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REVIEW

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Male hypogonadism and testosterone therapy: current clinical evidence and controversies

Alfonso Romero Crespo[1,*], Javier Fernández Siles[1], Juan Manuel Martí Flores[1], Juan Antonio Rivero Esteban[1,2], Emilio García Galisteo[1,2], Rodrigo España Navarro[1,3]

[1]Department of Urology, Regional University Hospital of Málaga, 29010 Málaga, Spain
[2]Lyx Institute of Urology, 29016 Málaga, Spain
[3]TAUS Clinic, 29016 Málaga, Spain

***Correspondence**
alfonromero@usal.es
(Alfonso Romero Crespo)

Abstract

Male hypogonadism, also referred to as testosterone deficiency (TD) in several clinical guidelines, is a common but frequently underdiagnosed condition that affects multiple domains of male health. This narrative review summarizes current evidence on the diagnosis and management of male hypogonadism, with emphasis on testosterone replacement therapy (TRT). Advances in the understanding of testosterone physiology, particularly the saturation model, have reshaped clinical perspectives. We review the effects of TRT on sexual function, metabolic health, bone density, mood, and physical function. Its relationship with cardiovascular risk, prostate safety, and lower urinary tract symptoms is also examined, highlighting the reassuring findings of the landmark TRAVERSE trial (Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy trial). Evidence also supports cautious use in men with comorbidities such as obstructive sleep apnea and previously treated prostate cancer. A guideline-based, individualized approach, prioritizing symptomatic men with confirmed biochemical deficiency, remains essential to optimize outcomes while minimizing risks.

Keywords

Testosterone replacement therapy; Controversies; Hypogonadism; Cardiovascular risk; Prostate cancer; Male sexual health; Hormone therapy safety; Aging male; Andrology

Hipogonadismo masculino y terapia con testosterona: evidencia clínica actual y controversias

Resumen

El hipogonadismo masculino, también denominado déficit de testosterona (DT) en diversas guías clínicas, es una condición frecuente pero a menudo infradiagnosticada que afecta múltiples dominios de la salud del varón. Esta revisión narrativa sintetiza la evidencia actual sobre el diagnóstico y manejo del hipogonadismo masculino, con especial énfasis en la terapia de reemplazo con testosterona (TRT). Los avances en la comprensión de la fisiología androgénica, en particular el modelo de saturación, han modificado la perspectiva clínica contemporánea. Se revisan los efectos de la TRT sobre la función sexual, la salud metabólica, la densidad mineral ósea, el estado de ánimo y la función física. Asimismo, se examina su relación con el riesgo cardiovascular, la seguridad prostática y los síntomas del tracto urinario inferior, destacando los resultados tranquilizadores del ensayo TRAVERSE (Ensayo sobre la terapia de reemplazo de testosterona para la evaluación de eventos vasculares a largo plazo y su eficacia). La evidencia también respalda un uso cauteloso en pacientes con comorbilidades como apnea obstructiva del sueño o cáncer de próstata tratado. Mantener un enfoque individualizado, basado en guías y centrado en varones sintomáticos con confirmación bioquímica del déficit androgénico, sigue siendo esencial para optimizar los beneficios y minimizar los riesgos.

Palabras Clave

Terapia de reemplazo con testosterona; Controversias; Hipogonadismo; Riesgo cardiovascular; Cáncer de próstata; Salud sexual masculina; Seguridad de la terapia hormonal; Varón envejecido; Andrología

1. Introduction

Testosterone is a critical hormone in male health, influencing sexual function, muscle and bone mass, mood, cognition, and overall vitality [1, 2]. Over recent years, its role has become a subject of growing scientific interest and intense societal debate [3, 4]. Beyond its well-established physiological functions, testosterone has emerged at the intersection of medicine, aging, and lifestyle culture, especially as part of a broader trend toward the medicalization of aging and male performance [3, 4].

The resurgence of interest in testosterone has introduced both clinical opportunities and critical challenges. On one hand, there is growing recognition of late-onset hypogonadism and the potential therapeutic benefits of its management [2, 5]. On the other hand, concerns have intensified regarding the non-therapeutic use of testosterone, often propelled by direct-to-consumer marketing, fitness-oriented subcultures, and the proliferation of so-called "longevity clinics" [3, 4]. The increasing prevalence of testosterone replacement therapy (TRT) in men without well-defined clinical indications—frequently initiated based solely on nonspecific symptoms, such as fatigue or diminished libido, has raised substantial concerns about overdiagnosis, overtreatment, and the dissemination of misleading information [3].

Given this clinical and societal context, throughout this review we use the term testosterone replacement therapy (TRT), in line with major clinical guidelines from the American Urological Association (AUA), the European Association of Urology (EAU), and the Endocrine Society, which consistently adopt TRT rather than testosterone supplement therapy (TST), as the therapeutic aim is to restore physiological testosterone levels rather than provide supraphysiological supplementation. Likewise, we use the term hypogonadism as the primary diagnostic entity, while acknowledging that several guidelines (AUA, EAU) employ the term testosterone deficiency (TD) to describe the same clinical syndrome of low serum testosterone combined with compatible symptoms.

While hypogonadism encompasses rare pathological causes (*e.g.*, congenital hypogonadotropic hypogonadism, or pituitary tumors), the most prevalent and clinically challenging form in urological and general practice is Late-Onset Hypogonadism (LOH). LOH is primarily a form of functional secondary hypogonadism that affects older men, driven largely by common comorbidities, such as obesity, type 2 diabetes, and chronic illness. This functional presentation, which forms the basis of the large cardiovascular safety trials (*e.g.*, the Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy (TRAVERSE) trial), is the central focus of the clinical controversies and guideline discrepancies addressed in this review.

The scientific literature reflects this complexity. Multiple clinical trials and meta-analyses have investigated the benefits and risks of TRT in domains such as metabolic health, cardiovascular safety, sexual function, and mental well-being—often yielding conflicting or inconclusive findings [6–9]. Furthermore, endocrine societies and urological guidelines continue to evolve in their recommendations, revealing ongoing controversy regarding diagnostic thresholds, target populations, and long-term safety [3, 5].

