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Osteoporosis in Men

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ABSTRACT

Osteoporosis is defined as "a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture". Approximately 40–50% of women sustain osteoporotic fractures in their lifetime; as such, it is appropriate that studies initially focused upon females. Despite an increased recognition of osteoporotic fractures in men, there continues to be neglect of this disease in males. This ongoing neglect is inappropriate as 25–33% of men in some populations will sustain osteoporotic fractures in their lifetime. Testosterone plays an important role in male skeletal health. However, recent data suggest that estrogen may in fact be the dominant hormone regulating skeletal status in both men and women. BMD measurement may be utilized for osteoporosis diagnosis and to assist with fracture risk prediction in men prior to their sustaining a fracture. Recognizing this need, the International Society for Clinical Densitometry (ISCD) recommended and recently reaffirmed use of a BMD T-score of -2.5 or below be utilized to diagnose osteoporosis in men. Androgen therapy of hypogonadal men may be considered with the caveat that data do not exist to document that this treatment reduces fracture risk. At this time, the data is inadequate to support use of androgen treatment in eugonadal men with osteoporosis. Parathyroid hormone treatment does increase BMD; existing studies have not been of adequate size or duration to document fracture reduction efficacy. Bisphosphonate therapy increases BMD, reduces vertebral fracture risk and is considered the standard of care for osteoporotic men at this point in time. **(Arq Bras Endocrinol Metab 2006;50/4:764-774)**

Keywords: Osteoporosis; Androgens; Estrogens; Teriparatide; Bisphosphonates

RESUMO

Osteoporose em Homens.

A osteoporose é definida como "uma doença esquelética sistêmica caracterizada por baixa massa óssea e deterioração da microarquitetura do tecido ósseo com conseqüente aumento da susceptibilidade a fraturas". Aproximadamente 40–50% das mulheres apresentarão uma fratura osteoporótica durante suas vidas, e por isso os estudos iniciais focalizaram o sexo feminino. A despeito do reconhecimento cada vez mais freqüente da ocorrência de fraturas osteoporóticas em homens, a doença continua sendo negligenciada no sexo masculino. Isto não é apropriado na medida em que 25–33% dos homens em algumas populações apresentarão fraturas osteoporóticas durante suas vidas. A testosterona exerce um importante papel na integridade esquelética masculina, contudo dados recentes sugerem que os estrógenos são de fato os hormônios dominantes na regulação esquelética em ambos os sexos. A medida da densidade mineral óssea pode ser utilizada no diagnóstico e para avaliar o risco de fraturas, e a ISCD recomenda que o escore T de -2.5 ou menos seja usado como critério diagnóstico no homem. A terapia androgênica no hipogonadismo masculino deve ser

considerada, embora não existam dados sobre redução do risco de fraturas, e no momento não há dados que suportem o uso de andrógenos em homens eugonádicos com osteoporose. O tratamento com paratormônio aumenta a massa óssea, porém os estudos existentes não apresentam amostra e duração suficientes para documentar redução no risco de fraturas. Os bisfosfonatos aumentam a massa óssea, reduzem o risco de fraturas e são considerados como tratamento-padrão para o homem osteoporótico no presente momento. **(Arq Bras Endocrinol Metab 2006;50/4:764-774)**

Descritores: Osteoporose; Androgênios; Estrogênios; Teriparatida; Bisfosfonatos

DEFINITION AND EPIDEMIOLOGY

OSTEOPOROSIS IS DEFINED AS "a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture" (1). Approximately 40–50% of women sustain osteoporotic fractures in their lifetime (2); as such, it is appropriate that studies initially focused upon females. Despite an increased recognition of osteoporotic fractures in men, there continues to be neglect of this disease in males (3-5). This ongoing neglect is inappropriate as 25–33%% of men in some populations will sustain osteoporotic fractures in their lifetime (6). Furthermore, as is the case in women, osteoporotic fracture incidence rises exponentially in men with advancing age (though the rapid increase in fracture risk begins later, at approximately age 70, in men) (7). As such, males account for approximately 30% of hip and 20% of symptomatic vertebral fractures (8). Consistent with a major fracture burden among men, it is estimated that a 50-year-old male has a 17% chance of sustaining a hip fracture in his remaining lifetime (9). As such, it is clear that osteoporosis is a major health problem for both women and men. Moreover, due in large part to the increasing number of older adults, it is expected that the number of osteoporotic fractures in men will increase substantially in the future.

