Conferences and Reviews

Androgen Deficiency and Aging in Men

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Androgen levels decrease with age in men. Androgen deficiency in men older than 65 years leads to asthenia, a decrease in muscle mass, osteoporosis, and a decrease in sexual activity. Androgen deficiency has been reported to cause changes in mood and cognitive function. The combination of these factors results in impaired quality of life in older men. Androgen replacement therapy in hypogonadal men increases bone and muscle mass, enhances muscle and cardiovascular function, and improves sexual function and general well-being; whether elderly men experience benefits of androgen replacement is not known. These benefits have to be weighed against the possible adverse effects of prostate and cardiovascular diseases. Careful long-term studies are needed to assess the risk-to-reward ratios of androgen or other hormone replacement therapy before treatment strategies similar to estrogen therapy for postmenopausal women are implemented.

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In women, acute clinical symptoms of estrogen deficiency frequently accompany the onset of menopause. Sex hormone replacement therapy is generally recommended for postmenopausal women to diminish symptoms such as hot flashes and to reduce long-term manifestations such as osteopenia and bone fracture.

In men, the decline in androgen secretion occurs more gradually than the decline in estrogen secretion in women, and it has fewer acute clinical manifestations. Long-term androgen deficiency, however, leads to impaired sexual function, a decrease in muscle mass, and osteoporosis. The last two problems may predispose to frailty and an increased fracture rate. The beneficial effects of androgen substitution in men older than 65 years* have not been adequately documented, nor have the potential adverse effects of androgens on the prostate, plasma lipids, and red cell mass been studied in older men. Androgens may have direct actions in some tissues. In others, they may interact with other growth factors to manifest their full biologic activities. In this review, we describe the changes in spermatogenesis, sexual function, cognitive ability, bone mass, muscle strength and mass, cardiovascular function, and levels of androgens (such as testosterone) and nonandrogenic anabolic hormones such as growth hormone and insulinlike growth factor-I (IGF-I) with aging in men. We also consider the risk-to-reward ratio of possible benefits and adverse effects of androgen therapy in elderly men.

*Men differ from women in the time of onset and the development of senescent changes in the reproductive hormonal system. Menopause (in women) occurs over a few months to years, but the decline in men is slow and progressive, beginning sometime after age 30 and declining slowly thereafter. For many years the decrease in serum testosterone levels is not clinically discernible, but during the seventh decade symptoms and metabolic effects are common.

Androgen Levels in Elderly Men

A decline in serum levels of testosterone with aging has been reported in multiple cross-sectional studies of elderly men, with a considerable proportion falling below the normal range for young men.[1-7]* The metabolic clearance and production rates of testosterone have been shown also to be lower in elderly men.[1,4] The circadian rhythm in serum testosterone levels—higher in the morning, lower in the evening—observed in younger men is also lost in older men.[8] This may explain the inability to show an age-related decline in testosterone levels in some studies using specimens obtained in the afternoon. When integrated 24-hour or morning testosterone levels are measured, the concentrations are lower in the elderly. Limited longitudinal data on a small number of subjects confirm the decline of hormonal secretion with aging reported in cross-sectional studies.[5] This decline in total serum testosterone levels may be influenced by the health and physical fitness of the subjects. In studies where exceptionally healthy old men are studied, hormonal levels may be in the normal range despite advancing age.[9-11] Even though serum total testosterone levels may be normal in some elderly men, the levels of free (non-protein bound) or bioavailable (non-sex hormone-binding globulin bound) testosterone are often decreased. This is because levels of sex hormone-binding globulin increase with age, leading to lower levels of free or bioavailable testosterone.[2-4,6,12-15] Longitudinal data are limited on the relative change of serum-free or bioavailable testosterone levels in individual persons as they age. Some investiga-

*See also the editorial by A. M. Matsumoto, MD, "'Andropause'—Are Reduced Androgen Levels in Aging Men Physiologically Important?" on pages 618-620.