This narrative review aims to explore the current landscape of TRT from a multidisciplinary perspective. We provide a critical synthesis of the evidence surrounding its therapeutic use. Special attention is paid to the controversies that dominate the field, including its relationship with prostate cancer, cardiovascular disease, male fertility, and non-medical enhancement [3, 7–10]. In light of rising public interest and polarized opinions, this review seeks to offer clinicians a balanced, evidence-informed approach to navigating the modern "testosterone era" [3, 7–10].

A summary of the main findings and controversies regarding testosterone therapy is provided in Table 1 (Ref. [11–41]).

2. Detecting, indications, evaluation, and monitoring

2.1 Testosterone: reference values and indications for testing

Testosterone circulates predominantly bound to plasma proteins: ~60% to sex hormone-binding globulin (SHBG), 38% to albumin, and only 0.5–2% as free testosterone (FT). The sum of FT and albumin-bound fractions is bioavailable testosterone, which represents the biologically active pool [11, 12]. SHBG, produced in the liver, strongly modulates testosterone availability and is influenced by age, obesity, thyroid status, liver disease, and medications [12, 42, 43]. Measurement of SHBG is, therefore, valuable when total testosterone (TT) and clinical presentation are discordant, enabling the calculation of calculated FT (cFT) and improving diagnostic accuracy [4, 13, 38].

Reference values for TT in healthy, non-obese young men range from 264–916 ng/dL (9.2–31.8 nmol/L) [13, 38]. The AUA defines hypogonadism at TT <300 ng/dL, confirmed by symptoms [11]. During TRT, guidelines recommend targeting mid-normal levels (400–700 ng/dL; 13.9–24.3 nmol/L) to maximize efficacy while minimizing risks [11, 13]. Similar thresholds are endorsed by the EAU and Endocrine Society, emphasizing that biochemical evidence must always be interpreted in conjunction with clinical features [12, 13].

TT is the first-line test, ideally with two early morning samples under fasting, stable conditions. Liquid chromatography-tandem mass spectrometry (LC-MS/MS), remains the gold standard, though automated immunoassays are widely used, despite lower accuracy [12, 19, 37]. FT assessment is indicated when TT is borderline (230–350 ng/dL), SHBG is abnormal, or clinical features and TT are discordant [12, 13, 20]. FT can be measured directly (equilibrium dialysis, ultrafiltration) or calculated (Vermeulen, Zakharov), though assay variability affects accuracy [12, 21, 41]. Salivary testosterone is not recommended due to poor standardization [12].

Screening is not advised in asymptomatic men, but TT measurement should be considered in those with suggestive symptoms or conditions, such as unexplained anemia, bone loss, type 2 diabetes, human immunodeficiency virus (HIV), chronic opioid use, infertility, pituitary dysfunction, or prior testicular damage [11, 12, 43]. Clinical questionnaires, such as the Androgen Deficiency in the Aging Male (ADAM) ques-

TABLE 1. Key areas of consensus and ongoing controversies in testosterone therapy.

Clinical Domain	Consensus (Established Evidence)	Controversies (Ongoing Debate)
Diagnosis and thresholds	Hypogonadism requires both symptoms and low testosterone confirmed by two early-morning samples. Free T is relevant when TT borderline or SHBG abnormal [11–13].	Lack of unified diagnostic cutoff (300 *vs.* 350 ng/dL) and variability between endocrine *vs.* urological guidelines creates a "grey zone" of eligibility [14–18].
Metabolic syndrome	TRT improves body composition, insulin sensitivity and glycemic parameters in hypogonadal men; strong pathophysiological link with visceral adiposity [19–21].	Whether TRT should be considered metabolic therapy or prevention strategy (*e.g.*, T4DM results) remains debated; not endorsed for diabetes prevention [21].
Bone health and fractures	TRT increases BMD (mainly lumbar spine) and reduces bone turnover in hypogonadal men [22, 23].	TRAVERSE substudy showed higher fracture incidence despite BMD gains, questioning translation into fracture prevention in older functional hypogonadism [24].
Cardiovascular safety	TRAVERSE confirms no increase in MACE in appropriately selected men under guideline-based TRT [25].	Long-term safety beyond ~3 years, very elderly men, and applicability to those WITHOUT biochemical hypogonadism remain uncertain. Historical observational risk signals still influence perception [26–30].
LUTS/BPH	Mild–moderate LUTS are not a contraindication; some evidence suggests neutral or even favorable effect (metabolic + detrusor mechanisms) [31, 32].	Fear of prostate enlargement persists in clinical practice; concerns remain in men with severe obstruction or high-risk BPH phenotype despite lack of strong evidence.
Prostate cancer	Modern evidence and saturation model: TRT does not increase PCa incidence in appropriately selected men; cautious use possible post-treatment [33–37].	Active surveillance and long-term oncologic safety in younger candidates remain insufficiently studied; some societies still contraindicate TRT entirely [14–18].
OSA/erythrocytosis	OSA is a major risk factor for TRT-induced erythrocytosis; guidelines advise caution or delay until appropriately treated [38–41].	Whether TRT directly worsens OSA *vs.* amplifies pre-existing hypoxia remains debated; severity thresholds for "contraindication" differ between guidelines.
Fertility	TRT suppresses spermatogenesis; alternatives (SERMs, hCG, AIs) recommended in men seeking to preserve fertility [12, 13].	No consensus on when to transition from medical restoration (SERMs/hCG) to TRT; limited long-term safety of fertility-sparing strategies.

TT: total testosterone; SHBG: sex hormone-binding globulin; TRT: testosterone replacement therapy; T4DM: Testosterone for Diabetes Mellitus trial; BMD: bone mineral density; TRAVERSE: Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy trial; MACE: major adverse cardiovascular events; LUTS: lower urinary tract symptoms; BPH: benign prostatic hyperplasia; PCa: prostate cancer; OSA: obstructive sleep apnea; SERMs: selective estrogen receptor modulators; hCG: human chorionic gonadotropin; AIs: aromatase inhibitors.

tionnaire and the Aging Males' Symptoms (AMS) scale, may support assessment but should not replace laboratory confirmation [12, 20].

2.2 Prolactin, erythrocytosis, and alternative strategies

Secondary hypogonadism may arise from multiple hypothalamic or pituitary disorders. Among these, hyperprolactinemia is clinically relevant because elevated prolactin can suppress gonadotropin release and reduce testosterone production. For this reason, baseline prolactin measurement is recommended in men with suspected central hypogonadism, although it should be interpreted within the broader context of pituitary function [11, 12].

