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Review

Testosterone deficiency and treatments: common misconceptions and practical guidance for patient care

Mohit Khera, MD[1,*], James M. Hotaling, MD MS FECSM[2], Martin Miner, MD[3]

[1]Baylor College of Medicine, Houston, TX 77030, United States
[2]University of Utah, Salt Lake City, UT 84112, United States
[3]Men's Health Center, Miriam Hospital, Providence, RI 02906, United States
*Corresponding author: Department of Urology, Baylor College of Medicine, Houston, TX 77030, United States. Email: mkhera@bcm.edu

Abstract

Introduction: Misconceptions about testosterone therapy are prevalent and there is an unmet need for a review of current literature that can be leveraged by physicians to deliver safe and effective care for men with hypogonadism.

Objectives: This review aims to address common misconceptions about testosterone therapy using current literature and synthesize practical guidance for clinicians with patients who are starting testosterone therapy.

Methods: A literature search of PubMed, Embase, CINAHL was carried out to identify associations between testosterone therapy and prostate cancer, cardiovascular risk, and hepatic toxicity; definitions of hypogonadism; and practical guidance for clinician with patients starting testosterone therapy.

Results: There is no evidence to support the misconception that testosterone therapy leads to or promotes progression of prostate cancer, no evidence that testosterone therapy increases cardiovascular risk, no evidence that newer oral testosterone therapy formulations (eg, testosterone undecanoate) are associated with hepatic toxicity, and no consistent definition of hypogonadism among regulatory agencies and expert bodies. Clinicians should diagnose hypogonadism using testosterone concentrations and/or symptoms of testosterone deficiency, help patients select a testosterone therapy formulation that best fits their needs and preferences (including considerations for dose adjustment), ensure appropriate laboratory monitoring before and during treatment, and assess how patients are feeling during treatment.

Conclusions: Testosterone therapy is not associated with increased prostate cancer or increased cardiovascular risk, newer oral testosterone therapy formulations are not associated with hepatic toxicity, and a strict definition of hypogonadism is difficult because patient individualization is required. Each patient in real-world clinical practices has unique baseline characteristics and will likely respond differently to testosterone therapy. As the primary goal of testosterone therapy is to provide relief from symptoms of hypogonadism, physicians should work with their male patients to create a comprehensive treatment plan that suits the patient's specific needs and preferences.

Keywords: hypogonadism; oral; guidelines; cardiovascular; testosterone undecanoate; monitoring.

Introduction

A study that estimated the crude prevalence of hypogonadism, defined using symptoms and calculated free testosterone (T) and based on data from a randomly sample population-based cohort of middle-aged and older men, reported rates up to 12%, with prevalence increasing significantly with age.[1] The European male aging study that recruited 3369 men aged 40–79 years found that 11.8% and 2.0% of men were classified into the secondary hypogonadism category (hypothalamic–pituitary failure with low T and low or normal gonadotropins), and primary hypogonadism category (testicular failure characterized by low T and elevated gonadotropins.), respectively.[2] Symptoms of hypogonadism include decreased energy, reduced endurance, diminished work and/or physical performance, fatigue, depression, reduced motivation, irritability, infertility, reduced sex drive, and changes in erectile function.[3] The 2018 AUA guidelines state that a large proportion of men in need of T therapy (TTh) remain untreated due to clinician concerns, primarily regarding the increased risk of prostate cancer and cardiovascular events, although current evidence does not support the validity of these concerns.[3]

Untreated T deficiency imposes a substantial cost to health-care systems, as it may be a risk factor for a number of chronic conditions such as osteoporosis, diabetes mellitus, and cardiovascular disease.[4] These comorbidities can cause considerable economic impact.[5] A cost-modeling study using data from 6 national databases and large cross-sectional studies found that T deficiency may be directly accountable for ~$190 to $525 billion in United States health care expenditures over a 20-year period.[4]

Although use of TTh has increased significantly in the US,[6] misconceptions about TTh are still prevalent. Therefore, there is an unmet need for a review of current literature that can be leveraged by practitioners to deliver safe and effective care for patients with hypogonadism. The objective of this review is to address common misconceptions about TTh using up-to-date literature and synthesize practical guidance for clinicians with patients who are starting TTh.

