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Risks Versus Benefits of Testosterone Therapy in Elderly Men

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Abstract

'Andropause', like menopause, has received significant attention in recent years. It results in a variety of symptoms experienced by the elderly. Many of these symptoms are nonspecific and vague. For this reason, many authors have questioned the value of androgen replacement in this population. Also in dispute is the normal cutoff level for testosterone beyond which therapy should be initiated, and whether to measure free or total testosterone. Testosterone levels decline with age, with the lowest level seen in men older than 70 years. This age-related decline in testosterone levels is both central (pituitary) and peripheral (testes) in origin. With aging, there is also a loss of circadian rhythm of testosterone secretion and a rise in sex hormone binding globulin (SHBG) levels. Total testosterone level is the best screening test for patients with suspected hypogonadism. If the total testosterone concentration is low, free testosterone levels should be obtained. Prostate cancer remains an absolute contraindication to androgen therapy. Testosterone replacement results in an improvement in muscle strength and bone mineral density. Similar effects are observed on the haematopoietic system. Data on cognition and lipoprotein profiles are conflicting. Androgen therapy can result in polycythemia and sleep apnoea. These adverse effects can be deleterious in men with compromised cardiac reserve. We recommend that elderly men with symptoms of hypogonadism and a total testosterone level <300 ng/dl should be started on testosterone replacement. This review discusses the pros and cons of testosterone replacement in hypogonadal elderly men and attempts to answer some of the unan-

swered questions. Furthermore, emphasis is made on the regular follow-up of these patients to prevent the development of therapy-related complications.

'Andropause' or male climacterium is a term used to describe a collection of symptoms associated with a decline in male gonadal function with aging. At the time of menopause in women, there is an abrupt and complete loss of ovarian function, often leading to a relative sudden onset of drastic symptoms such as hot flashes or flushes, behavioural changes, variations in sleep cycle and dyspareunia. In contrast, men experience a gradual decline in testicular function leading to nonspecific complaints of decreased muscular strength, energy and libido, erectile dysfunction, and depression. Another feature which differentiates andropause from menopause is that the decline in biologically active androgens is only moderate and many elderly men have free androgen levels that are at the lower end of the normal range. In this review we will discuss the actions of testosterone, the changes in testosterone levels associated with aging, and the risks and benefits of testosterone supplementation.

1. Androgen Production and Aging

1.1 Normal Metabolism

Testosterone, synthesised and secreted by Leydig cells of the testes,[1] is regulated by a negative feedback system involving the hypothalamus and the pituitary. The testes produce 0.24 μmol/day of testosterone. Testosterone is metabolised to dihydrotestosterone (DHT) by 5-α reductase. Most of the circulating testosterone (80%) is bound to sex hormone binding globulin (SHBG). The remaining is bound to albumin and other plasma proteins. Only 2% of total testosterone is free and is bioactive.[2-4] There is a diurnal variation in serum testosterone levels in young men, which is highest at about 08.00 hours and lowest in the late afternoon.[5]

Testosterone secretion begins *in utero* with a peak in the male fetus at 12 weeks. The second peak occurs after birth. From this time until puberty, the levels are low and equal to the female. At puberty, there is a pulsatile secretion of luteinising hormone (LH) leading to maturity of the Leydig cells resulting in increased testosterone synthesis.

1.2 Changes in Hormone Levels With Age

Numerous cross-sectional and longitudinal studies have found that beginning in the fifth decade of life, serum total testosterone levels progressively decline with age with the lowest levels noted in men older than 70 years.[6-10]

Serum SHBG levels increase gradually as a function of age.[11] This effect may be mediated by enhanced estradiol production due to increased adiposity with age. Since most of the testosterone is bound to serum proteins, a decline in levels of free testosterone with increasing age is of greater magnitude than that of serum total testosterone.[11,12] Morley et al,.[13] in their longitudinal study of 77 elderly men, showed a significant decline in testosterone levels with aging. They also observed an increase in gonadotropin and SHBG levels. Furthermore, the normal diurnal variation of testosterone levels observed in young men is lost in elderly men with values throughout the day similar to those of young men at 20.00 hours.[5]

On the other hand, plasma DHT levels do not vary significantly with age.[10] Harman et al.[14] found no effect of age on serum testosterone levels in male members of the Baltimore Longitudinal Study on Aging (BLSA) group. The only drawback of this study was that testosterone levels were checked in the afternoon (14.00 to 15.00 hours), the time when the testosterone levels are at their nadir. Measuring serum testosterone levels in the morning between 06.00 to 08.00 hours may have shown lower values in the older population compared with their younger counterparts.

