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Androgen Replacement in Men with Hypogonadism and Erectile Dysfunction

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The prevalence of hypogonadism and erectile dysfunction (ED) increases with age. Hypogonadism also is frequently associated with decreased libido and ED. Testosterone replacement therapy for hypogonadal ED is effective in restoring sexual desire and erectile function, especially in younger and healthy men. It appears to be less effective in older men with comorbid diseases that may cause ED. Therapy should be individualized, considered carefully, and closely monitored because of potential risks, especially in older men. The FDA has approved several testosterone delivery systems. These include a buccal testosterone tablet, intramuscular injections, transdermal and subcutaneous forms. There also are several promising experimental androgens under investigation including non-steroidal selective androgen receptor modulators (SARMs).

Key Words: Testosterone; androgen; hypogonadism; libido; erectile dysfunction.

Introduction

Testosterone and its metabolites, dihydrotestosterone (DHT) and estradiol (E_2), have a critical role in the development and maintenance of normal male genitalia, testes, accessory sex organs, skeletal muscle mass, bone growth mass, male hair patterns, and libido and erectile function *(1)*. Testosterone is also thought to influence central nervous system gender identification *(2)*. DHT as well as testosterone can maintain libido and erectile function, indicating that estrogen is not required for their maintenance in men *(3)*.

Androgens and the Brain

Sex steroids can modulate secretion and release of neurotransmitters within hypothalamic and other brain areas *(4)*. Androgen receptors (ARs) are present in the amygdala, lateral septum, and premamillary bodies in male primates *(5)*. AR-linked brain sites in the hypothalamus, pituitary gland and preoptic areas appear to influence male sexual behavior. For instance, stimulation of forebrain, hippocampus, and hypothalamic nuclei causes penile erection and/or mating behavior in laboratory animals *(6–8)*. Contemplating or imagining a sexually stimulating condition, by visual and/or auditory stimuli and by tactile or osmic stimuli, can stimulate sexual arousal. Presumably, each of these sensations is mediated by the cerebral cortex. These stimuli are important for libido, and available evidence indicates that androgens affect libido. Imaging studies using positron emission tomography and cerebral blood flow have been used to correlate brain activation with visual sexual stimuli in healthy men *(9)*. Other studies indicate that the hypothalamic paraventricular nuclei could be the main source of a descending spinal erection pathway to the spinal erection generator *(10)*.

A number of observations demonstrate that androgen also can affect erections by acting on peripheral neural pathways. We were able to demonstrate increased penile rigidity during sleep-related erections in hypogonadal men soon after testosterone replacement as compared to 7 to 8 wk later when testosterone levels were subnormal *(11)*. These findings have been confirmed *(12)*. Additionally, visually stimulated erections are reported to be firmer in testosterone-treated hypogonadal men *(13)*. More recently, animal studies have demonstrated that ARs are located in peripheral neurons responsible for mediating penile erections (see the article by Lewis and Mills in this issue). Castration decreases electrically stimulated erections, and testosterone replacement increases the response. Finally, penile nitric oxide, the major smooth muscle relaxor responsible for penile erections, is in part regulated by testosterone. At this time it is not known if the peripheral androgenic effects observed in animals also are present in man. Although ARs are prevalent in the penis during development of animals and man, ARs are reduced in the adult penis. This suggests that the peripheral effects of androgen on the adult penis are more likely to be mediated by neuronal mechanisms as opposed to direct effects on either the endothelium or trabecular smooth muscle.

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Table 1
Plasma Testosterone and AFTC Levels and Body Mass Index According to Age Group[a]

Age (yr)	Testosterone (ng/dL)	AFTC (ng/dL)	Body Mass Index
20–39 (mean 26 ± 5) (*n* = 70)	683 ± 209	10.75 ± 2.68	23.0 ± 2.8
40–59 (mean 45 ± 5) (*n* = 54)	599 ± 167	11.93 ± 3.70	25.5 ± 2.9
60–69 (mean 65 ± 3) (*n* = 41)	575 ± 134	6.23 ± 2.58	26.6 ± 4.5
70–79 (mean 74 ± 1) (*n* = 51)	428 ± 128	5.28 ± 2.22	26.2 ± 4.3
80–89 (mean 84 ± 3) (*n* = 76)	434 ± 174	—	24.6 ± 4.4
90–101 (mean 93 ± 3) (*n* = 9)	391 ± 189	4.72 ± 1.24	25.2 ± 5.4

[a]All values are mean ± SD. (Adapted from ref. *19*.)

