Testosterone and Andropause: The Feasibility of Testosterone Replacement Therapy in Elderly Men

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Andropause, a syndrome in aging men, consists of physical, sexual, and psychologic symptoms that include weakness, fatigue, reduced muscle and bone mass, impaired hematopoiesis, oligospermia, sexual dysfunction, depression, anxiety, irritability, insomnia, memory impairment, and reduced cognitive function. Free testosterone levels begin to decline at a rate of 1% per year after age 40 years. It is estimated that 20% of men aged 60–80 years have levels below the lower limit of normal. Although the causal relationship between declining testosterone levels and development of andropause symptoms is not firmly established, administration of testosterone to this population resulted in improvements in many areas. Most studies to date focused on physical benefits of testosterone replacement and failed to assess psychologic symptoms rigorously. Preliminary data suggest that therapy may benefit elderly men with new-onset depression. Testosterone administration is not without problems, the most worrisome being the potential for increased prostate cancer risk. Despite this concern, a limited number of studies administered the hormone weekly for up to 2 years, with only mild increases in prostate-specific antigen over control values. Currently, insufficient evidence, primarily regarding psychologic safety and efficacy, exists to warrant general administration of testosterone to elderly hypogonadal men. Further clinical investigations of this therapy in men with low testosterone levels and andropause symptoms are justified and necessary.
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OUTLINE

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Menopause is a well-described syndrome of somatic and psychologic symptoms associated with a decline in circulating estrogenic hormones.[1] Data from several disciplines including endocrinology, urology, and gerontology suggest the existence of a similar syndrome in men, referred to as andropause, male climacteric, viropause, or low-testosterone syndrome.[2] Andropause was defined by at least one investigator as "an indefinite syndrome…in

middle-aged and elderly men…composed of several constellations of physical, sexual, and emotional symptoms brought about by a complex interaction of hormonal, psychological, situational, and physical factors."[3] Physical findings include weakness, fatigue, reduced muscle and bone mass, and impaired hematopoiesis; sexual dysfunction can include oligospermia, diminished libido, and impotence; the psychologic and emotional component may involve depression, anxiety, irritability, insomnia, memory impairment, and reduced cognitive function.[2]

Testosterone and Aging

Testosterone production in men is controlled by the hypothalamic-pituitary-gonadal (HPG) axis. Secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulates the pituitary gland to release luteinizing hormone, which acts on testicular Leydig cells to produce testosterone. Testosterone is metabolized by 5α-reductase to dihydrotestosterone and then metabolized to estradiol by aromatase. Increasing concentrations of testosterone inhibit further secretion of GnRH through a negative feedback mechanism. Testosterone is highly bound (80%) to sex-hormone-binding globulin (SHBG) and, to a lesser extent, to other serum proteins including albumin. Only 2% exists unbound as free testosterone. Bioavailable testosterone refers to non-SHBG-bound forms (including free testosterone) and generally is considered to be the biologically active fraction.[4]

Reductions in total testosterone are not usually observed in men until the sixth decade; however, decline in free concentrations are seen earlier, at a rate of approximately 1% per year between ages 40 and 70 years.[5] This is explained by increasing SHBG concentrations at a rate of about 1.2% per year. As the number of testosterone-binding sites on SHBG increases, the unbound fraction of the hormone decreases. As a result of declines in both Leydig cell function and HPG axis sensitivity, aging men appear unable to compensate for the reduction in circulating testosterone.[6] In fact, 7% of men aged 40–60 years, 20% of those 60–80 years, and 35% over 80 years have total concentrations below the lower limit of normal (350 ng/dl).[6] The insidious nature of this reduction does not mirror the rapid hormone decline in women during menopause. Thus the physiologic and emotional effects of declining hormone concentrations in men are significantly less dramatic and obvious than those experienced by women.

