

**Sponsored by**

**Schering**

**Sidney Glina**



# Testosterone and erectile dysfunction

Sidney Glina

## Abstract

### Keywords

Androgen  
Hormone replacement therapy  
Hypogonadism  
Impotence  
Testosterone

The role of testosterone on sexual desire, interest and motivation is well established, but its effects on erectile function remain controversial. Animal data show that experimental or medical castration results in loss of the intracavernosal pressure, smooth muscle/connective tissue balance, and penile tissue concentration of nitric oxide synthase-containing nerves, which alter the fibroelastic properties of penile tissue compliance, leading to veno-occlusive dysfunction and therefore erectile dysfunction. Castration also induces apoptosis of penile erectile tissue, and new DNA synthesis is induced by treatment with testosterone. In an animal model of venogenic erectile dysfunction, intracavernous vascular endothelial growth factor (VEGF), in addition to testosterone, restores the smooth muscle/connective tissue balance, endothelial cell hypertrophy and hyperplasia and normalizes the diameter of the dorsal nerve fibres, thereby preventing veno-occlusive dysfunction. There is some evidence that treatment with testosterone may be beneficial to men with erectile dysfunction who have low baseline testosterone levels. Androgens may also control the expression and activity of phosphodiesterase type-5 (PDE-5) in the penile corpus cavernosum. Oral drug therapy with PDE-5 inhibitors fails in some patients with erectile dysfunction. However, when testosterone is used together with a PDE-5 inhibitor, sexual function is restored in these patients, creating the potential for pharmacological combination therapy with testosterone for the treatment of erectile dysfunction. WPMH GmbH. Published by Elsevier Ireland Ltd.

## Introduction

Male erectile function involves a complex interplay between physiological, behavioural and interpersonal factors. Androgens have a profound effect on male development and sexual function in general and erectile physiology in particular. The prevalence and severity of erectile dysfunction progressively increase with age in healthy men [1,2]. Although testosterone has been associated with erectile dysfunction, it remains unclear whether it maintains sexual function at all ages. This review highlights the role androgens play in sexual function, with particular emphasis on erectile function and penile erectile tissue in ageing men.

injury/disease, medications and hormones. Thus, hormonal changes (loss of androgens) may ultimately lead to erectile dysfunction. In addition, erectile function is dependent on the tissue structure and fibroelastic properties of the corpus cavernosum. Any alteration in the structural, vascular or neural components of penile tissue will modify erectile function.

Androgens play a key role in male sexual development and function. It is clearly established that testosterone affects sexual desire, interest and motivation, but its role in erectile function remains controversial. Although declining androgen levels and reduced sexual interest and activity appear to be related to the natural ageing process in men, there is little evidence of any clear association between androgen levels and erectile function [2]. Most studies investigating the role of androgens on erectile function have focused on androgen modulation of the nitric oxide/cyclic guanylate monophosphate biochemical pathway. Few studies have investigated the effects of

