The American Journal of Medicine (2006) 119, 373-382

ELSEVIER

THE AMERICAN JOURNAL of MEDICINE®

REVIEW

AJM Theme AJM Theme Issue: Men's Health

Does Testosterone Have a Role in Erectile Function?

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ABSTRACT

PURPOSE: Despite the well-established role of testosterone in enhancing libido, its exact contribution to erections in men remains unclear. The main objectives of this review are to clarify the role of testosterone in erectile function and evaluate its therapeutic value in men with erectile dysfunction (ED).

METHODS: Review of the relevant literature (English, French, and Spanish) from 1939 to June 2005 was conducted using data sources from MEDLINE, endocrinology text books, and hand searching of cross-references from original articles and reviews. Clinical trials, animal studies, case reports, reviews, and guidelines of major associations were included.

RESULTS: Animal and preliminary human studies suggest that testosterone may facilitate erection by acting as vasodilator of the penile arterioles and cavernous sinusoids. Following castration, most, but not all, men had partial or complete loss of erection. Hypogonadism is not a common finding in ED, occurring in about 5% of cases, and in general, there is lack of association between serum testosterone levels, when present in normal or moderately low levels, and erectile function. Most trials using testosterone for treatment of ED in hypogonadal men suffer from methodological problems and report inconsistent results, but overall, suggest that testosterone may be superior to placebo. Erectile function is more likely to improve with testosterone therapy in patients with severe degrees of hypogonadism. Testosterone treatment may ameliorate the response to the phosphodiesterase 5 (PDE5) inhibitors in hypogonadal men and men with low-normal serum testosterone. Repeated measurement of morning serum total testosterone is a fairly accurate and easy method to evaluate androgenecity, but measurement of free or bioavailable testosterone is recommended in conditions that alter the levels of sex-hormone-binding globulin (SHBG), such as in the elderly and in obesity.

CONCLUSIONS: Available data suggest that in most men circulating levels of testosterone, well below the normal range, are essential for normal erection and that higher levels of serum testosterone may not have major impact on erectile function. Screening for hypogonadism in all men with ED is necessary to identify cases of severe hypogonadism and some cases of mild to moderate hypogonadism, who may benefit from testosterone treatment.

KEYWORDS: Testosterone; Hypogonadism; Erection; Erectile function; Erectile dysfunction

Erectile dysfunction is defined as the persistent inability to sustain erection.[1] It is a complex and, frequently, a multifactorial disorder that leads to low self-esteem and decreased quality of life.[2] The majority of cases of ED are closely linked to cardiovascular disease and its risk factors.[3,4] The introduction of phosphodiesterase 5 (PDE5) inhibitors for treatment of ED was a major step forward due to their efficacy, safety and simple use. However, approximately one third of patients do not respond to PDE5 inhibitors.[5] Moreover, patients taking nitrates cannot take PDE5 inhibitors.[6-8] In addition, these agents have no effect on libido,[5-8] an essential component of sexual function. Although the role of testosterone in improving libido is well known,[9-17] its exact function in the pathophysiology of erection is still ill-defined. In the

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0002-9343/$ -see front matter
doi:10.1016/j.amjmed.2005.07.042

following review, the author summarizes evidence related to the role of testosterone in the etiology and treatment of ED.

DEFINITION OF HYPOGONADISM

There is no universal agreement regarding the exact definition of hypogonadism. However, it is generally accepted that hypogonadism refers to the presence of persistently low circulating testosterone compared with the normal range derived from healthy young and middle-aged men. This range is approximately 300-1000 ng/dL or 10.4-34.7 nmol/L in most assays of serum total testosterone,[18] although wide variation may exist between different commercial assays.[18-19] Frequently, hypogonadism is associated with nonspecific clinical features such as fatigue, weakness, decreased libido and energy, ED, reduced muscle and bone mass, and increased abdominal fat. In the elderly, the diagnosis of hypogonadism is sometimes problematic because of the difficulty to know to what extent the previous features are due to aging, hypogonadism, or both. Furthermore, because serum total and free testosterone levels decrease slowly with age,[20] it is unclear whether the reference range of serum androgens derived from younger men is also appropriate for the elderly population.[21] Based on prospective data from the Massachusetts Male Aging Study, Mohr et al[20] recently proposed the following age-specific thresholds below which a man is considered to have an abnormally low total testosterone: 251, 216, 196, and 156 ng/dL (8.7, 7.5, 6.8, and 5.4 nM) for men in their 40s, 50s, 60s, and 70s, respectively.

