THE JOURNAL OF
SEXUAL MEDICINE

ORIGINAL RESEARCH

Testosterone Deficiency: A Review and Comparison of Current Guidelines

Jethro C. C. Kwong, BMSc,[1] Yonah Krakowsky, MD,[2] and Ethan Grober, MD[2]

ABSTRACT

Background: There is much controversy regarding the appropriate evaluation and management of testosterone deficiency (TD).

Aim: To compare current guidelines on the evaluation and management of TD to provide clarity for patients and clinicians, as well as to highlight areas of controversy.

Methods: A literature search of MEDLINE, Embase, Cochrane Library, and various association websites was performed to identify guidelines for TD.

Outcomes: Key aspects in the approach were compared, with a focus on the biochemical definition (cutoff) for low testosterone (T), principles of management, and recommendations for testosterone therapy (TTh) in special patient populations.

Results: Guidelines from the Canadian Medical Association Journal, American Urological Association, European Association of Urology, Endocrine Society, International Society for Sexual Medicine, and British Society for Sexual Medicine were included for review. Recommendations were generally consistent across guidelines. Key differences include the biochemical cutoff for low T, and recommendations for patients with low to normal T, prostate cancer, or cardiovascular disease. We highlight several case scenarios in which management differs depending on the guideline adopted.

Clinical Implications: Although general diagnostic and management principles are in agreement across the guidelines, notable differences may impact patient diagnosis and eligibility for TTh.

Strengths & Limitations: Only guidelines written in English were included. The quality of the included guidelines was not evaluated, but this was beyond the scope of this review.

Conclusion: We highlight the limitations of relying exclusively on guidelines in managing patients with TD. **Kwong JCC, Krakowsky Y, Grober E. Testosterone Deficiency: A Review and Comparison of Current Guidelines. J Sex Med 2019;XX:XXX–XXX.**

Key Words: Testosterone Deficiency; Male Hypogonadism; Testosterone Therapy; Prostate Cancer; Cardiovascular Disease; Low to Normal Testosterone

INTRODUCTION

Testosterone deficiency (TD) is a clinical and biochemical syndrome characterized by low levels of testosterone (T) with associated signs and symptoms. This condition can have a profound impact on a patient's quality of life.[1] The estimated prevalence of symptomatic TD is 2.1% overall and increases with age, reaching 5.1% for men age 70–79 years.[2]

The diagnosis and management of TD remain controversial owing to concerns regarding the development of prostate cancer (PCa) and cardiovascular events and the identification of appropriate candidates for therapy. Despite this, there has been a surge in the use of testosterone therapy (TTh), as evidenced by a 3-fold increase in the United States[3], a 90% increase in Europe over the last decade,[4] and a 4.5-fold increase over the last 20 years in Australia.[5] In an attempt to provide clarity for patients and practitioners, a number of panels from North America and Europe have released guidelines for the diagnosis and management of TD. The aims of the present review were to highlight the similarities and differences in recommendations among the available guidelines and to demonstrate the practical implications of using guidelines for TD management in clinical practice.

Received January 16, 2019. Accepted March 18, 2019.

[1]Faculty of Medicine, University of Toronto, Toronto, ON, Canada;

[2]Division of Urology, Department of Surgery, University of Toronto, Women's College Hospital and Sinai Health System, Toronto, ON, Canada