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Materials and methods

PubMed, Embase, and CINAHL were searched. The following eligibility criteria guided the literature search and selection: English language; patients receiving TTh; associations between TTh and prostate cancer, cardiovascular risk, and hepatic toxicity; definitions of hypogonadism; considerations before starting TTh; factors in selecting a TTh; monitoring during TTh; alternatives to TTh; and androgen abuse.

The titles and the abstracts were reviewed. If the abstracts reported associations between TTh and prostate cancer, cardiovascular risk, and hepatic toxicity; definitions of hypogonadism; considerations before starting TTh; factors in selecting a TTh; monitoring during TTh; alternatives to TTh; or androgen abuse, full texts were read. If the pre-established eligibility criteria were met, they were included in the review. Of the thousands of publications captured in the initial search, 47 studies were selected for inclusion. Reference lists of relevant studies were examined manually to identify additional relevant studies.

Results

Testosterone therapy: common misperceptions versus evidence and guidelines

Testosterone therapy causes prostate cancer: no

Although one of the many concerns about TTh treatment is the risk of prostate cancer (PCa), there is no evidence that TTh leads to or promotes progression of PCa in men with hypogonadism and normal prostate-specific antigen (PSA) concentrations. The 2018 AUA guidelines state that there is no evidence TTh increases risk of PCa.[3] Furthermore, a 2023 study (n = 5246), the largest randomized trial of TTh conducted to data with prospectively recorded and adjudicated prostate safety outcomes, found no significant difference in the incidences of high-grade or any PCa between men treated with TTh and placebo (0.2% vs. 0.1%, $P = 0.51$ for high-grade PCa).[7] However, it is important to note that this study excluded men at high risk of PCa (defined as PSA concentrations >3 ng/mL and International Prostate Symptom Score >19). Therefore, the results are not generalizable to all men treated with TTh. Additionally, a 2014 meta-analysis of 22 randomized clinical trials (n = 2351) found that TTh does not promote PCa development or progression.[8]

In fact, some studies suggest a potential benefit for patients with PCa on TTh. A 2016 cohort study (n = 10 311) reported that long-term TTh was associated with reduced risk of mortality and PCa.[9] A 2020 retrospective study (n = 850, median follow-up of 3.5 years) indicated that TTh significantly reduced biochemical recurrence after radical prostatectomy, although the authors specify that "these findings are hypothesis-generating and require confirmation with multicentred, prospective randomised controlled trials."[10] Similarly, a separate study in men treated with TTh following radical prostatectomy found that mean T values increased from 255 to 459 ng/dL, with no biochemical PSA recurrence.[11] Furthermore, several studies of TTh after brachytherapy or external beam radiotherapy found increased serum T levels and improvement in hypogonadal symptoms without PCa recurrence or progression.[12-14] Taken together, these study results suggest that TTh does not increase risk of PCa and may be beneficial for PCa patients with hypogonadal symptoms post-radical prostatectomy and/or radiotherapy. That said, TTh in PCa requires careful multidisciplinary care by specialists and primary care physicians.

Testosterone therapy increases cardiovascular risk: no

The association between TTh and increased CV risk is controversial: some labels and agencies warn of potential increased CV risk with administration of TTh, but recent studies found that TTh does not impact CV outcomes. First, it must be acknowledged that various government agencies have published warnings regarding TTh and increased CV risk. Testosterone therapy prescribing information includes a warning that TTh can cause blood pressure increases that can increase the risk of major adverse cardiovascular events (MACE).[15] This is likely due to TTh causing an increase in red blood cell production, which in turn elevates blood pressure and may increase CV risk.[12] In 2014, Health Canada issued a warning about the association between use of TTh and increased CV risk.[13] In 2015, the FDA mandated that labels for all T products add a warning against the possible increased risk of heart attacks and strokes,[16] based on four studies that suggested increased CV risk with TTh.[178] However, the strength of evidence was weak and the European Medicines Agency declined to add a CV warning after performing an independent literature review.[179] Moreover, the recent TRAVERSE study of men with hypogonadism and CV disease or high CV risk found no difference in MACE risk between patients treated with TTh and a placebo.[17] A 2024 meta-analysis of 26 randomized clinical trials (n = 10 941) reported that TTh does not worsen CV outcomes or increase mortality risk in hypogonadal men.[18] In a review of all articles relating to T and CV disease that identified over 200 studies, only four suggested increased CV risk and several dozen found normal T levels benefited CV health and mortality.[19] This large meta-analysis concluded that there is no convincing evidence of the association between TTh and increased CV risk.[19] According to Canadian Urological Association guidelines, hypogonadal men with stable CV disease can be treated with TTh.[17]