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ABBREVIATIONS USED IN TEXT

FSH = follicle-stimulating hormone
HDL = high-density lipoprotein
IGF-I = insulinlike growth factor-I
LDL = low-density lipoprotein
LH = luteinizing hormone

tors think that most men have a progressive decrease in serum testosterone concentrations as they get older. In contrast to testosterone, serum 5α-dihydrotestosterone levels are either slightly reduced or unchanged with aging, perhaps reflecting an increased production of dihydrotestosterone by the prostate in elderly men.[6,11,12] Levels of other androgens and metabolites such as androstanediol, androstanediol glucuronide, and dehydroepiandrosterone have been reported to decline between ages 40 and 70.[6] In most studies, levels of estrogens are not changed in elderly men.[4,6,9,13,16]

The mechanisms causing lower testosterone levels in healthy elderly men include a decreased responsiveness of Leydig cells to luteinizing hormone (LH) and a blunted compensatory elevation of LH to the lower testosterone levels. The primary testicular defect in the elderly is evidenced by a low Leydig cell mass,[17] a low testosterone production rate,[1] and a diminished testosterone response to exogenously administered LH or human chorionic gonadotropin.[3,9,18] Although most studies show elevated mean levels of LH and follicle-stimulating hormone (FSH) in aged men,[3,4,13,19] the increase in gonadotropins may be inappropriately low compared with the levels found in younger men with similarly decreased testosterone levels.[15,16] The occurrence of a secondary hypothalamic-pituitary defect in elderly men is further supported by the reports of decreases in the relative responsiveness of LH and FSH to gonadotropin-releasing hormone.[3,11,19,20] Low bioactive versus immunoreactive levels of LH and FSH[21,22] and alterations in LH pulse frequency and amplitude have been reported in elderly men.[23,24] The consensus from these studies is that serum testosterone and in particular bioavailable testosterone levels decrease with aging in men and that hypogonadism in elderly men is consequently a combination of testicular and hypothalamic-pituitary dysfunction.

Reproductive Function

An abrupt cessation of reproductive capacity, comparable to the menopause, does not occur with aging in men. Studies on spermatogenesis from autopsy specimens in elderly men showed substantial decreases in daily sperm production rates, testicular parenchyma tissue, seminiferous tubule volume, Sertoli cell numbers, and round spermatids compared with younger men.[17] Studies examining semen measurements from elderly men generally confirm the histomorphometric findings. Nieschlag and co-workers reported that healthy older men had higher sperm concentrations and lower sperm motility than younger men.[11] The ejaculate volume, sperm structure, and sperm fertilizing capacity as assessed by the zona-free hamster oocyte test did not decrease with aging. The duration of abstinence was longer in the older men and could have accounted for the increased sperm concentration and decreased motility. In another study Tsitouras showed that when the duration of abstinence was controlled at between two and three days, lower ejaculate volume, greater sperm motility, and percentage of spermatozoa with normal structure were reported in elderly men.[25] The actual fecundity of elderly men is not known, although a gradual decrease in fertility with aging has been reported.[26] The relationship between reduced androgen production and altered spermatogenesis in elderly men remains unclear.

Androgens, Psychosexual Function, and Cognitive Ability

Similiar to serum androgen levels, sexual activity and libido decrease with age in elderly men.[18,25,27] In most men with age-related sexual decline, however, factors other than decreased hormonal secretion (impaired penile vasculature, depression, chronic illness, pharmacotherapy) may also play a role. Well-controlled research has shown that testosterone therapy enhanced sexual desire and sexual fantasy in nonelderly hypogonadal men.[28] In elderly men, decreased libido and impotence present a common and important clinical problem. Although androgen replacement has been shown to enhance sexual function in many elderly men with low testosterone levels,[29,30] it cannot be assumed that androgen deficiency is responsible for impaired potency in older men when testosterone levels are in the normal range. Furthermore, no data are available to judge the effect of falling testosterone levels as men age when testosterone concentrations are still within the normal range. The threshold for testosterone effects on the libido in young men and young adult animals appears to be lower than that for many other metabolic functions,[31] but well-designed similar studies in older men are limited.

Evidence for hormonal effects on cognitive functions comes from studies showing relationships between testosterone and visuospatial ability in young men[32] and from a study showing changes in cognitive abilities with seasonal changes in testosterone levels.[33] In addition, a recent study found that hormonal treatment enhanced performance on the block design subtest of the Wechsler Adult Intelligence Scale in elderly men, whereas placebo treatment did not.[34] Similarly, in women with surgically induced menopause, memory and sexual functioning have improved following estrogen-androgen administration.[35] Thus, it is possible that age-dependent decreases in visuospatial ability, memory, and sexual functioning relate in part to a decline in testosterone levels.