https://doi.org/10.1016/j.jsxm.2019.03.262

Table 1. Current guidelines for the diagnosis and management of TD

	Topic	ISSM (2015)	CMAJ (2015)	BSSM (2017)	AUA (2018)	ES (2018)	EAU (2018)
Evaluation	Definition of TD	Signs and symptoms of TD with low TT					
	Biochemical cutoff for low TT	<231 ng/dL (<8 nmol/L); 2 measurements	No specific cutoff; 1 measurement	<231 ng/dL (<8 nmol/L); 2 measurements	<300 ng/dL (<10.4 nmol/L); 2 measurements	<264 ng/dL (<9.2 nmol/L); 2 measurements	<231 ng/dL (<8 nmol/L); 2 measurements
Management	Principles of management	Symptomatic improvement with minimal side effects. Include lifestyle modifications and optimize comorbidities. Consider contraindications to TTh. Shared decision making in selecting appropriate formulation.					
	Target T range for TTh	Mid-normal	404–505 ng/dL (14–17.5 nmol/L)	433–865 ng/dL (15–30 nmol/L)	450–600 ng/dL (15.6–20.8 nmol/L)	350–600 ng/dL (14.1–24.5 nmol/L)	Mid-normal
	Contraindications to TTh	Desire to have children; current or history of PCa, polycythemia, erythrocytosis; male breast cancer; untreated severe OSA; uncontrolled life-threatening condition	Desire to have children; high risk for recurrent PCa; metastatic PCa; Male breast cancer; no improvement despite adequate TTh trial	Desire to have children; locally advanced or metastatic PCa; NYHA class IV heart failure; Hct >54%; male breast cancer; untreated severe OSA; severe LUTS (IPSS >19)	Desire to have children; within 3–6 mo after cardiovascular event; no improvement despite adequate TTh trial	Desire to have children; history of PCa; prostate nodule, induration; PSA >4 ng/mL or >3 ng/mL in high-risk patients; uncontrolled heart failure, MI, stroke in last 6 mo; Hct >48%, thrombophilia; male breast cancer; untreated severe OSA; severe LUTS (IPSS >19)	Desire to have children; locally advanced or metastatic PCa; NYHA class IV heart failure; Hct >54%; male breast cancer; no improvement despite adequate TTh trial
	Follow-up monitoring	T: 3, 6, and 12 mo, annually Hct: 3, 6, and 12 mo, annually PSA: 3, 6, and 12 mo, annually Lipid profile: 3, 6, and 12 mo, annually	T: 3 and 6 mo, annually Hct: 3 and 6 mo, annually PSA: 3 and 6 mo, annually DRE: 6 mo, annually	T: 3, 6, and 12 mo, annually Hct: 3, 6, and 12 mo, annually PSA: 3, 6, and 12 mo, annually	T: every 6–12 mo	T: 3–6 mo, 12 mo, annually Hct: 3–6 mo, 12 mo, annually PSA: 3–12 mo, then follow prostate screening guidelines Urology consult if PSA >1.4 ng/mL above baseline, PSA >4.0 ng/mL, or abnormal DRE within first 12 mo of TTh	T: 3, 6, and 12 mo, annually Hct: 3, 6, and 12 mo, annually PSA: 3, 6, and 12 mo, annually

(continued)

Table 1. Continued

	Topic	ISSM (2015)	CMAJ (2015)	BSSM (2017)	AUA (2018)	ES (2018)	EAU (2018)
Special populations	Low-to-normal TT	Measure LH, SHBG, and PRL; trial of TTh for 6–12 mo if symptomatic	Trial of TTh for 3 mo if symptomatic	Measure FT, LH, FSH, SHBG, and PRL; trial of TTh for 6 mo if symptomatic	Further hormonal evaluation	Measure FT	Measure FT
	Prostate cancer	Case-by-case basis	Recommend TTh: treated localized PCa with no active disease Against TTh: metastatic PCa; high risk for recurrent PCa	Recommend TTh: Treated localized PCa with no active disease; must be low-risk for recurrent PCa Against TTh: metastatic PCa; locally advanced PCa	Case-by-case basis	Against TTh: history of PCa; palpable prostate nodule, induration; PSA >4 ng/mL or >3 ng/mL in high-risk patients	Recommend TTh: Treated localized PCa with no active disease; brachytherapy or external beam radiation therapy for low-risk PCa; must be low risk for recurrent PCa Against TTh: metastatic PCa; locally advanced PCa
	Cardiovascular disease	Insufficient evidence linking TTh and CVD risk	Insufficient evidence linking TTh and CVD risk Recommend TTh: stable CVD	Insufficient evidence linking TTh and CVD risk Against TTh: NYHA class IV heart failure; Hct >54%	Low T increases CVD risk Against TTh: within 3–6 mo after cardiovascular event	Insufficient evidence linking TTh and CVD risk Against TTh: Hct >48%	Insufficient evidence linking TTh and CVD risk Against TTh: NYHA class IV heart failure; Hct >54%

AUA = American Urological Association; BSSM = British Society for Sexual Medicine; CMAJ = Canadian Medical Association Journal; CVD = cardiovascular disease; DRE = digital rectal exam; EAU, European Association of Urology; ES = Endocrine Society; FSH = follicle-stimulating hormone; FT = free testosterone; Hct = hematocrit; IPSS = International Prostate Symptom Score; ISSM = International Society for Sexual Medicine; MI = myocardial infarction; NYHA = New York Heart Association; LH = luteinizing hormone; LUTS = lower urinary tract symptoms; OSA = obstructive sleep apnea; PCa = prostate cancer; PRL = prolactin; PSA = prostate-specific antigen; SHBG = sex hormone–binding globulin; T = testosterone; TD = testosterone deficiency; TT = total testosterone; TTh = testosterone therapy.

MATERIALS AND METHODS

We conducted a literature search in Ovid MEDLINE, Embase, and the Cochrane Library for guidelines published after January 2010. Key search terms included "testosterone deficiency," "male hypogonadism," and "guidelines." In addition, we conducted a manual search of the websites of major professional organizations. Only guidelines that provided evidence-based recommendations using levels of evidence or GRADE (Grading of Recommendations, Assessment, Development and Evaluation) were included. For organizations with multiple iterations of guidelines, the most recent version was used.

