fracture for inclusion. In these studies, such men responded to the treatment regimen with improvements in the standard surrogates for fracture. It is also interesting that the Rotterdam study (6) mentioned above also used sex-specific normative databases for the DXA diagnosis of osteoporosis. Had they used the female database for all participants, the group with osteoporosis by

DXA at baseline would have accounted for an even smaller percentage of the hip fractures observed. A practical approach to the diagnosis is provided below.

There are other potential tools for determining fracture risk. For example, FRAX Plus (15) will be released soon. It will add falls, diabetes mellitus, and other risk factors to the fracture risk prediction. Trabecular Bone Score (16) can be derived from DXA of the spine. It reflects bone architecture and can be added to FRAX calculations. It is thought to be a reflection of bone quality (17). The reader is directed to the chapters on osteoporosis in women, which will include other methods to better quantify fracture risk.

Epidemiology of Osteoporosis in Men

Fractures in men occur about 10 years later in life than in women (18). Men, with generally bigger bones, have more to lose over time. In addition, men do not undergo the rapid increase of bone turnover that occurs with menopause and the marked drop in estradiol secretion. Instead, it is well-accepted that the loss of sex steroids in men is a much more gradual process (19), and it is interesting to note that, with aging, BMD is more closely associated with serum bioavailable estradiol levels than with any serum measure of testosterone (20). Nonetheless, in middle-aged men presenting usually with vertebral fractures or low spine BMD by DXA, one of the causes of osteoporosis earlier in life is hypogonadism. This type of osteoporosis is analogous to what Riggs and Melton labelled postmenopausal osteoporosis in a seminal paper (21) many years ago. They described osteoporosis in women soon after menopause as loss of mostly trabecular

bone (and thus vertebrae were particularly at risk) and associated with the dramatic drop in ovarian estrogen production. Men with organic causes of hypogonadism (for example, pituitary tumors) may also present with very low serum testosterone levels and osteoporosis. There are other causes of this earlier type of osteoporosis in men, including hypercalciuria (22) and secondary causes, which may not be very apparent clinically. An example of the latter is celiac disease, which may not bring the patient to clinical attention but can lead to early fracture risk. (See below for other secondary causes of osteoporosis in men). Finally, there have been reports of genetic disorders leading to so-called idiopathic osteoporosis in men, such as low levels of IGF-I without abnormalities in growth hormone (23) and low serum bioavailable estradiol levels (24). It is much more likely for a man to experience an osteoporotic fracture after age 75 than at middle age, but the clinician needs to know that early osteoporosis occurs and that it should lead to evaluation and treatment.

The majority of fractures in men occur later in life. The Rotterdam Study (6) assessed only nonvertebral fractures because the date of vertebral fractures was much more difficult to ascertain. In men the incidence of nonvertebral fracture accelerates after about age 75. The incidence of nonvertebral fractures in men at ages 80 to 84 is about the same as the incidence in women ages 70 to 74. This observation is the basis for stating that fractures occur about 10 years later in men than women, and it may explain why men come to fracture with more co-morbidities than women, a possible explanation for why men do relatively poorly after hip fracture in particular. As used in FRAX, risk factors for fracture, presumably reflecting bone quality, magnify the impact of bone quantity (DXA) on fracture risk. In the FRAX calculation age, prior fracture, and history of parental fracture are the most important variables. Not well known is a report (25) from Leslie and colleagues proposing that the age at which a parent has fractured a hip is important. If the parent has fractured before age 80, this adds greatly to the patient's risk of fracture, whereas if the parental hip fracture occurred late in life, the impact on fracture risk is much less. The analogy with familial heart disease is striking: early heart disease, particularly in a patient's mother, makes the patient at much increased risk for cardiac events.

Risk Factors and Secondary Causes of Osteoporosis

Table 1 summarizes potential risk factors and secondary causes of osteoporosis, most of which pertain to men as well as to women. Aspects specific to men are discussed below.