Testicular function may be affected by many conditions seen more frequently in the elderly such as stress, illness, medications, obesity, malnutrition and psychiatric conditions. Therefore, serum testosterone levels may be even more profoundly suppressed in elderly experiencing the above men-

tioned conditions than in those who are not.[8-10] However, decreased testosterone levels have also been reported in carefully screened exceptionally healthy elderly men.[15] Morley et al.,[16] in their cross-sectional study of 56 healthy men belonging to different age groups, showed a significant decline in bioavailable testosterone levels with aging.

1.3 Mechanism of Age-Related Changes in Hormone Levels

It is generally accepted that the decline in testosterone levels with age is primarily testicular in origin. This belief is supported by the decreased number and volume of Leydig cells,[17-20] impaired testicular perfusion[21,22] and impaired steroid biosynthesis in aging men.[23]

Although the above evidence supports testicular failure, several alterations in the hypothalamic-pituitary compartment of the hypothalamic-pituitary-gonadal axis have been noted. These include loss of nycthemeral variations in testosterone levels,[5,24] decreased frequency of large amplitude LH pulses in elderly men[25] and increased sensitivity of the gonadotrophs to sex hormone feedback.[26,27]

Based on the above evidence, it may be concluded that hypogonadism in elderly men is both central and peripheral in origin.

2. Androgens, Target Organs and Elderly Men

2.1 Prostate

The development of both benign prostatic hyperplasia (BPH) and prostatic cancer requires the presence of functional testes in fetal life, puberty and, at least part of, adulthood.[28] Neither of these conditions occur in men who undergo prepubertal castration.[29] After sexual maturation, both androgens and estrogens are important in maintaining the structure and integrity of the prostate. Although testosterone is the main circulating androgen, a peripheral conversion product, DHT, binds to the main nuclear androgen receptor in sexual tissue.[30-33] DHT is the major androgen for prostatic growth.

The role of androgens in the aetiology of preclinical prostate cancer is not known. Hulka et al.[34] showed that there was no statistically significant association between testosterone levels and occurrence of prostatic cancer. Carter et al.[35] also found no significant difference in LH, total testosterone, free testosterone and SHBG levels between men who developed prostate cancer and those free of disease by evaluating sera collected over many years.

The pathogenesis of BPH is also not completely understood. Contrary to the study by Hulka et al.,[34] Gann et al.[36] failed to show any relation between circulating androgen levels and BPH. On the other hand, a number of studies show improvement in symptoms of patients with BPH when treated with anti-androgens. Finasteride, a 5-α reductase inhibitor, has been shown to statistically significantly decrease the size of the prostate,[37] especially in those men who have gland size >40ml at baseline.[38] Treatment with other anti-androgens such as flutamide and the gonadotropin releasing hormone (GnRH) agonist nafarelin, have shown similar results.[39,40]

Although it is known that the clinical course of prostate cancer is accelerated by testosterone, its incidence is not increased by its administration.[41] The other way to put it would be that testosterone does not cause prostate cancer. There is even no clear evidence that testosterone replacement accelerates the development of BPH.[42] A recent study showed no symptoms of bladder outlet obstruction in hypogonadal men receiving intramuscular testosterone and followed for 2 years.[43] Another study by Tenover[41] in elderly men (mean age 67.5 years) receiving testosterone enanthate 100mg weekly for 3 months, showed no increase in total prostate volume determined by suprapubic ultrasound. Behre et al.[44] showed that men receiving various modalities of testosterone replacement therapy had an increase in prostate size which was comparable with, but not higher than, those in age-matched eugonadal men. Another recent study found no abnormal prostate growth in hypogonadal men (aged 21 to 65 years) when treated with transdermal testosterone.[45] The mean prostate volume in treated

patients was similar to age-matched eugonadal men. The prostate specific antigen (PSA) levels also remained in the normal range. Many other studies have shown no effect of testosterone replacement therapy on serum PSA values, changes on prostate examination or prostate volume in elderly men.[46,47]

To summarise, testosterone replacement therapy slightly increases prostate size and increases PSA levels, but they remain within the normal range. However, testosterone therapy remains an absolute contraindication in patients with known prostate cancer (but not for BPH). More long term studies are needed to demonstrate the effect of androgen replacement on benign or malignant growth of the prostate.

