Volume 2 Number 2

TU TIMES
E-NEWSLETTER

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Editor's Letter

Dear Colleague:

As men's life expectancy increases, there is a critical need to address the burgeoning health concerns associated with an aging population.

Although traditionally considered a women's health issue, awareness is growing that osteoporosis significantly affects men. Gaining a fuller understanding of the epidemiology, pathogenesis, diagnosis, and treatment of osteoporosis in men and how it relates to comorbidities, such as hypogonadism, is increasingly important. It is imperative for clinicians to recognize male osteoporosis as a serious health concern and develop a protocol for how to best manage it.

After the age of 50, one in three osteoporotic fractures occur in men, and fracture-related morbidity and mortality rates are higher than in women. The majority of male osteoporosis cases are considered secondary, due to an underlying cause or contributing risk factor, such as hypogonadism, that can be identified and potentially modified. Therefore, male patients presenting with symptoms of hypogonadism should be evaluated for low bone mineral density (osteopenia) or osteoporosis and vice versa.

In this issue of *TU Times*, we examine the relationship between bone health and hypogonadism. The feature article describes our current understanding of osteoporosis and examines how treating hypogonadism may improve both conditions and lead to better overall health. In the interview, my distinguished colleague, John E. Morley, MB, BCh, explains how he manages concomitant osteoporosis and hypogonadism for his patients in the Division of Geriatric Medicine at Saint Louis University Medical Center.

We hope that you find this newsletter informative and applicable in your clinical practice to improve patient care. Please provide us with feedback and earn CME credit by completing the evaluation and posttest.

Sincerely,

Adrian S. Dobs, M.D., M.H.S.

Feature Article

Adrian S. Dobs, MD, MHS

Osteoporosis, defined as a systemic skeletal disease characterized by low bone mass and micro architectural deterioration of bone tissue with a consequent increase in fragility and susceptibility to fractures, is an escalating public health concern.[1] Although most research has focused on the pathogenesis, diagnosis, and treatment of osteoporosis in women, interest in understanding the impact and pathophysiology of osteoporosis within the male population is increasing and supported by epidemiologic and observational studies.[2]

Between 25% and 33% of men will sustain osteoporotic fractures during their lifetimes.[2] Although fracture-related morbidity and mortality rates are higher in men than in women and after the age of 50 years and approximately one in three osteoporotic fractures occur in men,[3] male osteoporosis remains significantly underdiagnosed and undertreated.[2,4]

Often preventable, osteoporosis is a silent disease until it is complicated by fractures.[1] Whereas female osteoporosis is frequently related to abrupt changes in hormone profiles, triggering osteoporosis testing, the onset of male osteoporosis is often subtle and goes undetected.[5] Compared with the age-related skeletal changes in women, namely, the loss of trabeculae, skeletal changes in the aging male include less micro structural damage, greater endocortical expansion, and thinning of the trabeculae.[4,6]

Measurements of changes in bone mineral density (BMD) vary across longitudinal and cross-sectional studies, but generally, peak bone mass in men is achieved by the early to mid 20s and declines thereafter.[7] Men gradually lose BMD at a rate of between 0.5% and 1% per year with advancing age.[8-10] Declining androgen levels, particularly testosterone, are thought to play a role.[11,12]

Studies currently indicate that more than 50% of male osteoporosis cases have an identifiable cause, with hypogonadism one of the most common.[3,11] Present thinking is that the causes of male osteoporosis are more correctable than the causes of osteoporosis in women, which is increasing the impetus for clinical vigilance to improve diagnosis, laboratory evaluation, and subsequent treatment.[5,11] Additional studies are essential to elucidating the precise pathogenesis and the optimal treatment paradigm.[2]

To investigate the factors that contribute to osteoporosis in men, Ryan and colleagues evaluated the prevalence of risk

factors, potential causes, and laboratory abnormalities in men with or without previously known contributors to osteoporosis.[5] Using a retrospective chart review of 234 men with osteoporosis diagnosed by BMD testing, they found that 75% of the cases were associated with modifiable risk factors, such as hypogonadism, subclinical hyperthyroidism, hypercalciuria, hyperparathyroidism, and vitamin D deficiency. While recognizing the limitations of a retrospective investigation in which not all laboratory results and records were available, the authors concluded that nearly half of the men had multiple risk factors for osteoporosis. Patients thought to have primary osteoporosis at the time of referral were recognized as having secondary osteoporosis in 45% of cases. This study demonstrates the need for appropriate assessment for risk factors that are potentially modifiable. The authors proposed that a reasonable evaluation for men presenting with osteoporosis would include a complete blood count, serum evaluation, and appropriate assessment for comorbidities, such as hypogonadism and thyroid conditions.

