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Testosterone and the Aging Male

Minireview

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Over the past several years, the popular press has become enamored with the idea that testosterone and other androgens might be among the "superhormone" candidates so eagerly being sought as means to prevent or reverse aging in the male. Clearly, all the media attention has not been without either its audience or its promoters, and the demand for more information on the use of testosterone in men during mid-life and beyond far outstrips the information there is to relay. Solid clinical and scientific information regarding testosterone "replacement" therapy in the older adult male is really only in its nascent stages yet, at this point, a review of available data is perhaps useful.

Background

That there is an age-associated decrease in serum-testosterone concentrations in healthy adult men has only been generally accepted within the past decade, which may help to explain why research on hormone replacement in the older male is limited (Gray et al, 1991; Vermeulen, 1991). Data on the rate of change in serum testosterone with age are scarce and largely based on cross-sectional studies. There is great inter-individual variability in serum-testosterone levels among healthy older men, and these levels can be impacted by both disease and medication. Consequently, unlike women, not all men are destined to become "hypogonadal" as they age; in fact, how one defines an older adult male as testosterone "deficient" has not been established. For example, in the Massachusetts Male Aging Study, if "hypogonodal" is defined as those men who have serum-testosterone levels in the lowest quintile and gonadotropin levels in the highest quintile, then about 4% of men in the 40–70-year age range would be "hypogonadal" (McKinlay, personal communication). If one were to just look at healthy men 55 years and older who have serum-testosterone levels below the lower range of normal for young adult men, then the percentage would be closer to 20% (Tenover, 1996). If one were to evaluate men not by their serum level of total testosterone, but by their serum level of testosterone that is not bound to sex-hormone-binding globulin (sometimes called "bioavailable" testosterone), then the prevalence of testosterone deficiency in older men might be as high as 50%.

The more practical question at this point, however, is not so much if there is a particular level of testosterone that defines an older man as testosterone deficient; it may be that the answer to this will vary by individual and the androgen-target organ of interest. The real question is whether older men respond in a favorable manner, in terms of some measurable androgen-target-organ response, to testosterone "replacement" therapy. In this regard, androgen-target organs of particular interest in the older male include bone, muscle, penis, and brain. Can testosterone prevent or reverse some of the changes that commonly occur in men as they age, such as thinning bones, decline in muscle mass and strength, or impotence? Can testosterone help some older men who have begun to experience symptoms often euphemistically described as the "male menopause", decreased libido, mild fatigue, or decreased sense of well-being? Another question is whether testosterone-replacement therapy in the older man carries any significant risks and just what the risk/benefit ratio for such replacement therapy might be.

Limitations of Studies on Androgen Therapy in Aging Men

A search for studies on androgen therapy in older men finds that large, well-designed evaluations are lacking. Many studies to date are (1) not controlled (sex steroids are notorious for their placebo effect), (2) generally short term (most studies are 12 months in duration or less), (3) involve small numbers of participants (the total number of men evaluated is well under 500), (4) lack uniformity in participant characteristics, (5) involve a variety of treatment regimens, (6) utilize a variety of assessment techniques, and (7) reported in abstract form only. Nonetheless, by organizing available data by target-organ response, some interesting and meaningful outcomes can be evaluated.

Androgens and Muscle

Androgens, long noted for their anabolic effects, have begun to be evaluated as a possible way to reverse or prevent some of the body composition changes seen in the older man since normal male aging results in an increase in upper- and central-body fat, a decrease in muscle mass, and a decline in muscle strength. The total number of

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study participants from the various trials that have evaluated androgen replacement and body composition has been small (<150 men), study treatment duration has varied greatly (1–24 months), and a wide variety of methods for evaluating body composition and strength have been utilized. Nevertheless, the data on body-composition changes in the older male with androgen therapy show consistent results. The large majority of these studies have reported an increase in lean-body mass, a decline in fat mass, and an increase in either hand-grip or lower-extremity strength with testosterone therapy (Tenover, 1992, 1996; Marin et al, 1993; Morley et al, 1993; Urban et al, 1995). While these data are suggestive of the fact that testosterone may have a beneficial impact on body composition in the older man, larger studies will be needed to corroborate these data, to determine if effects are sustained, and to elucidate if the increase in muscle strength with testosterone will be of such magnitude as to have clinically meaningful impact on function.