Table 1. Conditions, Diseases and Medications that Cause or Contribute to Osteoporosis and Fractures

Lifestyle Factors

Low Calcium Intake	Vitamin D Insufficiency	Excess Vitamin A	High Caffeine Intake
High Salt Intake	Aluminum (in antacids)	Inadequate Physical Activity	Immobilization
Smoking	Falling	Thinness	Alcoholism

Genetic Factors

Cystic Fibrosis	Homocystinuria	Osteogenesis Imperfecta	Ehlers-Danlos Syndrome
Hypophosphatasia	Gaucher's Disease	Idiopathic Hypercalciuria	Porphyria
Glycogen storage diseases	Marfan Syndrome	Riley-Day Syndrome	Hemochromatosis
Menkes Steely Hair Syndrome	Parental History of Hip Fracture	Androgen Insensitivity	Turner's & Klinefelter's Syndromes

Endocrine Disorders

Adrenal Insufficiency	Diabetes Mellitus	Hyperthyroidism	Cushing's Syndrome
Hyperparathyroidism	Hypogonadal States	Panhypopituitarism	Athletic Amenorrhea
Anorexia Nervosa and Bulimia	Hyperprolactinemia	Premature Ovarian Failure	

Gastrointestinal disorders

Celiac Disease	Inflammatory Bowel Disease	Primary Biliary Cirrhosis	Gastric Bypass
Malabsorption	GI Surgery	Pancreatic Disease	

Hematologic Disorders

Hemophilia	Multiple Myeloma	Systemic Mastocytosis	Leukemia
Lymphoma	Sickle Cell Disease	Thalassemia	

Rheumatic and Autoimmune Diseases			
Ankylosing Spondylitis	Lupus	Rheumatoid Arthritis	
Miscellaneous Conditions and Diseases			
Chronic Obstructive Pulmonary Disease	Muscular Dystrophy	Amyloidosis	End Stage Renal Disease
Parenteral Nutrition	Chronic Metabolic Acidosis	Epilepsy	Post-Transplant Bone Disease
Congestive Heart Failure	Idiopathic Scoliosis	Prior Fracture as an Adult	Depression
Multiple Sclerosis	Sarcoidosis	HIV/AIDS	
Medications			
Anticoagulants (heparin)	Cancer Chemotherapeutic Drugs	Gonadotropin Releasing Hormone Agonists	Anticonvulsants
Lithium	Aromatase Inhibitors	Depo-medroxyprogesterone	Barbiturates
Glucocorticoids (> 5mg of prednisone or equivalent for > 3 months)	Cyclosporine A	Tacrolimus	

Table from the Endotext chapter entitled "Osteoporosis: Clinical Evaluation" by E. Michael Lewiecki.

The Osteoporotic Fractures in Men Study (MrOS) has provided a great deal of information. This long-term US observational study included about 6000 men for more than 15 years (26). Of the many important findings from the study, one is of particular interest. What are the characteristics of men, in addition to DXA, that predict hip fracture? In this excellent report (1), several surprising factors were discovered and others were expected. Of the latter group, age ≥75, current smoking, Parkinson's disease, hyperthyroidism, hyperparathyroidism, and decreased cognitive function were risk factors that greatly increased the fracture risk prediction, when added to BMD. More interestingly, several other risk factors were found: low dietary protein, any fracture after age 50, divorce, tricyclic anti-depressants or hypoglycemic agents, tall stature, and the inability to do chair stands. Having 4 of these risk factors increased hip fracture risk 5-fold in men with osteoporosis by DXA.

Secondary causes of osteoporosis are thought to be particularly important in men, but there is overlap between what might be called a secondary cause of osteoporosis and in another

context a risk factor for primary osteoporosis. In addition, while treatment of a secondary cause may be adequate to lower fracture risk, a man will possibly be at risk for primary osteoporosis as he ages – and need osteoporosis specific treatment. Hyperthyroidism, hyperparathyroidism, and hypercalciuria are well-characterized secondary causes of osteoporosis in men. A particularly important cause is glucocorticoid excess, usually due to treatment of an inflammatory disorder with systemic glucocorticoids. Glucocorticoid-induced osteoporosis (GIOP) is considered the most important medication-related type of osteoporosis and is of particular concern because fracture risk is increased (27) after 3 months of prednisone equivalent doses of 5 to 7.5 mg daily – and maybe earlier (28) and maybe even lower doses. There is evidence that men are less likely to be evaluated and treated for GIOP (29), perhaps because clinicians again do not think that osteoporosis happens in men. While endogenous Cushing's syndrome leads to GIOP, most cases are due to exogenous glucocorticoids, and about 1% of the adult population may be taking such medications at any particular time.

Multiple myeloma may present with osteoporosis-like vertebral fractures; hence, this diagnosis must be in the differential diagnosis of the new patient presenting this way. Malabsorption, particularly celiac disease, is another potential secondary cause of osteoporosis. While type 2 diabetes mellitus is clearly associated with increased fracture risk (30), bone density is usually not decreased, whereas in type 1 diabetes mellitus, BMD is variable. Celiac disease is associated with type 1 diabetes mellitus, and thus it should be considered in men with type 1 diabetes mellitus and a fracture. Mastocytosis is associated with osteoporosis, although the mechanism is not fully understood. Hemochromatosis, presumably via some of its consequences is also on the list of secondary causes. Immobilization leads to loss of bone. Spinal cord injury is much more common in men than women, and bone is lost distal to the cord lesion and may be worse than immobilization *per se* because of comorbidities (31). The fracture risk is high in men with spinal cord injury, and other types of decreased mobility should be considered when assessing men: stroke, Parkinson's disease, multiple sclerosis, etc.