MECHANISM OF ERECTION

Normally, various sexual stimuli result in the release of the vasodilator nitric oxide (NO) from the nonadrenergic noncholenergic nerve fibers in the penile cavernous tissue and from the endothelial cells of the penile arterioles.[22] Nitric oxide activates the enzyme guanylyl cyclase, resulting in the generation of the second messenger, cyclic guanosine monophosphate (cGMP). cGMP decreases calcium uptake into cavernous and vascular smooth muscle leading to the dilation of cavernous sinusoids and penile erection. Expansion of the blood-filled sinusoids against the tunica albuginea compresses the veins carrying the blood out of the penis. The decreased venous outflow from the penis helps maintain erection. Subsequently, degradation of cGMP by the PDE5 leads to loss of arteriolar dilation and penile detumescence.[22]

CLINICAL SIGNIFICANCE

- Although evidence suggests that testosterone plays an important role in erectile function, testosterone levels below the lower limit of normal range may be sufficient to retain normal erection in most men.
- The minimal circulating level of testosterone necessary to maintain erection is unknown.
- Approximately 65% of hypogonadal men may have improvement in erectile function with testosterone replacement therapy.
- Testosterone replacement therapy may improve the response of hypogonadal men to PDE5 inhibitors such as sildenafil citrate.

ROLE OF TESTOSTERONE IN THE PHYSIOLOGY OF ERECTION

Animal Studies

Animal data suggest that testosterone may act as a vasodilator in the penis[23] and in other vascular beds such as the coronary arteries,[24] in part by activation of NO synthase. Chamness et al[23] showed that NO synthase activity in the penis of castrated rats was reduced by 45% and that testosterone replacement prevented such reduction.[23] Noradrenaline is one of the putative vasoconstrictors of penile arterioles and sinusoids that help maintain the penis in the flaccid state.[25] Reilly et al[26] have shown that the responsiveness to phenylephrine, an α_1-adrenergic agonist, was nearly 6 times greater in castrated rats than in rats with normal testosterone levels. Therefore, testosterone could indirectly enhance erection by attenuation of the alpha-adrenergic vasoconstrictor activity in vascular smooth muscles of the corpus cavernosum. Testosterone may also contribute to the penile venous occlusion mechanism that maintains erection.[27]

In addition to its peripheral action at the penis level, testosterone may affect erection through central mechanisms.[28,29] Animal studies in rats suggest that testosterone may facilitate erection at the level of the mesolimbic dopamine area.[29]

Human Studies

In humans, the effects of testosterone on the vasculature were first reported in 1939 by Edwards and colleagues,[30] who observed that treatment of castrated men with testosterone was associated with increased "arterialization" of the cutaneous vasculature, as assessed by spectrophotometry. In addition, testosterone therapy led to marked improvement in the walking ability and intermittent claudication in men with peripheral vascular disease and thromboangiitis obliterans.[30] Later, several noncontrolled studies in the 1940s recorded the use of testosterone for treatment of angina in men, with variable success.[31-33] More recently, intracoronary administration of testosterone at physiological or greater concentrations induced coronary vasodilation and increased coronary blood flow acutely in men with coronary artery disease.[34] Moreover, in a placebo-controlled trial oral testosterone administration improved endothelium-depen-

dent and endothelium-independent vasodilation of brachial artery in eugonadal men with coronary artery disease.[35] Similar findings were reported in postmenopausal women who received testosterone for 6 weeks to achieve plasma concentrations of approximately 150 ng/dL or 5.2 mmol/L of total testosterone, suggesting that the vasodilator effect of the hormone may be sex-independent.[36]

Human studies designed to examine a possible direct vasodilator effect of testosterone on penile arterial circulation are lacking, but some indirect evidence suggests that this may be the case. Aversa et al[37] demonstrated a direct correlation (correlation coefficient, r = 0.37) between serum levels of free testosterone and cavernous vasodilation assessed by duplex ultrasound in 52 eugonadal men with ED. In a randomized, placebo-controlled trial of 10 men with arteriogenic ED and low-normal plasma testosterone levels, the same investigators reported that testosterone supplementation for 1 month was associated with increased blood flow (by about 27%) to cavernous arteries.[38] Becker et al[39] showed that plasma testosterone levels increased during penile tumescence after sexual arousal in the systemic and cavernous vasculature in both healthy men and patients with ED having low-normal or mildly decreased plasma total testosterone levels (mean ± SD 300 ± 100 ng/dL, or 10.4 ± 3.5 nmol/L). However, the percentage increase in testosterone levels from the flaccidity to the tumescence stages of erection was less pronounced in men with ED compared with subjects without ED, 15% and 48%, respectively.[39]