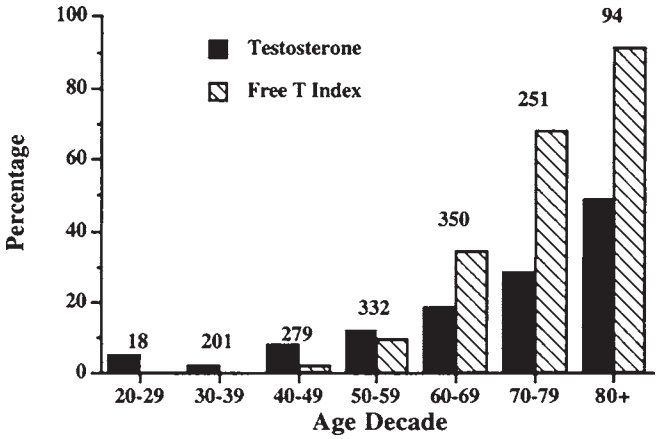

Fig. 1. Percentage of age group that was hypogonadal by decade using total and free testosterone index. Bar height indicates the percentage of men in each 10-yr interval, from the third to the ninth decades, with at least one testosterone value in the hypogonadal range, by the criteria of total testosterone <11.3 nmol/L (325 ng/dL) (shaded bars), or testosterone/SHBG (free testosterone index) <0.153 nmol/nmol (striped bars). Numbers above each pair of bars indicate the number of men studied in the corresponding decade. T, testosterone. (Adapted from ref. *20*.)

Prevalence of Erectile Dysfunction

In a recent national survey, 31% of 1410 men ages 18–59 yr reported sexual dysfunction *(14)*. Sexual function includes libido, penile erection, ejaculation, and orgasm. While each of these parameters may be of concern to an individual patient, the vast majority of men complain of erectile dysfunction (ED). Testosterone deficiency frequently is associated with decreased libido and ED.

ED is a clinical problem that is underdiagnosed, underevaluated, and undertreated. Kinsey *(15)* reported in 1948 that ED affected about 10% of men, mostly men over 75 yr of age. Nowadays, there is increasing recognition of this condition. ED is a common complaint in the primary care setting. The Massachusetts Male Aging Study was conducted from 1987 to 1989. It was designed as a community-based, random sample observational survey of 1290 noninstitutionalized men 40–70 yr old. It found that the combined prevalence of minimal, moderate, and complete ED was 52%. The prevalence of complete ED tripled from 5 to 15% between subjects 40 and 70 yr of age *(16)*. The prevalence of ED increases with age, and it is associated with multiple medical conditions including diabetes, hypertension, and heart disease that also increase with age.

The frequencies of associated causes of ED vary depending on the patient population. A study of 121 men *(17)* with a mean age of 68 yr described the causes of ED as follows: vascular (21%), neurogenic (28%), combined vascular and neurogenic (30%), drug-induced (4%), hypogonadism (2.9%), and Peyronie disease (1.3%). Hypogonadism is more common in older populations; however, it frequently is associated with comorbid diseases that also can cause ED.

Prevalence of Hypogonadism

Testosterone is synthesized within the Leydig cells under the influence of a glycoprotein produced in the anterior pituitary gland, luteinizing hormone (LH). Testosterone circulates in serum bound to sex hormone–binding globulin (SHBG) and albumin (approx 44 and 54%, respectively) and only 2% is free *(18)*.

Serum levels of testosterone, dehydroepiandrosterone (DHEA), and DHEA sulfate undergo age-related changes. After the fifth decade of life, a significant percentage of men have low total and free testosterone levels (Table 1; Fig. 1) *(19,20)*. Total E_2 levels usually are within normal limits, but some studies indicate that they also fall with aging. Aging is associated with an increase in SHBG; how-

ever, obesity causes a reduction in SHBG levels, so levels are not predictable in aging obese men. Testosterone is secreted in a circadian manner in younger men, but diurnal fluctuation is reduced and may disappear in aging men *(21)*.