Guidelines that met our inclusion criteria were compared in terms of diagnosis, management, and special considerations for specific patient populations with TD. Diagnosis included a definition of TD and a biochemical cutoff for low T. For management, we compared principles of management, target therapeutic range for TTh, contraindications to TTh, and follow-up monitoring. We also examined recommendations for patients with low to normal total T (TT), PCa, or cardiovascular disease (CVD).

RESULTS

The initial search yielded 25 articles, of which 4 met our inclusion criteria. Two additional articles were included from websites of major professional organizations. A total of 6 clinical practice guidelines from the following organizations were selected for full text review: Canadian Medical Association Journal (CMAJ; 2015),[6] International Society for Sexual Medicine (ISSM; 2015),[7] British Society for Sexual Medicine (BSSM; 2017),[8] American Urological Association (AUA; 2018),[9] European Association of Urology (EAU 2018),[10] and the Endocrine Society (ES; 2018).[11] These guidelines are summarized in Table 1.

Definition of TD

The formal definition of TD was consistent across all guidelines and included abnormal clinical findings and biochemistry. Signs and symptoms of TD include impacts on physical, cognitive, and sexual function, sleep, and affect. Low TT is used to support the diagnosis of TD.

Biochemical Cutoff for Low TT

Although all guidelines recommend using TT as part of the initial diagnostic workup, there were notable differences in the biochemical cutoff for low TT. The AUA recommends 2 separate morning measurements with a cutoff of <300 ng/dL (<10.4 nmol/L). The EAU also suggests 2 measurements made between 7:00 and 11:00 AM, ideally in the fasting state, with a cutoff of <231 ng/dL (<8 nmol/L). The BSSM recommends two measurements obtained between 8:00 and 11:00 AM 4 weeks apart, with a cutoff of <231 ng/dL (<8 nmol/L). Similarly, the ISSM suggests 2 measurements obtained between 8:00 AM and 12:00 noon at least 1 week apart, with a cutoff of <231 ng/dL (<8 nmol/L). The ES recommends 2 morning measurements in the fasting state, with a cutoff of <264 ng/dL (<9.2 nmol/L). In contrast, the CMAJ calls for only 1 measurement obtained between 7:00 and 11:00 AM or less than 3 hours after waking for shift workers, with no specific cutoff.

All guidelines agree that liquid chromatography/mass spectrometry (LCMS) is the gold standard for TT measurement but also recognize that this might not be feasible at every institution. The CMAJ, BSSM, ES, and EAU recommend the use of validated immunoassays if LCMS is not available. The ES specifies the use of a harmonized reference range for immunoassays certified by the Centers for Disease Control and Prevention Hormone Standardization Program for Testosterone. In contrast, the EAU recommends using laboratory-specific references ranges, whereas the AUA and BSSM advise using the absolute TT value.

Principles of Management and Therapeutic T Range

The treatment goal for patients on TTh is symptomatic improvement with minimal side effects. Most guidelines recommend lifestyle modifications, including weight loss and optimizing management of comorbidities, as first-line treatment. Although all guidelines aim for a mid-normal T range with pharmacotherapy, a few subtle differences should be noted, including AUA, 450−600 ng/dL (15.6−20.8 nmol/L); BSSM, 433−865 ng/dL (15−30 nmol/L); CMAJ, 404−505 ng/dL (14−17.5 nmol/L); and ES, 350−600 ng/dL (14.1−24.5 nmol/L). All guidelines share similar contraindications to TTh, notably the desire to have children and male breast cancer, and advocate for shared decision making with patients to select the appropriate T formulation after consideration of safety, efficacy, patient preference, product availability, and cost. Only the BSSM and ISSM specify a minimal treatment duration of 6 months; however, there is consensus that TTh should be discontinued if there is no improvement in symptoms despite an adequate therapeutic trial.

Recommendations for Patients with Low to Normal TT

There are significant variations in the recommendations for patients with low to normal TT, ranging from further hormonal evaluation to initiation of a trial of TTh. Whereas the AUA (low to normal TT: >300 ng/dL [>10.4 nmol/L]) recommends a comprehensive panel of investigations guided by the clinical findings, the EAU (low to normal TT: 231−346 ng/dL [8−12 nmol/L]) and ES (low to normal TT: 200−400 ng/dL [6.9−13.9 nmol/L]) specifically recommend free testosterone (FT) as the next investigation of choice. In contrast, the CMAJ (low to normal TT unspecified), ISSM (low to normal TT: 231−346 ng/dL [8−12 nmol/L]), and BSSM (low to normal TT: 231−346 ng/dL [8−12 nmol/L]) recommend initiating a trial of TTh for 3 months, 6−12 months, and 6 months, respectively. In addition, the ISSM suggests measuring

luteinizing hormone (LH), sex hormone—binding globulin (SHBG), and prolactin (PRL). Similarly, the BSSM recommends further workup of FT, LH, follicle-stimulating hormone (FSH), SHBG, and PRL.