Erythrocytosis is the most frequent dose-limiting adverse effect of TRT. Elevated hematocrit (>54%) increases the risk of thromboembolic events, and major guidelines recommend monitoring hematocrit at baseline, at 3–6 months, and annually thereafter [11, 16]. If erythrocytosis develops, management includes dose adjustment, switching formulation, temporary discontinuation, or therapeutic phlebotomy [11, 13].

2.3 Fertility preservation: alternatives to exogenous TRT

"In selected cases, particularly in younger men wishing to preserve fertility, alternatives to exogenous testosterone can be considered. Agents such as selective estrogen receptor modulators (SERMs), human chorionic gonadotropin (hCG), or aromatase inhibitors may enhance endogenous testosterone production, by selectively stimulating the hypothalamic–

pituitary–testicular (HPT) axis. However, their long-term safety and efficacy remain less well established compared with TRT." [12, 13, 20, 21].

Figs. 1,2 proposes a Diagnostic and therapeutic algorithm for male hypogonadism and testosterone deficiency, outlining the clinical evaluation, biochemical confirmation, and subsequent management strategy.

3. Testosterone and male health

3.1 TD and metabolic syndrome

Well-documented association exists between low testosterone levels and metabolic dysfunction, including obesity, insulin resistance, type 2 diabetes mellitus (T2DM), and metabolic syndrome [12, 20, 43]. Up to 40% of men with T2DM exhibit serum testosterone levels below 300 ng/dL, most often as a form of hypogonadotropic (functional) hypogonadism linked to excess adiposity and systemic inflammation [13, 38].

Visceral obesity, particularly abdominal fat accumulation, is strongly correlated with low testosterone levels. Adipose-derived factors, such as leptin, pro-inflammatory cytokines (*e.g.*, interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α)), and dysregulation of the hypothalamic–pituitary–testicular (HPT) axis contribute to this relationship [13]. Insulin resistance may be both a consequence and a driver of hypogonadism, as low testosterone reduces insulin receptor expression in adipose tissue and impairs glucose transporter type 4 (GLUT4)-mediated glucose uptake in skeletal muscle [20].

Weight loss, improved glycemic control, and reduction of inflammation have been shown to restore endogenous testosterone levels. Lifestyle interventions remain the first-line approach for men with obesity-related or functional hypogonadism. Studies have shown that both caloric restriction and bariatric surgery can significantly raise serum testosterone, even leading to normalization in some men [39].

Testosterone replacement therapy (TRT) aims primarily to alleviate symptoms of hypogonadism, but it also exerts metabolic effects. In hypogonadal men with obesity, metabolic syndrome, or T2DM, TRT has been shown to improve several cardiometabolic risk factors, including body composition, insulin sensitivity, lipid profiles, and glycemic control [19–21]. Meta-analyses and observational cohorts have reported:

- Improved glycemic control (reduction in fasting glucose and glycated hemoglobin A1c (HbA1c)).
- Increased insulin sensitivity.
- Decreased visceral fat and waist circumference.
- Increased lean body mass.
- Improved lipid profile, with reductions in triglycerides and LDL cholesterol, though accompanied by a consistent reduction in high-density lipoprotein (HDL) cholesterol.

The landmark the Testosterone for the Prevention of Diabetes Mellitus (T4DM) trial further explored whether TRT could prevent the development of T2DM in high-risk men. In this 2-year, double-blind, placebo-controlled study, more than 1000 overweight or obese men aged 50–74 years with abdominal obesity and testosterone $\leq$14 nmol/L, but without pathological hypogonadism, were randomized to intramuscular testosterone undecanoate or placebo. All participants received an intensive lifestyle programme. At 2 years, TRT significantly reduced the incidence of new-onset diabetes compared with the placebo (12% *vs.* 21%; relative risk 0.59, 95% confidence interval (CI) 0.43–0.80), independent of baseline testosterone [21]. However, approximately 22% in the TRT arm triggered the hematocrit safety threshold (>54%), versus ~1% with placebo, despite both arms receiving an intensive lifestyle program. These findings suggest that while TRT may reduce diabetes risk beyond lifestyle measures, its long-term safety, durability, and cardiovascular effects remain to be determined.

Despite promising results, TRT is not indicated for diabetes prevention, and major guidelines (*e.g.*, American Diabetes Association (ADA)) do not support its use solely to improve metabolic outcomes. Evidence on cardiovascular benefits remains inconclusive, and risks such as erythrocytosis or exacerbation of sleep apnea must be considered [11, 19, 38]. Professional societies (Endocrine Society, AUA, European Academy of Andrology (EAA)) recommend restricting TRT to men with consistent hypogonadal symptoms and confirmed low testosterone on two separate morning samples. In men with functional hypogonadism—often related to obesity or T2DM—lifestyle modification is first-line, as it may restore endogenous testosterone without the risks of exogenous therapy [19, 38, 40, 44, 45].

3.2 Bone health and fracture risk

Testosterone plays a fundamental role in male bone physiology, promoting bone formation and maintaining bone mineral density (BMD). Its effects are mediated both directly through androgen receptors and indirectly via aromatization to estradiol (E2), which is especially important for trabecular bone preservation [12, 22, 42].

Hypogonadism is a well-established secondary cause of male osteoporosis, and fracture risk related to low testosterone is most evident in older, often obese men with mildly reduced T and non-elevated Luteinizing hormone (LH) (functional, age-related hypogonadism).

Some studies suggest a nearly threefold higher risk of fractures in older men with low testosterone [46, 47]. The European Male Ageing Study (EMAS) and the Osteoporotic Fractures in Men Study (MrOS) Sweden cohorts demonstrated that low serum testosterone is independently associated with decreased BMD and greater fracture risk [46, 47]. A population-based study confirmed that testosterone levels predict fracture risk even in men without overt hypogonadism, reinforcing the hormone's role in skeletal aging [46].