Hypogonadism and Penile Erections

Many studies have associated testosterone levels and sexual activity. Epidemiologic studies have demonstrated reduced sexual activity in boys with low serum testosterone levels compared with those having higher levels even when pubertal development is considered *(22)*. Testosterone treatment in boys with delayed puberty increases nocturnal emissions and touching behaviors *(23)*.

One objective means for evaluating the effects of testosterone on erections is to assess nocturnal penile tumescence (NPT). Karacan et al. *(24)* evaluated penile erections throughout the age spectrum. They noted that prepubertal boys do have penile erections and that NPT increases in frequency at the time of puberty. Consistent with the importance of testosterone on NPT are the observations of Burris et al. *(25)*. They studied young men with severe testosterone deficiency. NPT was absent or greatly diminished, and increasing serum testosterone levels normalized nocturnal erections. Serum testosterone levels below 200 have been associated with reduced NPT *(26)*.

Testosterone deprivation also is associated with reduced sexual activity. Bagatell et al. *(27)* administered the gonadotropin-releasing hormone (GnRH) antagonist Nal-Glu to 10 sexually healthy young men. They observed significant decreases in the frequency of sexual desire, sexual fantasies, and intercourse by 4–6 wk. Men who received the antagonist plus testosterone enanthate (either 50 or 100 mg intramuscularly each week) did not experience a change in these parameters. Similarly, Hirshkowitz et al. treated 10 sexually healthy young men with a GnRH agonist. They noted a significant decline in sleep-related duration of erections at 8 and 12 wk when testosterone levels were very low.

Other confusing issues regarding gonadal function and erections are reports indicating that some men continue to have erections sufficient for intercourse for months to years following castration *(29)*. This emphasizes the social and learned aspects of sexual activity in men. Furthermore, Rhoden et al. *(30)* found a direct relationship between the prevalence of ED and aging; however, there was not a consistent correlation between low serum total testosterone and ED *(30)*. Finally, further confounding the relationship of low testosterone and ED are observations that effective, nonhormonal treatment of ED can increase testosterone levels in some men *(31)*.

Testosterone Supplementation for Hypogonadal ED

There are multiple potential causes of hypogonadism in both younger males and aging men. They include primary hypogonadism (primary testicular disease), secondary hypogonadism (pituitary disease), and tertiary hypogonadism (hypothalamic disease). Moreover, several common clinical conditions are associated with dysfunction at both a hypothalamic and a testicular level. Patients having a total testosterone level <150 ng/dL and an LH level that is not increased should undergo magnetic resonance imaging (MRI) to look for an anatomic abnormality in the pituitary or hypothalamic area *(32)*.

Androgen treatment for ED is effective in younger men, but less effective in men with comorbid diseases associated with ED. Nonetheless, restoring normal levels of testosterone can produce a favorable outcome in a considerable number of patients.

Several placebo-controlled clinical studies have demonstrated that testosterone replacement improves libido and erectile function. One of the first objective studies to assess the effects of testosterone on sexual activity was conducted in six hypogonadal men who were treated with parenteral testosterone every 4 wk. Testosterone increased the number of total erections, nocturnal erections, and coital attempts compared with placebo *(33)*. In another report, hypogonadal men treated with oral testosterone undecanoate experienced an increased number of sexual acts per week, increased number of ejaculations per week, and increased frequency of sexual thoughts and excitement compared with placebo *(34)*. Nankin et al. *(35)* treated impotent men with low testosterone levels. Testosterone cypionate compared with placebo increased libido and potency. Both scrotal testosterone patches *(36)* and torso testosterone patches *(12)* improved libido and sexual activity. Improved sexual function was also noted when hypogonadal men were treated with transdermal testosterone gel *(37)*.

Androgen treatment increases nocturnal and spontaneous erections as well as sexual interest. Burris et al. *(25)* evaluated nocturnal erections in severely hypogonadal young men before and during hormone replacement. Nocturnal erections were increased in frequency and in quality. We evaluated six hypogonadal men 4–7 d after they were given an IM injection of testosterone cypionate and again 5 to 6 wk later. The number of NPT episodes, maximum penile circumference, total tumescence time, and penile rigidity decreased significantly at the later time point when serum testosterone levels had fallen to the hypogonadal range *(11)*. Similar effects were noted when hypogonadal men were treated with transdermal testosterone *(12)*.