Another study, by Bours et al, suggested that more than 25% of patients (both male and female) presenting with fractures had previously unknown contributors to secondary osteoporosis and metabolic bone diseases (SECOB).[13] Many of these risk factors were treatable, reinforcing the importance of systematic screening and follow-up of patients with a recent fracture and the need to identify early those with potentially reversible contributors to SECOB.

The prevalence of osteopenia (low BMD) and osteoporosis in men has been a challenge to assess because definitions and criteria vary among studies, such that 8 to 13 million men in the United States are estimated to have low BMD and 1 to 2 million are estimated to have osteoporosis.[14] Using the World Health Organization (WHO) definitions and Third National Health and Nutrition Survey (NHANES III) data, one analysis found that osteoporosis occurred in 3% to 6% of men older than age 50 years and 28% to 47% had osteopenia.[15] Based on the magnitude of the population at risk, it is urgent to address osteopenia and osteoporosis.

Because osteoporosis is a heterogeneous condition affected by multifactorial variables, it is important to consider potential causes and risk factors discretely to better understand its natural history and pathogenesis.[16] Classic risk factors for osteoporosis are diverse, for example, smoking, excessive alcohol consumption, chronic liver disease, low calcium intake, inactivity, thin build, and hypogonadism[17,18] (Table).

In men, hypogonadism contributes to osteopenia and osteoporotic fractures. Studies have shown that low BMD in men with hypogonadism is improved by testosterone therapy, but there is marked variability in response among individuals and the mechanisms are not yet clearly differentiated.[19,20]

Because most bone cells contain androgen receptors, it has been hypothesized that diminishing testosterone levels contribute to the pathophysiology of bone loss.[11] Testosterone acts on bone directly via androgen receptors and indirectly following aromatization via estrogen receptors. These two receptor pathways appear to work on bone structure in tandem to produce similar and additive outcomes during skeletal remodeling. More importantly, testosterone, but not estradiol, appears to directly inhibit differentiation of osteoclasts.

Based on the assertion that hypogonadism is a common cause of secondary osteoporosis, it has been suggested that symptomatic hypogonadal men with osteoporosis should be treated with testosterone therapy.[11] Reinforcing the need to attain eugonadal serum testosterone levels is the recognition that suboptimal testosterone therapy can allow hypogonadism to persist, potentially contributing to decreased bone mineralization and osteoporosis.[21] However, because of the lack of specific data related to osteoporosis parameters and endpoints, agents other than testosterone (eg, parathyroid hormone and bisphosphonates) are generally considered first-line therapy for men with declines in both testosterone and BMD.[11]

Numerous studies have shown that testosterone therapy increases muscle mass and BMD.[20-25] Zacharin and colleagues assessed BMD in hypogonadal men receiving long-term (mean, 6.6 years) long-acting testosterone therapy in a cross-sectional study of 37 patients.[21] Testosterone therapy resulted in adequate bone mass accumulation and maintenance of normal BMD. The authors suggested that, by providing sustained physiologic testosterone levels, exogenous testosterone therapy may contribute to increased androgen receptor effects.

Aminorroaya and colleagues conducted a retrospective review of serial results of dual-energy x-ray absorptiometry (DEXA) of the lumbar spine and proximal femur in men with hypogonadism requiring testosterone therapy.[19] After a baseline DEXA scan, all men received testosterone 800 mg approximately every 6 months and underwent BMD monitoring at 2- to 3-year intervals. Men who received adequate treatment (n=77) had significantly better age-adjusted BMD at all 4 DEXA sites (L1 to L4, Ward's triangle, femoral neck, and trochanter) compared to those who were inadequately treated (n=66) or untreated (n=24). Further, proportionately greater improvements in BMD were seen among previously untreated or inadequately treated men. This study confirms a positive effect of testosterone therapy on BMD in men with hypogonadism and showed that optimal treatment to achieve eugonadal testosterone levels rendered BMD values similar to those of age-matched men without hypogonadism.