Routine evaluation of bone health in hypogonadal men includes dual-energy X-ray absorptiometry (DXA) scanning, particularly in those over 50, with previous low-trauma fractures, or additional risk factors, such as corticosteroid use, smoking, or alcohol intake. DXA is also advised before starting TRT in men with severe deficiency or osteopenia, and should be repeated after 12–24 months to monitor response [11, 46].

TRT has consistently been associated with improvements

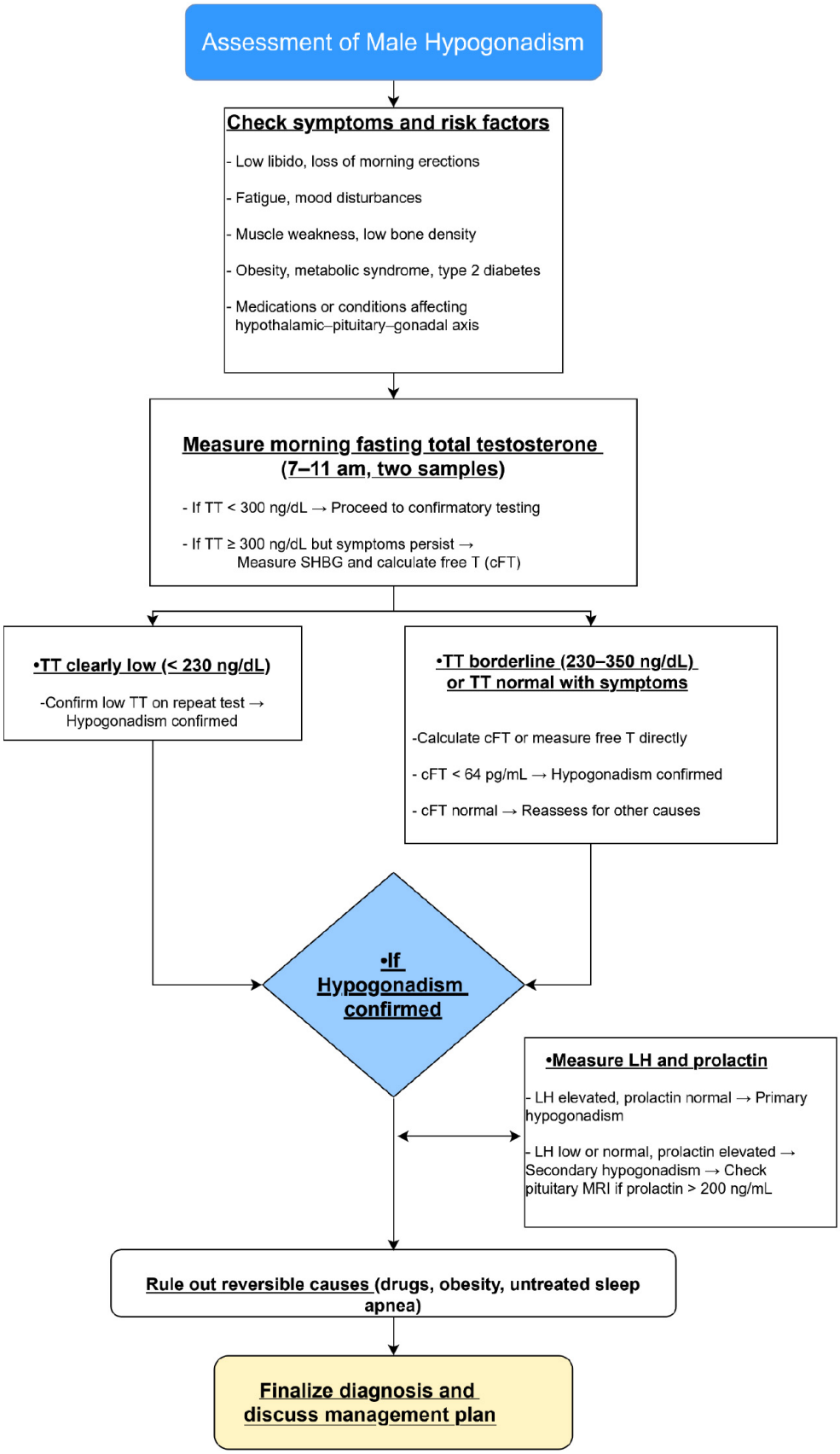

FIGURE 1. Assessment of male hypogonadism: stepwise evaluation including symptoms, risk factors, biochemical confirmation with total testosterone (TT) and free testosterone (cFT), and subsequent endocrine workup (LH and prolactin) to distinguish primary from secondary hypogonadism. Hct: hematocrit; PSA: prostate-specific antigen; DEXA: dual-energy X-ray absorptiometry; CPAP: continuous positive airway pressure.