Other studies also have noted that androgen replacement in men with low testosterone levels does not increase daytime erections but can improve daytime erectile rigidity *(13)*. Although untreated hypogonadal men had erections while observing erotic films, penile rigidity of erections stimulated by visual erotic material increased significantly after testosterone therapy.

Jain et al. *(38)* conducted a meta-analysis of 16 studies from 73 publications to assess the effectiveness of androgen replacement for ED. They concluded that patients with

Table 2
Delivery Systems for Testosterone

Oral	Intramuscular	Subcutaneous	Transdermal
Fluoxy-mesterone	Testosterone cypionate	Testosterone pellets	Testosterone patch
Methyl testosterone	Testosterone enanthate		Testosterone gel
Testosterone undecanoate	Testosterone decanoate		
Buccal testosterone[a]	Testosterone propionate		
	Testosterone undecanoate[a]		

[a]Experimental.

primary hypogonadism responded favorably more frequently than those with secondary testicular failure (64 vs 44%) and that transdermal testosterone was more effective than either IM or oral forms of replacement. These conclusions need confirmation in a prospective study.

In summary, hypogonadism often is difficult to diagnose purely on a clinical basis. Biochemical measurements usually are needed to support the diagnosis. Measurement of two early morning levels of serum total testosterone may be sufficient if the level is <200 ng/dL. However, values between 200 and 400 ng/dL require additional testing because of the effects of aging and obesity on SHBG. Measurement of bioavailable testosterone, free testosterone by equilibrium dialysis, or calculated free testosterone (based on total testosterone and SHBG) is useful and necessary for diagnosis in patients with borderline low levels of total testosterone. Treatment with testosterone must be considered carefully because of potential risks, especially in older men.

Testosterone Treatment

The goal of testosterone therapy is to normalize serum testosterone levels in patients with hypogonadism. Therapy should maintain or restore libido and erectile function; improve or maintain virilization, muscle mass and strength, and bone density; and alleviate other symptoms related to hypogonadism. Of note, ED associated with hypogonadism may not improve after adequate androgen replacement. This should prompt the physician to reconsider the diagnosis and to look for other possible causes of ED. There is some evidence that the addition of type 5 phosphodiesterase inhibitor can potentiate the effects of testosterone replacement in some hypogonadal men *(39)*. If this is unsuccessful, one should consider other treatments for ED.

Testosterone Delivery Systems

The Food and Drug Administration (FDA) has approved several testosterone delivery systems (Table 2). Some of them were "grandfathered" and have not undergone careful evaluation, including the oral alkylated androgens that were developed by adding a 17-α alkyl group to testosterone. This modification reduced first-pass catabolism by the liver, a problem that eliminates the effectiveness of oral testosterone. Oral 17-alkylated androgens are not used commonly today because of poor efficacy unless given in split doses of 40–50 mg/d. These doses can cause side effects including cholestasis, cystic disease of the liver, and hepatoma *(40,41)*. Oral testosterone undecanoate is available in Canada and Europe. It is administered in capsules containing oil. The oil is absorbed into the intestinal lymphatics, bypassing first-pass metabolism by the liver. Nonetheless, divided doses of 160–240 mg/d are required to provide replacement, and nocturnal levels of testosterone usually are subnormal. Testosterone also can be delivered into the systemic circulation by means of a bioadhesive tablet that releases testosterone into the oral cavity where it is absorbed through the oral mucosa *(42)*.

The injectable lipophilic esters (testosterone propionate, enanthate, and cypionate) are suspended in oil, producing a depot with slow release when injected intramuscularly. Testosterone propionate is too short acting to be used for replacement therapy. After administration of either testosterone cypionate or testosterone enanthate, peak levels occur within 72 h. Although IM administration of testosterone cypionate or testosterone enanthate is biologically effective, these treatments can be associated with symptoms, especially when the interval between injections is more than 2 wk. Pharmacokinetic studies indicate that the injection of 100–200 mg of testosterone enanthate every 1 or 2 wk, respectively, provides the most physiologic serum levels of testosterone *(43)*. One goal is a midnormal serum level of testosterone midway between injections. As a general guide, the level of testosterone at the nadir should be somewhat above the lower limit of normal. The dose or frequency of injections can be adjusted to achieve this level. Some patients can self-inject a T ester. Some have a spouse of friend do this for them, and some men return to the physician's or nurse's office for injections. The latter increases the cost of testosterone replacement; however, this delivery system is the least costly.

