Testosterone therapy: where do the latest guidelines agree and differ?

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Purpose of review
The incidence of testosterone deficiency and number of men on testosterone therapy (TTh) has increased significantly over the past 3 decades. This rise has been accompanied by controversies surrounding the indications and possible adverse effects of therapy. To better inform prescribing habits among providers, many major medical associations have devised guidelines regarding the diagnosis and management of testosterone deficiency. While these guidelines agree in many areas, there are some key differences that should be identified. This review will explore the similarities, differences, and rationale for these guidelines.

Recent findings
Over the past 7 years, much attention has been devoted to the implications of TTh on cardiac health. All reviewed guidelines include dedicated sections discussing these implications and the society's position on prescribing testosterone considering recent findings, however, differ on specific contraindications to TTh and when to initiate therapy after a cardiovascular event. In addition, the American College of Physicians released its first guideline earlier this year which may impact prescribing habits among primary care physicians.

Summary
The differences between testosterone deficiency guidelines may indicate gaps in our knowledge of testosterone deficiency and focuses of future research efforts. Prescribers should be aware of these differences and discuss all treatment options with their patients.

Keywords
cardiovascular disease, hypogonadism, testosterone, testosterone deficiency

INTRODUCTION

Testosterone deficiency (also known as male hypogonadism) is a clinical syndrome characterized by low serum levels of circulating testosterone in addition to one or more associated symptoms. The estimated prevalence of testosterone deficiency worldwide ranges from 2 to 10% and increases with age and presence of comorbidities [1–4,5▪]. The introduction of improved testosterone formulations in the 1990s led to a four-fold rise in new testosterone prescriptions and 10-fold increase in market share during the early-2000s, although prescriptions sharply declined after 2013 following the publication of divisive studies suggesting an association with adverse cardiovascular events [6,7▪]. These findings prompted the Food and Drug Administration (FDA) to mandate inclusion of a warning on all testosterone packaging cautioning of the potential cardiovascular risks of prescription testosterone in 2014. In 2016, another FDA warning was added to alert prescribers of the potential for testosterone abuse and associated adverse outcomes. Due to these controversies and the high rate of off-label testosterone prescriptions, testosterone therapy (TTh) remains contentious [8]. To improve consistency in prescribing habits among providers, multiple major medical associations have release guidelines for the diagnosis and treatment of testosterone deficiency. This review will compare the recommendations from these guidelines and discuss the rationale behind their similarities and differences.

An Internet search was conducted for published guidelines from major medical associations regarding the diagnosis and treatment of testosterone deficiency. Guidelines from the American Urological Association (AUA), European Association of Urology

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KEY POINTS

- The diagnosis of testosterone deficiency requires the presence of both symptoms and biochemical confirmation of low testosterone.
- The decision to initiate TTh should only occur after appropriate counseling and informed discussion of possible risks (e.g., cardiovascular events, prostate cancer, and infertility).
- The choice of a testosterone formulation should be patient-specific and based on cost, patient convenience, and clinical reasoning.
- Although the guidelines share many similarities, there are key differences among them which may reflect topics needing further research.

(EAU), Endocrine Society, and International Society for Sexual Medicine (ISSM) were chosen due to their comprehensiveness, recency, and popularity [9–12]. The guidelines from the American College of Physicians (ACP) published in 2020 were also included when appropriate because they are the first guidelines produced by a nonspecialty association and may have significant ramifications on testosterone prescribing habits by primary care physicians [13]. Notably, the ACP guidelines do not contain recommendations regarding diagnosis of testosterone deficiency or monitoring of testosterone levels and will not be discussed in these sections.