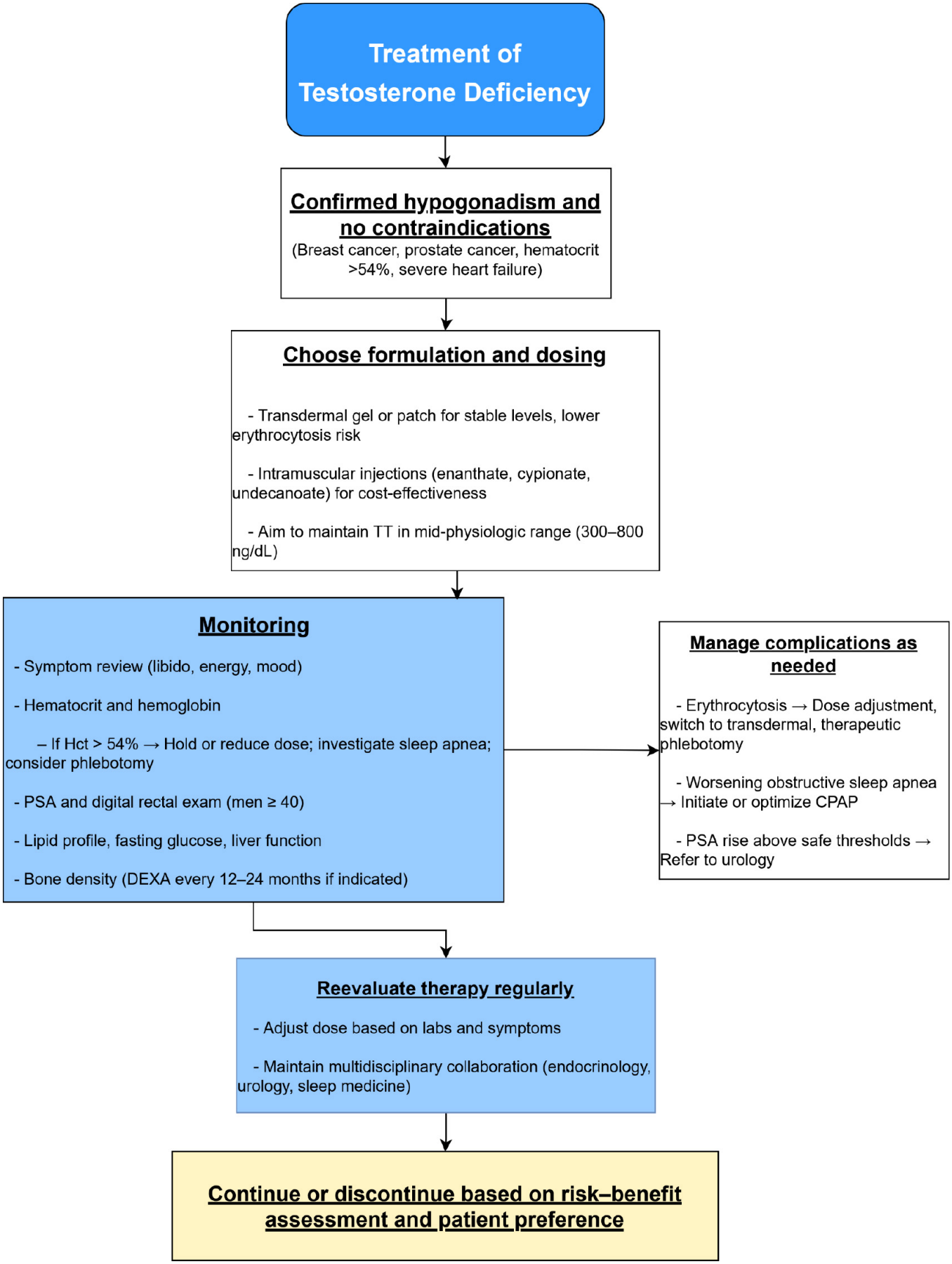

FIGURE 2. Treatment of testosterone deficiency: selection of formulation and dosing, monitoring of efficacy and safety (hematocrit, PSA, lipid profile, and bone density), management of complications, and periodic reevaluation to balance risks, benefits, and patient preferences. SHBG: sex hormone-binding globulin; TT: total testosterone; cFT: calculated free testosterone; LH: luteinizing hormone; MRI: magnetic resonance imaging.

in BMD, especially in the lumbar spine [22, 23]. A meta-analysis reported TRT has consistently been associated with modest but significant increases in BMD at the lumbar spine (≈+3.7% *vs.* placebo; 95% CI 1.0–6.4%), with no significant change at the femoral neck, and concomitant reductions in bone resorption markers, with the greatest benefits in younger men and those with lower baseline testosterone [22]. Transdermal testosterone has also shown efficacy in increasing both bone and muscle mass in older hypogonadal men [23]. However, these anabolic effects on BMD do not necessarily translate into fracture prevention. In the bone substudy of the TRAVERSE trial—the largest randomized trial of TRT to date—the incidence of clinical fractures was higher in the testosterone group than in placebo (3.50% *vs.* 2.46%; hazard ratio (HR) 1.43, 95% CI 1.04–1.97) among 5204 hypogonadal men aged ≥45 years [24]. This paradox may reflect improved BMD, which is primarily seen at the lumbar spine, without parallel improvements in bone quality, potentially reflecting an increased fall risk in older, more active men with underlying frailty. The findings underscore that TRT is not a primary osteoporosis treatment, particularly in the LOH population.

Therefore, TRT is not a primary osteoporosis treatment. This is particularly important for older, obese men with functional hypogonadism (mildly low T, non-elevated LH), where TRAVERSE data suggest fracture risk may outweigh BMD benefits.

Fracture prevention evidence in men is limited. Intravenous zoledronic acid is the only drug with proven efficacy for reducing vertebral fractures in randomized controlled trials (RCTs), though data on hip fractures are lacking. Treatment must be individualized: TRT is key for bone mass accrual in young men with pathological hypogonadism (*e.g.*, Klinefelter syndrome), while older men with established osteoporosis may require added bone-specific therapy, considering its finite duration and long-term strategic use.

3.3 Mental health

Testosterone modulates brain regions responsible for mood, cognition, and motivation, including the prefrontal cortex, hippocampus, and amygdala [48–50]. Low testosterone levels have been consistently associated with increased depressive symptoms, particularly in older men. The European Male Ageing Study (EMAS) reported a higher risk of incident depression among men with hypogonadism (or low testosterone), even after adjustment for comorbidities [6, 47].

Psychological symptoms—irritability, low mood, reduced motivation, subjective cognitive difficulties, poor memory, and decreased concentration—are frequently reported in men with late-onset hypogonadism (LOH). While these features are nonspecific, their presence together with low serum testosterone should prompt clinical evaluation [12, 45].

Several trials show that TRT improves depressive symptoms in men with confirmed hypogonadism. In one RCT, remission occurred in 53% with TRT versus 19% with placebo among men with dysthymia [31]. A meta-analysis confirmed a significant reduction in depressive symptoms, with greater benefits in those with lower baseline testosterone or comorbid mild depression [6].

Evidence on cognition remains inconclusive. Some studies suggest modest improvements (*e.g.*, spatial memory, verbal fluency), whereas others find no significant changes. Marked cognitive impairment is mainly observed in contexts of profound androgen deprivation, such as long-term androgen-deprivation therapy (ADT) for prostate cancer [51].

