

The role of testosterone in erectile dysfunction

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Abstract | Erectile dysfunction (ED) is a clinical disorder that results from a continuous spectrum of clinical factors, including physical illness (comprising the organic component of ED), reaction to stress (the intrapsychic component of ED) and relationship difficulties (the relationship component of ED). Testosterone clearly has a relevant role in all three causes of ED; the usefulness of this hormone in the treatment of ED has not, however, been completely clarified. The main physiological action of testosterone in the male sexual response is to regulate the timing of the erectile process as a function of sexual desire, thereby coordinating penile erection with sex. The link between ED, hypogonadism and underlying disorders (such as metabolic syndrome and type 2 diabetes mellitus) is nowadays well documented. The recognition of underlying disorders might be useful in motivating men with ED to improve their health-related lifestyle choices. Hence, patients with ED might be considered 'lucky', because their disorder offers the opportunity to undergo medical examinations to detect underlying disease. Both ED and hypogonadism are treatable conditions. A range of testosterone preparations are available for supplementation; their combination with phosphodiesterase 5 inhibitors might improve outcomes in some cases.

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Introduction

Erectile dysfunction (ED) is a very common multi-dimensional disorder that has a detrimental effect on sexual and reproductive activity, and can thereby considerably impair the quality of life of both the patient and his partner. A 2009 analysis of all population-based studies conducted in the US indicates that ED is indeed the most common endocrine disorder in men.¹ A European survey showed that ED affects almost 30% of men in an age-dependent manner.²

In 1993, the NIH Consensus Development Panel on Impotence defined ED as "...the persistent inability to achieve and/or maintain a penile erection adequate for satisfactory sexual activity".³ Penile erection (Box 1) is a neurovascular event that can be seen as a feed-forward event with a biologic dimension (with cardiovascular, neuronal and hormonal determinants), an intrapsychic dimension (the individual's sexual identity and sense of well-being) and a marital dimension (the context for a sexual relationship). In each patient with ED, biological, psychological and lifestyle factors are present in varying degrees, and interact with each other. Thus, ED is a frustrating disorder that derives from a continuous spectrum of clinical elements, including physical illness, reaction to stress and relationship difficulties.⁴ We strongly believe that the male hormone testosterone makes a considerable contribution to all three of these dimensions of ED.

In this Review, we aim to outline the role of testosterone in the pathogenesis and treatment of ED, highlighting both the molecular pathways and the clinical symptoms influenced by this hormone. Current

guidelines for testosterone replacement therapy (TRT) will be presented, together with a discussion of the currently available testosterone preparations for treatment. We conclude by providing a brief overview of the use of combination therapy in cases in which TRT might not be adequate owing to the multifactorial pathophysiology of ED.

Testosterone and sexual dysfunction Linking ED with testosterone

ED, low testosterone levels and metabolic and cardiovascular diseases are now recognized to be closely linked, and this association might have a relevant impact on patient morbidity and mortality (reviewed elsewhere^{5–8}). Accordingly, these disorders are all associated with the condition known as metabolic syndrome. Metabolic syndrome constitutes a diagnostic category based on a cluster of risk factors (hyperglycemia or diabetes, abdominal obesity, hypertriglyceridemia, low HDL cholesterol, and hypertension), and specifically identifies individuals who are at high risk for metabolic and cardiovascular diseases. The link between metabolic syndrome and hypogonadism and ED is now well recognized, as this syndrome is highly prevalent in patients with ED and low testosterone levels.^{5–8} A clear negative relationship exists between the presence of risk factors for metabolic syndrome (defined according to the National Cholesterol Education Program—Third Adult Treatment Panel [NCEP—ATPIII] criteria)⁹ and levels of circulating testosterone in patients with ED.

We previously reported this association between the number of metabolic syndrome risk factors and low testosterone in consecutive series of 803¹⁰ and 1,491⁶ men

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Competing interests

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with ED. We have now extended this analysis to a larger series ($n = 1,922$; unpublished data), the characteristics of which do not differ significantly from the previous sample. Patients were interviewed before treatment, and before any specific diagnostic procedures, using the structured interview on sexual dysfunction (SIEDY) and ANDROTEST.^{4,11} In these patients, an increasing number of risk factors for metabolic syndrome was associated with decline in testosterone levels (Figure 1a).

The recognition of underlying conditions that are associated with ED, such as hypogonadism, metabolic syndrome and diabetes, might be useful in motivating men to improve their health-related lifestyle choices. The presence of ED, which was previously considered to be no more than a frustrating condition, should now be regarded as a unique opportunity to screen for the presence of comorbidities. Hence, patients with ED might be considered 'lucky', because their disorder offers the opportunity to undergo medical examinations. Thus, not only might these patients improve their sexual health, but also—perhaps more importantly—their overall health might be ameliorated,¹² even though the pathogenetic mechanisms linking low testosterone to metabolic syndrome and ED seem complex.^{5–8}

In an animal model of metabolic syndrome with ED and hypogonadism, metabolic syndrome is specifically associated with hypogonadism of central origin (at pituitary–hypothalamus level), which is characterized by a decreased number of gonadotropin-releasing hormone neurons in the hypothalamus and reduced levels of circulating gonadotropins.¹³ Available clinical data in humans also indicate an impairment of the hypothalamic–pituitary axis in some patients with metabolic syndrome or type 2 diabetes, with the consequence of the insulin resistance associated with both disorders manifesting peripherally.^{5–8,14–17}

Testosterone and penile erection

The relationship between penile blood flow (as assessed by dynamic penile Doppler ultrasonography) and levels of circulating testosterone in individuals with ED is weak overall, although it is statistically significant when adjusted for age. When smoking and the number of metabolic syndrome factors were included in a multivariate model, the positive relationship between testosterone and stimulated penile blood flow remained significant, indicating an independent association between testosterone levels and penile blood flow (Figure 1b). Much weaker is the age-adjusted negative association between total testosterone levels and the ability to obtain an erection that is sufficient for penetration (Figure 1c). By contrast, the age-adjusted association between total testosterone and reported frequency of spontaneous (morning or nocturnal) erections in the same sample of patients was highly significant (Figure 1d). Overall, these data indicate that penile erection is somehow associated with the androgen milieu, even though such an association can be obscured by other clinical factors.