COMPARISON OF GUIDELINES

Definition of testosterone deficiency

All reviewed guidelines agree that a diagnosis of testosterone deficiency should only be made in men with both clinical signs/symptoms of hypoandrogenism *and* laboratory evidence of low testosterone levels. Most signs and symptoms of testosterone deficiency are highly nonspecific, and consequently making the initial diagnosis can be challenging. Sexual symptoms, including reduce libido, erectile dysfunction, decreased spontaneous erections, and delayed ejaculation are common presenting complaints of men with testosterone deficiency. The ACP guidelines currently recommend initiating TTh only in men with sexual dysfunction as measured by the Aging Males' Symptoms or International Index of Erectile Function scales. Other frequent symptoms include decreased physical strength, fatigue, depressed mood, concentration difficulties, or sleep disturbances. It is important to note that none of these symptoms are specific to testosterone deficiency and could result from one or more other comorbid conditions.

Populations to test

All guidelines recommend against screening in the general population but rather only performing workup in certain subpopulations of men who would benefit from TTh. It is generally accepted that all men with signs and symptoms of testosterone deficiency should be further evaluated but the guidelines differ on other patient populations that should be screened. These are detailed in Table 1. Previous editions of the EAU guidelines recommended screening men with several conditions that can commonly cause testosterone deficiency, but this list is absent in the 2020 guidelines.

Laboratory evaluation of testosterone deficiency

Although all guidelines require biochemical evidence of low testosterone levels to diagnose testosterone deficiency, they differ in their total testosterone cutoff values and recommendations for free T and sex-hormone binding globulin (SHBG) testing. The AUA, EAU, Endocrine Society, and ISSM recommend two separate morning measurements of serum total testosterone in the absence of acute illness prior to diagnosing testosterone deficiency. Although only ISSM formally recommends liquid chromatography–mass spectrometry (LC/MS) as the preferred method for assessing serum T levels, the AUA, EAU, and Endocrine Society all acknowledge the inherent advantages to this technique in their remarks. These four guidelines also note that

Table 1. Indications for testosterone deficiency screening

Patient population	AUA	EAU	ES	ISSM
Signs/symptoms of TD	R	R	R	R
Unexplained anemia	R	–	R	–
Bone density loss	R	–	R	R
Diabetes	R	–	NR	R
Exposure to chemotherapy	R	–	–	–
Exposure to radiation	R	–	–	–
HIV/AIDS	R	–	R	–
Chronic narcotic use	R	–	R	–
Infertility	R	–	R	–
Pituitary dysfunction	R	–	R	–
Chronic steroid use	R	–	R	–
Metabolic syndrome	–	–	–	R
Obesity	–	–	–	R

R, recommended. NR, not recommended. –, no recommendation provided. AUA, American Urological Association; EAU, European Association of Urology; ES, Endocrine Society; ISSM, International Society for Sexual Medicine; TD, testosterone deficiency.

standardized, approved immunoassays produce reasonably accurate results if LC/MS is not available.

The AUA states that 300 ng/dl is a reasonable cutoff for diagnosis, while the EAU suggests a value of 350 ng/dl. The Endocrine Society recommends further workup if a patient has 'unequivocally and consistently low serum total testosterone' and defines a lower limit of normal as 264 ng/dl. The ISSM does not provide a definitive cutoff but instead recognizes that men with total *T* less than 231 ng/dl are likely to have testosterone deficiency, whereas men with total *T* more than 346 ng/dl are unlikely to have testosterone deficiency. Those with values between these two should have additional evaluation performed. All guidelines agree that these T cutoffs are not absolute and that values should be contextualized on an individual basis.

None of the guidelines recommend measurement of free T as an initial diagnostic test. The Endocrine Society does recommend measurement of SHBG and free T (either directly or calculated) in all patients with borderline total testosterone (between ~200 and 400 ng/dl) or those with conditions causing altered SHBG concentrations (e.g., obesity, hypothyroidism, or HIV). Both ISSM and EAU guidelines suggest measuring SHBG and calculating free T in men with persistent symptoms and borderline total testosterone levels or conditions that alter SHBG. The AUA has no official recommendation on usage of free T but the unabridged guidelines recognize the value of free T calculation in highly symptomatic men with equivocal total testosterone levels.

