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·Review·

Recent insights into androgen action on the anatomical and physiological substrate of penile erection

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Abstract

Erectile response is centrally and peripherally regulated by androgens. The original insights into the mechanisms of action of androgens were that androgens particularly exert effects on libido and that erections in response to erotic stimuli were relatively androgen-independent. It was shown that sexual functions in men required androgen levels at the low end of reference values of testosterone. So it seemed that testosterone was not useful treatment for men with erectile difficulties, particularly following the advent of the phosphodiesterase type 5 (PDE5) inhibitors. However, approximately 50 % of those treated with PDE5 inhibitors discontinue their treatment. A number of recent developments shed new light on testosterone treatment of erectile dysfunction (ED) in aging men. (1) A recent insight is that, in contrast to younger men, elderly men might require higher levels of testosterone for normal sexual functioning. (2) Several studies have indicated that PDE5 inhibitors are not always sufficient to restore erectile potency in men, and that testosterone improves the therapeutical response to PDE5 inhibitors considerably. (3) There is growing insight that testosterone has profound effects on tissues of the penis involved in the mechanism of erection and that testosterone deficiency impairs the anatomical and physiological substrate of erectile capacity, reversible upon androgen replacement. The synthesis of PDE5 is upregulated by androgens, and the arterial inflow into the penis is improved by giving androgen. The above invites a re-examination of the merits of giving testosterone to aging men with ED. The beneficial effects of PDE5 inhibitors may only be optimally expressed in a eugonadal environment. *(Asian J Androl 2006 Jan; 8: 3-9)*

Keywords: testosterone; erection; corpus cavernosum; phosphodiesterase type 5 inhibitors

1 Introduction

Since testosterone became pharmaceutically available, clinicians have been impressed with the powerful effects it exerts on a man's sexual functioning. The evidence for testosterone-induced masculinization of sexual behavior in men is indeed persuasive. Most of the information has been collected from androgen withdrawal/replacement studies of hypogonadal men. The distinction between sexual interest and erectile function and its subdivision initially helped considerably in clarifying the role of androgens in male function [1]. In the first studies,

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spontaneous erections, particularly those that occur during sleep, and probably fantasy-induced erections, were thought to be exquisitely androgen-dependent, whereas erections in response to erotic (e.g. visual or tactile) stimuli were less so [1, 2]. This led to the hypothesis that the neural circuitries subserving nocturnal erections and erections in response to sexual arousal were not identical, explaining their distinctly different androgen dependence. The original studies [1], however, monitored only penile circumference but not stiffness, and later observations showed that androgens do affect penile responses to erotic stimuli with regard to the duration of response, maximal degree of rigidity, and speed of detumescence [3, 4], all significant aspects of androgen effects on sexual functioning. Nevertheless, this observation did not change the view that in men the principal target of androgen was sexual interest or appetite [1]. The influence on the penis was believed to be indirect, through the effects on libido, rather than direct on penile tissues.

The blood level of testosterone critical for restoring sexual interest, though varying between individuals, appeared to be 60 %–70 % of the reference values for eugonadal men [5–8]. It is of note that these observations were done in men in a wide age range. Consequently, it was assumed that in men with erectile dysfunction (ED) and normal or slightly lower-than-normal androgen levels, usually an elderly population, additional testosterone was likely to be of no help, which was in agreement with the clinical experience of many practitioners. However, Schiavi and Rehman [9], based on their vast clinical experience, hypothesized that the threshold for the biological actions of testosterone might be higher in elderly men compared to young men. Recently, their hypothesis was convincingly confirmed experimentally by Gray *et al*. [10] showing that in elderly men libido and erectile function respond only to higher levels of circulating testosterone compared with younger men.

