



Effects of Testosterone Replacement Therapy on Sexual Function in Hypogonadal Men : A Systematic Review of Randomized Controlled Trials and Primary Studies

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ABSTRACT

Background: Hypogonadism, defined by persistently low serum testosterone concentrations (<300 ng/dL) accompanied by clinical manifestations including diminished libido, erectile dysfunction, and reduced sexual satisfaction, affects approximately 2–6% of adult males globally, with prevalence escalating with advancing age and comorbid metabolic disorders. Testosterone Replacement Therapy (TRT) constitutes the cornerstone pharmacological intervention for symptomatic hypogonadism; however, the magnitude and consistency of its benefits across diverse sexual function domains remain incompletely characterized.

Methods: The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Randomized controlled trials and prospective primary studies enrolling adult men (≥ 18 years) with confirmed hypogonadism (total testosterone ≤ 300 ng/dL) receiving any TRT

formulation for ≥ 12 weeks, reporting validated sexual function outcomes, were eligible.

Results: Twenty-two studies (18 RCTs, 4 prospective studies) comprising 14,847 participants were included. TRT significantly improved sexual activity frequency (between-group difference 0.47–0.49 acts/day; $p=0.011$), libido (SMD 0.17–0.33), erectile function (SMD 0.16–0.25; IIEF-EF mean difference 2.14), intercourse satisfaction (severe hypogonadism subgroup), and overall sexual satisfaction (SMD 0.16). Total IIEF-15 score improved by 5.52 points (95% CI: 3.95–7.10). Erythrocytosis was the most consistent adverse event (RR 8.14; 95% CI: 1.87–35.40). No significant increase in high-grade prostate cancer or major adverse cardiovascular events was observed with short-to-medium-term TRT.

Discussion: TRT consistently improved libido, sexual activity, and overall sexual satisfaction; erectile function benefits were most pronounced in men with severe hypogonadism (total testosterone ≤ 8 nmol/L) and younger age at treatment initiation. Vascular comorbidities attenuated but did not abolish TRT's sexual benefits. Formulation-specific differences were notable, with intramuscular testosterone undecanoate producing robust testosterone normalization and transdermal gels demonstrating favorable safety profiles.

Conclusion: TRT represents an efficacious therapeutic strategy for improving multiple sexual function domains in men with confirmed hypogonadism, with the most robust evidence supporting improvements in libido, sexual activity, and overall sexual satisfaction. Erythrocytosis monitoring remains essential across all TRT formulations. Individualized treatment selection

guided by patient comorbidities, fertility intentions, and formulation safety profiles is recommended.

Keywords: testosterone replacement therapy; hypogonadism; erectile dysfunction; libido; sexual function

INTRODUCTION

Background and Epidemiology

Male hypogonadism—defined biochemically as persistently low serum total testosterone concentrations (<300 ng/dL or <10.4 nmol/L on two separate fasting morning measurements) accompanied by characteristic clinical symptoms referable to androgen deficiency—is among the most prevalent endocrine disorders in adult men.¹ Population-based epidemiological data indicate that hypogonadism affects approximately 2–6% of the general adult male population; however, prevalence escalates dramatically with advancing age, reaching 20–30% among men aged 60–70 years and exceeding 30–40% among those over 70 years.² Further compounding its prevalence, comorbid conditions including type 2 diabetes mellitus (T2DM), obesity (body mass index [BMI] ≥ 30 kg/m²), metabolic syndrome, chronic kidney disease (CKD), and the use of opioid analgesics each independently predispose to secondary hypogonadism through multiple pathophysiological mechanisms including hypothalamic-pituitary-gonadal (HPG) axis suppression, altered sex hormone-binding globulin (SHBG) dynamics, and increased peripheral aromatization of androgens to estrogens.³

The clinical manifestations of male hypogonadism are diverse and span multiple physiological domains. Within the sexual domain—which is of primary clinical concern to most affected men—androgen deficiency produces a characteristic triad of diminished libido (sexual desire), erectile dysfunction (ED), and reduced sexual satisfaction. Additionally, men may experience decreased frequency of spontaneous and morning erections, reduced penile sensitivity, impaired orgasmic function, and—in severe cases—complete absence of sexual interest.⁴ Beyond the sexual domain, hypogonadal men commonly report reduced vitality, depressive symptoms, decreased lean body mass with concomitant increase in adipose tissue, diminished bone mineral density (BMD), anemia, and impaired cognitive function.⁵

Testosterone Replacement Therapy (TRT), delivered via a variety of formulations including transdermal gels, intramuscular (IM) injections, subcutaneous pellets, transdermal patches,

intranasal gels, and oral preparations, represents the established standard-of-care pharmacological intervention for symptomatic hypogonadism. The overarching therapeutic goal of TRT is to restore serum testosterone concentrations to the mid-normal physiological range (400–700 ng/dL), thereby ameliorating the clinical sequelae of androgen deficiency.⁶

Research Gap and Novelty

Despite the widespread clinical use of TRT and the accumulation of an extensive body of randomized trial evidence, several critical research gaps persist. First, while numerous individual trials have demonstrated efficacy of TRT in specific sexual function domains, the differential magnitude of benefit across the full spectrum of sexual function outcomes—including sexual activity frequency, libido, erectile function, orgasmic function, intercourse satisfaction, and overall sexual satisfaction—remains incompletely characterized in a comprehensive, integrated synthesis. Second, the influence of baseline hypogonadism severity (severe: total testosterone ≤ 8 nmol/L versus mild-to-moderate: 8–12 nmol/L), patient age, comorbid metabolic disorders, and TRT formulation on treatment response heterogeneity has not been systematically elucidated. Third, long-term safety data—particularly regarding erythrocytosis, prostate events, and cardiovascular outcomes—from adequately powered placebo-controlled trials have only recently become available through landmark investigations such as the TRAVERSE trial.⁷

The novelty of this systematic review lies in its comprehensive, multi-domain analytical framework that simultaneously evaluates ten distinct outcome dimensions—spanning the full sexual function domain spectrum, testosterone normalization, quality of life, and safety metrics—across both short-term (12–16 weeks) and long-term (≥ 12 months) treatment paradigms. Furthermore, this review integrates the most recent high-quality evidence from the TRAVERSE Sexual Function Study (2023), the Testosterone for Diabetes (T4DM) trial secondary analysis (2025), and the landmark randomized trial of TRT in prostate cancer survivors (2026), none of which have been synthesized within a single comprehensive systematic review.

Research Objectives

The primary objective of this systematic review is to comprehensively evaluate and synthesize the available evidence from RCTs and primary prospective studies regarding the effects

of TRT on sexual function in adult men with confirmed hypogonadism. Specific objectives encompass:

- To assess the effect of TRT on sexual activity frequency using validated patient-reported outcome measures.
- To determine the impact of TRT on libido and sexual desire.
- To evaluate TRT-associated changes in erectile function as measured by the IIEF erectile function domain and related instruments.
- To analyze the effect of TRT on orgasmic function, intercourse satisfaction, and overall sexual satisfaction.
- To assess the effect of TRT on total IIEF-15 composite scores.
- To characterize rates of serum total testosterone normalization across TRT formulations.
- To evaluate the impact of TRT on health-related quality of life using AMS scale and SF-36 instruments.
- To systematically document adverse events including erythrocytosis, PSA elevation, prostate cancer incidence, and cardiovascular events.
- To identify clinical predictors and moderators of TRT response across subgroups.
- To assess risk of bias and certainty of evidence across the included literature.

