

Review Article

Diagnosis and Treatment of Sexual Dysfunctions in Late-Onset Hypogonadism

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Testosterone is the principal androgen in the human male. The decline of testosterone with aging was recognized to be associated with a number of symptoms and signs that reduce the quality of life and that may even have severe, debilitating consequences. Clinically, late-onset hypogonadism (LOH) is diagnosed by use of biochemical and clinical measures. Despite published guidelines and recommendations, however, uncertainty surrounds the profile of clinical symptoms as well as the biochemical threshold of diagnosis. Clinicians should be aware of these shortcomings while adhering to the guidelines. Current treatment methods are centered on restoring testosterone to mid to lower levels of young men with natural testosterone replacements. Although recent studies have highlighted possible additional benefits involving improvement of systemic disorders, the goal of treatment is to improve sexual function, while observing for adverse effects in the prostate. Overall, the problem of LOH in debilitating the quality of life and well-being is real, and by following proper guidelines with attentiveness to the results of treatment trials, testosterone replacement therapy presents a safe and effective treatment option.

Key Words: *Erectile dysfunction; Hormone replacement therapy; Hypogonadism; Libido; Testosterone*

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INTRODUCTION

Testosterone is the principal androgen synthesized in the testis and the adrenal cortex in men. Its major physiologic roles include the development of the normal male, as well as maintenance of many male characteristics, including muscle mass, strength, bone mass, libido, potency, and spermatogenesis. The classic effects of testosterone replacement therapy were first noted in Brown-Sequard's self-injection of fluid extracted from the testicles of dogs and guinea pigs before the Societe de Biologie in Paris, 1889. He reported increased physical strength, mental abilities, and appetite [1]. Although his claims were never substantiated, his experiment led to a rash of endocrinologic research. Recent years have seen a revival in interest in the rejuvenating properties of testosterone. Epidemiologic studies have found a decrease of serum testosterone with normal aging [2,3]. Aging itself is typically associated

with lack of energy, reduced strength, loss of libido, and decreased sexual performance; many of these symptoms are similar to the presentation of testosterone deficiency [4,5]. A number of guidelines have since been published in an attempt to define the condition and to recommend appropriate treatment [6,7]. However, much confusion remains as to the appropriate approach to the diagnosis and treatment of late-onset hypogonadism (LOH).

LATE-ONSET HYPOGONADISM

1. Difficulty in defining the clinical syndrome of late-onset hypogonadism

The decrease of serum testosterone with age has been widely documented. Cross-sectional studies, such as the Massachusetts Male Aging Study, showed a 0.8% per year decline with total testosterone and a 2% per year decrease with bioavailable testosterone [2]. Longitudinal follow-up

showed a decline of 1.6% per year with total testosterone and 2% to 3% per year for bioavailable testosterone [3]. However, the clinical milieu of the age-related decrease in testosterone is varied in both its presentation and significance.

Aging is typically associated with a decline in sexual activity. However, these changes have not been well documented. Recently, large cross-sectional studies have described a sharp decrease in sexual activity with old age [8,9]. Whereas 73% of respondents aged 57 to 64 years reported sexual activity, only 26% were sexually active by 75 to 85 years of age. Male responders in the survey reported a steady decline in sexual interest with increasing age, from 28.2% to 24.2%, but showed larger changes in inability to climax, from 16.2% to 33.2%, and erectile dysfunction (ED), from 30.7% to 43.5%. Although decrease in sexual interest may accompany ED, the survey also showed that sexual activity not requiring vaginal penetration also showed an abrupt decrease [8]. Another large-scale survey showed that an isolated category of 'thinking about sex' decreased abruptly for respondents replying 'every day,' from about 40% for men in their 40s to about 12% for men in their 70s; respondents who replied that they thought about sex 'never or less than once a month' increased from about 2% for men in their 40s to about 36% for men in their 70s [9]. These data suggest that not only the physical function of sexuality but also its mental appetite is severely hindered with age.

The results of studies identifying these patients with evaluation of serum testosterone levels concurred with the general presentation of decreased sexual activity but described a divergence between erectile function and libido in their specificity [2,10,11]. The Massachusetts Male Aging Study confirmed that, in general, testosterone levels decreased with erectile function and libido [2,11]. The Boston Area Community Health Survey showed that, whereas ED was more prevalent in the overall population than decreased libido, the proportion of patients with decreased libido was higher among patients with decreased total and free testosterone [10]. The recent European Male Aging Study showed that, although sexual symptoms were all associated with age to some degree, after factoring for age, ED was also more dependent than libido on the presence of comorbidities, such as cardiovascular diseases, diabetes, and depression [12]. The study also concurred that whereas both sexual symptoms were associated with low total and free testosterone, there was a higher correlation with the decrease of libido than with ED [13].