The introduction of intracavernous injections of smooth muscle relaxants, such as papaverine and prostaglandin E1, was a step forward in the treatment of ED. This is even more true for the phosphodiesterase type 5 (PDE5) inhibitors. The identification of pathways in the physiology of erection and the discovery of the importance of nitric oxide and its downstream effects lay at the basis of their development [11, 12]. The introduction of highly efficacious and relatively safe compounds such as the PDE5 inhibitors has had a profound impact on the diagnosis and treatment of ED. Patients who had failed to respond to androgen or other types of treatment could be successfully treated with PDE 5 inhibitors. The success of the PDE 5 inhibitors rendered androgens, as treatment for erectile problems, something of the past. This seemed rational in view of the assumption that the primary effects of testosterone were on libido, in other words, on the central nervous system. Furthermore, it had become established that less-than-normal circulating levels of testosterone were sufficient to maintain sexual functioning; this notion, however, is no longer tenable [9, 10]. ED, once the domain of the urologist or andrologist, attempting to define the precise etiology, is now often treated by first-line physicians, often without much of a diagnostic work-up. Despite the initial euphoria of a panacea for ED, and the simplicity and safety of PDE 5 inhibitors, approximately 50 % of patients discontinue treatment [13, 14]. The reasons for discontinuation lie for a large part in an incomplete evaluation of the sexual problem. These may be somatic factors, such as diabetes mellitus, cardiovascular or neurological disease and smoking [13, 14], or psychological, such as unrealistic expectations and emotional aspects of the sexual relationship [15, 16].

There is a multitude of factors leading to discontinuation of PDE inhibitors, however, the focus of this paper is on recent studies that have arrived at the conclusion that large proportions of men who had failed to respond to treatment with PDE5 inhibitors appeared to be testosterone deficient. All studies on ED unanimously agree that aging is the most significant factor in the etiology of ED [17]. Over the last 15 years the age-related decline of circulating testosterone in men has received abundant attention and its pathophysiological significance is still hotly debated, although recently consensus on its approach has been reached by a number of professional bodies [18]. These two factors together, the age-related increase in ED and the age-related decline in testosterone in men, warrant reconsideration of the significance of testosterone in ED.

Moreover, new research has presented convincing evidence, mainly in laboratory animals, that testosterone has profound effects on tissues of the penis involved in the mechanism of erection and that testosterone deficiency impairs the anatomical and physiological substrate of erectile capacity. This study reviewed recent findings and arrived at the conclusion that the full therapeutical potential of PDE5 inhibitors can only become manifest in a eugonadal state, providing some needed nuance to the earlier beliefs that the effects of testosterone are pri-

marily and predominantly exerted on libidinous aspects of the male, and not directly on the penis as well.

2 New insights into the actions of testosterone on erectile function

We will review recent findings on the following three topics:

1 The recent results of testosterone replacement studies showing that restoration of androgen levels to normal has a beneficial effect on erectile function. These studies provide no insight into the primary targets of androgen action, libido or penile structures, but confirm that normal or near-normal levels of testosterone benefit erectile function.

2 Failures of restoration of erectile function in men receiving PDE5 inhibitors due to testosterone deficiency and the success rates of addition of androgen to the treatment of men who failed to respond to PDE5 inhibitors or, *vice versa*, of addition of PDE5 inhibitors to men who failed to respond to testosterone treatment.

3 Mechanism of action of androgens on penile structures related to erectile function. This has been mainly studied in animals but there is limited evidence obtained in human studies as well.

2.1 Testosterone replacement in elderly men

The effects of testosterone replacement in younger men on parameters of sexual functioning have been convincingly demonstrated, however, studies of the effects in elderly men are more problematic. These studies have been reviewed [19, 20]. The review by Morley and Perry [20] concluded somewhat optimistically that testosterone supplementation increased libido in 7 of 8 studies and improved erections in 5 of 6 studies. Recently, in a large cohort of 406 men (mean age 58 years; total testosterone = 300 ng/dL) a clear relationship was reported between restoring serum testosterone to the normal range and improving certain parameters of sexual functioning, such as sexual desire, nocturnal erections and frequency of intercourse [21]. Remarkably, in this study the results of testosterone administration with a 100 mg gel were superior to those of 50 mg gel or a testosterone patch, raising the issue of threshold values of testosterone for sexual functioning in elderly men. As indicated above, this assumption was recently substantiated in a study by Gray *et al*. [10] showing that the threshold for androgens on sexual functions in elderly men is higher than in younger men.

2.2 Combined treatments

Park *et al*. [13] reported recently that the success rate of treatment with sildenafil in a cohort of 162 men (> 60 years) was only 47 %. It could further be established that among the risk factors predicting a poor response to sildenafil were smoking and hypogonadism (plasma testosterone < 3 μg/L). In line with this, Aversa *et al*. [22] reported that the circulating levels of free testosterone, independent of age, positively correlated with the degree of relaxation of the corporal smooth muscle cells and the cavernous endothelial cells, giving support to the potential role of androgens in regulating smooth muscle function in the penis.