Experimental studies in animals and human cell cultures indicate that testosterone controls, directly or

Key points

- Testosterone levels can reflect perturbations in all three dimensions (organic, intrapsychic and relationship) of erectile dysfunction (ED)
- Testosterone is important not only in controlling the mechanical process of penile erection, but it also controls male sexual behavior and attitudes
- Testosterone replacement therapy (TRT) should be considered the first-line treatment in hypogonadal patients with ED
- TRT monotherapy might not be adequate in all cases of ED because of the multifactorial pathophysiology of this disorder
- In these cases, combination therapy with phosphodiesterase 5 inhibitors might improve outcomes

Box 1 | Mechanism of penile erection

Penile erection occurs when the two sponge-like cavernous bodies (corpora cavernosa) become engorged with blood. The amount of blood flow to the corpora cavernosa is regulated by the activity of smooth muscle cells (SMCs); these cells are arranged in a syncytium, lining the penile arteries and cavernous spaces while maintaining tight communication with the overlying endothelial cells. The penis is flaccid when SMCs are contracted and becomes rigid when they are relaxed. A series of biochemical and hemodynamic events, which are associated with activation of the central nervous system, control the switch between muscle contraction and relaxation.¹⁰³ Sympathetic nerve activity is mainly responsible for maintaining SMCs in a contractile state. When released from nerve endings, norepinephrine binds to its cognate receptors. Receptor binding activates two separate pathways within the cells—one leading to the activation of Rho kinase and the other causing increased levels of inositol trisphosphate—which result in an increase in intracellular calcium levels and calcium sensitization.

SMC relaxation is primarily driven by the activity of parasympathetic and nonadrenergic/noncholinergic neurons, which control the formation of nitric oxide (NO) through NO synthase, present in both endothelial cells and neurons. NO diffuses into SMCs and increases the formation of cyclic GMP (cGMP), which, through cGMP-dependent protein kinase G, promotes SMC relaxation by decreasing intracellular calcium levels. Relaxation of cavernous SMCs increases blood flow to cavernosal sinuses and mediates venous occlusion, resulting in penile engorgement and rigidity. The formation of cGMP is actively counteracted by a series of phosphodiesterases (PDEs), the most important of which is PDE5. In the human corpora cavernosa, PDE5 alone accounts for the breakdown of the majority (~70%) of cGMP²⁸

indirectly, several of the mechanisms that lead to erection and detumescence (Box 1; Figure 2). First, it controls the commitment of penile stem cells to a smooth muscle phenotype, thereby promoting the functional and structural integrity that is necessary for penile erection (reviewed elsewhere^{18–20}). In addition, testosterone also controls numerous enzymatic activities within the corpora cavernosa. A role for testosterone in regulating the formation of nitric oxide (NO), by acting on endothelial and neuronal nitric oxide synthase (eNOS and nNOS), has been demonstrated in numerous animal models of hypogonadism induced by surgical or chemical castration^{21–23} (see reviews^{19–24}) or by metabolic disorders such as type 1 diabetes²⁵ or metabolic syndrome.¹³ In addition, testosterone also negatively regulates the activity of the RhoA–ROCK (Ras homolog gene family member A–Rho-associated, coiled-coil containing protein kinase) pathway, such that sensitivity to calcium within penile smooth muscle cells in both castration-induced²⁶ and diabetes-induced hypogonadism²⁷ is reduced overall

