

## Diagnosis and Treatment of Testosterone Deficiency: Recommendations From the Fourth International Consultation for Sexual Medicine (ICSM 2015)



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### ABSTRACT

**Introduction:** Testosterone deficiency (TD), also known as hypogonadism, is a condition affecting a substantial proportion of men as they age. The diagnosis and management of TD can be challenging and clinicians should be aware of the current literature on this condition.

**Aim:** To review the available literature concerning the diagnosis and management of TD and to provide clinically relevant recommendations from the Fourth International Consultation for Sexual Medicine (ICSM) meeting.

**Methods:** A literature search was performed using the PubMed database for English-language original and review articles published or e-published up to January 2016.

**Main Outcome Measures:** Levels of evidence (LoEs) and grades of recommendations are provided based on a thorough analysis of the literature and committee consensus.

**Results:** Recommendations were given for 12 categories of TD: definition, clinical diagnosis, routine measurement, screening questionnaires, laboratory diagnosis, threshold levels for the biochemical diagnosis of TD, prostate cancer, cardiovascular disease, fertility, testosterone (T) formulations, alternatives to T therapy, and adverse events and monitoring. A total of 42 recommendations were made: of these, 16 were unchanged from the Third ICSM and 26 new recommendations were made during this Fourth ICSM. Most of these recommendations were supported by LoEs 2 and 3. Several key new recommendations include the following: (i) the clinical manifestations of TD occur as a result of decreased serum androgen concentrations or activity, regardless of whether there is an identified underlying etiology [LoE = 1, Grade = A]; (ii) symptomatic men with total T levels lower than 12 nmol/L or 350 ng/dL should be treated with T therapy [LoE = 1, Grade = C]; (iii) a trial of T therapy in symptomatic men with total T levels higher than 12 nmol/L or 350 ng/dL can be considered based on clinical presentation [LoE = 3, Grade = C]; (iv) there is no compelling evidence that T treatment increases the risk of developing prostate cancer or that its use is associated with prostate cancer progression [LoE = 1, Grade = C]; and (v) the weight of evidence indicates that T therapy is not associated with increased cardiovascular risk [LoE = 2, Grade = B].

**Conclusion:** TD is an important condition that can profoundly affect the sexual health of men. We provide guidance regarding its diagnosis and management. Men with TD who receive treatment often experience resolution or improvement in their sexual symptoms and non-sexual health benefits.

*J Sex Med* 2016;13:1787–1804. Copyright © 2016, International Society for Sexual Medicine. Published by Elsevier Inc. All rights reserved.

**Key Words:** Testosterone Deficiency; Androgens; Hypogonadism; Prostate Cancer; Cardiovascular Disease

Received October 1, 2016. Accepted October 21, 2016.

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<http://dx.doi.org/10.1016/j.jsxm.2016.10.009>

## INTRODUCTION AND DEFINITION

Testosterone deficiency (TD), also known as hypogonadism, is a common medical condition affecting men, characterized by clinical signs and symptoms in conjunction with decreased serum androgen concentrations or activity. Men with TD often present with sexual symptoms, hence its importance to specialists in sexual medicine. The purpose of this article is to provide clinically relevant recommendations on the diagnosis and treatment of TD from the Fourth International Consultation on Sexual Medicine (ICSM 2015). The authors of this report were selected to serve as members on the committee of Pharmacotherapy for Erectile Dysfunction, Testosterone Deficiency and Sexual Rehabilitation after Treatment for Prostate Cancer. The members were selected based on their clinical knowledge and experience and on their reputation as key opinion leaders. This committee reviewed all the available evidence published in the literature, assigned level of evidence (LoE) for all data, and provided recommendations based on LoEs. It should be emphasized that recommendations were obtained after attempts at achieving consensus, but unanimity was not achieved for all recommendations or comments. Throughout this report recommendations are given on the diagnosis and treatment of hypogonadism. The new recommendations from the Fourth ICSM are highlighted in *italic typeface*.

Serum testosterone (T) levels below the normal range are common in men, especially after 50 years of age. However, low T levels are not associated with symptoms of TD in every case. For example in the Boston Area Community Health (BACH) study, 47.6% of men older than 50 years who had low T levels had no symptom of TD.<sup>1</sup> In this context, data from three large cohort studies demonstrated that less than one third of men who had a low level of total T (TT) reported at least two or three symptoms of TD<sup>1–3</sup> (Table 1). This outlines the importance of considering TD a clinical and biochemical syndrome deserving laboratory and clinical criteria to be defined and prevent overdiagnosis, as supported by all major currently available guidelines and recommendations.<sup>4–7</sup>

TD can result from:

- Decreased testicular synthesis of T owing to impaired Leydig cell function (hypergonadotropic hypogonadism; primary hypogonadism)
- Decreased testicular synthesis of T owing to inadequate gonadotropic stimulation of Leydig cells (hypogonadotropic hypogonadism; secondary hypogonadism)

In addition, TD symptoms, in the presence of a TT level within the reference range, can result from (i) impaired androgen receptor function, (ii) androgen receptor blockade, and (iii) increased SHBG, resulting in a decrease in free T (FT) or bioavailable T.

## RECOMMENDATIONS: DEFINITION OF TD

1. TD is a clinical AND a biochemical syndrome associated with age and comorbidities [LoE = 2, Grade = B] and characterized by a deficiency in T AND relevant symptoms.

2. TD can affect the function of multiple organ systems and result in significant detriment in quality of life, including alterations in sexual function [LoE = 2, Grade = B].
3. TD results from defects at various levels of the hypothalamus-pituitary-testis (HPG) axis: abnormality in the testes (primary TD), pituitary or hypothalamic failure (secondary TD), or a combination of the two (mixed TD) [LoE = 1, Grade = A].
4. TD also can result from an impairment of T action because of decreased bioavailability of the hormone (owing to SHBG variations) or because of androgen receptor alterations that can influence androgen activity [LoE = 2, Grade = A].
5. The clinical manifestations of TD occur as a result of decreased serum androgen concentrations or activity, regardless of whether there is an identified underlying etiology [LoE = 1, Grade = A].

## CLINICAL DIAGNOSIS AND SIGNS AND SYMPTOMS

The signs and symptoms of TD can vary considerably from individual to individual. TD varies from various defects in virilization to an almost complete female phenotype in case of “very early-onset TD” during the fetal life from milder central or peripheral defects (ie, delay in puberty, eunuchoidism) in “early-onset (peri-pubertal) TD.”<sup>8</sup> Other common terms used to describe TD include late-onset hypogonadism or adult-onset hypogonadism.<sup>9</sup> These definitions support the fundamental concept that low androgen serum concentrations or activity can produce a clinical syndrome associated with characteristic symptoms and signs in adult men.

Several studies have demonstrated that the T threshold at which TD symptoms and signs occur differs according to the symptom or sign,<sup>3,10</sup> with differences as large as, for example, 320 ng/dL (11 nmol/L) for the decrease of morning erections and 245 ng/dL (8.5 nmol/L) for erectile dysfunction (ED).<sup>3</sup> Owing to interindividual variations, some men can have these same symptoms with serum concentrations beyond these group thresholds.

## Signs and Symptoms of TD

The clinical manifestations of TD are variable. The main symptoms of TD are listed in Table 2. Because T regulates all steps of the male sexual response (including sexual desire, arousal, and to a lesser degree orgasm and ejaculation), sexual dysfunctions are a prominent symptom of TD and often the presenting symptom.<sup>3,4,8</sup> Low sexual desire and decreased nocturnal and morning erections are clearly associated with TD, whereas the association with impaired sex-induced erections is less evident.<sup>3,4,8</sup> However, after having analyzed the large European Male Aging Study (EMAS) database of more than 3,000 men 40 to 79 years old using mass-derived data, Wu et al<sup>3</sup> found that late-onset hypogonadism could be clinically defined by the presence of the three preceding sexual symptoms associated with a TT level lower than 320 ng/dL (11 nmol/L) and an FT level

**Table 1.** Rates of men with low T and of men with symptomatic low T (low T plus clinical symptoms of TD) in three random sample populations of subjects at least 30 years old\*

Study; subjects	Lower limit of normal T (ng/dL)	Men with low T, %	Clinical criteria	Men with low T and clinical criteria, %
MMAS <sup>2</sup> ; 1,667 men ≥40 y old	TT = 400, FT = 8.9	TT = 25.3, FT = 19.4	≥3 of 8 symptoms	6
BACH <sup>1</sup> ; 1,475 men 30–79 y old	TT = 300, FT = 5	TT = 24, FT = 11	≥1 of 3 specific or ≥2 of 4 non-specific symptoms	5.6
EMAS <sup>3</sup> ; 3219 men ≥40 y old	TT = 320, FT = 6.4	TT = 17, FT = not reported	3 sexual symptoms	2.1

BACH = Boston Area Community Health; EMAS = European Male Aging Study; FT = free testosterone; MMAS = Massachusetts Male Ageing Study; T = testosterone; TD = testosterone deficiency; TT = total testosterone.