Recommendations for Patients with Prostate Cancer

Most guidelines recommend against TTh in patients with metastatic or locally advanced PCa and in patients at high risk for recurrent PCa. The ES has the strictest guidelines, advising against TTh in patients with an unevaluated prostate nodule, PSA >4 ng/mL, or PSA >3 ng/mL in high-risk patients (i.e., African Americans or first-degree relative with PCa). Only the AUA and ISSM recommend offering TTh on a case-by-case basis for all patients with PCa. Patients treated for localized PCa with no evidence of active disease (eg, measurable PSA, abnormal digital rectal examination [DRE] findings, evidence of bone or visceral metastases) are candidates for TTh under the CMAJ, EAU, and BSSM guidelines. However, an additional caveat for the EAU and BSSM guidelines is that there must be a low risk for recurrent PCa (eg, Gleason score <8, pT1-2, preoperative PSA <10 ng/mL). The EAU also recommends TTh in patients treated with brachytherapy or external-beam radiation therapy for low-risk PCa.

Recommendations for Patients with CVD

All the current guidelines state that there is insufficient evidence linking TTh with the risk of CVD, although the AUA guideline notes that low T may be associated with an increased risk of myocardial infarction, stroke, and cardiovascular-related mortality. However, TTh is contraindicated in patients who had a cardiovascular event within the past 3—6 months. The CMAJ guideline supports the use of TTh in patients with stable CVD. Several guidelines recommend against TTh in patients with elevated hematocrit: ES, >48% and EAU and BSSM, >54%. In addition, TTh is contraindicated in patients with New York Heart Association (NYHA) class IV heart failure under the EAU and BSSM guidelines.

Follow-Up Monitoring

There is strong agreement among the evaluated guidelines in terms of recommendations for follow-up monitoring. The consensus panel of investigations includes TT, hematocrit, and PSA at varying intervals. Most groups advise checking these levels at 3, 6, and 12 months and then annually thereafter. In addition, the ISSM and CMAJ recommend regular lipid monitoring and DRE, respectively. The ES also recommends a urologic consultation for patients with PSA >1.4 ng/mL above baseline, PSA >4.0 ng/mL, or abnormal DRE results within first 12 months of TTh. In contrast, the AUA does not recommend any other laboratory testing beyond serial TT measurements every 6—12 months.

DISCUSSION

This review highlights and contrasts the current guidelines for the diagnosis and management of TD. Despite a general consensus, differences were evident in the biochemical cutoff for low TT, target T range for TTh, and follow-up monitoring. Recommendations varied considerably for special patient populations, namely those with low to normal TT, PCa, or CVD. Importantly, these differences can significantly impact the diagnosis and eligibility for TTh. These discrepancies may be attributed to the availability of T formulations within each region, time of guideline publication relative to available scientific evidence, influences of healthcare and insurance funding models, and potential bias among guideline committee members.

The variation in low TT cutoffs and studies supporting these values is quite striking. The BSSM and ISSM cutoffs are based on a cross-sectional cohort study (age 50—86 years) conducted by Zitzmann et al,[12] who reported a significantly increased prevalence of erectile dysfunction at a TT level <231 ng/dL (8 nmol/L), with other symptoms occurring at a TT level <433 ng/dL (15 nmol/L). The ES cutoff is the 2.5th percentile value of a harmonized reference range for healthy nonobese men (age 19—30 years) based on 100 men from each of 4 cohorts: the Framingham Heart Study, European Male Aging Study, Osteoporotic Fractures in Men Study, and Male Sibling Study of Osteoporosis.[13] The EAU cutoff is based on a survey of middle-aged men (age 40—79 years) by Wu et al[2] that found an increased probability of symptoms with lower TT levels, with diminished libido at 231 ng/dL (8 nmol/L) and other symptoms at higher thresholds.[2] The AUA cutoff is based on their meta-analysis of randomized controlled trials (RCTs) with morning TT<350 ng/dL as the inclusion criterion, with a median baseline TT of 249 ng/dL and an interquartile range of 233—283 ng/dL.[9]

The attitudes toward monitoring lipid profiles at follow-up have evolved over the years. The ISSM includes several studies demonstrating improvement in the metabolic syndrome following normalization of TT,[14,15] and uses lipid profile values to monitor improvement in dyslipidemia. While the BSSM and EAU acknowledge that these benefits may occur, they do not mandate testing for safety. The CMAJ and AUA reference 5 randomized trials and several meta-analyses, respectively, to conclude that the effects of TTh on lipid profiles are inconclusive and thus there is no added value of lipid profile monitoring. Interestingly, the ES offers no recommendation for this topic.

