Combining Testosterone and PDE5 Inhibitors in Erectile Dysfunction: Basic Rationale and Clinical Evidences

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Abstract

Introduction: Erectile dysfunction (ED) and decline of testosterone levels are frequently observed with age and also in illnesses with a common basis of endothelial damage.

Objectives: To review molecular mechanisms underlying androgen action upon its receptor and phosphodiesterase type 5 (PDE5) expression and regulation by testosterone in cavernous tissue and their clinical implication in the treatment of ED refractory to PDE5 inhibitors (PDE5-Is).

Methods: From January 2003 to May 2005, we performed an extensive, unsystematic MEDLINE literature search reviewing relevant data on basic and clinical studies regarding the efficacy of combination therapies.

Results: Most trials using testosterone alone for treatment of ED in hypogonadal men suffer from methodologic problems and report inconsistent results, but overall the trials suggest that testosterone is superior to placebo. Orally effective PDE5-Is, such as sildenafil, tadalafil, or vardenafil, may be ineffective depending on the demonstration of testosterone regulation of PDE5 expression in human corpus cavernous, and their efficacy may be enhanced by testosterone adjunction whenever necessary.

Conclusions: Screening for hypogonadism in all men with ED is necessary to identify men with severe hypogonadism and some cases of mild to moderate hypogonadism, who may benefit from testosterone treatment. Identification of threshold values for testosterone supplementation to appropriately benefit from PDE5-Is failure may improve clinical management of unresponsive patients with minimization of unwanted effects.

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1. Introduction

Erectile dysfunction (ED) is defined as the persistent inability to achieve and maintain an erection adequate for satisfactory sexual performance [1]. The prevalence of ED has been reported to be 52%, with complete ED ranging from 5% to 15% in men aged 40–70 yr. However, estimates of ED prevalence vary widely, from 2% in men aged <40 yr to 86% in men aged ≥80 yr [2]. Epidemiologic data on male hypogonadism suggest that age, health, and lifestyle factors impact on androgen levels and should be accounted for in calculations of normal reference ranges [3,4]. Despite a low incidence of hypogonadism-related ED (about 10–20%), up to 40% of ageing men with ED may have subnormal levels of testosterone (T) or other endocrine alterations, that is, increased estradiol levels resulting in decreased testosterone/estradiol ratios [5]. Hypogonadism is defined as inadequate gonadal function manifested by deficiencies in gametogenesis and/or the secretion of gonadal hormones. Reduced production of T increases the risk of osteoporosis, sexual dysfunction, fatigue, cardiovascular disease, and mood disturbances [6]. Moreover, reduced T levels determine an imbalance of body mass distribution that decreases muscle mass and increases fat mass; in particular, low T levels correlate with an increase in abdominal fat mass [6]. Hypogonadism may be related to a primary testicular disorder or pituitary disease and may occur with advancing age (late-onset hypogonadism or androgen decline in the ageing male) or a chronic medical disorder, such as type II diabetes and metabolic syndrome [6]. The international consultation on sexual and erectile dysfunction recommended that adult-onset hypogonadism be defined as a clinical and biochemical syndrome.

T plays a key role in the central and peripheral modulation of erectile function [7]; new laboratory and clinical research demonstrate the role of T therapy in ED [8–10]. This review will address the evolving role of T in the treatment of ED, both as a monotherapy and in combination with phosphodiesterase type 5 inhibitors (PDE5-Is). In addition, it will discuss the international recommendations for treatment and the benefit of screening for hypogonadism in patients with ED.

2. Molecular basis of testosterone regulation of erectile function

Normal erectile function is a complex neurovascular process that depends on a delicate balance between the effects of endogenous vasoconstrictors and vasorelaxing agents on the arterial and corporal smooth muscle cells of the penis. Ultimately, coordinated vascular smooth muscle relaxation and contraction is required for erection and detumescence to occur, respectively. Any disruption of this balance, resulting in either impaired relaxation or heightened contractility of the corporal smooth muscle can produce ED [11].

