Sex and Gender Considerations in Male Patients With Osteoporosis

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Abstract

Background Osteoporosis remains underrecognized and undertreated in both men and women, but men who sustain fragility fractures experience greater morbidity and mortality. While men exhibit advanced comorbidity at the time of hip fracture presentation, there are distinct sex- and gender-specific factors related to the pathophysiology and treatment of osteoporosis that further influence morbidity and mortality.

Questions/purposes With a selective review of the literature, we evaluated sex- and gender-based differences contributing to increased morbidity and mortality in men with osteoporosis.

Where are we now? Sex-specific differences in bone biology and morphology may affect the pathophysiology of osteoporosis, choice of pharmacotherapy, and surgical implant selection. Additionally, estrogen metabolism may play a key role in both fracture prevention and healing. Gender-based differences in recommendations for screening

and prevention between men and women may influence the severity at which osteoporosis is recognized. Primary, secondary, and tertiary prevention efforts in men lag behind those of women. This may be due to a lack of consensus regarding screening guidelines for osteoporosis in men but may be attributed to lack of awareness in the physician and patient about osteoporosis and its potentially debilitating consequences.

Where do we need to go? These disparities are a call to action for healthcare providers to raise awareness for early prevention and treatment of this potentially debilitating disease, particularly in men.

How do we get there? Continued prospective research on the differences between men and women diagnosed with osteoporosis is needed, as well as sex-specific stratification of data in all studies on osteoporosis.

Introduction

Osteoporosis affects both aging women and men but remains an underrecognized and undertreated disease. Despite its prevalence across both sexes, osteoporosis does not affect men and women equally [19, 30, 34]; there are important sex- and gender-based distinctions between men and women that should be acknowledged. The Institute of Medicine recognized the importance of using the term “sex” to refer to factors that are primarily biologic in origin and “gender” to refer to social and cultural influences based on sex [18]. This distinction is important to understand, as both sex- and gender-based characteristics influence the pathophysiology, diagnosis, prognosis, and treatment of osteoporosis and its sequelae. These sex and gender differences ultimately influence the rates of morbidity and mortality in men who sustain a hip fracture [8, 27, 30], as

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men are more likely than women to have osteoporosis that is undiagnosed or undertreated [19, 30, 34].

Sex-specific differences in the development of bone exist [58] and may have consequences on the later pathophysiologic process of osteoporosis in men and women. Gender-based differences in awareness of osteoporosis, the utilization of screening tests, and subsequent recognition of decreased bone quality influence the manner in which men and women present with osteoporotic fractures. While initiation of medical treatment for individuals at risk for future fragility fractures is paramount, there may be sex-specific factors influencing the pharmacologic efficacy and utilization. Additionally, men and women may experience disparate clinical outcomes after fragility fractures due to differences in fracture healing related to biologic reasons or choice of surgical implant.

In this review, we explore the following research questions: (1) What are the sex-based differences in bone biology, bone morphometry, osteoporosis pathophysiology, and fracture healing that may influence morbidity and mortality in patients with osteoporosis? (2) What are the gender-based differences in screening and primary prevention for osteoporosis? (3) What are the gender-based differences in medication response and adherence to treatment recommendations for osteoporosis?

Search Strategy and Criteria

Articles were found through MEDLINE and Google Scholar. Initial search criteria included “osteoporosis” AND “sex” or “gender.” Initially 336 articles were identified. The search was further refined to identify articles discussing osteoporotic fractures. Addition of “fracture” as a search criterion narrowed the number of articles down to 135. Further analysis of these articles for content on the influence of sex and gender on osteoporosis and for clinically applicable screening and treatment guidelines yielded a total of 60 articles to be included in our selective literature review.

Sex-based Differences

Bone Biology

Differences in clinical outcomes of osteoporosis in men and women may be rooted in the biologic properties of bone. Work by Barrett-Connor et al. [5] suggests there are sex-specific differences in the number of osteoprogenitor cells, hormone response, and hormone regulation between sexes [33, 44], which could potentially influence the normal growth of bone and the remodeling that occurs after a fracture.