The effects of testosterone on sexual function at the level of higher centers of the nervous system are poorly studied in humans. Preliminary studies in young healthy men using positron emission tomography (PET) suggest that the paralimbic zones may be activated during visually evoked sexual arousal.[40] Furthermore, activation of some of these areas correlated with the increase in plasma testosterone levels during sexual arousal.[40] Clearly, further investigations are needed to clarify the effects of testosterone on erectile function at the level of the penile vasculature and higher centers of nervous system.

PREVALENCE OF HYPOGONADISM IN PATIENTS WITH ERECTILE DYSFUNCTION

The prevalence of hypogonadism in men with ED varies widely from 1.7%[41] to 35%.[42] Causes of this wide variation include characteristics of patient populations, definition of ED and hypogonadism, method, timing and frequency of testosterone measurement, which was performed only once in most studies. In two large series of patients with ED, repeated testosterone sampling yielded a prevalence close to 5%.[43,44] To what extent the prevalence of hypogonadism in patients with ED is different from that in men without ED remains unclear because most studies lacked adequate controls. In one controlled study of men older than 50 years, Korenman et al[45] reported that the prevalence of hypogonadism (defined as repeated serum total testosterone less than 2.5 SD below the mean value in young healthy men) was unexpectedly lower in patients with ED compared with age-matched controls, 12% and 22%, respectively. They concluded that both ED and hypogonadism were common but independently distributed disorders.

Indeed, most[3,46-49] but not all[50] studies failed to demonstrate a significant correlation between plasma testosterone levels and erectile function. In the Massachusetts's Male Aging Study, a large population study, serum levels of dehydroepiandrosterone (DHEA) and its sulfated form (DHEA-S) but not those of testosterone (either free or total) were strongly associated with erectile function.[3] In 92 male army recruits aged 18-22 years, serum dihydrotestosterone, the potent metabolite of testosterone, was an independent hormonal predictor of increased frequency of orgasms, with an average increase of one orgasm per week per 2 SD increase in serum dihydrotestosterone concentrations.[51] Erectile function was not specifically addressed.

Thus, available correlation studies do not support a major role of testosterone in erection. However, most men included in these studies were either eugonadal,[3,46,48] or mildly hypogonadal.[47] In men with more severe degrees of hypogonadism, the relationship between ED and serum testosterone levels might yield different results and deserves further investigations.

HYPOGONADISM AS CAUSE OF ERECTILE DYSFUNCTION

Castration Studies

The strongest evidence of a possible role of testosterone in erection in humans comes from studies of castrated men. In the early series reported by McCullagh and Renshaw[52] of 12 castrated adult men, sexual potency was diminished in all patients, with complete loss of erection in 6 subjects. In subsequent studies of elderly men who underwent bilateral orchiectomy or estrogen therapy for treatment of prostate cancer, 22 of 38 (58%) men who had normal erection before castration reported ED after castration.[53] The remaining 42% reported persistence of erection by direct questioning.[53] In another series of 16 men with prostate cancer, all men reported good erection before therapeutic castration, and all of them experienced ED that started a few weeks after castration.[54] Yet, 4 of the 16 men (25%) could still achieve functional erection during visual sexual stimulation.[54] Thus, overall, 58%[53] to 100%[52,54] of men suffer from partial or complete ED following castration.The persistence of apparently adequate erection in some castrated men suggests that markedly decreased serum concentrations of testosterone may be sufficient to maintain erection. The wide interindividual variation in erectile capacity after castration could reflect the existence of different degrees of comorbidities (eg, aging, diabetes, vascular disease, smoking, etc), differences in levels and sensitivity to the remaining circulating testosterone, persistence of the adrenal an-

drogens DHEA and androstenediones that can be converted to testosterone,[55] and possibly other unknown factors.

