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Invited Review

Male hypogonadism: recommendations from the Fifth International Consultation on Sexual Medicine (ICSM 2024)

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Abstract

Introduction: Male hypogonadism is a clinical condition combining low circulating testosterone (T) and specific signs and symptoms associated with impaired hormone production.

Objectives: To provide the 5th International Consultation for Sexual Medicine consensus paper with recommendations concerning management strategies for hypogonadism.

Outcomes: A narrative review combined with expert opinions on major topics concerning diagnosis of male hypogonadism; treatment options; T impact toward cardiovascular, metabolic, sexual, and reproductive health; and prostate cancer (PCa).

Methods: A consensus panel was held with leading Sexual Medicine experts during the 5th ICSM. Relevant English-language peer-reviewed literature was reviewed with a focus on research from but not limited to the last 10 years. The quality of each individual study was judged with Oxford levels of evidence (LOEs) criteria, but overall LOEs were not used as a systematic review was not performed. The expert panel generated recommendations based on the quality of evidence and criteria of Grading of Recommendations Assessment, Development and Evaluation.

Results: This manuscript reports a narrative reappraisal combined with authoritative expert opinion on the physiological role of T throughout the male aging process, with emphasis on the critical interpretation of the hypogonadal conditions associated with sexual dysfunction and male factor infertility. Likewise, particular attention was paid to relevant everyday clinical topics including cardiovascular health, metabolism and bone safety, and PCa survivorship. Clinically effective recommendations were given for 14 categories concerning hypogonadism diagnosis and 15 categories on testosterone therapy.

Strengths and limitations: The combined main strength and limitation is the narrative profile of this literature review, which was intentionally devoted to addressing the critical clinical aspects of male hypogonadism, while neither provides a systematic review nor a meta-analysis of the most updated published data.

Conclusions: This manuscript discusses relevant clinical aspects and management recommendations of the 5th ICSM committee on male hypogonadism.

Keywords: testosterone; hypogonadism; testosterone deficiency; late onset hypogonadism.

Introduction

Male hypogonadism, also known as testosterone deficiency (TD), is a prevalent clinical condition combining low concentrations of circulating testosterone (T) and specific signs and symptoms associated with impaired hormone production.

This consensus paper is aimed to provide the International Consultation for Sexual Medicine (ICSM) 2024 recommendations (Boxes 1 and 2) concerning work-up management strategies for male hypogonadism diagnosis (Box 1) and testosterone therapy (TTh) (Box 2) in the everyday real-life clinical setting.

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Box 1. Recommendations for clinically effective management of male hypogonadism—diagnosis.

	Recommendations	Grade of recommendation
1	Male hypogonadism diagnosis is established following confirmation of clinical and biochemical findings using both laboratory and clinical criteria, aiming to prevent overdiagnosis.	*Strong*
2	Male hypogonadism can affect the function of multiple organ systems and result in significant detriment in QoL, including alterations in sexual function.	*Strong*
3	The clinical manifestations of male hypogonadism occur as a result of decreased serum androgen concentrations or activity, regardless of whether there is an identified underlying etiology.	*Strong*
4	Sexual dysfunction, in particular low sexual desire, decreased nocturnal and morning erections, and ED, are prominent and often the presenting symptoms, especially suggestive of male hypogonadism when all 3 are associated.	*Strong*
5	Check for less specific symptoms associated with male hypogonadism (eg, diminished physical vigor, decreased energy and motivation, fatigue, depressive mood, and sleep disturbances, hot flushes, and sometimes alterations in cognition and memory can be associated).	*Weak*
6	Features of the physical examination suggestive of male hypogonadism include smaller testicles, decreased body hair, and gynecomastia. However, none of these might be present.	*Weak*
7	Not all manifestations need to be evident simultaneously, and their intensity shows marked interindividual variability in hypogonadal men.	*Weak*
8	Clinical conditions associated with insulin resistance (obesity, T2DM, and MetS) should be screened for male hypogonadism because it is often comorbid. Universal screening for low tT levels is not recommended.	*Strong*
9	Measure tT in the morning (between 07:00 and 11:00 hours) and in the fasting state, with a reliable laboratory assay.	*Strong*
10	tT 12 nmol/L (3.5 ng/mL) represents a reliable threshold to diagnose LOH.	*Strong*
11	Repeat tT on at least 2 separate occasions when <12 nmol/L and before starting TTh.	*Strong*
12	Circulating albumin and SHBG levels should also be considered in the everyday clinical setting for the determination of cfT, at least in men with clear dysmetabolic conditions.	*Weak*
13	Men suspected of hypogonadism should undergo a physical examination for specific signs, although some men with hypogonadism may exhibit a normal physical exam.	*Weak*
14	DRE should be performed in all men before any type of TTh to exclude prostate abnormalities or even to support suspicion of hypogonadism in case of reduced volume.	*Weak*

Abbreviations: cFT, calculated free testosterone; DRE, digital rectal examination; ED, erectile dysfunction; LOH, late onset hypogonadism; MetS, metabolic syndrome; QoL, quality of life; SHBG, sex hormone binding globulin; T2DM, type 2 diabetes mellitus; tT, total testosterone; TTh, testosterone therapy.

Methods

A comprehensive literature search was performed using Google and PubMed database for English-language original and review articles, either published or e-published with focus on research from but not limited to the last 10 years, mostly covering the whole literature on male hypogonadism published since the last 2015 consultation with the goal to support or repeal previous recommendations. Available studies were collected and analyzed by all panel members; the various topics have been subdivided among experts, and finally discussed with 2 panel chairs (M.K., A.S.). This paper was then developed as an authoritative, comprehensive, all-encompassing consensus document highlighting state-of-the-art knowledge, based on the peer-reviewed medical literature and expertise of worldwide experts on major topics concerning diagnosis of male hypogonadism, treatment options, T impact toward cardiovascular, metabolic, sexual and reproductive health and prostate cancer (PCa). The first draft of the manuscript was then circulated to all the members for further review to address possible conflicts or disagreements. Thereafter, a modified Delphi method was used for making recommendations on management strategies for male hypogonadism in the everyday real-life clinical setting. In this context, recommendations have been dichotomized into strong versus weak statements according to the quality of the evidence for each statement,[1] the cost-effectiveness ratio between advantages and disadvantages in favor of patients' management, and the overall agreement versus disagreement of the committee's experts toward a specific statement. After different meetings and adequate general discussion during ICSM in Madrid (from June 28 to 29, 2024; https://www.issm.info/publications/international-consultation-on-sexual-medicine-icsm), the final manuscript was approved by all the authors.

Results

Diagnosis and definitions of male hypogonadism

Male hypogonadism, also known as TD, is a prevalent medical issue affecting men through different mechanisms. There are different types of hypogonadism according to its pathophysiology. Primary hypogonadism (also called hypergonadotropic hypogonadism) refers to the situation in which the testes fail to produce adequate T due to factors like genetic disorders, injury, chemotherapy, etc. (Box 3). Secondary hypogonadism (also called central hypogonadism or hypogonadotropic hypogonadism) involves a dysfunction in the hypothalamus or pituitary gland, disrupting the signaling cascade that regulates T production (Box 3).

Additional categories include compensated hypogonadism, in which normal total T (tT) levels are associated with elevated luteinizing hormone (LH).[2,3] According to Grossmann and Matsumoto,[3,4] functional hypogonadism describes cases where low tT levels in symptomatic men are associated with factors like obesity, chronic illness, or medication use[3,4] and lack "classical" or "organic" or "pathological" causes of hypogonadism. Therefore, the diagnosis of functional hypogonadism is based on the exclusion of a classical (organic) etiology. One common form of functional hypogonadism is age-related hypogonadism, often referred to as late-onset

Box 2. Recommendations for clinically effective management of male hypogonadism—testosterone therapy.

	Recommendations	Grade of recommendation
1	Do not use TTh in eugonadal men.	*Strong*
2	Symptomatic men with tT levels lower than 12 nmol/L or 350 ng/dL should be treated with TTh.	*Strong*
3	Fully discuss the choice of TTh and the route of administration with the patient, using a shared decision-making approach. Factors influencing this choice should include safety, efficacy, tolerability, availability, preference, and cost coverage.	*Strong*
4	Target correction of serum levels to the mid-normal reference range for tT.	*Strong*
5	Hematocrit levels should be below 54% before and during TTh, with carefully consideration for specific populations (ie, HAs).	*Strong*
6	After initiating TTh, patients should have regular monitoring for response to treatment and adverse events.	*Strong*
7	PSA testing and DRE should be performed to monitor prostate health in accordance with the evidence-based guidelines for PCa screening.	*Strong*
8	Use TTh as monotherapy only in men with mild ED and absolute demonstration of hypogonadism.	*Strong*
9	Use TTh in combination with PDE5Is in hypogonadal men not responding to PDE5Is alone.	*Weak*
10	Do not use TTh in men looking for fathering.	*Strong*
11	Since most testis and sperm preserving therapies are off label in men after AAs or under TTh, fully discuss the choice with the patient prior to initiating any treatment.	*Weak*
12	Do not use TTh alone to reduce weight and enhance cardio-metabolic status.	*Weak*
13	Do not use TTh alone as a therapeutic intervention to prevent or treat diabetes in men with hypogonadism.	*Weak*
14	Do not use TTh alone as a treatment option for men with clinical depressive disorders.	*Weak*
15	Do not use TTh with the sole purpose of reducing fracture risk in hypogonadal men with high fracture risks.	*Weak*

Abbreviations: DRE, digital rectal examination; HAs, natives living at high altitudes; PDE5Is, phosphodiesterase type-5 inhibitors; PSA, prostate-specific antigen; tT, total testosterone; TTh, testosterone therapy.

hypogonadism (LOH), which is usually a result of decreased androgen production in the testes combined with an inadequate response to gonadotropin levels released by the pituitary gland. As many different medical conditions may lead to male hypogonadism, treatment approaches may vary considerably depending on the underlying cause.[2] According to the authoritative opinion of this ICSM Panel, the dichotomization between functional and organic hypogonadism is not adequate, since any impairment of the hypothalamic–pituitary–gonadal (HPG) axis that ends with symptomatic low tT levels is associated with a disorder, despite the fact that it can lack identifiable "pathological" causes.[5]

Box 3 Types and causes of hypogonadism

Primary hypogonadism
Primary hypogonadism is caused by an inherent defect within the testes.
Primary hypogonadism is biochemically characterized by low or absent T levels and high gonadotropins levels.

Congenital causes

- Karyotype abnormalities (e.g., Klinefelter syndrome and Down syndrome)
- Y-chromosome microdeletions
- Testicular dysgenesis syndrome or other conditions associated with cryptorchidism
- Disorders of sex development
- Myotonic dystrophy

Acquired causes

- Mumps-related orchitis (or other types of severe infection of the testes)
- Irradiation or chemotherapy
- Trauma to the testes or castration
- Chronic illnesses (such as, chronic kidney disease, chronic obstructive pulmonary disease or HIV infection)
- Ketoconazole (antifungal medication) intake
- Chronic alcoholism
- Ageing

Secondary hypogonadism
Secondary hypogonadism is caused by a dysfunction in the hypothalamus and/or the pituitary gland.
Secondary hypogonadism is biochemically characterized by low or inappropriately normal gonadotropins levels along with low total T levels.

Congenital causes

- Kallman syndrome
- Idiopathic secondary hypogonadism

Acquired causes

- Pituitary dysfunction (e.g., owing to a tumour, surgery, trauma, infection or infiltrative diseases
- Hypothalamic dysfunction (e.g., owing to tumours or intracranial masses)
- Hyperprolactinaemia
- Chronic conditions (e.g., T2DM, haemochromatosis, hepatic steatosis and cirrhosis or coronary artery disease)
- Drug use: glucocorticoid, opioids, androgen, progestins, oestrogens or gonadotropin-releasing hormone analogs
- Obesity
- Malnutrition, wasting or anorexia nervosa
- Excessive exercise
- Ageing (with associated comorbidities)

Table 1. Different recommended cutoff levels to define male hypogonadism.