Sidney Glina, MD  
Instituto H. Ellis,  
Sao Paulo, Brasil

E-mail:  
glinas@terra.com.br

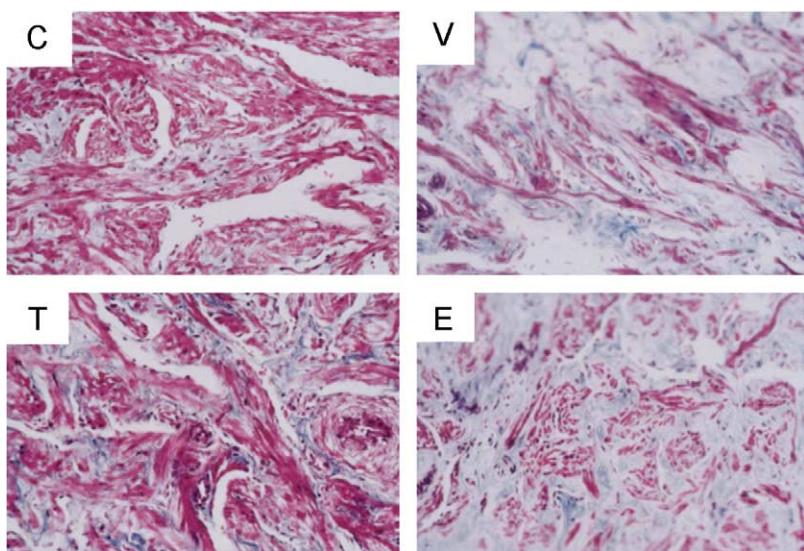
Online 8 December 2004

## Physiological role of testosterone in erectile dysfunction

Erectile function is a neurovascular event that is modulated by several factors, including penile

androgens on the smooth muscle/connective tissue balance and the changes in the compliance of the corpus cavernosum. To explore this further, the effect of androgen depletion and replacement on the functional responses of the penile corpus cavernosum in the rabbit [3,4] was examined.

Depletion of androgens by surgical or medical castration significantly reduced the intracavernosal pressure; testosterone replacement restored the intracavernosal pressure. In the castrated rabbits, phosphodiesterase type-5 (PDE-5) activity was not significantly reduced. Similarly, treatment with a PDE-5 inhibitor alone was ineffective in restoring erectile function. However, androgen replacement restored erectile function and increased PDE-5 activity, suggesting that PDE-5 is an important regulator of this pathway, and that testosterone may normalize the function of erectile tissue by upregulating PDE-5. Castration significantly reduced the trabecular smooth muscle content by about 20–23% and increased the connective tissue matrix in the corpus cavernosum. In the castrated rabbits treated with testosterone, the trabecular smooth muscle content was maintained (Figure 1). Androgens therefore regulate the synthesis and deposition of the connective tissue matrix in the penis.



**Figure 1** Effects of castration and androgen replacement on trabecular smooth muscle and connective tissue content in the rat corpus cavernosum. Panels are representative sections from: top left intact control; top right castrated treated with vehicle; bottom left castrated treated with testosterone; bottom right castrated treated with oestradiol (magnification 200 $\times$ ). Reprinted with permission from [3].

In the rat model of venogenic erectile dysfunction, systemic testosterone replacement or intracavernous vascular endothelial growth factor (VEGF) restores the smooth muscle/connective tissue balance, endothelial cell hypertrophy and hyperplasia and normalizes the diameter of the dorsal nerve fibres, thereby preventing veno-occlusive dysfunction ([5], personal communication). These findings suggest that testosterone acts via a paracrine mechanism involving VEGF to maintain the fibroelastic properties of the penile tissue, smooth muscle content, physiological function and ultimately erectile activity.

### Clinical experience with testosterone in non-responders to PDE-5 inhibitors

Experimental evidence supports the role of androgens in erectile function through a direct effect on penile tissue [6,7]. Denervation of the rat penis results in apoptosis of penile erectile tissue, suggesting that androgens have an important role in maintaining smooth muscle cell growth and functional integrity [6]. Testosterone replacement in the castrated rat results in new DNA synthesis, confirming the androgen dependence of erectile function. The primary action of androgens on trabecular smooth muscle of the rat is believed to be via the stimulation of nitric oxide synthase. Castration reduces, and testosterone replacement increases, the concentration of nitric oxide synthase-containing nerves innervating the corpus cavernosum of the rat [7]. These findings, in addition to the observation that free and total testosterone concentrations decrease with age, prompted the examination of the effect of testosterone on erectile dysfunction when used as adjuvant therapy with the PDE-5 inhibitor sildenafil in hypogonadal men who had failed to respond to sildenafil treatment alone.