In a later well-designed intervention study Aversa *et al*. [23] provided support for this mechanism of action of testosterone on the erectile tissues of the penis. They assessed the effects of androgen in 20 patients with arteriogenic ED (confirmed with dynamic colour duplex ultrasound) not responding to treatment with sildenafil 100 mg. The patients' testosterone levels were in the lower quartile of the normal range. In this placebo-controlled study, treatment with transdermal testosterone raised plasma testosterone levels and led to an increase of arterial inflow into the cavernous tissue and to an improvement of ED, thus improving the response to treatment with PDE5 inhibitors. In line with the above, Foresta *et al.* [24] have documented that normal plasma testosterone levels are required for erectile function. In severely hypogonadal men (plasma testosterone < 2.0 ng/mL) the nocturnal penile tumescence, ultrasound measurement of arterial carvernous inflow and visually stimulated erection in response to sildenafil 50 mg or apomorphine 3 mg were minimal. The responses to these pharmacological stimuli normalized after they were given testosterone gel for six months, evidence of the significant role of normal levels of testosterone for erectile function. The notion that testosterone and PDE5 inhibitors have synergistic effects on nocturnal erections was also confirmed in men in a laboratory setting by Rochira *et al.* [25].

There are clinical studies of large cohorts of patients to support this notion. Kalinchenko *et al*. [26] found in a cohort of 120 men with diabetes mellitus type 2 and ED that men who had failed to respond to sildenafil 100 mg had lower plasma testosterone levels than controls. Upon androgen replacement with oral testosterone undecanoate restoring testosterone levels to the normal range, 84 of

120 men experienced considerable improvement of their erectile function. Similar findings were reported by Shabsigh *et al.* [27] in their randomized placebo-controlled double blind study of 75 men with plasma testosterone levels < 400 ng/dL who had responded poorly to treatment with sildenafil. Testosterone gel improved their erectile function compared to placebo, reaching significance after 4 weeks of treatment, and improved orgasmic function and overall satisfaction. There were no significant correlations between plasma testosterone levels and improvements in sexual function, probably indicating individual thresholds to the action of testosterone.

Conversely, it could be shown that testosterone replacement alone is not always satisfactory with regard to restoring erectile potency. Mulhall *et al.* [28] noted in a study of 32 men who were testosterone deficient, and whose testosterone levels were pharmacologically restored to normal, that there was an improvement in erectile function in the first month after reaching normal plasma testosterone. This subsequently declined in the following months of the follow-up. In a study of 178 men with secondary hypogonadism and ED, testosterone levels were raised following administration of clomiphene, with beneficial effects on sexual function in 75 % of men. In the 25 % who experienced no improvement, aging, diabetes and cardiovascular disease were factors that emerged as significant [29]. That addition of PDE5 inhibitors may be helpful for such men was demonstrated by Greenstein *et al.* [30]. These authors assessed the effects of testosterone replacement in 49 hypogonadal men with ED. Treatment with testosterone gel led to an improvement of ED in 31 of the 49 participants. When the non-responders received sildenafil, the ED of these men also responded favorably. A number of these studies suggest favorable effects of testosterone administration to elderly men in addition to PDE5 inhibitors, however, it has to be remembered that not all of these studies were blinded and placebo-controlled. Until more definitive data are available, the interpretation of the results must be cautious.

2.3 Mechanism of action of androgens on penile structures

Animal experiments and, to a much more limited degree, human observations suggest that androgens are necessary to maintain the integrity of the anatomical structures of the penile erectile tissue and, furthermore, that androgens are significant in the biochemical mechanisms subserving penile erection.

In a rat model, Shen *et al.* [31] demonstrated that androgen deprivation leads to loss of elastic fibers in the tunica albuginea and of smooth muscle fibers in the corpus cavernosum which were replaced by collagenous fibers in both structures. Similar findings were reported in the rabbit by Traish *et al.* [32], noting a reduced trabecular smooth muscle content, reversible upon androgen replacement.

Singh *et al.* [33], analyzing the increase of muscle mass and decrease of fat mass upon replacement of testosterone in hypogonadal subjects, found as an explanation that the mesenchymal pluripotent cells follow a myogenic lineage or adipogenic lineage, depending on circulating levels of testosterone. Traish *et al.* [34] could demonstrate a similar mechanism in the rabbit with an accumulation of adipocytes in the subtunical region of the corpus cavernosum, thus impairing the veno-occlusive mechanism if testosterone levels are low. This study also confirmed that androgen deprivation leads to loss of trabecular smooth muscle and increase of connective tissue fibers.