Although the relationship between sexual symptoms and decreased testosterone may seem intuitive, the difficulty in delineating the clinical boundaries of the age-associated decrease in testosterone is confounded by the fact that several nonsexual age-related symptoms and diseases are also associated with decreased testosterone to a varying degree. Testosterone deficiency has been associated with decreased muscle mass [14], decreased bone mineral density [15-17], and increased risk of cardiovascular disease, type 2 diabetes, and metabolic syndrome [18].

Increase of inflammatory cytokines and changes toward unfavorable lipid profiles are associated with the incidence of atherosclerosis and cardiovascular disease and eventually increased mortality [18].

However, the array of features is not usually presented in a uniform profile of a typical hypogonadal patient. In a cross-sectional cohort study of 434 patients, excluding patients who received previous therapy for hypogonadism and selecting for ages above 50, Zitzmann et al attempted to define categorical groups of features [19]. Although the prevalence of sexual symptoms, such as libido and vigor, significantly differed at testosterone levels of 430 ng/dl (15 nmol/l), metabolic and psychosomatic risk factors accumulated with decreasing testosterone levels. ED contributed to the symptoms only below 230 ng/dl (8 nmol/l). The study also suggested a syndromic association through cluster analysis, whereby patients could distinctively be grouped into clusters characterized by psychosomatic complaints, metabolic disorders, or sexual health problems on the basis of testosterone level, age, and body mass index. Analysis revealed three clusters characterized as being predominantly psychosomatic, metabolic and psychosomatic, and predominantly ED. The European Male Aging Study, a cross-sectional survey of 3,369 men (range, 40 to 79 years) from a random population, also suggested a syndromic association with decreased testosterone levels [13]. Although symptoms of poor morning erection, low sexual desire, ED, inability to perform vigorous activity, depression, and fatigue were all significantly related to testosterone level, only the three sexual symptoms had a syndromic association with decreased testosterone levels. Incorporating low testosterone levels, morning erections, ED, and decreased sexual thoughts showed a clustering of patients. Furthermore, two or more of the three symptoms had an increased odds ratio compared with single symptoms combined with higher power of exclusion by testosterone.

Owing to the difficulty in delineating a clear-cut patient group, earlier studies used the questionnaires available at the time [20]. Diagnostic tools such as the Aging Male Survey and the Saint Louis University Androgen Deficiency in Aging Males are highly sensitive but suboptimal in specificity [21-23]. The International Society for the Study of the Aging Male (ISSAM) and the Endocrine Society both recommend against the use of questionnaires because of this lack of specificity and suggest instead a formal method of symptom assessment [6,7]. However, even this approach has been criticized as being equally ineffective in improving specificity [23,24]. Recently, newer diagnostic tools, such as the European Male Aging Study Sexual Function Questionnaire [13,25] and the New England Research Institute hypogonadism screener (Screener) have specifically been structured to meet the needs of diagnosing LOH [26]. These tests boast good correlation with serum total testosterone as well as high specificity. Whether these newer tools can assist in clarifying the diagnostic presentation of LOH requires further validation.

2. Difficulty in determining LOH by biochemical levels of testosterone

The testis secretes more than 95% of circulating testosterone in the male, producing up to 6 to 7 mg per day [27]. Biosynthesis takes place within the Leydig cells, stimulated by luteinizing hormone. In the serum, testosterone is mainly bound to albumin (50%) and sex hormone-binding globulin (SHBG, 45%), leaving only a small physiologically active free fraction [28]. However, testosterone binds loosely to albumin, making this testosterone and free testosterone available to tissues, i.e., bioavailable testosterone. Testosterone is tightly bound to SHBG, rendering it biologically inactive.

The difficulty in presenting a cohesive diagnosis of LOH on the basis of biochemically defined levels of serum testosterone lies with the complexity by which testosterone is regulated and actuates function. Beginning with variables associated with determining the level of biologically active testosterone as a result of the fluctuating amounts of SHBG produced, as well as tissue responsiveness to testosterone depending on site, the activity of the androgen receptor and the expression of the androgen receptor itself all function to present a clinical picture not easily represented by bioavailable testosterone or total testosterone.