Androgens and Bone

Loss of bone mass with age becomes more clinically significant as men live longer. Hypogonadism is a risk factor for minimal-trauma hip fracture in the elderly male, and treatment of older men with gonadotropin-releasing-hormone (GnRH) analogs or castration can lead to a rapid decline in vertebral-bone density. The effect of testosterone supplementation on bone density and bone turnover in older men, therefore, is an important area for research.

As long ago as 1948, Albright reported that testosterone given to a 72-year-old man with osteoporosis resulted in a decline in total-calcium excretion (Albright and Reifenstein, 1948). Since that time at least ten studies, involving just over 100 total participants, have evaluated the effects of testosterone supplementation on bone in older men (Lafferty et al, 1964; Francis et al, 1986; Tenover, 1992; Morley et al, 1993). These studies have involved testosterone replacement for periods from 6 weeks to 18 months and have evaluated either biochemical parameters of bone turnover or bone-mineral density. Again, although the methodology is often quite different among the studies, the results are generally quite consistent.

For the shorter-term testosterone-supplementation studies, bone formation, as evaluated by serum osteocalcin or bone-specific alkaline phosphatase, and bone degradation, as evaluated by urinary-calcium, hydroxyproline, or pyridinoline excretion, were assessed. For the longer-term studies (therapy for >6 months), bone-mineral density (BMD) was measured. In all studies where biochemical parameters of bone degradation were evaluated, those measurements showed a decline with testosterone therapy; of the studies that evaluated biochemical markers for bone formation, one-half reported an increase and one-half reported a decrease in those markers with testosterone therapy. All four of the studies evaluating BMD reported an increase in bone mass with therapy.

Therefore, there are data to suggest that androgen therapy may have beneficial effects on bone density and bone turnover in older men. Similar to the data with testosterone and muscle mass, however, more and longer-term studies are needed to confirm that testosterone therapy can sustain a stabilization or reversal of bone loss seen in the older man.

Androgens and Sexual Behavior, Cognition, and Mood

Measures of sexual function, such as potency, orgasmic frequency, and sexual thoughts have been reported to decline with age. While studies of androgen replacement in hypogonadal young men have shown that some testosterone is necessary for normal libido, ejaculation, and spontaneous erections, data to support a relationship between androgen levels and age-related declines in sexual function are often contradictory. Some studies in older men have shown a mild correlation between serum-testosterone levels and sexual activity.

In older men, the effects of testosterone therapy on mood, aspects of cognition, and sexual behavior have not been extensively or carefully evaluated. Several studies have shown improvement in spatial cognition with androgen therapy, while others have reported improvement in sense of well-being and/or an increase in libido with testosterone supplementation (Tenover, 1992, 1996; Marin et al, 1993). The relationship between testosterone levels and erectile function, especially in older men, is complex, and only a small percentage of erectile dysfunction in this age group appears secondary to "testosterone deficiency".

Potential Risks of Androgen Therapy

For all medical or surgical treatments, both physicians and patients would like to know not only what might be the benefits of therapy but also what the prevalence and magnitude of potential adverse outcomes might be. At this point, assessments of adverse effects of testosterone supplementation in older men have been made on the basis of data obtained over relatively short periods of time (most studies are for 12 months or less) and in a limited number of men (<300 total). The areas of adverse effects that have been assessed include those selected on the basis of experience with androgen therapy in young adult men, as well as those inferred on the basis of knowledge about androgen-target organs. The two areas of most concern in regards to adverse effects in the older man are potentiation of cardiovascular disease and acceleration of benign or malignant prostate disease. Other areas of concern include water retention, hepatotoxicity, exacerbation of sleep apnea, and development of polycythemia or gynecomastia.

Part of the increased cardiovascular disease in men, compared with premenopausal women, may be due to androgens. Some of this increased cardiovascular risk in men, compared with women, may be mediated through androgen effects on serum lipoproteins but clearly other factors, such as direct effects on atherogenesis or modulation of vasoconstriction, may play a role.

