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The evolving role of testosterone in the treatment of erectile dysfunction

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SUMMARY

Hypogonadism may play a significant role in the pathophysiology of erectile dysfunction (ED). A threshold level of testosterone may be necessary for normal erectile function. Testosterone replacement therapy is indicated in hypogonadal patients and is beneficial in patients with ED and hypogonadism. Monotherapy with testosterone for ED is of limited effectiveness and may be most promising in young patients with hypogonadism and without vascular risk factors for ED. A number of laboratory and human studies have shown the combination of testosterone and other ED treatments, such as phosphodiesterase type 5 (PDE5) inhibitors, to be beneficial in patients with ED and hypogonadism, who fail PDE5 inhibitor therapy alone. There is increasing evidence that combination therapy is effective in treating the symptoms of ED in patients for whom treatment failed with testosterone or PDE5 inhibitors alone. Testosterone replacement therapy has potentially evolved from a monotherapy for ED in cases of low testosterone, to a combination therapy with PDE5 inhibitors. Screening for hypogonadism may be useful in men with ED who fail prior PDE5 inhibitors, especially in populations at risk for hypogonadism such as type 2 diabetes and the metabolic syndrome.

Keywords: Hypogonadism; erectile dysfunction; testosterone

INTRODUCTION

The pathophysiology of erectile dysfunction (ED) is multifactorial, involving vascular, neurologic, hormonal and/or psychological causes. The prevalence of hypogonadism in men with ED varies depending on the study populations, comorbidities and diagnosis methods. Approximately 12% of patients with ED may have hypogonadism (1). Hypogonadism is defined as a state of deficiency in gonadal function manifested by deficient secretion of gonadal hormones and/or gametogenesis (2). For the purpose of this paper, review and discussion will be limited to hypogonadism as testosterone deficiency. Reduced production of testosterone may increase the risk of osteoporosis, sexual dysfunction, fatigue, cardiovascular disease and mood disturbances, and may decrease muscle mass (2). Hypogonadism may be classified as hypergonadotrophic in cases of testicular failure or hypogonadotrophic in cases of hypothalamic/pituitary failure (2). Ageing is associated with gradually declining levels of testosterone (late-onset hypogonadism or androgen decline in the ageing male) (3). In addition, chronic medical disorders are also frequently associated with hypogonadism, such as type 2 diabetes (4), the metabolic syndrome, chronic renal failure and chronic hepatic failure. The International Consultation on Sexual and Erectile Dysfunction recommended that adult-onset hypogonadism be defined as a clinical and biochemical syndrome (3).

Testosterone plays a key role in the central and peripheral modulation of erectile function (5) New research in the laboratory and in humans is shaping a refinement of the role of testosterone replacement therapy in ED. This paper

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will address the evolving role of testosterone in the treatment of ED, both as a monotherapy and in combination with phosphodiesterase type 5 (PDE5) inhibitors.

METHODS

Several sources of information were used to write this article. The multidisciplinary international group of authors provided clinical knowledge and expert consultation on the current literature. Review articles and recent research studies were obtained from author archives and online journals. A scientific literature search was a key source of information. Appropriate studies were identified from PubMed, IngentaConnect, Scirus, and Kluwer Online. Full-text online sources for articles included FreeMedicalJournals.com, PubMed Central, and Directory of Open Access Journals. Cochrane reviews were also searched.

BASIC SCIENCE OF TESTOSTERONE AND ED

Androgens Modulate NOS and PDE5 Expression and Activity in Erectile Tissue

The nitric oxide (NO) pathway is critical for initiation and maintenance of erectile function (6,7). In animals, the expression of NO synthase (NOS) isoforms in the corpus cavernosum is regulated by androgens. Further, NOS activity and protein expression are markedly decreased in erectile tissue of castrated animals, as is the erectile response to pelvic nerve stimulation. Testosterone restores the erectile response and normalises NOS protein expression and activity (8–11).

Following sexual stimulation, PDE5 inhibitors reduce the hydrolysis of intracellular cyclic guanosine monophosphate (cGMP), thus maintaining greater cGMP levels and enhancing smooth muscle relaxation. This results in improved penile erection in men with ED. In the animal model, castration resulted in reduced protein expression and activity of PDE5, and androgen treatment upregulated the expression of PDE5 activity (12,13). Furthermore, castration had a negative effect on the efficacy of PDE5 inhibitors on erections induced by electrostimulation of the cavernous nerves (12,13). Medical castration (luteinizing hormone releasing hormone agonist-treated) or surgical castration of rabbits caused reduction in the otherwise enhancing effect of PDE5 inhibitors on erections induced by electrostimulation of the cavernous nerves (12,14). This facilitation of neurogenic relaxation by PDE5 inhibitors was restored in castrated animals treated with testosterone (12,13). Recent studies also showed that chronic or acute administration of the PDE5 inhibitor tadalafil to castrated animals did not restore erectile response to pelvic nerve stimulation (15). Mounting evidence from laboratory experiments shows that the erectile physiology is testosterone dependent at multiple levels, including the regulation of the expression and activity of neuronal NOS with the consequent regulation of smooth muscle relaxation/contraction. In addition, testosterone is involved in the regulation of smooth muscle PDE5 expression and activity.