\*The factor to convert nanograms per milliliter to nanomoles per liter, or picograms per milliliter to picomoles per liter, is 3.467. The factor to convert nanomoles per liter to nanograms per liter, or picomoles per liter to picograms per milliliter, is 0.2884: 2.31 ng/mL = 231 ng/dL = 8 nmol/L and 12 nmol/L = 3.46 ng/mL = 346 ng/dL.

lower than 6.4 ng/dL (6.4 pg/mL, 220 pmol/L). These three sexual symptoms were the only symptoms that had a syndromic relation with decreased T levels. Preliminary evidence also indicates that a delayed ejaculation<sup>11</sup> and a perceived ejaculate volume decrease<sup>12</sup> also might underlie TD.

In the EMAS study, three additional symptoms (ie, inability to perform vigorous activity, fatigue, and depression) were significantly related to low T levels.<sup>3</sup> Likewise, in the second psychometric validation of the NERI Hypogonadism Screener, in addition to the sexual symptoms, the most prevalent symptoms and signs in the TD group were fatigue, muscle weakness, depressed mood, and increased body fat. Other symptoms that significantly discriminated the TD group from the control group were excessive irritability and difficulties remembering things read and directions.<sup>10</sup> An association of low T with several cognitive symptoms also has been reported, but these data seem inconsistent (Table 2).<sup>8,13</sup>

Physical signs of TD, and the LoE of their association with a low T level, are listed in Table 3. Men with suspected TD should have a physical examination to identify such physical signs. However, the physician must be mindful that this examination could be normal in men with TD. The most prevalent sign of TD are weight gain, increased visceral obesity, characterized by an increase in waist circumference, and smaller prostate volume. Secondary TD has been recently considered one of the many adverse consequences of being overweight and having obesity, especially in aging men. Conversely, low T levels could contribute to the accumulation of excess fat, establishing a vicious cycle. Decrease in muscle mass is less prevalent and difficult to confirm.

**RECOMMENDATIONS: CLINICAL DIAGNOSIS**

1. Sexual dysfunction, in particular low sexual desire, decreased nocturnal and morning erections, and ED, are prominent and often the presenting symptoms especially suggestive of TD when all three are associated [LoE = 1, Grade = A].

2. Diminished physical vigor, decreased energy and motivation, fatigue, depressive mood, and sleep disturbances are often present [LoE = 1, Grade = B].
3. Hot flushes and sometimes alterations in cognition and memory can be associated with TD [LoE = 3, Grade = C].
4. Visceral obesity is often observed, and muscle mass and bone mineral density are often decreased [LoE = 1, Grade = A].
5. Features of the physical examination suggestive of TD include smaller testicles, decreased body hair, and gynecomastia. However, none of these might be present [LoE = 1, Grade = B].
6. Not all manifestations need to be evident simultaneously and their intensity shows marked interindividual variability [LoE = 2, Grade = D].

**Table 2.** Symptoms of testosterone deficiency

Domain	Symptoms
Sexual	Decreased sexual desire and activity
	Decreased frequency of sexual thoughts
	Decreased frequency of morning erections
	Erectile dysfunction
	Delayed ejaculation
	Smaller volume of ejaculation
Physical	Inability to perform vigorous activity
	Decreased physical vigor and muscle strength
	Decreased bending
	Fatigue
Psychological	Hot flushes, sweats
	Decreased energy, motivation, initiative
	Depressive mood
	Sadness
	Excessive irritability
Cognitive	Sleep disturbances, insomnia, sleepiness
	Poor self-rated health
	Impaired concentration
	Impaired verbal memory
	Impaired spatial performance

**Table 3.** Physical signs of TD and level of evidence of their association with a low T level

Domain	Signs	Remark
Sexual development	Incomplete, eunuchoidism	Peri-pubertal TD
	Smaller testicle	Not specific
	Varicocele	
	Gynecomastia	T might increase after surgery
	Loss of pubic hair	Prolonged TD
Body composition	Decreased need for shaving	Prolonged TD
	Increased BMI, obesity	Late-onset TD
	Visceral obesity	Late-onset TD
Signs suggestive of osteoporosis	Decreased muscle mass	
	Height loss	Prolonged TD, infrequent
	Low trauma fractures	Prolonged TD
General	Decreased bone mineral density	
	Anemia	Could contribute to fatigue

BMI = body mass index; T = testosterone; TD = testosterone deficiency.

7. Although the prevalence of TD increases with each decade of life, TD can occur in adult men of all ages [LoE = 1, Grade = B].

## CONDITIONS ASSOCIATED WITH A HIGH PREVALENCE OF LOW T LEVELS

Table 4 presents a list of conditions associated with a high prevalence of low T levels. Overall, T is often low in men with chronic diseases.<sup>4</sup> Screening for low T should be recommended only in those conditions for which discovering a low T level could have important consequences for the management of the patients, whether they are symptomatic or not. In this context, TD screening should be restricted to patients with medical conditions associated with insulin resistance (obesity, type 2 diabetes, and metabolic syndrome [MetS]) and TD signs and/or symptoms. Similarly, screening for TD should be suggested for men with HIV-associated weight loss, osteoporosis (or height loss or low trauma fracture), or using opioids or glucocorticoids. Most researchers recommend against routinely screening for low T in the absence of signs or symptoms of TD. Conversely, for a patient presenting with TD symptoms or signs, the presence of any of these conditions reinforces the presumption of low T and the requirement for a T measurement.

## CIRCUMSTANCES REQUIRING ROUTINE MEASUREMENT OF T

### Sexual Symptoms

T plays a key role in male sexual function. In the EMAS, Wu et al<sup>3</sup> found that the best predictors of TD were men presenting with all three of following sexual problems: ED, decreased libido, and decreased frequency of morning erections. Other investigators have found that men with TD are more likely to have decreased sex-induced erections, delayed ejaculation and decreased semen volume, decreased nocturnal and morning erections, and hypoactive sexual desire.<sup>4,21,22</sup> Rosen et al<sup>23</sup> found

that decreased spontaneous erections and low libido were the most prevalent clinical symptoms in hypogonadal younger and older men.

### Metabolic Diseases

The association between low T and impaired fasting glucose, insulin resistance, type 2 diabetes mellitus, and MetS in men with and without ED has recently emerged.<sup>4,24,25</sup> Conversely, type 1 diabetes mellitus is not associated with an increased prevalence of TD or of risk factors associated with TD.<sup>26</sup> MetS-associated TD is characterized by the hypertriglyceridemic waist phenotype, which combines high triglyceride levels and increased waist circumference.<sup>4</sup> Low T is associated not only with MetS but also with each of its individual components, including type 2 diabetes mellitus, visceral obesity, insulin resistance, dyslipidemia, and high blood pressure.<sup>27</sup> In addition, several prospective cohort studies and their meta-analyses have found that low T predicts the occurrence of incidental type 2 diabetes and MetS, which suggests that low T could be causally related to the two metabolic diseases. A meta-analysis of randomized placebo-controlled trials found that T therapy (TTh) could improve body composition, leading to an improvement in the glyco-metabolic profile.<sup>28</sup> In addition, these same investigators found through another meta-analysis of type 2 diabetics that TTh could improve body weight and waist circumference.<sup>29</sup> It is important to recognize that obesity and low T are associated and have a bidirectional relation.