The role of T in the development and propagation of PCa has been controversial since Huggins and Hodges[16] first described a link between PCa and T in 1941. The Saturation Model, initially described by Morgentaler and Traish,[17] postulates that androgen

Table 2. Management of TD in selected clinical scenarios

Clinical scenario	ISSM (2015)	CMAJ (2015)	BSSM (2017)	AUA (2018)	ES (2018)	EAU (2018)
1. Low to normal TT: Mr. A with symptomatic TD and 2 measurements of TT = 288 ng/dL (10 nmol/L)	Use caution	Initiate TTh	Use caution	Initiate TTh	Use caution	Use caution
2. Prostate cancer: Mr. B with symptomatic TD and 2 measurements of TT = 215 ng/dL (7.5 nmol/L), previously treated with radical prostatectomy for a pT1, Gleason score 7 PCa with a preoperative PSA of 12 ng/mL	No treatment	Initiate TTh	Use caution	No treatment	Use caution	Use caution
3. Cardiovascular disease: Mr. C with symptomatic TD and 2 measurements of TT = 220 ng/dL (7.6 nmol/L), previous myocardial infarction 4 mo earlier	Initiate TTh	Initiate TTh	Initiate TTh	Use caution	Initiate TTh	Initiate TTh
4. Single TT measurement: Mr. D with symptomatic TD and 1 measurement of TT = 190 ng/dL (6.6 nmol/L)	Use caution	Initiate TTh	Use caution	Use caution	Use caution	Use caution
5. Symptomatic but normal TT: Mr. E, a 27-year-old patient with severe symptoms of TD but 2 measurements of TT = 360 ng/dL (12.5 nmol/L)	Use caution	Initiate TTh	Use caution	No treatment	Use caution	Use caution

AUA = American Urological Association; BSSM = British Society for Sexual Medicine; CMAJ = Canadian Medical Association Journal; EAU = European Association of Urology; ES = Endocrine Society; ISSM = International Society for Sexual Medicine; PCa = prostate cancer; PSA = prostate-specific antigen; TD = testosterone deficiency; TT = total testosterone.

Initiate TTh | Use caution | No treatment

receptors within the prostate are saturated at relatively low levels of T, and thus T supplementation above the saturation threshold does not appear to fuel PCa growth. Over the past 2 decades, accumulating evidence has continued to support this model,[18] and studies have demonstrated the safety of TTh in men after radical prostatectomy,[19] after radiation therapy,[20] and during active surveillance.[21]

Reflecting a conservative approach, clinical practice guidelines and physician attitudes have lagged slightly behind the scientific evidence. Guidelines published in the early 2000s still advised against initiating TTh in men with PCa.[22–24] In an international survey on TD management, >50% of physicians surveyed in 2006 and 2010 expressed concerns regarding the development of PCa.[25] Although recent evidence has influenced the paradigm of offering TTh to selected patients with PCa, current guidelines still reflect this controversy, as evidenced by a lack of consistent recommendations. The ES guideline acknowledges data supporting the safety and efficacy of TTh following radical prostatectomy for organ-confined disease[26] but errs on the side of caution owing to the lack of RCTs on this topic. Similarly, the BSSM and EAU mention the lack of RCTs and cite other studies, including a case report of an 80-year-old patient with localized PCa (Gleason 4+3, stage pT1c) who was safely treated with TTh following iatrogenic TD from androgen deprivation therapy.[27] How these studies support their recommendations against TTh in patients with locally advanced PCa is unclear, however. The CMAJ recognizes that studies have demonstrated a lack of association among TTh, biochemical recurrence, and progression of PCa but nonetheless includes contraindications to TTh based on the 2010 ES and 2012 EAU guidelines. In contrast, the ISSM and AUA recommendations for TTh are expert opinions based on recent evidence supporting the Saturation Model. Overall, these discrepancies in recommendations appear to be largely related to philosophical differences and opposing stances with respect to the Saturation Model.

Patients with CVD represent another group that has been subject to a firestorm of controversy. Initial studies suggested that low levels of endogenous T are associated with an increased risk of atherosclerosis[28,29]; however, a 2013 observational study reported a 25.7% rate of adverse cardiovascular events at 3 years in patients receiving TTh, compared with 19.9% in the untreated group.[30] Although that study has been seriously challenged owing to its several methodologic errors, subsequent work has shown a mixed picture; some studies suggest that TTh may be cardioprotective,[31–33] whereas others suggest a correlation with an increased risk of CVD.[34–37] Current recommendations for this patient group reflect these contemporary studies by acknowledging the insufficient evidence linking TTh with the risk of CVD and thus are based largely on expert opinion. For instance, the AUA recommendation against TTh within 3–6 months of a cardiovascular event is based on the expert opinion from a previous review due to the uncertainty of CVD risk[38] and 2 trials in which patients with a cardiovascular event within 3 months of the studies were excluded.[34,39] Why these time cutoffs were chosen is unclear, however. The BSSM and EAU recommendations against TTh in patients with NYHA class IV heart failure are based on 2 trials in which exacerbation of heart failure was documented as an adverse event in the treatment groups. In the first trial, 1 patient in the TTh group (10%) was hospitalized for "breathlessness" 8 weeks into the treatment.[40] In the second trial, 2 patients in the TTh group (5.4%) experienced exacerbation of heart failure, although 2 patients in the placebo group

(5.1%) experienced the same adverse event.[41] However, the BSSM and EAU have not explained how these findings support their decision to use NYHA class IV as a contraindication, but not NYHA class III. It is interesting to note that despite the lack of a clear causal relationship between TTh and CVD, several guidelines include such caveats against TTh.

