A Review of the Use of Testosterone in Male Osteoporosis

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Introduction/Epidemiology

Osteoporosis is a common, serious disease in older adults. Until recently, osteoporosis research and treatment have focussed on postmenopausal women. Recently, however, the epidemiology of this condition in elderly men has become clearer and it is evident that osteoporosis is also prevalent in this population. In fact, men over the age of 50 years have a 19–25% lifetime risk of an osteoporotic fracture, as compared to women who have a 50% lifetime risk. In addition, it is estimated that 30% of hip fractures that occur worldwide occur in men, and lead to significant mortality and loss of independence. Indeed, post-hip fracture, men have a higher mortality rate than do women.[1,2,3,4] The role of androgens in bone physiology has suggested that testosterone may be one arm in the treatment regimen. The following article will review the place of testosterone in the management of osteoporosis in males.

Bone Physiology and Pathophysiology

Osteoporosis is a "disease characterized by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture incidence."[5] The origin of idiopathic osteoporosis lies in the aging process and normal bone physiology. Throughout life, bone repairs itself by the opposing forces of bone formation and bone resorption. Bone remodeling begins with osteoclast activation, which comes about by such conditions as mechanical forces, microfractures and hormonal changes or other factors such as parathyroid hormone, interleukin-1, prostaglandin E2, and 1,25-dihyroxyvitamin D. Fully differentiated osteoclasts undertake bone resorption, after which osteoblasts migrate, differentiate and begin new bone formation at the resorption site, likely brought about by the local release of growth factors from the cells involved in the resorption of the bone matrix.[2] The ability of osteoblasts to multiply and create new bone decreases with age, resulting in a net loss of bone.[2]

Androgen receptors are present on osteoblasts,[6] and androgens are important determinants of peak bone mass in men.[2] Stimulation of androgen receptors in osteoblastic bone marrow stromal cells inhibits the differentiation of osteoclasts in the bone marrow cavity. Androgens also allow the creation of cortical bone by stimulating periosteal bone formation. Androgen action is necessary for the increases in bone mass seen in puberty, as well as the maintenance of bone mass after puberty.[6]

In women, bone mass peaks in the mid-20's to mid-30's, is stable for a few years, then decreases slowly until the onset of more rapid loss of about 3–7% per year at the time of the estrogen deficiency that accompanies menopause.[2] Men also lose bone with age, at a rate of approximately 1% per year. However, men retain the potential to gain cortical bone through periosteal bone deposition, thereby increasing the cross-sectional area and thus the maximal load levels of the vertebrae until age 75, at which time their increased bone strength is reversed by thinning of cortical bone. This is the approximate time that men begin to present with vertebral fractures.[2] In part, the slow, age-related declines in male bone mass are related to the slow decline in androgen levels. Recently, however, it has been suggested that declining estrogen levels in men may be even more closely related to the reduction in bone mass than are declining androgen levels, and that androgens may possibly exert their effect after aromatization to estrogens.[3,7]

Etiology of Osteoporosis in Males

The exclusion of disease states that present with low bone mass or fractures is an essential part of the evaluation of an individual with osteoporosis. Men are more likely than women to have a secondary cause of osteoporosis, such as an underlying metabolic abnormality.[2,8] It is estimated that 40–50% of men with osteoporosis have a secondary cause, compared with only 20% of women.[2] The most commonly reported secondary causes in men include hypogonadism and malabsorption syndromes, such as status post-gastrectomy. These each account for approximately 16% of cases of spinal osteoporosis in males.[2,9]

Table 1 lists causes of secondary osteoporosis in males. Other conditions that contribute to osteoporosis in men include deficient dietary calcium, smoking, excessive alcohol intake and

Table 1
Secondary Causes of Osteoporosis in Males

Hypogonadism
Malabsorption syndrome
Primary hyperparathyroidism
Multiple myeloma
Hyperthyroidism/excess thyroid replacement
Paget's disease
Osteomalacia

Modified from: Kenny AM, Prestwood KM. Osteoporosis: Pathogenesis, diagnosis and treatment in older adults. Rheumatic Diseases Clinics of North America. 2000;26(3):569-91.

sedentary lifestyle. Certain medications can also be contributory, including glucocorticoids, excess thyroid supplementation, anticonvulsants, methotrexate, cyclosporine and heparin.[3]

While the extent to which certain hormonal and biochemical parameters are involved in the pathogenesis of osteoporosis in males remains controversial, a panel of factors was found to be significantly correlated to the presence of osteoporosis in men, as determined by bone mineral density. These include free testosterone, estradiol, sex hormone-binding globulin, 25-dihyroxy vitamin D, parathyroid hormone and insulin-like growth factor. A subject with any one abnormal serum parameter had a four-fold increase in the risk of osteoporosis, whereas three abnormal parameters were associated with an 11-fold increased risk.[10]