## OTHER CHRONIC DISEASES WITH INCREASED PREVALENCE OF LOW T

### Osteoporosis

Low T can be found in up to 20% of men with symptomatic vertebral fractures and 50% of elderly men with hip fractures.<sup>30</sup>

**Table 4.** Conditions associated with an increased prevalence of low T and Level of Evidence of this association

Domain	Condition	Prevalence of low T and remarks
Andrology and endocrinology	History of cryptorchidism	
	History of delayed puberty	
	History of pituitary disease	
	Varicocele	T can increase after surgery
	History of male infertility	Can show hypog hypogonadism
Metabolic diseases associated with insulin resistance	Obesity	TD in 52% of men with BMI > 30 kg/m <sup>2</sup>
	Type 2 DM	Not increased in type 1 DM <sup>14</sup>
	Metabolic syndrome	Type 2 DM = 50%, hyper-lipid = 40%
Cardiovascular diseases	Hypertension	42% role in associated obesity
	Coronary artery disease	Low T related to severity
	Cerebrovascular disease	Low T related to severity
	Chronic heart failure	
	Atrial fibrillation	Low T associated with 10-y risk of incident atrial fibrillation
Other chronic diseases	Chronic obstructive pulmonary disease	Only moderate and severe cases = 38–43%, role for glucocorticoids
	Obstructive sleep apnea syndrome	Low T mainly due to associated obesity <sup>15</sup>
	End-stage renal disease, hemodialysis	Low T in 22–66% of men according to degree of renal failure <sup>16</sup>
		Tth effects inconsistent <sup>17</sup>
	Cirrhosis	Low T in up to 90%, SHBG increase
	(Low trauma) fractures	Vertebral = 20%, hip = 50%
	Osteoporosis	44% T effect mediated by low E2 and SHBG
	Rheumatoid arthritis	20–47% moderate hypog hypogonadism
	HIV-associated weight loss	16–70%, linked to poor health status, significant benefit of tth
		Associated with weight loss and poor quality of life
Pharmacologic	Chronic opioid use	Low T in 53%, 74% on long-acting
	Treatment with glucocorticoids	Contributes in associated myopathy and osteoporosis <sup>18–20</sup>

BMI = body mass index; DM = diabetes mellitus; E2 = estradiol; hypog = hypogonadotropic; T = testosterone; TD = testosterone deficiency; TTh = testosterone therapy.

However, T effects on men's bone are mostly linked to its aromatization into estradiol (E2).<sup>31</sup> In a cohort study of men at least 65 years old, the major predictor of non-vertebral fracture risk was a low bioavailable E2 followed by the association of low bioavailable T with high SHBG levels. This finding would support the measurement of SHBG levels in addition to T in cases of low trauma non-vertebral fractures.<sup>32</sup> Although several randomized controlled trials have shown a significant increase of bone mineral density after TTh in men with low T, currently there are no data on the effect of TTh on the incident risk of bone fractures.<sup>32</sup>

### Human Immunodeficiency Virus

The prevalence of low T in men with HIV infection and have lost weight has decreased since the availability of antiretroviral therapy. TD is still prevalent in 20% to 25% of HIV-infected men<sup>14</sup> and up to 70% of HIV-infected men in certain series.<sup>33</sup> In hypogonadal HIV-infected men, low T seems to be a marker of frailty and poor health.<sup>34</sup> Randomized controlled trials have demonstrated that TTh rapidly improves lean and muscle mass, red blood cell count, depression, and perception of

well-being.<sup>14</sup> This could justify routine screening of T in HIV-infected men.<sup>6,35</sup> A recent 12-month registry study also reported beneficial effects of T on sexual function in HIV-infected men.<sup>36</sup> Long-term follow-up studies are limited in this population.<sup>36</sup>

## PHARMACOLOGIC CAUSES OF LOW T

### Opioids

According to a recent meta-analysis of 17 studies, T levels are suppressed in men with regular opioid use, regardless of opioid type, including methadone and tramadol.<sup>37</sup> This meta-analysis found a mean T difference of 165 ng/dL (5.7 nmol/L) between opioid users and controls.<sup>37</sup> In a retrospective cohort study of 81 men treated with opioids for chronic pain, 53% of men had a morning T level lower than 250 ng/dL (8.66 nmol/L). TD was found in 74% of patients on long-acting opioids and 34% of patients on short-acting opioids. Body mass index (BMI) also was significantly associated with low T. After adjustment for BMI and daily dosage, men on long-acting opioids were 4.78

times more likely of becoming hypogonadal than men on short-acting opioids.<sup>38</sup> A registry study found that sexual function and mood of men with low T improved significantly in opioid users and non-users over a 12-month course of T gel administration.<sup>39</sup>

### Glucocorticoids

In a cross-sectional study of men with respiratory disease, mean T was 33% lower in those treated with long-term oral prednisolone than in age-matched controls. T levels of men on long-term inhaled glucocorticoid therapy were not different from those of controls.<sup>15</sup> Acute administration of dexamethasone has been shown to significantly decrease T in serum and at the muscle level. These defects could contribute to the development of the well-known steroid-induced myopathy.<sup>16</sup>

### RECOMMENDATIONS: ROUTINE MEASUREMENT OF T

- Men presenting with the following conditions should be screened for low T:
  - Sexual symptoms including decreased libido, ED, and decreased frequency of morning erections [LoE = 1, Grade = B].
  - Clinical conditions associated with insulin resistance (obesity, type 2 diabetes, and MetS) should be screened for TD because it is often comorbid [LoE = 2, Grade = B].
  - Infertility [LoE = 2, Grade = B] (this is discussed in more detail in subsequent section).
  - Osteoporosis and height loss or low trauma fractures likely indicate TD because asymptomatic low T can be a negative contributor and can be corrected with TTh [LoE = 1, Grade = B].
  - HIV-associated weight loss [LoE = 2, Grade = B].
  - Long-acting opioid use [LoE = 2, Grade = B].
  - High-dose glucocorticoid use [LoE = 1, Grade = B].
- Screening for low T is not recommended in the absence of TD symptoms in all other populations, although they are potentially associated with an increased prevalence of low T (cardiovascular [CV] diseases, chronic pulmonary diseases, end-stage renal diseases, cirrhosis, rheumatoid arthritis, and cancer), because of the lack of evidence of benefit resulting from TTh in non-symptomatic individuals [LoE = 3, Grade = B].

### QUESTIONNAIRES TO SCREEN FOR TD

Several questionnaires have been proposed to screen for TD in aging men. These questionnaires include the Androgen Deficiency in Aging Males (ADAM) Questionnaire, the Aging Male Survey (AMS),<sup>17</sup> and the Massachusetts Male Ageing Study (MMAS) screening questionnaire.<sup>17,40</sup> All these questionnaires have good sensitivity, although they are not effective in the diagnosis of TD in daily practice because of their low specificity.<sup>17</sup> The ADAM and AMS instruments are not significantly associated with circulating TT levels. Moreover, ADAM and

AMS scores did not increase in some studies of men with TD after TTh.<sup>41</sup> A recent systematic review found that of the multiple-item instruments, the AndroTEST showed the most favorable positive likelihood ratio (range = 1.9–2.2) and the most favorable negative likelihood ratio (range = 0.37–0.49).<sup>42</sup>

### RECOMMENDATIONS: QUESTIONNAIRES TO SCREEN FOR TD

- Different questionnaires have been proposed to help with screening or diagnosing TD. Most are sensitive but not adequately specific [LoE = 1]. Overall, questionnaires are not recommended as a screening tool for TD because of poor specificity [Level 2, Grade = B].
- The clinical diagnosis of TD should not be based exclusively on questionnaires or structured interviews [LoE = 5, Grade = B].
- In men with sexual dysfunction, structured interviews such as the AndroTEST demonstrated enough sensitivity and specificity to raise the suspicion of TD [LoE = 2, Grade = B].

### LABORATORY DIAGNOSIS OF TD

#### Indications for a Laboratory Diagnosis of TD

Measuring serum T is justified in the presence of any of the signs and symptoms listed in [Tables 2](#) and [3](#).<sup>4,6</sup> Measuring serum T levels are especially required in men with sexual dysfunction, which has been strongly associated with low T levels. TD has been associated with low sexual desire,<sup>3,4,6,10,43</sup> delayed ejaculation,<sup>23</sup> decreased perceived ejaculate volume,<sup>12</sup> and poor morning erections.<sup>3,4,6,10,43</sup>

Measuring T also is required in some general conditions frequently associated with TD, including obesity, diabetes, MetS,<sup>4</sup> osteoporosis,<sup>4,6</sup> HIV-associated weight loss,<sup>4,6,44</sup> long-term use of long-acting opioids,<sup>4,6</sup> and treatment with glucocorticoids.<sup>4,6,44,45</sup> Conversely, there is no indication for a routine measurement of T in the general population in the absence of these signs, symptoms, or particular general conditions.<sup>4,6</sup>

#### Methods to Measure Serum T

[Table 5](#) lists the advantages and drawbacks of the methods to measure T.