Based on a meta-analysis of prospective cohort studies with at least 5 years of follow up investigating the relationship between sex hormones and CV disease and mortality in men, men with low T levels had higher risk of all cause mortalities and CV disease mortality.[20] This may be because CV disease is one of the comorbidities associated with hypogonadism.[21] A study of men with hypertension concluded that MACE risk was higher in men with low T levels.[22] Therefore, although there is little to no evidence that TTh increases CV risk, and indeed TTh may even offer CV benefits for men with hypogonadism,[23] men with hypogonadism may have higher baseline CV risk compared to men with normal T concentrations. Specialists should carefully assess CV risk factors before initiating TTh, and monitor and manage CV health during TTh administration.

All oral testosterone therapies are associated with hepatic toxicity: no

Unlike older formulations, newer oral TTHs (eg, testosterone undecanoate) have unique delivery systems that avoid first-pass metabolism in the liver and therefore prevent hepatic toxicity. Methyltestosterone (Testred [discontinued in the US], Android, METHITEST), an older TTh formulation, can cause hepatotoxicity when administered orally because the drug is directly transported to the liver,[24] and because of the oxidative stress caused by methylated formulations.[25] However, the

Table 1. There is no consistent definition of hypogonadism.

Definition of Hypogonadism by Institution/Journal	
Source	**Definition**
FDA	Average **morning serum T** (at least 2 draws) **<300 ng/dL**
AUA Guidelines	**Low T level < 300 ng/dL** combined with **symptoms and/or signs**
Association of Family Practitioners	Although there is no universal laboratory definition of hypogonadism, in most laboratory reference ranges, the **lower limit of normal is between 250 and 350 ng per dL**
Endocrine Society Guidelines	The threshold testosterone level below which **symptoms** of androgen deficiency **and adverse health outcomes** occur and testosterone administration improves outcomes in the general population is not known

Source: Nguyen CP. FDA. 2019; Mulhall JP, et al. J Urol. 2018; Data on file [Although there is no universal laboratory definition of hypogonadism, in most laboratory reference ranges, the lower limit of normal is between 250 and 350 ng per dL].

newer oral therapy testosterone undecanoate (JATENZO, TLANDO, KYZATREX), a nonmethylated prodrug of endogenous T, uses a novel lymphatic delivery system that avoids first-pass metabolism in the liver.[24] A 2-year study of oral testosterone undecanoate reported no clinically significant changes from baseline in liver function tests.[258]

Hypogonadism can be simply defined as a testosterone level: No

There is no consistent definition of hypogonadism among regulatory agencies and expert bodies. Some definitions are based solely on T concentrations: the FDA uses a threshold of morning T <300 ng/dL[26] and the Association of Family Practitioners uses a T range of 250 to 350 ng/dL.[27] The AUA guideline definition includes a T threshold <300 ng/dL and also symptoms of T deficiency.[3] In contrast, the Endocrine Society guideline states that the T threshold below which symptoms of androgen deficiency and adverse health outcomes occur and T administration improves outcomes in the general population, is not known").[28] (Table 1) Thus, it is clear that T <300 ng/dL is not a universally agreed upon definition of hypogonadism, and that both T concentrations and symptoms should be considered when diagnosing hypogonadism.

A quantitative definition of hypogonadism is difficult, with patient individualization required. Each patient in real-world clinical practices has unique baseline characteristics and will likely respond differently to TTh. First, "normal" testosterone levels may vary by age, and T levels decrease by age naturally,[24] so age-specific definitions for low T may be more useful. More importantly, the goal of treatment with TTh is symptom relief, not a specific target T (eg, if a patient feels back to "normal" with T = 325 ng/dL, the clinician does not need to aim for T = 900 ng/dL).