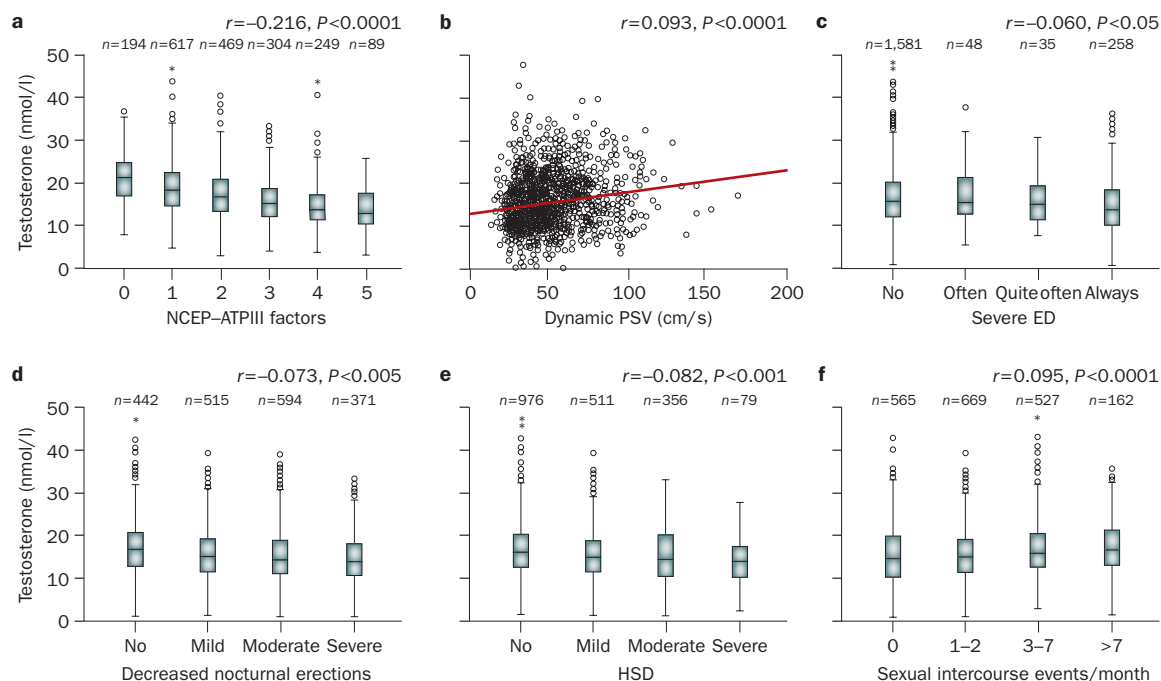


Figure 1 | Correlation between testosterone plasma levels and different clinical, instrumental and sexual parameters. These data are from 1,922 patients who sought medical care at our andrology unit for sexual disorders. The inset reports the age-adjusted correlation. **a** | Number of metabolic syndrome components according to NCEP-ATPIII criteria.⁹ **b** | Dynamic (after PGE1 stimulation) PSV. **c** | Lack of erection during sexual intercourse as derived from SIEDY appendix A:⁴ sometimes $\leq 25\%$ of cases; quite often, 26–50%; often, 51–75%; always $> 75\%$. **d** | Decreased nocturnal erections as derived from SIEDY structured interview:⁴ no, the patient reports spontaneous nocturnal or morning erections, with the same frequency as previously observed; mild, nocturnal or morning erections are present, but their frequency is somewhat lower than that observed previously; moderate, the frequency of nocturnal or morning erections is reduced by at least 50%; severe, no nocturnal or morning erections are present. **e** | HSD as derived from SIEDY structured interview:⁴ no, the patient's desire is unmodified or increased; mild, desire is reduced in less than 50% of potential occasions; moderate, desire is reduced in more than 50% of potential occasions; severe, the patient has had no sexual desire. **f** | Frequency of sexual intercourse per month. Abbreviations: ED, erectile dysfunction; HSD, hypoactive sexual desire; NCEP-ATPIII, National Cholesterol Education Program–Third Adult Treatment Panel; PGE1, prostaglandin E1; PSV, peak systolic velocity; SIEDY, Structured Interview on Erectile Dysfunction.

through increased RhoA–ROCK activity. However, under the same experimental conditions (surgical or chemical castration, diabetes-induced or metabolic-syndrome-induced hypogonadism), testosterone also regulates the expression of phosphodiesterase type 5 (PDE5).^{13,25,27–30} As testosterone positively controls both the enzymatic steps necessary for the initiation (positive effect on NOS and negative effect on RhoA–ROCK) and the end (positive effect on PDE5) of the erectile process, its net effect on erection ends up as modest overall.

Hypogonadism and erection

Erections are indeed still possible under hypogonadal conditions; in these circumstances, decreased cyclic GMP (cGMP) formation, owing to impaired NO production, is most probably counterbalanced by reduced PDE5 activity and reduced cGMP hydrolysis. The main physiological action of testosterone is, therefore, to regulate the timing of the erectile process as a function of sexual desire, thereby coordinating erection with sex.^{19,24} Accordingly, Rhoden *et al.*,³¹ in a large consecutive series of almost 1,000 elderly men with or without ED, have documented a lack of association between

total testosterone and erectile condition (as measured by the International Index of Erectile Function [IIEF-5] score). Historical reports note that in ancient Rome, women used potent eunuchs for pleasure with no risk of procreation.³²

Testosterone and sexual behavior

Testosterone is important not only in controlling the mechanical process of penile erection but in regulating aspects of male sexual behavior and attitudes. Several brain areas, including the amygdala, medial preoptic area, paraventricular nucleus of the hypothalamus and periaqueductal gray matter, express the androgen receptor.³³ As in penile erection, testosterone has a permissive effect on sexual behaviors, increasing the likelihood that sexual behavior occurs in the presence of an appropriate stimulus. Sexual behavior in humans is indeed multifactorial, but hormonal cues have a distinct role.^{34,35}

Sexual desire

Results from a large series of men who presented to our unit with ED indicate that patients with decreasing levels of sexual desire have progressively lower concentrations

of testosterone than those who maintain their sexual desire (Figure 1e). Sexual thoughts and motivations are universally accepted as the most testosterone-dependent aspects of male sexual behavior.^{34–36} Nonetheless, we have previously demonstrated that, in addition to low levels of testosterone, other intrapsychic and relationship factors, as well as medical conditions, might significantly influence male sexual desire.³⁷ For instance, mood depression or hyperprolactinemia have a greater negative effect on sexual drive than hypogonadism.³⁷ In particular, severe (>35 ng/ml), but not mild, hyperprolactinemia is associated with a relevant impairment in sexual desire.^{37–41} Although hypogonadotropic hypogonadism is often associated with severe hyperprolactinemia,^{37–41} current evidence indicates a direct, testosterone-independent, effect of prolactin on sexual desire.^{38,40} Accordingly, in hyperprolactinemic patients, testosterone treatment is not able to restore libido,⁴² whereas prolactin-lowering drugs can.^{40,43} Thus from these aforementioned associations, it can be deduced that frequency of sexual intercourse—which is related to both sexual interest and erectile function—is obviously androgen-dependent (Figure 1f).

Autoeroticism and fidelity

Other sexual behaviors and attitudes are also associated with the androgen milieu. Autoeroticism, the practice of sexually stimulating oneself, is indeed androgen-dependent.⁴⁴ Masturbation is a more frequent habit in individuals with higher levels of testosterone than in those with lower levels (Figure 3a). In fact, higher androgen levels were one of the main factors associated with an increased frequency of masturbation.⁴⁴ In addition, self-defined unfaithful men have higher levels of testosterone, even after adjustment for age, than do their faithful counterparts (Figure 3b), confirming previous findings from other studies.^{45–48} Potentially, looking for additional partners is a competitive situation, which might be associated with higher testosterone levels.^{45–48} Competitiveness⁴⁹ and dominance^{50–52} are well-known androgen-dependent behaviors.