2.2 Bone

Osteoporosis is a major health problem resulting in more than 1.3 million fractures annually in the US.[48] 20% of all hip fractures occur in men. The hip fracture rates in men increase dramatically after the age of 60 years and double with each decade thereafter. According to the cross-sectional and longitudinal studies, typical bone loss rates for vertebral bone in men (aged 30 to 80 years) have been 1.2 to 2% per year.[49-52] Cortical bone loss is less rapid. Hypogonadism is a well established cause for male osteoporosis[53-55] and a risk factor for fractures.[56] Jackson et al.[57] reported testosterone deficiency in 71% of elderly men with hip fractures compared with 32% of controls. Ongphiphadhanakul et al.[58] reported a clear association between decrease in serum free testosterone levels and decline in bone mineral density (BMD) at the femoral neck and Ward's triangle. Finkelstein et al.[59] showed lower cortical and trabecular bone densities in young hypogonadal men than their age-matched controls. Furthermore, a rapid decline in vertebral bone density after castration or treatment with a GnRH analogue illustrates the beneficial role of testosterone on bone.[60,61] Reversal of hypogonadism is associated with improvement in bone mass and maintenance of skeletal integrity.[62]

Loss of bone mass in men becomes more clinically significant as they live longer. The work on hypogonadism and male osteoporosis goes back to 1948 when Fuller Albright studied the results of testosterone replacement therapy in a 72-year-old man with osteoporosis. He noted that androgen replacement resulted in a decline in total calcium excretion.[63] Following in Albright's footsteps, Lafferty treated a 75-year-old osteopenic man with testosterone for 3 months and observed a decrease in urinary calcium excretion and an increase in calcium retention.[64]

Oppenheim et al.[65] studied 6 hypogonadal osteopenic men with a mean age of 61 years. Testosterone replacement therapy for 6 to 8 months resulted in increased spinal BMD in all patients. In her study on 13 elderly men treated with testosterone enanthate (100 mg/week for 3 months), Tenover[41] showed significant decline in urinary excretion of hydroxyproline. No changes in serum alkaline phosphatase or osteocalcin levels, or in urinary calcium excretion, were noted in this study. In his 3-month study, Morley et al.[66] also reported an increase in serum osteocalcin levels in elderly hypogonadal men treated with testosterone. Another study showed an increase in spinal BMD of 5% and trabecular BMD of 14% in hypogonadal men treated with testosterone.[67] Bone specific alkaline phosphatase and urinary hydroxyproline levels also decreased significantly.

Behre et al.[68] recently studied the effect of transdermal testosterone on BMD. In this study of 72 hypogonadal men, aged 18 to 74 years, testosterone replacement was given either intramuscularly or transdermally. Significant increases in BMD were seen during the first year of testosterone therapy independent of the route of administration. Long term testosterone therapy maintained BMD in age-dependent reference range. Transdermal testosterone scrotal patches were as effective as intramuscular testosterone in this study.

To summarise, androgens are as important in maintaining BMD in elderly men as they are in young hypogonadal men. Long term studies on larger number of elderly men are needed to ascertain whether testosterone replacement therapy can reverse bone loss in this population.

2.3 Body Composition

About 50 years ago, Kochakian demonstrated that testosterone increases nitrogen retention in castrated male rats.[69] Both cross-sectional and longitudinal studies show that aging is accompanied by an increase in upper and central body fat, decreased muscle mass, increased muscle fibrous tissue and decreased muscle strength.[70-72] Studies have shown that men with abdominal accumulation of body fat often have low testosterone concentration.[73] Marin et al.[74] and Rogers et al.[75] have shown that testosterone induces a decrease in abdominal fat and increases fat free mass male volunteers.