#### Total Testosterone

The main screening test for hypogonadism is the measurement of serum TT. The immunoassays—performed by most laboratories in the everyday clinical setting—are relatively inexpensive and readily available. Due to the variability of results with immunoassays, some experts have encouraged the use of liquid chromatography-tandem mass spectrometry, which provides more reliable results from one laboratory to another. However, this expensive methodology is still mostly available only in research settings or in large referral laboratories. An additional problem is the lack of consistent and clinically relevant reference ranges.

**Table 5.** Methods to measure testosterone

Laboratory test	Advantages	Drawbacks
TT: LC-MS	Reference method; most accurate, especially for low values	More expensive, available in few laboratories (reference laboratories)
Immunoassays: RIA, chemiluminescence	Less expensive, more widely available	Less accurate, especially when TT in low range
FT: ED	Gold standard, most accurate	Expensive, labor intensive, limited availability
Analog immunoassay	Less expensive, easily accessible	Assay provides lower values, thus requiring different set of reference values
cFT: based on T and SHBG values	Good correlation of some formulas with equilibrium dialysis, less expensive	Needs accurate TT (LC-MS), right formula debated
BT: ammonium-sulfide precipitate	Measures 1–2% FT + 30–35% albumin bound	Expensive, labor intensive, prone to errors
Calculated BT: calculated with TT and SHBG	Less expensive	Same requirements as cFT, overestimates BT

BT = bioavailable testosterone; cFT = calculated free testosterone; ED = equilibrium dialysis; FT = free testosterone; LC-MS = liquid chromatography-mass spectrometry; RIA = radioimmunoassay; T = testosterone; TT = total testosterone.

### Free Testosterone

T circulates in the blood mainly bound to proteins, especially to SHBG. It is widely believed that the SHBG-bound T is not readily available to most tissues, whereas albumin-bound T and FT are bioavailable. Because unbound T readily crosses the cell membrane and bound T does not, many experts consider FT and bioavailable T to be more accurate indicators of androgen status than TT. However, data are lacking to demonstrate that FT or bioavailable T is more strongly associated with TD symptoms than TT.

### Measuring Serum T Levels

It has been recommended that blood samples for diagnosing TD should be obtained in the morning, usually from 8:00 to 11:00 AM, because of the diurnal rhythm of serum T in which values are highest in the early morning. Measurement of T before 11:00 AM is important for men younger than 40 years. However, the diurnal variation of T is attenuated in men older than 40 years,<sup>45</sup> suggesting that an afternoon blood test in these older men is more likely to be accurate. However, diurnal variation can be evident even in elderly men.<sup>44</sup>

Several studies have tried to quantify the risk of over-diagnosing TD in case of late blood sampling. In three large retrospective studies, no influence of draw time on mean TT values was observed until after 2 PM in men older than 45 years.<sup>46–48</sup> After 2 PM T levels decreased by roughly 13%.<sup>49</sup> However, these data have serious limitations because of their retrospective nature, with one study restricted to a population of men with ED<sup>48</sup> and another study with a population of men with predominantly poor health.<sup>47</sup> A morning blood test remains the usual recommendation for TT. It is important to note that there are no data indicating whether morning or afternoon TT values better predict the clinical manifestations of TD or response to TTh. In addition, some investigators have found that T levels are better assessed in the fasting condition.<sup>50</sup>

It is important to note that men presenting with low serum T levels ( $T < 150$  ng/dL) and increased prolactin levels or suppressed luteinizing hormone (LH) and follicle-stimulating hormone levels should undergo pituitary magnetic resonance imaging rule out a pituitary adenoma.<sup>6</sup>

### RECOMMENDATIONS: LABORATORY DIAGNOSIS OF TD

The following investigations are recommended in patients with suspected TD:

- Steps for diagnosis of TD
  - Step 1. Morning determination of TT [LoE = 2, Grade = A].
  - Step 2. In case of a low level (defined as  $TT < 12$  nmol/L or 350 ng/dL), we recommend:
    - Repeating the TT measurement [LoE = 3, Grade = A].
    - Measuring with serum LH and prolactin measurements [LoE = 1, Grade = B].
- In individuals with clinically suspected TD, SHBG levels should be assessed if TT is low to normal or borderline, especially in obese or older men [LoE = 2, Grade = C].

### CONTROVERSY WITH SERUM T THRESHOLD LEVELS

#### Association Between T Levels and Hypogonadal Symptoms

There is no universally agreed threshold for “normal” serum T levels. In addition, there are no generally accepted lower limits of normal TT below which TTh is eventually justified if symptoms of TD are associated.<sup>5</sup> Most routine laboratories do not establish normal T ranges and thus rely on normal ranges provided by the manufacturers of T assay kits. In addition, this principle of a single threshold does not take into account the variability of the sensitivity to circulating T.

TT levels below 200 ng/dL (7 nmol/L) are in most cases associated with impairment of sexual function and nocturnal erections, and the effect of T seems to reach its maximum benefit from levels of at least 350 to 400 ng/dL (12–16 nmol/L).<sup>51</sup> There seems to be a gray zone, from 200 to 400 ng/dL, within which the effect of T on sexual activity might or might not be maximal according to the sensitivity to androgens of the individual.

## RECOMMENDATIONS: THRESHOLD LEVELS FOR BIOCHEMICAL DIAGNOSIS OF TD

There are no generally accepted lower limits of normal TT.

1. Symptomatic men with TT lower than 12 nmol/L or 350 ng/dL should be treated with TTh [LoE = 1, Grade = C].
2. A trial of TTh in symptomatic men with TT higher than 12 nmol/L or 350 ng/dL can be considered based on clinical presentation [LoE = 3, Grade = C].

## INDICATIONS FOR TTH

There are two primary widely considered indications for TTh in adult men with low TT circulating levels. One indication is for the treatment of men with substantially decreased serum T concentrations as a consequence of a significant disruption of the HPG axis, such as after hypophysectomy, or in men with absent or atrophic testes.<sup>6</sup> Lifetime TTh is indicated in these men. A second more common indication is for the treatment of men exhibiting signs or symptoms of TD associated with low circulating TT values irrespective of age.<sup>4,6,7</sup>

A 3- to 6-month trial of empiric TTh can be considered in men with suggestive symptoms but without definitive diagnostic blood test results, because there is no absolute T concentration that reliably distinguishes who will or will not respond to treatment and because of substantial interindividual variations in T physiology.<sup>4,6,7</sup> One study of hypogonadal men undergoing TTh showed similar subjective response rates whether TT was lower than 200 ng/dL, 200 to 300 ng/dL, or higher than 300 ng/dL as long as all men had FT levels lower than 15 pg/mL as measured by radioimmunoassay with a T analog.<sup>52</sup>

## CONTRAINDICATIONS TO TTH

The controversies surrounding TTh in men with TD have been magnified by uncertainty on its safety. The two major concerns are those related to prostate and CV safety.

Contraindications to the use of TTh include the following<sup>6</sup>:

- History of prostate cancer (PCa)
- Breast cancer
- Unevaluated prostate nodule or induration
- Prostate-specific antigen (PSA) higher than 4 ng/mL
- Severe lower urinary tract symptoms (LUTS) associated with benign prostate hyperplasia (BPH) as indicated by an

American Urological Association International Prostate Symptom Score higher than 19

- Hematocrit higher than 50%
- Uncontrolled or poorly controlled congestive heart failure

These historical contraindications must be re-evaluated in light of more recent evidence. Numerous studies have shown no increased PCa progression or recurrence in men after radical prostatectomy, external beam radiation therapy, brachytherapy, and even in small groups of men on active surveillance.<sup>53</sup> Most experts would accept the use of TTh in men with a PSA higher than 4.0 ng/mL as long as the patient has undergone adequate evaluation to exclude the presence of PCa, which will usually require prostate biopsy examination. Several studies have shown improvement in voiding symptoms with TTh,<sup>18,19</sup> in contrast to the historical assumption that increasing T would necessarily cause prostate growth and thus worsen obstructive voiding symptoms.