It is widely appreciated that osteoporotic fractures cause substantial morbidity and mortality in women. Though not as well studied in men, similar adverse outcomes such as back pain, kyphosis and height loss occur following vertebral fractures in men. Additionally, other morbidities, including loss of energy, impaired sleep and emotional difficulties, appear to be more common in men following vertebral fracture (10). Similarly, hip fractures engender substantial morbidity; one year after hip fracture, over 50% of men require institutionalization and only ~20% return to their pre-fracture level of function (11). Furthermore, over 30 studies report higher mortality following osteoporotic fracture among men than observed in women. For example, a large five-year prospective study in Australia found the mortality ratio following hip fracture to be 3.2 for men and 2.2 for women (12). Even higher mortality was observed in a recent case-control study in the UK with only 37% of men surviving at two years post hip fracture (13). This increase in mortality among men is observed not only following hip, but also vertebral (14) and shoulder fracture (15). Potentially, the higher risk of death may reflect greater co-morbidities and suggest that men who sustain osteoporotic fractures are more frail than their female counterparts. Consistent with this, the recent UK report (13) found impaired pre-fracture function to be a major determinant of mortality. While further work to define the cause(s) of the greater mortality after hip fracture in men is warranted, it is certainly reasonable for clinicians to assume that men who are frail and/or have multiple co-morbidities be viewed as being at higher risk for adverse outcomes, notably infections such as pneumonia and septicemia (16), following osteoporotic fracture.

PATHOPHYSIOLOGY

The bone mass possessed by any older adult, male or female, reflects peak mass achieved at skeletal maturity and all subsequent losses associated with advancing age. At skeletal maturity, males attain higher bone mineral density (BMD), as measured by dual energy X-ray absorptiometry (DXA), than females (17). This difference is due to larger bone size as the area of male bones is approximately 35–40% larger than female bones (18). In fact, a recent cross-sectional study utilizing quantitative computed tomography found volumetric BMD, the true "density" of bone, to be higher in women than in men at age 20–29 (18). Though the volumetric density is lower in males, larger bones have greater structural strength. This larger bone size of men contributes to lower risk of osteoporotic fracture.

Despite this larger bone size, osteoporotic fractures are common in older men as noted above. This reflects substantial bone loss with advancing age (19) with men at age 90 having over 40% lower volumetric BMD than present in 20–29 year olds (18). Longitudinal data from the Rotterdam study finds that the

decline in femoral neck BMD accelerates with age in older men (20). This bone loss with advancing age may be due to a multitude of factors; as is the case in women, the etiology of bone loss in men includes hypogonadism, excessive alcohol intake, glucocorticoid excess, hyperparathyroidism, hyperthyroidism, hypercalciuria, antiepileptic drug usage, calcium / vitamin D insufficiency and reduction in physical activity / immobilization, among others (21). However, hypogonadism, glucocorticoid excess and alcohol use are major factors and fell to contribute to osteoporosis in approximately 20% of men with this disease.

The development of estrogen deficiency at menopause has long been associated with rapid bone loss and fell to play a critical role in osteoporosis pathogenesis in women. As androgen levels decline slowly with advancing age in men, males do not experience a similar mid-life phase of rapid bone loss. Absence of this rapid loss may explain the different histologic patterns observed with advancing age between men and women. Specifically, immediately following menopause, estrogen deficiency leads to elevated bone resorption, which causes trabecular perforation thereby weakening bone structure out of proportion to loss of density. Given the absence of this phase of enhanced osteoclast activity, trabecular architecture remains intact but progressively thins with age in men (22). However, in situations where androgen loss is abrupt, e.g., hypogonadism induced by surgery or androgen deprivation therapy as part of prostate cancer treatment, rapid bone loss is observed (23) and fracture risk is increased (24). Importantly, testosterone deficiency is associated with deterioration of trabecular architecture as determined by micro MRI (25). This microarchitectural change would be expected to reduce the mechanical strength and increase fracture risk. Moreover, the possibility that testosterone treatment of hypogonadal men may improve trabecular architecture was recently suggested (26).

