Testosterone therapy in erectile dysfunction

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ABSTRACT

Studies in animals have indicated that the nitric oxide erectile pathway is testosterone-dependent. Castration induces erectile dysfunction and a reduction in nitric oxide synthase-stained nerves in erectile tissue. Furthermore, castration adversely affects penile hemodynamics and smooth muscle content, leading to veno-occlusive dysfunction. Testosterone replenishment reverses these physiological, biochemical and structural changes. Several clinical studies have demonstrated the benefits of a combination of testosterone and sildenafil. A recently published, multicenter study evaluated the safety and efficacy of testosterone gel 1% (Testogel®; Schering AG, Germany/AndroGel®; Solvay Pharmaceuticals) vs. placebo gel in conjunction with sildenafil, in producing an erectile response in hypogonadal men who did not respond to treatment with sildenafil alone for erectile dysfunction. The selection criteria required subjects to have had erectile dysfunction for at least 3 months, to be non-responsive to 100 mg sildenafil and to have low testosterone levels (< 400 ng/dl). The primary efficacy measurement was the mean change from baseline in the Erectile Function domain of the International Index of Erectile Function (IIEF). Secondary outcome measures included the mean change from baseline in the other domains and the total sum of the IIEF. Subjects were randomized to receive either testosterone gel + sildenafil, or placebo gel + sildenafil for 12 weeks. Testosterone therapy with testosterone gel improved the erectile response to sildenafil. Therefore, testosterone therapy may be considered for the treatment of erectile dysfunction in men with low to low-normal testosterone levels, who have failed prior treatment with sildenafil alone. Consequently, it is important to screen for hypogonadism in men who fail PDE5 inhibitors.

INTRODUCTION

Testosterone is the main sexual hormone in human males, and has a pharmacological effect on the physiology of sexual function. It is known that suppression of testosterone in eugonadal adult males leads to reduced sexual desire and activity³, and may result in erectile dysfunction.

The prevalence of erectile dysfunction is high, affecting approximately 30% of men in the US². Erectile dysfunction is defined as the consistent inability to achieve and/or maintain an erection sufficient for satisfactory sexual activity⁴. Erectile dysfunction is clearly associated with a decrease in quality of life, and may lead to depression and, eventually, the avoidance of sexual activity⁴,⁵.

Although erectile dysfunction is multifactorial in etiology, it is strongly associated with age. The incidence of complete erectile dysfunction increases from 5% in men 40 years of age to 15% in...
men 70 years of age. With aging, there is a decline in serum testosterone that may lead to symptomatic late-onset hypogonadism (SLOH), of which erectile dysfunction is often a symptom. While some data suggest that erectile dysfunction and hypogonadism are independent, it is thought that a certain threshold of testosterone may be required for full sexual function. Testosterone replacement is indicated in men with SLOH, and has been demonstrated to significantly increase sexual desire and activity, and the frequency of erections. Thus, although testosterone deficiency may not always be the causative factor in cases of age-related erectile dysfunction, it is certainly a potential cause, and should be investigated in patients presenting with erectile dysfunction.

**ANDROGEN REGULATION OF CELLULAR PROLIFERATION**

Castrated rats provide a good, albeit not perfect, animal model of hypogonadism, and studies have shown that, in rats, penile erection is androgen-dependent. Studies in castrated rats have provided morphological evidence of the effects of testosterone on the penis. Castration induced apoptosis in specific cells in the corpora cavernosa (erectile tissue) of the rat penis, suggesting that certain cell types are dependent on testosterone for survival. Replenishment of testosterone after castration induced new DNA synthesis in the smooth muscle cells, stroma and blood vessels, and there was a pan-cellular proliferative effect in the penis.

**ANDROGEN REGULATION OF NITRIC OXIDE**

The physiology of the erectile response is mostly understood, although gaps in our knowledge remain. In rats, it has been demonstrated that penile erections are mediated by nitric oxide (NO) and are androgen-dependent. Direct or indirect stimuli can trigger an erectile response that starts with the release of relaxing substances, primarily the neurotransmitter NO, from the nerve endings in the corpora cavernosa. The effects of NO are mediated via two distinct second messenger systems: the cyclic guanosine monophosphate (cGMP) pathway and the cyclic adenosine monophosphate (cAMP) pathway. NO stimulates the synthesis of cGMP, leading to the phosphorylation of cellular membrane proteins and the efflux of calcium. Calcium efflux leads to vasodilation of the penile arteries and sinusoidal spaces, resulting in an erection. In addition, NO activates other second messengers such as prostaglandin E1, leading to the synthesis of cAMP and an increase in calcium efflux.