Men with HIV now have life expectancies close to those without HIV, but the risk of osteoporosis and fracture is greater. Fractures appear about 10 years earlier than in men without HIV. In a systematic review of large numbers of people living with HIV (mostly men), the relative risk of a low trauma fracture was 1.51 and the relative risk of a hip fracture was 4.09 (32). In a meta-analysis of bone mineral density testing (33), low bone mass (osteopenia) and osteoporosis by dual energy x-ray absorptiometry (DXA) was more prevalent in persons (again mostly men) with HIV compared to non-infected controls. Interestingly, initiation of antiretroviral therapy (ART) appeared to be associated with lower bone density, confirmed by a subsequent randomized trial (34). ART with tenofovir alafenamide appears to have better renal safety than tenofovir disoproxil fumarate (35) and may have less impact on bone. Fortunately, men with HIV appear to response well to bisphosphonate therapy for osteoporosis 36).

Osteoporosis and Hypogonadism

As mentioned above, men with organic causes of hypogonadism are at risk for fracture and may present at middle age or later with fracture or low BMD. More common and more controversial is the parallel decrease in BMD and serum testosterone levels with aging. While not proven, it is reasonable to assume that as testosterone and muscle mass diminish with age, falls will increase, leading to fractures. The relationship between serum testosterone and BMD is less clear. As previously mentioned, Khosla and colleagues reported (20) that BMD was more strongly related to bioavailable estradiol levels than any measure of testosterone. Of course, in men the major source of estradiol is aromatization of testosterone. The importance of estrogen is illustrated by the impact of iatrogenic hypogonadism. Prostate cancer often responds to androgen withdrawal, and for men with rising PSA levels or other evidence of recurrence or spread, androgen withdrawal may be accomplished by orchiectomy (not done very often today) or by use of analogs of gonadotropin releasing hormone (GnRH). Some GnRH analogs acutely increase gonadotropins LH and FSH such that an androgen receptor blocker such as bicalutamide or nilutamide is given on a short-term basis until the pituitary is down regulated. GnRH analog treatment results in serum testosterone levels that are essentially zero and in very low levels of estradiol (the remaining estrogens are presumably from conversion of adrenal androgens). Some men are treated with an androgen blocker alone. In most studies (37) bone loss is much more profound in the men treated with GnRH analogs compared to men treated with only androgen receptor blockers, who have normal estradiol levels. Abiraterone (38) blocks conversion of precursors to androgens and

may be used in concert with GnRH analogs. Prednisone is needed to prevent mineralocorticoid excess due to the enzyme blockage caused by abiraterone. The dose is 5 mg twice daily, a little more than a replacement dose. This potentially adds to the risk that men treated with this combined androgen deprivation therapy (ADT) will have particularly increased fracture risk. However, the most widely cited study (39) of fracture in men on ADT is several years old, done before abiraterone was approved. The important finding from this study was that while ADT given to a man who has a rising PSA level after primary treatment of prostate cancer leads to a 10-year survival rate of 80 to 90%, the 5-year fracture rate was almost 20% in Caucasian men and 2/3 or ¾ of that rate in African-Americans. Thus, the profound hypogonadism of ADT is clearly a major risk for fracture.

This still leaves unanswered whether testosterone given to men with decreased serum testosterone levels associated with aging would benefit from testosterone replacement. There are no studies large enough to show a fracture benefit of such treatment. In a careful study (40) of older men with low serum testosterone levels, testosterone gel or placebo gel was used for one year. At the end of the year, there was a modest increase in BMD by DXA and also by quantitative computed tomography (qCT). More importantly, there was an increase in bone strength by finite element analysis of the qCT data. The Endocrine Society Male Osteoporosis Guideline (41) states that older men at risk for fracture should be treated with osteoporosis-specific medications but those who also have symptomatic hypogonadism can be considered for testosterone replacement. The likely impact of

testosterone deficiency on muscle and the bone strength response to testosterone replacement make it plausible that testosterone replacement will lead to fewer fractures. The TRAVERSE study (42) is a large study of testosterone replacement on cardiovascular safety in older hypogonadal men. There was no increase in cardiovascular events in the men treated with testosterone gel (43), nor was there evidence of increased prostate cancer risk or urinary retention (44). Interestingly, there were more fractures in the men receiving testosterone replacement (45). However, the fractures occurred soon after starting replacement, and the majority were ankle and risk fractures (45, 46). This suggested to Grossmann and Anawalt (46) that testosterone-induced changes in behavior may have been the etiology of the fracture increase.