Testosterone and Factors Other than Aging

The decline of testosterone concentrations is confounded by a number of factors such as smoking, obesity, alcohol use, lifestyle, and concomitant disease states. Critics of the characterization of andropause as a clinical syndrome maintain that signs and symptoms are related to these confounders and that nonspecific changes in physical, sexual, and emotional states are better explained by declining health, which leads to reduced testosterone levels.[7] It also may be argued that declining levels and andropause-like symptoms occur simultaneously but share no causal relationship.

Smoking

When data are matched for age and body weight, they show that smoking most commonly increases total testosterone.[8, 9] The mechanism of this effect is not clear.[6]

Obesity

Massively obese men (200–380% ideal body weight) had substantially reduced total testosterone concentrations, 63% lower than that of control subjects, and SHBG concentrations were also markedly reduced.[10] Thus, free testosterone concentrations were decreased by only 21%, a difference that was not significant in this group of 10 patients. A study of mildly obese patients (> 20% ideal body weight) without other disease states reported reductions in total and free testosterone concentrations of 25% and 19%, respectively.[5] It appears that the degree of obesity correlates with total testosterone, but free concentrations may be less affected.

Alcohol

Ethanol use in chronic alcoholics caused dose-dependent reductions in testosterone concentrations of 19–27%. Reduction was reversible with discontinuation of alcohol consumption.[11]

Lifestyle

Diet (conventional vs vegetarian) and residency (care facility vs home) had no effect on testosterone.[8] Stress effects were evaluated in patients after myocardial infarction. Young patients had large drops in testosterone initially,

but concentrations rebounded with recovery. This effect was not observed in elderly patients. Elderly men had less circadian variation in testosterone concentrations than their younger counterparts. Morning concentrations were the most significantly reduced and may be the most accurate estimate of deficiency.

Medical Illness

The most significant confounder in the characterization of andropause is the influence of medical illness. This issue was addressed in a cross-sectional study of 1709 men aged 39–70 years. Patients were categorized as healthy or unhealthy. The unhealthy group was composed of 1294 patients who were obese, alcoholic, taking prescription medication(s), and/or chronically ill.[5] Both groups had parallel declines in free testosterone with increasing age (~ 1% per yr), however, concentrations in unhealthy men were consistently about 10% lower at any given age. It appears that poor health and chronic disease do not affect the rate of reduction in free testosterone but may affect baseline production.

The more difficult question is whether a causal relationship exists between low concentrations and symptoms of andropause. The only means to assess this relationship is to observe the effect of testosterone replacement therapy (TRT) on elderly hypogonadal men.

Effects of Physiologic Restoration of Testosterone

Several dosages and dosage forms of TRT were studied in several patient populations. Studies involved men aged 55 years or older with preexisting "low" concentrations unless otherwise specified. The hormone was administered intramuscularly 100 mg weekly or 200 mg biweekly as either the enanthate or cypionate ester. These doses were chosen to restore levels from hypogonadal (compared with middle-aged men) to normal physiologic values.

Physical Effects

Replacement therapy in elderly hypogonadal men consistently and significantly increased skeletal muscle strength. Improvements were observed in grip strength,[12, 13] hamstring and quadricep strength, and biochemical measures of muscle synthesis.[14] Increases in lean body mass also were reported.[15]

Androgens reduce bone resorption and may promote bone formation.[16] These effects could prove clinically significant, as low serum testosterone is a risk factor for hip fractures in elderly men.[17]

Testosterone replacement can significantly increase hematocrit,[12, 13, 15, 18] in some patients to the extent of exceeding the upper limit of normal.[13, 15] Some men had to discontinue the hormone temporarily, but no serious complications occurred with proper monitoring.[18]

The effect of TRT on lipids varies. Of seven articles reviewed, four reported a significant lowering of total cholesterol,[12, 15, 19, 20] one insignificant lowering,[14] and two no significant change.[13, 18] None of the studies reported an increase in low-density lipoprotein (LDL) fraction, whereas a significant reduction was observed in three studies.[15, 19, 20] Effects on high-density lipoprotein (HDL) also varied. Of the seven studies, one reported significant lowering,[14] two insignificant lowering,[15, 19] and three no change.[12, 13, 18] The remaining study reported an increase in HDL but was conducted in eugonadal elderly men given daily oral testosterone undecanoate.[20] When it occurred, the average decline in HDL ranged from 2–9 mg/dl. Monitoring is appropriate in men with low baseline HDL, especially those at risk for cardiovascular disease. Administration of testosterone varied, and inconsistent effects on lipids were both beneficial (decreased LDL) and detrimental (decreased HDL). The implication for long-term TRT is unclear.