It is generally accepted that, in animals, testosterone stimulates the production of NO. More specifically, androgens are thought to stimulate the synthesis of the neuronal isoform of nitric oxide synthase (nNOS). Studies in castrated rats have demonstrated a smaller increase in intracavernosal pressure in response to electrical

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**Figure 1** Castration causes apoptosis in the rat penis. Adapted from Shabsigh R. The effects of testosterone on the cavernous tissue and erectile function. *World J Urol* 1997;15:21–6. Copyright Springer-Verlag 1997.

stimulation, compared with uncastrated rats, suggesting an androgen-dependent portion of the erectile response. In addition, molecular studies have demonstrated that the castrated animals had a reduction in the level of nNOS mRNA expression, compared with uncastrated animals. These results suggest that androgens mediate the erectile response in the rat penis by stimulating the expression of nNOS, thus maintaining an adequate supply of NO.

Although NO is considered to be the predominant vasodilator in the penis, there are other vasodilatory pathways in the erectile response that are independent of NO but are androgen-regulated. When castrated rats were treated with a combination of testosterone and a competitive inhibitor of NOS (L-nitro-L-arginine methyl ester), there was an increase in intracavernosal pressure in response to electrical stimulation, similar to that observed in uncastrated rats.

In order to elucidate further the effect of testosterone on NO and penile innervation, Baba and colleagues assessed three groups of rats: castrated; castrated with testosterone replacement; and sham-operated. The rats were subjected to three types of induced erections: apomorphine (to study centrally mediated erections), electrical stimulation and papaverine injections (to study peripherally induced erections). All three types of stimulation resulted in significantly fewer erections in the castrated rats, compared with rats that received testosterone treatment or were sham-operated. After sacrifice, castrated rats were found to have fewer nerve fibers in the corpora cavernosa and dorsal root containing NOS (as demonstrated by NADPH–diaphorase staining of penile histological sections), compared with the other two groups. Thus, testosterone acts on the nervous system to mediate erection, and, in its absence, the production and activity of NO may be down-regulated. Testosterone replacement can preserve erectile function and NOS-containing neurons in the rat.

The role of testosterone in the human erectile response is less well understood. Some severely hypogonadal men continue to have an erectile response, and, although testosterone therapy in hypogonadal men with erectile dysfunction may increase the number and quality of erections, improvements are observed in only 40–60% of patients.

**TESTOSTERONE THERAPY**

Testosterone therapy can improve certain aspects of male sexual function, including erectile function. Intramuscular injections of testosterone enanthate and testosterone cypionate have been widely prescribed. However, this form of treatment is not always ideal, as it may lead to wide variations in serum testosterone levels.

The first transdermal mode of testosterone application was a scrotal patch, which had to be applied once daily on shaved scrotal skin. Although effective, the scrotal patch did not become readily accepted, due to the concomitant supraphysiological levels of dihydrotestosterone and the unpleasantness of scrotal skin shaving. Adding an absorption enhancer to the patch made application on non-scrotal skin possible.

In a 16-month investigation in 34 hypogonadal men, a non-scrotal testosterone transdermal system was shown to increase the frequency, duration and rigidity of erections, and enhance patient assessment of sexual desire, compared with during the withdrawal period. Thus, transdermal testosterone treatment in hypogonadal men significantly enhanced both objective and subjective parameters of sexual function, relative to the hypogonadal state, while achieving physiologically normal levels of serum testosterone and major metabolites.

Despite the efficacy of the transdermal testosterone system, a large number of patients experienced considerable skin reactions due to the enhancer. In addition, the reservoir patches were generally judged to be too large, uncomfortable, visually obtrusive and noisy; therefore, the non-scrotal patch has not become well established.

These problems in delivery have led to the development of an open testosterone delivery system using a 1% hydroalcoholic testosterone gel (Testogel; Schering AG, Germany/AndroGel; Solvay Pharmaceuticals), which can be applied to the abdomen, shoulders or upper arms, and delivers between 5 mg and 10 mg testosterone/day. This formulation of testosterone has been demonstrated to increase rapidly serum and free testosterone levels in hypogonadal men to within the normal range, and to improve sexual function and mood. The open system provided flexibility in dosing, with little skin irritation, and was well tolerated.

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TESTOSTERONE THERAPY IN COMBINATION WITH PDE5 INHIBITORS

Phosphodiesterase 5 (PDE5) inhibitors, such as sildenafil (Viagra), prevent the degradation of cGMP by PDE5 in the corpora cavernosa, thereby enhancing erection. Thus, in order to obtain an erection, a level of testosterone is required that supports both NO synthesis and cGMP synthesis. PDE5 inhibitors help to maintain an erection by preventing cGMP degradation and, therefore, principally act to improve vasodilation, as opposed to libido, sexual interest and activity. Consequently, the efficacy of drugs such as sildenafil may depend on the presence of adequate levels of testosterone.