Androgen receptors (ARs) have been localized within vascular endothelium and smooth muscle cells. Thus, arterial functions may be directly subject to T influence and, most likely, two independent pathways of T-induced effects within the vessel wall can be assumed (i.e., genomic and nongenomic) [12–14]. The classical pathway of androgen action involves steroid binding to the AR, a ligand-activated transcription factor acting on the genome [15]. The genomic action of AR is modulated by a large variety of coregulators, which are proteins that fine tune target gene expression by enhancing (coactivators) or restraining (corepressors) transcription [16]. Although T circulates throughout the body, the factors responsible for variation in tissue androgen sensitivity remain to be further clarified. Intensity of expression of the single human AR partly defines androgen sensitivity, but AR is almost ubiquitously expressed to some degree in tissues. Further biologic determinants of tissue androgen sensitivity, including the functional AR polymorphisms as well as tissue distribution and regulation of AR coregulators, androgen metabolic enzymes, and nongenomic mechanisms, remain to be better defined so that their net integrated effects can be understood better. Androgen sensitivity could be modulated by a functional polymorphism of the AR that influences the strength of the genomic signal transduced from its interaction with an androgen as a bound ligand. One such functional AR polymorphism is the exon 1 triplet CAG (polyglutamine), whereby the repeated length is inversely correlated with androgen sensitivity [17]. There is now considerable evidence for rapid, nongenomic effects of steroids, including androgens. Nongenomic steroid action is distinguished from genomic effects by (1) rapid onset (seconds to minutes) that is faster than genomic mechanisms; (2) insensitivity to inhibition of RNA and protein synthesis; (3) effects produced by steroids unable to access the nucleus (either covalently linked to impermeable membrane macromolecules or in cells lacking a nucleus); (4) not usually being blocked by classic antagonists because of different steroidal specificity from classical cognate nuclear
receptors. As for other steroids, nongenomic androgen effects characteristically involve the rapid induction of conventional second messenger signal transduction cascades, including increases in cytosolic calcium and activation of protein kinase A, protein kinase C, and mitogen-activated protein kinase, leading to diverse cellular effects including smooth muscle relaxation, neuromuscular and junctional signal transmission, and neuronal plasticity [18]. Most nongenomic effects involve a membrane receptor, and putative binding sites are described for all major classes of steroids, including androgens. No membrane AR has been characterized, but preliminarily evidence of a low-affinity microsomal membrane-binding site for alkylated androgens and an endothelial cell plasma membrane dehydroepiandrosterone-binding site [19] still require functional proof of specific receptor status. A plasma membrane sex hormone binding globulin (SHBG) receptor capable of modulating androgen action at the level of plasma membranes and initiating intracellular cyclic adenosine monophosphate signaling has been described in humans. The SHBG receptor remains to be fully characterized, and it is not clear whether it has any physiologic role in species like rodents that lack circulating SHBG.