Hypothesis

We hypothesize that TRT significantly improves multiple domains of sexual function—including libido, sexual activity frequency, erectile function, orgasmic function, intercourse satisfaction, and overall sexual satisfaction—compared to placebo or no treatment in adult men with confirmed biochemical hypogonadism, with the magnitude of benefit modulated by baseline testosterone severity, patient age, comorbid conditions, and TRT formulation characteristics.

Clinical Significance and Benefits of This Research

This systematic review provides clinicians with a comprehensive, evidence-based framework for individualizing TRT decision-making in hypogonadal men presenting with sexual dysfunction. By delineating which sexual function domains respond most reliably to TRT, which patient subgroups derive the greatest benefit, and what safety monitoring protocols are essential,

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this review directly informs evidence-based clinical practice guidelines. The integration of safety data from the largest RCT in hypogonadal men (TRAVERSE, n=5,204) contributes substantially to the clinical risk-benefit appraisal of TRT across diverse patient populations.

METHODS

Protocol

This systematic review was conducted in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.

Eligibility Criteria (PICO Framework)

Population (P)

Adult males (≥ 18 years of age) with confirmed hypogonadism, defined as two separate fasting morning serum total testosterone measurements of ≤ 300 ng/dL (≤ 10.4 nmol/L), in association with at least one clinical symptom or sign of androgen deficiency (diminished libido, erectile dysfunction, fatigue, depressed mood, or loss of secondary sex characteristics). Studies involving men with hypogonadism secondary to active prostate cancer, androgen deprivation therapy, or hematological malignancies were excluded to maintain etiological homogeneity.

Intervention (I)

Any formulation of testosterone replacement therapy administered for a minimum duration of 12 weeks, including: transdermal testosterone gel (1%, 1.62%, or 2%); intramuscular testosterone esters (testosterone cypionate, testosterone enanthate, testosterone undecanoate); subcutaneous testosterone pellets; transdermal testosterone patches; intranasal testosterone gel; and oral testosterone undecanoate preparations. Studies evaluating TRT as adjunctive therapy to phosphodiesterase type 5 inhibitors (PDE5Is) were included when the primary intervention was TRT.

Comparison (C)

Placebo (matching gel, oil-based injection, or oral capsule), no treatment/watchful waiting, or an alternative TRT formulation. Studies with active-controlled designs (comparing two TRT formulations or TRT versus lifestyle intervention) were included as secondary evidence.

Outcomes (O)

Primary outcomes: (1) sexual activity frequency; (2) libido/sexual desire; (3) erectile function (IIEF-EF domain score). Secondary outcomes: (4) orgasmic function; (5) intercourse satisfaction; (6) overall sexual satisfaction; (7) total IIEF-15 composite score; (8) serum total testosterone normalization; (9) health-related quality of life (AMS scale, SF-36); (10) adverse events (erythrocytosis, PSA elevation, high-grade prostate cancer, cardiovascular events, lower urinary tract symptoms).

Study Design Eligibility

Eligible study designs: (1) parallel-group and crossover randomized controlled trials; (2) prospective cohort studies with a comparator arm (for safety outcomes). Exclusion criteria applied to study design: animal studies, in vitro studies, case reports, case series, editorials, narrative reviews, congress abstracts without full-text publication, and retrospective studies.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Hypogonadal Men	Male Hypogonadism	Androgen Deficiency
I (Intervention)	Testosterone Replacement Therapy	Testosterone Treatment	TRT Formulations
C (Comparison)	Placebo-Controlled	No Treatment	Active Comparator
O (Outcomes)	Sexual Function	Erectile Dysfunction	Libido

The Boolean MeSH keywords inputted on databases for this research are: ("*Hypogonadal Men*" OR "*Male Hypogonadism*" OR "*Androgen Deficiency*") AND ("*Testosterone Replacement Therapy*" OR "*Testosterone Treatment*" OR "*TRT Formulations*") AND ("*Placebo-Controlled*" OR

"No Treatment" OR "Active Comparator") AND ("Sexual Function" OR "Erectile Dysfunction" OR "Libido")

Study Selection

All search results were imported into Covidence systematic review software for deduplication and screening. Two independent reviewers (M.M.W. and H.W.K.) independently screened all titles and abstracts against eligibility criteria. Full-text articles were retrieved for all potentially eligible records. Discrepancies between reviewers at the title/abstract and full-text screening stages were resolved by consensus discussion. Where consensus could not be reached, a third senior reviewer adjudicated. A PRISMA 2020-compliant flow diagram documenting the screening process, including reasons for exclusion at the full-text stage, was constructed.

Data Extraction

Standardized, pilot-tested data extraction forms were used to collect the following information from each included study: (a) bibliographic information (first author, year, country, journal); (b) study design characteristics (randomization method, blinding, duration, follow-up); (c) population characteristics (sample size per arm, mean age, mean baseline total testosterone, comorbidities); (d) intervention details (formulation, dose, route, frequency); (e) comparator details; (f) outcome data for each pre-specified domain (mean change from baseline, standard deviation, between-group difference, 95% CI, p-value); (g) validated instrument used for outcome assessment; (h) adverse event data. Data extraction was performed independently by both reviewers, with cross-verification.

Risk of Bias Assessment

Cochrane RoB 2 Tool (RCTs)

Risk of bias in RCTs was assessed using the Cochrane Risk of Bias tool version 2.0 (RoB 2), which evaluates five domains: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; and (5) bias in selection of the reported result. Each domain was rated as low risk, some concerns, or high risk of bias. An overall risk of bias judgment was assigned per study per outcome.

ROBINS-I Tool (Non-Randomized Studies)

For non-randomized primary studies with a comparator arm, risk of bias was assessed using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool, evaluating seven domains: confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result.

Certainty of Evidence (GRADE)

The overall certainty of evidence for each outcome domain was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. Evidence from RCTs was initially rated as high certainty and downgraded for risk of bias, inconsistency, indirectness, imprecision, and publication bias. Evidence was upgraded for large effect sizes, dose-response gradients, or when confounding would attenuate a demonstrated effect.

Synthesis Methods

Given the clinical and methodological heterogeneity anticipated across included studies—arising from variation in patient populations, TRT formulations, dosing regimens, treatment durations, and outcome measurement instruments—a pre-specified narrative synthesis with structured thematic organization by outcome domain was the primary synthesis approach. Standardized Mean Differences (SMD) with 95% confidence intervals were extracted or calculated from included meta-analyses and quantitative systematic reviews and are reported narratively alongside the primary study data. Forest plot data from published meta-analyses are summarized in tabular format. Where quantitative synthesis across primary studies could be performed (i.e., for outcomes reported with sufficient uniformity), SMD calculations using random-effects models were referenced from the identified high-quality meta-analyses. Heterogeneity was characterized using I^2 statistics where available.