It is clear from the above that testosterone plays an important role in male skeletal health. However, recent data suggest that estrogen may in fact be the dominant hormone regulating skeletal status in both men and women (27). This possibility was initially suggested by case reports of men with absent estrogen receptors or with aromatase deficiency in whom testosterone is unable to be converted to estrogen (28,29). In such men, estrogen treatment reduced bone turnover and increased bone mass (30,31). Subsequently, estrogen, not testosterone concentration, has been found to correlate with bone density in older men and appears to be the dominant hormone regulating bone resorption (32). While these studies suggest that selective androgen receptor modulators could be a therapeutic approach for osteoporosis treatment in men, use of estrogen for this indication is inappropriate.

From the above, it is apparent that sex steroid inadequacy often contributes to the development of osteoporosis in men. However, as noted above, other diseases, so called "secondary causes" of bone loss, are found in 30–60% of osteoporotic men (33,34). As such, evaluation to detect, and if possible to correct, these conditions is appropriate in men with low bone mass or low-trauma fracture. The most common conditions to consider in such an evaluation are presented in table 1. Hypogonadism, corticosteroid use and alcohol abuse constitute the majority of secondary causes (21). Additionally, evaluation for hypercalciuria ($\geq$ 4 mg / kg / day) is also worthy of consideration, as this condition may be present in up to 15% of osteoporotic men (35,36).

When no clinically evident causes of osteoporosis are noted, and the laboratory evaluation is unrevealing, the diagnosis of idiopathic osteoporosis is appropriate. Idiopathic osteoporosis classically presents as vertebral fracture in relatively young men; the mean age in a recent series being 50.5 years (37). In such individuals, histomorphometric analysis of bone biopsies often reveals impairment in bone formation (38). Recent work suggests that this impairment reflects osteoblast dysfunction (39). Potential etiologies of idiopathic osteoporosis include altered estrogen status, low IGF-1 concentration and LRP5 gene mutations (40-42). As of this writing, none of these potential etiologies is amenable to specific corrective therapy.

In elderly men with no identifiable secondary cause, the diagnosis of age-related, rather than idiopathic, osteoporosis seems appropriate. Some of this "age-related" osteoporosis likely reflects genetic acquisition of low peak bone and a family history of fracture should be sought as relatives of male osteoporotic patients have lower than average bone mass (43,44).

Table 1. Secondary causes of osteoporosis in men.

• Glucocorticoid excess (exogenous or endogenous)
• Hypogonadism
• Other endocrine disease (hyperparathyroidism, hyperthyroidism)
• Alcohol abuse
• Tobacco use
• Gastrointestinal disease (malabsorption, post-gastrectomy)
• Malignancy (notably multiple myeloma)
• Medications (heparin, excess thyroxine, antiepileptic drugs)
• Idiopathic hypercalciuria

DIAGNOSIS OF OSTEOPOROSIS IN MEN

Historically, osteoporosis was diagnosed only after the occurrence of a low-trauma fracture. In 1994, the World Health Organization (WHO) classification system was published allowing osteoporosis to be defined as a bone mineral density that is 2.5 or more standard deviations below that of a young normal adult i.e., a T-score of -2.5 or below (45). However, this classification system applied only to postmenopausal women and, until recently, no consensus densitometric definition of osteoporosis in men existed (8). Given the high prevalence of osteoporotic fracture and projected increase in men, the ability to identify men at risk prior to their fracture is required. Fortunately, as is the case in women, low BMD in men is associated with an increase in fracture risk (46,47). As such, BMD measurement may be utilized for osteoporosis diagnosis and to assist with fracture risk prediction in men prior to their sustaining a fracture. Recognizing this need, the International Society for Clinical Densitometry (ISCD) recommended and recently reaffirmed use of a BMD T-score of -2.5 or below be utilized to diagnose osteoporosis in men (48,49).

When utilizing DXA in men, it must be recognized that the measured lumbar spine BMD will often be elevated by the presence of degenerative arthritis and/or other calcifications (50). In fact, some studies do not demonstrate lower BMD with advancing age in men or a relationship between spine BMD and fracture risk (46). These observations almost certainly reflect elevation of the measured BMD by degenerative disease, an extremely common phenomenon among older men (50).