Non-prescription testosterone boosting supplements are safe and effective: likely not

Patients may believe that taking over-the-counter T boosting supplements is a safe and effective way to naturally raise T level.[25] However, many of the ingredients in "T boosters" have never been tested for safety and/or efficacy in human trials.[26] A study of 50 "T booster" supplements found that only 25% had data to support T boosting claims, and 10% contained ingredients with data suggesting a negative effect on T.[25] According to the FDA, supplements are not intended to treat, diagnose, prevent, or cure diseases.[27] Additionally, supplements may have the potential to interact with other drugs.[29] Therefore, physicians should educate their patients and correct the misconception that all "natural" products are safe and effective.

Discussion

Practical guidance for starting testosterone therapy

It should be noted that each patient's healthcare team should be determined by individual needs and preferences. For hypogonadal patients who are generally healthy without comorbidities, a primary care physician (PCP) will likely be the best option. However, for more complicated cases, for example, patients who have been treated for localized PCa and patients with CV risk factors and/or other co-morbidities, a multidisciplinary team incorporating specialists and the PCP should always be considered the best care.

Before starting testosterone therapy

Before starting treatment in potential TTh candidates, healthcare providers (HCPs) should confirm the diagnosis of hypogonadism and ensure that the patient does not have contraindications for TTh. First, HCPs should check that the patient has two separate early morning T measurements with T <300 ng/dL[5] and/or symptoms of T deficiency such as fatigue, insomnia, decreased libido, mood changes, erectile dysfunction.[30] The presence of clinical symptoms or signs suggesting hypogonadism is vital for diagnosis as T levels vary by patient age and the potential medical co-morbidities. Next, HCPs should rule out contraindications for TTh (eg, severe untreated sleep apnea, breast cancer, prolactinoma, or prostate cancer).[31] Primary care providers should also consider the patient's baseline cardiovascular risk and ensure blood pressure is adequately controlled before initiating TTh.[32,33] A multidisciplinary approach with specialists and PCPs may be beneficial for patients with PCa and/or CV risk factors.

It is also important to note that men may be hesitant to initiate a discussion about TTh with their HCP. Therefore, HCPs should work to establish a strong rapport with patients so that patients feel comfortable talking about all health conditions. Additionally, HCPs should proactively discuss the benefits of TTh with patients who are experiencing symptoms of T deficiency.

Treatment selection

While all TThs should offer similar benefits, such as improved sexual function,[359] improved mood,[34,35] increased motivation,[36] improved quality of life,[35] increased bone mineral density,[37] reduced body fat,[37] and potentially improved cardiovascular health,[31,38] different formulations have unique characteristics (eg, duration of action), so HCPs should help patients select a formulation that best fits their needs and preferences. For patients with more complicated cases (eg, those who have been treated for localized PCa), treatment selection should be done by a specialist or a multidisciplinary team.

Some key factors to consider for treatment selection include whether patients would benefit from dose adjustment, duration of action, convenience of administration, and financial considerations. First, as men likely have different needs based individual patient factors such as BMI and baseline T, a TTh that allows for dose adjustment should be considered. Additionally, shorter-acting formulations (eg, oral) may be preferred over long-acting depot formulations as clinicians can quickly discontinue therapy should an adverse event develop. Furthermore, oral, transdermal, and pellet formulations may be more convenient because they avoid clinic visits to receive injections and self-injections. A study published in 2024 reported that patients switching from other TTh formulations to oral testosterone undecanoate experienced increased measures of effectiveness, convenience, and global satisfaction relative to previous TTh.[39] Finally, financial considerations may also impact treatment selection. The cost of TTh depends on factors such as TTh type, dosage, route of administration, third-party coverage, and clinician and laboratory fees.[40] Some of these expenses may be covered by insurance companies. However, out-of-pocket costs can still represent a financial burden to patients, potentially incentivizing patients to seek out cheaper, unregulated, non-prescription, and/or herbal products, which may be dangerous in addition to being ineffective for addressing T deficiency symptoms. As pharmaceutical companies may offer patient assistance programs and free or discounted TTh products to help patients pay for their medications,[41] HCPs should educate themselves about these programs and work with patients to offset the financial burden of TTh, with the goal of ensuring that patients are treated with regulated, approved, and tested TTh formulations. Patients with a valid prescription but without insurance coverage can also obtain branded FDA-approved medications through manufacturers' programs, often at cash prices that are comparable to or even lower than those offered by online stores.[42-45] Clinicians should work with patients to select a TTh that meets their needs, preferences, and financial circumstances.