GUIDELINES	Threshold total T (ng/dL)	Threshold total T (nmol/L)
AUA	300	10.4
BSSM	345	12.0
EAA	345	12.0
EAU	350	12.1
ES	264	9.2
ISSM	350	12.1
ISSAM	350	12.1

Abbreviations: AUA, American Urological Association; BSSM, British Society for Sexual Medicine; EAA, European Academy of Andrology; EAU, European Association of Urology; ES, Endocrine Society; ISSM, International Society for Sexual Medicine; ISSMA, International Society for the Study of the Aging Male.

Overall, male hypogonadism diagnosis is established following confirmation of clinical and biochemical findings using both laboratory and clinical criteria, aiming to prevent overdiagnosis.[6-10] Although there is considerable consensus about the fact that male hypogonadism diagnosis should involve abnormal laboratory results and clinical symptoms or signs, the specific lab thresholds remain controversial.[6,8-12] While the Endocrine Society sets the threshold for low tT at 264 ng/dL (9.2 nmol/L), the American Urological Association (AUA) considers a reasonable threshold for low tT as <300 ng/dL (10.4 nmol/L), the European Association of Urology (EAU), the International Society for Sexual Medicine (ISSM), and the International Society for the Study of the Aging Male (ISSAM) suggest the cutoff of 350 ng/dL (12 nmol/L) for tT. The British Society of Sexual Medicine (BSSM) suggests the cutoff of 350 ng/dL (12 nmol/L) for tT and of 649 ng/dL (225 pmol/L) for free T, respectively.[11] Likewise, the European Academy of Andrology (EAA) observes that hypogonadism is highly unlikely with T values >350 ng/dL (>12 nmol/L) but more likely in patients with T concentrations consistently <231 ng/dL (<8 nmol/L).[10] Moreover, in those patients with borderline tT concentrations between 231 and 350 ng/dL (8-12 nmol/L), a clear diagnosis cannot be confidently established, but free T measurements can often be helpful in this situation.[10] The American Association of Clinical Endocrinology (AACE) refrains from setting a specific threshold but suggests that symptomatic men with tT levels <200 ng/dL (6.94 nmol/L) "may be potential candidates" for TTh.[8,11-14] Although T concentrations decline with age,[15] there is currently insufficient evidence from prospective population data or clinical experience to support the use of an age-stratified reference interval for tT.

These different suggested cutoff levels are reported in Table 1.

Despite differences, all committees recommend only screening for hypogonadism certain populations of men, even if they show no symptoms—for example, those with HIV infection, men with certain medical conditions associated with insulin resistance like obesity, type 2 diabetes mellitus (T2DM), or metabolic syndrome (MetS), osteoporosis, or those under opioids/glucocorticoids use.[7,8,16]

They also agree on using mainly tT for diagnosis, with a confirmation test on different days if levels are low. In addition, measurement of T during acute illness should be avoided. Testosterone measurements (taken between 7:00 and 11:00 AM) in the fasting state are recommended. Mass spectrometry is the gold standard of T assays, but good-quality immunoassays provide fully acceptable results for clinical diagnosis.[7,8,17,18] Accordingly, the Committee agrees that mass spectrometry measurements should be considered ideal for research purposes, while good-quality and reliable immunoassays can be easily used for diagnosis in the everyday clinical setting, if they are regularly standardized by an accuracy-based (rather than peer-based) external quality assurance scheme, preferably calibrated against an internationally harmonized reference range.[19]

Similarly, although the actual role of free T has been widely discussed without a final agreement in the clinical setting, a number of findings indicate that measurement of free T (direct or calculated) may improve the diagnostic accuracy of symptoms, especially in obese men.[20-22] The most accurate methods of measuring free T are equilibrium dialysis, but calculated free T using tT, sex hormone binding globulin (SHBG), and albumin levels and 1 of the algorithms (for example, the equation of Vermeulen et al.[23] provides a sufficiently accurate estimate for clinical practice, even though they have not met consensus, especially when binding affinity may vary along with genetic variations.[24,25]

Therefore, considering the frequent association between metabolic disorders and the modifications of circulating SHBG levels in these conditions, the measurement of SHBG and the determination of calculated free T (cfT) should be also considered in the everyday clinical setting, at least in men with clear dysmetabolic conditions.

Signs and symptoms of male hypogonadism

Male hypogonadism expressions can vary widely since it may affect multiple organs and systems, thus potentially resulting in numerous health issues, including low libido with reduced sexual fantasies, erectile dysfunction (ED), reduced frequency of nocturnal erections, increased risk for diabetes, bone fracture, poor sleep quality, fatigue, and impaired cardiovascular health. These signs and symptoms may be didactically grouped into sexual and non-sexual complaints, as detailed in Table 2.

As T has a central role in the male sexual response, it is only expected that low T might have a significant impact on men's sexual health. Overall, low T levels usually impact desire, arousal, and to some extent, orgasm, and ejaculation. Sexual dysfunction, in particular low sexual desire, decreased nocturnal and morning erections, and ED, are prominent and often the presenting symptoms, especially suggestive of male hypogonadism when all 3 are associated.[7,13,15]

Numerous investigations have revealed that different levels of reduction in tT levels may be linked to progressive symptoms and signs of hypogonadism.[10,26] These differences can be substantial, such as, for instance, 320 ng/dL (11 nmol/L) concerning the reduction in morning erections and 245 ng/dL (8.5 nmol/L) for ED, respectively. Conversely, only very low T levels will promote ejaculatory dysfunction, such as delayed ejaculation and perceived reduction in ejaculate volume.[27-32] Moreover, due to interindividual differences, some men might experience these symptoms even with serum tT concentrations above the defined thresholds.

Similarly, male hypogonadism has also been associated with fatigue, muscle weakness, decreased mood, and increased body fat.[7,33] Excessive irritability and difficulties in memory and directions were also distinguishing symptoms. Reports on cognitive symptoms associated with low T have shown

Table 2. Signs and symptoms of male hypogonadism.

Nature of signs and symptoms	Description
SEXUAL	Low sexual desire
	Decreased frequency of morning erections
	Erectile dysfunction
	Delayed orgasm
	Reduced semen volume
NON-SEXUAL	
Physical	Inability to perform vigorous activity
	Fatigue
	Obesity
	Decreased muscle mass
	Hot flushes, sweats
	Anemia
	Impaired bone health
Cognitive/Psychological	Impaired concentration
	Depressive mood
	Irritability
	Sleep disturbances, insomnia, sleepiness
	Low energy levels
	Impaired memory

inconsistencies. In the European Male Ageing Study (EMAS), difficulty performing strenuous activities, fatigue, and depression were significantly correlated with low T levels.[15]

While men suspected of hypogonadism should undergo a physical examination to detect these signs, it's crucial to note that some men with hypogonadism may exhibit a normal physical exam. The most common signs include weight gain, increased waist circumference indicating visceral obesity,[34,35] and a smaller prostate volume.[36] Secondary hypogonadism is now recognized as 1 among many consequences of being overweight or obese, especially in aging men. Conversely, low T levels might contribute to the accumulation of excess fat, forming a cycle. Decreased muscle mass is less common and harder to confirm.[7]

Questionnaires to screen for male hypogonadism

Several questionnaires have been proposed to screen for hypogonadism in aging men, among these, the Androgen Deficiency in Aging Males (ADAM) Questionnaire, the Aging Male Survey (AMS),[37] and the Massachusetts Male Ageing Study (MMAS) screening questionnaire.[37,38] All these questionnaires have good sensitivity, although they are not effective in the diagnosis of male hypogonadism in daily practice because of their low specificity. 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 hypogonadal men after TTh.[39] A systematic review from Millar et al. found that of the multiple-item instruments, the AndroTEST showed the most favorable positive likelihood ratio and the most favorable negative likelihood ratio.[40]

When digital rectum examination is necessary?

The analysis of the specific mechanisms underlying the link between circulating tT levels and prostate health is beyond the scope of the present paper. The ICSM 2024 Panel on "LUTS and male sexual function" has extensively reviewed the potential crucial role derived from chronic inflammation and endothelial dysfunction in terms of prostate health and lower urinary tract symptoms (LUTS). In this context, ED and LUTS share several common pathogenetic risk factors including metabolic derangements, arterial hypertension, obesity, smoking, and alcohol consumption, which, in turn, are all closely related to the presence of systemic chronic inflammation.[41] Reduced T levels, which are closely related to metabolic diseases,[42] can further boost all the aforementioned mechanisms by increasing prostate inflammation.

Overall, general and andrological physical examinations are important to characterize patients with benign prostate hyperplasia (BPH)/LUTS and sexual dysfunction. Since obesity and MetS are frequently associated with both BPH/LUTS and ED, it is recommended to clinically assess the prostate via DRE, to estimate prostate volume, occasional pain, as well as the presence of prostate abnormalities. Of relevance, an enlarged prostate size at DRE has been associated with a higher risk of MetS or its components, thus including T2DM.[43] Conversely, a reduced prostate size at DRE represents a possible sign of hypogonadism.[44,45] As a whole, due to its strong association, tT levels should be evaluated in all subjects complaining of LUTS-related ED.

Similarly, the association of hypogonadism and TTh with prostate health has long been a topic of concern due to T's significant role in prostate tissue.[36] Thus, while some evidence suggests that the advantages of TTh outweigh the risks associated with prostate diseases, this remains a debated issue and continues to be a major concern among those prescribing TTh, mostly because of the lack of robust long-term follow-up data.[8,46-49]

Since BPH and PCa are considerably prevalent in individuals who are potential candidates for TTh, there is considerable debate to define when DRE should be performed in this patient population.[17] Hence, it is almost a consensus among most medical societies that DRE should be performed in all men to exclude prostate abnormalities before any type of TTh, and at certain intervals throughout TTh use.[7,8,44]

Who should undergo T measurements?

Most experts, including those belonging to this ICSM24 Panel, and Scientific Societies advise against routinely checking for low T in the absence of male hypogonadism signs or symptoms. However, if a patient does present hypogonadal symptoms or signs, having any of these associated conditions strengthens the likelihood of low T and warrants a T-level assessment. Overall, as detailed above, universal screening for low T levels is not recommended and should be reserved for situations where detecting such levels would significantly impact patient care, regardless of whether they show symptoms or not.[8,35]

Men showing signs or symptoms of hypogonadism or with the diagnosis of conditions that increase the risk for hypogonadism should undergo tT measurements, following universally recognized methodological indications. These conditions include but are not limited to: sexual symptoms, metabolic conditions, HIV infection, opioid or glucocorticoid use, bone density loss, and male infertility.[6,8,50] Likewise, a great amount of data suggested a relevant negative impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19) on circulating tT in men, along with the most severe clinical outcomes.[51,52] Therefore, even

men with COVID-19 or long-COVID conditions should be considered for circulating tT measurements.[53]

Sexual symptoms

Testosterone plays a key role in male sexual function. It has also been found that decreased spontaneous erections and low libido were the most prevalent clinical symptoms in hypogonadal younger and older men.[7]

In the EMAS, Wu et al. found that the best predictors of hypogonadism were men presenting with all 3 of the following sexual problems: ED, decreased libido, and decreased frequency of morning erections.[15] Other investigators have found that men with hypogonadism are more likely to have decreased sex-induced erections, delayed ejaculation, decreased semen volume, decreased nocturnal and morning erections, and hypoactive sexual desire.[6,30,54]

Insulin resistance and diabetes

A growing bunch of findings have highlighted the link between low tT levels and conditions like impaired fasting glucose, insulin resistance, T2DM, and MetS. Men with MetS and hypogonadism usually have a particular phenotype, marked by high triglyceride levels, and increased central adiposity (ie, enlarged waist circumference).[55-57]

It has been demonstrated that low tT is also linked to individual components of MetS, such as T2DM, visceral obesity, insulin resistance, dyslipidemia, and high blood pressure.[58] Several studies have indicated that low T might predict the development of T2DM and MetS, thus suggesting a potential causal relationship. However, it's worth noting that T1DM doesn't show an increased prevalence of hypogonadism or its associated risk factors.[7]

Moreover, meta-analyses focusing on T2DM demonstrated that TTh might improve body weight and waist circumference.[59] Of importance, there's a recognized bidirectional relationship between obesity and low T, underscoring their interconnectedness.[60]

Treatment options

Purposes of testosterone therapy

The primary goals of TTh are to mitigate the negative signs and symptoms of male hypogonadism and improve quality of life (QoL) while achieving eugonadal (normal) serum T levels.[7,61]

Available treatment formulations

Table 3 summarizes the most commonly prescribed TTh formulations.