SCREENING AND DIAGNOSTIC EVALUATION IN MEN

DXA Testing Men

From this extensive review of pathogenesis and epidemiology of osteoporosis in men, it is possible to postulate which men should be screened for osteoporosis and how they should be evaluated. Age is a major risk factor for fracture. At what age should a man undergo DXA testing and does such testing lead to fewer fractures? The Endocrine Society Guideline (41) suggests DXA testing in most men at age 70 or above. The United States Preventive Services Task Force (47) states that there is insufficient evidence to recommend DXA testing in men, although it supports DXA testing in women by age 65. There are few studies demonstrating that DXA screening in women leads to fewer fractures. The recent SCOOP study (48) from the UK revealed that a two-stage method of choosing women for testing by first calculating FRAX using BMI as a surrogate for femoral neck BMD resulted in fewer hip fractures. In this study, women at low risk for fracture by FRAX were not screened further. Those at high risk were treated, and those in the middle had a DXA. Based on DXA results and recalculation of FRAX with femoral neck DXA results, women at risk were placed on therapy and had fewer fracture than those not screened for osteoporosis. There are no similar prospective studies in men, but Colon-Emeric and colleagues (49) used the Department of Veterans Affairs and Medicare databases to determine the impact of screening men with DXA. Overall, screening did not lead to fewer fractures. However, strategic screening did. Men aged 80 or older, men on systemic glucocorticoids or ADT, and men with FRAX calculated with BMI (somewhat like the SCOOP study women) had fewer fractures if they were screened by DXA. In addition, men over age 65 with several other risk factors (including rheumatoid arthritis, alcohol or tobacco abuse, chronic obstructive pulmonary disease, chronic liver disease, stroke, Parkinson's disease, gastrectomy, hyperthyroidism, hyperparathyroidism, or traditional anti-seizure drug use) were also likely to benefit, should they have a DXA done. This study was observational and done with the Department of Veterans Affairs population, which tends to be sicker than the general population and from the population of the prospective study, MrOS. Nonetheless, the findings are compatible with the epidemiology of fractures in men and can serve as a basis for clinical care. It is unrealistic to expect that a study like SCOOP will be done in men. The SCOOP population was about 12,500 women; a male

version would likely need approximately 40,000 participants. Based on the Colon-Emeric observational study (49) and studies from MrOS (1), Table 2 suggests which older men that should be screened for osteoporosis by DXA.

Table 2. Which Men Should Be Screened (by DXA) for Osteoporosis?
Men > 50 Years Old
After a fragility fracture (usually vertebral in younger group)
On chronic glucocorticoids
Organic causes of hypogonadism
Hypercalciuria
Men > 65 Years Old
All of the above plus:
On androgen deprivation therapy for prostate cancer
High risk for fracture based on FRAX using BMI
Current smoking/COPD
Alcohol abuse/chronic liver disease
Rheumatoid arthritis
Parkinson's disease or other mobility disorder
Gastrectomy/bariatric surgery
Hyperthyroidism
Hyperparathyroidism
On enzyme-inducing anti-seizure medications for > 2 years
Men > 80 Years Old
If not already screened, all men over 80 should have a DXA (unless there is a contraindication).

In the United States, reimbursement for DXA testing is limited. This may be one reason that so few men are assessed for fracture risk. One potential method to identify men at risk for fracture is to assess bone density from CT scans done for other reasons. There are several methods of so-called opportunistic bone density evaluation that have been used (e. g. 50), including a study done in male veterans (51). It is likely that artificial intelligence can be harnessed to make this

process even more efficient. Whether finding men at risk this way will lead to more clinical evaluation and treatment and fewer fractures remains to be determined.