Monitoring during treatment

Appropriate monitoring is required to ensure effective and safe treatment with TTh. Laboratory parameters that should be monitored at baseline include total and free T, luteinizing hormone (LH), hemoglobin/hematocrit, sex hormone binding globulin (SHBG), estradiol, PSA, lipid profiles, and glucose.[40] During the stable phase of TTh treatment, T, hemoglobin/hematocrit, and PSA should be measured in all patients.[3] Patients should also be monitored for signs of edema, gynecomastia, sleep apnea, lower urinary tract symptoms, low bone mineral density,[35] blood pressure increase,[39] CV symptoms,[3] and depression symptoms or other mental illnesses.[46] In addition to laboratory assessments, HCPs should be sure to ask patients how they are feeling, as symptom relief is the primary goal of TTh. Exact timing of follow-up monitoring will depend on the TTh duration of action, but in general, patient responses should be assessed at two to three months after starting TTh, then annually. Clinicians should also be aware of and monitor for unique adverse events for specific products. For example, the prescribing information for AVEED, an intramuscular testosterone undecanoate injection, recommends that patients should be observed in the healthcare setting for 30 minutes following each injection in the event of serious pulmonary oil micro-embolism reactions or anaphylaxis.[47] For patients with PCa or who have been treated for PCa, CV risk factors, and/or other co-morbidities, a multidisciplinary team incorporating specialists and the PCP should always be considered the best care.

Alternatives to testosterone therapy

For patients with contraindications or who prefer not to initiate TTh, HCPs can recommend alternative ways to reduce or manage symptoms that negatively impact quality of life. Some symptoms of T deficiency can be managed with lifestyle modifications such as increased exercise and improved diet. Corona and Maggi reported that 72% and 71% of primary and secondary hypogonadism, respectively, can be attributed to the chronic conditions of obesity, metabolic syndrome, and diabetes.[44] Thus, these authors recommended that the first therapeutic approach should be lifestyle changes and treatment of overweight/obesity or other underlying conditions, with TTh as a secondary or supportive strategy.[44] As there is a risk of low adherence to lifestyle modifications such as increased exercise and improved diet,[30] better treatment outcomes can be achieved when TTh is combined with lifestyle changes in patients with obesity and other comorbidities.[45]

Clinicians can also educate patients with hypogonadism, especially those who want to preserve fertility, about drugs other than TTh, such as aromatase inhibitors,[48,49] human chorionic gonadotropin,[50] and selective estrogen receptor modulators.[51] There are also medications other than TTh that are used off-label to treat hypogonadism, for example, clomiphene citrate (Clomid), which is indicated for the treatment of ovulatory dysfunction in women desiring pregnancy. Clomiphene citrate is a selective estrogen modulator that modulates estrogen receptors at the hypothalamus and pituitary gland, blocking the negative feedback of estrogen and therefore enhancing the secretion of LH and follicle-stimulating hormone. The increase in LH stimulates endogenous testosterone production. One study of 153 hypogonadal men treated with clomiphene (starting dosage of 25 mg every other day or 25 mg/day for men with bodyweight >100 kg, increased to 50 mg/day when there was little biochemical response) found that T increased from 9 to 16 nmol/L and 74% experienced hypogonadal symptom improvement. The mean duration of treatment was 10 months.[52] In men who continued treatment, the increased T concentrations persisted after 8 years of treatment.[52] A second study of hypogonadal men who wanted to preserve fertility found that serum total T concentrations increased from 235.5 to 438 ng/dL with clomiphene treatment and hypogonadal symptoms were improved (dosage and follow-up period were not reported).[53] For men who elect to start TTh and want to preserve fertility, clinicians may recommend freezing his sperm before treatment initiation. As the primary goal is to provide relief from symptoms of hypogonadism, HCPs should work with patients to create a treatment plan that suits their needs and preferences.