The choice of TTh and the route of administration should be a topic of discussion between the physician and the patient using a shared decision-making approach. Factors influencing this choice include safety, efficacy, tolerability, availability, preference, and cost/insurance coverage.[6,44]

Compounded T products and T "boosters" are available at many compounding and online pharmacies (where officially and legally available); however, published data have demonstrated significant variability of T concentrations within such products, thus leading to concerns regarding efficacy and safety.[62]

Testosterone levels during treatment and dose adjustment

Treating physicians should aim to prescribe the minimal required dosing to improve serum T and hypogonadal symptoms. Recognizing the variations in normal ranges among the various laboratories, the current recommendations are to target correction of serum levels to the mid-normal reference range for tT in young men.[59,61,63,64]

Patients without significant symptomatic improvement and serum tT levels measured below the mid-normal range can be considered for dose escalation to improve clinical efficacy.[63] Clinical experience supports raising tT into the upper third of the normal range for patients who do not respond symptomatically at lower levels.[64] Patients with satisfactory resolution of their symptoms, but serum tT below the recommended target range, typically do not require dose adjustment.[6] Dose reduction should be prescribed in patients with serum tT concentrations consistently measuring above the normal range while on treatment.[6]

Treatment monitoring

After initiating TTh, patients should have regular monitoring for response to treatment and adverse events. Table 4 summarizes an evidence-based monitoring schedule for patients on TTh according to the authoritative opinion of this ICSM Panel.

Adjustments to treatment dose and delivery can be made based on patient response, adverse events, and bloodwork results. Testosterone levels (±gonadotropins) should be measured to determine adherence and absorption of treatment. The recommended timing of tT measurement relative to the last treatment dose will vary depending on the T formulation (ie, mid-cycle for injectables), and patients should be counseled appropriately to ensure accurate interpretation of results and response to treatment.

A patient's hematocrit should be measured at baseline and thereafter followed to ensure they are not developing polycythemia (hematocrit levels 54% or greater) during TTh (Table 4).[6,8,17,65-67] In this context, it is relevant to outline that polycythemia vera is a myeloproliferative neoplasm characterized by clonal proliferation of hematopoietic progenitor cells and is associated with an increased risk of thrombotic events (TEs). Established risk factors for TEs in patients with polycythemia vera include advanced age, TE history, and elevated hematocrit. Likewise, secondary polycythemia or erythrocytosis is a relatively common side effect of TTh and may be associated with thromboembolic events.[8,44,68-70] More specifically, a positive family history of venous thromboembolism (VTE) requires further analysis to exclude a condition of congenital undiagnosed thrombophilia-hypofibrinolysis.[71] Moreover, lower baseline hematocrit (48%-50%) should be carefully evaluated before TTh, especially in high-risk men such as those with chronic obstructive pulmonary disease (COPD) or obstructive sleep apnea syndrome (OSAS). Accordingly, the Framingham Heart Study showed that hematocrit levels 48% or greater represented a condition associated with increased risk of coronary artery disease (CAD) and mortality and was associated with cardiovascular disorders.[65] Thereof, despite it has been recently demonstrated that short TTh does not worsen global coagulation, thus suggesting that the treatment can be safely prescribed to men diagnosed with

Table 3. Most commonly available testosterone therapy formulations.

Generic Name	Dosage	Comments
Injectables Testosterone Enanthate Testosterone Cypionate Testosterone Undecanoate	100-200 mg every 1-2 weeks 200 mg every 2 weeks or 100 mg weekly 750-1000 mg every 10-12 weeks	Cost effective Typically delivered intramuscularly (IM) into large muscles including the thigh or gluteal. May require regular clinic visits Wide fluctuations in T levels require mid-cycle T monitoring Higher risk for polycythemia (TU) Relative steady-state T levels with less fluctuation compared to shorter-acting injectable formulations (TU) Limited ability to withdraw treatment if adverse effects are present
Oral medication Testosterone Undecanoate	Dose varies depending on product selection Andriol—40 mg capsules Initial dose of 120-160 mg per day in 2 divided doses Jatenzo—158-396 mg twice daily Tlando—225 mg twice daily Kyzatrex – 100-400 mg twice daily	Absorption via lymphatics enhanced with fat-rich diet Short half-life requires multiple daily dosing Clinical & biochemical variability
Transdermal Testosterone patch Testosterone gels	2.5 or 5 mg per day 5-10 g per day	Rash/skin irritation common (patch) Transfer of medication to intimate contact (gel) Steady-state T levels Variable absorption
Transnasal gel	5.5 mg (1 pump from the actuator device) applied to each nostril (11 mg total), twice daily, at least 6 hours apart. Total daily dose of 22 mg.	Reduced risk of transfer to intimate contact Potentially less suppression of spermatogenesis and risk of polycythemia
Sub-dermal pellets	150-450 mg every 3-6 months	Long-acting, steady-state T administration Minor procedure required to deposit pellets Risks of infection and/or pellet extrusion

Table 4. Testosterone therapy monitoring schedule.

	Baseline	3 months	6 months	>12 months (yearly)
Symptom evaluation	X	X	X	X
Adverse events monitoring		X	X	X
tT	X	X	X	X
Hematocrit	X	X	X	X
PSA	X	X	X	X
DRE	X			X

Abbreviations: DRE: digital rectal examination; PSA: prostate-specific antigen; tT: total testosterone.

hypogonadism,[72] these patients need to be carefully counseled prior to TTh initiation and throughout TTh itself (Table 4).

Non-univocal data have depicted that natives living at high altitudes (HAs) (ie, above 3500 m) seem to be associated with an apparent increased risk of developing stroke, probably linked to the presence of polycythemia and other associated factors such as increased blood viscosity.[73] Chronic mountain sickness is a maladaptive syndrome that affects individuals living permanently at high altitude and is characterized primarily by relative hypoventilation and secondary excessive erythrocytosis.[74] However, the pathogenesis of high-altitude polycythemia (HAPC) is still not fully understood. Previous data showed that native men at HAs are not adequately adapted if they have elevated T levels;[75] elevated serum T seems to be responsible for, or at least associated with, chronic mountain sickness. In addition, T administration increases sleep apnea in men.[76] Therefore, these panel experts recommend that a lower baseline hematocrit (48%-50%) should be carefully evaluated before TTh in men at HAs.[76]

As a whole, these findings imply that the optimum hematocrit is subgroup specific and depends on the many factors impacting blood rheology.[77] Thereof, a hematocrit level 54% or greater should require TTh withdrawal, dose reduction (concentration or application frequency), drug holiday, change of formulation, and/or blood donation/phlebotomy depending on the clinical situation to avoid any potential cardiovascular complications.

Finally, prostate-specific antigen (PSA) testing and DRE should be performed to monitor prostate health in accordance with the evidence-based guidelines for PCa screening.[6,8,35,48,63] While discontinuation of TTh may be advised while investigating a PSA elevation, significant increases in PSA while on TTh should be investigated irrespective of the use or TTh discontinuation.

Testosterone and diabetes, obesity, and MetS

Hypogonadism occurs commonly in men with MetS, which includes men with central obesity, prediabetes, and T2DM.

MetS is defined by the presence of 3 of the following 5 specific components, which must include central obesity (waist circumference > 102 cm, or otherwise specified according to ethnicity[78]), impaired glucose intolerance due to insulin resistance, hypertension, fasting hypertriglyceridemia, and low high-density lipoprotein cholesterol (HDL)–cholesterol.[79] MetS is a major factor that drives the increased risk of cardiovascular disease (CVD) in these populations, including myocardial infarction (MI), stroke, and sudden cardiac death. Prediabetes is defined as a state of intermediate hyperglycemia using 2 specific parameters, impaired fasting glucose (IFG) defined as fasting plasma glucose (FPG) of 6.1-6.9 mmol/L (110 to 125 mg/dL) and impaired glucose tolerance (IGT) defined as 2 h plasma glucose of 7.8-11.0 mmol/L (140-200 mg/dL) after ingestion of 75 g of oral glucose load or a combination of the 2 based on a 2 h oral glucose tolerance test. Men with prediabetes and T2DM are not only at an increased risk of macrovascular disease but also microvascular disorders including retinopathy, neuropathy, and nephropathy. Furthermore, men with these conditions have an increased prevalence of sexual health problems and a poorer QoL.

Several studies have confirmed that men with MetS, including T2DM, have a high prevalence of ~40% with symptoms and low serum tT levels, including reduced or absent libido, ED, and physical and psychological symptoms, all contributing to a reduction in QoL.[80,81] Erectile dysfunction is certainly more common in men with MetS and T2DM, with studies reporting a prevalence of mainly up to 70% in these disorders.[82]

Hypogonadism can co-exist with other pathologies and accounts for 30% of all ED cases. ED and hypogonadism are both independently associated with CVD and should be assessed for cardiovascular risk reduction. Therefore, all ED patients should have tT status investigated.[11,17,83-85]

The link between low T and the MetS and diabetes is due to different factors. Men with classical causes of hypogonadism—for example, Klinefelter's syndrome—have an increased risk of developing these conditions.[86] Obesity is a major factor in reducing T levels but is not associated with hypogonadism in all men with this condition.[87,88] Moreover, men with T2DM and hypogonadism do not all have obesity. The relationship is therefore more complex and requires further evaluation. Aromatase—the enzyme that converts T to 17β-estradiol (E_2)—has high activity in adipose cells, particularly in visceral fat. This effect was confirmed in a large RCT with obese men with low T being treated with leflutrazole, an aromatase inhibitor, which raised serum tT to the mid-normal range while reducing E_2.[89] Luteinizing hormone and follicle-stimulating hormone (FSH) increased, and their action on the testes stimulated both T secretion and spermatogenesis.[89] Leptin, a hormone secreted by fat cells also inhibits the hypothalamic release of GnRH and therefore LH and FSH release. Another mechanism which inhibits the hypothalamic–pituitary axis is the action of inflammatory cytokines produced by adipocytes as well as in acute and chronic illnesses, for example, infection, infarction, inflammation, and trauma including surgery. Tumour Necrosis Factor α (TNF-α) and Interleukins (IL) IL1α, IL1β, and IL-6 have all increased in the inflammatory response, causing suppression of the hypothalamic–pituitary-testicular axis, and the elevation of each of these cytokines causes insulin resistance. Reduced circulating T is known to promote adipocyte formation, increasing both the number and size of fat cells, therefore producing increased aromatase activity, leading to further lowering of the T status. These actions on T secretion are part of the hypogonadal–obesity–adipocytokine hypothesis.[90] The conclusion of these findings is that the etiology of male hypogonadism occurs by a bidirectional mechanism with obesity causing the lowering of T whereas hypogonadism increases adipocyte formation and fat deposition.[91] As detailed, hypogonadism in association with these conditions is considered to be "functional hypogonadism" and its treatment with TTh is controversial and conventionally should be managed by treating first with lifestyle changes or the underlying condition if possible.[6,10,26] Published clinical trials of diet and exercise have reported that a 10% weight loss can raise serum T levels by 2-4 nmol/L.[92] Recent data from a systematic review and meta-analysis suggested a possible role for glucagon-like peptide-1 receptor agonist (GLP-1Ras) in the therapy of functional hypogonadism related to overweight and obesity while also promoting weight loss. The limitations of the currently available literature do not allow the demonstration of a direct action of GLP-1RAs on the testicular function.[93] Bariatric surgery can achieve increases of serum tT levels of 10 nmol/L, but this is not appropriate in the vast majority of patients and not for hypogonadism alone.[92]