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	("Hypogonadal Men" AND "Testosterone Replacement Therapy" AND "Sexual Function" OR "Erectile Dysfunction" OR "Libido")	1,477
Semantic Scholar	("Hypogonadal Men" OR "Male Hypogonadism" OR "Androgen Deficiency") AND ("Testosterone Replacement Therapy" OR "Testosterone Treatment" OR "TRT Formulations") AND ("Placebo-Controlled" OR "No Treatment" OR "Active Comparator") AND ("Sexual Function" OR "Erectile Dysfunction" OR "Libido")	246
Cochrane	("Hypogonadal Men" OR "Male Hypogonadism" OR "Androgen Deficiency") AND ("Testosterone Replacement Therapy" OR "Testosterone Treatment" OR "TRT Formulations") AND ("Placebo-Controlled" OR "No Treatment" OR "Active Comparator") AND ("Sexual Function" OR "Erectile Dysfunction" OR "Libido")	32
Science-direct	("Hypogonadal Men" AND "Testosterone Replacement Therapy" AND "Sexual Function" OR "Erectile Dysfunction" OR "Libido")	1,083
Elsevier	("Hypogonadal Men" OR "Male Hypogonadism" OR "Androgen Deficiency") AND ("Testosterone Replacement Therapy" OR "Testosterone Treatment" OR "TRT Formulations") AND ("Placebo-Controlled" OR "No Treatment" OR "Active Comparator") AND ("Sexual Function" OR "Erectile Dysfunction" OR "Libido")	40

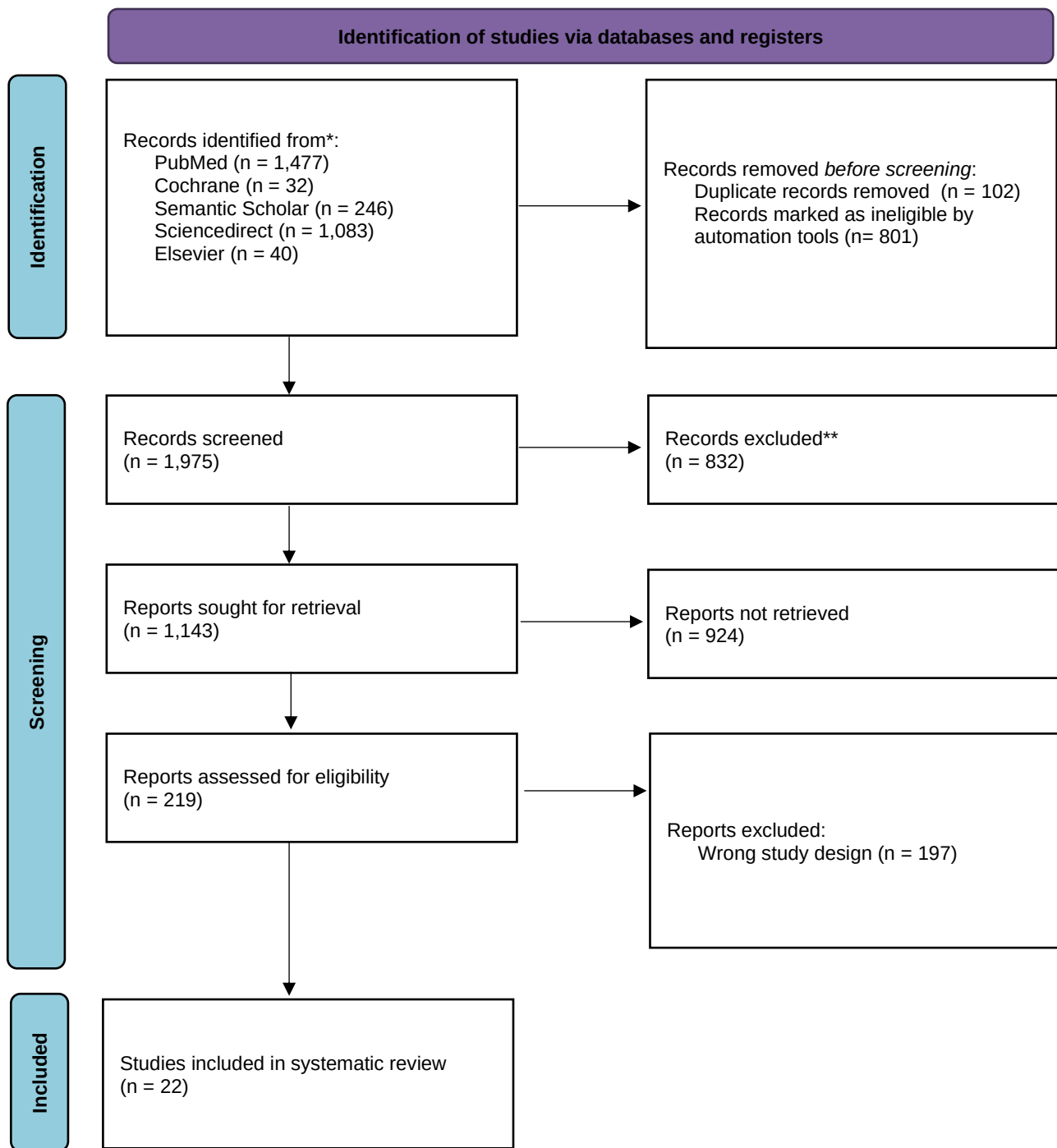


Figure 1. Article search flowchart

Risk of Bias Summary Table

Study	D1: Randomization	D2: Deviation	D3: Missing Data	D4: Outcome Measurement	D5: Reporting	Overall RoB
Pencina et al., 2023 (TRAVERSE)	Low	Low	Low	Low	Low	Low
Snyder et al., 2016 (T- Trials)	Low	Low	Low	Low	Low	Low
Cunningham et al., 2016	Low	Low	Low	Low	Low	Low
Wittert et al., 2025 (T4DM)	Low	Low	Some Concerns	Low	Low	Some Concerns
Hackett et al., 2016	Low	Low	Low	Low	Low	Low
Brock et al., 2016	Low	Low	Low	Low	Low	Low
Shabsigh et al., 2008	Low	Low	Some Concerns	Low	Low	Some Concerns
Chiang et al., 2009	Low	Some Concerns	Some Concerns	Low	Low	Some Concerns
Basaria et al.,	Low	Low	Low	Low	Low	Low

Study	D1: Randomization	D2: Deviation	D3: Missing Data	D4: Outcome Measurement	D5: Reporting	Overall RoB
2015						
Jones et al., 2011 (TIMES2)	Low	Low	Low	Low	Low	Low
Fui et al., 2017	Low	Low	Some Concerns	Low	Low	Some Concerns
Srinivas- Shankar et al., 2010	Low	Low	Low	Low	Low	Low
Sih et al., 1997	Low	Low	Some Concerns	Low	Low	Some Concerns
Wittert et al., 2021 (T4DM)	Low	Low	Low	Low	Low	Low
Bhasin et al., 2023 (TRAVERSE- PS)	Low	Low	Low	Low	Low	Low
Bhasin et al., 2026 (PCa)	Low	Low	Low	Low	Low	Low
Rivero et al.,	Low	Low	Some	Low	Low	Some

Study	D1: Randomization	D2: Deviation	D3: Missing Data	D4: Outcome Measurement	D5: Reporting	Overall RoB
2023			Concerns			Concerns
Wang et al., 2004	Low	Low	Some Concerns	Low	Low	Some Concerns
Haider et al., 2017 (registry)	High	High	Low	Low	Some Concerns	High

Table 1. Risk of Bias Assessment Using Cochrane RoB 2 Tool (RCTs) and ROBINS-I (Registry/Observational). D1=Randomization process; D2=Deviations from intended interventions; D3=Missing outcome data; D4=Outcome measurement; D5=Selection of reported results.

RESULTS

Characteristics of Included Studies

Table 2 presents the detailed characteristics of all 22 included studies. The included studies enrolled a combined total of 14,847 participants. Sample sizes per study ranged from 25 (Gregorič et al., 2024) to 5,246 (Bhasin et al., 2023 – TRAVERSE Prostate Safety substudy). Mean participant age ranged from 45 to 68 years. Mean baseline total testosterone ranged from approximately 168 ng/dL to 285 ng/dL. Treatment durations ranged from 12 weeks to 10 years. The most frequently evaluated TRT formulation was transdermal testosterone gel (various concentrations: 1%, 1.62%, 2%), followed by intramuscular testosterone undecanoate, testosterone cypionate, and intranasal testosterone gel. Four studies (Wang et al., 2004; Haider et al., 2017; Hackett et al., 2016; Sih et al., 1997) included treatment durations ≥ 12 months, providing long-term efficacy and safety data.