Androgens Maintain Penile Structural and Functional Integrity

Erectile function depends on the integrity of the structural and cellular components regulating the veno-occlusive mechanism (16). In particular, trabecular smooth muscle is an important component of the penis, regulating detumescence and erection (17,18). Surgical castration results in apoptosis of the rat penile cavernous and spongiosal cells (19). Experimental testosterone deficiency caused significant reduction in trabecular smooth muscle and significant increase in connective tissue deposition concomitant with loss of erectile function (12,14,20). The corpus cavernosum from orchiectomised animals contained disorganised trabecular smooth muscle, with a large number of cytoplasmic vacuoles containing flocculent materials and decreased amounts of cytoplasmic myofilaments (20). In castrated animals, the tunica albuginea was significantly thinner and the elastic fibres were mostly replaced by collagenous fibres (21). In the control animals, the tunica was thicker and the elastic fibres were very rich and regularly arranged (21). A recently described, very interesting observation was the accumulation of adipocytes in the subtunical resion of the corpora cavernosa in castrated animals (22). In experiments utilising double staining technique (staining nuclei and cytoplasm), testosterone therapy of castrated rats was shown to induce new DNA synthesis in the various cell types in the corpora cavernosa (23).

Castration also produced profound ultrastructural changes in the penile dorsal nerve. The myelinated and non-myelinated nerve bundles were reduced in diameter and the axons appeared smaller with increased numbers of nucleated Schwann cells (21). Testosterone treatment restored the nerve fibres and myelin sheath structure. Administration of vascular endothelial growth factor to castrated animals also restored these structural elements, suggesting that androgens may act via a paracrine mechanism (21).

Low free testosterone may correlate independently of age with the impaired relaxation of corporeal smooth muscle cells to a vasoactive challenge (24). This finding gives clinical support to the experimental knowledge of the importance of androgens in regulating smooth muscle function and the regulation of the veno-occlusive mechanism in the penis. These data suggest that androgens have a profound effect on the functional and structural integrity of the corpus cavernosum.

CLINICAL EXPERIENCE: TESTOSTERONE MONOTHERAPY AND ED

Testosterone replacement therapy was associated with significant efficacy in the treatment of hypogonadism and ED, with improvement in sexual attitudes and performance in 61% of patients (25). A meta-analysis has indicated a 57% efficacy for testosterone replacement therapy in patients with ED and hypogonadism, ranging from 64% for primary hypogonadism to 44% for secondary hypogonadism (26). In another study, testosterone monotherapy improved erectile function and penile vascular abnormalities in 36% and 42% of cases respectively (27). In general, testosterone monotherapy for the treatment of ED is efficacious in men with hypogonadism when it is the sole cause of ED, but is often not efficacious in men with ED, hypogonadism and other pathophysiologies such as vascular disease and neuropathy.

Testosterone replacement therapy may have more significant effects on sexual desire than erectile function (28,29). In one study, normalisation of serum testosterone in hypogonadal men with ED fostered only short-term improvement (1 month) in erectile function and sexual satisfaction, with long-term therapy (6 months) showing a decrease in effectiveness compared with results at 1 month. The use of testosterone replacement therapy alone for ED was questionable in this population (30). In clinical studies of testosterone replacement therapy, testosterone gel significantly improved sexual performance, sexual desire and sexual motivation (31). A significant effect of testosterone replacement therapy on sexual function was observed at 30 days and subsequently throughout the duration of the 6 month treatment period (31).

Isidori et al. (32) recently performed a meta-analysis on the effects of testosterone on sexual function, showing that in studies carried out in men with a mean testosterone level below 12 nmol/l, testosterone moderately improved the number of nocturnal erections, sexual thoughts and motivation, number of instances of successful intercourse, erectile function scores, and overall satisfaction compared with placebo. In eugonadal men, testosterone had no effect on erectile function. In this elegant study, a cut-off value of 10 nmol/l for the mean testosterone level of the study populations failed to predict the effect of treatment, whereas the presence of risk factors for vasculogenic ED, comorbidities and shorter evaluation periods was associated with greater treatment effects in studies performed in hypogonadal, but not in eugonadal, men. The effects of testosterone on erectile function, but not libido, were inversely related to baseline testosterone concentration. These findings must be tempered by the caveats that the effects of testosterone tend to decline over time and to diminish progressively as baseline testosterone levels increase, and that long-term safety data are not available.