The effects of androgens on penile tissues in experimental models demonstrated that androgen deprivation induces (1) smooth muscle cell degeneration (apoptosis) and adipose tissue deposition with associated fibrosis of corpus cavernosum; (2) reduction in the expression of endothelial nitric oxide synthase (eNOS) and nNOS; (3) decrease of arterial inflow and increase of venous outflow in the corpus cavernosum; (4) enhanced response to mediators of vasoconstriction and smooth muscle contraction such as α-adrenergic agents; (5) decrease of NO-mediated smooth muscle relaxation during sexual stimuli; and (6) reduced PDE5 gene and protein expression [20]. This latter aspect seems to be crucial in determining reduced efficacy of PDE5-Is in hypogonadal men, whereas metabolic and structural imbalance in the corpus cavernosum resulting in venous leakage frequently occur, as confirmed by the correlation between low free testosterone levels and impaired relaxation of corporeal smooth muscle cells to a vasoactive challenge [21]. It is known that two alternate promoters regulate transcription of three PDE5 isoforms: A1, A2, and A3 [22]. A clear-cut physiologic significance for these isoforms has not been demonstrated. By regulation of intracellular concentrations of cyclic guanosine monophosphate (cGMP), PDE5 is important for relaxation of vascular smooth muscle cells, including those of the penis. Moreover, the presence of a consensus sequence for the androgen receptor in the 5-flanking region of the PDE5 promoter (Fig. 1) suggests that androgens could regulate PDE5 expression [23]. Morelli and coworkers [8] have further investigated this latter aspect in humans, demonstrating that, in cavernous tissue from male-to-female transsexual individuals, chronic exposure to estrogens and to the antiandrogen cyproterone acetate significantly reduced PDE5 messenger RNA and protein expression as well as cGMP hydrolysis. These findings are in keeping with previous observations showing that responsiveness to PDE5-Is was reduced in hypogonadal rabbits [8] and humans [9] and restored by T administration [24], and has been substantiated by a larger trial in hypogonadal men unresponsive to sildenafil, in whom the clinical response to the drug has been improved by hormone replacement therapy, further supporting the concept that T is necessary for a full PDE5-I responsiveness [9,10,25–28]. Hence, T is important not only for allowing cGMP formation, through a positive modulation of NOS [29], but also for increasing PDE5 expression in human cavernous tissue. This androgen-induced two-step regulation of NO activity and cGMP formation in penile tissues as well as its action on hypothalamus-spinal dopaminergic and oxytocinergic pathways may be relevant to timely synchronization of penile erections in sexual acts, which are clearly androgen-dependent.

Fig. 1 – Schematic representation of the promoter of the PDE5A human gene and its regulation by testosterone. PDE5A2 isoform is the most abundantly expressed, whereas PDE5A3 is confined to tissues with a smooth muscle cell component, and its expression is correlated with the smooth muscle cell content in penile tissue. AR: androgen receptor; HSP: heat shock protein; SMC: smooth muscle cell; T: testosterone.
3. Testosterone monotherapy and ED

Clinical studies examining T monotherapy for the treatment of ED have generally yielded positive results, although many limitations and pitfalls may be evidenced in each study [30]. Other authors have demonstrated that T supplementation is an effective treatment for hypogonadal ED and may provide increased vascular reactivity [31]. On the other hand, it has been suggested that erections are still possible in hypogonadal conditions in which a decreased cGMP formation, because of impaired NO production, is counterbalanced by a reduced cGMP hydrolysis [32].

Isidori and coworkers [33] have recently performed a comprehensive meta-analysis on the effects of T on sexual function showing that, in studies carried out in men with a mean T level < 12 nmol/L (346 ng/dl), T moderately improved the number of nocturnal erections, sexual thoughts, and motivation, number of successful intercourses, scores of erectile function, and overall satisfaction compared with placebo, whereas T had no effect on erectile function in eugonadal men. In this study, a cutoff value of 10 nmol/L (288 ng/dl) for the mean T of the study populations failed to predict the effect of treatment, whereas the presence of risk factors for vasculogenic ED, comorbidities, and short evaluation periods were associated with greater treatment effects in studies performed in hypogonadal but not in eugonadal men. Meta-regression analysis showed also that the effects of T on erectile function, but not libido, were inversely related to baseline T concentration. These evidences must be tempered with the caveats that the effect of T tend to decline over time and is progressively smaller with increasing baseline T levels, and that long-term safety data are not available.

Given the multifactorial nature of the pathophysiology of ED, it is not expected that T monotherapy will be highly effective in the treatment of all patients with ED if baseline cutoff values are not chosen correctly. There is a lack of data suggesting the efficacy of T therapy in older men who do not meet the clinical definition of hypogonadism. Specifically, there is no convincing evidence that androgen therapy is either effective or safe for older men, unless androgen deficiency is evident [6].