Beyond DXA: Laboratory Evaluation of Osteoporosis in Men

If a man has osteoporosis by DXA or meets other criteria for osteoporosis or has low bone mass (osteopenia) but may be at higher risk for fracture, what other tests should be done? Spine x-rays or vertebral fracture analysis (images of the spine by DXA machines) may reveal vertebral fractures that increase subsequent fracture risk. There are no specific blood tests for osteoporosis, and the evidence base for the tests that follow may be weak. Nonetheless, it makes clinical sense to do a few laboratory tests to look for secondary causes/risk factors for osteoporosis and to ensure the safety of treatment, should it be indicated. Many patients will have had some of these tests as part of their general medical care, so the actual addition to routine testing may be small. For all patients, assessments of serum calcium and phosphate and renal function are necessary to look for hypercalcemia (which might signal hyperparathyroidism) and to determine if some osteoporosis treatments can be safely given. Avoiding controversies about ideal levels of serum 25-OH vitamin D in the general population, there is consensus that for the patient with osteoporosis, the target level should be 30 ng/ml (52). All of those tests mentioned may help to identify the unusual patient with osteomalacia. Serum alkaline phosphatase reflects bone formation and turnover, among other things. It is interesting that low serum alkaline phosphatase may be a sign of hypophosphatasia (53), a

disorder of variable severity that may present as osteoporosis. Such patients should not be treated with anti-resorptive agents. An automated complete blood count should be done, particularly if there is any suspicion of multiple myeloma because about 75% of such patients will have anemia. All of the above tests, with the exception of 25-OH vitamin D, may be done as routine screening tests in many people visiting primary care clinicians, although measurement of 25-OH vitamin D has become very common as well. Once the 25-OH vitamin D level is at goal, a 24-hour urine for calcium and creatinine (and possibly sodium) may help to signal hypercalciuria, or in in the case of low urinary calcium excretion, may reflect malabsorption. For a patient suspected of hyperparathyroidism or hyperthyroidism, appropriate testing for parathyroid hormone (PTH) or thyroid hormones/TSH should be done. Similarly, for patients in whom there is a suggestion of another secondary cause of osteoporosis, specific tests such as serum protein electrophoresis, celiac antibodies, cortisol, tryptase, etc. can be done. More controversial is whether serum testosterone should be measured. Most symptoms of hypogonadism are non-specific, such as fatigue. Decreased libido is considered the most specific symptom, but decreased muscle mass and decreased beard growth might be present. For the symptomatic man, measurement of early morning testosterone is reasonable. Many experts may suggest measurement of free and bioavailable testosterone as well as gonadotropins. The diagnosis of hypogonadism requires two early morning (preferably fasting) testosterone measurements (54). We would also measure PSA and review the hematocrit and hemoglobin before considering testosterone

replacement. In addition, measurement of testosterone should only be done if the clinician would consider testosterone replacement, likely in addition to an osteoporosis-specific treatment. In the Veterans Affairs population, routine laboratory testing was found to reveal new secondary causes and/or osteoporosis risk factors (55). In contrast, in the healthier MrOS cohort, routine testing was found to be less helpful (56).

Table 3. Practical Approach to the Man with Osteoporosis
History and Physical Exam
Evidence of secondary causes of osteoporosis, risk factors
Family history
Height versus maximum attained height
Gait
Kyphosis
General condition of teeth
Evidence of significant visual abnormalities
Ability to rise from chair without using hands
Tenderness to percussion of spine
Standard Laboratory Tests
Serum Chemistries: Calcium, Phosphate, Alkaline Phosphatase, Albumin
Measure of Renal Function (e.g. serum creatinine, eGFR)
Complete blood count
Serum 25-OH vitamin D
When 25-OH vitamin D is at goal: 24-hour urine calcium, creatinine, and maybe sodium
Laboratory Tests in Specific Cases (triggered by history and physical exam)
Thyroid function tests (TSH, Free T4, maybe Total T3)
Parathyroid hormone (PTH)
Ionized Calcium
Total, Free, and Bioavailable Testosterone
LH, FSH, Prolactin

CTX or other marker of bone resorption
Bone Specific Alkaline Phosphatase (or other marker of bone formation)
Celiac antibodies
Serum/Urine Protein Electrophoresis
Magnesium
Tryptase
Tests for cortisol excess (e.g. urinary free cortisol, dexamethasone suppression test, midnight salivary cortisol)
Images
X-rays of thoracic and lumbar spine
X-rays of fractured bone
Pituitary imaging (usually MRI)

MANAGEMENT OF OSTEOPOROSIS IN MEN

Non-Pharmacologic Management of Osteoporosis

One criticism heard about current osteoporosis treatment is that it focuses only on pharmacologic methods. A more comprehensive approach to osteoporosis treatment is preferred. Indeed, there are ways to reduce fracture that do not involve prescription of drugs, and they should be an important part of the therapeutic regimen. While there has been controversy about the role of calcium and vitamin D on fracture risk and on potential side effects, such as cardiovascular events, discussion of these controversies can be found in other chapters. One recent meta-analysis (57) concluded that daily calcium and vitamin D are likely to be salutary for osteoporosis. The widely-cited Institute of Medicine report (58) suggested 1000 to 1200 mg of elemental calcium in the diet and vitamin D intake of 400 to 800 units per day. As stated above, most experts would suggest that a target vitamin D level of 30 ng/ml is reasonable for patients with osteoporosis. From MrOS (1) we learned that the protein content of the diet is also important. A liquid protein supplement might be a good source of calcium and protein for some older men. In my own experience, older men who live alone may have poor diets, and such protein supplements may be an easy way to augment their diet.