Histrionic or hysterical trait

We found that, of different personality traits, the histrionic or hysterical trait is most tightly linked to levels of testosterone (Figure 3c).⁵³ Men who show a greater tendency towards histrionic or hysterical traits have higher levels of testosterone. Accordingly, they reported a higher prevalence of extramarital affairs.⁵³ Individuals with histrionic or hysterical traits display a number of characteristics, including self-centeredness, inappropriate appearance or behavior, and excess concern with physical appearance.⁵³ We have speculated that high levels of testosterone favor behaviors that are characterized by high self-ranking, exaggerated emotionality, seductiveness and the tendency to crave novelty and excitement.⁵³

Linking testosterone and relationships

In light of these findings, a key question arises: are testosterone levels higher in mating males in order to

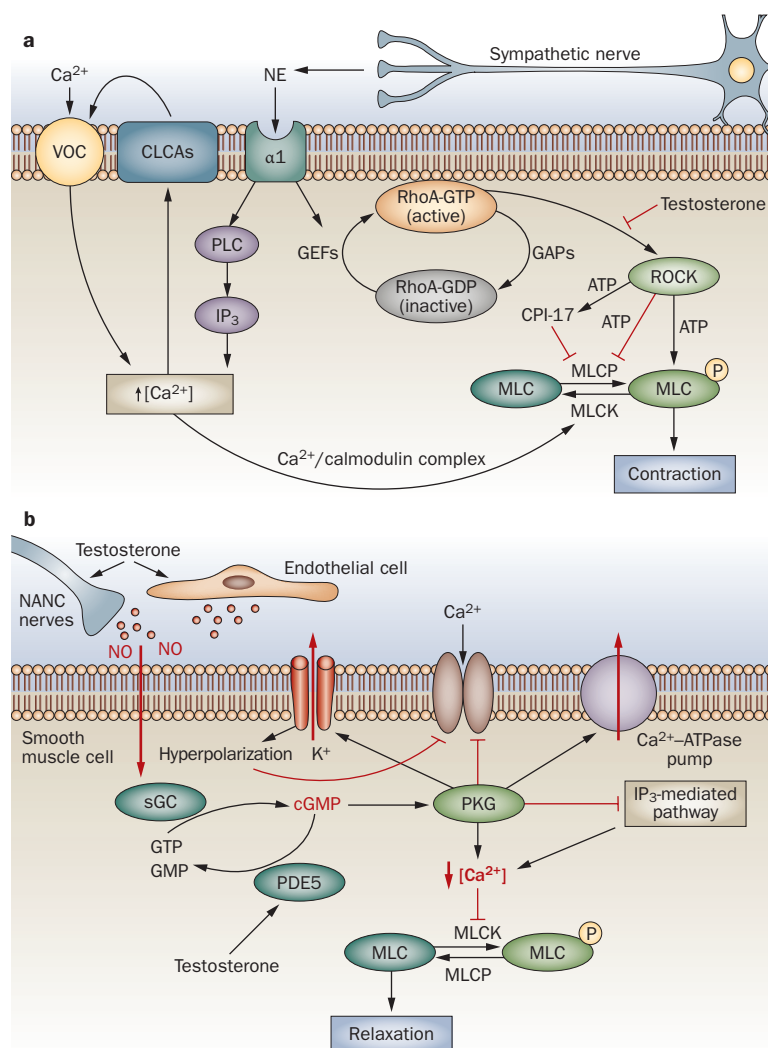


Figure 2 | The putative role of testosterone in the mechanism of penile flaccidity and erection. **a** | Smooth muscle cell contraction in the corpora cavernosa. NE binding to $\alpha 1$ receptors generates IP_3 , which, by increasing intracellular calcium (Ca^{2+}) levels, activates Ca^{2+} -sensitive CLCAs resulting in membrane depolarization, with the diffusion of the stimulus to the neighboring cells and the opening of VOC. The increased Ca^{2+} flow promotes, through calmodulin, activation of MLC kinase and cell contraction. Cell contraction is also obtained by altering the Ca^{2+} sensitivity through a NE-induced activation of a second pathway, RhoA/ROCK, which increases, through a series of kinase activation, the sensitivity of MLC to Ca^{2+} . Testosterone is proposed to negatively regulate this second pathway. **b** | Smooth muscle cell relaxation in the corpora cavernosa. NO is generated by NO synthases in either NANC neurons (nNOS) or endothelial cells (eNOS). Both steps are positively regulated by testosterone. NO diffuses into smooth muscle cells and activates sGC, which in turn transforms GTP into cGMP. cGMP activates PKG, which, through various pathways, ultimately decreases intracellular Ca^{2+} levels, leading to relaxation. PDE5 metabolizes cGMP into GMP, thereby limiting its effects. This event is positively controlled by testosterone. Abbreviations: cGMP, cyclic GMP; CLCA, Ca^{2+} -sensitive chloride channel; CPI-17, protein phosphatase 1 regulatory subunit 14A; eNOS, endothelial nitric oxide synthase; GAP, GTPase activating protein; GEF, guanine nucleotide exchange factor; IP_3 , inositol 1,4,5-trisphosphate; MLC, myosin light chain; MLCK, myosin light chain kinase; MLCP, myosin light chain phosphatase; NANC, nonadrenergic-noncholinergic; NE, norepinephrine; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; PDE5, phosphodiesterase type 5; PKG, protein kinase G; PLC, phospholipase C; RhoA, Ras homolog gene family member A; ROCK, Rho-associated, coiled-coil containing protein kinase; sGC, soluble guanylate cyclase; VOC, voltage-operated channels.