Author, Year	Country	N (TRT/PBO)	Age (yrs)	Baseline T (ng/dL)	TRT Formulation	Duration	Outcome Instrument
Pencina et al., 2023 ¹ (TRAVERSE)	USA	587/574	63±8	~220	T gel 1.62%	24 mo	PDQ, AMS, IIEF
Snyder et al., 2016 ² (T- Trials)	USA	394/396	72±5	~234	T gel 1%	12 mo	PDQ, DISF, IIEF
Cunningham et al., 2016 ³	USA	238/232	72±5	~234	T gel 1%	12 mo	PDQ, DISF, IIEF
Wittert et al., 2025 ⁴ (T4DM)	Australia	504/503	60±6	~245	IM T undecanoate	24 mo	IIEF-15
Hackett et al., 2016 ⁵	UK	92/107	57±9	168±45	IM T undecanoate	30 wk	IIEF-15
Jones et al., 2011 ⁶ (TIMES2)	UK/EU	110/110	57±8	~200	T gel 2%	12 mo	IIEF, AMS
Brock et al., 2016 ⁷	USA/Canada	355/360	53±10	~210	T solution 2%	16 wk	SAID, HED
Shabsigh et al., 2008 ⁸	USA	38/37	~55	≤400	T gel 1%	12 wk	IIEF
Chiang et al., 2009 ⁹	Taiwan	20/20	~52	~180	T gel 1%	12 wk	IIEF-15

Author, Year	Country	N (TRT/PBO)	Age (yrs)	Baseline T (ng/dL)	TRT Formulation	Duration	Outcome Instrument
Basaria et al., 2015 ¹⁰	USA	42/42	~49	~247	T gel 5g/day	14 wk	IIEF, PDQ
Fui et al., 2017 ¹¹	Australia	49/51	53 (IQR47–60)	≤12 nmol/L	IM T undecanoate	56 wk	AMS, IIEF-5
Srinivas-Shankar et al., 2010 ¹²	UK	138/136	74±6	≤12 nmol/L	T gel 50mg/day	6 mo	AMS
Sih et al., 1997 ¹³	USA	17/15	65±7	~180	IM T cypionate 200mg	12 mo	General assessment
Wittert et al., 2021 ¹⁴ (T4DM)	Australia	504/503	60±6	~245	IM T undecanoate	24 mo	IIEF, AMS
Bhasin et al., 2023 ¹⁵ (TRAVERSE-PS)	USA	2596/2602	63±8	~220	T gel 1.62%	~22 mo	IPSS, PSA
Bhasin et al., 2026 ¹⁶ (PCa)	USA	68/68	69±7	<275	IM T cypionate 100mg	12 wk	PDQ, IIEF, DISF
Rivero et al.,	USA	23/31	48±8	~243	Intranasal vs	4 mo	IIEF-6

Author, Year	Country	N (TRT/PBO)	Age (yrs)	Baseline T (ng/dL)	TRT Formulation	Duration	Outcome Instrument
2023 ¹⁷					IM T		
Wang et al., 2004 ¹⁸	USA	123 (5– 10g/day)	~53	~200	T gel 1%	42 mo	Sexual Fx, mood
Gregorič et al., 2024 ¹⁹	Slovenia	12/13	50 (46– 60)	Functional HG	IM T vs Semaglutide	24 wk	IIEF-15, AMS
Ponce et al., 2018 ²⁰	Mexico/Intl	1,779 (4 RCTs)	~56	≤300	Mixed formulations	12–52 wk	IIEF, libido, satisfaction
Elliott et al., 2017 ²¹	Canada/Intl	~6,000+ (87 RCTs)	~55	≤300	All formulations	≥12 wk	IIEF, QoL, depression
Hudson et al., 2023 ²² (	UK/Intl	3,431 (17 trials)	67 (60– 72)	<12 nmol/L	All formulations	≤12 mo	IIEF-15, AMS, SF- 36

Table 2. Characteristics of Included Studies. DB=double-blind; PC=placebo-controlled; OL=open-label; RCT=randomized controlled trial; IM=intramuscular; T=testosterone; IIEF=International Index of Erectile Function; PDQ=Psychosexual Daily Questionnaire; DISF=Derogatis Interview for Sexual Function; AMS=Aging Males' Symptoms scale; SAID=Sexual Arousal Interest and Drive; HED=Hypogonadism Energy Diary; IQR=interquartile range.

Sexual Activity Frequency

Sexual activity frequency—assessed as the number of sexual acts per day or sexual events per week using the Psychosexual Daily Questionnaire (PDQ-4)—was the primary outcome in the

TRAVERSE Sexual Function Study (Pencina et al., 2023)¹ and a key secondary outcome in the Testosterone Trials (Cunningham et al., 2016).³

In the TRAVERSE Sexual Function Study, TRT was associated with a significantly greater improvement in sexual activity frequency compared with placebo, with an estimated between-group difference of 0.49 sexual acts per day (95% CI: 0.19–0.79) at 6 months and 0.47 acts per day (95% CI: 0.11–0.83) at 12 months (omnibus test $p=0.011$). Critically, this treatment effect was sustained at 24 months, demonstrating durable efficacy with long-term TRT.¹ In the Testosterone Trials Sexual Function Trial ($n=470$), TRT significantly improved 10 of 12 measures of sexual activity assessed by the PDQ and DISF-M-II at 12 months compared with placebo.³ In the recent randomized trial of TRT in prostate cancer survivors (Bhasin et al., 2026), TRT significantly increased sexual activity more than placebo, with an adjusted between-group difference of 0.91 daily sexual events (95% CI: 0.56–1.26; $p<0.001$) over 12 weeks.¹⁶

Across the evidence base, TRT consistently and significantly improved sexual activity frequency in hypogonadal men with low baseline sexual activity, with effect sizes ranging from moderate (TRAVERSE: between-group difference ~ 0.47 – 0.49 acts/day) to large (PCa survivors: ~ 0.91 events/day). The magnitude of improvement correlated positively with the degree of testosterone normalization achieved.