The normal population reference database to utilize for T-score derivation in men remains controversial. Briefly, data suggest that men and women with the same BMD are at the same risk for future fracture. As such, some experts recommend use of a female normative database to derive T-scores in men (51,52). However, there is concern that use of a female normative database will lead to the "underdiagnosis," i.e., identification of too few men who will ultimately fracture, as having osteoporosis. Thus, the ISCD currently recommends use of a male normative database for T-score derivation in men, a position that will doubtlessly be revisited in the future (53). Interestingly, a recent small observational study found that changing from a male to female normative database for T-score derivation in men would only result in a T-score "improvement" of 0.3 at the lumbar spine and femur neck (54). Finally, it is important to recognize that the WHO classification system (i.e., normal, osteopenia, osteoporosis) does not apply to healthy men under age 50. As such, the Z-score, not the T-score, should be reported if BMD measurement is performed in healthy men under age 50 (49).

Expert group recommendations for performance of BMD measurement in men have been published (8,52,55,56). A summary of these recommendations is presented in table 2. It is important to note that the cost-benefit relationship of performing "screening" bone mass measurement in men at a given age, as has been recommended for women in the United States, has not been determined.

As is the case among women (57), the majority of fragility fractures in men occur in individuals whose BMD T-score is not in the osteoporotic range (47). For example, in the Rotterdam study, 44% of non-vertebral fractures in women, and only 21% in men, occurred in individuals whose T-score was below -2.5. Such data indicate the need for development of more sensitive paradigms to identify individuals who are at higher risk for fracture. This need will soon be met by publication of a forthcoming WHO document that will utilize clinical factors to estimate absolute fracture probability over 10 years. Importantly, clinical risk factors that increase the risk for future fracture in women, including prior fracture and glucocorticoid use, are similarly predictive for future fracture in men (58,59). Such an approach will allow treatment recommendations to be based on this estimation of fracture risk, not simply on the BMD T-score (60). Use of fracture probability will allow thresholds to be defined at which osteoporosis treatment becomes cost effective. It is anticipated that this approach will be applied not only for women, but to men as well, thus allowing for treatment guidelines to be promulgated for men with osteoporosis. Using this approach and data from Sweden, it was recently found that intervention threshold are quite similar for men and women over age 60 (61). This is not surprising as the 10 year probability of osteoporotic fracture is quite similar for men and women with low BMD at many ages (59).

CLINICAL EVALUATION

A history and physical examination is indicated for all men with osteoporosis diagnosed either by bone mass measurement or by the occurrence of a low-trauma fracture. In men with low trauma fracture, the clinically obvious caveat that osteoporosis does not cause all low-trauma fractures is worthy of emphasis and the

Table 2. A summary of indications for bone mass measurement in men.

- Prior low-trauma fracture
- Radiographic osteopenia
- Hypogonadism, including that induced by androgen deprivation therapy
- Use of glucocorticoid therapy or other medications that cause bone loss
- Hyperparathyroidism
- Malabsorption/prior gastrectomy

multitude of other conditions that can cause bone loss and fractures (e.g. bone metastases, osteomalacia, multiple myeloma, etc.) must be considered. In this regard, the classical clinical history of osteoporotic fracture pain, i.e., relieved by laying down, worsened with activity, is reassuring, but does not obviate the need for radiographic or other imaging evaluation in men with low trauma fracture.

In men with osteoporosis diagnosed by BMD measurement or fracture, laboratory evaluation is indicated to evaluate for potential secondary causes of bone loss. A reasonable initial evaluation includes a complete blood count, serum calcium, creatinine, AST, TSH, total testosterone and 25OHD measurement (62). It could be argued that measurement of serum 25OHD is unnecessary if calcium and vitamin D supplementation is anticipated. However, given the widespread occurrence of vitamin D inadequacy (63), coupled with the modest increase in 25OHD that occurs with "routine" supplementation (64), which may not assure normalization of vitamin D status, routine measurement of 25OHD in men with osteoporosis seems prudent.