Recognize potential abuse of testosterone products

Androgen abuse is the use of androgens, usually bought illegally and often used in high doses, for non-medical reasons.[54] Androgen abusers are mostly young men who are engaged in body building, weightlifting, and martial arts sports. The main reasons to use these products are increasing muscle mass and improving physical strength and performance.[52] Illegal products are cheap and can be purchased online or

Table 2. Testosterone therapy: common misperceptions versus evidence and guidelines.

Misperception	Evidence & Guidelines
TTh causes PCa	**No,** there is no evidence that TTh leads to or promotes PCa progression[1,2,3,4]
TTh increases CV risk	**No,** in fact TTh may improve CV health[5,6,7,8]
All oral TThs are associated with hepatic toxicity	**No,** unlike older formulations (e.g., methyltestosterone), newer oral TThs (e.g., testosterone undecanoate) have unique delivery systems that avoid first-pass metabolism in the liver and therefore prevent hepatic toxicity
Hypogonadism is universally defined as T < 300 ng/dL	**No,** there is no consistent definition of hypogonadism among regulatory agencies and expert bodies, and a strict definition of hypogonadism is difficult and patient-dependent as each patient in real-world clinical practices has unique baseline characteristics and will likely respond differently to TTh[9,10,11]

[1]Mulhall JP, et al. J Urol. 2018; [2]Cui Y, et al. Prostate Cancer Prostatic Dis. 2014; [3]Wallis CJ, et al. Lancet Diabetes Endocrinol. 2016; [4]Ahlering TE, et al. BJU Int. 2020; [5]Miner M, et al. Clin Endocrinol (Oxf). 2018; [6]Morgentaler A, et al. Mayo Clin Proc. 2015; [7]Sood A, et al. Endocr Pract. 2024; [8]Lincoff AM, et al. N Engl J Med. 2023; [9]Petering RC, et al. Am Fam Physician. 2017; [10]Bhasin S, et al. J Clin Endocrinol Metab. 2010; [11]Zhu A, et al. J Urol. 2022.

Table 3. Practical guidance for healthcare providers.

Diagnosis	Treatment Selection	Monitoring
a) Confirm the diagnosis of hypogonadism using T concentrations and/or symptoms of T deficiency (e.g., fatigue, insomnia, decreased libido, mood changes, erectile dysfunction)[1] b) Rule out contraindications for TTh (e.g., severe untreated sleep apnea)[2] c) Consider the patient's baseline cardiovascular risk and ensure blood pressure is adequately controlled before initiating TTh	a) Shorter-acting formulations (e.g., oral) may be preferred over long-acting depot formulations as clinicians can quickly discontinue therapy should an adverse event develop b) Oral, transdermal, and pellet formulations avoid clinic visits to receive injections and self-injections	a) Laboratory parameters that should be monitored at baseline include total and free T, H/H, SHBG, LH, E2, PSA, lipid profiles, Glc, and liver function tests[2] b) During the stable phase of TTh treatment, T, H/H, and PSA should be measured in all patients c) Ask how patients are feeling, as symptom relief is the primary goal of TTh d) Exact timing of follow-up monitoring will depend on the TTh duration of action, but patient responses should be assessed at 2-3 months after starting TTh, then annually e) Clinicians should also be aware of unique adverse events for specific products e.g., serious pulmonary oil microembolisms or anaphylaxis for AVEED®

Abbreviations: T = Testosterone; H/H=Hemoglobin/hematocrit; SHBG = Sex hormone binding globulin; LH = Luteinizing hormone; PSA = Prostate-specific antigen; Glc = Glucose [1]Morales A, et al. Can Urol Assoc J. 2010. [2]Bassil N, et al. Ther Clin Risk Manag. 2009.

from local suppliers. Testosterone and other anabolic steroids are included in Schedule III of controlled substances because they can be abused by adults and adolescents.[55] Testosterone abuse is associated with serious risks such as heart attack, stroke, infertility, and depression.[55] Thus, the FDA labeling information for T products to include new safety information about T abuse associated risks.[55] Differentiating between a lawful prescription for a controlled substance and one that might be used illegally is one of the most difficult challenges facing prescribers,[56] and one that can make them hesitant to prescribe controlled substances. Clinicians should be aware of proper patient assessment and the possibility of abuse and diversion of controlled substances.[56] They also should be trained to prevent and recognize androgen abuse side effects.[52] Studies on approaches to prevent T abuse have underscored the importance of using nutrition and appropriate training as effective alternatives to anabolic steroid abuse,[57] and support the use of sex-specific, team-centered education in a school athletic team environment.[58] A balanced education program that presented both potential risks and benefits was also found to be more effective compared to a risks-only (negative or "scare tactics") presentation.[58]