Fall risk reduction is also very important. In most cases, patients fall first, fracture second. Thus, attention to eyesight, avoidance of drugs that affect standing blood pressure or cause sleepiness or confusion, and home safety are very important parts of a comprehensive osteoporosis treatment program. Treatment of cataracts, for example, leads to fewer fractures (59). In MrOS (1) use of hypoglycemic agents was associated with increased hip fracture risk.

People with seizure disorders fall; thus, control of epilepsy is important. Avoidance of alcohol, opiates, benzodiazepines, and psychiatric drugs is suggested, but of course some patients may require medications that can cause drowsiness or imbalance. Anti-hypertensive medications need to be titrated such that postural hypotension does not occur. Convincing a man to use a walking aid may be challenging. Night lights, elimination of loose throw rugs and extension cords, and care with pets are also important to avoid falls. Consultation with Occupational Therapy and/or Physical Therapy should be considered in many cases. Exercise prescriptions should aim to improve muscle strength as well as balance. Risk factors for falls are listed in table 4.

Table 4. Risk Factors for Falls Adapted From Guidelines of the National Osteoporosis Foundation
Environmental Risk Factors
Lack of assistive devices in bathrooms, loose throw rugs, low level lighting, obstacles in the walking path, slippery outdoor conditions
Medical Risk Factors
Age, anxiety and agitation, arrhythmias, dehydration, depression, female gender, impaired transfer and mobility, malnutrition, orthostatic hypotension, poor vison and use of bifocals, previous fall, reduced mental acuity and diminished cognitive skills, urgent urinary incontinence, Vitamin D insufficiency (serum 25-OH-D < 30ng/ml (75nmol/l)), medications causing over-sedation (narcotic analgesics, anticonvulsants, psychotropics), diabetes
Neurological and Musculoskeletal Risk Factors
Kyphosis, poor balance, reduced proprioception, weak muscles
Other Risk Factors; Fear of falling
The presence of any of these risk factors should trigger consideration of further evaluation and treatment to reduce the risk of falls and fall-related injuries.

Table from the Endotext chapter entitled "Osteoporosis: Clinical Evaluation" by E. Michael Lewiecki.

Medications for Osteoporosis in Men

The pharmacologic treatment of osteoporosis in men is by and large the same as treatment in women. Alendronate, risedronate, zoledronic acid, denosumab, teriparatide, and abaloparatide are all FDA approved for men with osteoporosis. Most men have been treated with bisphosphonates, similar to women. Alendronate was the first modern bisphosphonate approved by regulatory agencies in the mid-1990's; it was shown to change surrogates of fracture (BMD and bone turnover markers) in men similarly to women (60). Although fracture risk reduction was not the primary outcome of the study, there were fewer morphometric vertebral fractures in the men randomized to alendronate compared those on placebo. Similarly, risedronate and zoledronic

acid have been shown to increase bone density in men to a similar degree as in women (61, 62). A criticism by some is that current surrogates for fracture may not be adequate, and that raising BMD or suppressing bone turnover markers in men is not enough evidence to conclude that fracture risk will be lowered by bisphosphonates. In a two-year study (63) with morphometric vertebral fractures as the primary outcome, Boonen et al demonstrated that zoledronic acid not only increased BMD in men, compared to placebo infusions, but it also led to fewer vertebral fractures. Specifically, at 2 years there was a 67% relative risk reduction and 3.3% absolute risk reduction in morphometric vertebral fractures. Thus, the clinician can be confident that if the patient is compliant and adherent to bisphosphonate treatment, fracture risk should be decreased.

All of the cited studies in men used a male normative database for calculation of the T-score. Men were eligible for the studies if they had osteoporosis by this criterion or had osteopenia (usually a T-score of -2) plus history of a low trauma facture. In women treated with bisphosphonates, vertebral fractures are decreased by about half and hip fractures by a third. In the zoledronic acid registration trial in women (64), at 2 years the relative risk reduction of morphometric vertebral fractures was 71% and the absolute risk reduction was 5%. Compared to the study in men, at baseline the women were older, were more likely to have had a previous fracture, and had lower BMD. It is impossible to compare results between the two gender-specific studies in any meaningful way, other than to conclude that zoledronic acid works similarly in men and women.