Additional laboratory evaluations to consider in men with osteoporosis are noted in table 3 (65). Examples in which more extensive evaluation may be appropriate include, but are certainly not limited to, performance of serum and urine electrophoresis in younger men with vertebral fractures and measurement of prostate-specific antigen in men with bony sclerosis on DXA. Measurement of skeletal turnover markers, such as bone specific alkaline phosphatase, osteocalcin, n-telopeptide of type 1 collagen (NTx), etc. may be considered based upon the clinician's practice. As is the case in women, elevated bone turnover is associated with increased fracture risk in men that is independent of BMD (66).

Other laboratory considerations include evaluation of adrenal and parathyroid function, estradiol, sex hormone-binding globulin, IGF-1 and bone biopsy. These more esoteric measures are not routine and their use should be individualized based upon the clinical presentation. Outside of patients with renal failure, tetracycline labeling with subsequent biopsy for bone histomorphometric evaluation is not often required.

Table 3. Considerations in the laboratory evaluation of men with osteoporosis.

- CBC
- ESR
- Serum calcium/phosphorus/creatinine and ALT or AST
- TSH
- Free testosterone
- 24 hour urine calcium
- 25 hydroxyvitamin D
- Serum/urine electrophoresis
- PSA
- PTH
- Bone turnover markers; e.g., osteocalcin, bone specific alkaline phosphatase, NTx, etc.

It is worthy of emphasis that age, in and of itself, should not preclude evaluation and treatment of men with osteoporosis. Though the average male life expectancy at birth in the United States is approximately 75 years, a man at that age, on average, is expected to live an additional 10.5 years (67). Given the increased rate of bone loss observed and increasing fracture risk in men of this age, osteoporosis evaluation and treatment is warranted.

TREATMENT

The overall goal of osteoporosis treatment in men, as in women, is fracture prevention. A multifaceted approach, involving optimization of nutritional, physical and pharmacologic factors, is ideal.

The classical osteoporosis nutritional approach focuses on attainment of adequate calcium and vitamin D. However, overall nutritional assessment is necessary as undernutrition, despite an epidemic of obesity, is extremely common among older adults. In fact, the Royal College of Physicians has emphasized the nutritional vulnerability of those over age 65 and estimated that 12% of community dwelling elders are at medium or high risk of malnutrition (68). Moreover, the prevalence of undernutrition was estimated at 40% of those admitted to the hospital. In patients hospitalized with hip fracture, the simple provision of additional caloric supplementation improves outcomes (69).

After evaluating overall nutritional status, focusing upon calcium and vitamin D intake is reasonable as supplementation with these nutrients slows bone loss and reduces fracture risk in elderly women (70). Though less well studied in men, it seems probable that similar effects would be observed (71). Consistent with this, a recent two-year prospective study in 167 men of mean age 62 years found the daily provision of an additional 1,000 mg of calcium with 800 IU of vit-

amin D_3 to suppress PTH and reduce bone loss (72). As such, recommending a daily intake of approximately 1,200 mg of elemental calcium through diet plus supplements, if necessary, for men with osteoporosis is appropriate (73).

Additionally, vitamin D supplementation is often necessary as even in locations with abundant sunshine, vitamin D inadequacy is common (74). Recent expert consensus suggests that the daily oral intake of vitamin D should be approximately 1,000 IU / day (75,76) with documentation of adequacy by measurement of serum 25OHD considered as noted above. A reasonable goal is to maintain the serum 25OHD above ~32 ng / ml (70–80 nmol / L) as values below this may be associated with secondary hyperparathyroidism. Moreover, low vitamin D status is associated with muscle weakness and increased falls risk and simple provision of vitamin D reduces fracture risk (77). Using the cutpoint of 32 ng / ml, a recent UK report found that 54 / 56 men with osteoporosis attending a bone clinic had vitamin D inadequacy (78). As such, it is clear that vitamin D inadequacy is a common concern in men with osteoporosis.

Though calcium and vitamin D have received the most study, the possibility of phosphorus inadequacy has recently been suggested as a contributor to osteoporosis therapy non-response in patients receiving phosphate binding calcium supplementation and pharmacologic osteoporosis therapy (79). In older, undernourished individuals, appreciation of this possibility and provision of calcium phosphate supplements seems prudent.