Conclusions

1) **Testosterone Therapy: Common Misperceptions Versus Evidence and Guidelines** (Table 2)
   - **TTh Causes PCa: No,** there is no evidence that TTh leads to or promotes PCa progression
   - **TTh Increases CV Risk: No,** in fact TTh may potentially improve CV health
   - **All Oral TThs Are Associated with Hepatic Toxicity: No,** unlike older formulations, newer oral TThs (eg, testosterone undecanoate) have unique delivery systems that avoid first-pass metabolism in the liver and therefore prevent hepatic toxicity
   - **Hypogonadism Is Simply Defined as T Level: No,** there is no consistent definition of hypogonadism among regulatory agencies and expert bodies, and a quantitative definition of hypogonadism is difficult, with patient individualization required. Each patient in real-world clinical practices has unique baseline characteristics and will likely respond differently to TTh
   - **Non-Prescription T Boosting Supplements Are Safe and Effective: Likely not,** there is not enough evidence to support the efficacy or safety of T boosting supplements
2) **Practical Guidance for HCPs** (Table 3)
   - **Before Starting TTh:**
     a) Confirm the diagnosis of hypogonadism using T concentrations and/or symptoms of T deficiency (eg, fatigue, insomnia, decreased libido, mood changes, erectile dysfunction)
     b) Rule out contraindications for TTh (eg, severe untreated sleep apnea)
     c) Consider the patient's baseline cardiovascular risk and ensure blood pressure is adequately controlled

Table 4. Practical guidance for monitoring during testosterone therapy.[a]

Parameter	Measure at Baseline	Measure at 3 and 6 Months Then Annually After Starting TTh
Laboratory		
Total Testosterone	X	X
Free Testosterone	X	X
Hematocrit/Hemoglobin	X	X
Sex Hormone Binding Globulin	X	
Luteinizing Hormone	X	
Estradiol	X	
Prostate-Specific Antigen	X	X
Lipid Profiles	X	X
Glucose	X	
Potential Adverse Effects Associated with Testosterone Therapy		
Edema		X
Gynecomastia		X
Sleep Apnea		X
Lower Urinary Tract Symptoms		X
Bone Mineral Density		X
Cardiovascular Health (eg, Blood Pressure)	X	X
How Patients Are Feeling During Testosterone Therapy		X

[a] Bassil N, et al. Ther Clin Risk Manag. 2009.

- **Treatment Selection:**
  a) Shorter-acting TTh formulations (eg, oral) may be preferred over long-acting depot formulations as clinicians can quickly discontinue therapy should an adverse event develop
  b) Oral, transdermal, and pellet TTh formulations avoid clinic visits to receive injections and self-injections
- **Monitoring During Treatment (Table 4):**
  a) Check the following laboratory parameters at baseline: total and free T, LH, hemoglobin/hematocrit, SHBG, estradiol, PSA, lipid profiles, and glucose. Check the following laboratory parameters at 3 and 6 months then annually after starting TTh: total/free T, hemoglobin/hematocrit, PSA, and lipid profiles
  b) Ask how patients are feeling, as symptom relief is the primary goal of TTh
  c) In general, patient responses should be assessed at two to three months after starting TTh, then annually
  d) Clinicians should also be aware of unique adverse events for specific products, for example, serious pulmonary oil micro-embolisms or anaphylaxis for AVEED

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Author contributions

All authors participated in writing and editing the manuscript. All authors have reviewed the manuscript, believe it represents valid work, and approved it for submission.

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Conflict of Interest

M Khera served on steering committee for TRAVERSE trial. He is also a consultant for Endo, AbbVie, Halozyme, Marius, Tolmar, Inc. and Besins. JM Hotaling served on the scientific advisory board for Maximus and Carrot. M Miner is a consultant for Halozyme Therapeutics, Inc. and Tolmar, Inc. Editorial support was funded by Tolmar, Inc.

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