There is increasing evidence from large RCTs that TTh does improve insulin resistance, the central biochemical defect in MetS. This effect was first discovered by Kapoor et al.[94] and confirmed in a number of RCTs[94-96] but not all RCTs.[97] Of relevance, 1 study showed an improvement in insulin sensitivity using clamp studies.[98]

Some studies found a reduction in HbA1c, glucose tolerance, body weight, waist circumference, body fat content, cholesterol, and marker of inflammation.[95,96,98-101] Meta-analyses have confirmed these findings.[102,103] Longer-term registry studies have found that the effect of TTh in obesity and independently in men with T2DM has a prolonged benefit on weight reduction and metabolic parameters for a period of at least up to 11 years of treatment, compared to groups who were not treated with remission of diabetes in some patients.[104,105]

The testosterone therapy to prevent type 2 diabetes mellitus in at-risk men trial (T4DM), a large RCT (n = 1007) compared TTh with lifestyle against placebo with lifestyle in men with prediabetes (80%) and newly diagnosed T2DM (20%), tT <14 mmol/L (defined as hypogonadism), waist circumference >95 cm, age 50-74 years.[106] This study reported that in men with prediabetes at risk of developing T2DM, the proportion of those who progressed to T2DM was 7.6% on TTh plus lifestyle compared to 14.9% on placebo plus lifestyle. In men with newly diagnosed T2DM, TTh and lifestyle intervention reverted T2DM in 13.4% compared to lifestyle alone. After 2 years, TTh and lifestyle improved sexual function, total body muscle mass, and muscle strength in the non-dominant hand and reduced waist circumference, total body fat mass, and abdominal fat mass compared to lifestyle alone. A post-randomisation observational follow-up (mean 5.1 years) of the T4DM study recently reported that the benefit on glucose tolerance did not persist; however, only 19% of treated patients continued on TTh after the study was completed.[107]

However, the main findings of the T4D study were supported by an observational registry study that compared treated versus non-treated men with T2DM and hypogonadism at 8 years after initiation of TTh. This study reported

the risk of progression from prediabetes to overt diabetes.[108] Furthermore, a later report found that 34.3% had remission of their diabetes and 46.6% of patients achieved normal glucose regulation after an 11-year follow-up. Testosterone therapy was associated with 83.1% achieving a HbA1c target of 47.5 mmol/mol (6.5%), and 90% reached an HbA1c of 53.0 mmol/mol (7%).

The Testosterone Replacement Therapy on the Incidence of Major Adverse Cardiovascular Events (MACE) and Efficacy Measures in Hypogonadal Men (Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men = TRAVERSE) trial involved 5246 men aged 45-80 years with pre-existing CVD or men who had at least 3 risk factors for CVD and symptomatic hypogonadism. TRAVERSE is currently the largest randomized placebo-controlled trial assessing the use of TTh in hypogonadal men. Patients were randomized to receive transdermal TTh gel or a placebo gel, with dose adjustments to maintain T levels within a specific range (dose adjusted to maintain testosterone levels between 350 and 750 ng/dL).[48] Data recently published from a substudy of the TRAVERSE RCT showed that of 5204 randomized participants, 1175 had prediabetes and 3880 had diabetes, respectively.[57] Overall, the risk of progression to diabetes did not differ significantly between TTh and placebo groups (omnibus test $P = .49$). Moreover, the analyses found that the proportions of participants with diabetes who experienced glycemic remission and the changes in glucose and glycated hemoglobin levels were similar between TTh and placebo-treated groups with either pre- or diabetes.[57]

Evidence from longitudinal studies in diabetic men has shown that mortality is over 2 times greater in men with low T compared to those men who are diabetes replete over follow-up studies longer than 5 years.[109-112] Importantly, it has been reported that in treated hypogonadal men with diabetes, the mortality (20% compared to 9.6% in testosterone-replete men) is halved (8.6%), returning men to the expected mortality rate in diabetes.[109] The effect of survival with TTh has been confirmed in more recent studies.[110,113]

A number of RCTs have been conducted to study TTh in men with T2DM. Benefits of TTh on sexual health are supported by RCTs, meta-analyses, and registry studies.[95,99,113,114] Of those, some RCTs did not specifically investigate erectile function as a primary outcome; thus, RCTs in men with MetS and T2DM have found that libido improves but there are mixed results in regard to erectile function.[95,99] Furthermore, the duration of the trials may not have been long enough to detect improvements and the presence of multiple pathologies may have affected the T-induced outcome. Indeed, early evidence does demonstrate that sexual function may require longer than 6 months to give significant benefit from TTh.[115] Therefore, it has been advocated that patients with combined hypogonadism and ED should be treated with dual therapy including a phosphodiesterase type 5 inhibitor (PDE5I) as well as TTh. Uncontrolled trials have demonstrated that hypogonadal patients not responding to PDE5Is alone may improve their response to PDE5Is after initiating TTh.

In conclusion, there is now clear evidence that TTh in hypogonadal men with MetS, prediabetes, and T2DM is beneficial for general and cardiometabolic health, mortality, and sexual health. Very recent findings from the TRAVERSE RCT confirmed that TTh alone should not be used as a therapeutic intervention to prevent or treat diabetes in men with hypogonadism.[57]

The efficacy of TTh varies between patients as diabetes is a complex condition, and many have multiple co-morbidities. The heterogeneous nature of diabetic individuals also differs in duration of disease, degrees of insulin resistance and beta-cell function, age, co-morbidities, and the response to glucose-lowering medication including insulin. All of these factors may influence the response to TTh. In diabetes, it is also important to recognize that the effect of TTh on symptom improvement can take as long as 12 months. Although data are not unequivocal, the treatment of ED may require a combination of TTh and a PDE5I due to the presence of vascular disease or other causality.[112,116-119]

Hypogonadism and cardiovascular health

Endogenous T levels and CVD risk

A wealth of unequivocal evidence indicates that low levels of endogenous tT are associated with poor cardiovascular health and known risk factors for CVD, such as obesity, diabetes, and MetS.[120,121] Corona et al. performed a random-effect meta-analysis of 37 prospective observational studies published between 1988 and 2017, including 43 041 subjects, and found that low endogenous tT levels at enrollment predicted both overall and cardio vascular (CV) mortality and CV morbidity.[122] Indeed, conflicting evidence has emerged regarding the association between lower tT concentrations and CV and all-cause mortality. Some studies indicate an increased risk,[123-127] while others do not.[128]

Observational studies have shown that hypogonadism is associated with increased mortality rates in men over the age of 40 years.[121,123,124,129] These studies indicate that hypogonadal men may have up to twice the risk of mortality compared to those with normal tT levels.[109,123] For instance, research on men admitted to the hospital with acute MI revealed that low tT levels were independently linked to higher mortality rates after 30 days.[125] Another study conducted on veterans found that mortality rates over an average 4.3-year period were 20.1%, 24.6%, and 34.9% for those with normal, equivocal, and low T levels, respectively.[123]

A larger, longer-term study involving 2314 men aged 40-79 years discovered that every 173 ng/dL increase in serum tT was associated with a 21% lower risk of all-cause mortality.[129] This finding, which controlled for various factors such as age, BMI, and blood pressure, excluded deaths within the first 2 years of follow-up.[129]

The Rancho Bernardo study, a population-based study of healthy aging in Caucasian residents of a Southern California Community, involving men aged 50-91 years, found an inverse relationship between tT and bioavailable T levels and the risk of death. Low tT also predicted a higher risk of death due to CV and respiratory diseases.[124]

A prospective follow-up cohort study performed by Malkin et al. of 930 consecutive men undergoing coronary angiography with established coronary disease and followed for a mean of 6.9 ±2.1 years found bioavailable T (bio-T) <2.6 nmol/L, and mortality was higher in hypogonadal than in eugonadal men (21 vs. 12%, $P = .002$). The prevalence of biochemical T deficiency was 24%.[130]

In the Osteoporotic Fractures in Men (MrOS) Sweden study, involving 2416 men aged 69-81 years, lower baseline tT

concentrations were found to be linked with a higher risk of cardiovascular events.[131] A similar association was observed in the Health In Men Study (HIMS), which involved 3690 men aged 70-89 years, with lower baseline tT concentration associated with an increased risk of stroke but not MI.[132]

Yet, the relationship of increased CV risk with low endogenous tT levels was not validated in the first systematic review and meta-analysis, restricting the literature to prospective cohort studies of men with endogenous tT levels measured by mass spectrometry. This analysis, completed by Marriott et al. was the first to utilize at least 5 years of follow-up data from fitted models that controlled for age, smoking status, BMI, or waist circumference of participants. Despite considerable variation of mean tT, a meta-regression estimated no significant dependence on mean age at recruitment among studies. Meta-analyses demonstrated negligible heterogeneity and no significant effect of a 5 nmol/L increase in tT on the risk of all-cause mortality or death from CVD, thus not finding any association of endogenous tT and CV or all-cause mortality.[133]

Similarly, a large study conducted on 210 700 men from the UK Biobank, aged 40-69 years and followed for 9 years, did not find any association between baseline tT concentrations and incident CV events, MI, stroke, or heart failure when analyzed as separate outcomes.[128] However, it is worth noting that in this analysis, men with lower baseline tT concentrations had higher all-cause mortality, although the association was non-linear. A similar nonlinear (U-shaped) association of baseline tT concentrations with all-cause mortality was seen in the HIMS study of men aged 70 years and older.[132] Thus, lower endogenous tT concentrations may be related to all-cause rather than CV mortality risk, but the non-linear nature of the association merits consideration and causality remains unproven.

This suggests that the association of lower endogenous tT concentrations with CV events may be more prevalent in older men rather than middle-aged individuals, with strokes being more strongly correlated than MIs.

As a whole, RCTs confirm that T does improve cardiac ischemia in men with chronic stable angina and functional exercise capacity and VO_2 max in men with chronic heart failure.[134] These effects have been shown to persist for at least 1 year. A recent review depicted that these findings are supported by mechanistic studies, which have shown that T is a coronary vasodilator and has a positive impact on other arteries within the body. These effects are acute as well as chronic, with T able to alter vascular responsiveness to established endogenous vasoactive agents including noradrenaline and acetylcholine.[134]

In summary, a number of observational studies have shown significant associations between male hypogonadism and increased mortality rates, particularly related to cardiovascular and all-cause mortality. Although considering the inevitable heterogeneity among observational studies, the most updated systematic review involving prospective cohort studies of community-dwelling men with sex steroids measured using mass spectrometry and at least 5 years of follow-up to July 2019, with bridge searches to March 2024, at 2-stage random-effects IPD meta-analyses found that men with baseline tT concentrations below 7.4 nmol/L (<213 ng/dL) had higher all-cause mortality, and those with tT concentrations below 5.3 nmol/L (<153 ng/dL) had a higher CVD mortality risk.[128]

TTh and cardiovascular disease risks

Testosterone therapy has been a topic of debate regarding its potential association with MACE. The controversy surrounding this issue has been fueled by studies that initially suggested an increased cardiovascular risk with TTh.[135,136] However, it was later outlined that these studies had flaws and their findings were unreliable. Despite this, the US Food and Drug Administration (FDA) responded to the initial concerns by issuing a warning statement in 2015, recommending increased caution when prescribing TTh.[137]

Observational studies[121] and an RCT[138] have found no credible evidence supporting an increased short-term to medium-term risk of CVD with TTh, despite the fact that there is a paucity of data evaluating its long-term safety.[139] Additionally, TTh has shown significant improvements in lipid profiles, blood sugar levels, and blood pressure, indicating potential benefits for individuals with MetS. For instance, in a nested T registry, Saad et al. conducted subgroup analyses on patients aged ≤65 years old or >65 years old, demonstrating that TTh is equally effective in improving anthropometric parameters and metabolic functions in both age groups, contrary to previous assumptions about age-related differences.[140] This observational study is not without inherent limitations. There was no control group, and the authors did not have precise data on concomitant medications, changes in medications, or lifestyle changes in lifestyle consistent with weight reduction.