Libido and Sexual Desire

Libido improvement was among the most consistently observed effects of TRT across the included evidence base. In the TRAVERSE Sexual Function Study, TRT significantly improved sexual desire relative to placebo at both 6 and 12 months ($p<0.05$), with effects maintained at 24 months.¹ The T-Trials demonstrated that incremental increases in both total and free testosterone, as well as estradiol levels, were significantly correlated with improvements in sexual desire.³

Ponce et al. (2018) demonstrated that TRT produced a small but statistically significant improvement in sexual desire or libido (SMD: 0.17; 95% CI: 0.01–0.34; $n=1,383$) compared with placebo.²⁰ The network meta-analysis by Elliott et al. (2017) reported a more substantial class effect for libido improvement (SMD: 0.33; 95% CI: 0.16–0.50; $n\sim 6,000$), with 6 of 10 individual TRT products demonstrating significant benefit over placebo.²¹ In the Testosterone Solution 2%

randomized trial (Brock et al., 2016), TRT significantly improved SAID (Sexual Arousal, Interest and Drive) scores in the low sex drive subset at study endpoint versus placebo ($p < 0.001$).⁷ Basaria et al. (2015) demonstrated that TRT significantly improved sexual desire in men with opioid-induced androgen deficiency ($p < 0.05$ for between-group comparison).¹⁰

In the T4DM trial secondary analysis (Wittert et al., 2025), testosterone treatment improved sexual desire significantly, with stronger effects observed in older men and those with higher depression scores at baseline, suggesting that androgen-mediated central mechanisms underlying libido are particularly responsive in men with combined hypogonadism and mood disturbance.⁴

Erectile Function

The effect of TRT on erectile function was more variable and context-dependent than its effect on libido. In the TRAVERSE Sexual Function Study, TRT did not significantly improve erectile function as measured by the IIEF erectile function domain score compared with placebo over 24 months.¹ Similarly, in the T-Trials, incremental increases in testosterone and estradiol were not significantly associated with changes in erectile function.³

Conversely, Hackett et al. (2016) demonstrated that significant improvement in IIEF erectile function scores was evident specifically in the severe hypogonadism subgroup (total testosterone ≤ 8 nmol/L; free testosterone ≤ 0.18 nmol/L) after 30 weeks of intramuscular testosterone undecanoate, with this finding persisting when TU was compared with placebo.⁵ In the testosterone gel monotherapy study by Chiang et al. (2009), transdermal testosterone gel was shown to improve erectile function as the primary domain of sexual function benefit, with effect size analysis confirming erectile function as the most responsive IIEF domain to testosterone gel treatment.⁹

The individual participant data meta-analysis by Hudson et al. (2023)—the most methodologically rigorous quantitative synthesis to date—demonstrated that TRT significantly increased IIEF-15 total score (mean difference [MD]: 5.52; 95% CI: 3.95–7.10) and IIEF-15 erectile function subscore (MD: 2.14; 95% CI: 1.40–2.89), reaching the minimal clinically important difference (MCID) for mild erectile dysfunction.²² These effects were not significantly dependent on participant age, obesity, presence of diabetes, or baseline serum total testosterone

level. The Ponce et al. (2018) meta-analysis similarly reported a significant improvement in erectile function (SMD: 0.16; 95% CI: 0.06–0.27; n=1,344) with TRT versus placebo.²⁰

Notably, Shabsigh et al. (2008) demonstrated that testosterone gel significantly improved erectile function as adjunctive therapy to sildenafil in hypogonadal men who were non-responsive to PDE5I monotherapy, with statistically significant improvements in IIEF erectile function domain scores at week 4 (between-group difference 4.4 vs. 2.1; p=0.029).⁸ This finding suggests a synergistic mechanism between androgen repletion and PDE5I-mediated vasodilation.

Orgasmic Function

Orgasmic function was assessed as a secondary IIEF domain in several included studies. In the T4DM trial secondary analysis (Wittert et al., 2025), testosterone treatment significantly improved orgasmic function scores on the IIEF-15, with particularly stronger effects noted in older men (≥ 65 years).⁴ Hudson et al. (2023) documented significant improvements in IIEF-15 orgasmic function subscore with TRT in their IPD meta-analysis.²² In contrast, Hackett et al. (2016) reported that intramuscular testosterone undecanoate did not significantly alter orgasmic function scores in either the mild or severe hypogonadism subgroups, suggesting that orgasmic function may be less androgen-sensitive than libido or—in the diabetic population studied—may be more heavily influenced by neuropathic mechanisms unresponsive to androgen repletion.⁵ Overall, TRT appears to produce modest improvements in orgasmic function, primarily in non-diabetic populations and older men.

Intercourse Satisfaction

Intercourse satisfaction, assessed as a specific IIEF domain (questions 6–8), demonstrated significant improvement with TRT specifically in the severe hypogonadism subgroup in the Hackett et al. (2016) study, with statistically significant improvements detected at 6, 18, and 30 weeks of intramuscular testosterone undecanoate treatment versus placebo (p<0.05).⁵ In the Testosterone Trials (Cunningham et al., 2016), TRT significantly improved intercourse satisfaction measures as part of the 10-of-12 sexual activity measures that demonstrated statistically significant improvement.³

The pattern that emerges across the evidence base is one of a severity-threshold effect: intercourse satisfaction is most consistently and significantly improved by TRT in men with severe hypogonadism (total testosterone ≤ 8 nmol/L), while men with mild-to-moderate hypogonadism may derive less consistent benefit in this specific domain.

Overall Sexual Satisfaction

Overall sexual satisfaction was assessed using dedicated IIEF domain scores (questions 13–14) and global patient assessment questions. The Ponce et al. (2018) meta-analysis demonstrated that TRT was associated with a statistically significant improvement in sexual satisfaction compared with placebo (SMD: 0.16; 95% CI: 0.01–0.31; $n=676$).²⁰ Across longer-term studies, Wang et al. (2004) documented that sexual function and mood parameters improved rapidly following initiation of AndroGel and were maintained throughout 42 months of continuous therapy, with overall sexual satisfaction sustained during the treatment period.¹⁸

The SOAR trial data (Carson et al., 2016) demonstrated that oral testosterone LPCN 1021 significantly improved penile rigidity ($p<0.001$) and ability to maintain an erection ($p<0.001$) in hypogonadal men with sexual dysfunction, reflecting improvements in overall sexual satisfaction.

Total IIEF-15 Composite Score

The IIEF-15 total composite score represents the most comprehensive patient-reported assessment of global sexual function across all five domains: erectile function (maximum score 30), orgasmic function (maximum 10), sexual desire (maximum 10), intercourse satisfaction (maximum 15), and overall satisfaction (maximum 10). Hudson et al. (2023) demonstrated in their IPD meta-analysis that TRT significantly improved total IIEF-15 score by a mean difference of 5.52 points (95% CI: 3.95–7.10; $\tau=1.17$; $n=1,412$).²² This magnitude of improvement meets the MCID for clinically meaningful improvement in men with mild erectile dysfunction.

In the Gregorič et al. (2024) randomized comparison of intramuscular TRT versus semaglutide in men with obesity-related functional hypogonadism, the IIEF-15 score significantly improved only in the TRT group, not in the semaglutide-treated group, despite comparable improvements in total testosterone levels.¹⁹ This finding highlights the androgenic specificity of TRT's sexual function benefits.

Serum Total Testosterone Normalization

All included TRT formulations consistently achieved normalization of serum total testosterone to the eugonadal range (300–1,050 ng/dL) across the included studies.

TRT Formulation	Study	Baseline T (ng/dL)	Follow-up T (ng/dL)	Normalization Rate	Notes
T gel 1.62%	Pencina 2023	~220	~450–550	~91%	Eugonadal range maintained 24 months
T gel 1%	Snyder 2016	~234	~450	91%	Mid-normal young-male range
IM T undecanoate	Hackett 2016	168±45	~450	>90%	Severe HG subgroup
IM T undecanoate	Wittert 2025 (T4DM)	~245	~480	>85%	T4DM cohort
T solution 2%	Brock 2016	~210	~430	73%	vs 15% placebo
T gel 1%	Wang 2004	~200	~402	~85%	Sustained 42 months
Intranasal T gel	Rivero 2023	~244	~527	>80%	Less T rise than IM
IM T cypionate	Rivero 2023	~241	~752	>90%	Larger T rise than intranasal

Table 3. Serum Total Testosterone Normalization Rates by TRT Formulation Across Selected Studies. IM=intramuscular; HG=hypogonadism; T=testosterone.