Several factors are associated with the regulation of SHBG. In humans, SHBG is produced by hepatocytes [29]. Hepatocytes are the primary site of plasma SHBG biosynthesis [30]. Thyroid and estrogenic hormones and a variety of drugs, including the anti-estrogen tamoxifen, the phytoestrogen genistein, and mitotane, increase SHBG production. In contrast, monosaccharides effectively decrease production by inducing lipogenesis, and production is influenced by hormonal, metabolic, and even nutritional status [31]. Furthermore, SHBG has been shown to have signaling function of its own; SHBG activates cAMP-mediated pathways associated with a variety of downstream effects, including estrogen-induced androgen receptor activation of prostate-specific antigen (PSA) gene transcription and cancer growth and inhibition [32]. It is clear that several factors are interconnected with the level of plasma SHBG, which in turn is closely associated with functional levels of testosterone. It is all the more important in the elderly, in whom the factors that affect SHBG accumulate. Epidemiologic studies show that whereas the level of total testosterone gradually decreases with age, the level of free testosterone decreases more sharply [33].

The androgen receptor is also subject to various forms of effect modification both in tissue-wise distribution and in its molecular activity and expression. The main component that imbues variability to the function of testosterone in the cell is its conversion to a more metabolically active form, dihydrotestosterone, or its aromatization to estrogen. Dihydrotestosterone, although similar in interactions with testosterone on the androgen receptor, differs in androgen receptor and coactivator motif interactions [34]. Aromatization to estrogen has been implicated in various age-related adiposity-increasing mechanisms and behav-

ioral changes [35]. These differing potencies are thus in part reliant on the conversion ability of each tissue, organ, or individual, whereas the activities of 5 α -reductase or aromatase are dependent on various conditions or drugs, most notably 5 α -reductase inhibitors and anticonvulsants [36]. Other modifications, evident through androgenic anabolic steroids and selective androgen receptor modulators, are some examples of the variability of pre-receptor activity modification that is possible [37].

Finally, the androgen receptor has been shown to have various modifications through coactivators or genetic mutations. Coactivators are proteins that enhance ligand-dependent transcriptional activity. As stated above, the affinity of dihydrotestosterone derives in part from different activities pertaining to coactivators. Several coactivators with various functions have been found, and their specific activities are currently under investigation [38]. The most studied androgen receptor genetic mutations affecting pathophysiologic presentations have been the polymorphism of CAG repeats. The mutations vary in length of between 18 and 24 tandem repeats that influence expression. These mutations have been implicated in a variety of pathologic states, including androgen insensitivity syndrome, genetic muscular atrophy diseases, and even prostate cancer, whereas normal variations have been implicated in explaining racial differences in the incidence of these pathologic states [38,39].

The complexity of physiologic regulation has led to a difficulty in determining appropriate reference levels for diagnosing LOH. Testosterone is known to have a circadian variation, reaching peak values in the morning; however, this circadian variation is blunted with aging [40]. Both ISSAM and the Endocrine Society recommend early morning timed measurement of total testosterone, between 700 and 1100 [6,7], because some studies showed that intra-individual variation remained relatively consistent, despite wide inter-individual variation in the emergence of symptoms [41]. However, other studies presented wide weekly and between-day intra-individual variation greater than within-day intra-individual variation [40,42].

Further complicating the issue is that the physiologically optimal form of diagnosis is also impractical to implement. Despite the fact that numerous reports have substantiated that free testosterone better correlates with symptoms of LOH, free testosterone is difficult to measure and standardize [40,42]. The gold standard for determination of free testosterone is equilibrium dialysis [43]. However, equilibrium dialyses are costly, requiring more expertise and time than is considered feasible for local laboratories [44]. Vermeulen et al introduced the method of calculating bioavailable testosterone on the basis of measurements of total testosterone, SHBG, and albumin [43]. These values correlate well with those obtained by equilibrium dialysis, presenting a practical alternative, yet this method requires measurement of both total testosterone and SHBG. Hence, the standard recommendation for decreased levels of testosterone is an arbitrary balance be-

tween pragmatism and accuracy. The practical clinical steps of diagnosis would be to first estimate total testosterone and then to weigh the need to evaluate free testosterone levels by use of SHBG assays.

With the confusion resulting from the inherent wide-reaching and varied nature of testosterone, several international organizations have presented guidelines

and recommendations for the diagnosis and treatment of LOH (Table 1 and Fig. 1) [6,7].