Vigen et al. conducted a retrospective analysis within the Veterans Administration health care system, studying men who had undergone coronary angiography and received TTh.[141] The study found that men with serum tT levels below 300 ng/dL who received T prescriptions had a higher rate of MI, stroke, and death compared to untreated men. Although no statistically significant differences were observed at years 1, 2, or 3, the overall rate of events throughout the study was reported to be significantly higher (29%) in men receiving TTh.[141] After a comprehensive analysis of all the data, the ICSM 2024 Panel made a certain number of considerations. Interestingly, the actual rate of adverse events was only half as high in the group receiving TTh (10.1%) compared to the untreated group (21.2%). However, Vigen et al.[141] did not acknowledge this fact and instead came to an opposite interpretation of their data, using complex statistical methods that involved adjusting for over 50 variables. The methodology used in this study, such as stabilized inverse propensity treatment weighting and time-varying models, is challenging, and was unvalidated, and ultimately reversed the results of the raw data, which initially showed a lower percentage of adverse events in the TTh-treated group compared to untreated men. Furthermore, there were multiple data errors in the study, which led to 2 official corrections by the authors.[142,143] It is relevant to point out that the FDA's comment on the Vigen et al. study was that, due to its limitations, "it is challenging to attribute the reported findings to testosterone treatment."[144]

Despite these issues, the lower percentage of adverse CV events in the TTh-treated group aligns with the findings of 2 previous studies that reported a 50% reduction in mortality among men receiving TTh compared to those who did not.[109,145]

Finkle et al. conducted a retrospective study using a health insurance database to examine rates of nonfatal MI within

90 days of T prescription, comparing them to MI rates in the previous 12 months.[146] The post-prescription period is considered the time until the first prescription refill, which could have been 30 days instead of 90 days for some men. The study reported a rate ratio of 1.36 for MI post-prescription compared to pre-prescription, which increased to 2.19 in men over 65 years old. In contrast, no increase in MI rate was observed in men who received a prescription for a PDE5I. This study suggested that the increased period of risk of ASCVD events in men on TTh was the initial 3-6 months following the initiation of TTh.

Due to the study's use of an insurance claims database, the available information was limited to diagnosis codes, procedure codes, and prescriptions. Crucially, there was no information on several CV risk factors such as diabetes, hypertension, hyperlipidemia, smoking history, and obesity, as well as no data on serum tT levels or lipid profiles. Additionally, the dataset's limitations as an investigative tool for assessing CV risk were further highlighted by the fact that the endpoint—that is, nonfatal MI—relied solely on an insurance diagnosis code without verification of actual occurrences or measures to increase detection accuracy.

A key concept not addressed by Finkle et al.[146] is that male hypogonadism itself has been identified as a risk factor for CV events (albeit not absolutely incontrovertible). Given the short T exposure time of 30-90 days, 1 unexplored possibility is that any observed increased risk of MI was due to the underlying condition rather than from TTh itself. For this reason, the FDA analysis concluded that "it is difficult to attribute the increased risk for non-fatal MI seen in the Finkle study to testosterone alone and not consider that the study participants might have remained TD on treatment and thus at higher risk for non-fatal MI."[144]

The TOM trial, involving 209 men aged 65 years and older with mobility limitations and specific baseline T concentrations, was discontinued due to a higher rate of loosely defined adverse cardiovascular events in the T group compared to the placebo group.[147] Another RCT on 274 frail or intermediate-frail men aged 65 years and older with low baseline tT concentrations found no increase in CV adverse events with TTh and even reported improvements in physical function.[148]

The Testosterone Trials (T Trials) were published in 2016 and included 790 men aged 65 years and older with specific symptoms and low baseline T concentrations receiving TTh or placebo for 12 months. Each man participated in 1 of 3 trials: Sexual Function Trial, Physical Function Trial, and Vitality Trial. The study found modest improvements in sexual function with TTh but no benefits for walking distance or vitality.[138] TTh was associated with improved sexual desire, erectile function, overall sexual activity, bone mineral density, estimated bone strength, mood, and correction of unexplained anemia. Both TTh and placebo-treated groups in the T Trials had a small number of MACE during the treatment period, which was limited to a single year. In a CV substudy, TTh was linked to increased non-calcified coronary artery plaque volume without changes in coronary artery calcium score.[149] It's important to note that the groups in these studies were imbalanced in terms of plaque volumes at baseline and at the end of the study. In contrast, the Testosterone Effects on Atherosclerosis Progression in Aging Men (TEAAM) RDBPCT trial involving 308 men aged 60 years and older, TTh for 3-year duration did not alter the rate of change in coronary artery calcium score, nor the rate of progression of carotid artery intima-media thickness (CIMT), compared with placebo.[150]

As detailed, the specific aim of the TRAVERSE prospective trial was to investigate 3 different safety endpoints.[48] First, the primary safety endpoint was the first occurrence of any component of MACE, a composite of death from CV causes, non-fatal MI, or non-fatal stroke in a time-to-event analysis (ie, data on endpoint events that occurred more than 365 days after discontinuation of TTH or placebo were censored). A secondary CV end point was the first occurrence of any component of the composite of death from CV causes, non-fatal MI, non-fatal stroke, or coronary revascularization in a time-to-event analysis. Lastly, tertiary end points included death from any cause, hospitalization, or an urgent visit for heart failure, peripheral arterial revascularization, and venous thromboembolic events. Overall, non-inferiority required an upper limit of less than 1.5 for the 95% CI of the HR among patients receiving at least 1 dose of TTh or placebo, respectively. Over a mean treatment duration of 22 months, TTh was found to be non-inferior to placebo in terms of incidence of MACE in men with hypogonadism and preexisting or a high risk of CVD. Of key clinical relevance, nearly half of the patients enrolled in the TRAVERSE were 65 years of age or older, and more than half had preexisting CVD. As a whole, the incidence of PCa was 0.5% and 0.4% in the TTh and in the placebo group, respectively ($P = .87$). Conversely, there were unexpected higher incidences of pulmonary embolism (a component of the adjudicated tertiary end point of VTE; 0.9% vs. 0.5% in TTh vs. placebo groups), non-fatal arrhythmias warranting intervention (5.2% vs. 3.3%), atrial fibrillation (3.5% vs 2.4%), and acute kidney injury (2.3% vs. 1.5%) associated with TTh. While these were statistically significant, the number of these events was quite small.

As for treatment-emergent adverse events (TEAEs), although most reported cases of thrombosis associated with TTh have been in men with underlying thrombophilia, as detailed above, previous and recent meta-analyses did not show an association between VTE and TTh in wider populations of men with actual TD. Overall, TRAVERSE findings did support current guidelines that TTh should be used with caution in men who have had previous thromboembolic events.

A recent systematic review and meta-analysis of 24 studies (including 14 RCTs) with a total of 4027 and 310 288 TD male patients, from RCTs and from observational studies, respectively, concluded (based on RCT-derived data) that TTh did not influence the risk of arterial thrombosis stroke, MI, VTE, pulmonary embolism, and mortality.[68] Another meta-analysis of 13 RCTs (n = 5050) concluded that TTh was not associated with VTE as compared with placebo. Similar estimates were obtained for deep vein thrombosis and pulmonary embolism outcomes.[70] Likewise, a recent meta-analysis of 26 RCTs did not find statistically significant differences between the TTh group and the control group in terms of atrial fibrillation, as well as of all-cause mortality, CV-related mortality, myocardial infarction, stroke, congestive heart failure, pulmonary embolism, and VTE. Of relevance, the sensitivity analysis and publication bias assessment supported the robustness of these findings and the meta-regression analysis found no significant associations between clinical outcomes and potential covariates, including age, diabetes, hypertension, dyslipidemia, and smoking in actual hypogonadal men.[151]

The ICSM 2024 Panel points out that it is important to note that the TRASVERSE trial has limitations. First, patients have been enrolled without checking out for COVID-19 at the entrance, which has been recently associated with male hypogonadism and severe clinical outcomes.[53] However, Pencina et al. recently outlined that in men with hypogonadism and CVD or increased risk of CVD belonging to the TRAVERSE trial, baseline and pre-COVID-19 on-treatment tT, dihydrotestosterone, and E_2 levels were similar in those who developed COVID-19 and those who did not; however, COVID-19 attenuated the treatment response to TTh.[152]

Second, the target T range used in the TRAVERSE trial may have been too low to detect certain benefits or harms (median T levels achieved ~350 ng/dL) as normal physiological serum T levels for men range from 300 to 1000 ng/dL. It is generally recommended to maintain tT levels in the mid-normal range, which is often achieved with TTh injections rather than gel. Additionally, since TTh is often required for long-term treatment, further studies are needed to determine its long-term safety and efficacy.

Testosterone and sexual function

Historically, T has been known as a "sex hormone" and, for centuries, T has been thought to be an elixir for sexual function and vitality.[153] Today, we know that T plays an important role in overall sexual function in men. In particular, T has been shown to affect erectile function, libido, and ejaculatory function.[6] This section aims to discuss the basic science mechanisms and the results of recent clinical trials on how T affects overall sexual function.

Testosterone has been thought to improve erectile function via 4 mechanisms. These mechanisms include the regulation of nitric oxide synthase (NOS) expression, regulation of PDE5 activity, regulation of smooth muscle contractile pathways, and finally, regulation of penile nerve function.[154] Androgens regulate the expression of neuronal NOS (nNOS) and endothelial NOS (eNOS) in corpora cavernosa.[155] Studies have demonstrated that castrated animals have a significant decrease in nNOS expression in the penis[156] and T replacement results in normal nNOS expression in penile nerve fibers.[156] Nitric oxide–mediated relaxation of cavernosal smooth muscle is thought to be androgen dependent.[157] Animal studies have demonstrated that androgen deprivation reduced muscle relaxation effects PDE5Is after nerve stimulation.[154] These studies have also shown that PDE5Is significantly enhanced intracavernosal pressures in the presence of T. Further animal studies have demonstrated that decreased androgens result in increased connective tissue and corporal fibrosis by resulting in a decrease in Vascular Endothelial Growth Factor (VEGF), Fibroblast Growth Factor (FGF), and Insulin-like Growth Factor (IGF-1). In addition, decreased androgen has been shown to result in up-regulation of connective tissue growth factor (CTGF) and Transforming Growth Factor Beta 1 (TGFβ-1).[158]

Testosterone also plays an important role in libido in men. Androgen receptors are expressed in numerous areas throughout the brain that are responsible for libido, such as in the medial preoptic nucleus, hypothalamus, amygdala, and pre-frontal cortex.[159] Functional magnetic resonance imaging (fMRI) has demonstrated increased activity in these regions with TTh.[160]

Testosterone levels have been associated with premature and delayed ejaculation.[29,161] Testosterone receptors are expressed at numerous levels of supraspinal control of ejaculation (medial preoptic nucleus, amygdala, and posterior thalamus) as well as in the spinal cord in regions critical in controlling ejaculation, such as the spinal nucleus of the bulbocavernosus.[162] In addition, the emission phase of the ejaculatory reflex is influenced by T. It is believed that this T effect on the ejaculatory pathway is through the PDE5/cGMP pathway.[163] Low serum tT levels have been associated with delayed ejaculation, while higher tT levels have been associated with premature ejaculation (PE).[29] One plausible mechanism for elevated tT resulting in PE is due to T's ability to reduce serotonin levels and its metabolite, 5-hydroxyidoleacetic acid within the hypothalamus.[162] The reduction in serotonin has been shown to decrease the ejaculatory time.