The usual starting treatment for osteoporosis is oral alendronate 70 mg by mouth once weekly. As in women, oral alendronate (or most preparations of risedronate) has to be taken on an empty stomach with just a glass of water, and the patient is instructed to take nothing else by mouth for at least 30 minutes. In general, this is not a problem, but for men also taking levothyroxine and/or proton pump inhibitors, timing may be difficult. In patients on levothyroxine, one strategy is to have them take the levothyroxine in the middle of the night, when older men are likely to need to urinate. This does not work for bisphosphonates because lying down after taking the bisphosphonate may lead to esophageal irritation. For the man with gastro-esophageal reflux disease (GERD), avoidance of oral bisphosphonates is indicated if the GERD is not under good control. For such men and for those unable or unwilling to adhere to the correct oral regimen, intravenous zoledronic acid, 5 mg given over 15 minutes or more, is a reasonable choice. The FDA-approved interval for zoledronic acid is one year. In our experience (65, 66), increasing the interval to 1.5 years or so allows all bisphosphonate patients to have a 5-year initial treatment period. Long-term management of osteoporosis in men is discussed below. An alternative oral treatment is risedronate given as a monthly 150 mg tablet. For some men, particularly those with a high pill burden, this may be an attractive regimen.

As an alternative to bisphosphonates, another anti-resorptive or anti-bone turnover medication is denosumab, an antibody against RANK Ligand. Among the earliest uses of this medication was a study of a high-risk group, men on ADT for

prostate cancer. In this important study, Smith and colleagues (67) randomized men receiving GnRH analogs to profoundly suppress testosterone secretion to denosumab or placebo. There were fewer morphometric vertebral fractures in the men who were given denosumab as a subcutaneous injection every 6 months compared to men receiving placebo injections. After a study (68) showing that denosumab altered surrogates for fracture in men similarly to the effect in women, the drug was approved for osteoporosis in men, regardless of etiology. Interestingly, denosumab increases forearm bone density, something not found with bisphosphonate treatment (60). In long term studies of bisphosphonates in women (69, 70) BMD rises and then plateaus after a few years of treatment. In contrast, studies in women have shown continued increases in BMD for at least 10 years with continued denosumab treatment (71). The consequences of this plus the impact of withdrawal of osteoporosis treatment will be discussed below.

As men age, there is thinning of trabeculae, whereas in women there is loss of trabecular number and the spacing between trabeculae increases (72). Thus, while the changes in vertebral fracture risk appear very similar in men and women, the impact on fracture could be different. DXA does not capture all of the changes with time. More recent studies (73) with high resolution peripheral quantitative computed tomography (HR-pQCT) also show sex-specific changes, but the studies are small. To my knowledge, there are no bone biopsy or HR-pQCT studies that demonstrate sex-dependent differences in response to therapy.

In women anabolic agents increase trabecular thickness and connectivity and increase cortical bone thickness. Of late, increased use of such agents as the initial treatment has been advocated for those patients at highest risk for fracture based on recent studies in women (74) demonstrating benefits to starting with anabolic treatment. In the United States, only teriparatide and abaloparatide are FDA approved for osteoporosis in men. There is another anabolic agent, romosozumab, that is approved for women, but there is no reason to believe that it would not work in men. There is one published report of improved fracture surrogates in men given romosozumab (75). Abaloparatide works similarly in men and women (76, 77). The use of anabolic agents, regardless of the patient's sex, is limited by inconvenience of treatment (both teriparatide and abaloparatide are administered as a daily subcutaneous injection) and cost. While romosozumab is given as a monthly injection in a clinician's office, its cost in the United States is similar to that of abaloparatide, which is somewhat cheaper than teriparatide. In Japanese women, a higher dose of teriparatide given weekly or semi-weekly has been found to be effective (78), but there have been no studies of similar preparations in Europe or the United States. Based on studies in women, anabolic agents should be considered, including off-label use, for men at the highest risk of fracture. In a 3-year study (79) of men and women with glucocorticoid-induced osteoporosis, teriparatide was shown to result in fewer spine fractures than alendronate. More recently, a study in women (80) showed that anabolic treatment led to fewer fractures than anti-resorptive treatment with risedronate. Until there are better surrogates for fracture, there will never be a study comparing fracture risk in men

treated with anabolic agents compared to anti-resorptives. The data from studies in women are convincing, and there is no physiological reason to question whether men would respond differently. A recent systematic review and meta-analysis of randomized controlled trials (81) led to the conclusion that osteoporosis drugs work the same in men and women.