## SPECIAL CONSIDERATIONS ASSOCIATED WITH TTH

### TTh and PCa

For several decades the greatest concern among physicians regarding the use of TTh has been the risk of PCa.<sup>20</sup> Although androgen deprivation has been proved effective in causing regression of advanced PCa, evidence is lacking to support the contention that increasing serum T is associated with increased PCa risks. A large study of 3,886 men with PCa and 6,448 without PCa showed no increased risk with higher serum T, dihydrotestosterone, or E2.<sup>54</sup> Similarly, the placebo arm of the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial investigated 3,255 men with correlation of prostate biopsy examinations performed at years 2 and 4 with baseline serum T and dihydrotestosterone.<sup>55</sup> Rates of PCa did not correspond with serum androgen concentrations. A meta-analysis of 19 placebo-controlled T studies found no increased risk of PCa in men who received T compared with men who received placebo.<sup>56</sup>

A major advance in explaining why higher T levels do not appear to increase PCa risk was the development of the saturation model, which recognizes that maximal androgenic stimulation of prostate tissue is achieved at relatively low serum T concentrations.<sup>53</sup> Once the threshold for maximal androgen stimulation is reached, further increases in serum androgen concentrations appear to cause little or no additional growth.<sup>57</sup>

Considerable evidence supports the saturation model, with data indicating that the saturation point is approximately 8 nmol/L (250 ng/dL).<sup>53</sup> In a 6-month placebo-controlled T gel study, a significant increase in PSA was noted for those with baseline serum T lower than 250 ng/dL (8.7 nmol/L) but not in men with baseline serum T above this concentration.<sup>58</sup> A similar result was seen in a T registry trial.<sup>59</sup> In an observational study of men presenting to an andrology center, serum PSA increased with increasing serum T until concentrations reached

approximately 8 nmol/L (231 ng/dL), at which point a plateau was reached and there was no further increase in serum PSA even at the highest serum T concentrations.

One of the most controversial topics is the use of TTh in men with TD and a history of PCa. A modest number of case series have shown no apparent increased rate of PCa recurrence or progression with TTh in men after radical prostatectomy<sup>53</sup> or brachytherapy.<sup>60,61</sup> In addition, no PSA increase or cancer progression was noted in a group of 13 men on active surveillance for untreated PCa who received TTh for a mean of 2.5 years.<sup>62</sup> Definitive conclusions regarding the safety of TTh in men with a history of PCa must await larger trials.

## RECOMMENDATIONS: PCA

1. There is no compelling evidence that T treatment increases the risk of developing PCa or that its use is associated with PCa progression [LoE = 1, Grade = C].
2. Men older than 45 years with TD should be informed before treatment that safety data regarding TTh and prostate safety are limited but that current data are reassuring [LoE = 3, Grade = C].
3. Men successfully treated for PCa with confirmed, symptomatic TD are candidates for TTh after a prudent interval (depending on the type of cancer treatment), if there is no evidence of residual cancer [LoE = 3, Grade = C].

## TTh and CV Disease

The possibility that TTh could be associated with increased CV risk initially arose in 2010 based on a 6-month T gel study in elderly frail men that reported 23 CV events in men who received T gel for 6 months compared with five events in men who received placebo.<sup>63</sup> The practical implications of these results were limited by the fact that the large majority of reported “events” were of uncertain clinical significance, including pedal edema, palpitations, syncope, and premature ventricular contractions on electrocardiogram. In addition, the study was not designed to investigate CV risks, and as a result the collection of data regarding events was anecdotal, unsystematic, and unverified.

However, concerns were again raised when two observational studies, one published in November 2013<sup>64</sup> and the other in January 2014,<sup>65</sup> reported increased CV events in men who received T prescriptions. Regulatory agencies in Canada and the United States added warnings regarding CV risks to T product labels. All these events received wide media attention, leading to the impression among health care providers and the public that TTh is associated with CV risks.

However, a careful analysis of these articles and a broader review of the literature failed to support the view that TTh is associated with increased CV risks.<sup>66</sup> In fact, the weight of evidence strongly suggested the very opposite conclusion, namely that TTh can offer CV benefits. Published analysis by the Food and Drug Administration showed only four articles in total

suggesting any concern, with each of these failing to provide convincing evidence of increased risk.<sup>67</sup> In contrast, there is a rich literature of more than 80 studies demonstrating that low values of serum T are associated with increased mortality and atherosclerosis; TTh improves known CV risk factors such as obesity, fat mass, and insulin resistance; and several randomized controlled trials in men with known heart disease (angina, heart failure) have demonstrated improved functional responses in men who received T compared with men who received placebo.<sup>66</sup> It is important to note that after a full investigation, the European Medicines Agency found no consistent evidence of an increased risk of heart problems with TTh.

The study by Vigen et al<sup>64</sup> in November 2013 was a retrospective analysis of data collected from 8,709 men in the Veterans Administration health system who underwent coronary angiography and were found to have T concentrations lower than 300 ng/dL (10.4 nmol/L). They reported that the absolute rate of adverse events (cumulative for myocardial infarction [MI], stroke, and death) at 3 years after angiography was 25.7% for those who received a T prescription compared with 19.9% for untreated men. However, they misreported their results, because the absolute rate of adverse events was actually lower by half (10.1% vs 21.2%) for men who received a T prescription compared with untreated men (10.1% vs 21.2%, respectively).<sup>68</sup> In a correction, they replaced “absolute rate of events” with “Kaplan-Meier estimated cumulative percentages with events.” Their application of a little-known methodology, stabilized inverse propensity weighting, resulted in having each event in the T group count for approximately three events, whereas each event in the untreated group counted as less than one event. In a second correction, they reviewed data for a subgroup of 1,132 men and discovered that nearly 10% were women. Because of these errors, 29 medical societies called for retraction of the article citing “gross data mismanagement” that rendered the study results “no longer credible.”<sup>66</sup>

The study by Finkle et al<sup>65</sup> in January 2014 appeared at first glance to confirm the recently published results reported by Vigen et al.<sup>64</sup> This also was a retrospective analysis of data obtained from a large insurance database. Using only diagnosis codes and prescription data, they reported that of men who received a T prescription, there was a 36% higher rate of non-fatal MI in the 90 days after receipt of a T prescription compared with the 12 months before the prescription. However, there was no control group, so it is unknown whether untreated men with T deficiency would have had a rate of MI that was higher, lower, or the same.

More importantly, the result was based entirely on the ratio of the rate of MI before receiving a prescription to the rate after the prescription; however, as performed by Finkle et al,<sup>65</sup> these rates were unrelated. It is critical to understand that as a retrospective analysis, the data reflected what actually happened, and was not an experimental study. Although it can be reasonably assumed that the post-prescription rate represents a true MI rate, the

period before the prescription measures only the willingness of practitioners to prescribe T to men with a recent history of MI. These two periods measure different things, and it is therefore meaningless to compare them. Perhaps most importantly, actual reported rates after the T prescription were substantially lower than expected using the Heart Attack Risk Calculator provided by the National Institutes of Health.<sup>66</sup>

Thus, it is difficult to conclude from these studies that TTh is associated with increased CV risks. In fact, the studies by Vigen et al<sup>64</sup> and by Finkle et al<sup>65</sup> could be reasonably interpreted as demonstrating decreased CV risks with TTh, because the absolute rate of events was lower in the T group in the study by Vigen et al, and Finkle et al reported unexpectedly low MI rates after a T prescription. Those studies are consistent with studies by Shores et al<sup>69</sup> in a Veterans Administration population and by Muraleedharan et al<sup>70</sup> in a diabetic population that reported that in men with TD mortality was lower by approximately half in T-treated men compared with untreated men. A meta-analysis of 75 placebo-controlled randomized trials found no increased risk of CVD in men receiving TTh, but rather a protective effect of TTh in men with metabolic disorders.<sup>71</sup>

In the absence of a large-scale, long-term study, it must be acknowledged that it is impossible to draw definitive conclusions regarding the CV safety of TTh. Nonetheless, there appears to be no compelling current evidence to suggest that TTh is associated with increased CV risks.<sup>66</sup>

## RECOMMENDATIONS: CV DISEASE

1. The weight of evidence indicates that TTh is not associated with increased CV risk [LoE = 2, Grade = B].
2. Preliminary evidence suggests the possibility of beneficial effects of TTh on CV function [LoE = 2, Grade = B].