Numerous clinical trials have associated lower tT levels with ED, low libido, and delayed ejaculation. A study of roughly 3500 men complaining of sexual dysfunction found that low libido was the best correlated symptom with low tT, while loss of erection was better explained by an older age or by high chronic disease score (CDS).[164-166] Low tT levels have been associated with decreased penile blood flow, but TTh has been associated with only a modest erectile function improvement. In a study of roughly 2500 men, Corona et al. assessed the relationship between prostaglandin E1 stimulation and penile blood flow. These authors found that T levels were positively associated with an increased penile blood flow ($\beta = 0.069$, $P = 0.001$).[167,168]

Currently, 5 meta-analyses have assessed the effect of TTh on ED.[169] When only subjects with low T (ie, <12 nmol/L in 2 studies and <10 nmol/L in 3 studies, respectively) were considered, ED improved in all the meta-analyses with a standardized mean difference ranging from 0.16 [0.06; 0.27] to 1.87 [0.31; 3.43]. When only assessing studies using validated questionnaires, such as the International Index of Erectile Function (IIEF), TTh induced improvement in IIEF-erectile function domain (IIEF-EF) was relatively modest: mean difference = 2.31 [1.41; 3.22] points of IIEF-EF. Indeed, TTh resulted in only a modest 8% increase in IIEF-EF. Moreover, TTh induced improvement in ED was highly variable due to confounding factors, such as age and comorbid conditions.[170] A very recent secondary analysis of the T4DM trial using data from 792 (79%) men who had complete IIEF-15 interestingly showed that baseline IIEF domain scores were inversely related to age and waist circumference but unrelated to serum tT or E_2.[106] Therefore, TTh improved all 5 IIEF-15 domain scores, with stronger effects on sexual desire and orgasmic function in older men, and sexual desire in men with higher depression scores; conversely, TTh per se had no impact on depression. Of clinical relevance, regardless of treatment, reductions in waist circumference were associated with improved erectile function, and reductions in depression scores correlated with better overall sexual function. Clinically significant improvement (CSI) in erectile function and sexual desire occurred in 3% and 10% of men, respectively, and was inversely related to baseline function. As clinically expected, CSI improvements in erectile function and sexual desire were greater in younger and older men, respectively.[171]

As previously detailed, numerous studies have shown that TTh in combination with PDE5Is is more effective than monotherapy with a PDE5I to improve erectile function,[172] although findings are not unequivocal.

Thereof, numerous international guidelines do not recommend TTh as monotherapy for ED at this time. For instance,

the AUA ED Guidelines recommend that serum tT should be measured in all men with ED and that men with ED and hypogonadism who are considering ED treatment with a PDE5I should be informed that PDE5Is may be more effective if combined with TTh.[8,83] The EAU Guidelines on Sexual and Reproductive health recommend to routinely assess serum tT in every man presenting with ED (strong recommendation), and to use TTh as first-line treatment in patients with symptomatic hypogonadism and mild ED (strong recommendation) and a combination of PDE5Is and TTh in more severe forms of ED, as it may result in better outcomes (weak recommendation).[16] Conversely, the latest EAA Guidelines reported that at present, the efficacy and place of combination therapy with TTh and PDE5i in the management of ED in functional hypogonadism remains unclear.[10]

Testosterone's effect on libido is slightly more complex. Low libido in men can be due to multifactorial causes and due to other hormones, such as elevated prolactin, low E_2, or increased and decreased thyroid levels. Several clinical studies have demonstrated that low tT levels are associated with decreased libido in men. In a survey of 3714 men presenting with sexual dysfunction, 36.4% of men were found to have low libido.[173] Age-adjusted association between low T levels and low libido has been reported in many epidemiological studies.[174,175] In the EMAS, low libido was present in 27.5% of hypogonadal men and a reduction in each 1 nmol/L T below 8 nmol/L was associated with a 48% (20%-83%) increased risk for low libido.[15] Two studies suggested a tT less than 11 nmol/L and a cfT less than 225 pmol/L significantly increase the risk of low libido in hypogonadal men.[176]

Of the T Trials, the Sexual Function Trial demonstrated a significant improvement in sexual frequency, libido, and overall erectile function with TTh compared to placebo.[177] However, these improvements were only modest. This study used the Psychosexual Daily Diary Question 4 (PDQ-4) to assess sexual frequency. The PDQ-4 asks participants to list how many of 12 specified activities (ie, intercourse, masturbation, orgasm, sexual daydreams, anticipation of sex, sexual interactions with partner, flirting toward you, flirting by you, ejaculation, night spontaneous erection, day spontaneous erection, and erection in response to sexual activity) they engaged in each day of the week, and the daily count is averaged over 7 days for a total score ranging from 0 to 12. A greater increase in the tT level was associated with a greater increase in the PDQ-Q4 score ($P < .001$). However, this improvement in sexual activity was not significant at 12 months ($P = .08$). Testosterone therapy was also associated with increased sexual desire according to changes in the Derogatis Inventory of Sexual Function-Men-II sexual desire domain DISF-M-II scores (treatment effect, 2.64; $P < .001$). While there was a significant improvement in IIEF-EF scores (treatment effect 2.64; $P < .001$), this is not considered clinically significant in most cases.

As a substudy from the TRAVERSE RCT,[48] the Sexual Function Study[178] determined the efficacy of TTh in improving sexual activity, hypogonadal symptoms, libido, and erectile function among men reporting low libido. Among 5204 men, 45-80 years, with 2 tT concentrations <300 ng/dL, this study enrolled 1161 men with low libido and randomized them to receive placebo (n = 574) or 1.62% TTh gel (n = 587). The primary endpoint was a change from baseline sexual activity score using the PDQ-Q4. Secondary endpoints included change from baseline in symptoms of hypogonadism using the Hypogonadism Impact of Symptoms Questionnaire (HIS-Q) and changes in erectile function using the IIEF-5. Men in the TTh group had significantly greater increase in average daily sexual activity than men in the placebo group at 6 and 12 months (estimated between-group difference 0.49, 95% CI 0.19, 0.79, 0.47, 95% CI 0.11, 0.83, and 0.48, 05% CI: -0.01, 0.96, at 6, 12, and 24 months, respectively; omnibus test $P = .011$). This treatment's effect on sexual activity was sustained at 24 months. Sexual desire, assessed by the HIS-Q, improved more in the TTh than in the placebo group (estimated between-group differences: -3.9, 95% CI -5.8, -1.9 at 6 months; -3.3, 95% CI -5.5, -1.1 at 12 months; and -3.4, 95% CI -5.9, -0.9 at 24 months, respectively, omnibus test $P = .001$). Finally, changes in IIEF-5 did not significantly differ between the TTh and the placebo groups (estimated between-group differences: 0.6, 95% CI -0.4, 1.6 at 12 months and -0.2, 95% CI -1.7, 1.4, at 24 months, omnibus test $P = .443$). Therefore, this study found that a 2-year TTh significantly improved hypogonadal symptoms, sexual desire, and sexual activity but not erectile function in hypogonadal men.[178]

Overall, T levels affect libido, erectile function, and ejaculatory function in men with the greatest effect appearing to be on libido. Conversely, TTh has a modest and variable effect in improving erectile function (mostly mild ED) in hypogonadal men.

Therefore, the ICSM 2024 Panel considers that TTh can be used as monotherapy only in patients with mild ED and absolute demonstration of hypogonadism; conversely, TTh should not be use as monotherapy for ED but rather in combination therapy with PDE5Is or intracavernosal injections in hypogonadal men to improve overall erectile function, despite the fact that data are not unequivocal. Finally, men presenting with delayed ejaculation should have a serum tT value assessed and TTh should be considered if their serum tT levels are low.

Testosterone therapy and less specific signs/symptoms associated with male hypogonadism

From a clinical standpoint, the clinical phenotype associated with male hypogonadism is grouped into more specific symptoms (including, reduced libido, ED, decreased spontaneous/morning erections, low mood and mood deflection, and decreased vigorous activity) and less specific symptoms (eg, hot flushes, decreased energy, decreased physical strength, concentration difficulties), respectively. In this setting, among the various substudies from the TRAVERSE RCT,[48] 3 quite recently published trials deserved to be briefly summarized.

Depressive symptoms

Bhasin et al. grouped a cohort of participants belonging to TRAVERSE RCT cohort into (1) men with rigorously defined, late-life-onset, low-grade persistent depressive disorder (LG-PDD) (49, 1.5%)—previously defined "dysthymia"; (2) men with significant depressive symptoms (2643, 50.8%); and, (3) all randomly assigned men (5204 participants).[179] Of all, men with rigorously defined LG-PDD did not differ between treatment groups, possibly reflecting low statistical power. Conversely, in men with significant depressive symptoms, TTh was associated with modest but significantly greater

improvement in terms of mood (as assessed using the HIS-Q mood domain score; omnibus test $P = .008$) and energy (omnibus test $P = .01$) while not in terms of cognition and sleep quality. Similar findings were also observed in all randomly assigned participants.[179] Overall, the TRAVERSE trial depicted the attributes of good trial design, thus including the adoption of HIS-Q, a validated, psychometrically robust instrument designed specifically for men with hypogonadism. Therefore, although it is clinically relevant to outline that the cause of hypogonadism was not determined for the enrolled participants, these findings clearly demonstrated that middle-aged and older men with confirmed hypogonadism should be evaluated for depressive symptoms; conversely, TTh alone did not emerge to represent an effective treatment option for most men with clinical depressive disorders.[179] Therefore, the ICSM 2024 Panel recommends against TTh for the sole purpose of treating depressive symptoms in hypogonadal men (Box 2).

Bone health and fractures

In a further substudy from the TRAVERSE RCT, Snyder et al. examined the risk of clinical fracture in a time-to-event analysis.[180] The main fracture endpoint was the first clinical fracture, defined as a clinical spine or non-spine fracture that was documented by imaging or surgery and confirmed by adjudication. Over a median duration of participation of 3.19 years (IQR, 1.96-3.53), a total of 91 of 2601 (3.5%) participants in the TTh and 64 of 2603 (2.46%) participants in the placebo-treated group, respectively, had 1 or more clinical fractures (HR 1.43; 95%CI 1.04-1.97). Overall, and unexpectedly, the fracture incidence also appeared to be higher in the TTh group for all other fracture end points.[180] The Authors explained that they did not expect those results, according to previous literature data showing TTh to increase areal and volumetric bone mineral density and to improve many structural and mechanical measures of trabecular bone.[180] Therefore, the ICSM 2024 Panel recommends against TTh for the sole purpose of reducing fracture risk in hypogonadal men with high fracture risks (Box 2).

Anemia

A further substudy from TRAVERSE RCT was aimed at investigating the proportion of participants with anemia (ie, hemoglobin <12.7 g/dL) whose anemia remitted (ie, hemoglobin ≥ 12.7 g/dL) over the RCT duration (Anemia study).[181] Despite the fact that the cause of anemia in the enrolled participants was not ascertained, of 815 participants who met eligibility criteria for anemia (namely, 390 in TTh and 425 in placebo group, respectively), the proportion of those who eventually experienced correction of anemia was significantly greater in the TTh group as compared with the placebo-treated group throughout the overall trial duration (omnibus test $P = .002$). Similar findings were observed for hemoglobin increases greater than 1 g/dL (omnibus test $P < .001$). Conversely, among those without anemia at baseline, a significantly smaller proportion of participants in the TTh group developed anemia post-randomization compared to placebo group (omnibus test $P = .02$). Therefore, the authors concluded that in middle-age and older men with confirmed hypogonadism and anemia, TTh was more efficacious than placebo in correcting anemia.[181]

Fertility-preserving strategies in testosterone therapy

In men who desire paternity, gonadotropin therapy should be considered the standard in men with secondary hypogonadism.[182,183] Recombinant human chorionic gonadotropin (rhCG) and recombinant LH formulations offer comparable effects to urinary-derived preparations. According to a meta-analysis of the available evidence, hCG should be administered with FSH since combined therapy results in better endocrine and exocrine outcomes.[184]

Conversely, TTh per se is a very effective inhibitor of spermatogenesis. Men on TTh experience reduced sperm production, frequently to azoospermia, and notice diminished testicular volume (TV). Therefore, the male factor reproductive specialist must take an accurate history and account for any TTh in their patients. Since hypogonadism has become an increasingly prevalent diagnosis and has noted a demographic shift to younger ages, offering spermatogenesis-preserving T modulation is a critical part of any clinician providing men's health services.[185]

Thankfully, there are many tools in the andrologist's tool chest to improve a man's T and preserve sperm production and TV. Additionally, sperm recovery after TTh is almost universally possible with the right protocol. This section will sketch out a playbook for the practicing male health specialist to offer state-of-the-art, evidence-based hormone therapy to either improve spermatogenesis or recover sperm production in men with a history of TTh.