This review also reveals several gaps in our current understanding of TD, which are described in greater detail in the AUA guideline. The role of FT in aiding the diagnosis of TD remains a subject of debate. The BSSM, AUA, ES, and EAU guidelines recommend FT as an adjunctive test in the setting of low to normal TT. In contrast, the ES guideline lists additional conditions that alter SHBG levels where FT measurement may be beneficial. Furthermore, the long-term adverse events of TD and TTh are unknown. As such, there are currently no evidence-based recommendations on the maximum duration of therapy and the age at which TTh should be discontinued.

The following are some clinical scenarios that highlight how diagnosis and management may differ depending on the guidelines used (Table 2):

- Case 1: Mr. A, with symptomatic TD and 2 measurements of TT = 288 ng/dL (10 nmol/L). This patient meets the biochemical cutoff for low TT under the AUA guideline and thus may be eligible for TTh. Because the CMAJ guideline has no specific cutoff, Mr. A also may be a candidate for TTh under this guideline. In all other guidelines, further hormonal evaluation is warranted, because his TT level is classified as low to normal, and thus he is at risk of being denied TTh. The ISSM recommends measuring LH, SHBG, and PRL, whereas the BSSM recommends measuring FT, LH, FSH, SHBG, and PRL. Both the ES and EAU suggest measuring FT.
- Case 2: Mr. B, with symptomatic TD and 2 measurements of TT = 215 ng/dL (7.5 nmol/L), previously treated with radical prostatectomy for a pT1, Gleason Score 7 PCa with a pre-operative PSA of 12 ng/mL. This patient might not be a candidate for TTh according to the EAU, BSSM, and ES guidelines. However, he is eligible under the CMAJ guideline and would be considered on a case-by-case basis under the AUA and ISSM guidelines.
- Case 3: Mr. C, with symptomatic TD and 2 measurements of TT = 220 ng/dL (7.6 nmol/L), who sustained a myocardial infarction 4 months earlier. The AUA guideline specifically recommends against TTh for up to 6 months after a cardiovascular event. In contrast, TTh would be considered for Mr. C under the CMAJ, EAU, ES, ISSM, and BSSM guidelines. If his cardiac health progresses to NYHA class IV heart failure, he may no longer be a candidate for TTh according to the EAU and BSSM guidelines.
- Case 4: Mr. D, with symptomatic TD and 1 measurement of TT = 190 ng/dL (6.6 nmol/L). Owing to the requirement for 2 TT measurements in most guidelines, this patient is at serious risk of being denied TTh at this visit until he completes his repeat TT. He is eligible for TTh only under the CMAJ guideline.
- Case 5: Mr. E, a 27-year-old patient with severe TD symptoms but 2 measurements of TT = 360 ng/dL (12.5 nmol/L). Considering this patient's age, there is consensus among the guidelines to first ascertain his desire for children, which is an absolute contraindication for TTh. The challenge with this patient is that he does not meet all the criteria for TD because of his normal TT level. As such, the ISSM guideline states that TTh is not indicated, and other causes must be ruled out. The AUA guideline recommends using clinical judgment and additional testing where applicable (FT, LH, FSH, hemoglobin A1c, PRL, estradiol, pituitary magnetic resonance imaging, bone densitometry, karyotype, and hematocrit) to support the use of TTh. The EAU, ES, and BSSM guidelines recommend measuring FT and considering other causes of the patient's symptoms, such as HIV or conditions that increase SHBG concentrations. The ES guideline further specifies that the diagnosis of TD is confirmed by low FT despite normal TT; however, an FT cutoff value is not provided. In contrast, the BSSM guideline includes a FT cutoff of <65 pg/mL (<225 pmol/L) as an indication for TTh. The CMAJ guideline recommends a 3-month trial of TTh after other causes have been ruled out and suggests monitoring the response to TTh to support the diagnosis of TD.