Transdermal administration of testosterone was introduced in the United States in 1994 as a scrotal patch. Scrotal testosterone patches were available as 40- and 60-cm^2 patches, delivering 4 and 6 mg of testosterone daily, respectively *(44)*. Serum levels peak 3–5 h after application *(45,46)*. The patch is applied daily after bathing and worn continu-

ously for 24 h. Patients must dry shave their scrotal hair twice a week to enhance adherence of the patch.

The nonscrotal form of patch (Androderm) is worn on the arm, hip, or trunk. This patch is designed to deliver 5 mg of testosterone every 24 h, and serum level peaks in 3–8 h after application *(47)*. Skin rash is common with the Androderm patch. Applying triamcinolone cream on the skin side of the patch can reduce contact dermatitis. The annual cost for testosterone patches ranges from $800 to $1500.

The FDA approved the first testosterone gel for daily application to nongenital skin in 2000. It dries quickly, and it is available in packets of 2.5 g (25 mg of testosterone) and 5 g (50 mg of testosterone). Skin rashes are uncommon, but, theoretically, close skin contact can transfer testosterone to a female or child. Patients are advised to apply the gel to the upper arm or abdomen, where it can be covered to prevent possible transfer. Serum levels plateau within a few days and are relatively stable when the gel is applied every 24 h *(48)*. The FDA recently approved a second gel. Pharmacokinetics appear to be somewhat different from the first gel, emphasizing the need to monitor serum levels of testosterone and to adjust doses accordingly.

Testosterone pellets also are available in the United States, Europe, and Australia. Although the need to make a small incision and use a retention suture to keep them in place limits their acceptance, they can be effective *(49)*. Pellets have not been very popular in the United States but are in Australia.

Several experimental androgens are under investigation. They include an IM form of testosterone undecanoate and selective androgen receptor modulators (SARMs). The latter can provide normal serum testosterone levels for 6–12 wk. A long-acting IM preparation probably is safer in younger men. Because it would be desirable to avoid stimulation of the prostate in older men, several pharmaceutical companies are working to develop SARMs. Such agents may be able to target some tissues and avoid others; however, it is not clear if they will be able to cross the blood-brain barrier or if they will have beneficial effects on bone because metabolism to E_2 appears to be required for the full effects of testosterone on bone.

Monitoring

Documentation that testosterone therapy achieves adequate serum levels of testosterone is essential. This should be done 1–3 mo after starting therapy. Testosterone levels can be determined midway between IM ester injections or at the nadir. Peak levels should be determined after application of a patch and at any time with the testosterone gels. Ideally, testosterone therapy should provide physiologic range serum testosterone levels (between 400 and 600 ng/dL) and physiologic DHT and E_2 levels.

Periodic follow-up of patients on replacement is essential. In men over age 50, the clinical response and potential side effects should be monitored at 3, 6, and 12 mo and then annually. The side effects of therapy are related to the delivery system and to testosterone, *per se*. They include skin rashes, acne, worsening of lower urinary tract symptoms, exacerbation of erythrocytosis, and sleep apnea. Gynecomastia may result from aromatization of testosterone to E_2. Lipid disturbances are generally not problematic. It is possible that androgen replacement can cause a nonclinical prostate cancer to increase in size and to become clinically detectable. It also is possible that androgen replacement will cause growth of an occult prostate cancer. It will suppress follicle-stimulating hormone/LH and may cause a noticeable reduction in testicular size. Absolute contraindications to therapy include prostate cancer and breast cancer.

The physician should inquire about symptoms of urinary tract obstruction and obstructive sleep apnea before and after initiation of therapy in patients over 40 yr of age. If suspected, urine flow rate, a postvoid residual urine volume, or a sleep study to document sleep apnea may be warranted. In addition, a hematocrit, prostate-specific antigen (PSA) level, digital rectal examination, and breast examination should be performed at baseline, 3, 6, and 12 mo and then annually in men over age 50 and in any man having a first-degree relative with prostate cancer or who is African American. Referral to a urologist is indicated if a prostate nodule or induration is detected, if PSA is >4.0 ng/mL or PSA changes more than 0.45 ng/mL per year over 2 yr *(50)*. The potential risk of androgen replacement on cardiovascular disease remains uncertain. Long-term prospective studies are needed to assess this risk as well as the risk of prostate diseases.

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