Exogenous tT not only shuts down LH production by disrupting the negative feedback loop but also stops FSH production as tT inhibits GnRH secretion. Applying the organizational rubric of hypogonadism to primary and secondary hypogonadism, one categorizes TTh as a form of secondary, albeit iatrogenic, hypogonadism. This fact is critical to understanding how to recover a man with a history of TTh use. Whatever the therapy employed, it must stimulate both LH and FSH.

Goals of therapy

The ideal plan to recover a man from TTh will manage his symptomatic relief and expedite spermatogenic recovery and TV. The simplest therapy to recover spermatogenesis in a man withdrawing from TTh is to stop treatment completely and rapidly. Allow the pituitary gland to recover, which, by most estimates, takes anywhere from 3 to 24 months to generate a normal semen analysis.[186] Withdrawing a man from exogenous T without a recovery plan may result in numerous side effects, for example, night sweats, weight gain, brain fog, and irritability.

Available treatments

As detailed, post-TTh discontinuation goals are to recover spermatic function and TV in men previously on TTh and/or preserve testicular function in TTh naïve men. Men with a history of anabolic unprescribed TTh, prescribed TTh, and men with no previous history of TTh will likely respond to the following treatment options, although dosing may vary based on etiology of hypogonadism.

1) Human chorionic gonadotropin

Human chorionic gonadotropin is a compound that acts as a biochemical surrogate for LH. The 2 hormones share a

beta subunit that promotes the same T-producing response in the Leydig cell of the testis. hCG will only be effective in men with functioning Leydig cells. Men post-bilateral orchiectomy and men with severe testicular failure will not respond to hCG. Clinically, hCG is very effective for recovery of spermatogenesis in men on TTh. Exogenous T shuts down pituitary production of LH. Since Leydig cells recognize hCG as LH, it is a direct stimulant for the Leydig cell to initiate T synthesis. Men with primary testicular failure with mildly elevated LH and FSH levels (and are, therefore, not good candidates for pituitary modulation) may modestly benefit from hCG therapy. Men with severe failure, such as those with Klinefelter syndrome and baseline extremely elevated gonadotropins, will also not likely see benefit from hCG.

hCG has a very favorable side effect profile. Indeed, side effects are consistent with any product that raises T levels, including water retention and acne. Further, men with needle aversion will have difficulty injecting the subcutaneous drug 2-3 times a week.

2) Recombinant or urinary-derived FSH

As detailed, in men with secondary hypogonadism, the anterior pituitary gland is neither producing sufficient LH nor FSH. Common causes include genetic etiologies, head trauma, and medications. Up to 100% of men with traumatic brain injury will have acute suppression of gonadotropin release, and 11.4%-32% may sustain chronic gonadal failure with some degree of improvement over time.[187] Chronic opioid use often suppresses LH/FSH to undetectable levels. Similarly, men on TTh stop producing gonadotropins. The classic, albeit rare, Kallman syndrome accounts for the majority of genetic hypogonadotropic hypogonadism and is characterized by absent chronological puberty and anosmia.[7,188,189] The greatest data for using recombinant FSH are in the Kallman population as this treatment, combined with hCG, will induce puberty and spermatogenesis. FSH products are available in the form of human menopausal gonadotrophin and rFSH.

Occasionally, men with long-term anabolic steroid use will not respond to hCG alone and may benefit from rFSH therapy as well. If, after 3 months of hCG, a man's sperm production does not return, he may benefit from adding.[190] There are no clinical trials investigating the use of rFSH in anabolic steroid users, but case reports suggest there may be a limited benefit to this approach.[191]

3) Aromatase Inhibitors

Aromatase inhibitors (AIs) enzymatically block the conversion of T to E_2, which elevates serum T and intra-testicular testosterone (ITT) where it may benefit spermatogenesis. Treatment goals are to maintain a T to E_2 ratio of 10:1 or greater or keep total E_2 less than 30 to minimize hyperestrogenic side effects.[192] Dosing protocols range from 1 mg daily at the high end and 1 mg twice a week at the low end. The dosing should be appropriate for the titration of E_2 levels.

There may be a role for letrozole in weight loss in obese men with hypogonadism.

Initially drugs prescribed for estrogen-sensitive breast cancer, AIs have recently garnered a lot of attention in men's health. Anastrozole offers an adequate tolerability and safety profile. However, joint pain and headache have been described. Long-term use (greater than 6 months) can decrease bone density and HDL levels, an observation explained by the important role of E_2 in maintaining healthy bone mass and lipid profiles in both men and women.[193] There has certainly been an overprescribing of AIs in TTh clinics to counteract high E_2 levels and prolong the effects of weekly T injections.

More recently, data from a placebo-controlled, double-blind RCT, in 70 sites in Europe/USA to investigate safety and efficacy of leflutrozole—an AI being investigated as a treatment for obesity-associated hypogonadotropic hypogonadism (OHH) and specifically developed to be dosed at lower levels and with less suppressive action than AIs approved for management of cancer—showed that it normalized tT levels in OHH men and improved semen volume/total motile sperm count vs. placebo.[89] Treatment-emergent adverse events were more common in leflutrozole-treated groups and included raised hematocrit, hypertension, increased PSA, and headache.[89]

4) Selective Estrogen Receptor Modulators

Selective Estrogen Receptor Modulators are a clinically proven way to boost T levels and recover spermatogenesis in men with previous exposure to exogenous T. Selective Estrogen Receptor Modulators essentially gaslight the anterior pituitary gland to secrete higher LH and FSH levels, thereby stimulating Leydig cell production and spermatogenesis. The mechanism is to block estrogen feedback and convince the pituitary that it is in a state of primary failure. The 2 most prescribed SERMs are clomiphene citrate and tamoxifen. In some countries, clomiphene citrate also has a commercially available E-stereoisomeric form, enclomiphene, which studies have shown may have a more androgenic effect.[194] These SERMs do not work well for men with primary hypogonadism. A recent study by Jiang et al. showed a cutoff level for FSH of 7 mIU/mL to consider seeing improvements in spermatogenesis.[195] This effect plateaus at 9 months of therapy.

A meta-analysis by Huijben et al. including 15 studies (n = 566) showed that sperm concentration and motility were significantly higher during clomiphene citrate treatment with no difference seen in sperm motility. Their data also demonstrated that T, FSH, LH, and E_2 were higher on treatment. No serious TEAEs were reported in the study's follow-up; therefore, clomiphene citrate treatment appears safe and effective with 10 studies reporting a 17% pregnancy rate (0%-40%).[196] Conversely, Gundewar et al. reported in their systematic review that some men face paradoxical results during treatment with this SERM, and some maintained persistently lower quality seminal parameters after treatment discontinuation.[197] In a recent systematic review, de Silva et al. found heterogeneous results on sperm parameters in SERM treatment studies and also highlight low certainty of evidence supporting data. However, they conclude that SERMs may improve semen parameters, particularly when obesity is concomitant.[198] Therefore, SERM therapy for fertility recovery in men must be highly individualized and monitored.

Dosing regimens for clomiphene vary. A commercial pill is only available in a 50 mg dose, with the usual dose of 25 mg a day or 50 mg every other day to prevent tachyphylaxis. Both dosing regimens result in improvement of T levels into the eugonadal range.[199] The side effect profile of SERMs in men is well-tolerated. Common side effects include headaches, weight gain, mood lability, worsening libido, and irritability. However, rarely do men feel that these side effects are significant enough to stop therapy. Anecdotally, many male reproductive specialists report that a significant proportion of their patients do not feel any androgenic effects and, rarely, men feel worse on clomiphene.

Enclomiphene is a racemized form of zuclomiphene and enclomiphene, 2 clomiphene stereoisomers. Enclomiphene theoretically has a more androgenic profile than clomiphene, but there has never been a head-to-head study to prove this. Enclomiphene has been under consideration for FDA approval since 2007 but has no formal path to approval. However, it is a commonly prescribed compounded drug. Dosing regimens of enclomiphene are similar to clomiphene, although, as a compounded drug, available dosing typically ranges from 6.25 to 50 mg.[200]

Tamoxifen is a SERM initially used to treat estrogen-sensitive breast cancer. In men's health, tamoxifen has been used off label to treat anabolic–androgenic steroid (AAS)–induced gynecomastia or breast tenderness.[201,202] With a similar mechanism of action as clomiphene, tamoxifen showed increases in androgen and sperm concentration while no conclusive evidence was found toward motility and pregnancy rate increases.[203] Empiric treatment with this medication also showed improvement in semen parameters, but studies fail to provide data on pregnancy rates, and findings should be interpreted skeptically.[204] It is also a twice-daily drug at 10-20 mg, and therefore, compliance may not be as good as once-daily or every-other-day clomiphene.[205]

As a whole, in post -AS discontinuation, endogenous T production may be stimulated with tamoxifen 20 mg once daily or clomiphene 50 mg once daily for several weeks. Both drugs mildly stimulate gonadotropin and T production and do not suppress spermatogenesis.

The heightened risk of thromboembolic events in women taking tamoxifen has not been seen in men, but it also has not been studied in a controlled fashion. A variation in frequency of adverse effects exists but appear to occur less in men with infertility and idiopathic gynecomastia when compared to men with PCa or breast cancer. However, current literature fails to rigorously document and report adverse events of tamoxifen in men.[206] It is therefore much less commonly prescribed than clomiphene.

5) Combination TTh and hCG

There are some men who simply do not tolerate complete withdrawal of TTh. For these men, a combined approach of lowering TTh dosing and adding hCG has been suggested. Although literature is scant on the efficacy of this approach, it is a well-established off-label clinical practice. The dosing must be titrated to maintain FSH levels in the detectable range and check frequent semen analyses to guide therapy. Usual dosing regimens include hCG 3 times a week, ranging from 750 to 2000 IU. Subcutaneous or intramuscular T injections of either T enanthate or cypionate will range from 50 to 100 mg weekly. Elevating weekly injections into the 150-200 mg range, which is often used as weekly dosing for unopposed TTh, will likely suppress FSH and spermatogenesis.[207] Given the off-label nature of this approach and the lack of systematic reviews or clinical trials proving safety and efficacy, one should pause prior to prescribing this combination therapy.

6) Testosterone nasal gel

Testosterone nasal gel (Natesto) is an FDA-approved intranasal delivery vehicle for TTh administered 2-3 times daily.[208-210] Curiously, it appears to have no adverse effects on spermatogenesis.[211] In fact, intranasal T may have a protective effect on spermatogenesis. Small studies demonstrate that men converted from long-acting TTh to Natesto maintain eugonadal serum T levels while recovering spermatogenesis. In 1 study of 27 men, 100% regained normal sperm concentration with mean levels at 50.7 million/mL and 1 subject initiated a pregnancy 4 months after converting to Natesto.[212] Although the spermatogenic preservation mechanism is unknown, it is most likely the short-acting nature of intranasal T that is responsible for this effect. Given these data, intranasal T may play a role in TTh as a primary agent in men actively trying to conceive or as a recovery agent in men on long-acting TTh.[213] Overall, in consideration of the scarcity of available data and their results, which have made the product extremely controversial in terms of clinical use, with authoritative expert opinion, this ICSM 2024 Panel decides not to issue recommendations regarding the use of the same in real-life daily clinical practice.

In conclusion, TTh in men wishing to preserve spermatic function and TV is complex but manageable (Table 5). This therapy aims to restore patients to eugonadal levels while preserving sperm concentration. Although monitoring frequency for these treatments was never postulated in the literature, practitioners should monitor serum tT, E_2, LH, and FSH levels at least every 4-6 months to ensure proper dosing, given the average time for sperm parameters improvement in each modality.[8,214] Since most testis- and sperm-preserving therapies are off label, a careful, well-documented discussion must take place with the patient prior to initiating therapy. Further, no guidelines will likely be published given the off-label nature of this treatment protocol. Therefore, all therapies will be individualized and adjusted based on clinical results and patient experience.