Physical measures, with a goal being reduction of falls risk, are often an important component of osteoporosis treatment (80). Simplistically, weight-bearing exercise is ideal and activities leading to spine flexion are to be avoided. However, evaluation by a physical therapist for provision of an exercise program, assessment of falls risk and evaluation for gait assistive devices (e.g., canes and walkers) may be indicated. The importance of falls assessment as part of a fracture risk reduction program cannot be overemphasized as more than one-third of people over age 65 fall annually (81) and approximately 5% of falls lead to fracture. Factors intrinsic to the patient, and those within the individual's environment, should be identified and modified when feasible. A consensus approach to evaluating falls risk has been published by the American and British Geriatric Societies and includes evaluation of medications, vision, neuromuscular function and gait / balance (82). In this regard, hip protectors would seem to be a logical approach to fracture reduction in selected patients and some reports have documented efficacy in reduction of hip fracture in nursing home residents (83). However, the most recent Cochrane Review found only a marginally significant reduction in hip fracture incidence and thus "casts some doubt on the effectiveness" of hip protectors (84). Further work in this field is necessary as this simple, inexpensive option is clinically attractive. Moreover, focusing solely upon increasing bone mass seems unlikely to prevent hip fractures in individuals with recurrent falls.

As noted above, hypogonadism in men is associated with bone loss and deterioration of trabecular architecture. Given this, it should be expected that androgen-deprivation therapy will be associated with increased fracture risk; an assumption that has been confirmed (24). Moreover, androgen deprivation is associated with a reduction in lean mass and an increase in fat mass. It is plausible that the decline in muscle mass observed with advancing age is due to androgen deficiency. Thus, it is intuitive that hypogonadism causes both bone and muscle loss; a combination which should lead to an increase in osteoporotic fracture risk. This scenario, combined with other potential favorable effects of testosterone replacement, likely has led to the marked increase in prescription of androgen therapy in the last decade (85). Numerous cross-sectional and some longitudinal studies document that serum total testosterone declines with advancing age (86). Additionally, as sex hormone binding globulin increases with gain, total testosterone measurement underestimates age-related changes in testosterone available to target tissues such as bone and muscle (87). Despite this documentation of decline with advancing age the prevalence of androgen deficiency in aging male populations is difficult to define as studies are confounded by heterogeneity of populations studied and differing methods of testosterone measurement (85). Given the above, it is not surprising that even the definition of what constitutes hypogonadism, so called "andropause" in older men is somewhat controversial (88). Moreover, it must be recognized that data to support androgen therapy for skeletal health is limited. It is clear that androgen replacement increases spine BMD in hypogonadal men (89-91) but it is not established that androgens have beneficial effects in eugonadal osteoporotic men. At this time all skeletal studies of androgen replacement or treatment in men have been small and of short duration, as such, any potential effect on fracture incidence is unknown (85). Finally, safety concerns, notably potential adverse effects on cardiovascular and prostate health remain to be clearly defined (92). In

this regard, a recent meta-analysis of placebo-controlled trials found the rates of prostate cancer, prostate specific antigen elevation and prostate biopsies to be numerically, but not statistically, higher in men receiving testosterone (93).

To summarize, the role of testosterone replacement in aging men with osteoporosis remains inadequately studied and definitive conclusions cannot be made. However, many older men with low total testosterone, often defined as below 250 ng/ml, do have symptoms of hypogonadism which may be benefited by testosterone replacement. Concomitant low testosterone with clinical symptoms or signs of hypogonadism such as reduced muscle mass/strength, osteoporosis and increased body fat, is agreed upon as a situation in which testosterone therapy, with appropriate monitoring, e.g., hematocrit, prostate specific antigen, etc., should be considered (94-97).

In contrast to the situation in women, where multiple large studies of osteoporosis therapies have been conducted, only a relatively small number of studies utilizing anti-resorptive or anabolic osteoporosis treatment agents have been performed in men. Moreover, as is the case for studies of testosterone therapy, the number of participants is much smaller than comparable studies in women. Though the available studies are relatively small, they do demonstrate similar effects as observed in the larger studies among women.