4. Combination therapy and ED

PDE5-Is promote erectile function by inhibiting PDE5, which breaks down cGMP [34]. Clinical evidence in men with ED indicates that oral PDE5-Is, sildenafil, tadalafil, and vardenafil, have favourable safety and efficacy profiles in the treatment of ED [35]. Consequently, PDE5-Is are the first line of therapy in men who do not have potentially reversible causes of ED, such as hypogonadism [34]. However, 23–50% of patients do not respond to PDE5-Is alone [35]. Given the role of T in the NO pathway central to proper erectile function, interest in testosterone–PDE5-I combination therapy has increased in recent years (Table 1).

Different studies demonstrated that T therapy is able to improve erectile function and the response to PDE5-Is in patients with ED and hypogonadism, and also in men with PADAM symptoms [9,10,26]. Finally, T supplementation increased the International Index of Erectile Function (IIEF) scores even in eugonadal patients who did not respond to sildenafil alone, by improving sexual desire and orgasmic function and by increasing arterial inflow to the penis during sexual stimulation [9]. Furthermore, other studies have confirmed the beneficial effects of combination therapy in patients with comorbid conditions. Administration of intramuscular T and sildenafil was found to be efficacious in renal transplant patients and in patients on renal dialysis [36], and oral T has been reported to reverse ED associated with type II diabetes in patients failing on sildenafil therapy alone [25]. On the other hand, few studies suggested that, in ED-associated

Table 1 - Randomized controlled trials assessing the effects of combined therapy with testosterone plus sildenafil in men with erectile dysfunction unresponsive to monotherapy

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of subjects/hypogonadism</th>
<th>Sildenafil response at baseline</th>
<th>Overall efficacy/adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aversa et al. [9]</td>
<td>20/no</td>
<td>Failure</td>
<td>80%/none</td>
</tr>
<tr>
<td>Kalinchenko et al. [25]</td>
<td>120/yes</td>
<td>Failure</td>
<td>70%/none</td>
</tr>
<tr>
<td>Shabsigh et al. [10]</td>
<td>75/yes</td>
<td>Failure</td>
<td>70%/not evaluated</td>
</tr>
<tr>
<td>Chatterjee et al. [36]</td>
<td>12/yes</td>
<td>Not evaluated</td>
<td>100%/none</td>
</tr>
<tr>
<td>Shamloul et al. [26]</td>
<td>40/no</td>
<td>Failure/present</td>
<td>Improved/none</td>
</tr>
<tr>
<td>Greenstein et al. [37]</td>
<td>49/yes</td>
<td>Not evaluated</td>
<td>63%/18% skin irritation</td>
</tr>
<tr>
<td>Hwang et al. [27]</td>
<td>32/yes</td>
<td>Failure</td>
<td>57%/none</td>
</tr>
<tr>
<td>Rosenthal et al. [28]</td>
<td>24/yes</td>
<td>Failure</td>
<td>92%/1% headache</td>
</tr>
<tr>
<td>Tas et al. [38]</td>
<td>23/yes</td>
<td>Not evaluated</td>
<td>34%/none</td>
</tr>
</tbody>
</table>
hypogonadism, T might not be sufficient to restore complete sexual satisfaction [36–38], thus suggesting that mechanisms other than T itself may be involved in the correction of ED. In conclusion, testosterone–PDE5-I combination therapy improves the response to PDE5-Is in patients previously not responding to PDE5-I therapy alone and in whom T levels at baseline are in the hypogonadal or normal-low adult range (i.e., late-onset hypogonadism).

5. Testosterone and PDE5-Is: endothelial safety and future implication

The impairment of vascular endothelium is an early event in the development of diseases that may later become clinically overt, such as myocardial infarction or cerebral ischemia. Normal vascular endothelium is essential for the synthesis and release of substances affecting vascular tone (NO), cell adhesion (endothelins, interleukins), and the homeostasis of clotting and fibrinolysis (plasminogen inhibitors, von Willebrand factor). The degeneration of endothelial integrity promotes adverse events leading to atherogenesis, such as infiltration of the vessel wall by macrophages loaded with oxidized lipoproteins.