The current ISSAM and Endocrine Society recommendations agree that serum total testosterone below 230 ng/dl (8 nmol/l) delineates a state of severe testosterone deficiency and that correlating free testosterone measurements of below 65 pg/ml (225 pmol/l) would assist in con-

TABLE 1. Evolution of guidelines for late-onset hypogonadism and testosterone replacement therapy

ISSAM ^a	Endocrine Society
Personal expert opinion	Evidence-based guidelines
1996	2006
Morales et al. Clinical practice guidelines for screening and monitoring male patients receiving testosterone supplementation therapy. <i>Int J Impot Res</i>	Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline. <i>J Clin Endocrinol Metab</i>
ISSAM official recommendations	2010
2002	Testosterone Therapy in Men with Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline. <i>J Clin Endocrinol Metab</i>
ISSAM recommendations.	
2004	
ISA ^b , ISSAM and EAU ^c recommendations.	
KOSAR Recommendations. <i>Korean J Aging Male</i> 2006, <i>Korean J Androl</i> 2008	
Evidence-based guidelines	
2008	
ISA, ISSAM, EAU, EAA ^d and ASA ^e recommendations.	
Park NC. <i>Korean J Androl</i> 2009	

^a: International Society for the Study of the Aging Male, ^b: International Society of Andrology, ^c: European Association of Urology, ^d: European Association of Andrology, ^e: American Society of Andrology

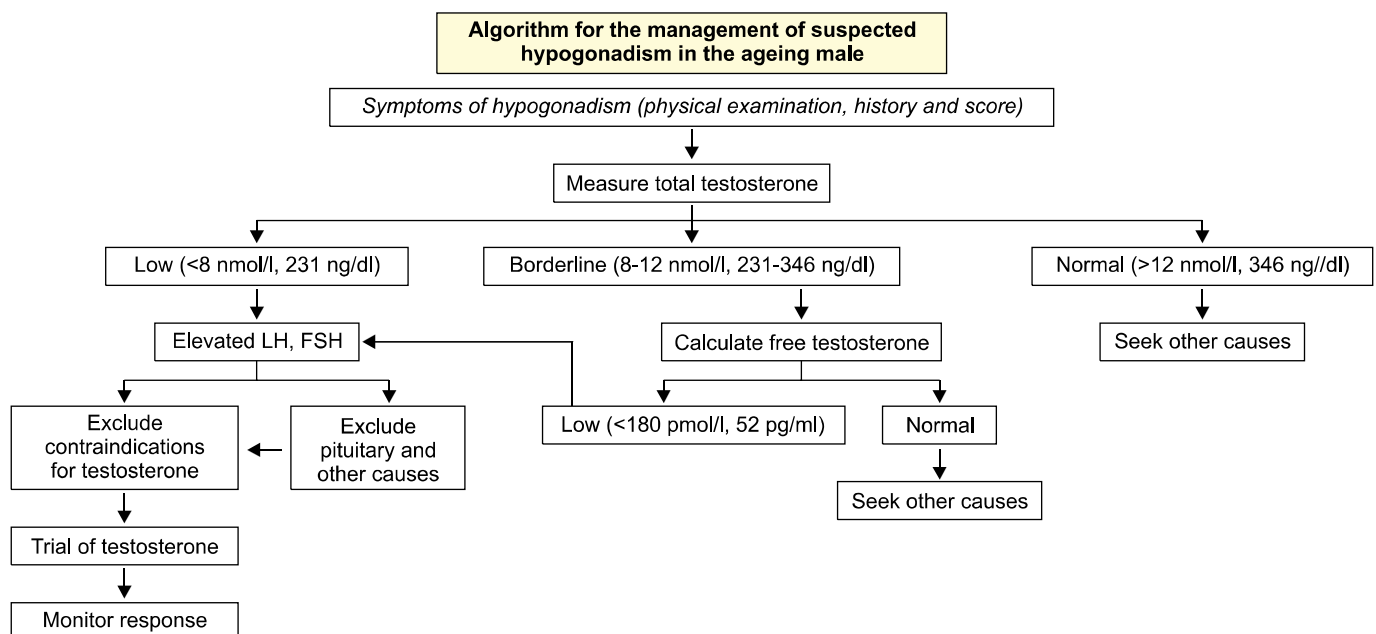


FIG. 1. Diagnostic algorithm for late-onset hypogonadism [95]. Recommendations by the ISSAM suggest a serum sample for total testosterone, taken between 700 and 1,100 hours, for patients who are at risk or suspected of hypogonadism. Total testosterone above 12 nmol/l does not require treatment. Patients with serum total testosterone below 8 nmol/l will usually benefit from treatment. If the total testosterone is between 8 and 12 nmol/l, the measurement of total testosterone should be repeated with sex hormone-binding globulin to calculate free testosterone. Measurements of serum LH will assist in differentiating between primary and secondary hypogonadism. LH: luteinizing hormone, FSH: follicle stimulating hormone.

firming the diagnosis for total testosterone measurements below 350 ng/dl (12 nmol/l) [6,7]. While appreciating these guidelines, clinicians should be aware of the pitfalls surrounding a biochemical diagnosis based on an arbitrary level of total testosterone as well as the disadvantage of lacking questionnaire tools that could aid in a cohesive approach to a syndromic pathology.