Finally, it is important to highlight that the product inserts of many commercially available T agents include statements and recommendations that are in stark contrast to many of the presented guidelines. Regulators like the US Food and Drug Administration and Health Canada may be more conservative and slow to change, particularly in relation to such "hot button" patient safety issues as PCa and CVD.[42] This discrepancy adds another source of confusion when interpreting and practicing according to published guidelines. For example, a patient with PCa may be a candidate for TTh under the AUA guideline but might not qualify for therapy according to the product insert. Therefore, additional advocacy is needed to ensure that product information is consistent with the latest clinical evidence.

This study must be interpreted within the context of its limitations. First, our initial search results might have been limited by our search strategy. However, we mitigated this issue by performing a comprehensive manual search of association websites for additional guidelines. Second, only guidelines written in English were included, and those written in other languages were excluded from our review. Finally, we did not assess the quality of the guidelines with validated tools, such as the Appraisal of Guidelines for Research and Evaluation II (AGREE-II) instrument, because this was beyond the scope of this review.

CONCLUSION

With increasing popularity of TTh, many professional organizations have developed clinical practice guidelines for the diagnostic evaluation and management of TD. The CMAJ, AUA, EAU, ES, ISSM, and BSSM have provided considerable

consensus in the approach to TD; however, we have highlighted notable differences in which diagnosis of TD and eligibility for TTh may vary depending on the guidelines used. These variations in approach may be attributed to differences in T formulation availability, time of publication, funding models across healthcare systems, and philosophical differences in the workup of TD. The presented guidelines are not without shortcomings and controversies, as shown in our clinical scenarios. Although they are helpful, their current state leaves much to be desired. Therefore, we encourage careful clinical judgement of each patient rather than strict adherence to guidelines.

Corresponding Author: Ethan Grober, MD, Mount Sinai Hospital, Sinai Health System, 600 University Avenue, Toronto, ON, Canada M5G 1X5. Tel: +1 (416) 586-4800, ext. 5374; E-mail: Ethan.Grober@sinaihealthsystem.ca

Conflicts of interest: The authors report no conflicts of interest.

Funding: None.

STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design
Jethro C.C. Kwong; Yonah Krakowsky; Ethan Grober
(b) Acquisition of Data
Jethro C.C. Kwong
(c) Analysis and Interpretation of Data
Jethro C.C. Kwong; Yonah Krakowsky; Ethan Grober

Category 2

(a) Drafting the Article
Jethro C.C. Kwong
(b) Revising It for Intellectual Content
Jethro C.C. Kwong; Yonah Krakowsky; EthanGrober

Category 3

(a) Final Approval of the Completed Article
Jethro C.C. Kwong; Yonah Krakowsky; Ethan Grober

REFERENCES

1. Buvat J, Maggi M, Guay A, et al. Testosterone deficiency in men: Systematic review and standard operating procedures for diagnosis and treatment. **J Sex Med 2013;10:245-284.**
2. Wu FCW, Tajar A, Beynon JM, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. **N Engl J Med 2010;363:123-135.**
3. Baillargeon J, Urban RJ, Ottenbacher KJ, et al. Trends in androgen prescribing in the United States, 2001 to 2011. **JAMA Intern Med 2013;173:1465.**
4. Gan EH, Pattman S, H S Pearce S, et al. A UK epidemic of testosterone prescribing, 2001-2010. **Clin Endocrinol (Oxf) 2013;79:564-570.**
5. Handelsman DJ. Trends and regional differences in testosterone prescribing in Australia, 1991-2001. **Med J Aust 2004; 181:419-422.**
6. Morales A, Bebb RA, Manjoo P, et al. Diagnosis and management of testosterone deficiency syndrome in men: Clinical practice guideline. **CMAJ 2015;187:1369-1377.**
7. Dean JD, McMahon CG, Guay AT, et al. The International Society for Sexual Medicine's Process of Care for the Assessment and Management of Testosterone Deficiency in Adult Men. **J Sex Med 2015;12:1660-1686.**
8. Hackett G, Kirby M, Edwards D, et al. British Society for Sexual Medicine Guidelines on Adult Testosterone Deficiency, with statements for UK practice. **J Sex Med 2017;14:1504-1523.**
9. Mulhall JP, Trost LW, Brannigan RE, et al. Evaluation and management of testosterone deficiency: AUA guideline. **J Urol 2018;200:423-432.**
10. Dohle GR, Arver S, Bettocchi C, et al. EAU guidelines on male hypogonadism. Available at: https://uroweb.org/guideline/male-hypogonadism/. Accessed March 16, 2019.
11. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: An Endocrine Society Clinical Practice Guideline. **J Clin Endocrinol Metab 2018;103:1715-1744.**
12. Zitzmann M, Faber S, Nieschlag E. Association of specific symptoms and metabolic risks with serum testosterone in older men. **J Clin Endocrinol Metab 2006;91:4335-4343.**
13. Travison TG, Vesper HW, Orwoll E, et al. Harmonized reference ranges for circulating testosterone levels in men of four cohort studies in the United States and Europe. **J Clin Endocrinol Metab 2017;102:1161-1173.**
14. Mårin P, Holmäng S, Gustafsson C, et al. Androgen treatment of abdominally obese men. **Obes Res 1993;1:245-251.**
15. Kapoor D, Goodwin E, Channer KS, et al. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. **Eur J Endocrinol 2006;154:899-906.**
16. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. **CA Cancer J Clin 1972;22:232-240.**
17. Morgentaler A, Traish AM. Shifting the paradigm of testosterone and prostate cancer: The saturation model and the limits of androgen-dependent growth. **Eur Urol 2009; 55:310-321.**
18. Khera M, Bhattacharya RK, Blick G, et al. Changes in prostate specific antigen in hypogonadal men after 12 months of testosterone replacement therapy: Support for the prostate saturation theory. **J Urol 2011;186:1005-1011.**
19. Pastuszak AW, Pearlman AM, Lai WS, et al. Testosterone replacement therapy in patients with prostate cancer after radical prostatectomy. **J Urol 2013;190:639-644.**
20. Pastuszak AW, Khanna A, Badhiwala N, et al. Testosterone therapy after radiation therapy for low-, intermediate-, and high-risk prostate cancer. **J Urol 2015;194:1271-1276.**
21. Kacker R, Hult M, San Francisco I, et al. Can testosterone therapy be offered to men on active surveillance for prostate cancer? Preliminary results. **Asian J Androl 2016;18:16.**