Androgens and Osteoporosis

Although far greater attention has been given to the incidence of osteoporosis and fractures in aging women, an increasing incidence of osteoporotic fractures in aging men has been documented[36,37] and poses a major health problem. Bone density measurements show a progressive

decline with age in elderly men.[38-41] The risks of fractures in both men and women about double every five years after the age of 50.[37] A recent study of 30,000 men older than 40 years and 27,000 women older than 55 years in Finland showed that with aging, men had a greater risk of sustaining a thoracic vertebral fracture than women.[42] Because of the relatively few studies of aging in men, the pathogenesis of male osteoporosis is unclear; it has been suggested that declining gonadal function may be a major factor. Androgen receptors have now been demonstrated in human osteoblasts,[43] and androgens have been shown to induce the replication of human osteoblasts in vitro[44] and to modulate osteoblast function.[45]

Hypogonadism in men is associated with an increased risk of fractures.[46] Premature osteoporosis occurs in hypogonadal men in association with hypothalamic dysfunction, hyperprolactinemia, anorexia nervosa, Klinefelter's syndrome, and castration.[47-51] Androgen replacement therapy in osteoporotic men with clinically apparent hypogonadism[52,53] or correction of the low serum testosterone levels of hyperprolactinemia[48] is associated with an improvement in bone density. The few studies reporting bone histomorphometry do not agree on whether the osteoporosis of androgen deficiency is a low-turnover or high-turnover state.[48,49,52] In some patients urinary hydroxyproline excretion, a marker of bone resorption, has been found to be elevated.[47,51] In only one study have the newer tests of osteoblast function, including serum osteocalcin and bone-specific alkaline phosphatase activity, been assessed, and they were found to be elevated.[51]

Although decreased androgen secretion (low serum androgen levels) and osteoporosis are commonly seen in aged men, the causal relationship of the altered androgen levels and osteopenia are less clear. In men with vertebral crush fractures, 16% were found to have hypogonadism.[54] Early studies by Foresta and associates showed a positive linear correlation between the percentage of cortical area of the left second phalanx and serum testosterone or androstenedione levels in 30 elderly men.[55] Another study showed that vertebral bone density assessed by computed tomography in 60 healthy men (ages 30 to 92 years) correlated strongly with the free testosterone levels.[56] In another cross-sectional study of 48 healthy men (ages 21 to 79 years), bone mineral density at the spine and femoral neck (measured by dual-photon absorptiometry) was not correlated with sex hormone levels, but the bone mineral density at the radius was predicted by free testosterone levels and by body weight.[57] In one study in a nursing home population of white men older than 65 (mean age 77), 27% of the men had free testosterone concentrations below the normal range for the general population. In those with minimal-trauma hip fractures, 59% had hypogonadism as compared with 18% of the controls.[58] A recent study of 13 elderly men showed that testosterone replacement led to decreases in urinary hydroxyproline levels, suggesting a decrease in bone turnover. A preliminary report in 5 hypogonadal elderly men showed an increase in bone mineral density after testosterone replacement therapy.[60]

Androgens, Physical Exercise, Muscle Strength, and Function

Testosterone replacement in elderly men may have other benefits. Cross-sectional and longitudinal studies in elderly men show that lean body mass decreases and body fat increases with aging.[61-63] Although androgens are widely used by athletes and body builders, the evidence that their use increases muscle mass and muscle strength in normal men remains inconclusive.[64,65] A recent study in a small number of healthy men suggests that testosterone may increase muscle mass by increasing muscle protein synthesis.[66] The treatment of young healthy men and men with muscular dystrophy with testosterone administration for three months increased the basal metabolic rate and lean body mass.[67] In hypogonadal men, the replacement of androgens led to nitrogen retention, an increase in muscle mass, and a loss of adipose tissue.[64] Although it is not certain whether androgen replacement therapy will increase lean body mass, improve muscle strength, and decrease body fat in elderly men, some data are supportive. Tenover reported that short-term replacement therapy increases lean body mass and muscle mass in elderly men.[59] Muscle mass has been shown to be predictive of muscle strength in the elderly.[68] Muscle strength and physical activity are predictors of bone mass in women.[69,70] In elderly men, body composition, aerobic capacity, and muscle strength correlate strongly with bone mineral density.[71] Thus, improved muscle strength with androgens, physical activity, or both may also contribute to increases in the bone mineral density.[72]

Endogenous androgen levels are substantially influenced by physical exercise. As with growth hormone, the increase in circulating testosterone levels occurs within a short period of time (minutes) of the start of exercise.[73-75] Factors like nutritional status and the degree of exercise training are known to influence the testosterone response. Researchers have suggested that the increase in testosterone after exercise may be due to dehydration or to reduced hepatic flow with resultant decreased metabolic clearance. Exercîse-induced secretion of testosterone is less in the elderly, similar to the growth hormone response to exercise.[76] There is some evidence that exercise-induced testosterone plays a role in the training effect—the phenomenon of muscle growth and hypertrophy that accompanies physical training. Thus, a cycle of physical inactivity, reduced endogenous testosterone secretion (or other growth factors), and decreased muscular function could likely contribute to the physical frailty that worsens the quality of life of many elderly people. Whether exercise alone or exercise in combination with exogenous testosterone administration can mitigate the well-described age-related reduction in exercise capacity is not known. Moreover, although training programs in older persons clearly improve cardiorespiratory fitness,[77] the mechanism of these changes remains unknown.