Sexual Effects

Changes in men's sexual functioning occur with age and include decreased libido, decreased sexual arousal, and erectile dysfunction.[21] Although TRT may increase libido and arousal,[18, 22] it does not necessarily improve erectile functioning.[22] This finding is consistent with many potential etiologies of sexual dysfunction in aging men, of which hypogonadism is only one. Therefore, TRT would not be expected to have widespread efficacy in erectile dysfunction, although individual patients may experience a benefit.

Psychologic Effects

The ability of estrogen replacement therapy (ERT) to improve cognition and prevent development of dementia in postmenopausal women has received considerable attention in the past decade.[23] A meta-analysis estimated that

ERT results in a 29% decrease in the risk of developing dementia.[23] Similarly, TRT is associated with improved cognition, particularly spatial cognition.[24–26] Spatial cognition refers to tasks that include visual perception, spatial attention, object identification, and visual memory processes, and declines with age.[24]

In a study of female-to-male transsexuals, cognitive assessments were performed before and 3 months after testosterone administration.[25] The authors observed significant improvement in tasks involving spatial cognition, which men typically perform better than women. Also noted was a corresponding decline in word and sentence production, tasks that women typically perform better. In another study, testosterone concentrations were negatively correlated with cognitive tasks involving verbal production.[26]

Psychologic changes associated with andropause include dysphoria, anxiety, and irritability, but these symptoms have not been rigorously assessed.[2] Some authors made statements regarding improved energy and mood but made no attempt to quantify these improvements.[15, 18] For example, patients receiving TRT were described as having "a general increase in sense of well-being."[15] In a preliminary study in middle-aged hypogonadal men, testosterone enanthate 400 mg intramuscularly every 2 weeks was effective in relieving depression refractory to selective serotonin reuptake inhibitor antidepressant therapy.[27]

The potential to relieve depressive symptoms is important, as depression and suicide are common among elderly men.[28, 29] The highest suicide rates in the United States are in men over age 65 years.[29] They continue to increase after age 65, doubling by age 85, which is 4–10 times greater than in women of similar ages.[29] Furthermore, the trend is consistent among different nations and cultures.[30] Of countries reporting suicide data to the World Health Organization, the highest rate in men was in those older than 75 years in all but one country.[30] The most common explanation of this phenomenon revolves around declining health and quality of life with age.

An analysis was performed in 9181 patients older than 65 years taken from the 1986 National Mortality Followback Survey. This study compared various demographic factors and health-related measures among people who committed suicide, those who died of natural causes, and those who died of injury (e.g., motor vehicle accident).[31] Persons who committed suicide were most likely to have had a mental or emotional disorder and to have seen a psychiatrist in the year before death. Of interest, compared with the other two groups, they tended to have less significant impairment in activities of daily living and had a similar if not lower frequency of diabetes, hypertension, myocardial infarction, angina, stroke, and Alzheimer's disease. In fact, the only medical risk factor for suicide was a history of cancer. However, this explanation is questionable, since people committing suicide actually have lower cancer rates than those dying of natural causes.

Based on these analyses, it appears that the presence of chronic disease does not fully account for the increased suicide rate in elderly men. Moreover, if poor health was the most important determinant underlying suicide risk, a similarly elevated rate should be observed in women. However, the highest rate for women occurs between ages 45 and 54 years and actually declines after age 65.[28, 29] Therefore, it appears that something specific to elderly men increases their risk of suicide. Unlike women, men are not exposed to late-life hormone replacement therapy. Depression associated with declining testosterone concentrations may be a significant determinant of suicide risk. Unfortunately, the safety and efficacy of TRT in the treatment of depression in elderly hypogonadal men is limited to preliminary research. If found to be beneficial, TRT could have a dramatic impact on suicide in this population.