TESTOSTERONE REPLACEMENT THERAPY

There are several cautionary issues surrounding the proper treatment of LOH. Despite the multiple steps at which the effect of testosterone may become diminished, at present, there is no substantial evidence-based treatment for LOH other than replacement of the deficient hormone [6,7]. Furthermore, owing to the arbitrary nature of defining a diagnostic threshold of total testosterone as a mid to lower level in young men, patients may be subjected to unnecessary testosterone replacement, complicated by the risk of increased testosterone levels possibly masking an underlying pathology [45].

The expected treatment outcome in LOH patients with testosterone replacement therapy is primarily improvement of libido and erectile function [7]. With the uncertainty over the effects of replacement, previous guidelines suggested that ideally testosterone replacement should mimic normal physiological circadian changes [46]. However, no substantial evidence has shown significant benefit of such a method, and subsequent recommendations do not support its necessity [6,7]. A number of natural testosterone replacements have been developed. Currently available routes of delivery consist of oral, buccal, intra-

muscular, and transdermal (patches and gels) routes (Table 2). There is no overall optimal therapeutic regimen. The clinician should consider the patient's preference, pharmacokinetics, treatment burden, and cost when prescribing treatment [7]. Considering the possibility of treating false-positive patients, clinical trials lasting 3 to 6 months to observe for short-term improvement in sexual function is pertinent [47]. This trial of treatment is also beneficial for observing for adverse effects, because such cases warrant rapid discontinuation.

1. Libido

Animal studies have demonstrated testosterone-related changes in the central nervous system. Neurophysiological studies of rats have shown that testosterone affects libido in the sexually dimorphic nucleus of the preoptic area [48]. A recent study demonstrated that, whereas middle-aged rats had significant impairments of sexual behavior compared with young rats, castration and exogenous testosterone treatment restored sexual activity [35]. The study observed that exogenous testosterone stimuli restored the androgen receptor density in the preoptic area to levels comparable to those of a young rat.

There is some difficulty in assessing treatment effects on libido in the clinical setting. Studies comparing results in humans rely on subjective assessment of libido. Comparison of studies is difficult because of the differences in methods of treatment and response. However, several clinical trials have documented the effect of testosterone replacement therapy in improving sexual desire. Several clinical trials showed consistent results of increased sexual frequency and libido in hypogonadal men with testosterone

TABLE 2. Current available regimens for testosterone replacement therapy

Route	Formulation	Drug	Dose	Advantage	Disadvantage
Oral	Capsule	Testosterone undecanoate	40 mg, 4/d	Convenience of oral administration	Variable serum levels, high DHT ^a :T ^b ratio
Buccal	Bioadhesive tablet	Testosterone	30 mg, 2/d		Gum related adverse events in 16%
Intramuscular	Oily suspension	Testosterone enanthate	250 mg, 1/2-3 wk		Wide variation of serum T
		Testosterone cypionate	200 mg, 1/2 wk		
		Testosterone undecanoate	1,000 mg, every 2-3 mo	Infrequent administration	
Subcutaneous	Pellets/rods	Testosterone	3-6 (200 mg each) every 6 mo	Infrequent administration	Requires surgical incision for insertions
Transdermal	Scrotal patch	Testosterone	10-15 mg, 1/d	Ease to stop treatment	High DHT:T ratio, scrotal shaving
	Non scrotal patch		2.5-5 mg, 1/d	Ease to stop treatment, ease of application	Skin irritation
	Gel		1%, 10 g/d	Ease of application, good skin tolerability	Potential transfer by contact

^a: dihydrotestosterone, ^b: testosterone

replacement [49,50].

Other studies have noted varying responses to treatment depending on the deficiency of testosterone before treatment. A meta-analysis of placebo-controlled trials reported that most studies enrolling documented hypogonadal patients showed improvement in libido [51]. The review noted, however, significant inconsistencies in the response to oral agents. Treatment in the low-normal range of testosterone for decreased libido also showed non-significant or inconsistent effects on libido. A retrospective study of 211 men with various degrees of initial testosterone showed high response rates to total testosterone below 300 ng/dl but considerably lower response to low-normal testosterone levels [52]. However, a recent placebo-controlled, randomized double-blind study of otherwise-healthy nonobese men with low-normal testosterone and symptoms of LOH reported improvement of libido after 12 months [53]. The variable outcome among patients in the low-normal testosterone population may be due to underlying low bioavailable testosterone not evident in results shown by total testosterone.