In a retrospective analysis of 220 diabetic men presenting with erectile dysfunction, 120 sildenafil nonresponders were found to have hypogonadal testosterone levels (mean 6.9 nmol/L) whereas the responders had testosterone in the normal range (mean 18.6 nmol/L). Following treatment with testosterone, significant improvements as measured by

**Table 1** Mean changes from baseline in the International Index of Erectile Function (IIEF) after treatment with testosterone or placebo in combination with sildenafil for 4 weeks in hypogonadal men with erectile dysfunction who were unresponsive to sildenafil alone<sup>a</sup>

IIEF Domain	Mean (+/– SD) Change from BL		p-value
	T + sildenafil	Placebo + sildenafil	
Erectile Function	5.65 (6.66)	2.97 (5.13)	0.037
Orgasmic Function	1.53 (2.38)	0.36 (2.03)	0.019
Sexual Desire	0.44 (2.02)	0.00 (1.68)	0.211
Intercourse Satisfaction	1.21 (2.33)	0.70 (1.94)	0.250
Overall Satisfaction	1.62 (2.26)	0.61 (1.98)	0.046
Total Score	10.44 (13.21)	4.62 (9.88)	0.022

Reprinted with permission from [9].

<sup>a</sup> Results: 4 week analysis (n = 67).

the International Index of Erectile Function (IIEF) were observed [8]. The first controlled study found that erectile function, as measured by the IIEF, improved significantly after 4 weeks of treatment with testosterone compared with placebo (Table 1). Similar findings were observed for improvements in orgasmic function, overall total satisfaction and total IIEF score. Hypogonadal men with erectile dysfunction who are unresponsive to sildenafil alone, or any other PDE-5 inhibitor, may therefore benefit from testosterone replacement therapy in combination with a PDE-5 inhibitor.

### Hypogonadism in ageing men with erectile dysfunction

The concentration of testosterone required to maintain normal sexual function appears to be relatively low. It is therefore not surprising that only weak associations have been observed between testosterone levels and sexual function. Studies investigating this possible relationship in healthy older men without erectile dysfunction have reported significant correlations between bioavailable and free testosterone levels and sexual function, including the erectile function domain of the IIEF [2]. However, there have been no reports of a correlation between sexual function and the levels of total testosterone.

Studies conducted among older men with erectile dysfunction in a clinical setting have failed to find a significant association between testosterone levels and erectile dysfunction [10]. Furthermore, replacing testosterone in

men with hypogonadism is only successful in improving erectile function in about 36% of men. Normalization of serum testosterone levels in men with hypogonadism and erectile dysfunction resulted in only a short-term improvement in erectile function and sexual satisfaction [11]. Most of the studies that have recorded improvements in sexual function with testosterone therapy have been in men with low baseline testosterone levels [12]. Studies in men with normal baseline levels have revealed mixed findings.

Many studies looking at the effects of testosterone therapy on sexual function have focused on young hypogonadal men, have not adjusted for age and have not been placebo controlled. Whether testosterone has a role in maintaining sexual function at all ages therefore remains unclear. Although a relationship has been reported between bioavailable levels of testosterone and sexual desire, arousal and nocturnal penile tumescence in healthy elderly men, the relationship lost its significance after adjusting for age [13].

Having a low testosterone level is only one of the many consequences of ageing and, therefore, may not be the only cause of erectile dysfunction. It has been hypothesized that low testosterone levels may be a consequence of erectile dysfunction, rather than a cause [14]. Overall, the mechanisms explaining erectile dysfunction may include reduced sexual activity, depression and/or stress, in addition to low testosterone levels.

Several studies have shown a beneficial effect of testosterone therapy in men with hypogonadism who are unresponsive to treatment with a PDE-5 inhibitor alone. In 20 men with

erectile dysfunction who had not responded to treatment with sildenafil, administration of transdermal testosterone, in combination with sildenafil on demand, significantly increased erectile function, intercourse satisfaction and overall satisfaction as measured by the IIEF. In addition, a significant increase in penile peak systolic velocity was assessed by ultrasound [15]. This was recently confirmed by Foresta et al. [16].

Based on these clinical findings, the 2nd International Consultation on Sexual Dysfunctions recommended to measure testosterone levels in all men presenting with erectile dysfunction. In case of hypogonadism, this should be corrected before further treatment options are pursued [17].