The anabolic effects of androgens have been known for a long time.[76] Cell culture studies have shown that androgens stimulate mitosis in myoblasts.[77-79] In studies of young hypogonadal men, muscle size, strength and lean body mass increase when they are given replacement doses of testosterone.[80] An increase in muscle protein synthesis, muscle mass and strength is also seen in young eugonadal men given pharmacological doses of testosterone.[81-83]

Several studies in elderly men have evaluated the effect of androgen on body fat, muscle mass and strength. Wang et al.[84] and others showed an increment in lean body mass and leg muscle strength in hypogonadal men after testosterone therapy.[84-86] Brodsky et al.[87] observed an increase in fat free mass, decrease in fat mass and a rise in muscle mass in 5 hypogonadal men on testosterone therapy.

Many studies in elderly men have shown similar results. In a 3 month crossover study of testosterone replacement in hypogonadal old men (57 to 76 years of age), Tenover[41] demonstrated an increase in bodyweight and lean body mass with subsequent declines in body fat. Urban et al.[88] showed testosterone administration increased muscle protein synthesis, muscle strength and mRNA concentration of intramuscular somatomedin-1 in elderly men. In a study by Sih et al.,[89] significant increases in upper body strength were seen in elderly hypogonadal men when treated with intramuscular testosterone enanthate for 1 year. The strength was evaluated by measuring hand grip strength. Another report also showed an increase in muscle functional strength in hypogonadal men (aged 69 to 89 years) on testosterone therapy.[66]

Finally, 2 other studies demonstrated decline in visceral fat with testosterone therapy in patients with acquired hypogonadism[67] and with obesity.[46] Since androgen receptors are present on adipose cells, testosterone may affect adipose metabolism directly by causing increased lipolysis.[90,91]

In summary, the evidence is reasonably robust that testosterone administration in elderly men may decrease body fat, increase muscle mass and enhance skeletal muscle strength. However, whether the increase in muscle strength would be of such magnitude to have a significant clinical impact on patients function and quality of life is a remaining issue.

2.4 Lipids

The effect of androgens on the lipid profile is of particular interest amongst physicians because it may explain, in part, the higher prevalence of atherosclerosis and shorter life span of men, relative to women. Epidemiological studies have revealed that high density lipoprotein cholesterol (HDL-C) levels are lower in men and triglyceride (TG) levels are higher compared with premenopausal women.[92,93] In prepubertal children, plasma levels of lipoproteins and TG show no gender difference. In boys during puberty, the HDL-C levels decline, while low density lipoprotein cholesterol (LDL-C) and TG levels increase slightly.[94] After menopause, there is no alteration in HDL-C levels in women, but LDL-C levels rise significantly resulting in a greater incidence of coronary artery disease (CAD) in postmenopausal than premenopausal women.[94] In addition, when young men are given a GnRH antagonist to suppress endogenous testosterone, their mean serum HDL-C levels increase by 20%.[95]

Although all of the above data point towards a negative impact of androgens on lipid profile, Hauner et al.[96] showed no significant role of sex steroids in the aetiology of CAD in men when assessed angiographically. Barrett-Connor[97] summarised interesting data showing that exogenous testoster-

one in physiological doses had no effect on HDL-C levels in clinical trials, while many cross-sectional epidemiological studies find that endogenous testosterone levels are positively associated with HDL-C levels.[98-103]

Data regarding effects of testosterone on cardiovascular risk factors in the elderly are conflicting and few. Administration of non-aromatisable oral androgens like stanozolol or methyltestosterone, cause profound decreases in HDL-C and significant increases in LDL-C.[94] One study showed a 7.6% decrease in HDL-C levels and a 9% rise in the total cholesterol/HDL-C ratio in adult hypogonadal men on testosterone replacement therapy.[104]

Although the above mentioned studies[94,104] report adverse effects of testosterone on lipids, other studies suggest otherwise. In one 4-year study in which testosterone cipionate at 25 mg/week was administered intramuscularly, no changes in HDL-, LDL- or total cholesterol were seen.[105] Tenover[41] reported 11% decline in total and LDL cholesterol in elderly hypogonadal men receiving testosterone therapy. Although HDL-C levels also decreased, the decline was insignificant. In their 3 year study, Hajjar et al.[43] also report no increase in angina pectoris, myocardial infarction or strokes in elderly patients on testosterone therapy. Zgliczynski et al.[106] exclusively studied the effects of testosterone on lipids in hypogonadal men and healthy elderly men. Testosterone replacement in both groups showed a beneficial effect on lipid metabolism as a decline in total cholesterol and atherogenic fractions of LDL-C without significant alterations in HDL-C or its subfractions (HDL_2-C and HDL_3-C).