3.4 Physical strength

Testosterone exerts anabolic effects on skeletal muscle, stimulating protein synthesis, satellite cell activation, and neuromuscular coordination. Hypogonadism leads to reductions in lean body mass, strength, endurance, and physical function, contributing to frailty and risk of falls [23, 52]. TRT has consistently been shown to increase lean body mass and, in some cases, improve muscle strength. The T-Trials, a multicenter series of RCTs, assessed the impact of TRT on physical function and vitality in older men with hypogonadism. The physical function trial reported modest improvements in walking distance and strength, though the magnitude of effect varied [53]. In the TEAAM study, long-term TRT improved leg press and chest press strength and enhanced stair-climbing power [27]. TRT may also improve self-reported energy and reduce fatigue, although some trials report minimal or placebo-driven effects on these domains [54]. While the benefits on muscle and vitality are relevant, it is important to emphasize that supraphysiologic doses of testosterone (*e.g.*, anabolic steroid abuse) carry serious risks, including cardiovascular events, mood instability, and infertility [13, 54].

3.5 TD and sexual function

Testosterone is considered the “fuel” of male sexual function. It plays a key role in regulating libido, erectile function, ejaculatory response, and sexual satisfaction, with androgen receptors distributed throughout the hypothalamus, limbic system, spinal cord, and penile tissue [12, 55, 56].

Sexual symptoms are among the most specific clinical indicators of hypogonadism, especially in men over 50. According to the European Male Ageing Study (EMAS), the presence of at least three sexual symptoms—reduced libido, fewer spontaneous/morning erections, and erectile dysfunction—combined with total testosterone <11 nmol/L (320 ng/dL) and free testosterone <220 pmol/L (64 pg/mL), is the minimum criterion for diagnosing late-onset hypogonadism (LOH) [57].

In the EMAS cohort of over 3400 men, sexual symptoms were the strongest predictor of low testosterone and the most common reason for medical consultation. The first sign to appear is typically the loss of morning erections, followed by decreased libido and, later, erectile dysfunction (ED) [57, 58].

Morning erections are closely related to circulating testosterone levels. Studies show that testosterone below 200 ng/dL is often associated with the complete disappearance of morning erections [39]. Libido is particularly sensitive to testosterone levels: a meta-analysis observed a 31% improvement in sexual desire with testosterone therapy, with the greatest gains in men with the lowest baseline testosterone [59].

Erectile dysfunction is one of the most frequent presenting complaint. About 30% of men with erectile dysfunction (ED) have concurrent testosterone deficiency, and in men

with suboptimal response to phosphodiesterase type-5 (PDE5) inhibitors, testosterone should always be assessed [55, 60].

TRT has been shown to improve libido and erectile function in hypogonadal men. Meta-analyses confirm significant improvements in sexual desire, satisfaction, and erectile rigidity, with greater effects in those with lower starting testosterone levels [56].

TRT can restore nocturnal erections, increase ease of initiating and maintaining erections, and improve erection quality sufficient for penetration [59]. In cases of incomplete response, combined therapy with PDE5 inhibitors is often recommended. TRT may enhance PDE5i responsiveness, likely through increased nitric oxide synthase expression and improved smooth muscle relaxation in the corpus cavernosum [60].

Experimental studies further support this: in androgen-deprived rats, testosterone restored cavernosal muscle and endothelial nitric oxide synthase (eNOS) expression, reversing erectile tissue damage [31, 35, 61].

4. Controversies and safety

4.1 Cardiovascular risk

The TRAVERSE Trial: Redefining the Evidence:

Published in 2023, the TRAVERSE trial represents a landmark in the evaluation of testosterone therapy, being the largest and most methodologically rigorous RCT to date addressing cardiovascular (CV) safety in hypogonadal men. This multicenter, placebo-controlled study enrolled over 5000 men with confirmed hypogonadism and high CV risk, with a median follow-up of 33 months.

Crucially, TRT did not increase the incidence of major adverse cardiovascular events (MACE) compared with placebo (HR 1.03; 95% CI 0.85–1.25), providing the most robust evidence to date that therapeutic testosterone does not raise CV risk when used appropriately [25]. The trial also confirmed neutral effects on stroke, myocardial infarction, and CV mortality, helping to resolve a decade-long controversy.

Clinical Implications and Risk Management:

The TRAVERSE findings support the CV safety of TRT in symptomatic, well-selected men, but clinical prudence remains essential. Testosterone should be avoided in the first 3–6 months following an acute cardiovascular event, and modifiable risk factors—such as hypertension, dyslipidemia, and smoking—should be optimized prior to initiating therapy [13, 23, 39].

Importantly, these safety data refer only to physiologic TRT, and should not be extrapolated to the misuse of anabolic androgenic steroids (AAS) at supraphysiologic doses, which are clearly associated with severe cardiovascular harm—including sudden death, arrhythmia, thrombosis, and cardiomyopathy [62].

4.2 TD and Obstructive sleep apnea

Obstructive sleep apnea (OSA) is an important comorbidity to consider in men being evaluated for TRT. OSA predisposes to nocturnal hypoxia, which may contribute to secondary polycythemia, a well-known adverse effect of testosterone therapy.

Chronic intermittent hypoxia, as observed in untreated OSA, stimulates erythropoietin production and increases the risk of erythrocytosis. In men receiving TRT, this effect may be amplified, particularly when additional risk factors, such as chronic pulmonary disease, are present [41, 51, 63]. One study reported that OSA is independently associated with polycythemia in men with hypogonadism on TRT, suggesting an additive effect [44].

Most clinical guidelines list untreated severe OSA as a relative or absolute contraindication to initiating TRT. Although the mechanisms are not fully established, the concern lies in the synergistic risk of hypoxia and testosterone-induced erythropoiesis, which may raise the likelihood of cardiovascular or thrombotic events [38–40, 63]. TRT should therefore be avoided in men with severe, untreated OSA until the condition is controlled—typically with continuous positive airway pressure (CPAP) therapy. In men with treated or mild OSA, TRT may be considered with close monitoring of hematocrit and respiratory symptoms.

Evidence suggests that TRT may worsen OSA in susceptible individuals by reducing upper airway muscle tone, altering central respiratory drive, and affecting sleep architecture. In a randomized trial, testosterone administration in older obese men with OSA worsened nocturnal oxygen desaturation and apnea severity [63]. This effect appeared dose-dependent and may be more relevant in men receiving higher doses or with borderline oxygenation at baseline.

Conversely, some studies evaluating the effect of CPAP on testosterone levels in men with OSA have shown modest increases in total testosterone after prolonged use, possibly due to improved sleep quality and reduced nocturnal hypoxia [64].