One way to elucidate the role of testosterone in erection independently of co-morbid conditions is to pharmacologically induce profound hypogonadism, comparable with that prevailing in the castration state, by means of administration of gonadotropin-releasing hormone (GnRH) antagonists[14] or long-acting GnRH agonists[48,49,56] in healthy men. Thus, administration of GnRH antagonist for 6 weeks to 9 young healthy men led to decreased libido and frequency of spontaneous erections.[14] Both abnormalities were reversible after withdrawal of the GnRH antagonist and restoration of normal testosterone serum levels.[14] There was also a trend toward impairment of maintenance of erection during intercourse, but the ability to achieve orgasm during masturbation was not affected.[14] In a placebo-controlled trial of 10 young healthy men, Hirshkowitz et al[56] showed that the duration of episodes of nocturnal erection was decreased in the 5 men who received luteinizing-hormone-releasing hormone agonist (LHRH-A) (leuprolide) compared with the 5 men assigned to placebo. However, the difference in the frequency of the episodes of nocturnal erection between the two groups did not reach statistical significance.[56] Taken together, the previous two small studies suggest that castration of young healthy men may result in partial defects in sexually stimulated and nocturnal erections. In addition to suppression of endogenous testosterone production by a GnRH agonist, Bhasin et al[48] treated 5 groups of healthy young men with five graded doses of testosterone ranging from 25 mg to 600 mg of testosterone enanthate intramuscularly per week to create different levels of serum testosterone concentrations extending from the subnormal to the supraphysiological range. These investigators found significant increases in fat-free mass and muscle strength, and significant decreases in fat mass and serum levels of high-density lipoprotein cholesterol in proportion to testosterone doses.[48] Meanwhile, sexual activity and sexual desire did not change significantly with any dose regimen.[48] Erection was not reported separately. More recently, the same group used a similar protocol in old healthy men.[57] Contrary to their data in the young population,[46] spontaneous erections and libido but not intercourse frequency or masturbation frequency correlated with serum testosterone levels.[57] Unfortunately, the authors did not report the serum testosterone levels achieved with different doses of exogenous testosterone.[57] However, the results obtained from their investigations in the young men[48] suggest that sexual function could still be maintained at subnormal serum total testosterone levels close to 253 ng/dL or 8.8 nmol/L, which corresponded to the mean trough testosterone value in the group receiving the smallest testosterone dose of 25 mg.[48] Although serum concentrations of total testosterone lower than 200 ng/dL or 7 nmol/L were not achieved in the previous investigations,[48] it is likely that lower circulating testosterone levels could still preserve erectile function. In fact, in one series of castrated elderly men, although the serum levels of free testosterone were profoundly decreased in all patients, the subgroup of men (n = 4) who maintained erection had relatively higher levels of free testosterone compared with the remaining patients (n=12) who lost the ability of erection.[54] Furthermore, in another small series of 6 men having severe hypogonadism with total serum testosterone below 170 ng/dL or 5.9 nmol/L, the erectile response to sexual visual stimuli was similar to that in normal men.[10] Likewise, Carani et al[58] found similar penile rigidity in 6 hypogonadal and 6 eugonadal men in response to visual erotic stimuli, but testosterone serum levels were not reported. Based on the above findings, many authors[13,49] have raised the possibility of the existence of a "threshold" serum testosterone level that lies below the normalcy, above which erectile function might still be intact.

THE THERAPEUTIC ROLE OF TESTOSTERONE IN ERECTILE DYSFUNCTION

In eugonadal men, testosterone administration to achieve supraphysiological serum testosterone concentrations had no significant effects on reported frequencies of waking erection, masturbation, sexual intercourse, and sexual interest, but increased sexual "arousability."[59] Studies that evaluated the effect of testosterone replacement therapy on erectile function in hypogonadal men yielded mixed results.[9,10,12,13,17,60-66] Unfortunately, data derived from these studies are difficult to interpret due to lack of placebo in most trials,[17,60,61-64,66] relatively small number (less than 20) of patients,[9,10,12,13,62] and with few exceptions,[13,61] the majority of studies did not report the response to testosterone therapy by the serum testosterone concentrations at baseline.