Combination therapy with sildenafil and testosterone in hypogonadal subjects may lead to an improved ability to achieve and maintain an erection. In a study by Kalinchenko and colleagues, 120 men with organic erectile dysfunction associated with type II diabetes mellitus, and receiving oral anti-diabetic drugs, were evaluated for the cause of failure to respond to treatment with sildenafil citrate. At baseline, these patients were found to have significantly lower levels of testosterone and depressed libido than controls (age-matched patients with diabetes mellitus, receiving treatment, but who responded positively to treatment with sildenafil citrate). After 2 weeks of treatment with oral testosterone undecanoate, testosterone levels were restored to normal and libido was increased. The subsequent use of 100 mg sildenafil citrate prior to coitus induced satisfactory erections in 70% of previous non-responders (p < 0.001).

More recently, the use of testosterone gel in combination with sildenafil citrate has been evaluated in men with erectile dysfunction and hypogonadism, who were previously refractory to monotherapy with sildenafil. A total of 75 men, who had experienced erectile dysfunction for a minimum of 3 months, had low to low-normal total testosterone (< 400 ng/dl) and had previously failed to respond to sildenafil, were randomized to 12 weeks of treatment with either testosterone (50 mg daily) + sildenafil citrate (100 mg), or placebo + sildenafil citrate (100 mg). The etiology of erectile dysfunction was either organic or mixed, and most patients (91%) had experienced erectile dysfunction for over 1 year – the majority had either moderate or severe erectile dysfunction. Baseline characteristics were similar in both groups; the mean age was 58.5 years and obesity was common (mean body mass index, 31.44 kg/m²). The primary efficacy outcome was the International Index of Erectile Function (IIEF), while secondary measures were sexual desire, orgasmic function, satisfaction (evaluated via a questionnaire) and serum testosterone levels. Evaluations were performed every 4 weeks.

After 12 weeks of treatment, serum testosterone had significantly increased in the group receiving testosterone, from a baseline level of 300 ng/dl to 500–600 ng/dl (p < 0.001, compared with placebo) (Figure 3). While there was a slight decrease at week 12, this was probably due to patient dropout. In contrast, the group who received placebo showed no change. An interim analysis at 4 weeks after the start of treatment demonstrated that erectile function had improved significantly from baseline in the group receiving the testosterone and sildenafil combination (mean change from baseline IIEF = 4.4), in contrast to those receiving placebo and sildenafil (mean change from baseline IIEF = 2.2) (p = 0.029) (Figure 4). In addition, the
group receiving the testosterone and sildenafil combination demonstrated significant improvements from baseline in orgasmic function ($p = 0.009$), overall satisfaction ($p = 0.02$) and total score of the sexual function questionnaire ($p = 0.011$), compared with the placebo and sildenafil group. The discovery that a combination of testosterone treatment and sildenafil could improve orgasmic function was an important finding of this study, as monotherapy with PDE5 inhibitors or prostaglandin E1 can only improve vasodilation and erectile function.

These findings are supported by a smaller study, in which 20 hypogonadal subjects were randomized either to testosterone treatment by patch administration or to placebo, indicating that transdermal administration of testosterone can improve response to sildenafil.

**CONCLUSIONS**

Erectile dysfunction is extremely common and can impact significantly on the quality of life and self-esteem of sufferers. Erectile dysfunction is often associated with aging and may be a symptom of late-onset hypogonadism. Many men do not respond adequately to treatment with PDE5 inhibitors or prostaglandin E1 unless testosterone levels are sufficient. It is important, therefore, to screen men who present with erectile dysfunction for low serum testosterone and hypogonadism, especially if they fail treatment with PDE5 inhibitors.

Clinical trials have demonstrated that testosterone replacement therapy, with products such as Testogel/AndroGel, can rapidly increase levels of testosterone and improve sexual function and mood in men with hypogonadism.

Testogel/AndroGel, in combination with the PDE5 inhibitor sildenafil, has been demonstrated to improve erectile response and orgasmic function in patients with erectile dysfunction and hypogonadism who had previously not responded to sildenafil monotherapy, compared with placebo. Therefore, testosterone treatment may be considered for the treatment of erectile dysfunction in men with low to low-normal total testosterone levels who have failed previous treatment with sildenafil.

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**References**