Growth Hormone and Insulinlike Growth Factors

In addition to low androgen levels, aging is associated

with low growth hormone and IGF-I secretion in men. Although baseline growth hormone levels appear to be unchanged, the total growth hormone peak area and the amplitude of the peaks are usually decreased in men older than 65 years.[78-80] In addition to the decreases in the pulsatile secretion of growth hormone, studies have shown low serum concentrations of IGF-I in elderly men.[79-81] It has been suggested that the reduced growth hormone levels in the elderly may be responsible for changes in body composition.[82] Recently cross-sectional studies showed that basal serum IGF-I levels were negatively correlated with indices of adiposity, the percentage of body fat, and indices of upper body fat and positively related to the cardiorespiratory response to exercise and physical activity.[83,84] Although this suggests that lower growth hormone and IGF-I secretion may contribute to the development of obesity in older men, other factors such as altered physical activity, caloric intake, and gonadal function are also important. Based on these observations, Rudman and colleagues treated a group of healthy men aged 61 to 81 years with growth hormone.[85] Preliminary studies showed small (less than 10%) increases in lean body mass, decreases in adipose-tissue mass, and minimal increases in lumbar vertebral bone density (1.6%). Parfitt recently reviewed the effects of growth hormone on adult bone remodeling.[86] The studies indicate a parallel increase in markers of bone resorption and formation, suggesting the activation of bone remodeling but a questionable net change in bone density. The risk-benefit ratio for long-term growth hormone therapy in elderly men has not been established, nor has it been shown conclusively that increased adiposity and decreased muscle mass are directly related to growth hormone or IGF-I deficiency. The possible risks of growth hormone and IGF-I therapy may include osteoarthritis and neoplasia.[87] In prepubertal boys and hypogonadal men, treatment with testosterone or human chorionic gonadotropin increases mean growth hormone levels, pulse amplitude, and serum IGF-I levels.[88,89] The low IGF-I and changes in growth hormone levels in aging men may be related to the hypogonadism. This possibility has not yet been adequately explored.

Possible Adverse Effects of Androgen Replacement Therapy

Although androgen replacement therapy may have benefits on bone mass, muscle strength, and psychosexual and cognitive function in elderly men with low testosterone levels, adverse effects may occur.[90] Androgen therapy is associated with mild weight gain of a few kilograms. Gynecomastia as a result of androgen therapy is mild and requires no treatment. Excessive oiliness of the skin and the development of acne are seen in younger men given androgen replacement. Whether these skin changes will occur in elderly men is not known. These changes in the skin usually require no treatment or the external application of cleansing soap. Other side effects may occur, including the aggravation of prostatic disease, alterations in lipid and carbohydrate metabolism, sleep apnea, and increased erythropoiesis and fibrinolysis.

Prostatic Disorders

Prostatic diseases (cancer and benign prostatic hypertrophy) are common problems of elderly men. Neither of these conditions develops without testosterone exposure during puberty and early adulthood. There is no direct relationship between serum androgen levels in adult or elderly men and the incidence of these disorders. Androgens in in vitro experiments regulate programmed cell death of prostate cells. The adult prostate maintains its size through a balance between the processes of cell death and cell renewal. Androgens modulate growth and differentiation of the prostate directly or may interact with a number of growth factors, their receptors, and binding proteins within the prostate.