## TTh and Male Fertility

TTh can lead to impaired spermatogenesis because T is a natural contraceptive. Men desiring to initiate a pregnancy in the future should be counseled appropriately before beginning TTh. T inhibits gonadotropin-releasing hormone and gonadotropin secretion and thus can cause lead to hypospermatogenesis.<sup>72</sup> Complete inhibition of intratesticular T can result in azoospermia.<sup>73,74</sup> Success rates of recovering spermatogenesis after TTh have been shown with human chorionic gonadotropin (hCG) alone or in combination with human menopausal gonadotropin.<sup>75</sup>

## RECOMMENDATIONS: MALE FERTILITY

1. TTh should not be used in men who are trying to produce a pregnancy [LoE = 2, Grade = A].
2. Exogenous T should not be used in men who are trying to preserve or enhance their fertility because TTh can result in azoospermia [LoE = 2, Grade = B].

3. hCG and human chorionic gonadotropin can be used to recover spermatogenesis and endogenous T production in young men who have abused anabolic steroids in the past [LoE = 3, Grade = C].

## T FORMULATIONS

There are many commercially available T compounds for use in TTh. They differ in their formulations, route of administration, dose and interval to be used (pharmacokinetics), and safety profiles. The most common available preparations to treat male TD are listed in Table 6.

### Oral Formulations

Oral administration of T is easy but T is almost completely inactivated by its first pass through the liver; therefore, it is difficult to achieve sustained blood levels with oral formulations and most are weakly active (eg, mesterolone).<sup>4,76</sup> The 17 $\alpha$ -alkylated derivatives of T (especially methyl T and fluoxymesterone) are more active, but because of potential hepatotoxicity (eg, hepatocellular adenoma, cholestasis, jaundice, and hemorrhagic liver cysts), these formulations should no longer be clinically used.<sup>4,76,77</sup> The only active and safe oral formulation is the T undecanoate, in oleic acid or in a mixture of castor oil and propylene glycol laurate (T undecanoate caps) encapsulated in soft gelatin.

### Buccal Formulation

Transbuccal administration provides absorption of T through the oral mucosa, thus avoiding the intestinal pass and liver inactivation. It is presented as a bio-pellet to be pressed on the gum above the incisor tooth: a buccal film is achieved and should be put between the lower gum and the cheek.<sup>4,77,78</sup> Men treated with 30 mg of the controlled release T buccal formulation (Striant; Auxilium Pharmaceuticals, Inc, Chesterbrook, PA, USA) twice a day compared with a group of patients given 5 mg of T gel formulation daily showed no differences in mean T serum levels.<sup>77,79</sup> Furthermore, its effect on sexual function was comparable when administering injectable T enanthate.<sup>80</sup> Recognized disadvantages are the potential oral irritation, the twice-daily dosing, and the unpleasant taste.<sup>77</sup>

### Transdermal Formulations

T transdermal gel formulations provide stable and normal serum T levels for 24 hours.<sup>81</sup> These formulations tend to be more expensive, carry the risk of transference, and can cause skin irritation.<sup>82,83</sup> Transdermal T preparations are available as skin patches or as hydroalcoholic gel and are designed to deliver 5 to 10 mg of T per day.<sup>4,77,79</sup> They should be used daily and normally provide uniform T serum levels during treatment. Their efficacy and safety are well documented.<sup>4,77,79</sup> Patient compliance with T gels seems much better than with T patches.<sup>4,77,84</sup> After 5 minutes, the gel dries and swimming or showering 2 hours after application does not affect serum T levels. Because gels achieve a

**Table 6.** Differences among available gel preparations

Formulation	Solution	Recommended starting dosage	Recommended application site
AndroGel 1%	Hydroalcoholic solution (carbomer 980, ethyl alcohol 67.0%, isopropyl myristate, purified water, and sodium hydroxide)	40.5 mg (2 pump presses or 2.5-g gel packet)	Upper arm and shoulder
AndroGel 1.62%	Hydroalcoholic solution (Carbopol 980, ethyl alcohol, isopropyl myristate, purified water, and sodium hydroxide)	50 mg (4 pump presses or 5-g gel packet)	Upper arm, shoulder, and stomach
Testim 1% (generic equivalent Vogelxo)	Hydroalcoholic solution (purified water, pentadecalactone, Carbopol, acrylates, propylene glycol, glycerin, polyethylene glycol, ethanol [74%], and tromethamine)	50 mg (1 tube)	Upper arm and shoulder
AXIRON 2%	Hydroalcoholic solution (ethanol, isopropyl alcohol, octisalate, and povidone)	60 mg (2 pump presses)	Axilla
Fortesta gel 2%, Tostrex 2%	Hydroalcoholic solution (propylene glycol, purified water, ethanol, 2-propanol, oleic acid, carbomer 1382, triethanolamine, and butylated hydroxytoluene)	40 mg (4 pump presses)	Thigh

steady-state level within a few days, timing of the application is generally not an issue. Transdermal formulations also have the advantage of flexible dosing, self-administration, and immediate decrease in T serum levels after cessation of treatment.

### Subcutaneous Formulations

Among TTh formulations, T pellets are reliable and a widely recognized delivery system.<sup>4,77,85</sup> A long-lasting option for TD treatment, T pellets were introduced in the United States more than 40 years ago and share some advantages compared with other available therapeutic options: (i) avoidance of the concentration peaks and variations found with injectable treatments; (ii) no risk of drug transference from the patient to others; and (iii) maintenance of a constant therapeutic serum T level. Moreover, the risk profile of the T pellet appears tolerable and similar to those reported for other T formulations.<sup>86</sup> A pharmacokinetic evaluation found that T pellets exert positive effects on serum T levels for approximately 3 to 4 months, followed by a decay.<sup>87</sup> Patient BMI has been found to be a major determinant for a starting dosage: men with a BMI lower than 25 kg/m<sup>2</sup> achieved therapeutic TT levels with fewer than 10 pellets, whereas men with a BMI of at least 25 kg/m<sup>2</sup> required at least 10 pellets to achieve therapeutic TT levels.<sup>86</sup> However, when prescribing pellets, physicians must take into account their relatively increased cost and the inability to control a patient's exogenous T dose once implanted. Furthermore, T pellets are not universally available in all countries.

### Injections (Intramuscular Formulations)

The intramuscular injection of T administered in oily depot is a route very often used. These formulations can be divided into short and long acting.

The more frequently used T injections are short-acting formulations, which are characterized by very similar

pharmacokinetics profiles. T enanthate and T cypionate are generally injected at 200 to 250 mg at intervals of 2 to 4 weeks. T propionate has a much shorter half-life and 50 mg is generally injected every 2 to 3 days.<sup>4,77,85</sup> Other formulations containing an association of T esters can be found in some countries. The short-acting T formulations induce serum peak T levels 2 to 3 days after injection at generally a transient supraphysiologic level. This is followed by an exponential decrease to subphysiologic levels in 10 to 14 days. The long-acting T formulation available (T undecanoate) shows more favorable kinetics than the short-acting ones; in practical terms, a first injection of 750 mg (AVEED; Endo Pharmaceuticals, Malvern, PA, USA) or 1,000 mg (Nebido; Bayer AG, Leverkusen, Germany) of T undecanoate is followed by a second injection 6 weeks afterward (loading dose) and then an injection every 12 weeks.

### RECOMMENDATIONS: T FORMULATIONS

1. Current commercially available preparations of T (with the exception of the 17 $\alpha$ -alkylated ones) are safe and effective [LoE = 1, Grade = A].
2. The treating physician should have sufficient knowledge and adequate understanding of the advantages and drawbacks of each preparation [LoE = 2, Grade = C].
3. The patient should be given the opportunity to actively participate in the choice of T formulation [LoE = 2, Grade = C].

### ALTERNATIVES TO TTH

Many young men with the diagnosis of hypogonadism desire to initiate TTh. However, many of these men are equally concerned about protecting their fertility. Therefore, TTh should be discouraged in these men because exogenous T impairs spermatogenesis. A more appropriate approach in these men is to increase their own endogenous T production.

## Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators (SERMs) inhibit estrogen feedback to the hypothalamus, which in turn results in an increase in the gonadotropins follicle-stimulating hormone and LH. SERMs also selectively modulate receptor subtypes. They are unique in that they are not pure receptor agonists and antagonists but have variable effects depending on the tissue type. Centrally SERMs are antagonists for the estrogen receptors and antagonize the effects of estrogen on the hypothalamus and anterior pituitary.