Bone Morphology

The bones of men have certain morphologic attributes that set them at a lower risk than women for developing osteoporosis. The diameter of bone is much greater in men and provides a greater moment of inertia [60], which is a strong determinant for torque strength. Additionally, men have a greater muscle mass [60], which gives them more agility and padding in case of a fall.

Pathophysiology of Osteoporosis

Qualitative and quantitative deficiencies in bone drive the development of osteoporosis. The strength of bone is related to the mass and quality of the bone. While dual-energy x-ray absorptiometry (DEXA) measurements are capable of defining bone mass, it is difficult to define the quality of bone, given the lack of standard laboratory tests to evaluate its microarchitecture. Men undergo a slow attrition of bone with age [50], but only women experience a profound period of rapid bone resorption as they enter into menopause [10], leading to loss of microarchitecture that may remain unreversed.

Additionally, osteoporosis is adversely affected by secondary diseases. Secondary causes for bone loss are remarkably common in patients with hip fractures, as Edwards et al. [17] found more than 80% of patients with hip fractures had an unrecognized cause for bone loss, with vitamin D deficiency being most common. Osteoporosis in men is more likely to be a marker of a systemic disease. While secondary causes for osteoporosis exist in 20% to 40% of women, 65% of men who have osteoporosis have other contributory diseases [15, 16, 38]. These secondary causes should raise concern on the part of the clinician to evaluate and treat the underlying disease process, which can include autoimmune diseases, such as rheumatoid arthritis, alcoholism, excessive smoking, and gonadal deficiencies, among others [25]. Men have a three times lower risk of hip fracture than women after adjusting for age and other risk factors [9], indicating those men who sustain fragility fractures must experience a substantially greater magnitude of bone loss compared to women. This amount of bone loss may be driven by a secondary cause of osteoporosis but may also serve as a reflection of the level of deconditioning and frailty seen in men with hip fractures.

Fracture Healing

The estrogen-deficient state experienced by osteoporotic individuals may adversely affect fracture healing [6]. Furthermore, animal studies suggest the presence of estrogen

will enhance fracture healing [31, 51, 55]. Both men and women experience lower estrogen levels as aging occurs [21], but the effects on bone quality may be more profound in men because of the lower likelihood of early diagnosis and primary prevention. The opportunity for the development of therapeutic agents that target estrogen metabolism in men was mentioned earlier in regard to primary prevention, but it should be noted the same agents may have a potential role in aiding fracture healing.

During the time of surgical repair of a fracture in a patient with osteoporotic bone, the surgeon's choice of implant is affected by the patient's bone morphology. As mentioned earlier, men generally have bones with a larger diameter, which influences the size of the implant used and the ability of the implanted device to gain purchase within the skeleton. The implant size may affect postoperative outcomes, as a man with a larger bone structure can be fitted with a larger implant that is stronger and less likely to experience failure regardless of the quality of underlying bone. This becomes more important for fractures of weightbearing bones fixed using load-bearing devices, such as a cephalomedullary device for an intertrochanteric fracture. The role of screw purchase becomes prominent in other fractures fixed with load-sharing constructs, such as tibial plateau fractures and proximal humerus fractures. These fractures are notorious for the potential of fixation failure with subsequent malalignment. The greater bone mass generally present in men should provide an advantage for fracture healing in appropriate alignment, as greater screw fixation can be obtained. The intramedullary canals in men are larger and can permit larger intramedullary implants. The larger-sized implants provide greater biomechanical stability than smaller-diameter implants [42], which aids in fracture healing. Despite these advantages in implant selection and screw fixation being more common in men, data from hip fracture studies suggest men continue to experience worse overall morbidity and mortality than women [28].

Gender-based Differences

Screening and Primary Prevention of Osteoporosis

Osteoporosis is common, with considerable morbidity and mortality. If decreased bone mineral density (BMD) can be recognized early, lifestyle modifications and pharmacologic interventions can be initiated for primary prevention of low-energy fractures. Many expert panels, including the National Osteoporosis Foundation (NOF) [53], International Society for Clinical Densitometry (ISCD) [53], Association of Clinical Endocrinologists (ACE) [24], the US Preventive Services Task Force (USPTF) [36], and the

American Academy of Family Physicians (AAFP) [3], recommend initiation of routine screening using BMD testing in women older than 65 years [4]. However, there is no consensus on recommendations for screening of men (Table 1). While the NOF and ISCD recommend using BMD screening in men older than 70 years or men older than 50 years when clinical risk factors are present, the ACE, USPTF, and AAFP do not recommend routine screening for men. The lack of emphasis on screening and primary prevention of osteoporosis in men leads to a failed recognition of those with decreased BMD, which later manifests with the findings of lower vitamin D levels in elderly men presenting with hip fractures [48]. Men at highest risk for fracture must be recognized early to allow for initiation of primary preventive strategies.