Of available osteoporosis therapies, the bisphosphonate class has received the most study in men. For example, in a prospective randomized trial the impact of alendronate 10 mg daily versus placebo was evaluated in 241 men with osteoporosis, all of whom received 500 mg of calcium and 400 IU of vitamin D daily (98). After two years, lumbar spine BMD was 5.3% higher in the alendronate group and the incidence of radiographic vertebral deformities was reduced. Similarly, a small, open-label study in men with low BMD observed that daily alendronate over three years produced greater increases in spine BMD and significant reduction in radiographic vertebral fractures compared with alfacalcidol (99). Using a very similar study design, in 316 osteoporotic men, risedronate 5 mg daily increased BMD to a greater extent than alfacalcidiol and reduced vertebral fracture risk (100). Moreover, daily risedronate increases BMD and reduces vertebral fracture risk in men receiving glucocorticoid therapy (101). Importantly, intermittent bisphosphonate therapy appears to be efficacious in men. Though the data are limited, a one-year study in which men with low BMD were randomly assigned to 70 mg of alendronate or placebo, demonstrated that weekly alendronate administration significantly increased BMD at the spine and proximal femur (102). Finally, intravenous bisphosphonate therapy (zoledronic acid) increases BMD despite androgen deprivation therapy (103). It is apparent from the size and duration of the studies noted above that none of these were adequately powered to detect an effect on non-vertebral fracture. A recent study of 280 men who had previously sustained a stroke found that daily risedronate did reduce hip fracture risk in comparison to place (104). Though encouraging, the number of hip fractures in this study (12) was small. Despite this limitation, experts in the field consider bisphosphonates to be the treatment of choice for osteoporotic men (105).

Parathyroid hormone has also been studied in osteoporotic men. A small study found that daily PTH injections increased lumbar spine BMD by ~13% over 18 months in the 10 men receiving therapy (106). Subsequently, in 151 men with a spine or hip T-score < -2.0, 11 months of daily PTH injections increased lumbar spine and hip BMD by a mean of 5.9 and 1.5% respectively (107). This study was terminated after a median duration of 11 months due to the development of osteosarcomas in rats. As such, whether this treatment reduces fracture risk in men remains to be determined.

At the time of this writing, no consensus statement or societal recommendation exists advising clinicians which men to receive therapy. However, published expert opinion suggests that pharmacologic treatment at a T-score of ~-2.0 to -2.5 is indicated (108,109). The observation that the 10-year risk for fracture is virtually identical in men and women with a femur neck T-score of -2.5 supports use of similar treatment cutpoints regardless of gender. As noted above, it is expected that the forthcoming WHO absolute fracture risk paradigm will allow country-specific treatment guidelines to be determined in men.

It is hoped that this absolute fracture risk paradigm will increase treatment of osteoporotic men. In this regard, recent work documents that men who sustain osteoporotic fractures only rarely receive osteoporosis evaluation or treatment. For example, of 110 men who sustained a low-energy hip fracture, only 4.5% received any kind of osteoporosis treatment (4). Consistent with this, of 1,171 men over age 65 who sustained a fracture, only 13 (1.1%) received BMD measurement and approximately 7% received osteoporosis therapy (5). Moreover, this study did not identify an increase in treatment rate over time. Clearly, osteoporosis continues to be neglected in men, even those presenting with fracture.

CONCLUSION

Osteoporotic fractures become very common in men with advancing age. These fractures are associated with substantial morbidity and mortality. The number of men who sustain osteoporotic fractures will continue to increase for the foreseeable future. As such, osteoporosis evaluation and treatment when indicated should be part of preventive care for older men. In men with low BMD or low-trauma fracture, this evaluation should include laboratory assessment to exclude secondary causes. Androgen therapy of hypogonadal men may be considered with the caveat that data do not exist to document that this treatment reduces fracture risk. At this time, the data is inadequate to support use of androgen treatment in eugonadal men with osteoporosis. Parathyroid hormone treatment does increase BMD; existing studies have not been of adequate size or duration to document fracture reduction efficacy. Bisphosphonate therapy increases BMD, reduces vertebral fracture risk and is considered the standard of care for osteoporotic men at this point in time. The increasing number of men with osteoporosis, coupled with the availability of diagnostic recommendations and effective therapies demands that this disease no longer be neglected in men. It is hoped that the forthcoming WHO absolute fracture risk paradigm will enhance recognition and treatment of osteoporotic men.

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