Table
Risk Factors for Osteoporosis

- L**O**w calcium
- **S**eizure medications
- **T**hin build
- **E**thanol
- Hyp**O**gonadism
- **P**rior fracture
- **O**ther drugs, eg, selective serotonin reuptake inhibitors, omeprazole, thiazolidinediones
- Thy**R**oid excess
- **O**ther relatives
- **S**teroids
- **I**nactivity
- **S**moking

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To date, studies of testosterone therapy in men with osteoporosis are limited and do not use fractures as a primary endpoint.[11] Although no specific evidence indicates that testosterone therapy reduces hip fracture (adequately powered studies have not been done), it is reasonable to treat men with hypogonadism and low BMD with testosterone therapy.[17] Randomized, placebo-controlled trials of testosterone therapy in men with declines in testosterone and osteoporosis should help elucidate the relationship and the potential for reducing fractures and improving overall health.[11]

To determine medically appropriate and cost-effective treatment according to risk stratification, clinicians can consult the WHO Fracture Risk Assessment Tool (Figure), or FRAX (World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, Sheffield, England). The FRAX algorithm considers clinical risk factors, BMD, and country-specific fracture

and mortality data to determine a patient's 10-year risk of experiencing a hip or major osteoporotic fracture.[26,27] Risk factors addressed by FRAX are femoral neck BMD, prior fractures, parental hip fracture history, age, gender, body mass index, ethnicity, smoking, alcohol use, glucocorticoid use, rheumatoid arthritis, and secondary osteoporosis.[26] Others, such as frequent falls, require individualized clinical attention. The National Osteoporosis Foundation clinician's guide recommends treating a patient to reduce his fracture risk if his FRAX hip fracture score is 3% or higher or major osteoporotic fracture score is 20% or higher.[1]

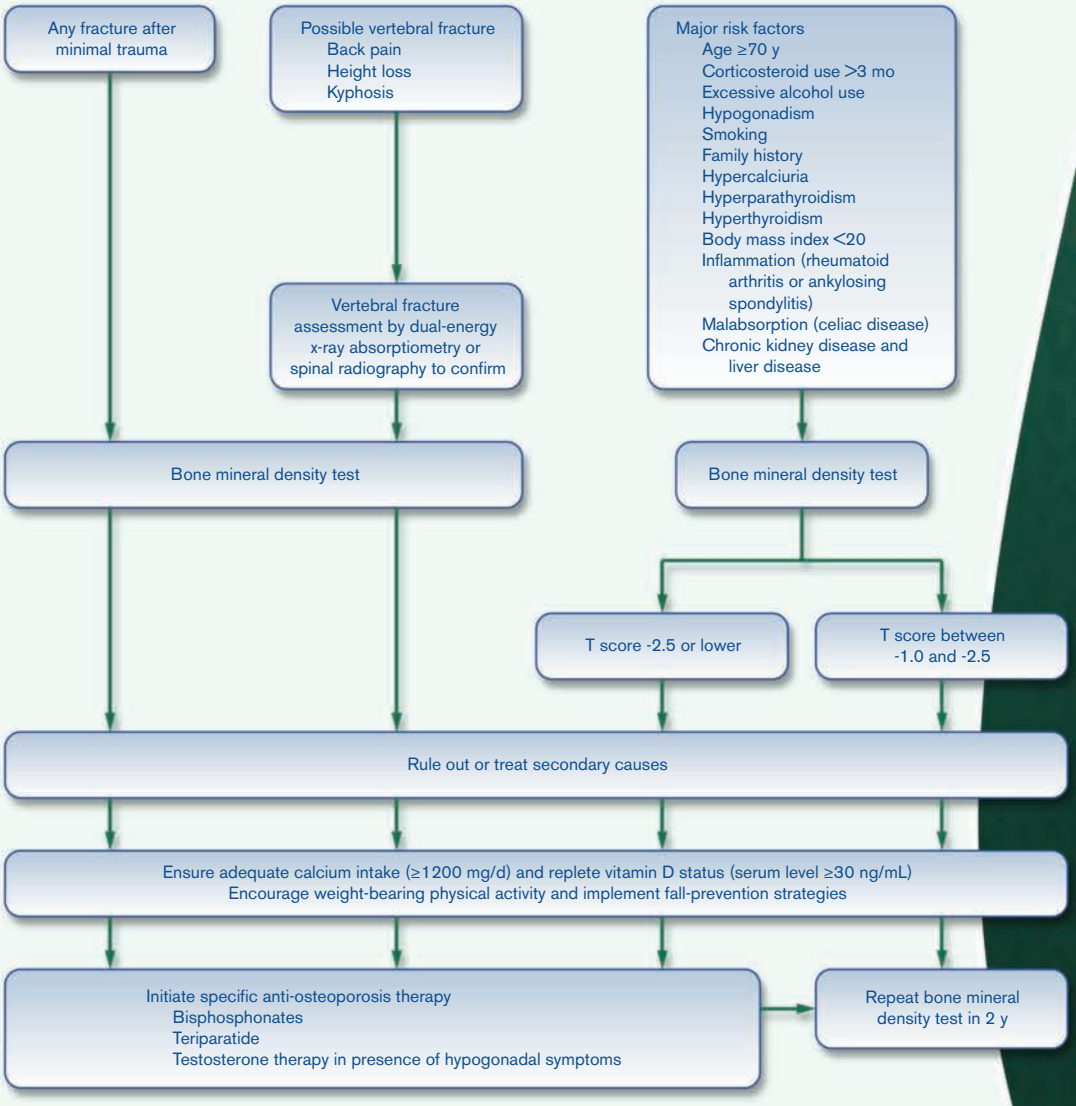
In conclusion, male osteoporosis continues to be under-recognized, and the majority of men with fragility fractures due to osteoporosis are not being treated. There is a need to improve awareness among both physicians and patients that male osteoporosis is underdiagnosed and undertreated and that causes of osteoporosis are prevalent in men and require clinical vigilance and treatment, including, most notably, hypogonadism.[11]