Clinical Presentation

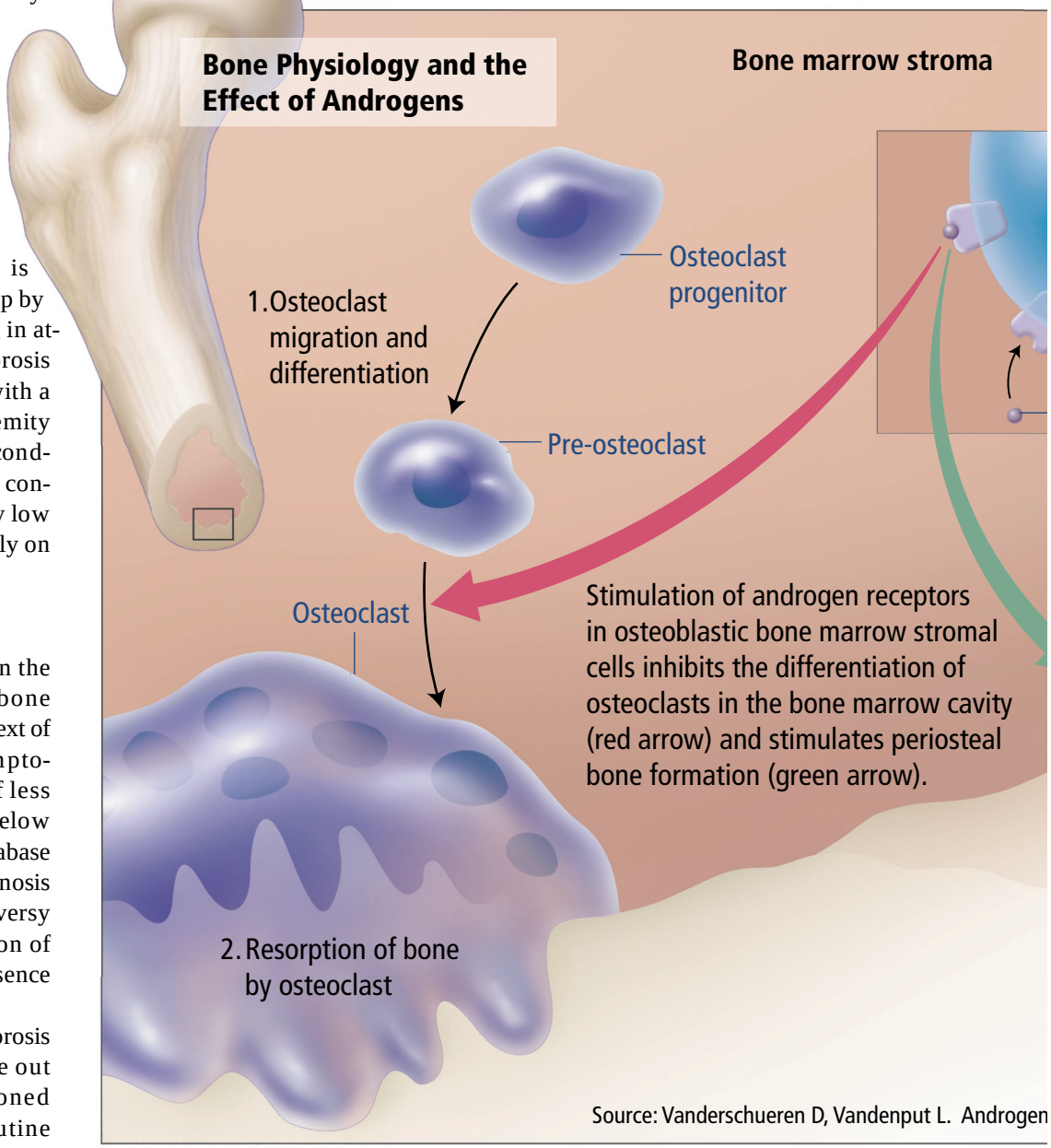
While female osteoporosis is increasingly likely to be picked up by bone mineral density screening in at-risk populations, male osteoporosis most often presents clinically with a symptomatic, low trauma extremity or hip fracture, or back pain secondary to a vertebral fracture.[3] The condition may also be suspected by low bone mass picked up incidentally on x-rays.