In summary, initial treatment of osteoporosis in men should be comprehensive, with attention to diet, exercise, vitamin D, fall risk reduction, and home safety. After vitamin D is satisfactory, and possibly after dental work is completed, most men can be treated with bisphosphonates, usually oral alendronate. For those who cannot take an oral preparation, intravenous zoledronic acid is the drug of choice. For men at the highest risk for fracture, based on fracture history, DXA, risk factors, and risk calculators, a 1 to 2-year course of anabolic treatment should be considered, although teriparatide and abaloparatide can be prescribed for more than 2 years, if needed. For very high-risk patients, the anabolic therapy can be followed by 2 years of denosumab treatment, followed by consolidation with a bisphosphonate. For those men with CKD 4, denosumab is a good choice but must be continued indefinitely. Denosumab is also appealing for men on ADT who receive long-acting GnRH analogs every 6 months because they can receive denosumab at the same visit. However, there are rapid bone loss and potential vertebral fractures in women who have recently withdrawn from denosumab (82, 83). In one observational study in men (84) zoledronic acid prevented the loss of bone after men had discontinuation of denosumab.

Long-Term Management of Osteoporosis in Men

There are no long-term studies of osteoporosis treatment in men. Hence, all suggestions for management must be made from the few studies in women. The FLEX trial (69) showed that 10 years of alendronate in women led to fewer clinical vertebral fractures than 5 years of alendronate followed by 5 years of placebo tablets. The HORIZON extension trial (70) showed that a plan of 6 annual infusions of zoledronic acid was associated with fewer morphometric vertebral fractures than 3 annual infusions of zoledronic acid followed by 3 placebo infusions. Based on these studies plus some other information, a task force of the American Society for Bone and Mineral Research recommended an approach to long-term osteoporosis management (85). While the approach was aimed mostly at postmenopausal women, the task force recommended that it be applied to men as well. In this approach, the initial treatment period is 5 years for oral bisphosphonates and 3 years for zoledronic acid. At the end of the initial treatment period, the patient is re-assessed by history, physical examination, and repeat BMD. Those patients remaining at elevated fracture risk should continue treatment and be re-assessed again in 2 to 3 years. Those patients whose fracture risk has been demonstrably decreased by treatment can interrupt therapy and be re-assessed at 2 to 3 years. Beyond 10 years of treatment there are no studies, and so clinical judgement will be necessary to manage such patients. I have proposed, based on studies in women (86, 87) and men (65), that the interval between zoledronic acid infusions can be lengthened such that each

patient would receive 3 infusions of zoledronic acid over 5 years. This creates a 5-year initial treatment plan for the majority of people with osteoporosis: all but those at highest risk for fracture. For the latter group, initial therapy should be anabolic for the first 1 to 2 years, and then the patient would be placed on anti-resorptive agents.

While this approach to long-term osteoporosis management makes sense, it will likely never be supported by large randomized trials.

A summary of a practical approach to the evaluation of osteoporosis in men is shown in Table 5.

Table 5. Approach to Osteoporosis Treatment in Men
For All Men: Conservative Treatment Fall risk reduction/home safety Adequate calcium, vitamin D, dietary protein Weight bearing exercise/balance training Smoking cessation/minimization of alcohol intake
Treat Secondary Osteoporosis with Specific Therapy
Men with Borderline Fracture Risk Conservative treatment Repeat DXA in 2 to 3 years Use FRAX to demonstrate low risk
Osteoporosis by DXA, Osteopenia + Fracture, High Risk by FRAX Oral alendronate or risedronate or intravenous zoledronic acid Clinical reassessment every year Repeat DXA at 2 to 3 years Change Rx if response inadequate Repeat DXA at 5 years to consider drug holiday versus continued Rx
Very High Risk by DXA, FRAX, Clinical Findings Anabolic Rx for 1 to 2 years Then denosumab for 2 years Then 1 year of alendronate or 1 infusion of zoledronic acid DXA at 2 to 3 and 5 years

Drug holiday versus continued treatment based on fracture risk after treatment

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CONCLUSIONS

Despite the overall paucity of evidence underpinning osteoporosis evaluation and treatment in men, it is important to identify men at risk for fracture, evaluate them efficiently, and treat them. As more men live long enough to fracture, the burden of male osteoporosis will increase. In addition, because men with hip fracture are more likely to die after fracture (88), compared to women of the same age, improving diagnosis and treatment is likely to save lives, decrease suffering, and lead to lower costs.

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