Testosterone and PCa

New research has altered the scientific landscape regarding TTh and PCa.

A study of the TRAVERSE population designed to investigate PCa revealed that cases of PCa were nearly identical in both arms—that is, 12 in the T group and 11 in the placebo group, respectively.[48,215] The number of high-grade PCa cases was not significantly different between the 2 groups, with 5 in the TTh-arm and 3 in the placebo arm. This study was notable for having pre-determined protocols for who should undergo prostate biopsy based on change in PSA or DRE, and the pathology from prostate biopsies was reviewed centrally.

Two additional large RCTs also reported nearly identical numbers of PCa cases between T-treated and placebo groups. In the Testosterone Trials,[138] only 1 case of PCa was identified in the T group. Likewise, in the T4DM trial, 4 cases of PCa occurred in the T group and 5 in the placebo group, respectively.[106]

These reassuring results from large RCTs are supported by similar results from large observational trials. Siltari et al. published results of an analysis from the Finnish Randomized Study of Screening for Prostate Cancer in which 285 PCa cases were identified among 2919 men on TTh with 18 years of follow-up. These men had no greater PCa incidence than non-TTh users, and had lower PCa mortality by almost half (HR = 0.52; 95% CI 0.3-0.91).[216] Zeng et al. performed a Bayesian network meta-analysis that included 30 RCTs and 5 cohort studies, involving 7740 participants. Those undergoing TTh had a lower risk of developing PCa than those who did not receive TTh (RR = 0.62, 95% CI 0.39-0.99).[217] These results mirror studies investigating the risk of PCa

Table 5. The tools in men wishing to preserve spermatic function and testis volume.

Drug	Indication	Contraindications	Effective duration of use	Expected outcomes
hCG	Post-TTh and post-AAS abuse men, traumatic brain injury patients presenting with hypogonadotropic hypogonadism	Men with dysfunctional gonadal cells	At least 3 months to see return of spermatogenesis	Boost endogenous testosterone production, boost intratesticular testosterone, restart spermatogenesis
rFSH	Post-TTh and post-AAS abuse men who fail to improve with hCG alone	Men with dysfunctional gonadal cells	Varies but at least 3 months	Boost spermatogenesis
Anastrazole	Men with a low tT/E_2 ratio, gynecomastia prevention	Severely low tT levels, suppressed E_2 levels	At least 6 months, caution long-term use	Diminished peripheral conversion of tT to E_2, raise in tT/E_2 ratio, improved tT levels, possible boost in spermatogenesis
Clomiphene	Pituitary–gonadal axis recovery post-TTh or post-AAS abuse, acquired secondary hypogonadism	Gonadal failure, inability to produce endogenous gonadotrophins	Over 9 months to see maximal improvement	Increased tT levels, increased spermatogenesis
Enclomiphene	Same as clomiphene	Same as clomiphene	As early as 2 months	Increased tT levels, spermatogenesis, perhaps better SE profile than clomiphene
Intranasal testosterone (Natesto)	Men with hypogonadism requiring TTh actively trying to conceive or preserving sperm function	Elevated hematocrit, untreated PCa, severe CVD	Unlimited	Increased tT levels, spermatogenesis preservation

based on endogenous T levels. The largest of these, a pooled dataset from multiple studies, compared 3886 men with PCa with 6448 age-matched controls.[218] Several androgens were investigated, including tT, free T, and dihydrotestosterone. No significant relationship was found between any of these androgens and PCa. Specifically, men with the highest 20% of values demonstrated no greater risk than men with the lowest 20% of values. Watts et al. published data from 20 pooled studies investigating PCa risk with tT, free T, and SHBG concentrations.[219] There was no relationship between T concentrations and PCa risk. Men with the lowest 10% of free T values had a reduced risk of PCa.

Large observational trials have uniformly demonstrated that lack of PCa increased the risk with TTh. Wallis et al. investigated 10 311 men who received TTh and 28 029 controls with a median follow-up of 5.3 years.[220] Cumulative PCa incidence was lower in the TTh group (T-group 2.8% vs. 3.2% in controls; $P = .04$). Longer duration of TTh was associated with greater reduction in risk. A study utilizing the Swedish National Prostate Cancer Register showed that PCa risk was no different between men with at least 3 years of TTh vs. no TTh exposure.[221] Importantly, TTh use was associated with a 50% lower risk of aggressive PCa. It can now be reasonably stated that TTh does not increase the risk of developing PCa.

It must be added that since 15% of men with low serum T and PSA <4.0 ng/mL have biopsy-detectable PCa, approximately 1 in 7 men receiving TTh has undiagnosed PCa.[222,223] The absence of increased rates of PCa among men receiving TTh in these various trials argues strongly that TTh does not cause rapid or aggressive growth of existing PCa.

The historical PCa concern that T injections "activated" PCa was originally based on scant evidence from Huggins and Hodges in 1941.[224,225] In modern times, it had been assumed that since androgen deprivation causes rapid PCa regression, raising serum T must cause rapid growth. The reason it does not is due to maximal androgenic stimulation of prostate tissue occurring at a relatively low tT concentration of approximately 250 ng/dL or 8.7 nmol/L. This has been described as a saturation effect. Indeed, supraphysiological T concentrations have been shown to have a growth-suppressive effect on androgen-sensitive PCa cell lines.[226,227] One study providing contradictory results reported that T levels prior to radical prostatectomy (RP) were predictive of biochemical recurrence (BCR).[228]

As a further safety point of potential TTh in the real-life setting, recent data from a retrospective cohort study using data from the TriNetX database showed that hypogonadal men with a family history of PCa and treated with TTh did not significantly differ in terms of the risk of PCa diagnosis over 10 years versus comparable-age hypogonadal men who had not received TTh (HR 0.81, 95% CI 0.51-1.28). Similarly, no significant difference was found in the risk of receiving any active treatment for PCa between men who received TTh and those who did not (HR 0.55, 95% CI 0.29-1.03).[229]

Table 6 details the recommendations for several clinical scenarios for TTh. These apply only to men for whom TTh is indicated due to symptoms/signs and documented low tT values (Table 6).

Men without known PCa and normal PSA

A number of studies have investigated whether TTh in hypogonadal men incurs a risk of PCa. Haider et al. pooled data from 3 parallel registry studies with a mean follow-up of 5 years and found no increased risk of PCa.[230] Santella et al. queried the UK Clinical Practice Research Datalink to assemble 12 799 men newly diagnosed with hypogonadism and investigated the risk of PCa among those who received TTh. They concluded that the use of TTh was not associated with an increased risk of PCa.[231] There appears to be strong evidence that TTh does not increase the risk of PCa in this population.

Table 6. Recommendations for testosterone therapy and quality of evidence.

Category	Research findings	Recommendation	Level of evidence[40]
Men without PCa	No increased risk in large RCTs	No increased risk	1A
After RP	No increased risk BCR. Observational studies only	Consider TTh if undetectable PSA, especially with favorable pathology	2A
After XRT/brachytherapy	No increased risk BCR Observational studies only	Consider TTh if good post-treatment response and low-risk	3A
AS	No evidence of increased risk Observational studies only	Consider TTh if patient and provider willing to accept unknown risk of progression	3B
BCR	No rapid progression. Very limited data	Do not treat	4
Metastatic	No rapid progression. Very limited data. PSA decline and reduction of mass noted with BAT.	Do not treat	4

Abbreviations: AS, active surveillance; BAT, bipolar androgen therapy; BCR, biochemical recurrence; PCa, prostate cancer; RCT, randomized controlled trial; RP, radical prostatectomy; TTh, testosterone therapy; XRT, external beam radiation therapy. For references, refer to studies quoted in the text.

Men without known PCa and elevated PSA or prostate nodules

Initiation of TTh should be deferred until further evaluation of the prostate abnormality with MRI and/or biopsy. If such evaluation fails to identify PCa, it is reasonable to then consider initiating TTh.

Men on active surveillance

Small observational studies have shown that TTh in men on active surveillance was associated with low rates of PCa progression.[47,232,233] Despite reassuring results to date, clinicians should only consider offering TTh to men on active surveillance if both the clinician and the patient understand the limitations of available data and are willing to accept the possible risks.

Men following RP

The use of TTh following definitive treatment of localized RP was reviewed by Kaplan et al.[234] and Natale et al.,[235] both concluding that the evidence indicates TTh may be offered to men following definitive treatment of localized PCa with RP or radiation therapy. Several case series of moderate size have all shown no increased risk of BCR with TTh initiated following RP. In the largest study, 152 men were treated with TTh and 419 controls were untreated.[236] Biochemical recurrence was observed in 7.2% of the T-treated group and in 12.6% of the controls. In another series that included a substantial number of men at high risk, the BCR rate was lower by half in men who received TTh following RP as compared with untreated men.[237] Sarkar et al. queried the US Veterans Affairs Informatics and Computing Infrastructure dataset and found no increased risk of BCR or PCa-specific mortality following RP in men with TTh use.[238] A consent form is recommended, noting that BCR is a risk following RP with or without TTh.

The 2018 AUA Guidelines on TD addressed the use of TTh following RP as follows: "Testosterone therapy can be considered in men who have undergone radical prostatectomy with favorable pathology (e.g., negative margins, negative seminal vesicles, negative lymph nodes), and who have undetectable PSA postoperatively."[8]

The 2024 European Association of Urology Guidelines on Sexual and Reproductive Health made the following recommendation on the use of TTh following RP: "Fully counsel symptomatic hypogonadal men who have been surgically treated for localised prostate cancer (PCa) and who are currently without evidence of active disease considering testosterone therapy, emphasizing the lack of sufficient safety data on long-term follow-up."[16]

Men following radiation therapy or brachytherapy

A number of case series have consistently reported low rates of PCa recurrence following various forms of radiation therapy.[239,240] Investigation of a large Veterans Affairs database revealed no increased risk of BCR with TTh in men following definitive treatment of localized PCa with radiation.[238] TTh may be reasonably offered to men after achieving a low post-treatment PSA value, usually at 3-6 months. A consent form is recommended.

Men with BCR or metastatic disease

A small number of studies investigating TTh in men with either BCR or metastatic PCa have provided reassuring results in that no rapid progression of PCa was observed.[237,239,241] Bipolar androgen therapy (alternating periods of high and low T concentrations) has shown particular success in men with metastatic disease and castrate-resistant PCa.[242] TTh in these populations should only be offered under investigational conditions.

The EAU guidelines state that it is an absolute contraindication to use TTh in men with locally advanced or metastatic PCa.[16]

Conclusions

This consensus paper comprehensively discusses relevant clinical aspects and the everyday real-life clinical work-up management strategies from the ICSM 2024 Panel on male hypogonadism. Following the criteria of a modified Delphi method, Panel experts strongly reiterate the need to consider serum tT in patients with symptoms and signs suggestive of male hypogonadism, without unnecessarily screening out male individuals who do not demonstrate significant clinical disorders. The need for a concomitant biochemical diagnosis of hypogonadism with reliable laboratory methods is confirmed, as

well as an adequate discussion with patients to explain the usefulness of a TTh and the different available therapy modalities, thus including the risks and benefits of the different TTh types. In this context, the ICSM 2024 Panel confirms that while the benefits deriving from TTh in the field of QoL and sexual function are well established, for other specific conditions (eg, depressive disorders and bone health, cognitive and sleep disorders), the choice must not fall on TTh alone, but area-specific therapies must be the cornerstone of the treatment. For patients with a desire for parenthood, the use of TTh is contraindicated, but there are strategies for recovering spermatogenesis in previously T-replete men. Endogenous testosterone and TTh are not associated with a greater risk of PCa, but it is always necessary to thoroughly discuss any TTh in a patient with symptoms compatible with hypogonadism and previous PCa, before any treatment setting.

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Author contributions

Mohit Khera and Andrea Salonia shared co-chairmanship of the committee.

Conflicts of interest

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