A meta-analysis of 16 trials, of which 5 were placebo-controlled, showed that testosterone supplementation in hypogonadal men may be superior to placebo in improving erection with mean response rates of 65.4 and 16.7%, respectively.[67] The same analysis showed that the response rate was higher in primary versus secondary testicular failure (64% and 44%, respectively), and with transdermal testosterone compared with intramuscular and oral testosterone (80.9% vs 51.3% and 53.2%, respectively).[67] In a more recent large (n = 406), short-term trial of 90-day duration, Steidle et al[65] reported improved sexual function, including erection and libido, in hypogonadal elderly men with administration of testosterone gel compared with placebo. However, in a non-placebo-controlled study that lasted 6 months, Mulhall et al[60] showed that improvement in erection with transdermal and intramuscular testosterone therapy decreased after 1 month of treatment. Meanwhile, in another non-placebo-controlled study, Wang et al[17] showed that the use of transdermal testosterone was associated

Table Conclusions Obtained From Studies of Treatment of ED With Testosterone

Comment	References
Most studies are of average quality (lack of placebo, inadequate statistical power, and no clear definition of hypogonadism and patient characteristics at baseline)	17, 60, 61-64, 66
Effectiveness of testosterone is variable, but generally superior to placebo	65, 67
Erectile function is more likely to improve with testosterone therapy in men with severe degrees of hypogonadism	13, 44, 61
Testosterone therapy may improve the response to PDE5 inhibitors	38, 68, 69

with significant amelioration of erectile dysfunction up to 42 months of follow-up.[17] The Table summarizes major characteristics and results of studies of testosterone replacement therapy for treatment of ED.

THE USE OF TESTOSTERONE IN CONJUNCTION WITH PDE5 INHIBITORS

Data from two placebo-controlled trials suggested that the use of transdermal testosterone may improve the response to the PDE5 inhibitor sildenafil citrate (Viagra) in men with low-normal testosterone levels.[38,68] However, in the latter study that lasted 12 weeks, the improvement in erectile function was significantly greater than with placebo at 4 weeks only.[68] In a 6-week non-placebo-controlled trial of hypogonadal diabetic men failing sildenafil citrate due to decreased libido (patients passively waited for the drug to take effect), the addition of oral testosterone significantly increased both libido and erectile function scores.[69] Two weeks after discontinuation of testosterone, ED recurred in the majority of patients.[69] Furthermore, the results of 2 pilot studies suggested that the combination of sildenafil citrate and testosterone (given as 250 mg intramuscular monthly injections of testosterone cypionate) had a beneficial effect on erectile function in mixed populations of eugonadal and hypogonadal men on renal dialysis,[70] and men with hematological malignancies.[71]

The mechanisms whereby testosterone improves the response to PDE5 inhibitors are unclear, but the enhancement of libido by testosterone is most likely a contributing factor. In turn, treatment of ED in men with PDE5 inhibitors may be associated with an increase in their serum levels of total and free testosterone.[72]

Based on animal studies suggesting that testosterone may activate NO synthase in the penis,[23] it is conceivable to assume that this androgen may increase the availability of NO and its second messenger, cGMP, in penile tissue. The latter concept may be relevant to the recent findings of Morelli et al[73] showing that the relaxation response of the corpus cavernosum derived from hypogonadal rabbits to sildenafil in vitro was abnormal but was markedly improved after testosterone replacement.[73] Thus, it is possible that both testosterone and PDE5 inhibitors act on the same pathway in the penis, ie, the NO-cGMP pathway.

SHOULD SERUM TESTOSTERONE BE MEASURED IN ALL CASES OF ERECTILE DYSFUNCTION?

Measurement of serum testosterone in all cases presenting with ED is still a matter of debate fueled by its unclear contribution to the erectile process, its inconsistent effectiveness in the treatment of ED, and the lack of long-term, placebo-controlled trials that address the efficacy and safety of testosterone replacement therapy. In addition, testosterone therapy is not free of risks such as enhancement of erythrocytosis, exacerbation of sleep apnea and benign prostate hyperplasia, and possible growth stimulation of occult prostate cancer.[74] Moreover, it requires more frequent prostate examination, and close monitoring of levels of hemoglobin and prostate specific antigen.[74]