4.3 TD and lower urinary tract symptoms (LUTS)

Lower urinary tract symptoms (LUTS) are highly prevalent among aging men and often attributed to benign prostatic hyperplasia (BPH). Given the androgen-dependence of the prostate, concerns have historically been raised about the potential for TRT to exacerbate LUTS or accelerate BPH progression [12, 38, 39].

The prostate is an androgen-sensitive organ. Testosterone is converted locally to dihydrotestosterone (DHT) via 5α-reductase, promoting epithelial proliferation. However, the saturation model suggests that androgen receptors in the prostate become fully activated at relatively low testosterone levels, such that further increases do not result in proportional prostatic growth [33, 65].

Multiple clinical trials and meta-analyses have evaluated the impact of TRT on LUTS, with no consistent evidence of symptom worsening. Some studies even suggest improvement, possibly due to enhanced detrusor muscle function, improved insulin sensitivity, or reduced systemic inflammation [31].

A 2016 meta-analysis by Cui *et al*. [32] reported no significant increase in International Prostate Symptom Score (IPSS) with TRT, and noted improvements in subgroups—particularly men with metabolic syndrome and mild LUTS. Current AUA guidelines state that mild LUTS are not a contraindication to TRT, although caution is advised in men with severe urinary

obstruction [17].

Additionally, TRT may confer indirect benefits through reductions in central adiposity and improvement in metabolic parameters, both of which are associated with bladder dysfunction and LUTS. TRT impact on BPH progression appears minimal when patients are appropriately selected and monitored [33].

4.4 Prostate cancer: risk, recurrence, and monitoring

The long-standing belief that testosterone "feeds" prostate cancer originated in 1941, when a seminal study showed that surgical castration reduced acid phosphatase levels in men with metastatic disease, while exogenous testosterone increased them [34].

Contemporary research has introduced a more nuanced understanding. The saturation model proposes that androgen receptors in the prostate become maximally activated at low testosterone concentrations (around <250 ng/dL), and further increases in serum testosterone do not stimulate additional prostate growth [33].

Current evidence does not support an increased incidence of prostate cancer (PCa) in appropriately selected men receiving TRT short-to-intermediate term. A meta-analysis of seven RCTs found no significant difference in prostate cancer diagnosis between TRT and placebo groups [35]. Although some observational studies report more frequent prostatic events—such as prostate-specific antigen (PSA) elevation—these have not translated into increased PCa detection rates [45].

TRT is contraindicated in men with metastatic or high-risk localized PCa. However, cautious use may be considered in select individuals with previously treated, organ-confined disease and undetectable PSA [36].

- Post-Radical Prostatectomy: Retrospective studies suggest that TRT does not increase the risk of biochemical recurrence in low-risk patients with undetectable PSA after surgery [36].
- Post-Radiation Therapy: Similarly, TRT after radiation does not appear to increase recurrence risk, though transient PSA rises may occur [37].
- Active Surveillance: Emerging data from small series suggest TRT may be used without disease progression, but long-term safety remains uncertain [66].

TRT may cause a modest increase in PSA levels, which typically stabilizes within the first year. Professional guidelines vary in their specific monitoring recommendations:

- The American Urological Association (AUA) advises obtaining a baseline PSA level, repeating it at 3–6 months after initiating therapy, and continuing annual monitoring thereafter, particularly in men over 40 or those with additional risk factors [39].
- Other societies, such as the Society for Endocrinology, recommend that men with hypogonadism should follow prostate cancer screening guidelines equivalent to those of the general population, without additional PSA testing solely based testosterone therapy.

Beyond PSA, clinicians should assess individual risk factors for prostate cancer before and during therapy, including age, family history, and genetic background (*e.g.*, Breast Cancer gene 2 (BRCA2) mutations). Current evidence does not support an increased risk of prostate cancer with testosterone therapy in appropriately screened men.

Interestingly, several studies suggest an inverse relationship between serum testosterone levels and prostate cancer aggressiveness. Low testosterone has been associated with higher-grade disease and adverse outcomes after prostatectomy [67].

The historical fear of testosterone promoting prostate cancer is increasingly being challenged by modern evidence. While TRT remains contraindicated in men with active or high-risk prostate cancer, data support its cautious use in selected individuals with treated, localized disease and stable PSA. Proper patient selection, risk stratification, and close PSA monitoring are essential to ensure safety.

5. Summary of differences between clinical guidelines on testosterone therapy

Although major international guidelines—such as those from the European Association of Urology (EAU), American Urological Association (AUA), International Society for Sexual Medicine (ISSM), Society for Endocrinology (SfE), Endocrine Society of Australia (ESA), and European Academy of Andrology (EAA)—share a common foundation in the diagnosis and management of male hypogonadism, they differ in key areas.

Diagnostic cutoffs for serum total testosterone vary among these societies, with the AUA defining testosterone deficiency at levels below 300 ng/dL [11], while the EAA and EAU use slightly higher cutoffs, typically <350 ng/dL [3, 11, 14, 15]. The ISSM specifies <231 ng/dL (8 nmol/L) as likely deficient, ≥346 ng/dL (12 nmol/L) as unlikely, and 231–346 ng/dL as requiring additional evaluation [16]. SfE emphasises evidence-based, lower biochemical thresholds derived from population studies (EMAS): sexual symptoms increase with total testosterone <8 nmol/L (231 ng/dL) or with <11 nmol/L (317 ng/dL) when combined with low calculated free testosterone (cFT <220 pmol/L [17]. ESA does not specify a strict diagnostic cutoff, instead emphasizing a pathological basis (*e.g.*, hypothalamic, pituitary, or testicular disease confirmed by elevated low/normal luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels alongside low total testosterone), with reference intervals cited as 10.4–30.1 nmol/L (300–870 ng/dL) for young men and 6.4–25.7 nmol/L (184–740 ng/dL) for healthy older men [18]. This disparity contributes to a clinical "gray zone", necessitating integration of biochemical results with clinical symptomatology to guide treatment initiation. Follow-up protocols reveal further differences: the AUA recommends initial PSA and hematocrit evaluation at 3 to 6 months post-therapy initiation, then every 6–12 months [11], while the EAU suggests more frequent early monitoring at 3, 6, and 12 months with risk-adapted surveillance thereafter [14]. The ISSM recommends symptom and side effect assessment at 3, 6, and 12 months then annually, with TT, hematocrit, PSA, and lipids at each visit [16]. The ESA proposes symptom-based monitoring [18]. The SfE aligns closely with EAU and ISSM, recommending monitoring of PSA, hematocrit, and symptoms at 3, 6, and 12 months

initially, then annually [17].