Adjunctive testing

After a diagnosis of testosterone deficiency is made, the AUA, EAU, Endocrine Society, and ISSM recommend obtaining luteinizing hormone (LH) alone (AUA, ISSM) or follicle stimulating hormone (FSH) with LH (EAU, Endocrine Society) to distinguish between primary and secondary hypogonadism. These four guidelines differ slightly on indications for obtaining a prolactin level as described in Table 2. Pituitary MRIs are recommended by AUA, EAU, and Endocrine Society for all men with severe secondary hypogonadism. The AUA also suggests measuring serum estradiol for men with testosterone deficiency who present with breast symptoms such as gynecomastia.

Validated questionnaires

There is consensus opinion among the AUA, EAU, Endocrine Society, and ISSM that validated

Table 2. Indications for adjunctive tests in the diagnosis of testosterone deficiency

Adjunctive test	AUA	EAU	ES	ISSM
Free T/SHBG	Persistent symptoms with equivocal TT	Persistent symptoms with equivocal TT Conditions which affect SHBG levels	All patients with borderline TT (200–400 ng/dl) Conditions which affect SHBG levels	Persistent symptoms with equivocal TT Conditions which affect SHBG levels
LH	Low TT	Low TT	Low TT	Low TT, at time of confirmatory TT test
FSH	–	Low TT	Low TT	–
Prolactin	Low TT and low or low-normal LH	Low desire and low or low-normal TT	Low TT and low or low-normal LH	Low TT, at time of confirmatory TT test
Estradiol	Low TD and breast symptoms	–	–	–
Pituitary MRI	Severe secondary hypogonadism ($T < 150$ ng/dl)	Severe secondary hypogonadism ($T < 175$ ng/dl) Hyperprolactinemia Symptoms of pituitary mass Anterior pituitary hormone deficiencies	Severe secondary hypogonadism ($T < 150$ ng/dl) Hyperprolactinemia Symptoms of pituitary mass	–
Hgb/Hct	Low TT, prior to initiating therapy	Low TT, prior to initiating therapy	Low TT, prior to initiating therapy	Low TT, prior to initiating therapy
Lipid profile	–	Low TT, prior to initiating therapy	–	Low TT, prior to initiating therapy

–, no recommendation provided. AUA, American Urological Association; EAU, European Association of Urology; ES, Endocrine Society; ISSM, International Society for Sexual Medicine; TD, testosterone deficiency; SHBG, sex hormone binding globulin; TT, total testosterone; LH, luteinizing hormone; FSH, follicle stimulating hormone; TD, testosterone deficiency.

questionnaires should not be used in the diagnosis or management of testosterone deficiency.

Goals of treatment

All guidelines agree that the ultimate goal of TTh is improvement in symptoms without adverse side-effects. They also promote lifestyle modifications such as weight loss and exercise as a first-line treatment that may improve symptoms of testosterone deficiency. For those patients who choose to pursue pharmacologic TTh, the AUA, EAU, Endocrine Society, and ISSM all define a goal total testosterone level as the mid-normal range for young men.

Formulations

The guidelines differ on their recommendations for initial TTh formulation that clinicians should prescribe. The EAU suggests using transdermals rather than long-acting depot administrations so that therapy can be adjusted or stopped quickly in the event of treatment-related side effects. Conversely, the ACP recommends starting treatment with intramuscular formulations due to the considerably lower cost. The AUA, Endocrine Society, and ISSM do not specify an initial treatment formulation but instead recommend starting with a preparation based on patient-driven factors such as cost and convenience. Of note, the AUA and ISSM both oppose the use of alkylated oral T due to the risk of hepatotoxicity. The AUA and EAU both warn of the possibility of transference when using topical testosterone gels.