The National Institutes of Health (NIH) Consensus Panel on ED recommended that measurement of morning serum testosterone is generally indicated in evaluating cases of ED.[1] In the author's opinion, the measurement of serum testosterone should be performed in every case of ED in order to establish the diagnosis of hypogonadism and assess the need for testosterone replacement therapy for the following reasons. First, the positive well-documented effects of testosterone therapy on libido,[9-17] a fundamental factor that motivates the patient to initiate the sexual act and could virtually facilitate erection at the level of higher centers. Second, some placebo-controlled trials showed that testosterone supplementation in hypogonadal men was associated with mild to moderate benefit in improving erection,[67] bone mineral density, lean body mass, and possibly mood (for recent review see reference[75]). Third, there is preliminary evidence that hypogonadism, particularly when severe, may be associated with decreased response to PDE5 inhibitors[76,77] and that testosterone replacement therapy may improve the response to PDE5 inhibitors[38] and convert nonresponders to these agents to responders.[68,69] Fourth, the diagnosis of hypogonadism cannot always be made on clinical grounds alone because the clinical picture may be subtle or nonspecific.[18] For instance, the important diagnosis of Klinefelter's syndrome is frequently delayed when symptoms and signs are mild,[78] and low serum testosterone levels may be the first clue for clinching the diagnosis. Furthermore, neither a history of decreased libido,[79,80] nor the presence of testicular atrophy[80] was shown to predict the existence of hypogonadism. Finally, the diagnosis of hypogonadotropic hypogonadism (low serum testosterone coupled with low or normal gonadotropin levels) can reveal serious treatable pathologies such as prolactinomas and nonsecretory pituitary macroadenomas. Although these abnormalities were found in less

than 5% of cases,[43,81,82] the yield of pituitary imaging to detect a significant anatomical finding increases with decreased testosterone levels reaching approximately 20% with serum testosterone levels less than 141 ng/dL or 4.9 nmol/L.[81]

WHAT IS THE BEST WAY TO MEASURE TESTOSTERONE?

Circulating testosterone consists of three fractions: testosterone bound with high affinity to sex hormone-binding globulin (SHBG) (44-65% of circulating testosterone),[83] testosterone bound with low affinity to plasma proteins, primarily albumin (33-50%),[83] and free testosterone (about 2% of circulating testosterone).[84] The testosterone component avidly bound to SHBG is believed to be biologically inactive.[83] However, at least part of the albumin-bound testosterone may be biologically active.[85] Thus, the two components, free testosterone and testosterone, bound to albumin are collectively referred to as the bioavailable testosterone.

The three main methods to evaluate androgenecity include the measurement of free testosterone, bioavailable testosterone, and total testosterone in serum. Measurement of free testosterone by equilibrium dialysis is considered the method of choice that reflects the biologically active circulating testosterone.[86,87] However, this method is time-consuming, expensive, and not widely available.[83,86] An acceptable and relatively simple alternative to the free testosterone assay consists of the measurement of bioavailable testosterone. The latter correlates well with free testosterone levels, with reported correlation coefficients (r) of 0.670[86] and 0.974.[88] In addition, bioavailable testosterone correlates strongly (and negatively) with increasing age ($r = -0.744$).[86] Unfortunately, the assay of bioavailable testosterone is time-consuming and expensive.[86]

The most commonly used method to diagnose hypogonadism is the measurement of serum total testosterone. In one study, serum total testosterone was shown to correlate moderately with free testosterone ($r = 0.484$).[86] Advantages of total serum testosterone measurement include the wide availability of reliable assays,[87] its low cost, and simplicity.[83] In addition, most data in the literature are based on total testosterone measurement. Wang et al[19] recently reported strong correlation between several commercial assays of total serum testosterone and total testosterone measured by liquid chromatography-tandem mass spectrometry (LC-MSMS) used as a gold standard method. However, at severely low serum testosterone concentrations, below 100 ng/dL or 3.5 nmol/L, the commercial assays lacked sufficient accuracy.[19] Similar results were generally obtained by Taieb et al,[89] who used gas chromatography-mass spectrometry (GC-MS) as gold standard method for measurement of serum total testosterone. Therefore, for practical purposes, most available commercial assays of total testosterone would be satisfactory for the diagnosis of hypogonadism in men. However, more accurate assays are needed to investigate the relationship between ED and serum testosterone levels in severely hypogonadal men.

It should be emphasized that circulating testosterone levels exhibit diurnal rhythm with peak levels in the morning and nadir levels in the afternoon,[83] and marked week-to-week intra-individual variation.[86] Marrama et al[90] were the first to report that the circadian rhythm of testosterone may be blunted in the elderly. Their observation has been replicated later by most,[91,92] but not all, groups.[93] Interestingly, one study of 26 men with hypogonadism showed absence of circadian variation in their testosterone profiles,[92] but these results need confirmation in a larger number of patients. Nevertheless, when measuring testosterone by any method, it is highly recommended to obtain 2-3 morning samples, preferably 1-2 weeks apart. Repeat testosterone measurements will help avoid misdiagnosis. In one series, repeat total testosterone testing showed normal results in 40% of subjects who initially had subnormal levels.[43] Consistently subnormal values, eg, total testosterone levels below 300 ng/dL or 10.4 nmol/L, should be obtained to make the diagnosis of hypogonadism.[18] The Figure shows the initial approach to the diagnosis of hypogonadism and its classification into two main categories, hypogonadotropic and hypergonadotropic hypogonadism. Discussion of the various causes of hypogonadism is beyond the scope of this review (for review, see reference[94]).