22. Petak SM, Nankin HR, Spark RF, et al. American Association of Clinical Endocrinologists Medical Guidelines for clinical practice for the evaluation and treatment of hypogonadism in adult male patients: 2002 update. **Endocr Pract 2002; 8:440-456.**
23. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in adult men with androgen deficiency syndromes: An Endocrine Society Clinical Practice Guideline. **J Clin Endocrinol Metab 2006;91:1995-2010.**
24. Traish AM, Miner MM, Morgentaler A, et al. Testosterone deficiency. **Am J Med 2011;124:578-587.**
25. Gooren LJ, Behre HM. Diagnosing and treating testosterone deficiency in different parts of the world: Changes between 2006 and 2010. **Aging Male 2012;15:22-27.**
26. Ory J, Flannigan R, Lundeen C, et al. Testosterone therapy in patients with treated and untreated prostate cancer: Impact on oncologic outcomes. **J Urol 2016;196:1082-1089.**
27. Aversa A, Francomano D, Lenzi A. Cardiometabolic complications after androgen deprivation therapy in a man with prostate cancer: Effects of 3 years intermittent testosterone supplementation. **Front Endocrinol (Lausanne) 2012;3:17.**
28. Hak AE, Witteman JCM, de Jong FH, et al. Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: The Rotterdam Study. **J Clin Endocrinol Metab 2002;87:3632-3639.**
29. Khaw KT, Dowsett M, Folkerd E, et al. Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men. **Circulation 2007;116:2694-2701.**
30. Vigen R, O'Donnell CI, Barón AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. **JAMA 2013; 310:1829.**
31. Sharma R, Oni OA, Gupta K, et al. Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. **Eur Heart J 2015;36:2706-2715.**
32. Wallis CJD, Lo K, Lee Y, et al. Survival and cardiovascular events in men treated with testosterone replacement therapy: An intention-to-treat observational cohort study. **Lancet Diabetes Endocrinol 2016;4:498-506.**
33. Cheetham TC, An J, Jacobsen SJ, et al. Association of testosterone replacement with cardiovascular outcomes among men with androgen deficiency. **JAMA Intern Med 2017;177:491.**
34. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. **N Engl J Med 2010;363:109-122.**
35. Xu L, Freeman G, Cowling BJ, et al. Testosterone therapy and cardiovascular events among men: A systematic review and meta-analysis of placebo-controlled randomized trials. **BMC Med 2013;11:108.**
36. Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. **PLoS One 2014;9:e85805.**
37. Layton JB, Meier CR, Sharpless JL, et al. Comparative safety of testosterone dosage forms. **JAMA Intern Med 2015; 175:1187.**
38. Kloner RA, Carson C, Dobs A, et al. Testosterone and cardiovascular disease. **J Am Coll Cardiol 2016;67:545-557.**
39. Snyder PJ, Bhasin S, Cunningham GR, et al. Effects of testosterone treatment in older men. **N Engl J Med 2016; 374:611-624.**
40. Pugh PJ, Jones RD, West JN, et al. Testosterone treatment for men with chronic heart failure. **Heart 2004;90:446-447.**
41. Malkin CJ, Pugh PJ, West JN, et al. Testosterone therapy in men with moderate severity heart failure: A double-blind randomized placebo controlled trial. **Eur Heart J 2006; 27:57-64.**
42. AndroGel® 1.62% [package insert]. North Chicago, IL: AbbVie Inc; 2016.