2. Erectile dysfunction

The classic etiology of ED consists of vascular, neurogenic, and psychological components. Recent studies have shown that ED, as a vascular phenomenon, is predictive of the development of serious cardiovascular insults [54]. Other systemic conditions, such as diabetes and obesity, also mediate pathophysiologic changes that result in peripheral neuropathy or microvascular injuries that result in ED in a significant number of patients in these populations [55]. Conversely, studies have shown that the majority of patients with ED suffer from these comorbidities [56]. The large proportion of patients with systemic comorbidities in ED is clinically significant, considering that these patients are the main constituents of nonresponders to PDE5 inhibitors [57].

ED is also the most common sexual dysfunction in patients with LOH [12]. Animal studies and human cell culture studies have shown that hypogonadism exerts a significant detrimental effect associated with peripheral mechanisms in the pathogenesis of ED. Testosterone has been shown to control commitment of penile stem cells to the smooth muscle cell lineage [58], whereas testosterone deprivation by castration results in reduced smooth muscle content and increased connective tissue matrix [59]. Testosterone has also been shown to increase nitric oxide synthase transcription [60] and to maintain normal RhoA/Rho-kinase activity [61]. However, testosterone has also been shown to increase the expression of PDE5 [62]. Thus, testosterone induces an overall modest effect on erection alone, as observed in studies that found no significant association between ED and hypogonadism in normal healthy populations [63]. This dual function has been suggested to allow testosterone to effectively regulate the timing of erection pertaining to sexual desire [58,64].

The complex association of the systemic etiology of ED,

as well as the pervasive effect of testosterone in erection, suggested the possibility of improving the treatment of ED in hypogonadal patients by combined treatment with PDE5 inhibitors and testosterone replacement. Clinical studies began with ED patients who were refractory to PDE5 inhibitors [65]. The studies showed not only improved overall sexual function with combination therapy, but most notably, improved erectile function presented as both components of subjective symptom scores and as physiologic indexes, such as resistive index values [65,66]. Studies have since shown various levels of success in erectile function [67]. This may be because most of these clinical trials varied in their definition of testosterone deficiency as well as in the degrees of concomitant comorbidities, thus making it difficult to derive a conclusive target group in which combination therapy may benefit [67]. Both the lowest reported success rate, 34%, and the highest, 100%, were from ED patients undergoing dialysis owing to renal failure [68]. Furthermore, the effect of testosterone does not seem to be uniform in these patients, as one study noted that the efficacy of combination therapy decreased as patients normalized in serum total testosterone [69]. Most of these studies were also limited in the length of treatment. Whereas early responses may be expected as late as 4 weeks [70], studies have rarely extended beyond 12 weeks [66,69], at which point one study even noted a decline in efficacy [69]. Hence, a longer period of observation of a more homogeneous cohort of patients is required to propound any definite conclusion. At present, combination therapy presents as a possible second-line treatment for patients failing PDE5 inhibitor monotherapy [71].

3. Adverse effects on the prostate

The most significant concern in prescribing testosterone replacement therapy is the effect on the prostate. Prostate tissue hypertrophy and progression to high-risk prostate cancer have been shown to be testosterone dependent [72]. The concern over the safety of testosterone replacement is understandable because androgen deprivation therapy is widely used to maintain prostate cancer regression [73]. However, observational studies have failed to find a correlation between serum testosterone levels and prostate pathology. Studies of normal men without prostate cancer showed no correlation between PSA or prostate volume and testosterone [74]. Studies of benign prostatic hyperplasia (BPH) patients also showed no correlation between testosterone and International Prostate Symptom Score (IPSS) scores, PSA, and prostate volume [75]. Measurement of prediagnostic testosterone levels and surveillance of prostate cancer also showed no additive effect of testosterone on cancer risk [76]. To address this concern, 18 study groups pooled patient data to identify prostate cancer risk against endogenous sex hormones [77]. The collected data represented 3,886 men with incident prostate cancer against 6,438 controls. Analysis of the data suggested no evidence that serum concentrations of sex hormones were associated with the risk of prostate cancer.