CONDITIONS THAT MAY ALTER LEVELS OF SEX HORMONE-BINDING GLOBULIN

Because SHBG forms a major part of the total testosterone in serum, conditions that alter the SHBG serum levels can also affect those of total testosterone. Conditions that can decrease levels of SHBG include obesity (see below), hypothyroidism, excess androgens, progestins, growth hormone, glucocorticoids, hyperinsulinemia, and nephrotic syndrome.[18,83] Conversely, aging, androgen deficiency, hyperthyroidism, hepatitis, alcoholic liver disease, antiepileptic agents, excess estrogens, and porphyria may be associated with increased levels of SHBG.[83] In the above situations, the biologically active testosterone is more accurately assessed by the measurement of free testosterone by equilibrium analysis[87] or by the measurement of bioavailable testosterone.

Importantly, in hypogonadism associated with old age, levels of the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are usually low-normal[75] (ie, a form of hypogonadotropic hypogonadism). This occurs in spite of a slight age-related increase in LH serum levels.[75] The "inappropriately" normal gonadotropin levels may indicate impairment of feedback regulation of testosterone by the pituitary gland or hypothalamus, suggesting dysfunction in the hypothalamo-pituitary-testicular (HPT) axis.[75] In cases of hypogonadotropic hypogonadism, the author recommends checking serum prolactin and performing imaging of the pituitary region to rule out prolactinoma and other pituitary/hypothalamic pathology (Figure).

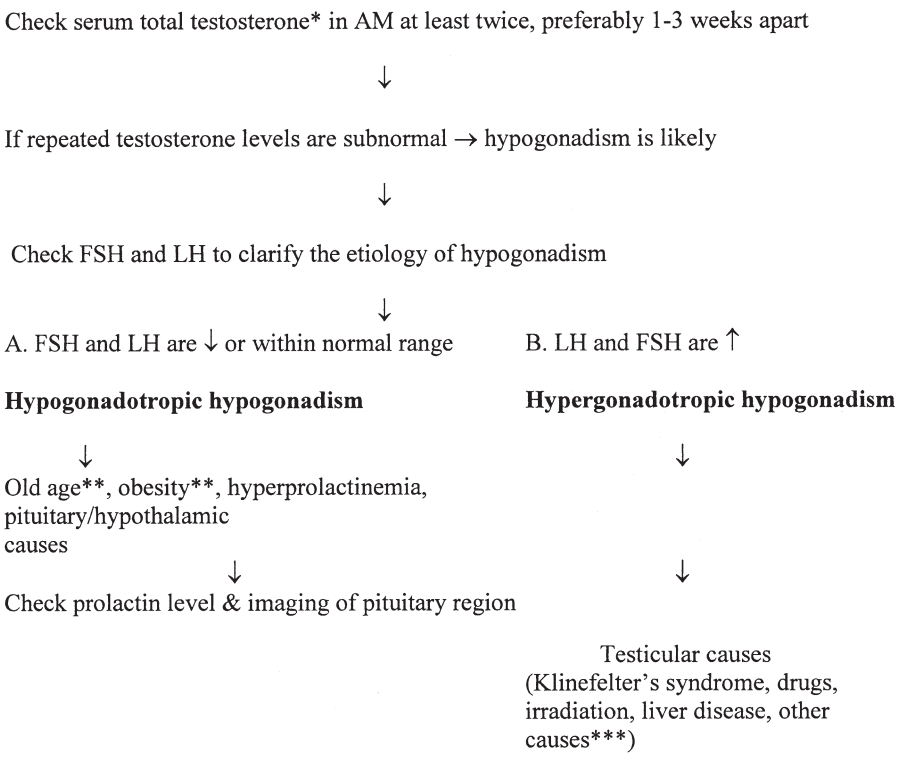

Figure Initial work-up for men with symptoms suggestive of hypogonadism (including ED). ED = erectile dysfunction; FSH = follicle-stimulating hormone; LH = luteinizing hormone. *See text for conditions requiring measurement of serum free or bioavailable testosterone. **In the elderly and obese men with low testosterone levels, FSH and LH are usually in the low-normal or within the normal range (see text). ***For a more detailed description of causes of hypogonadism, see reference.[94]