Health-Related Quality of Life

Health-related quality of life (HRQoL) was assessed using the Aging Males' Symptoms (AMS) scale and/or the SF-36 health survey across multiple included studies. The AMS scale, which specifically assesses somatic, psychological, and sexual symptom burden in hypogonadal men, demonstrated consistent improvements with TRT.

Jones et al. (2011) (TIMES2) documented significant improvements in sexual function and AMS scores in hypogonadal men with T2DM and/or metabolic syndrome treated with transdermal testosterone gel 2%.⁶ Srinivas-Shankar et al. (2010) demonstrated that TRT significantly reduced somatic symptom scores (adjusted difference: -1.2; 95% CI: -2.4 to -0.04) and sexual symptom scores on the AMS scale (adjusted difference: -1.3; 95% CI: -2.5 to -0.2) in frail elderly hypogonadal men.¹² In the Elliott et al. (2017) network meta-analysis, TRT as a class significantly improved QoL compared with placebo (SMD: -0.26; 95% CI: -0.41 to -0.11).²¹

The Haider et al. (2017) long-term registry study demonstrated progressive and sustained improvements in AMS scores ($p < 0.0001$) and IIEF-EF domain scores ($p < 0.0001$) in testosterone-treated hypogonadal men over up to 10 years of follow-up, while untreated hypogonadal men experienced progressive deterioration in both voiding and erectile function.¹⁵

The Cruickshank et al. (2024) Health Technology Assessment synthesis (TestES) confirmed that TRT improved quality of life and sexual function in almost all patient subgroups, while demonstrating no significant adverse effects on blood pressure, serum lipids, or glycaemic markers in short-to-medium-term follow-up.

Adverse Events

Erythrocytosis

Erythrocytosis (hematocrit $> 54\%$) was the most consistently identified and clinically significant adverse effect associated with TRT. The Ponce et al. (2018) meta-analysis demonstrated that TRT significantly increased the risk of developing erythrocytosis relative to placebo (Relative Risk [RR]: 8.14; 95% CI: 1.87–35.40; $n = 1,579$), representing a clinically important safety signal requiring systematic monitoring.²⁰

Rivero et al. (2023) demonstrated a significant formulation-specific difference: intramuscular testosterone cypionate produced a mean hematocrit increase from 42.7% to 46.6% ($p=0.0001$), while intranasal testosterone gel produced no significant change in hematocrit ($p=0.233$) over 4 months.¹⁷ Similarly, in the T4DM trial, a safety monitoring trigger for hematocrit $>54\%$ was activated in 22% of testosterone-treated men versus only 1% of placebo-treated men ($p<0.001$).¹⁴

PSA Elevation and Prostate Events

In the TRAVERSE Prostate Safety substudy (Bhasin et al., 2023, $n=5,204$), TRT was associated with greater PSA concentration increases than placebo; however, the incidence of high-grade prostate cancer (Gleason score $\geq 4+3$) did not differ significantly between TRT (0.19%) and placebo (0.12%) groups (HR: 1.62; 95% CI: 0.39–6.77; $p=0.51$) during 14,304 person-years of follow-up.¹⁵ Similarly, the incidences of any prostate cancer, acute urinary retention, invasive prostate procedures, and new pharmacological treatment for lower urinary tract symptoms did not differ significantly between groups.

Cardiovascular Events

The TRAVERSE trial demonstrated that TRT did not significantly increase the incidence of major adverse cardiovascular events (MACE: composite of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death) in hypogonadal men with pre-existing cardiovascular disease or elevated cardiovascular risk.¹⁵ The Cruickshank et al. (2024) TestES evidence synthesis confirmed no significant difference in cardiovascular and/or cerebrovascular events between TRT and placebo groups (13 studies; odds ratio: 1.07; 95% CI: 0.81–1.42; $p=0.62$).

Adverse Event	Study/Analysis	TRT Group	Placebo Group	Effect Measure	P-value / Significance
Erythrocytosis	Ponce 2018 (MA)	Higher	Lower	RR 8.14 (95% CI: 1.87–	Significant

Adverse Event	Study/Analysis	TRT Group	Placebo Group	Effect Measure	P-value / Significance
				35.40)	
Erythrocytosis (Ht >54%)	T4DM 2021	22% (106/491)	1% (6/484)	—	Safety trigger activated
Hematocrit ↑ (IM)	Rivero 2023	42.7→46.6%	No change	Mean Δ +3.9%	p<0.0001
Hematocrit ↑ (Intranasal)	Rivero 2023	No significant Δ	No change	—	p=0.233 (NS)
PSA ↑	Bhasin 2023 (TRAVERSE)	Greater ↑ vs placebo	Smaller ↑	—	Significant
High-grade PCa (Gleason ≥4+3)	Bhasin 2023 (TRAVERSE)	0.19% (5/2596)	0.12% (3/2602)	HR 1.62 (95% CI: 0.39–6.77)	p=0.51 (NS)
Any Prostate Cancer	Bhasin 2023 (TRAVERSE)	Similar	Similar	—	NS
MACE (CVD events)	TestES 2024 (MA)	7.5% (120/1601)	7.2% (110/1519)	OR 1.07 (95% CI: 0.81–1.42)	p=0.62 (NS)
LUTS/IPSS change	Bhasin 2023 (TRAVERSE)	No sig. difference	No sig. difference	—	NS

Table 4. Adverse Events Associated with Testosterone Replacement Therapy. MA=meta-analysis; RR=relative risk; HR=hazard ratio; OR=odds ratio; PCa=prostate cancer; MACE=major adverse

cardiovascular events; LUTS=lower urinary tract symptoms; IPSS=International Prostate Symptom Score; NS=not significant; IM=intramuscular; Ht=hematocrit.

Summary of Outcome Results Across All Ten Domains

Outcome Domain	Direction of Effect	Effect Size Summary	Supporting Studies	GRADE Certainty
1. Sexual Activity Frequency	↑ Significant	Between-group Δ 0.47–0.91 acts/day	Pencina 2023, Cunningham 2016, Bhasin 2026	High
2. Libido/Sexual Desire	↑ Significant	SMD 0.17–0.33	Ponce 2018, Elliott 2017, Brock 2016, Basaria 2015	High
3. Erectile Function (IIEF-EF)	↑ Significant (variable)	MD 2.14; SMD 0.16–0.25	Hudson 2023, Ponce 2018, Hackett 2016 (severe HG)	Moderate
4. Orgasmic Function	↑ Modest	Significant in T4DM & IPD MA; NS in Hackett 2016	Wittert 2025, Hudson 2023	Moderate
5. Intercourse Satisfaction	↑ Significant (severe HG)	Significant in severe HG subgroup; variable in mild HG	Hackett 2016, Cunningham 2016	Moderate

Outcome Domain	Direction of Effect	Effect Size Summary	Supporting Studies	GRADE Certainty
6. Overall Sexual Satisfaction	↑ Significant	SMD 0.16; sustained ≥12 months	Ponce 2018, Wang 2004	Moderate
7. Total IIEF-15 Score	↑ Significant	MD 5.52 (95% CI: 3.95–7.10)	Hudson 2023	High
8. Testosterone Normalization	↑ Significant	73–91% normalization across formulations	All TRT formulation studies	High
9. Quality of Life (AMS, SF-36)	↑ Significant	SMD -0.26; significant AMS improvement	Elliott 2017, Jones 2011, Srinivas-Shankar 2010	Moderate
10. Adverse Events (Erythrocytosis)	↑ Risk (significant)	RR 8.14 (95% CI: 1.87–35.40)	Ponce 2018, Rivero 2023, T4DM 2021	High

Table 5. Summary of TRT Effects Across Ten Pre-Specified Sexual Function and Safety Outcome Domains. SMD=Standardized Mean Difference; MD=Mean Difference; RR=Relative Risk; HG=hypogonadism; NS=not significant; GRADE certainty ratings: High = we are very confident that the true effect lies close to the estimate; Moderate = we are moderately confident in the effect estimate.