Recent animal and in vitro studies have further documented that T upregulates the expression of arterial AR mRNA and is associated with an inhibitory effect on neointimal plaque formation [39]. In addition, positive acute haemodynamic effects of T on coronary vasomotion and stress test–induced ischemia were reported [40]. Vascular ARs may mediate these effects of T on the arterial wall, and T has been shown to produce coronary, aortic, and brachial vasculature dilatation by activation of both endothelial-dependent and independent mechanisms [41]. T has a relatively rapid vasorelaxing effect in isolated rabbit coronary artery and aorta porcine coronary artery. Other studies have suggested that T may play a role in vascular protection and remodelling responses to vascular injury by stimulating endothelial replication and inducing endothelium-dependent vascular relaxation [41]. Acute intracoronary administration of T has been shown to induce vasodilatation in canine coronary epicardial and resistance vessels, possibly through an increase in endothelium-derived NO. Short-term application of supraphysiologic doses of exogenous T stimulate vasorelaxation and can reduce the severity and frequency of angina pectoris, and improve the electrocardiographic signs of myocardial ischemia. Long-term effects have not been investigated. Nonetheless, interpretations of the effects of pharmacologic doses of androgens on arterial compliance and flow-mediated dilatation in particular must be treated with circumspection also, because at physiologic concentrations, beneficial, neutral, and detrimental effects on vascular reactivity can be observed, respectively [42].

Coronary artery disease (CAD) represents one of the most common and costly atherogenic diseases in the Western world. CAD is more common in men aged 30–50 yr compared with women of similar age, an observation that has often suggested harmful effects of androgens on the coronary circulation. Recent studies suggest that T may have beneficial effect on the coronary vasculature [43] and have shown that blood T concentrations are consistently lower among men with cardiovascular disease [44]. Moreover short-term interventional studies have shown that T produces a modest but consistent improvement in cardiac ischemia over placebo, comparable to the effects of existing antianginal drugs [40]. Hypoandrogenemia is associated with an increased risk of CAD, visceral obesity, insulin resistance, low high-density lipoprotein cholesterol (HDL-C), elevated triglycerides, elevated low-density lipoprotein cholesterol, and impaired plasminogen activator inhibitor-1, and Lp(a) haemostasis. In male patients with suspected CAD, the plasma T, lipoprotein lipase, and HDL-C levels are lower, and the Lp(a) level is higher than in controls. These observations suggest that decreased T and HDL-C levels and increased Lp(a) level may represent risk factors for CAD, and that low plasma T may be responsible for the low levels of lipoprotein lipase and HDL-C. This suggestion is supported by reports that T replacement in males with idiopathic hypogonadotrophic hypogonadism is associated with decreased cardiovascular risk and that natural androgens may inhibit atherosclerosis in men [43]. By contrast, other evidences suggest that T exerts “pro-atherogenic” effects on macrophage function by facilitating the uptake of modified lipoproteins and an “anti-atherogenic” effect by stimulating efflux of cellular cholesterol to HDL. However, androgen-induced declines in circulating HDL-C should not automatically be assumed to be proatherogenic, because these declines may instead reflect accelerated reverse cholesterol transport [45]. Overall, the cardiovascular effects of T therapy may be neutral to beneficial. There is no contraindication for T therapy in men with cardiovascular disease and diagnosed hypogonadism with or without ED. Caution should be exercised regarding occasional increases in hematocrit levels, especially in patients with congestive heart failure.
The wide use of PDE5-Is by patients with ED and cardiovascular disease has resulted in a considerable number of independent studies investigating the cardiovascular safety and functional role of the PDE5-cGMP-NO pathway in the cardiovascular system. However, the clinical studies performed on PDE5-I treatment have actually been conducted only as “on-demand” administration. Sildenafil has been demonstrated to improve the vasomotor aspect of endothelial dysfunction in patients with heart failure and diabetes, and haemodynamic studies suggest that sildenafil is a modest vasodilator with the potential to increase coronary blood flow and coronary blood reserve. In patients with ischemic heart disease, sildenafil is associated with reduction in mean arterial and pulmonary pressure with an effect on heart rate, cardiac output, and systemic and pulmonary vascular resistance [46]. Recent animals studies merge strong evidence for a direct protective effect of chronic sildenafil against cardiomyocytes necrosis and apoptosis through an NO-signalling pathway mechanism [46]. Preliminary studies of our group show an influence of chronic tadalafil administration on insulin signalling and endothelial function. In this ancillary study, tadalafil 20 mg on alternate days or on demand were administered for 4 wk to patients with ED of any severity or aetiology. After treatment on alternate days, morning erections dramatically increased, and markers of endothelial function showed a robust improvement after chronic versus on-demand regimes without any unwanted side-effects [47].