In another study by Traish *et al.* [32] it was also found that intracavernosal pressure, expression of alpha1-adrenergic receptor and PDE5 activity were clearly dependent on androgen, which was also the case for neuronal nitric oxide synthase (nNOS) activity but not for nNOS protein expression. In a follow-up to this study in the rabbit model, Traish *et al.* [35] demonstrated that even a 50 % reduction in circulating testosterone reduced intracavernosal blood pressure, which was not enhanced by treatment with the PDE5 inhibitor vardenafil. NOS and arginase activities in the corpus cavernosum were not significantly affected by the reduction in circulating testosterone. This is in contrast with a study in the rat [36] where it could be shown that androgen upregulated neuronal and endothelial NOS, thus facilitating erectile responses upon stimulation of cavernosal nerves. Sato *et al.* [37] recently presented data on the powerful effects of testosterone on the central nervous system (medial preoptic area) and the peripheral cavernosal nerve of the rat.

What is known about the human? There are androgen receptors in the human corpus cavernosum [38]. The dependence of PDE5 on androgens in the muscular and endothelial compartment of the corpus cavernosum was confirmed in the rat but also in human tissue by Morelli *et al.* [39]. Furthermore, Yaman *et al.* [40] found in a series of penile biopsies that in men with ED, the

percentage of smooth muscle cells, endothelial cells and elastic fibers were substantially reduced compared to controls with normal erectile function. This could be an indication that structural alterations may play a similar role in humans as in animal models. Most recently, a case report by Yassin and Saad [41] showed that venous leak in a hypogonadal diabetic patient with ED was no longer manifest after three months of testosterone treatment, indicating that changes in penile structure may, at least in part, be reversible.

3 Summary and conclusion

Erectile response in mammals is centrally and peripherally regulated by androgens. Severe hypogonadism in men usually results in loss of libido and potency. It was repeatedly shown that sexual functions in men required androgen levels below or at the low end of reference values of testosterone [5–8].

The above considerations, the relative androgen-independence of erections in response to erotic stimuli and the relatively low androgen levels required, were reasons to believe that testosterone was not a useful treatment for men with erectile difficulties whose testosterone levels were usually only marginally low.

An even more important element in the disregard of testosterone as a treatment option was the advent of intracorporal smooth muscle relaxants (papaverine and prostaglandin E1), later superseded by the PDE5 inhibitors. When introduced in 1998, the latter were hailed as the ultimate successful treatment of ED. However, around 50 % of patients discontinue treatment because of a lack of success for somatic [13, 14] or psychological [15] reasons.

There are a number of recent developments which shed new light on testosterone treatment of ED in aging men:

1 The recent insight that, in contrast to the results obtained in younger men [5–8], elderly men might require higher levels of testosterone for normal sexual functioning [9, 10]. Actually, reviews of the literature on testosterone treatment in elderly men on libido and erectile potency were quite encouraging [19, 20].

2 Several studies have indicated that PDE5 inhibitors are not always sufficient to restore erectile potency in men [13, 23, 26, 27], and that testosterone improves the therapeutic response to PDE5 inhibitors considerably [23, 27].

3 There is growing insight that testosterone has profound effects on tissues of the penis involved in the mechanism of erection and that testosterone deficiency impairs the anatomical and physiological substrate of erectile capacity, reversible upon androgen replacement. These data come mainly from animal experimentation, but a number of studies support their relevance for the human as well. There are androgen receptors in the human corpus cavernosum [38].

Lewis and Mills [42], remarking that data on the testosterone effects on the penis in the human are still limited, find it reasonable to extrapolate animal dependency of androgens for molecular activity in the penile tissue to the human.

The above invites a re-examination of the merits of testosterone treatment in aging men with ED. It is becoming clear that the beneficial effects of PDE5 inhibitors are only optimally expressed in a eugonadal environment [43]. ED is strongly age-related, therefore it is evident that, inherent in the process of aging, etiology is multi-factorial, and combinations of drugs might be needed to restore it. In clinical practice PDE5 inhibitors will usually be tried first, but it is important to remember that insufficient success of one type of treatment might require the addition of the other. There is now consensus that measurement of serum testosterone is part of the diagnostic work-up of an elderly man with erectile difficulties [44], and in cases of proven testosterone deficiency there is now compelling reason to replace it.

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