Clomiphene citrate is a SERM that is commonly used off-label in men to increase endogenous T levels. It is composed of a trans-isomer and a longer acting zu-isomer. Clomiphene citrate is typically administered as 25 or 50 mg daily or every other day. Enclomiphene citrate is a non-steroidal isomer of clomiphene citrate that also results in increased endogenous production of T through inhibition of the hypothalamic-pituitary feedback mechanism. Enclomiphene citrate is a more potent, but shorter-acting, trans-isomer of clomiphene citrate. Dosages for enclomiphene have ranged from 6.25 to 25 mg/d.

## Aromatase Inhibitors

Aromatase inhibitors inhibit the conversion from T to E2. Examples of aromatase inhibitors include anastrozole, testolactone, and letrozole. There have been three randomized placebo-controlled trials assessing the use of 1 mg of anastrozole daily or twice weekly in elderly men.<sup>88–92</sup> After 3 to 12 months, the mean T value increased 123 and 229 ng/dL in the twice-weekly and daily treated groups, respectively. E2 in these studies decreased by 3.7 to 10 pg/mL. Other studies have demonstrated that even after 12 months of treatment with anastrozole, there was no improvement in strength or body composition despite a T increase of 202 ng/dL.<sup>88</sup>

## Human Chorionic Gonadotropin

hCG injections have been shown to increase endogenous serum T levels. hCG is made from the urine of pregnant women or through recombinant technology. It is an LH analog that stimulates Leydig cell production of T and is often administered intramuscularly or subcutaneously from 500 IU every other day to 10,000 IU twice weekly. hCG has been shown to increase T levels to the normal therapeutic range. Tsujimura et al<sup>93</sup> retrospectively analyzed 21 hypogonadal men using hCG injections. All men previously demonstrated a threefold increase in T levels after a stimulation challenge with two separate doses of 10,000 IU of hCG. Smaller doses of 3,000 IU of hCG every 2 weeks over 8 months resulted in only a modest increase in T by 80 ng/dL.

## RECOMMENDATIONS: ALTERNATIVES TO TTH

1. SERMS can be safely used to increase endogenous T levels in hypogonadal men [LoE = 2, Grade = B].

2. Aromatase inhibitors can result in a modest improvement in endogenous serum T levels in hypogonadal men [LoE = 2, Grade = B].
3. Hypogonadal patients should not be treated long term with aromatase inhibitors because of uncertain risks associated with bone health [LoE = 3, Grade = C].
4. hCG can be used to increase endogenous serum T levels in hypogonadal men [LoE = 3, Grade = B].
5. hCG can be used to improve spermatogenesis in men with impaired semen parameters [LoE = 3, Grade = C].

## ADVERSE EVENTS AND MONITORING WITH TTH

Serious adverse side effects secondary to TTh are relatively uncommon. Adverse effects appear to be particularly significant in elderly patients and are often dependent on the method of TTh. Some adverse effects reported with TTh are primarily reported with supraphysiologic levels of T. Often these adverse effects can be minimized or negated altogether by dose adjustment, switching to an alternative form of therapy, or discontinuation of androgen supplementation. Reported adverse effects include:

- Erythrocytosis
- Gynecomastia
- Hepatotoxicity (primarily with oral methylated formulations)
- Acne or oily skin
- Impaired sperm production and fertility
- Edema

Although obstructive sleep apnea is listed as a relative contraindication by most T formulations, there are poor data to support the association between obstructive sleep apnea and TTh. In a review of the literature, Hanafy<sup>94</sup> found only five case reports and one randomized placebo-controlled trial, suggesting that TTh resulted in worsening or development of obstructive sleep apnea.

For decades it has been believed that TTh exacerbates BPH-associated LUTS. Most package inserts of TTh state that clinicians should monitor patients with BPH for worsening of signs and symptoms, and that elderly patients treated with T could be at increased risk for BPH. Recent data suggest that TTh might actually alleviate BPH-associated LUTS. In fact, two meta-analyses reported no increased risk of worsening LUTS (odds ratio = 1.08, CI = 0.46–2.52) or impaired urinary flow (risk ratio = 0.86, CI = 0.13–5.53) with TTh.<sup>56,95</sup> Other studies have shown that TTh alleviates LUTS in men with mild BPH symptoms.<sup>19,96</sup>

## Follow-Up and Monitoring

Patients should be evaluated at 3 months after initiation of TTh and then every 6 to 12 months thereafter to assess serum T levels, symptomatic improvement, PSA and digital rectal exam changes, and changes in hematocrit. Follow-up might be

**Table 7.** Recommendations for the diagnosis and management of testosterone deficiency from the Fourth International Consultation for Sexual Medicine (ICSM 2015)

Recommendations: definition of TD
1. TD is a clinical AND biochemical syndrome associated with age and comorbidities [LoE = 2, Grade = B] and characterized by a deficiency in T AND relevant symptoms.
2. TD can affect the function of multiple organ systems and result in significant detriment in the quality of life, including alterations in sexual function [LoE = 2, Grade = B].
3. TD results from defects at various levels of the HPG axis: abnormality in the testes (primary TD), pituitary or hypothalamic failure (secondary TD), or their combination (mixed TD) [LoE = 1, Grade = A].
4. TD also can result from an impairment of T action because of decreased bioavailability of the hormone (from SHBG variations) or because of androgen receptor alterations that can influence androgen activity [LoE = 2, Grade = A].
5. Clinical manifestations of TD occur because of decreased serum androgen concentrations or activity, regardless of whether there is an identified underlying etiology [LoE = 1, Grade = A].
Recommendations: clinical diagnosis
1. Sexual dysfunction, in particular low sexual desire, decreased nocturnal and morning erections and erectile dysfunction are prominent and often the presenting symptoms, especially suggestive of TD when all 3 are associated [LoE = 1, Grade = A].
2. Decreased physical vigor, decreased energy and motivation, fatigue, depressive mood, and sleep disturbances are often present [LoE = 1, Grade = B].
3. Hot flushes, and sometimes alterations in cognition and memory, can be associated with TD [LoE = 3, Grade = C].
4. Visceral obesity is often observed, and muscle mass and bone mineral density are often decreased [LoE = 1, Grade = A].
5. Features of the physical examination suggestive of TD include small testicles, decreased body hair, and gynecomastia. However, none of these might be present [LoE = 1, Grade = B].
6. Not all manifestations need to be evident simultaneously and their intensity shows marked interindividual variability [LoE = 2, Grade = D].
7. Although the prevalence of TD increases with each decade of life, TD can occur in adult men of all ages [LoE = 1, Grade = B].
Recommendations: routine measurement of T
1. Men presenting with the following conditions should be screened for low T:
a. Sexual symptoms including decreased libido, erectile dysfunction, and decreased frequency of morning erections [LoE = 1, Grade = B].
b. Clinical conditions associated with insulin resistance (obesity, type 2 DM, MetS) should be screened for TD because it is often comorbid [LoE = 2, Grade = B].
c. Infertility [LoE = 2, Grade = B].
d. Osteoporosis and height loss or low trauma fractures likely indicate low T because asymptomatic low T can negatively contribute to these conditions and can be corrected with TTh [LoE = 1, Grade = B].
e. HIV-associated weight loss [LoE = 2, Grade = B].
f. Long-acting opioid use [LoE = 2, Grade = B].
g. High doses of glucocorticoid use [LoE = 1, Grade = B]
2. Screening for low T is not recommended in the absence of TD symptoms in all other populations, although they are potentially associated with an increased prevalence of low T (cardiovascular diseases, chronic pulmonary diseases, end-stage renal diseases, cirrhosis, rheumatoid arthritis, and cancer) because of the lack of evidence of benefit resulting from TTh in non-symptomatic individuals [LoE = 3, Grade = B].
Recommendations: questionnaires to screen for TD
1. Different questionnaires have been proposed to help with screening or diagnosing TD. Most are sensitive but not adequately specific [LoE = 1]. Overall, questionnaires are not recommended as a screening tool for TD because of poor specificity [LoE = 2, Grade = B].
2. Clinical diagnosis of TD should not be based exclusively on questionnaires or structured interviews [LoE = 5, Grade = B].
3. In men with sexual dysfunction, structured interviews such as the AndroTEST showed enough sensitivity and specificity to raise the suspicion of TD [LoE = 2, Grade = B].
Recommendations: laboratory diagnosis of TD
The following investigations are recommended in patients with suspected TD from the relevant symptoms and/or physical signs
1. Steps for diagnosis of TD
Step 1. Morning determination of TT [LoE = 2, Grade = A].
Step 2. For low-level TT (<12 nmol/L, 350 ng/dL, or 3.5 ng/mL), we recommend
Repeating the TT measurement [LoE = 3, Grade = A].
Measuring with serum LH and prolactin [LoE = 1, Grade = B].
2. In individuals clinically suspected of having TD, SHBG levels should be assessed if TT is low to normal or borderline, especially in obese or older men [LoE = 2, Grade = C].