Marks et al performed a randomized double-blind study in which hypogonadal men received testosterone or placebo and were observed for changes in prostate tissue testosterone after 6 months [78]. The study reported no change in histology, tissue markers, or gene expression specific to cancer and no significant changes in prostate volume, PSA, or voiding symptoms. Measurements of prostatic tissue testosterone levels remained at normal levels. Morgentaler and Traish suggested that the discrepancy between castration level testosterone inhibiting prostate cancer growth and normal levels not affecting incidence could be explained by the low threshold of androgen receptor binding achieving saturation [73]. They elaborated that testosterone exerts prostatic effects primarily by binding to the androgen receptor, and that maximal androgen-androgen receptor binding is achieved at serum testosterone concentrations well below the physiologic range. These observations suggest no clear correlation between testosterone replacement therapy and the incidence of prostate cancer, BPH, or progression of prostate cancer at normal serum levels. There is also evidence that testosterone suppression reduces growth or symptoms in men with advanced prostate cancer [72].

Despite the positive outlook for testosterone replacement therapy against the risk of prostate malignancies, the evidence also cautions vigilance. Recently, the growth of prostate cancer cells affected by testosterone, or dihydrotestosterone, suggests possible cross-talk with EGF-receptors and downstream pathways inducing MAPK signaling [79]. Through such nontranscriptional activities mediated by cross-talk between pathways, testosterone may affect a variety of physiologic functions including cell motility, metastasis, survival, and proliferation. Without clearly being able to discount these effects, cautious surveillance for the risk of prostate cancer development is warranted in patients receiving testosterone replacement therapy. The Endocrine Society recommends measurement of PSA at the initiation of treatment and at 3 to 6 months. An increase of the serum PSA concentration of more than 1.4 ng/ml within a 12 month period, a PSA velocity of higher than 0.4 ng/ml per year when observed for more than 2 years, detection of abnormalities on digital rectal examination, or an IPSS score above 19 should alert the urologist to consider the finding based on serum PSA and digital rectal exam when deciding on the need for a prostate biopsy. The ISSAM also recommends monitoring patients receiving testosterone treatment at 3 to 6 months, 12 months, and then annually. Findings on the digital rectal exam and PSA indicate the need for a prostate biopsy. Relative contraindications include an IPSS scores higher than 21, which is associated with a risk for exacerbation of lower urinary tract symptoms or acute urinary retention (Table 3).

4. Concern for safety of other systems

The initial concerns during the recent rediscovery of testosterone replacement therapy primarily centered on the sig-

nificant adverse effects of previous androgen therapies. Abuse of synthetic androgens in high doses by athletes has led to documented side effects, including accumulation of lean body mass and fluid retention, gynecomastia, sleep apnea, and hepatitis [80]. Most of these side effects have been found to be associated with modified testosterone products with alkylation at the 17-hydroxy position, which leads to exacerbation of anabolic effects over androgenic effects, and are further complicated by overdoses up to 100 times recommendations [81]. Alkylated androgens at high doses can cause hepatocellular and intrahepatic cholestasis that occasionally results in severe jaundice and hepatic failure. Peliosis hepatis, hepatocellular adenoma, and carcinoma may also result from the use of these compounds [82]. Because testosterone can be aromatized to estradiol in peripheral tissues, it occasionally induces mild gynecomastia, most commonly in adolescents. However, aromatization is common in men who take supraphysiologic doses of androgens, and these effects may persist for months after use of the alkylated agents has ceased [81]. Sleep apnea occasionally develops or worsens during androgen-replacement therapy [83], and erythrocytosis may also occur.

TABLE 3. Guidelines for monitoring prostate safety during testosterone replacement therapy

Prostate cancer
Contraindicated in P ca ^a . or breast ca.
Relatively CIx in high risk of developing P ca.
Unclear in localized low-grade (Gleason score < 7) P ca.
Successfully treated P ca. are potential candidates for TRT after a prudent interval of no clinical or lab. Evidence of residual ca.
BPH ^b
Relative CIx in severe LUTS ^c (high IPSS ^d > 21) for BPH
No CIx after successful Tx of lower urinary tract obst.
Careful monitor for prostate safety during treatment
DRE ^e , PSA ^f
Baseline, 3-6, 12 months and annually
Baseline, 3, 6, 9, 12 months and yearly in 2006
TR biopsies are indicated in sufficient high risk of P ca.
DRE: palpable prostate nodule or induration
PSA: > 4 ng/ml
> 3 ng/ml with high risk
A baseline PSA > 0.6 ng/ml
Age: > 40 yr
F/Hx: first-degree relatives with prostate cancer.
Ethnicity/race: African Americans
No conclusive evidence
TRT increases the risk of P ca.
TRT convert subclinical P ca. to clinically detectable P ca.
TRT increases the risk of BPH
Unequivocal evidence
Testosterone can stimulate growth and aggravate symptoms in locally advanced and metastatic P ca.