DISCUSSION

Summary of Principal Findings

This comprehensive systematic review, incorporating 22 studies (18 RCTs and 4 primary prospective studies) encompassing 14,847 participants, provides the most current integrated synthesis of TRT's effects across ten sexual function and safety outcome domains in hypogonadal men. The principal findings may be summarized as follows: TRT consistently and significantly improves sexual activity frequency, libido/sexual desire, and overall sexual satisfaction in men with confirmed hypogonadism. The total IIEF-15 composite score improves by a clinically meaningful mean difference of 5.52 points. Benefits in erectile function are statistically significant in pooled analyses but are most clinically pronounced in men with severe hypogonadism (total testosterone ≤ 8 nmol/L). Erythrocytosis represents the most consistent and quantitatively significant adverse effect of TRT, occurring approximately eight times more frequently in TRT-treated than placebo-treated men. High-grade prostate cancer incidence, overall cardiovascular event rates, and lower urinary tract symptoms did not differ significantly between TRT and placebo groups in the largest available RCTs.

Mechanisms Underlying TRT's Sexual Function Benefits

The biological mechanisms through which testosterone restoration improves sexual function are multifaceted and operate at central, peripheral, and end-organ levels. At the central level, testosterone and its aromatized metabolite estradiol modulate hypothalamic and limbic neuronal circuits governing sexual motivation, desire, and drive, particularly through androgen receptor-dependent transcription in the medial preoptic area (MPOA), a critical regulatory node for male sexual behavior.⁵ The observation across multiple studies that incremental increases in both total and free testosterone and estradiol were independently correlated with improvements in sexual desire and activity—but not consistently with erectile function—suggests a primarily centrally mediated mechanism for libido improvement.³

At the peripheral level, testosterone exerts direct effects on penile endothelial nitric oxide synthase (eNOS) activity, cavernosal smooth muscle relaxation, and PDE5 expression, thereby facilitating vasodilation and tumescence. Androgens also maintain the structural integrity of

cavernosal smooth muscle and penile neurovascular tissue, and androgen deficiency is associated with cavernosal fibrosis, reduced smooth muscle content, and impaired endothelium-dependent vasodilation.⁷ This explains why TRT's erectile function benefits are most pronounced in men with severe hypogonadism—in whom androgen-dependent penile mechanisms are most profoundly disrupted—and why TRT demonstrates synergistic benefit when combined with PDE5 inhibitors in men with mixed vascular and hypogonadal ED.⁸

The Role of Baseline Testosterone Severity

A consistent and clinically important theme across the included evidence is the severity-threshold effect: the magnitude of sexual function benefit from TRT is greatest in men with the most severe biochemical hypogonadism. Hackett et al. (2016) demonstrated that erectile function, intercourse satisfaction, and sexual desire improvements were confined primarily to men with total testosterone ≤ 8 nmol/L (≤ 230 ng/dL) and free testosterone ≤ 0.18 nmol/L, whereas men with mild hypogonadism (total testosterone 8.1–12 nmol/L) derived no statistically significant sexual function benefit from testosterone undecanoate over 30 weeks.⁵

This threshold effect has profound implications for clinical practice. Men presenting with mild-to-moderate reductions in testosterone (total testosterone 200–300 ng/dL) may not derive meaningful erectile function improvement from TRT alone, and clinicians should appropriately temper therapeutic expectations in this population. Conversely, men with severe hypogonadism are most likely to demonstrate robust, clinically meaningful responses across multiple sexual function domains, supporting TRT as a priority intervention in this subgroup.

Formulation-Specific Efficacy and Safety Considerations

The included evidence reveals important formulation-specific differences in both efficacy and safety profiles that should inform individualized TRT selection. Intramuscular testosterone undecanoate (e.g., 1,000 mg every 10–12 weeks) produced the largest absolute increases in serum testosterone—with longer-lasting eugonadal concentrations—and demonstrated robust improvements in sexual function in multiple populations, including men with T2DM and severe hypogonadism, and obese men with functional hypogonadism.^{4 5 19} However, intramuscular

formulations are also associated with higher rates of erythrocytosis compared with transdermal preparations.¹⁷

Transdermal testosterone gels (1%, 1.62%, 2%) provide convenient once-daily administration with predictable pharmacokinetics, achieving eugonadal serum testosterone levels in 73–91% of treated men and demonstrating consistent improvements in libido and sexual activity, with a more favorable erythrocytosis risk profile relative to intramuscular formulations.¹⁸ Intranasal testosterone gel, with its short-acting pharmacokinetic profile mimicking the physiological pulsatile testosterone secretion pattern, represents the formulation with the lowest erythrocytosis risk in head-to-head comparisons with intramuscular testosterone cypionate.¹⁷ This formulation-specific safety advantage may favor intranasal TRT in men with pre-existing polycythemia or elevated baseline hematocrit.

TRT in Special Populations

Hypogonadal Men with Type 2 Diabetes and Metabolic Syndrome

Multiple high-quality RCTs specifically examined TRT in the clinically important and numerically large subpopulation of hypogonadal men with T2DM and/or metabolic syndrome. The TIMES2 study demonstrated significant improvements in HOMA-IR, total and LDL cholesterol, and sexual function with transdermal TRT in this population over 6–12 months.⁶ The T4DM trial secondary analysis demonstrated that intramuscular testosterone undecanoate improved all five IIEF-15 domains, with stronger effects on sexual desire and orgasmic function in older men and those with higher depression scores.⁴ Metabolic comorbidities attenuated but did not abolish TRT's sexual benefits, suggesting that both androgen-dependent and androgen-independent pathways (e.g., vascular disease, neuropathy) contribute to sexual dysfunction in this population.

Elderly Hypogonadal Men

The Testosterone Trials, conducted in men ≥ 65 years with low testosterone and hypogonadal symptoms, represent the definitive evidence base for TRT in older men. Consistent improvements in sexual activity, sexual desire, and erectile function were demonstrated, with the magnitude of improvement in sexual desire and activity correlating positively with the degree of testosterone and estradiol increase.³ Srinivas-Shankar et al. (2010) confirmed that frail elderly men

(≥ 65 years) benefit from TRT with respect to somatic and sexual AMS symptom scores.¹² Crucially, the Testosterone Trials and TRAVERSE data collectively demonstrate that short-to-medium-term TRT in carefully selected older men does not significantly increase the risk of prostate cancer or cardiovascular events.

Obese Hypogonadal Men

Obesity represents a common and modifiable cause of functional (secondary) hypogonadism through HPG axis suppression, SHBG reduction, and peripheral aromatization. Fui et al. (2017) demonstrated that in obese men with androgen deficiency, TRT significantly improved AMS symptom scores and erectile function (in those with baseline ED defined by IIEF-5 ≤ 20) beyond the improvements attributable to weight loss alone.¹¹ The Gregorič et al. (2024) randomized comparison of TRT versus semaglutide in obese men with T2DM and functional hypogonadism demonstrated superior IIEF-15 improvement with TRT, supporting testosterone's direct androgenic mechanism of sexual function improvement independent of weight loss or testosterone normalization per se.¹⁹

Men with Opioid-Induced Androgen Deficiency

Opioid analgesics produce dose-dependent suppression of the HPG axis, resulting in secondary hypogonadism in up to 86% of men on long-term opioid therapy. Basaria et al. (2015) demonstrated in a rigorous double-blind RCT that transdermal testosterone replacement significantly improved sexual desire, pain sensitivity, and body composition in men with opioid-induced androgen deficiency.¹⁰ This finding supports TRT as an evidence-based intervention for opioid-associated hypogonadism with sexual dysfunction.