## Summary

- Testosterone regulates the synthesis and deposition of the connective tissue matrix in penile tissue to maintain its fibroelastic properties, possibly via a paracrine mechanism involving VEGF.
- The mechanisms involved in erectile dysfunction may include low testosterone levels, reduced sexual activity, depression and/or stress.
- Testosterone replacement therapy improves erectile function in hypogonadal men with erectile dysfunction, particularly in those with low baseline levels of testosterone and those who are unresponsive to a PDE-5 inhibitor alone.

## References

- [1] Davidson JM, Chen JJ, Crapo L, Gray GD, Greenleaf WJ, Catania JA. Hormonal changes and sexual function in aging men. *J Clin Endocrinol Metab* 1983;57:71–7.
- [2] Feldman HA, Goldstein I, Hatzichristou DG, Drane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol* 1994;151:54–61.
- [3] Traish AM, Park K, Dhir V, Kim NN, Moreland RB, Goldstein I. Effects of castration and androgen replacement on erectile function in a rabbit model. *Endocrinology* 1999;140: 1861–8.
- [4] Traish AM, Munarriz R, O'Connell L, Choi S, Kim SW, Huang YH, et al. Effects of medical or surgical castration on erectile function in an animal model. *J Androl* 2003;24:381–7.
- [5] Rogers RS, Graziottin TM, Lin CS, Kan YW, Lue TF. Intracavernosal vascular endothelial growth factor (VEGF) injection and adenovirus-mediated VEGF gene therapy prevent and reverse venogenic erectile dysfunction in rats. *Int J Impot Res* 2003; 15:26–37.
- [6] Klein LT, Miller MI, Buttyan R, Raffo AJ, Burchard M, Devris G, et al. Apoptosis in the rat penis after penile denervation. *J Urol* 1997;158:626–30.
- [7] Baba K, Yajima M, Carrier S, Morgan DM, Nunes L, Lue TF, et al. Delayed testosterone replacement restores nitric oxide synthase-containing fibres and the erectile response in rat penis. *BJU Int* 2000;85: 953–8.
- [8] Kalinchenko SY, Kozlov GI, Gontcharov NP, Katsiya GV. Oral testosterone undecanoate reverses erectile dysfunction associated with diabetes mellitus in patients failing on sildenafil citrate therapy alone. *Aging Male* 2003;6:94–9.
- [9] Shabsigh R, Kaufman JM, Steidle C, Padma-Nathan H. Randomized study of testosterone gel as adjuvant therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. *J Urol* 2004;172:658–63.
- [10] Buvat J, Lemaire A. Endocrine screening in 1,022 men with erectile dysfunction: clinical significance and cost-effective strategy. *J Urol* 1997;158:1764–7.
- [11] Mulhall JP, Valenzuela R, Aviv N, Parker M. Effect of testosterone supplementation on sexual function in hypogonadal men with erectile dysfunction. *Urology* 2004;63: 348–53.
- [12] Salmi P, Kockott G, Pirke KM, Vogt HJ, Schill WB. Effects of testosterone replacement on sexual behavior in hypogonadal men. *Arch Sex Behav* 1982;11:345–53.
- [13] Schiavi RC, White D, Mandeli J, Schreiner-Engel P. Hormones and nocturnal penile tumescence in healthy aging men. *Arch Sex Behav* 1993;55:207–15.
- [14] Jannini EA, Scroponi E, Carosa E, Pepe M, Lo Giudice F, Trimarchi F, et al. Lack of sexual activity from erectile dysfunction is associated with a reversible reduction in serum testosterone. *Int J Androl* 1999;22:385–92.
- [15] Aversa A, Isidori AM, Spera G, Lenzi A, Fabbri A. Androgens improve cavernous vasodilation and response to sildenafil in patients with erectile dysfunction. *Clin Endocrinol* 2003;58:632–8.
- [16] Foresta C, Caretta N, Rossato M, Garolla A, Ferlin A. Role of androgens in erectile function. *J Urol* 2004;171:2358–62.
- [17] Morales A, Buvat J, Gooren LJ, Guay AT, Kaufman JM, Tan HM, Torres LO. Endocrine aspects of sexual dysfunction in men. *J Sex Med* 2004;1:69–81.