Unfortunately, efforts for preventing future fractures are also failing; men believe osteoporosis is a more serious disease for women and they are less likely to develop osteoporosis [2]. These misconceptions are coupled with a lack of physician awareness [22] and a lack of consensus regarding screening guidelines. There is hope, however, as the implementation of standardized screening and treatment protocols in the emergency department setting have increased the diagnosis of osteoporosis, allowing for initiation of treatment [1].

Medication Response and Adherence

Pharmacologic therapy for osteoporosis is paramount to preventing fragility fractures. Oral calcium and vitamin D supplementation are the initial steps in treatment for both men and women, with no gender-based difference in recommendations to provide at least 1000 mg calcium and at least 800 IU vitamin D per day to decrease the risk of fracture [57]. The role of estrogen in preventing fractures and enhancing fracture healing has provided a promising basis for treatment possibilities [47]. Higher serum estrogen levels are associated with higher BMD in men [56], with the incidence of osteoporosis increasing as estradiol levels fall [20]. These findings present an opportunity to use medications that alter the metabolism of estrogen, such as selective estrogen receptor modulators (SERMs), for fracture prevention. While these medications have provided promising results in women [11, 13], they have no effect on men because they are degraded before reaching a functional level [14]. However, future generations of SERMs lack the feminizing effect and may affect men. While more data are available regarding the effects of estrogen levels on BMD in both sexes, the role of testosterone has also been explored. A study of middle-aged and older men found increased levels of bioavailable testosterone were linked to increased cortical density and muscle

Table 1. Recommendations for DEXA testing

Expert agency	Women	Both	Men
US Preventive Services Task Force	All women > 65 years; women 60 to 64 years at high risk (≤ 154 pounds, not on estrogen)		
National Osteoporosis Foundation	All women > 65 years; postmenopausal women discontinuing estrogen	Adults who have a fracture after age 50 years or who have a condition (eg, rheumatoid arthritis) or are taking medication (eg, glucocorticoids ≥ 5 mg/3 months) associated with low bone mass or bone loss; anyone being considered for pharmacologic treatment or on therapy	All men > 70 years
American Academy of Family Physicians	All women > 65 years; women > 60 years at increased risk of osteoporotic fractures		
American Association of Clinical Endocrinologists	All women > 65 years; all adult women with history of fracture not caused by trauma; younger postmenopausal women with clinical risk factors for fracture (≤ 127 pounds or family history of hip or spine fracture)		
American College of Obstetricians and Gynecologists	All postmenopausal women > 65 years or who have a history of fracture; postmenopausal women < 65 years who have one or more risk factors for osteoporosis		
Osteoporosis Society of Canada	Postmenopausal women		Men > 50 years with at least one major or two minor risk factors
American College of Physicians			Men at increased for osteoporosis who are candidates for drug therapy
International Society for Clinical Densitometry	Women > 65 years; postmenopausal women < 65 years with risk factors for fractures; women during menopausal transition with clinical risk factors for fracture, such as low body weight, prior fracture, or high-risk medication use	Adults with a fragility fracture or who have a disease or are taking medications associated with low bone mass or bone loss; anyone being considered for pharmacologic therapy or on therapy	Men > 70 years; men < 70 years with clinical risk factors for fracture

DEXA = dual-energy xray absorptiometry.

area [59]. However, the importance of estrogen levels over testosterone's influence on bone mineralization was emphasized in a case report of a 28-year-old man who was osteopenic due to lack of an estrogen receptor although he had normal testosterone levels [54].