Regarding safety, recommendations on hematocrit limits also differ: the EAU advises against initiating testosterone therapy if hematocrit exceeds 54% [3], whereas the AUA recommends discontinuing treatment if the hematocrit exceeds 50% and discontinuing treatment or reducing the dose at levels above 54% due to the risk of thrombosis [11].

Concerning prostate cancer, both the EAU and AUA cautiously permit testosterone therapy in men with previously treated, low-risk prostate cancer [11, 15], while the EAA considers testosterone therapy in this context controversial due to insufficient long-term safety data [14].

Regarding safety and hematocrit management, the guidelines show notable differences. The EAU advises against starting testosterone therapy when hematocrit is above 54%, while the AUA recommends discontinuing treatment if it exceeds 50% and either reducing or stopping therapy at levels above 54% due to thrombosis risk [3, 15]. The ISSM suggests hematocrit should remain within the laboratory reference range and managed according to local protocols, a stance that aligns with the EAA's caution on cardiovascular risks but offers greater flexibility than the numeric thresholds of the EAU and AUA [14, 16]. Meanwhile, the ESA and SfE do not set explicit cutoffs but emphasize regular monitoring for erythrocytosis as a safety measure, reflecting an approach closer to the ISSM, though ESA's focus on pathological hypogonadism suggests more conservative initiation criteria [17, 18].

With respect to prostate cancer, the EAU and AUA cautiously allow testosterone therapy in men previously treated for low-risk disease [11, 15]. The EAA cites insufficient long-term safety data [14]. The ISSM recommends that general practitioners avoid prescribing testosterone in men with active or prior prostate cancer and instead refer them to specialists [16]. In contrast, the ESA explicitly contraindicates therapy in men with prostate cancer, aligning with its stricter pathological requirements [18]. The SfE adopts a more permissive but structured approach, allowing therapy in selected low-risk, treated patients after multidisciplinary evaluation and with informed consent, thus balancing patient autonomy with medical caution [17].

These discrepancies (Table 2) underscore the importance of individualized clinical judgment and adherence to local guideline recommendations.

6. Conclusions

Male hypogonadism is a prevalent and often underrecognized condition that affects multiple aspects of male health. While testosterone replacement therapy (TRT) can offer significant clinical benefits in appropriately selected patients—particularly in terms of sexual function, mood, bone health, and metabolic parameters—its use remains

TABLE 2. Comparison of international clinical guidelines on testosterone therapy for male hypogonadism.

Aspect	AUA (2018)	EAU (2025)	ISSM (2015)	EAA (2020)	SfE (2022)	ESA (2016)
Diagnostic cutoff (total T)	<300 ng/dL (10.4 nmol/L)	<350 ng/dL (12 nmol/L)	250–350 ng/dL (8.7–12 nmol/L)	<350 ng/dL (12 nmol/L)	<231 ng/dL TD; ≥350 nmol/L unlikely TD	Based on pathological diagnosis, not threshold
Target serum T during therapy	450–600 ng/dL (mid-normal range)	280–873 ng/dL (full physiological range)	Individualized to clinical response	Full physiological range, symptom-guided	Mid-normal reference range for young adults	Physiological levels comparable to eugonadal men
Hematocrit—contraindication to start	>50%	>48–50%	>50%	>48–50%	>50% (untreated polycythemia)	Untreated polycythemia
Hematocrit—intervention/suspension	≥54%	≥54%	≥54%	≥54%	>50% (adjust treatment)	Not specifically defined
Prostate cancer (treated, low risk)	Permits with shared decision-making and undetectable PSA	Permits after ≥1 year recurrence-free and PSA <0.01 ng/mL	Permits with risk stratification	Permits under similar precautions as EAU	Joint management with urologist mandatory	May be acceptable after definitive treatment
Monitoring (PSA, Hct)	3–6 months, then every 6–12 months	3, 6, and 12 months first year; then risk-adapted	Similar to EAU with flexibility	Similar to EAU, risk-adapted	Variable based on formulation	Not specifically detailed

AUA: American Urological Association; EAU: European Association of Urology; ISSM: International Society for Sexual Medicine; EAA: European Academy of Andrology; SfE: Society for Endocrinology (UK); ESA: Endocrine Society of Australia; T: testosterone; TD: testosterone deficiency; Hct: hematocrit; PSA: prostate-specific antigen.

surrounded by controversy. Current evidence, including high-quality randomized trials such as TRAVERSE (cardiovascular safety) and T4DM (diabetes prevention), supports the efficacy and safety of TRT when prescribed judiciously. However, this must be tempered by findings such as the increased fracture risk observed in older men with functional hypogonadism, underscoring the need for careful patient selection. Therefore, a strict guideline-based approach is mandatory. TRT must be individualized, prioritizing symptomatic men with confirmed biochemical deficiency, and may include consideration of alternative therapies to stimulate endogenous production in selected cases. It requires rigorous ongoing monitoring to mitigate risks such as erythrocytosis, particularly in those with cardiovascular comorbidities, untreated sleep apnea, or a history of prostate cancer. In an era of evolving evidence and direct-to-consumer marketing, clinicians must navigate TRT with critical judgment, ensuring that therapeutic decisions are driven by robust evidence and individualized patient needs rather than anecdotal claims or non-medical demands.

AVAILABILITY OF DATA AND MATERIALS

Not applicable. This study is a narrative review and does not generate primary datasets. All data supporting the findings are derived from previously published literature cited within the article.

AUTHOR CONTRIBUTIONS

ARC—designed the research study and drafted the initial manuscript; performed the synthesis of the evidence. JFS and JMMF—contributed to literature search and data extraction. JARE and EGG—provided methodological guidance and critical expert input. REN—contributed to content validation and review of the clinical safety considerations. All authors contributed to editorial revisions, and all authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable. This article is a narrative review and does not involve human participants, human data, or animal experiments.

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The authors declare no conflict of interest.

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