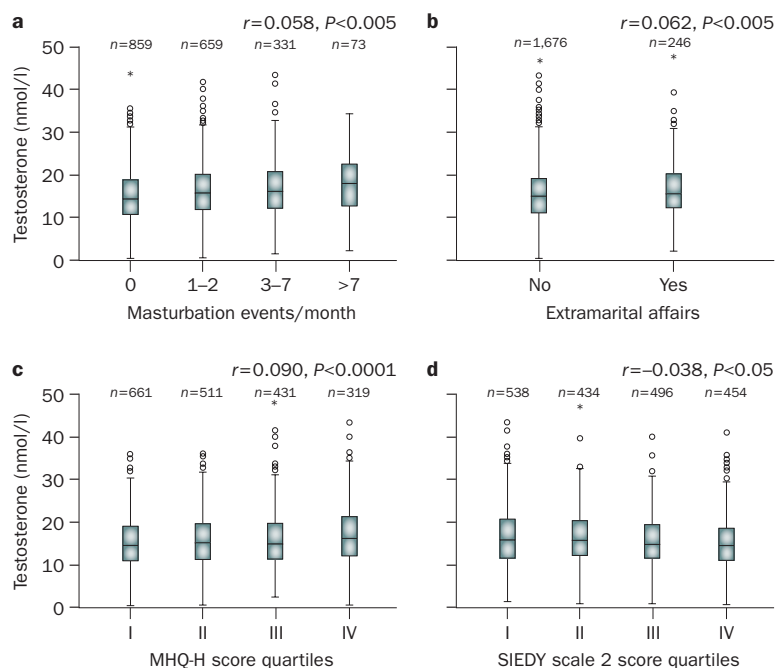


Figure 3 | Correlation between testosterone plasma levels and different clinical, instrumental and sexual parameters. These data are from 1,922 patients who sought medical care at our andrology unit for sexual disorders. The inset reports the age-adjusted correlation. **a** | Frequency of masturbation per month.⁴⁴ **b** | Presence or absence of extramarital affairs as derived from SIEDY structured interview.⁴⁵ **c** | MHQ-H score quartiles dealing with hysterical or hysterical traits.⁵³ **d** | SIEDY scale 2 score quartiles dealing with the relational component of erectile dysfunction.⁵⁴ Abbreviations: MHQ-H, Middlesex Hospital Questionnaire hysteria subscale; SIEDY, Structured Interview on Erectile Dysfunction.

allow better sexual and reproductive function (affecting libido, penile erections, sexual confidence and spermatogenesis); or is the reverse true, and might sexual activity positively affect the production of testosterone? Our view is that a reduction in sexual activity owing to relationship problems should be considered as a possible factor that influences testosterone levels.⁵⁴ A negative association between the SIEDY scale 2 (which scores problems in relationships) and testosterone levels has been reported,⁵⁴ with individuals in the highest score quartile showing the lowest level of circulating testosterone, even after adjustment for age (Figure 3d). We demonstrated, by iterative, alternative logistic modeling of several putative determinants of SIEDY scale 2, that the association between hypogonadism and impaired couple relationship seems to be exacerbated by ED and decreased intercourse frequency.⁵⁴ Hence, the greater the extent of ED, the lower the sexual activity and testosterone levels of the male partner, as previously suggested by others.^{55–59} Consistent with this result, we observed hypogonadotropic hypogonadism in a rat experimental model 3 months after bilateral denervation of the penis (by bilateral resection of the cavernous nerves),⁶⁰ and speculate that sexual inactivity, induced by cavernous denervation, could lead to a state of overt hypogonadism.⁶⁰ Importantly, however, our experimental model is an extreme model of cavernous nerve injury and other factors, such as

hypoxia and secretion of unidentified hypoxia-related factors, could be involved in the mechanism underlying the reduction of luteinizing hormone and testosterone levels. Accordingly, in men with obstructive sleep apnea, chronic hypoxia has already been demonstrated to be associated with decreased function of the pituitary–gonadal axis.⁶¹ In conclusion, current data suggest that successful sex is a prerequisite for a good relationship, and a good relationship is the cornerstone for successful sexual activity, which is accompanied by higher testosterone levels.

Diagnosis of hypogonadism

Guidelines on the use of TRT to treat hypogonadal men are available from professional societies (Table 1).^{36,62,63} Consensus among the major societies in the field recognizes that testosterone replacement should be offered when the levels of circulating total testosterone fall below 8 nmol/l (231 ng/dl).³⁶ There is also general agreement that a total testosterone level above 12 nmol/l (346 ng/dl) does not require TRT. When the levels of total testosterone are in the range 8–12 nmol/l and are accompanied by typical hypogonadal symptoms, the concentration of free testosterone (measured by equilibrium dialysis method or calculated according to Vermuelen's formula⁶⁴) should be evaluated. A free testosterone level of below 225 pmol/l (6.5 ng/dl) in conjunction with typical symptoms warrants consideration of a trial of TRT.³⁶ Guidelines proposed by the American Association of Clinical Endocrinologists⁶³ and by The Endocrine Society⁶² differ with respect to the proposed lower threshold for testosterone, with cut-off values of 7 nmol/l (200 ng/dl) and 10.4 nmol/l (300 ng/dl), respectively (Table 1).

Although they differ in the testosterone thresholds proposed for the definition of hypogonadism, all the society guidelines recognize that the presence of hypogonadism-related symptoms is the cornerstone to defining overt hypogonadism. Low sexual desire is considered the symptom that is most commonly associated with male hypogonadism, although ED has been considered the most common hypogonadism-related symptom that leads to a medical consultation.^{19,65,66} The prevalence of hypogonadism according to different criteria in a large series of subjects attending our unit for ED is summarized in Figure 4.

Although the prevalence of mild hypogonadism (total testosterone <12 nmol/l) is quite frequent, the presence of severe hypogonadism (total testosterone <7 nmol/l) is a rare event. Hence, the recognition of symptoms associated with hypogonadism is important for physicians dealing with patients with sexual dysfunction. For this purpose, at present, three different questionnaires have been developed to screen for hypogonadism: the St Louis University Androgen Deficiency in Aging Males (ADAM) questionnaire,⁶⁷ the Aging Males' Symptoms (AMS) scale,⁶⁸ and the questionnaire of the Massachusetts Male Aging Study (MMAS).⁶⁹ All these screening tools have demonstrated good sensitivity in cross-sectional surveys (compared to measured levels of bioavailable testosterone) but their relative specificity is rather low.⁷⁰ In addition,

they are not specifically designed for individuals with sexual dysfunction. We have recently developed a brief (12 items) structured interview (ANDROTEST) specifically to screen for hypogonadism in patients with sexual dysfunction.¹¹ In the validation sample, ANDROTEST showed a sensitivity and specificity of 68% and 65%, respectively, in detecting low total testosterone levels (<10.4 nmol/l) and of 71% and 65%, respectively, in screening for low free testosterone (<37 pmol/l).