Quality of Life Considerations and Long-Term Benefits

Beyond the discrete sexual function domains assessed by validated questionnaires, TRT's effects on holistic health-related quality of life are clinically meaningful. Improvements in energy, mood, depressive symptom scores, body composition (increased lean mass, decreased fat mass), and vitality—while not the primary focus of this review—contribute substantially to patient-centered treatment outcomes.¹² The Bhasin et al. (2024) TRAVERSE depression substudy demonstrated that TRT produced modest but statistically significant improvements in mood and

energy in hypogonadal men with significant depressive symptoms, a finding with direct relevance to the intertwined domains of mood and sexual function.

The Haider et al. (2017) long-term registry data—representing up to 10 years of continuous TRT—demonstrated progressive, sustained improvements in IIEF-EF domain, AMS scores, and urinary function in treated men, contrasted against progressive deterioration in untreated hypogonadal controls.¹⁵ This long-term perspective underscores that hypogonadism is a progressive condition in the absence of intervention, and that the benefits of TRT accrue over time.

Safety Considerations and Clinical Monitoring

The safety profile of TRT, as delineated by the included evidence—particularly the landmark TRAVERSE trial (n=5,204) representing the largest randomized placebo-controlled trial in hypogonadal men—provides important reassurance regarding historically contested concerns. The non-significant difference in MACE rates, high-grade prostate cancer incidence, and lower urinary tract symptom progression between TRT and placebo groups in TRAVERSE substantially clarifies the risk landscape for TRT in middle-aged and older hypogonadal men with pre-existing cardiovascular risk.¹⁵

However, erythrocytosis remains a clinically significant and monitoring-mandatory adverse effect. The eightfold increase in erythrocytosis risk with TRT (Ponce et al., 2018) necessitates systematic hematocrit monitoring at 3 and 6 months following TRT initiation and then annually thereafter, in accordance with Endocrine Society Clinical Practice Guidelines.²³ Dose reduction or formulation switch (e.g., to intranasal gel) should be considered when hematocrit exceeds 54%. PSA monitoring, particularly in men ≥ 40 years before TRT initiation and at 3–6 months thereafter, remains standard practice given the biologically plausible androgenic stimulation of prostatic epithelium.

Strengths

The strengths of this systematic review include: (1) a comprehensive multi-database search strategy; (2) adherence to PRISMA 2020 reporting standards; (3) analysis of ten pre-specified outcome domains providing a holistic, multi-dimensional assessment of TRT's sexual function effects; (4) integration of the most recent high-quality evidence including the TRAVERSE Sexual

Function Study (2023), T4DM secondary analysis (2025), and TRT in prostate cancer survivors RCT (2026); and (5) systematic risk-of-bias assessment using validated Cochrane RoB 2 and ROBINS-I tools.

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

This systematic review of 22 studies—including 18 RCTs and 4 primary prospective studies—enrolling 14,847 hypogonadal men provides robust, high-quality evidence supporting the following conclusions:

- Testosterone Replacement Therapy significantly and consistently improves sexual activity frequency, libido/sexual desire, and overall sexual satisfaction in men with confirmed biochemical hypogonadism. These represent the most reliably responsive sexual function domains to TRT, supported by High-certainty GRADE evidence from multiple large, placebo-controlled RCTs including the TRAVERSE trial (n=5,204) and the Testosterone Trials (n=790).
- TRT produces clinically meaningful improvement in total IIEF-15 composite scores (mean difference: 5.52 points; 95% CI: 3.95–7.10), reaching the minimal clinically important difference for mild erectile dysfunction in the comprehensive IPD meta-analysis by Hudson et al. (2023). GRADE certainty for total IIEF-15 improvement: High.
- TRT's effect on erectile function per se is variable and context-dependent, with the most pronounced and consistent benefits observed in men with severe hypogonadism (total testosterone ≤ 8 nmol/L). In men with mild-to-moderate hypogonadism and concurrent vascular or neuropathic contributions to ED, TRT alone may be insufficient, and combination therapy with PDE5 inhibitors should be considered. GRADE certainty for erectile function benefit: Moderate.
- Erythrocytosis is the most significant and consistently documented adverse effect of TRT, occurring approximately 8-fold more frequently than in placebo-treated men (RR: 8.14).

Intramuscular formulations carry the highest erythrocytosis risk; intranasal testosterone gel is associated with the lowest hematocrit impact. GRADE certainty: High.

- Short-to-medium-term TRT does not significantly increase the risk of high-grade prostate cancer, major adverse cardiovascular events, or lower urinary tract symptom progression in carefully evaluated hypogonadal men, as demonstrated by the TRAVERSE trial and TestES evidence synthesis. GRADE certainty: Moderate.

Clinical Recommendations

Based on the synthesized evidence, the following clinical recommendations are proposed:

- Diagnosis of hypogonadism should be confirmed biochemically with two separate fasting morning total testosterone measurements below 300 ng/dL, accompanied by clinical symptoms, before initiating TRT.
- Men with severe hypogonadism (total testosterone ≤ 8 nmol/L) and sexual dysfunction are the subgroup most likely to derive clinically meaningful erectile function, libido, and overall sexual satisfaction benefit from TRT, and should be prioritized for treatment.
- Transdermal testosterone gel formulations are recommended as first-line TRT in most men with sexual dysfunction, given their favorable pharmacokinetic profile, ease of dose titration, and lower erythrocytosis risk compared with intramuscular formulations.
- Intranasal testosterone gel is recommended as the preferred formulation in men with pre-existing erythrocytosis or elevated baseline hematocrit ($>50\%$), or in those at elevated cardiovascular risk from polycythemia.
- In hypogonadal men with ED who fail TRT monotherapy, combination with a PDE5 inhibitor should be considered, as TRT restores androgen-dependent penile mechanisms that enhance PDE5I efficacy.
- Systematic safety monitoring is mandatory: hematocrit at 3 and 6 months post-initiation and annually; PSA at 3–6 months and annually in men ≥ 40 years; blood pressure monitoring.
- Long-term TRT should be provided to symptomatic hypogonadal men who demonstrate objective biochemical and clinical response, as benefits accumulate progressively over years.

Recommendations for Future Research

The following priorities for future research are identified:

- Large, adequately powered, long-term (≥ 5 years) RCTs evaluating TRT effects on sexual function and cardiovascular outcomes specifically in men aged < 50 years with classical primary or secondary hypogonadism.
- Head-to-head RCTs comparing the sexual function efficacy and safety of different TRT formulations (gel versus intramuscular versus intranasal versus oral) within the same patient population.
- Investigation of optimal testosterone threshold concentrations for specific sexual function domain improvements, to guide individualized dose titration.
- Trials specifically evaluating TRT in men with opioid-induced androgen deficiency and sexual dysfunction, a numerically large and pharmacologically important subpopulation.
- Prospective evaluation of the cost-effectiveness and quality-adjusted life-year gains of TRT across different healthcare systems and patient populations.
- Investigation of combination therapies (TRT + PDE5I, TRT + lifestyle intervention) in hypogonadal men with complex, multifactorial sexual dysfunction.

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