Diagnosis

The diagnosis of osteoporosis in the male is typically made with bone densitometry (BMD) in the context of the above symptoms. In a symptomatic male, a BMD T-score of less than 2.5 standard deviations below the mean of a male standard database would be consistent with a diagnosis of osteoporosis. There is controversy regarding the T-score definition of osteoporosis in males in the absence of signs and symptoms.[3]

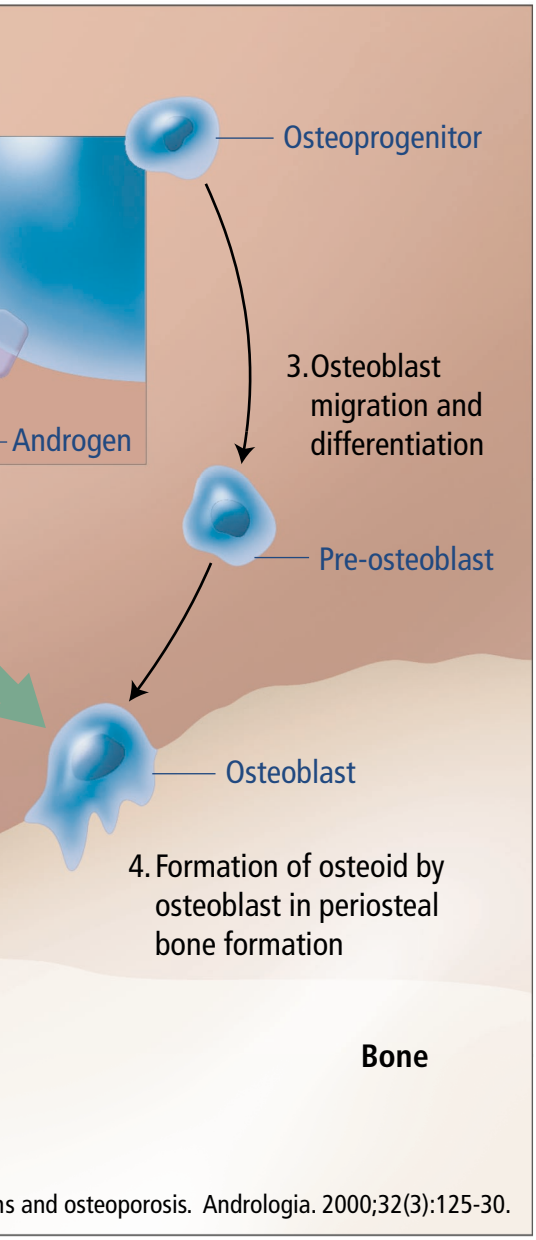
Once a diagnosis of osteoporosis is made, the next step is to rule out the secondary causes, mentioned above. This is done with a routine laboratory panel (which varies depending on the reference consulted) of calcium, phosphorous, alkaline phosphatase, serum proteins, liver, renal, adrenal, pituitary and thyroid function tests.[3] Sex steroid measurements, including testosterone, estrone, estradiol and sex hormone-binding globulin are advocated by some.[3] However, the recent Ontario Guidelines for the Prevention and Treatment of Osteoporosis suggest that routine screening of testosterone is not recommended in the absence of clinical findings suggestive of hypogonadism. In addition, bioavailable testosterone, if available, is the preferred test since free testosterone is a less sensitive measure of hypogonadism.[11]

The Androgen Deficiency in Aging Males (ADAM) questionnaire was developed to detect the complex of symptoms related to decreased testosterone levels in older men, and may be useful to assess clinical parameters suggestive of androgen deficiency.[12] The questionnaire contains 10 questions (See Table 2, page 22). Any man answering yes to question one or seven or any three other questions has a high likelihood of having a low testosterone level, and should have his androgen level



checked. The questionnaire was validated by 310 Canadian physicians and was shown to have a high sensitivity and adequate specificity as a screening questionnaire for testosterone deficiency in males over the age of 40 years.[12]

In addition, tests of the calciotropic axis including PTH, 25- and 1,25-dihyroxy vitamin D levels are recommended. A percutaneous bone biopsy may also be useful in certain situations to rule out other potential causes of male osteoporosis that are not readily apparent, such as occult forms of osteomalacia, acquired osteogenesis imperfecta, mastocytosis and malignancy.[3]



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Management

If the etiologic diagnosis of osteoporosis is not known, initial therapy is similar to that for osteoporotic women and includes an increase in dietary calcium to 1200 to 1500 mg with 400 to 800 IU Vitamin D per day. Adequate exercise is also strongly recommended. Smoking should be banned and excessive alcohol intake should be avoided.[3] If the etiologic diagnosis of osteoporosis is known, therapeutic measures are taken to deal with the underlying disorder. Such treatment, other than androgen therapy, is beyond the scope of this article.