Testosterone preparations

Native testosterone is absorbed well by the intestine, but it undergoes hepatic metabolism so rapidly that maintaining normal serum levels in a hypogonadal patient is difficult (see reviews^{71–75}). In an attempt to improve its bioavailability and pharmacokinetics, several structural modifications of testosterone have been carried out (Figure 5). Alkylation at the 17 α position prevents rapid breakdown in the liver; however, this modification causes hepatotoxicity and the use of these preparations is, therefore, no longer recommended. Alkylation at position 1 and esterification of the 17 β -hydroxyl group, which also prevent premature metabolism, do not induce this adverse effect. Esterification with carboxyl groups in the 17 β position increases lipophilicity and enables intramuscular administration in an oil solution. However, esters enter the circulation, and display a similarly short half-life to testosterone itself. The prolonged effect of this modified variant is, therefore, exclusively the result of its delayed release from the depot injection.

A wide range of testosterone preparations are commercially available, and these are summarized in Table 2.

Oral formulations

In view of this information, the only testosterone preparation that is available for oral administration is testosterone undecanoate, yet the absorption of this formulation is highly dependent on food intake and the considerable variation in the resulting testosterone levels (and, consequently, the clinical response) makes it an unsuitable therapy for hypogonadal patients.⁷² The manufacturer's recommendation to take it with meals is clearly insufficient: it must be taken with at least 20 mg of fat for optimum absorption.⁷²

Injections

Injectable esters comprise another possible testosterone formulation.^{71–75} The propionate testosterone ester is a short-term formulation, which is not widely used because it requires the administration of fractionated doses every 2–3 days. Cypionate and enanthate testosterone esters must be injected every 2–4 weeks. In general, levels of testosterone in the serum reach supra-physiologic levels 24 h after injection; this increase is followed by a gradual decline to hypogonadal levels over the following 2 weeks. This effect might create a sense of euphoria in the period immediately following injection and a subsequent rapid return of hypogonadal symptoms as testosterone levels fall. Furthermore, these wide fluctuations in testosterone concentrations could

Table 1 | Biochemical definitions of hypogonadism*

Guidelines	nmol/l	ng/ml	ng/dl
EAA, ISA, ISSAM EAU, ASA ³⁶	Mild <12	<3.40	<340
	Severe <8	<2.31	<231
Endocrine Society ⁶²	<10.4	<3.00	<300
AACE ⁶³	<7	<2.00	<200

*According to international societies. Abbreviations: AACE, American Association of Clinical Endocrinologists; ASA, American Society of Andrology; EAA, European Academy of Andrology; EAU, European Association of Urology; ISA, International Society of Andrology; ISSAM, International Society for the Study of the Aging Male.

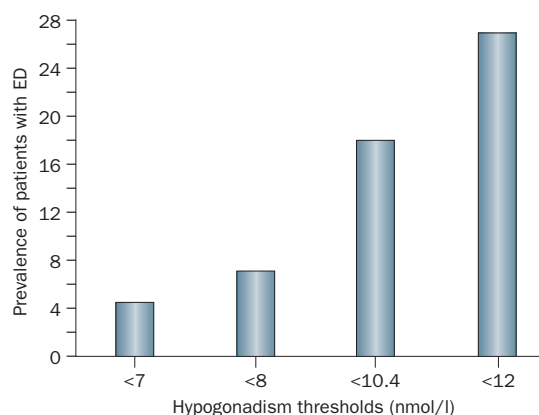


Figure 4 | Prevalence of hypogonadism according to different definitions. These data are from 1,922 consecutive patients who attended our andrology unit for treatment of ED. Abbreviation: ED, erectile dysfunction.

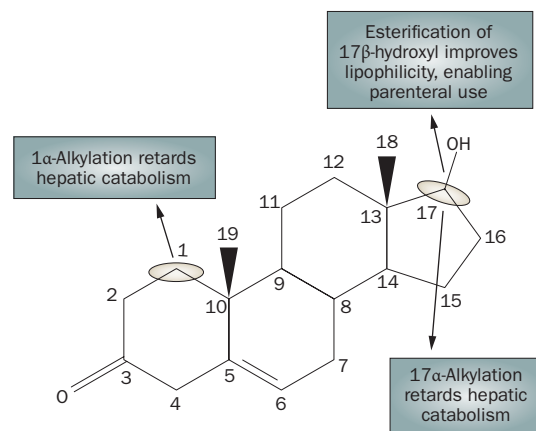


Figure 5 | Chemical structure of testosterone showing possible sites of structural modification to improve bioavailability and pharmacokinetics.

result in frequent, often dangerous, adverse effects, such as polycythemia.^{71–75} A new, even longer-lasting injectable formulation of testosterone undecanoate has been introduced. A longer hydrophobic side chain (11 versus 7 carbon atoms) confers an increased half-life in comparison with other esters. Testosterone undecanoate is injected with a castor oil carrier, which further improves the duration of its effect. A dosing regimen of 1,000 mg every 12 weeks following a 6-week loading dose has been recommended. This formulation has proven to