Given the multifactorial nature of the pathophysiology of ED, it is not expected that testosterone monotherapy will be highly effective in the treatment of all patients with ED. There is a lack of data suggesting the efficacy of testosterone replacement therapy in older men who do not meet the clinical definition of hypogonadism. Specifically, there is no convincing evidence that testosterone replacement therapy is either effective or safe for eugonadal older men (4). A further complexity is introduced by the finding that low testosterone levels may revert to normal as a consequence of improvement in sexual function, suggesting that low testosterone may, in some cases, be a consequence of ED (33).

COMBINATION THERAPY

Phosphodiesterase type 5 inhibitors are the first line of therapy in men who do not have potentially reversible causes of ED, such as hypogonadism (28). Nonetheless, 23–50% of patients do not respond to PDE5 inhibitors alone (34,35). Given the role of testosterone in the NO pathway central to proper erectile function, interest in PDE5 inhibitors and testosterone combination therapy has increased in recent years (36). Hypogonadism was found to be a risk factor for failure of PDE5 inhibitors (37). Testosterone was reported to positively regulate the expression of PDE5 in the corpus cavernosum of castrated rats and to increase responsiveness *in vivo* to the PDE5 inhibitor, tadalafil (38). In patients with ED and hypogonadism, testosterone replacement therapy improved erectile function and the response to PDE5 inhibitors in patients with ED and hypogonadism (36). In a randomised, placebo-controlled study of hypogonadal men with ED, the combination of sildenafil and 1% T-gel significantly improved erectile function and response to sildenafil (Figure 1). Additionally, the combination increased the International Index of Erectile Function (IIEF) scores at 4 weeks in patients who did not respond to sildenafil alone (34). Quality-of-life scores, however, were significantly improved at 12 weeks after combination therapy compared with placebo. In addition to improving erectile function, testosterone replacement therapy improved orgasmic function (34). In a randomised, placebo-controlled study, short-term transdermal testosterone administration improved the erectile response to sildenafil by increasing arterial inflow to the penis during sexual stimulation (39). Finally, testosterone was shown to improve arterial flow and subsequent response to tadalafil treatment, with a greater response after 10 weeks, compared to 4 weeks of pretreatment with testosterone (35).

Other studies have confirmed the beneficial effects of combination therapy in patients with comorbid conditions. The combination of testosterone and sildenafil was shown to improve sleep-related erections in hypogonadal men (40). This improvement was superior to sildenafil or testosterone

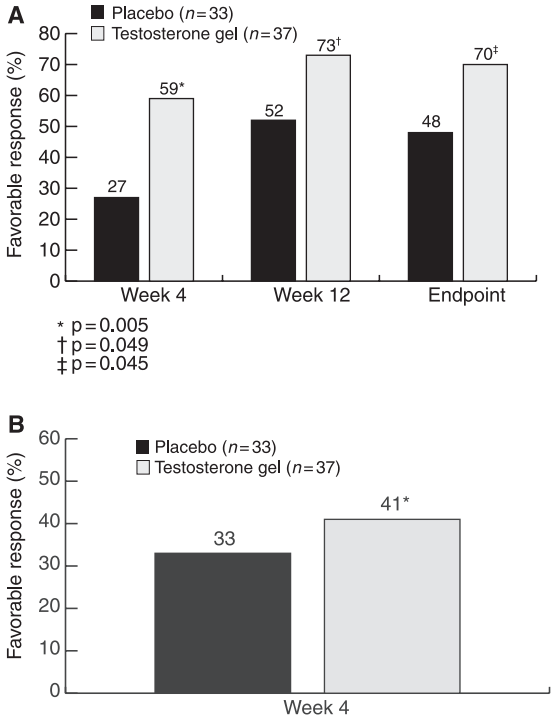

Figure 1 Testosterone therapy improved response to sildenafil, a PDE5 inhibitor. (A) A significantly higher percentage of subjects in the T-gel group answered 'yes' to 'Did your gel improve your response to sildenafil?' compared to the placebo group at week 4 (59% vs. 27%; p = 0.005), at week 12 (73% vs. 52%; p = 0.049), and at end-point (70% vs. 48%; p = 0.045) [adapted from Shabsigh et al. *J Urol* 2004]. (B) For the question, 'Did your gel improve your erections when sildenafil was not taken within 4 h before sexual activity?' the response 'yes' was numerically in favour of the T-gel group at each evaluation, but statistical significance was reached only at week 4 (41% vs. 33%; p = 0.009) [adapted from Shabsigh et al. *J Urol* 2005]