DIAGNOSIS OF HYPOGONADISM IN OBESITY

In obesity serum levels of total and free testosterone are decreased in proportion to the degree of obesity.[95-97] Multiple factors contribute to decreased androgen levels in obesity including hyperestrogenemia,[96] decreased SHBG-binding capacity,[97] attenuated LH pulse amplitude,[96,97] excess circulating leptin,[98] and insulin resistance.[99] As in age-related hypogonadism, the decrease in serum testosterone in obesity is not associated with a compensatory increase in serum gonadotropins, which are usually within normal limits,[98] implying dysfunction in the HPT axis. The few available preliminary data suggest that testosterone treatment of moderately obese men (body mass index 29-33 kg/m^2) with low-normal serum total testosterone levels may be associated with decreased visceral fat[100] and improvement in insulin sensitivity.[100,101] However, supraphysiological testosterone doses could impair glucose tolerance.[101]

SHOULD TESTOSTERONE THERAPY BE OFFERED TO ALL HYPOGONADAL MEN WITH ED?

Testosterone replacement therapy should be offered to all hypogonadal men with ED, provided that there are no contraindications (eg, history of prostate or breast cancer), in the following settings: when there is clear pathology causing testosterone deficiency such as the presence of pituitary tumors, Klinefelter's or Kallmann's syndrome; testicular damage by previous infection; chemotherapy; or radiotherapy, etc. In addition, most workers would initiate testosterone therapy in patients with severe hypogonadism (serum total testosterone consistently below 200 ng/dL, or 6.9 nmol/L) because this group will most likely benefit from replacement therapy.[13,44,61,75,87] For instance, in the retrospective analysis of Earle and Stuckey,[44] all responders to testosterone therapy in terms of erectile function had repeated baseline serum total testosterone below 210 ng/dL (7 nmol/L), and those who did not respond had higher testosterone levels ranging from 202 to 289 ng/dL (7 to 10 nmol/L).

When mild hypogonadism occurs in association with aging in absence of other clear reasons, testosterone replacement therapy is controversial due to the reasons mentioned earlier. In this setting, every case should be considered individually after discussion of possible benefits and risks with the patient. If testosterone therapy is initiated, a therapeutic trial of 3-4 months can be started,[1] then treatment may be continued or withdrawn depending on patient's response.

CURRENT DIRECTIONS AND FUTURE NEEDS

Although available evidence suggests that testosterone has an important role in erectile function, serum levels below the lower limit of normal range may be sufficient to retain normal erection in most men. However, the minimal circulating level of testosterone necessary to maintain erection is

unknown. At least three approaches can help identify such a level. First, by performing the same protocol of Bhasin et al[48] using GnRH agonist combined with exogenous testosterone administration in healthy men. Yet, much smaller doses of testosterone should be administered to achieve graded serum testosterone levels that lie well below the normal range. Second, by studying the correlation of circulating testosterone and erectile function in men with moderate and severe hypogonadism. Third, by analyzing the erectile response to testosterone therapy as a function of the baseline circulating testosterone levels in men with different degrees of hypogonadism.

In addition, the effects of testosterone on erection and other androgen-related outcomes must be assessed in hypogonadal men in well-designed trials of sufficient size and duration. Recently, the Institute of Medicine Committee on Assessing the Need for Clinical Trials of Testosterone Replacement Therapy[102] did not support embarking on a large-scale trial of testosterone replacement therapy in the elderly male population equivalent to the Women's Health Initiative in postmenopausal women.[103] Rather, the Institute recommended performing short-term, randomized, placebo-controlled trials of the effect of testosterone on several outcomes in elderly men with testosterone concentrations below 300 ng/dL or 10.4 noml/L.[102] The author strongly believes that erectile function should be included as one of these outcomes. A validated questionnaire for the evaluation of erectile function is readily available[104] and should simplify comparison between different trials. Well-designed trials can also help resolve the debate of whether one reference range of serum testosterone derived from young men or age-specific ranges should be used. In the meantime, the development of an accurate and properly validated testosterone assay with standardized normal reference range(s) is essential for the success of patient care and scientific research relevant to testosterone.

ACKNOWLEDGMENT

The author thanks the librarian Marsha Kmec for her help with the literature review.

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