Risks of Testosterone Replacement in Elderly Men

As with all pharmacologic treatments, TRT is associated with adverse effects. Most commonly reported are acne, gynecomastia, edema, and local reactions to injections and patches.[2, 16] The most worrisome risk of prolonged testosterone administration is prostate carcinoma. At least 50% of men over age 70 years have subclinical prostatic carcinoma.[32] Fortunately, most of these neoplasms do not progress to clinical disease during men's lifetime.[32] Several epidemiologic factors were investigated for an association with the development of prostate cancer, including concentrations of circulating androgens. Some studies found a positive correlation between high concentrations of testosterone and the risk of developing the disease,[33] and others did not.[34] The risk when administering testosterone to men with inherently low levels is unknown. However, progression to clinical disease and diagnosis of

adenocarcinoma during TRT was reported anecdotally.[35]

Three long-term studies ranging from 12–24 months suggest that TRT is relatively safe in elderly hypogonadal men.[13, 18, 19] One study administered testosterone enanthate 200 mg intramuscularly biweekly and reported an average increase in prostate-specific antigen (PSA) of 0.46 ± 0.2 ng/ml over 12 months. In no patient did the level exceed the upper limit of normal (4.0 ng/ml).[19] In a second study, administration of testosterone cypionate 200 mg intramuscularly biweekly for 12 months resulted in an insignificant increase in PSA of 0.7 ± 0.2 ng/ml at 12 months, with no patients exceeding 4.0 ng/ml.[13] The PSA in the placebo group increased 0.4 ± 0.2 ng/ml during the same time. In a third study, biweekly testosterone enanthate or cypionate 200 mg intramuscularly led to insignificant increases in mean PSA of 0.49 mg/dl in the treatment group and 0.25 mg/dl in the control group after 24 months.[18]

Baseline assessment of the prostate should be performed before beginning TRT. This should consist of transrectal ultrasound, digital palpation of the prostate, and measurement of total and free PSA levels.[36] Although these levels should be measured regularly, the sensitivity of the test in patients with low free testosterone levels was questioned.[37] The investigators performed fine-needle biopsy in patients with low free testosterone concentrations who had negative PSA and digital rectal examination, and found a 14% rate of adenocarcinoma.[37] They postulated that PSA concentrations are altered in patients with decreased androgenic stimulation and that PSA may not be a useful monitoring tool in hypogonadal men. Therefore, fine-needle biopsy and/or transrectal ultrasound may be useful before starting long-term TRT but is not necessary for routine monitoring.

Summary

Andropause is an indefinite syndrome of various physical, sexual, and psychologic symptoms in aging men. Steadily declining circulating testosterone levels in this population are implicated as a potential cause of symptoms. This relationship is confounded by several factors. Testosterone levels may be affected by other physiologic conditions and are consistently lower in patients with concomitant medical illnesses. However, data suggest that restoring testosterone to physiologic levels ameliorates symptoms associated with andropause.

Documented benefits from TRT in elderly men include increased bone and muscle mass, improved sexual function, reduced anxiety, improved mood and cognition, and improved quality of life. Furthermore, it may reduce the morbidity and mortality associated with depression and the increased rate of suicide in these men. Additional scientific research in this area is vital.

The most serious risk of TRT is a potential increase in prostate cancer. With proper monitoring of the prostate, TRT was administered safely for up to 2 years in elderly hypogonadal men. Because of insufficient evidence, particularly regarding psychologic safety and efficacy, general TRT in elderly hypogonadal men is not warranted. However, further clinical evaluation of TRT in men with low testosterone levels and symptoms of andropause is necessary.

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