alone (40). Administration of intramuscular testosterone and sildenafil was found to be efficacious in renal transplant patients and in patients on renal haemodialysis (41). Oral testosterone was reported to reverse ED associated with type 2 diabetes in patients failing on sildenafil therapy alone (42). In a recent study, a total of 49 hypogonadal men with ED received T-gel for 6 months. Sildenafil was added at 3 months to those with no efficacy of T-gel alone (43). A total of 31 patients reported significant improvement in the sexual desire and erectile function with testosterone alone. In spite of normalisation of total and bioavailable testosterone values, and significant improvement of sexual desire, the erectile function of 17 men did not improve. These men received combined T-gel and sildenafil, after which all reported improvement in erectile function. In conclusion, testosterone combination therapy with PDE5 inhibitors improves erectile function and the response to PDE5 inhibitors in patients with ED and hypogonadism. A prospective study included hypogonadal men failing to respond to sildenafil or partially responding to sildenafil (44). Men receiving both sildenafil plus testosterone replacement therapy showed significant improvement in erectile function (44).

Recommendations for Screening and Therapy

The Institute of Medicine (IOM) has noted an insufficient number of studies, particularly placebo-controlled, randomised trials, assessing the risks and benefits of testosterone replacement therapy in older men who have not been clinically diagnosed with hypogonadism but have lower testosterone levels than young adult males and show one or more symptoms of ageing and hypogonadism (45). Consequently, the IOM has recommended that the National Institute on Aging and other research agencies conduct short-term efficacy trials, and, if clinically significant benefits are documented, conduct long-term studies to evaluate risks and benefits (45). At present, there is no basis for large-scale testosterone replacement therapy in older men, unless they have symptomatic androgen deficiency (3,4).

Testosterone levels needed for normal sexual function vary among individuals. Some men may have normal sexual function even if their testosterone levels fall into the age-adjusted lower normal range (46). However, in patients with sexual dysfunction, testosterone testing is advised to screen for hypogonadism (36), and testosterone replacement therapy is appropriate when clinical symptoms and biochemical evidence of hypogonadism exist (3,36). Hypogonadal men with specific sexual dysfunctions such as ED, diminished libido, or both, are candidates for testosterone replacement therapy (3,36). Testosterone monotherapy may correct sexual dysfunction caused by hypogonadism, but absence of an adequate response may require further evaluation to exclude associated comorbidities, such as those causing vasculogenic or neurogenic ED (36).

Populations for Combination Therapy and Screening

Men with ED and hypogonadism could benefit from combination therapy with testosterone and PDE5 inhibitors. The 2nd International Consultation on Erectile and Sexual Dysfunction recommended that all men presenting with ED should be screened with a testosterone blood test, especially those who present with a history of failure of PDE5 inhibitors (3). Between 10% and 20% of ED cases may be attributed to hormonal abnormalities (28). Determining testosterone levels only in patients with ED and either low sexual desire or abnormal physical examination often overlooks those with low testosterone who do not have these additional symptoms but would benefit from androgen therapy. It has therefore been advocated that testosterone levels be determined in all men older than 50 years who have ED (27), in addition to populations at risk for hypogonadism, such as those with type 2 diabetes, metabolic syndrome,

chronic renal failure and other chronic diseases (47). A high prevalence of ED in patients with diabetes has been attributed mainly to vascular and neurological conditions, but also to hypogonadism (48), which has been observed to occur commonly with type 2 diabetes (49) and to result from metabolic syndrome in middle-aged men (50).

The decision to start a patient with ED and hypogonadism on testosterone replacement therapy, PDE5 inhibitor or on a combination of both deserves careful discussion, with medical and economic considerations. Testosterone replacement therapy is indicated in patients with hypogonadism. If ED is also present, it may be argued that hypogonadism may be a reversible cause of ED. However, PDE5 inhibitors alone may also be effective in some patients with ED and hypogonadism, especially those with borderline testosterone levels. At this point, individual evaluation of patients with benefit/risk assessment may be the most prudent course of action. Combination therapy is expected to be appropriate for those who failed initial monotherapy.

CONCLUSION

Hypogonadism is a pathophysiological and clinical factor in a substantial number of patients with ED, and data indicate that a threshold level of testosterone is necessary for normal erectile function. Testosterone replacement therapy is clearly indicated in hypogonadal patients and is beneficial in patients with ED and hypogonadism. However, testosterone monotherapy for ED is of limited effectiveness and may be restricted to young patients with hypogonadism and without vascular risk factors for ED. Combination therapy with testosterone and other ED treatments, such as PDE5 inhibitors, is valuable in patients with ED and hypogonadism who fail PDE5 inhibitor therapy alone. Consequently, testosterone replacement therapy has evolved from a monotherapy for ED in cases of low testosterone, to a combination therapy with PDE5 inhibitors. There is increasing evidence that combination therapy is effective in treating the symptoms of ED in patients for whom treatment failed with testosterone or PDE5 inhibitors alone. Screening for hypogonadism and combination therapy of ED may be particularly useful in men with type 2 diabetes or the metabolic syndrome.

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