Follow-up

All men who are started on TTh should be followed closely for efficacy and adverse side-effects, but the guidelines differ slightly regarding follow-up schedules. All of the guidelines advise clinicians to measure an initial follow-up total testosterone after an appropriate interval based on formulation. From the AUA guidelines, these intervals are: 2–4 weeks for gels, patches, or intranasal formulations, at least three to four cycles for short-acting intramuscular or subcutaneous formulations, and between the first two 10-week injections for long-acting intramuscular formulations. Those on long-acting subcutaneous pellets should have two follow-up measurements: one 2–4 weeks after implant and another 10–12 weeks after initiation. All guidelines recommend close monitoring of hemoglobin/hematocrit during treatment. There are small differences among follow-up schedules which are outlined in Table 3. Of note, both EAU and ISSM additionally recommend obtaining lipid and glycemic profiles at follow-up visits. There is consensus that PSA should be followed closely at follow-up visits for men who choose to engage in prostate cancer (PCa) screening, which will be discussed in a following section. All guidelines specify that signs of testosterone deficiency should be reevaluated at every appointment and therapy should be stopped if there is no symptomatic improvement. Although the ACP guidelines do not specifically address monitoring of TTh, they do recommend reevaluating symptoms within 12 months and discontinuing treatment in men with no improvement in sexual function.

Fertility

All committees recognize that exogenous testosterone impairs spermatogenesis and, consequently, men with testosterone deficiency who desire fertility should not start TTh. The AUA also recommends that the unknown long-term impact of TTh on

Table 3. Follow-up testing schedules

Follow-up testing	AUA	EAU	ES	ISSM
TT	Initial follow-up level based on formulation, then every 6–12 months	Initial follow-up level based on formulation, 3, 6–12 months, then annually	Initial follow-up level based on formulation, 3–6, 12 months, then annually	Initial follow-up level based on formulation, 3, 6, 12 months, then annually
Hgb/Hct	Every 6–12 months	3, 6–12 months, then annually	3–6, 12 months, then annually	3, 6, 12 months, then annually
PSA	Per screening guidelines	3, 6–12 months, then annually	3–12 months, then per screening guidelines	3, 6, 12 months, then annually
Lipid and glycemic profiles	–	6–12 months, then annually	–	3, 6, 12 months, then annually
DEXA	–	18–24 months	–	–

–, no recommendation provided. AUA, American Urological Association; EAU, European Association of Urology; ES, Endocrine Society; ISSM, International Society for Sexual Medicine; TT, total testosterone; PSA, prostate specific antigen; DEXA, Dual-energy X-ray absorptiometry.

spermatogenesis should be discussed with patients who may desire future fertility. This recommendation was based on multiple studies which demonstrated highly variable recovery rates of spermatogenesis following cessation of TTh [14–16]. For men with testosterone deficiency who are interested in fertility, the AUA, EAU, and ISSM all suggest either selective estrogen receptor modulators or aromatase inhibitors while acknowledging that this is an off-label indication for their use. Recombinant human chorionic gonadotropin (hCG) is also an option mentioned by AUA and EAU. The EAU emphasizes the importance of administering recombinant FSH in addition to hCG as it may result in a higher rate of spermatogenesis [17].

Prostate cancer

Guidelines regarding the use of TTh in men at risk for PCa can be broadly divided into recommendations for men with and without a history of PCa. For men without a personal history of PCa, all guidelines recommend assessing PCa risk prior to initiation of TTh with baseline prostate specific antigen (PSA) for all men over the age of 40. The EAU additionally recommends PSA screening for men under 40 using a shared decision-making approach after an informed discussion of screening risks and benefits. For men with elevated PSA, further urologic workup based on local guidelines (e.g., prostate parametric MRI or biopsy) is necessary before proceeding with TTh. In those men with negative workup, it is safe to begin TTh with close follow-up of PSA at each follow-up visit.