Androgen-replacement studies in older men have utilized parenteral therapy and have demonstrated that the major serum-cholesterol profiles are not adversely affected by this therapy (Tenover, 1992, 1996; Marin et al, 1993; Morley et al, 1993; Urban et al, 1995). Uniformly, such studies have shown either a decrease or no change in serum total cholesterol and low-density lipoprotein (LDL) cholesterol, while only one of five studies demonstrated a decline in high-density lipoprotein (HDL) cholesterol levels with testosterone treatment. Changes in other lipoprotein subfractions have not been well studied, and effects of testosterone therapy on factors impacting cardiovascular disease other than serum-lipoprotein levels have not been reported in the older man. Since cardiovascular disease remains the leading cause of mortality in this age group, even a small potentiation of disease by androgen therapy might lead to an unacceptable risk.

Benign prostatic hyperplasia (BPH) and prostate cancer are diseases of the aging male. Androgens have a role in promoting BPH and prostate cancer, and androgen deprivation has been used as a treatment for both. The role of androgen supplementation as a potential promoter of prostate disease in the older male is not known but remains a significant concern. There are at least eleven androgen-supplementation studies in older adult men that have evaluated the prostate in some manner during therapy. Of these eleven, only two reported any change in serum-prostate-specific antigen (PSA) levels with therapy (Tenover, 1992; Urban et al, 1995). All five studies in which prostate-size or urine-flow parameters were evaluated showed no change in these parameters with androgen therapy. Although these studies suggest that androgen supplementation may have no major immediate and obvious impact on the prostate in the older man, the studies represent <400 man-years of observation, which is too little experience to infer longer-term safety.

Fluid retention is known to occur with androgen therapy, and it is possible that testosterone supplementation in older men might lead to exacerbation of hypertension, peripheral edema, or precipitation of congestive heart failure. To date, however, none of the studies of androgen therapy in older men have reported fluid-overload problems in study participants. Similarly, although hepatotoxicity has been reported with the use of some oral androgens (especially methylated testosterone), all the studies in older men have used parenteral-androgen replacement and have reported no evidence of hepatotoxicity, as monitored by liver-enzyme blood tests. The development of gynecomastia with androgen therapy, especially in the older man, has been reported. This process is usually reversible and manageable, however.

The stimulatory effects of androgens on erythropoiesis are well documented. Studies in which young hypogonadal men have been supplemented with testosterone have shown an increase in hemoglobin and hematocrit with treatment. In older men, erythropoiesis also is affected by testosterone therapy that can result in a significant rise in hemoglobin levels, necessitating phlebotomy or testosterone-dosage adjustments (Krauss et al, 1991). Sleep apnea and elevated body-mass index may play a role in development of high hemoglobin levels in this age group (Drinka et al, 1995), but the method and extent of testosterone replacement also appear to have an effect. Those replacement methods that use lower, more frequent injectable-testosterone esters or the scrotal or transdermal patch have reported less of a problem with rising hemoglobin levels than those studies using higher, less frequent testosterone dosing regimens.

The relationship between androgens and sleep apnea is complex. There is data to show that pre-existing sleep apnea can be exacerbated by testosterone therapy (Sandblom et al, 1983), as well as data to suggest that sleep apnea can result in lower serum-testosterone levels (Santamaria et al, 1988). None of the studies on androgen therapy in older men have reported the development of sleep apnea in participants during therapy, but a number of the studies have prescreened study participants for presence of the disease.

Summary

The number and magnitude of studies involving testosterone-supplementation therapy in older men are limited. In addition, many studies to date have not been blinded or controlled, were reported in abstract form only, and had involved a variety of androgen-replacement regimens and outcomes measurements. Nonetheless, an overview of the data suggests there is real potential for supplementation therapy to improve bone mass and muscle mass and strength in this age group. Affects on mood, sexual function, and cognition are less clear but may be meaningful in certain men. Questions still remain, however, on the magnitude and longevity of the beneficial effects of testosterone supplementation in the older man and whether only certain subgroups of men would truly benefit from therapy. More importantly, the long-term risks of androgen therapy in this age group really are not known, especially in the areas of cardiovascular disease and prostate diseases. Presently, men who use androgen-supplementation therapy for age-related "testosterone deficiency" should consider this as a gamble.

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