^a: prostate cancer, ^b: benign prostatic hyperplasia, ^c: lower urinary tract symptoms, ^d: International Prostate Symptom Score, ^e: digital rectal examination, ^f: prostate specific antigen

With structural modifications, modern formulations prevent supraphysiological serum testosterone concentrations, thereby avoiding toxicologic risk to the liver. Gynecomastia is also rare under physiologic levels of testosterone [84]. Current guidelines include contraindication of therapy in case of breast cancer. Although sleep apnea is a predominantly male disease, recent studies have failed to provide compelling evidence that testosterone replacement is associated [83]. Testosterone versus placebo studies have shown no changes in respiratory disturbance index or upper airway caliber [85].

However, testosterone replacement therapy has consistently demonstrated stimulation of red blood cell production. The mechanism of action is through augmentation of erythropoietin and direct effects of testosterone on erythroblasts in the bone marrow [86]. Although the occurrence of thromboembolism has not been reported in studies of testosterone replacement, current guidelines contraindicate the initiation of treatment in patients with a hematocrit above 52% [84].

The effects of testosterone on the lipid profile are still being debated. Khaw et al followed 11,606 men aged 40 to 79 years in a nested case-control study and found that mean testosterone concentrations were lower in men who died of any cause, cardiovascular disease, or cancer than in control subjects [87]. Men who died of cardiovascular causes also had significantly higher mean body mass index, serum cholesterol, and low-density lipoprotein (LDL):high-density lipoprotein (HDL) cholesterol ratios. Testosterone concentrations were significantly inversely related to body mass index, waist-hip ratio, triglycerides, and the prevalence of diabetes mellitus and were positively related to total cholesterol, LDL cholesterol, and HDL cholesterol concentrations and to cigarette smoking. A meta-analysis of testosterone replacement pooled data from 29 randomized clinical trials and suggested that testosterone replacement reduced total cholesterol, with no change in LDL cholesterol [88]. There was also a reduction of HDL cholesterol, which was only found in studies with higher mean testosterone levels at baseline.

Testosterone has shown improvements in short-term cardiovascular function either directly or indirectly through aromatization [89]. Animal studies have also shown testosterone to have an acute effect in dilatation of the coronary and pulmonary arteries. It is believed that testosterone causes both endothelium-dependent and endothelium-independent vasodilatation. The former is achieved by an increased release of nitric oxide from the endothelium, whereas the latter is caused by blocking of calcium channels or opening of potassium channels [90]. A short-term study of testosterone in 12 men with coronary artery disease or proven myocardial infarction showed significant changes in improvement in ischemic threshold parameters [89]. Furthermore, this study showed concurrent evidence of total cholesterol and serum tumor necrosis factor- α reduction. A more recent trial studied the effects on ischemia for 12 months with a randomized parallel group

control trial [91]. At the end of follow-up, the testosterone group showed increased time to ischemia and decreased serum triglycerides and body mass index, with no significant effects on serum HDL.

Testosterone is also an important modulator of insulin sensitivity. Several clinical studies showed improved glucose metabolism in testosterone versus placebo trials of hypogonadal diabetic men [92-94]. Kapoor et al performed a double-blind cross-over study on 24 men with hypogonadism and type 2 diabetes [93]. Treatment periods lasted approximately 3 months. Testosterone therapy improved fasting insulin sensitivity and reduced glycated hemoglobin, fasting blood glucose, and total cholesterol as well as visceral adiposity as assessed by waist circumference and waist-hip ratio [94].

Currently, the overall effect of testosterone replacement has not been clearly established beyond safety under the recommended indications. Further investigations are required to claim any definite improvements to other associated systems.

CONCLUSION

Testosterone plays a significant role in the well-being of older men. Accumulating evidence even suggests a more vital role of testosterone replacement than improving the quality of life. Studies have consistently shown that testosterone deficiency leads to loss of libido and deteriorating erectile function, whereas replacement in testosterone-deficient patients provides symptomatic relief and improvement.

Because the diagnosis is not clearly delineated with an absolute biochemical threshold or pathognomic signs and symptoms, the early treatment period should be assessed for clear improvement of hypogonadic features. Although this may seem foreboding, such a recommendation merely dictates that therapy be accompanied by a short trial period with vigilance against possible adverse effects or underlying diseases. If there is no apparent danger of continuing treatment, maintaining and monitoring therapy within guidelines may significantly improve the patient's quality of life and well-being.

Conflicts of Interest

The authors have nothing to disclose.

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