Important differences exist within the guidelines regarding the management of men with a prior history of PCa. All guidelines urge against TTh in men with active locally invasive or metastatic disease due to high risk for disease progression. The ISSM and Endocrine Society do not have specific guidelines for TTh in men with a history of previously treated PCa, although ISSM does recommend referral to 'a physician with expertise in managing testosterone deficiency and PCa.' The AUA specifies that men with a history of localized PCa who have had prostatectomy or radiation with an appropriately low PSA value (undetectable for prostatectomy, <0.1 ng/ml for radiation) can be considered for TTh after a negotiated discussion with the patient. These recommendations were based on data which suggest that patients who responded well to definitive PCa treatment do not have an increased risk for PCa recurrence after starting TTh [18,19]; however, these studies were small and had short follow-up times which limits their clinical applicability. Men with PCa on active surveillance may also be candidates for TTh, but data for this population are similarly lacking [20]. The EAU allows for initiation of TTh in men with a history of PCa, but with stricter inclusion criteria than the AUA. In these guidelines, men with PCa considering TTh should have a low risk for recurrence (defined as preoperative Gleason score <8, pathological stage T1–2, and preoperative PSA < 10 ng/ml) and definitive treatment with prostatectomy. Ideally, treatment would be started at least 1 year after the patient's PSA nadirs under 0.01 ng/ml.

The relationship between TTh and PCa-related morbidity remains poorly understood, and this uncertainty is reflected in differences between guidelines. Several randomized controlled trials have demonstrated that TTh does not appear to increase the risk of PCa [21–23], although detection of subclinical PCa may rise due to higher rates of PSA screening and biopsy [24]. However, it is well known that androgen receptor signaling plays an essential role in PCa biology and androgen ablation halts growth of castrate-sensitive cancers. These two seemingly disparate findings may be explained by the 'Saturation Model,' which proposes that maximal androgenic stimulation of PCa occurs at a low plasma total testosterone 'activation threshold' [25]. In men with serum T under 250 ng/dl, topical TTh resulted in small increases in PSA but a similar rise was not found in men with baseline total testosterone greater than 250 ng/dl [26]. Similarly, a cross-sectional study observed that serum total testosterone correlated with PSA levels up to approximately 231 ng/dl, but over this threshold there was no correlation [27].

Cardiovascular disease

The relationship between TTh and cardiovascular disease remains a major focus of media attention and source of controversy in the clinical realm. The many facets of this relationship have been reviewed extensively [28–32] and a nuanced discussion is beyond the scope of this article. It is worth noting that the first randomized controlled trial adequately powered to assess for major adverse cardiovascular events as a primary outcome in hypogonadal men beginning TTh (TRAVERSE) began recruitment in 2018 and is slated to complete in mid-2022 [33▪▪].

All guidelines acknowledge that the data regarding cardiovascular risk in men on TTh is lacking but that risks factors should be assessed prior to starting therapy. The AUA recommends against starting TTh in men who have had a major adverse cardiovascular event [myocardial infarction (MI) or cerebrovascular accident] within the past 3–6 months. This timeframe was chosen because the cited studies excluded men who had a cardiovascular event in the preceding 3–6 months [34,35]. The Endocrine

Society similarly advised against starting TTh in men with a history of stroke or MI in the past 6 months. Although the EAU does not specify a timeframe, it does identify an 'acute cardiovascular event' as a relative contraindication and uncontrolled or poorly controlled congestive heart failure as an absolute contraindication to TTh. Conversely, the ISSM recommends that men with a history of cardiovascular disease be assessed and monitored in the same way as other men.

CONCLUSION

Due to the increased recognition of testosterone deficiency as a clinical entity and rise of testosterone prescriptions over the past 3 decades, professional organizations have sought to codify available evidence into practice guidelines. Although many of these guidelines share similar key recommendations for approaching testosterone deficiency, there are some notable differences especially regarding diagnosis, follow-up schedules, and treatment of special populations. As an example, a man with a history of MI 5 months ago may be a candidate for TTh based on the EAU and ISSM guidelines, but the AUA and Endocrine Society specifically recommend against TTh in this patient. Similar discrepancies exist for infertile patients or those with a history of PCa. The reasons for this variability may be attributed to time of publication, composition of the committee, local prescribing habits, or differences in available T formulations (e.g., in Europe versus North America). Importantly, disagreement among the guidelines highlights the need for well designed randomized trials to inform best clinical practices in the management of testosterone deficiency. When results of studies such as TRAVERSE are published in the coming decade, perhaps more congruent guidelines will also result.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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