Prostate cancer is one of the most commonly diagnosed cancers in the United States. It occurs in a preclinical (microscopic) and a clinical form. By the seventh decade, about 50% of men have microscopic prostate cancer. But the progression of preclinical cancer to clinical prostate cancer occurs in only a small proportion of these men. The progression to clinical disease is variable among ethnic groups and is associated with environmental as well as genetic factors. There are no data to show whether androgen therapy will enhance the progression of preclinical to clinical cancer. Androgens are known to stimulate the growth of clinically diagnosed prostate cancer.[91]

Benign prostatic hypertrophy occurs in more than 80% of men aged 70 years or older. It leads to urinary outflow obstruction that usually requires surgical intervention. Recent studies have shown that decreasing the production of testosterone and dihydrotestosterone in men with benign prostatic hypertrophy decreases the prostate size and improves urinary flow.[92] Despite the theoretical considerations, there is no evidence that the replacement of androgens in hypogonadal young or elderly men will lead to the development of hyperplasia or aggravate its clinical status. Clearly, careful monitoring of prostate size and abnormalities by rectal examination and prostatic ultrasonography, urinary flow studies, and markers of prostatic disease such as prostate-specific antigen are required in elderly men treated with androgen replacement therapy.[90,93]

Lipid and Carbohydrate Metabolism

The relationship of circulating androgens to lipid profiles is somewhat controversial. Correlative studies have suggested that both testosterone and high-density lipoprotein (HDL)-cholesterol levels decline with age. Data in younger men have also shown a direct correlation between serum testosterone and HDL-cholesterol levels. These data have recently been reviewed and have led to the suggestion that testosterone treatment may raise HDL-cholesterol levels and be beneficial to patients with coronary artery disease.[94] On the other hand, synthetic 17α-alkylated steroids have been shown to decrease HDL-cholesterol and apoprotein A-I and A-II levels and to increase low-density lipoprotein (LDL)-cholesterol levels.[95] The importance of this finding is that low HDL

levels and high LDL-to-HDL ratios are associated with an increased risk for coronary artery disease. When androgens such as testosterone and its esters are given to hypogonadal or eugonadal men, small decreases or no significant effects on LDL-cholesterol and mild decreases in HDL-cholesterol levels are seen.[59,95-97] It has been postulated that the difference in the effect of 17α-alkylated androgens and testosterone on lipids is that testosterone is converted to estradiol (aromatizable androgens), which has an opposite effect from androgens on blood apoproteins and cholesterol levels. The clinical significance of a small decrease in HDL-cholesterol levels is unknown.

Testosterone does not cause glucose intolerance or increased insulin secretion. This is in contrast to the effects of 17α-alkylated androgens, which increase the insulin response to glucose and impair glucose tolerance in men.[98]

Sleep Apnea

Sleep apnea is much more common in men than in women. Obese men, elderly men, patients with chronic obstructive pulmonary disease, and patients with acromegaly are predisposed to sleep apnea. Administering androgen to hypogonadal young men can precipitate or aggravate clinical symptoms of sleep-related breathing disorders.[99] The administration of androgens to elderly men could be a problem, especially in those who are overweight, heavy smokers, or who have chronic obstructive airway disease.

Erythropoiesis and Fibrinolysis

Androgens increase red cell mass mainly through a direct effect on erythropoietin. Androgens also have a direct effect on the bone marrow stem cells. Adult men have higher hemoglobin concentrations than male children, hypogonadal men have lower than normal red cell mass, and correcting androgen deficiency leads to a substantial increase in hemoglobin levels—all of which demonstrate the relationship between androgens and erythropoiesis.[100] Administering androgen to normal men also increases their hematocrit and red cell mass.[101] Elderly men have lower hematocrits than younger men. Androgen replacement in elderly men will stimulate erythropoiesis and increase red cell mass. It is unknown, however, whether the androgen-induced increase in hematocrit is beneficial to the elderly men or may lead to more frequent episodes of thromboembolism.[102]

Administering anabolic17α-alkylated androgens such as stanozolol may increase fibrinolytic activity and antithrombin III (a natural anticoagulant) levels.[100] The increase in fibrinolytic activity may neutralize some of the effects of increased hematocrits and altered HDL-to-LDL ratios by decreasing intravascular clotting ability.[90]

Summary

Aging in men is generally accompanied by a decrease in testosterone levels and, in particular, free testosterone levels. Androgen substitution in elderly men with low testosterone levels has been shown in recent reports on small numbers of patients to improve sexual function and prevent bone loss. Large prospective placebo-controlled studies are required to confirm the beneficial effects of androgens on bone and muscle mass, physical well-being, and psychosexual function. These studies will also help to clarify whether androgen substitution may stimulate prostate growth, leading to prostate disease. The effects of androgens on lipid levels, hematocrit, fibrinolytic activity, and the respiratory system can be carefully monitored. These studies will give a risk-to-benefit ratio of androgen replacement therapy in elderly men and will be a prerequisite to the development of treatment strategies of aging men.

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