The 2000 Ontario Guidelines for the Prevention and Treatment of Osteoporosis recommend that for: (a) men without osteoporosis but with risk factors, (b) glucocorticoid-treated men without osteoporosis, and (c) men with osteoporosis, testosterone should be added to the treatment regimen if the patient is hypogonadal.[11] For men with osteoporosis, testosterone would be added to the recommended therapies of calcium supplementation (calcium 1000 mg daily), vitamin D supplementation (800 mg IU daily) and a bisphosphonate.[11] In general, there is no role at present for androgen therapy for osteoporosis in individuals whose gonadal function is normal.[3]

Numerous studies have added to the body of evidence supporting these recommendations, although, in truth, relatively little is known about the successful treatment or prevention of osteoporosis in men compared to women.[2] Several studies show that androgen supplementation increases bone mass in hypogonadal men,[13,14,15,16] although normal adult bone mass is not reached with such treatment.[17] An early study revealed that in eugonadal men aged 34 to 73 years with vertebral fractures and established osteoporosis, treatment with testosterone esters (250 mg/2 weeks) over six months increased bone mineral density of the spine but not the femoral neck.[18] However, in a more recent study, increasing the serum testosterone concentrations of normal men over the age of 65 years to the midnormal range for young men did not increase lumbar spine bone density overall, although it did increase it in those men with low pretreatment serum testosterone concentrations.[19] Large, prospective, randomized studies are necessary to determine whether testosterone treatment in this context actually decreases the fracture rate.[20,21]

Before initiation of supplemental testosterone therapy in the hypogonadal male, several considerations are paramount:[22]

1. The diagnosis of hypogonadism is made by finding serum levels of bioavailable testosterone below the lower limits of normal (below 2 to 2.5 nmol/l), repeated on two or more occasions from morning blood samples.
2. If secondary hypogonadism is suspected, endocrine work up is warranted prior to the initiation of therapy.
3. Prior to therapy, patients should have their hematocrit and lipid profiles (serum triglycerides, HDL and LDL cholesterol) determined.
4. Prostate cancer is a contraindication for treatment. A digital rectal exam and serum prostate specific antigen (PSA) should be normal.
5. Mild benign prostatic hypertrophy is a relative contraindication to testosterone treatment.
6. Testosterone therapy may result in increased estrogen levels secondary to aromatization, and is contraindicated in men with breast cancer.
7. Sleep apnea is another contraindication for treatment.

After initiation of therapy, patients should be followed regularly, initially every three months, with digital rectal examination and PSA if the patient is over 40 years. After six months, the lipid profile, hemoglobin and hematocrit should be checked. Clinical assessment is a better marker of response than repeated serum hormone levels which can fluctuate during treatment.[22] Table 3 (page 22) details the testosterone preparations available in Canada at present.

Conclusions

This paper has reviewed the epidemiology, bone physiology and pathophysiology,

and etiology of osteoporosis in males, in an effort to describe the role of testosterone in the therapy. Caveats to consider in testosterone supplementation were also reviewed. While androgens are involved in normal male bone physiology, the role for testosterone therapy is currently limited to those patients who can be shown to be hypogonadal. Further research is needed to ascertain whether testosterone supplementation has a role in idiopathic osteoporosis.[23,24] ◆

Table 2

The ADAM Questionnaire

1.	Do you have a decrease in libido (sex drive)?
2.	Do you have a lack of energy?
3.	Do you have a decrease in strength, endurance, or both?
4.	Have you lost height?
5.	Have you noticed a decreased enjoyment of life?
6.	Are you sad, grumpy or both?
7.	Are your erections less strong?
8.	Have you noted a recent deterioration in your ability to play sports?
9.	Are you falling asleep after dinner?
10.	Has there been a recent deterioration in your work performance?

Reference: Morley JE, Perry HM. The aging male patient: Androgen deficiency in aging men. Medical Clinics of North America. 1999; 83(5): 1279-89.

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Table 3

Preparations of Testosterone in Canada

Administration	Generic name	Brand name	Dosage schedule
Injectable	Testosterone cypionate	Depo-testosterone	100-150 mg im q 2 weeks
	Testosterone enanthate	Delatestryl	100-150 mg im q 2 weeks
Oral	Testosterone undecanoate	Andriol	160-200 mg / day

Reference: Tremblay RR, Morales A. Canadian practice recommendations for screening, monitoring and treating men affected by andropause or partial androgen deficiency. The Aging Male 1998;1(3):213-8.