Table 2 | Available testosterone preparations

Formulation	Chemical structure	Half-life	Advantages	Disadvantages
Oral agents				
Testosterone undecanoate (Andriol Testocaps®)	17 α -hydroxyl ester	4 h	Oral convenience; modifiable dosage	Serum testosterone levels and clinical responses vary; must be taken with meals
Methyltestosterone (Android®, Testred®, Virilon®)	17 α -alkylated	3.5 h	Oral convenience; modifiable dosage	Potential hepatotoxicity; treatment considered obsolete
Mesterolone (Proviron®)	1-alkylated	8 h	Oral convenience; modifiable dosage	Not aromatizable to estrogen
Intramuscular agents				
Testosterone enanthate (Testo-Enant™, Testoviron™)	17 α -hydroxyl ester	4–5 days	Low cost	Wide fluctuations in circulating testosterone levels; multiple injections; relative higher risk of polycythemia
Testosterone cypionate (Delatestryl®)	17 α -hydroxyl ester	8 days	Low cost	Wide fluctuations in circulating testosterone levels; multiple injections; relative higher risk of polycythemia
Testosterone propionate (Testoviron™)	17 α -hydroxyl ester	20 h	Low cost	Wide fluctuations in circulating testosterone levels; multiple injections; relative higher risk of polycythemia
Testosterone undecanoate in castor oil (NEBIDO®)	17 α -hydroxyl ester	34 days	Testosterone levels maintained within normal range; long-lasting; less-frequent administration	Pain at injection site
Subcutaneous agents				
Surgical implants (Testopel®)	Native testosterone	NA	Treatment only twice per year	Placement is invasive; risk of extrusion and site infections
Controlled-release buccal agents				
Testosterone buccal (Striant®)	Native testosterone	12 h	Testosterone levels within physiologic range	Possible oral irritation; twice-daily dosing; unpleasant taste
Transdermal agents				
Testosterone patches (Androderm®, Testopatch®)	Native testosterone	10 h	Mimics circadian rhythm; simple administration	Skin irritation; daily administration
Testosterone gel (AndroGel®, Testogel®, Testim®, Fortigel®, Tostrex®)	Native testosterone	6 h	Testosterone levels maintained within normal range; flexible dose modification; skin irritation less common than with patches	Possible transfer during intimate contact; daily administration

The information in this Table has been adapted from several review articles.^{71–75}

attain normal testosterone levels without any significant adverse effects.^{71–75}

Slow-release preparations

An even longer-lasting option for hypogonadal men is the implantation of testosterone pellets, which are available in the US, UK and Australia. The pellets, made from pure crystals of testosterone, are inserted subcutaneously and held with a retention suture; erosion at the surface of the pellet leads to systemic absorption. The procedure is invasive and might not appeal to all patients. A slightly different option is a novel sustained-release muco-adhesive buccal testosterone tablet, which requires twice-daily application to the upper gums. This formulation has been demonstrated to restore physiological testosterone levels with minimal or transient local problems.

A variety of transdermal approaches have also been developed (see Table 2). Although the currently available transdermal testosterone patches facilitate consistent delivery of testosterone into the systemic circulation,

mimicking circadian rhythms, they are frequently associated with adverse skin reactions at the patch site. Hence, the use of these types of preparation is characterized by a reduced compliance rate.^{71–75} Transdermal testosterone gel, a colorless hydroalcoholic gel containing 1% or 2% testosterone, provides continuous delivery of testosterone for 24 h after a single daily application. Testosterone gels have an excellent safety profile, and have been shown to normalize serum testosterone levels. Furthermore, patient compliance using this formulation has been demonstrated to be markedly better than that of patch administration, owing to fewer cases of adverse skin reactions.^{71–75} A potential adverse effect of testosterone gel application is the transfer of testosterone to others during close contact with the skin. This transfer can be avoided by wearing clothing or removing the residual testosterone on the skin by showering; however, the maximal residence time on the skin (2–4 h, depending on the formulation) should also be considered to minimize the risk of possible transfer.

Table 3 | Trials of combined TRT and phosphodiesterase 5 inhibitors in men with erectile dysfunction

Study	Number of patients	Baseline testosterone (nmol/l)	Treatment	Overall efficacy rate
Aversa <i>et al.</i> ^{98*}	20	<13.9 (<400 ng/dl)	T-patch, sildenafil 100 mg	80%
Kalichenko <i>et al.</i> ^{89§}	120	<11.8 (<340 ng/dl)	Oral TU, sildenafil 100 mg	70%
Shabsigh <i>et al.</i> ^{99*§}	75	<13.9 (<400 ng/dl)	T-gel, sildenafil 100 mg	70%
Chatterjee <i>et al.</i> ⁹⁰	12	9 patients <13.9 (<400 ng/dl)	T-im, sildenafil 50–100 mg	100%
Foresta <i>et al.</i> ⁹¹	15	<6.94 (<200 ng/dl)	T-patch, sildenafil 50 mg	Normalized NPT
Shamloul <i>et al.</i> ^{92§}	40	<11.8 (<340 ng/dl)	Oral TU, sildenafil 50–100 mg	Improvement
Greenstein <i>et al.</i> ⁹³	31	<13.9 (<400 ng/dl)	T-gel, sildenafil 100 mg	63%
Tas <i>et al.</i> ⁹⁴	23	<13.9 (<400 ng/dl)	T-im, sildenafil 50–100 mg	34%
Rochira <i>et al.</i> ^{100*}	24	<6.94 (<200 ng/dl)	T-im, sildenafil 50 mg	Improvement in NPT
Hwang <i>et al.</i> ^{95§}	32	<10.4 (<300 ng/dl)	Oral TU, sildenafil 100 mg	57%
Rosenthal <i>et al.</i> ^{96§}	90	<12.1 (<350 ng/dl)	T-gel, sildenafil 100 mg	92%
Yassin <i>et al.</i> ^{97§}	69	<11.8 (<340 ng/dl)	T-gel, tadalafil 20 mg	65%
Buvat <i>et al.</i> ^{101*}	73	<10.4 (<300 ng/dl)	T-gel, tadalafil 10 mg/day	51%

*Indicates placebo-controlled studies. §Indicates phosphodiesterase 5 inhibitor treatment had previously failed. Abbreviations: NPT, nocturnal penile test; T-gel, testosterone gel; T-im, intramuscular testosterone; T-patch, testosterone patch; TRT, testosterone replacement therapy; TU, testosterone undecanoate.