Another potential class of therapeutic agents is antiresorptive medications, such as bisphosphonates. These medications provide relatively comparable prevention of vertebral and nonvertebral fractures in both sexes [23, 26, 43, 45, 46], although the data on men are limited due to

underenrollment of men in pharmacologic studies [39, 49]. Anabolic agents, such as parathyroid hormone (PTH) 1-34, PTH 1-84, and strontium ranelate, lead to comparable bone mass enhancement and fracture protection in both sexes [29, 35, 40]. Again, data are limited due to an underrepresentation of men in clinical trials.

Women and men may have different rates of side effects from the array of agents used for osteoporosis. The more notable adverse effects of bisphosphonates include hiatal hernias, dyspepsia, osteonecrosis of the jaw, and a newly

defined class of characteristic low-energy subtrochanteric fractures. Gastrointestinal side effects are well documented in women, although they are also seen in men but at an unclear ratio regarding disease incidence in each sex [12]. Osteonecrosis of the jaw is an exceptional rare entity without sex specificity [41]. The characteristic subtrochanteric fracture associated with bisphosphonate use over 5 years is newly reported and has been described mainly in women [32, 37, 52]. The true etiology of bisphosphonate-related fractures is unclear and may manifest in a different manner or time in men.

While established guidelines for the treatment of osteoporosis exist, compliance with prescribed treatment is a barrier to improved outcomes. Compliance with anti-osteoporosis medication improves immediately after hip fracture but diminishes over time [7]. The rate of medication noncompliance is influenced substantially by gender, as men were twice as likely to demonstrate non-compliance with antiosteoporosis therapy as women [7]. The importance of adherence to treatment must be emphasized, especially in the male population, in which there is decreased awareness and compliance.

Discussion

Osteoporosis is a disease affecting both men and women, but men experience greater morbidity and mortality [8, 27, 30] despite biologic advantages, such as greater bone size, more surrounding muscle mass, a steadier rate of bone loss, and the potential for better implant fixation. This may be at least partially driven by the fewer available pharmacologic treatments available to men. Osteoporosis remains unrecognized in all patients, especially in men, as primary, secondary, and tertiary prevention efforts in men lag behind those of women. Gender-influenced factors, such as the lack of consensus regarding screening guidelines for osteoporosis in men and a lack of awareness in the physician and patient about osteoporosis, certainly contribute to these disparities.

The reader should be aware of a number of limitations in the literature and this review. First, much of the data in the literature is focused on osteoporosis in women, and prospective data on men with osteoporosis are lacking. Second, the smaller number of men with osteoporosis makes comparisons between different outcomes more difficult. Overall, more powerful data on men with osteoporosis are needed to better understand why men suffer from increased morbidity and mortality after sustaining hip fractures.

Where are we now? There are sex-specific differences in bone biology and morphology that may influence the pathophysiology of osteoporosis in ways that are not yet understood. Men are more likely to have a secondary cause

of osteoporosis, but their risk of fracture is still less than that of women, after controlling for age. Despite this, men who present with hip fractures experience worse outcomes than women. While there are advantages toward bone healing afforded to men because of their greater bone size, these positive effects are likely negated by the magnitude of bone loss and general deconditioning affecting those who suffer a fragility fracture.

Where do we need to go? The disparities in clinical outcomes between men and women after hip fracture are disturbing. Despite a lower risk for fracture, men experience far more morbidity and mortality after hip fracture and are less likely to adhere to recommendations for primary, secondary, and tertiary prevention. These disparities in prevention, treatment, and outcomes are of great concern to the public health, as the sequelae and economic burden of osteoporotic fractures will grow as our population continues to age. Both patients and healthcare providers need to be made more aware of the need for education and outreach regarding osteoporosis, as protocols improve diagnosis and treatment. Osteoporosis needs to be recognized early in both men and women by initiating the appropriate diagnostic studies and effective therapeutic agents to avoid fragility fractures.

How do we get there? Well-constructed laboratory-based and clinical investigations that include sex and gender considerations are needed to better understand the driving factors behind disparities in the diagnosis and treatment of osteoporosis between men and women. Implementation of efforts to diagnose and appropriately treat all patients at risk for osteoporosis is paramount to reducing the tremendous burden to our healthcare system and society created by this potentially debilitating disease, but special emphasis should be placed on raising healthcare provider awareness about osteoporosis in men.

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