In both hypogonadal and eugonadal populations of men with bone loss due to causes such as androgen deprivation therapy, corticosteroid use, and rheumatologic disorders, bisphosphonates currently are considered first-line therapy because of their proven efficacy as potent antiresorptive medications, but there may be a role for testosterone therapy in appropriate patient populations.[4,11] Although some studies have shown that testosterone therapy improves BMD, larger trials are necessary, and it is advisable to consider which combinations of therapies are most appropriate for patients with low BMD and hypogonadism.

For men with osteoporosis and hypogonadism, testosterone therapy may be appropriate. Clinicians should encourage all men to consume adequate calcium and vitamin D to maintain bone mass or take supplements as necessary. Furthermore, all male patients should be educated about healthy lifestyle measures, including weight-bearing exercise, limited alcohol consumption, and smoking cessation, and in older men at risk of falls, prevention strategies should be initiated. Fragility fractures or early signs of osteopenia or osteoporosis in men should prompt screening for hypogonadism, and conversely, a hypogonadism diagnosis should prompt screening for low BMD and osteoporosis risk.[4]

Figure

Plan for Treatment of Men With Osteoporosis



Excessive alcohol use is defined as 18 oz (533 mL) or more of full-strength beer, 7 oz (207 mL) or more of wine, or 2 oz (59 mL) or more of spirits per day.

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An Interview With Dr Morley

Q In your clinical practice, how often do you screen patients with fragility fractures or early signs of osteoporosis for hypogonadism and vice versa? Should a hypogonadism diagnosis prompt screening for signs of low BMD?

A Males with hypogonadism are 6.5 times more likely to have minimal-trauma hip fractures than age-matched controls.[28] Hypogonadism is 2.08 times more prevalent in males with osteoporosis.[29] For these reasons, men with osteoporosis and/or fragility fracture should be screened for hypogonadism. Similarly, men with hypogonadism should be screened for osteoporosis. A 3-year study showed that testosterone therapy increased hip BMD in hypogonadal men.[20]

Q Within your clinical practice, how often do you refer patients with hypogonadism for BMD evaluation? Should this be considered a routine part of laboratory evaluation of patients with hypogonadism?

A All persons older than 50 years of age with hypogonadism should have their BMD evaluated.

Q Some patients with low BMD are frail; do you think there is a risk to treating older patients with frailty with testosterone therapy?

A There are always risks in treating frail patients. Overall, there is little clear risk with testosterone therapy in this population. The increase in heart failure is really due to increased water retention and edema, ie, not heart failure. Frail persons with heart failure have shown improved walking distance after receiving testosterone therapy.[30]

Q How frequently do you encounter edema in the older, frail patient population? How do you manage edema in this population?

A Edema is almost universal in this population. They are not very mobile, resulting in fluid accumulation in their legs. They have inadequate muscle strength to return blood from the legs and often, in addition, varicose veins. They may have low albumin and/or red cells leading to a decreased oncotic pressure.

Edema is mostly managed by doing nothing or prescribing elastic stockings. If it is troublesome, a low dose of a diuretic can be used.

Q Do you think it is appropriate to treat low BMD with testosterone therapy, even if the patient has not been diagnosed with low serum testosterone?

A No. However, he should have a free testosterone or bioavailable testosterone measurement taken to determine whether he is hypogonadal.

Q In what situations would you prescribe testosterone or bisphosphonates as monotherapy versus combination therapy with testosterone and bisphosphonates?

A In the patient who is hypogonadal but does not meet the criteria for osteoporosis, I would use testosterone therapy alone if he is symptomatic or has poor muscle mass and an increase in the FRAX chances of developing a hip fracture. I would use bisphosphonates together with testosterone therapy in the patient who meets the WHO criteria for osteoporosis and is hypogonadal.

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