Cardiovascular disease is a major cause of morbidity and mortality in an elderly population. It is important to study the long term effects of testosterone replacement on plasma lipoproteins and body fat distribution. Only after analysing the incidence of cardiovascular events in elderly men receiving androgens testosterone replacement for extended period, can testosterone replacement be considered safe.

2.5 Haematopoiesis

Over the last 3 decades numerous studies have shown that androgens may be beneficial in the treatment of primary anaemias and bone marrow failures.[107] It is a general observation that haemoglobin concentration increases in boys at puberty along with an increase in serum testosterone levels.[108] Adult men also have higher haemoglobin and red blood cell counts than do adult women.[109,110] These differences are not influenced by iron deficiency, pregnancy or blood loss. In addition, hypogonadal men have reduced haemoglobin levels compared with their age-matched controls and testosterone replacement restores the level to within the normal range for adult males.[111,112]

With age, haemoglobin and haemocrit (HcT) values decline and mild anaemia is prevalent in elderly men. Healthy older men tend to have slightly lower HcTs than healthy young adult men.[113] This has led many workers to explore the use of testosterone replacement to correct anaemia and also to monitor its complication, mainly polycythemia.

It is well known that testosterone therapy increases whole body Hct values.[114] Studies reviewed by Griggs et al.[82] involving healthy men of different ages supplemented with androgens show a significant increase in Hct. One short term study reported a rise in Hct of up to 7% in hypogonadal elderly men receiving testosterone therapy.[41] Another long term study in which older men were treated with testosterone for sexual dysfunction for 2 years also demonstrated a increase in Hct.[42] In their study on hypogonadal men, Sih et al.[89] also observed a significant rise in Hct values.

Although a rise in Hct may be beneficial for anaemic patients, polycythemia is a known complication of testosterone therapy.[43] This may have grave consequences in the elderly since increased blood viscosity can result in thromboembolic sequelae such as strokes, and add to cardiac afterload, which an aging heart is not equipped to handle. Hajjar et al.[43] in their study of testosterone therapy in hypogonadal men showed that 24% of the treated individuals developed polycythemia. Phlebotomy and withholding testosterone therapy was

required to reverse polycythemia. Another study demonstrated an increase in neurological complications secondary to polycythemia.[115] Drinka et al.[116] have implicated testosterone-induced polycythemia as a risk factor for sleep apnoea in a study on nursing home patients.

Testosterone usually increases the Hct within the normal range, but the risk of polycythemia should always be considered. Since it can add to cardiovascular burden, many authors believe phlebotomy or a decrease in testosterone dose when Hct reaches 51% and to stop treatment if it rises to 54%.[117]

2.6 Sexual Function and Cognition

Data on the relationship between androgen levels and declining sexual function are conflicting. There is a steady decline in orgasmic frequency and worsening erectile function with aging.[118] Increased detumescence, decreased vasocongestive responses and an increase in refractory period with aging have also been reported.[119] Davidson et al.[120] have also shown that there is a decrease in sexual thoughts and enjoyment with age. However, it is important to remember that hypogonadism is the sole cause of erectile dysfunction in only 10% of cases.[121]

Data on androgen replacement in hypogonadal men reveal that testosterone is necessary for spontaneous erections, normal libido and ejaculation.[122-124] Carani et al.[125] also found that nocturnal erections were substantially less in hypogonadal men in terms of both rigidity and tumescence compared with eugonadal men. Similarly, frequency of ejaculation and ratings of libido significantly increased in patients with hypopituitarism receiving testosterone and gonadotropins compared with those receiving placebo.[126]