Efficacy of TRT for ED

Data derived from studies evaluating the effect of TRT on patients with ED have yielded mixed results.^{76–83} Some of these trials enrolled only a few men, and the lack of treatment effect might reflect the limitations of their design. Systematic reviews and meta-analyses, however, can pool trial results and offer clinicians and patients the best estimate of the effect of TRT. In a meta-analysis of 17 randomized, placebo-controlled clinical trials carried out over the past 30 years, Isidori *et al.*⁷⁹ have shown that, in comparison to placebo, TRT resulted in a significant, but moderate, improvement in all aspects of sexual function in men with low or low-normal mean concentrations of testosterone at baseline (<12 nmol/l [<346 ng/dl]). The magnitude of the effect on erectile function was inversely related to the baseline concentration of testosterone. Hence, the more severe the hypogonadism before treatment, the more impressive the results obtained with TRT. More-severe hypogonadism is associated not only with functional defects in the penis (such as impaired regulation of NO and PDE5), but also with structural changes, which could explain why TRT induces such an impressive effect, in terms of improvement in erectile function, in more-severe instances of hypogonadism.^{18–20} By contrast, testosterone monotherapy might not be efficacious in all cases because of the multifactorial pathophysiology of ED.

An evaluation of eight observational studies, which included 258 hypogonadal (total testosterone <10.4 nmol/l [<300 ng/dl]) men who received consultation for ED, reported that TRT improved erectile function in only 36% of cases.⁸⁰ Interestingly, these patients were older and their hypogonadism was generally mild (fewer than 2% had total testosterone <7 nmol/l [<200 ng/dl]) when compared to pooled data derived from the meta-analysis described above.⁷⁹ In another meta-analysis focused on the effects of TRT in hypogonadal (total testosterone <10.4 nmol/l [<300 ng/dl]) men with sexual dysfunction at baseline, Bolona *et al.*⁸¹ reported similar conclusions. In particular,

they reported a sizeable and significant impact of treatment on libido (pooled effect size 1.31) but a moderate, nonsignificant and inconsistent effect on erectile function (pooled effect size 0.80). When the studies were stratified according to patient age, however, the effect of TRT on erectile function was sizeable and significant in the two trials that included young patients (mean age <40 years; effect size 1.80),^{84,85} and minimal and nonsignificant in the two that included older patients (mean age >50 years; effect size 0.10).^{86,87} Age has been considered to be an independent risk factor for ED.⁸⁸ Although hypogonadism can be the main cause of ED in younger patients, it generally comprises only one of many elements in older patients, in whom ED is often multifactorial.^{5–8} For this reason, combined therapy using testosterone and PDE5 inhibitors is often required for ED in older men (see below).

TRT plus PDE5 inhibitors for ED

As previously mentioned, androgens modulate the expression of both NOS and PDE5 (see Figure 2), and it is, therefore, easy to speculate that PDE5 inhibitors require that normal levels of androgens are present in order to show efficacy.^{28–30} Accordingly, results from several studies have suggested that hypogonadism is likely to contribute to a reduced efficacy of PDE5 inhibitors^{89–101} (also see reviews^{80,102}). All these observations emphasize the concept that hypogonadism must be ruled out or, if present, adequately treated, before PDE5 inhibitors are prescribed for ED. In other words, TRT should be considered the first line of treatment in patients with ED who have hypogonadism.

Several uncontrolled studies^{89–97} and four randomized, placebo-controlled trials^{98–101} have confirmed that hypogonadism hinders the effects of PDE5 inhibitors on erectile function (Table 3). The majority of studies published so far have tested the effect of TRT in individuals who were previously unresponsive to PDE5 inhibitors^{89,92,95–99} or to the combination of the two treatments.^{90,91,93,94,100,101}

Taken together, the results of these studies imply that the combination of TRT and PDE5 inhibitors can lead to an overall efficacy of therapy in the range 34–100%. In addition, one study suggested that the number of patients whose symptoms were improved by the combination of TRT and PDE5 inhibitors increased with increasing duration of treatment (65% at 10 weeks versus 43% at 4 weeks).⁸⁹ However, these studies are, without exception, weak in several respects. As shown in Table 3, only two studies^{91,100} included men who were unquestionably hypogonadal. In addition, in the study by Shabsigh *et al.*,⁹⁹ not only were the patients not hypogonadal, but the erectile response actually decreased when higher levels of testosterone were reached. Most of the studies involved small heterogeneous cohorts of participants with questionable diagnoses in terms of ED. The follow-up periods were almost invariably too short and the designs rarely included proper controls. Hence, placebo-controlled, longitudinal studies of adequate duration are needed to better clarify whether or not hypogonadism hinders the effects of PDE5 inhibitors.

Conclusions

Mild hypogonadism is frequent in patients with ED; however, its recognition on the basis of symptoms and

signs is not an easy task. Dedicated structured interviews such as ANDROTEST might help both inexperienced and more expert physicians to suspect and diagnose hypogonadism. Nonetheless, a biochemical confirmation of this disorder is mandatory. TRT should be considered the first-line treatment in patients with ED who have hypogonadism; however, this approach might not be adequate as a monotherapy in all cases because of the multifactorial pathophysiology of ED. In these cases, combination therapy with TRT and PDE5 inhibitors might improve the outcome. More, better designed studies are needed to corroborate the suggested benefit of TRT and PDE5 inhibitor combination therapy.

Review criteria

We searched the MEDLINE and PubMed databases for original articles published between 1969 and 2009. The search terms used were “testosterone”, “erectile dysfunction”, “autoeroticism”, “metabolic syndrome”, “testosterone replacement therapy” and “PDE5 inhibitors”. All papers identified were English-language full text articles. We also searched the reference lists of identified articles for further papers.

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