(continued)

Table 7. Continued

Recommendations: threshold levels for biochemical diagnosis of TD
There are no generally accepted lower limits of normal TT.
The ISSM recommends that
1. Symptomatic men with TT < 12 nmol/L or < 350 ng/dL should be treated with TTh [LoE = 1, Grade = C].
2. A trial of TTh in symptomatic men with TT > 12 nmol/L or > 350 ng/dL can be considered based on clinical presentation [LoE = 3, Grade = C].
Recommendations: prostate cancer
1. There is no compelling evidence that T treatment increases the risk of developing prostate cancer or that its use is associated with prostate cancer progression [LoE = 1, Grade = C].
2. Men > 45 y old with TD should be informed before treatment that safety data on TTh and prostate safety are limited but that current data are reassuring [LoE = 3, Grade = C].
3. Men successfully treated for prostate cancer with confirmed symptomatic TD are candidates for TTh, after a prudent interval (depending on type of cancer treatment), if there is no evidence of residual cancer [LoE = 3, Grade = C].
Recommendations: cardiovascular disease
1. The weight of evidence indicates that TTh is not associated with increased cardiovascular risk [LoE = 2, Grade = B].
2. Preliminary evidence suggests the possibility of beneficial effects of TTh on cardiovascular function [LoE = 2, Grade = B].
Recommendations: male fertility
1. TTh should not be used in men who are trying to produce a pregnancy [LoE = 2, Grade = A].
2. Exogenous T should not be used in men who are trying to preserve or enhance their fertility because TTh can result in azoospermia [LoE = 2, Grade = B].
3. hCG and hMG can be used to recover spermatogenesis and endogenous T production in young men who have abused anabolic steroids in the past [LoE = 3, Grade = C].
Recommendations: T formulations
1. Current commercially available preparations of T (with the exception of the 17 $\alpha$ -alkylated preparations) are safe and effective [LoE = 1, Grade = A].
2. The treating physician should have sufficient knowledge and adequate understanding of the advantages and drawbacks of each preparation [LoE = 2, Grade = C].
3. The patient should be given the opportunity to actively participate in the choice of T formulation [LoE = 2, Grade = C].
Recommendations: alternatives to TTh
1. SERMS can be safely used to increase endogenous T levels in hypogonadal men [LoE = 2, Grade = B].
2. AIs can result in a modest improvement in endogenous serum T levels in hypogonadal men [LoE = 2, Grade = B].
3. Hypogonadal patients should not be treated long term with AIs because of uncertain risks associated with bone health [LoE = 3, Grade = C].
4. hCG can be used to increase endogenous serum T levels in hypogonadal men [LoE = 3, Grade = B].
5. hCG can be used to improve spermatogenesis in men with impaired semen parameters [LoE = 3, Grade = C].
Recommendations: adverse events and monitoring
1. Hematocrit levels should be below 54% [LoE = 2, Grade = B].
2. Periodic hematologic assessment is indicated (i) before treatment, (ii) 3, 6, and 12 mo after initiating TTh, and (iii) with dose adjustments and change of preparation [LoE = 2, Grade = B].
3. TTh can be used in men with BPH and TTh might alleviate LUTS [LoE = 3, Grade = C].
4. Currently available preparations are largely free of hepatic toxicity. Liver function studies are not required before onset of therapy [LoE = 2, Grade = A].
5. Monitoring lipids and glycemia is not required for safety but might be required for monitoring the efficacy of other aspects of treatment [LoE = 2, Grade = A].

AI = aromatase inhibitor; BPH = benign prostate hyperplasia; DM = diabetes mellitus; hCG = human chorion gonadotropin; hMG = human menopausal gonadotropin; HPG = hypothalamus-pituitary-testis; ISSM = International Society for Sexual Medicine; LH = luteinizing hormone; LoE = Level of Evidence; LUTS = lower urinary tract symptoms; MetS = metabolic syndrome; SERMS = selective estrogen receptor modulators; T = testosterone; TD = testosterone deficiency; TT = total testosterone; TTh = testosterone therapy.

indicated every 3 months if clinically indicated, such as with suboptimal response to treatment, safety concerns (eg, high or increasing PSA or hematocrit), or other considerations. If a hematocrit level increases to higher than 54%, then the TTh dose can be lowered, or TTh should be discontinued until the hematocrit decreases, or the patient should consider therapeutic

phlebotomy. A patient receiving injectable T might consider switching to another TTh formulation that has a lower risk of erythrocytosis. Repeat dual-energy X-ray absorptiometry is indicated after 1 to 2 years of TTh in hypogonadal men with osteoporosis or low trauma fractures. Patients who report no symptomatic improvement after 3 to 6 months of TTh despite

adequate serum T levels should discontinue TTh. Those patients experiencing symptomatic benefits might attempt periodic trials of discontinuation of TTh to reassess benefits with TTh.

## RECOMMENDATIONS: ADVERSE EVENTS AND MONITORING

1. Hematocrit levels should be below 54% [LoE = 2, Grade = B].
2. Periodic hematologic assessment is indicated (i) before treatment, (ii) 3, 6, and 12 months after initiating TTh, and (iii) with dose adjustments or change of preparation [LoE = 2, Grade = B].
3. TTh can be used in men with BPH and TTh could alleviate LUTS [LoE = 3, Grade = C].
4. Currently available preparations are largely free of hepatic toxicity. Liver function studies are not required before onset of therapy [LoE = 2, Grade = A].
5. Monitoring lipids and glycemia is not required for safety but might be required for monitoring the efficacy of other aspects of treatment [LoE = 2, Grade = A].

## CONCLUSION

Forty-two recommendations on the diagnosis and management of TD were made during the Fourth ICSM (Table 7). Most of these recommendations were supported by LoEs 2 and 3. TD is a clinical and biochemical syndrome associated with age and comorbidities and characterized by a deficiency in T and relevant symptoms. TD results from defects at various levels of the HPG axis: abnormality in the testes (primary TD), pituitary or hypothalamic failure (secondary or tertiary TD), or a combination of the two (mixed TD). Sexual dysfunction, in particular low sexual desire, decreased nocturnal and morning erections, and ED, are prominent and often the presenting symptoms especially suggestive of TD when all three are associated. The laboratory diagnosis of hypogonadism should include two morning T levels. In individuals with moderately low or borderline TT, SHBG levels should be assessed (especially in obese or older men) if alterations of its circulating level are suspected. Symptomatic men with TT lower than 12 nmol/L or 350 ng/dL should be treated with TTh. However, a trial of TTh in symptomatic men with TT higher than 12 nmol/L or 350 ng/dL can be considered based on clinical presentation.

There are several special considerations when treating men with TTh. There is no compelling evidence that T treatment causes PCa or PCa progression. TTh is not associated with markedly increased CV risk and replacement can be advocated on conventional established clinical grounds. In fact, preliminary evidence suggests the possibility of beneficial effects of TTh on CV function. TTh should not be used in men who are trying to produce a pregnancy.

Current commercially available preparations of T (with the exception of the 17 $\alpha$ -alkylated ones) are safe and effective.

In addition, SERMS and hCG can be safely used to increase endogenous T levels in hypogonadal men.

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*Conflicts of Interest:* M.H. has served as a consultant for Abbvie, Lipocine, Repros, Boston Scientific, and Coloplast. A.M. has affiliations with Besins Healthcare, Endo Pharmaceuticals, Pfizer Inc, Repros, Abbvie, Bayer Pharma, BioTE, Akashi Therapeutics, Inc, Aytu Bioscience, Inc, Tolmar Pharmaceuticals Inc, and American Medical Systems. A.M. has affiliations with Pfizer Inc, Endo Pharmaceuticals, Repros, Tolmar Pharmaceuticals, Inc, Antares, Mero Biopharma, and Lipocine. S.C. has affiliations with Astellas, Sanofi, Pfizer Inc, Janssen, Milan, Repros, Boston Scientific, and Eli Lilly. K.H. has affiliations with Astellas, Janssen-Cilag, Amgen, and Recordati. The other authors report no conflicts of interest.

*Funding Sources:* None.

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