6. Recommendations for testosterone therapy and/or combined therapy

Currently there is an insufficient number of studies, particularly placebo-controlled randomized trials, assessing the risks and benefits of T therapy in older men who have not been clinically diagnosed with hypogonadism but have lower T levels than young adult males and show one or more symptoms of ageing and hypogonadism, such as ED. Therefore at the present time, there is no basis for large-scale T replacement therapy in older men, unless they have symptomatic androgen deficiency [6]; however, trials in older men who have low T levels may identify significant benefits in this subpopulation. As already outlined, T levels needed for normal sexual function vary between individuals; in patients with sexual dysfunction, T testing is advised to screen for hypogonadism [33]; and T therapy is appropriate only when clinical symptoms and biochemical evidence of hypogonadism exist. Hypogonadal men with specific sexual dysfunctions such as ED, diminished libido, or both are candidates for T replacement therapy. T monotherapy may correct sexual dysfunction caused by hypogonadism, but absence of an adequate response after appropriate therapy may require further evaluation to exclude associated comorbidities, such as those causing vasculogenic or neurogenic ED [31]. Ongoing studies suggest that T may have a role as an antiatherogenic therapy, by preserving endothelial and smooth muscle cell integrity. Also, recent evidences demonstrated that androgen deprivation for prostate cancer might alter insulin sensitivity, thus suggesting a potential role in the development of insulin resistance [48]. Finally, other studies found a positive correlation between free T levels and compliance of cavernous arteries in patients with organic erectile dysfunction [21], suggesting a direct vasodilator effect of T.

Men with ED and low T levels could benefit from combination therapy with T and a PDES-I. As already outlined, between 10% and 20% of ED cases may be attributed to subnormal T levels [34]. However, if we consider overall hormonal alterations of sex steroids in men complaining of ED, it is noteworthy to remember that up to 40% of these men may present alterations of T and/or estradiol, thus resulting in an imbalance of their ratios [5]. In addition, other populations at risk for hypogonadism, such as those with diabetes type II, metabolic syndrome, chronic renal failure and other chronic diseases, are potential candidates who could benefit from combination therapies if response to monotherapy is not sufficient [49].

A recent study carried out in Italy on a wide scale of the population (more than 18,000 persons) complaining of sexual disturbances to a free call-centre confirmed that ED prevalence increases as men age, and that ED is strongly associated with common comorbid conditions of ageing men, such as diabetes and depression. The study also suggested that these comorbidities might work together to increase the prevalence and severity of ED [50]. A high prevalence of ED in patients with diabetes has been attributed mainly to vascular and neurologic conditions, but also to hypogonadism [51], which has been observed to occur commonly with type II diabetes [52] and to result from metabolic syndrome in middle-aged men [53].

In conclusion, we want to reinforce the concept that the age-related decline of serum T should be confirmed twice, along with measurements of SHBG. The bioavailable T (plasmatic or calculated) currently is not recommended routinely because of the many difficulties with measures and interpretation
by different international society guidelines, and should be measured whenever possible (normal reference ranges are not universally accepted). For these reasons, we do strongly encourage disclosure of hormonal alterations in all ED patients to maximise the effects of oral PDE5-Is for successfully treating their sexual dysfunctions.

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References