One study showed that sexual behaviour is testosterone dependent and that the individual limit of plasma testosterone level below which sexual behaviour is impaired lies between 2.0 to 4.5 μg/L.[127] Arver et al.[128] studied the effects of testosterone on sexual function in 37 hypogonadal men aged 21 to 65 years. In this study, patients were treated with intramuscular testosterone, then withdrawn from therapy, and then retreated with transdermal testosterone. During testosterone therapy (both intramuscular and transdermal), the number of erectile events per day, mean duration of events, and mean penile rigidity increased significantly compared with during the testosterone withdrawal period. Furthermore, patients' libido, arousal, sexual desire, orgasm and satisfaction significantly decreased during testosterone withdrawal and returned with testosterone replacement. Kwan et al.[124] reported similar results, also in hypogonadal men. Recently Morales et al.[129] studied effects of oral testosterone undecanoate on 23 hypogonadal men (aged 30 to 72 years) with impotence. Testosterone replacement produced an improvement in sexual attitudes and performance in 61% of these patients.

Studies have shown an improvement in mood and sense of well being, and decreased anxiety in hypogonadal men receiving testosterone therapy.[130-132] Similarly many studies have reported an increased sense of well being in older men receiving androgen replacement therapy.[46,133] A few reports also report confusion in spatial cognition in the elderly population.[134,135] Janowsky et al.[136] reported that testosterone replacement enhances spatial cognition in elderly men. Similar results were obtained by Orwoll et al.[47] by using transdermal testosterone supplementation in healthy older men. Depression is more prevalent in the elderly population and studies, reviewed by Vogel et al.,[137] have shown that testosterone can has antidepressant properties. However, in their study in men (aged 45 to 74 years) with erectile dysfunction, Schiavi et al.[138] found no effect of biweekly testosterone enanthate administration on the affective state or psychological symptoms.

To summarise, evidence suggests that testosterone therapy in elderly men improves libido and sexual function. It also has a positive effect on spatial cognition and memory.[136]

2.7 Sleep Apnoea

Studies investigating androgen replacement and the development of sleep apnoea in the elderly are nonexistent. However, it is known that sleep ap-

noea is more common in men than women[139] and is more common in postmenopausal women than premenopausal women.[140] Matsumoto et al.[141] studied the development of obstructive sleep apnoea (OSA) in 5 hypogonadal men while receiving no therapy and after 6 weeks of intramuscular testosterone enanthate. Hypoxic ventilatory drive decreased significantly in all patients on testosterone therapy. OSA developed in 1 patient and markedly worsened in another in association with testosterone administration. There was also a marked decrease in nocturnal oxygen saturation with the development of cardiac arrythmias in both these patients.

In summary, the effects of testosterone replacement on the development of OSA needs to be studied in elderly men. Since nocturnal arterial desaturation is associated with cardiac arrythmias, it may lead to serious consequences in this population because of underlying CAD in many elderly patients.

3. Conclusion

Aging is associated with a decline in Leydig cell mass and free testosterone levels. Parameters such as muscle mass, Hct, and sexual desire and function also decline. Although total testosterone is the best screening test, free testosterone is a better parameter to evaluate elderly men with suspected hypogonadism since total testosterone levels are effected by a rise in SHBG levels with age. Although the number of studies of testosterone replacement in the elderly are limited, an overview of the data favours real potential for androgen therapy in a few areas such as BMD, muscle mass, muscle strength and Hct. Most of the studies also suggest a positive impact on mood and sexual behaviour. Data on the significance of lipid changes with testosterone replacement are conflicting. Although prostate cancer remains an absolute contraindication to testosterone therapy, one can say that testosterone therapy does not cause cancer. Sleep apnoea related to testosterone replacement can result in dire consequences secondary to increased Hct and arrythmias.

Since androgen replacement results in a constellation of positive and negative impacts on different body parameters, we do not recommend routine treatment of elderly men with testosterone. However, in elderly men who have manifestations of androgen deficiency and whose serum total testosterone level is < 300 ng/dl, testosterone administration is warranted. If treatment is undertaken, the patient should be screened before treatment for Hct and arrythmias, and monitored carefully during therapy.

The development of selective androgen receptor modulators is crucial, since their use may help target areas like bone and muscle tissue while avoiding any hazardous affect on the prostate and lipids. Similarly, it will be useful to explore a combination of testosterone with 5-α reductase inhibitors, since DHT is the major androgen in prostate growth. The use of an androgen preparation such as 7-α-methyl-19-nortestosterone, which is aromatised but not 5-α reduced, should be also studied in the elderly.

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