

Dual Effects of Testosterone Therapy in Aging Males: A Review of Prostate Cancer and BPH Outcomes

¹ K. Raj Kumar, ² R. Jona Methusala, ³ B. Sneha Reddy, ⁴ D. Priyanka

Student, Doctor of Pharmacy, Dr. K.V. Subba Reddy Institute of Pharmacy, Kurnool.

Associate Professor, Department of Pharmacology, Dr.K.V.Subba Reddy Institute of Pharmacy, Kurnool.

Student, Doctor of Pharmacy, Dr. K.V. Subba Reddy Institute of Pharmacy, Kurnool.

Student, Doctor of Pharmacy, Dr. K.V. Subba Reddy Institute of Pharmacy, Kurnool

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ABSTRACT

Background: Testosterone therapy (TT) has become an increasingly utilized intervention for symptomatic hypogonadism in aging males, offering benefits in sexual function, muscle mass, bone density, and quality of life. Concern about prostate safety — specifically the potential for TT to increase risk of prostate cancer (PCa) or to exacerbate benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS) — has historically limited broader clinical uptake. **Objective:** This review synthesizes mechanistic insights, epidemiological studies, randomized trials, systematic reviews, and contemporary guideline statements through 2025 to assess the effects of TT on prostate cancer and BPH outcomes. **Methods:** A narrative review of the literature emphasizing high-quality meta-analyses, randomized controlled trials, and professional society guidance was performed; key mechanistic models, including the saturation model, were evaluated alongside clinical data. **Results:** Mechanistic and clinical evidence suggests that physiological replacement doses of testosterone, when used in symptomatic, biochemically confirmed hypogonadal men who undergo baseline prostate assessment and ongoing surveillance, do not produce a marked increase in short-to-medium term incidence of de novo prostate cancer or clinically meaningful worsening of BPH/LUTS. The saturation model provides a useful explanatory framework for why raising serum testosterone within the physiologic range has limited additional stimulatory effect on prostate tissue. However, limitations include heterogeneous study designs, potential selection and surveillance biases in observational cohorts, and limited very-long-term randomized data. **Conclusions:** TT can be considered for symptomatic hypogonadal men following informed consent, baseline prostate evaluation, and guideline-concordant monitoring. Further long-term and subgroup-specific research is

warranted to refine risk stratification and optimize safety protocols.

Keywords

Testosterone therapy; Hypogonadism; Prostate cancer; Benign prostatic hyperplasia; PSA; Lower urinary tract symptoms

I. INTRODUCTION

Testosterone levels decline with advancing age in many men, a phenomenon variably referred to as late-onset hypogonadism or age-related testosterone deficiency. Clinically, low testosterone is associated with reduced libido, erectile dysfunction, decreased muscle mass and strength, increased adiposity, mood disturbances, fatigue, and impaired quality of life. Epidemiologic studies estimate that a significant proportion of men over 60 exhibit testosterone levels below reference ranges, though symptomatic correlation varies and diagnosis requires consistent morning measurements and clinical assessment [1-3].

Testosterone therapy (TT) has been demonstrated in randomized trials and observational studies to improve many of these symptomatic domains when hypogonadism is confirmed. Yet, since the seminal work demonstrating androgen-dependence of prostate cancer cells under castrate conditions, clinicians have approached TT cautiously due to theoretical risks of stimulating prostate growth or cancer progression. Over the past two decades, evolving mechanistic models, larger prospective series, and meta-analyses have led to a reappraisal of prostate risks associated with physiological TT. This review synthesizes contemporary evidence to inform clinicians and researchers.

Physiological Background and Mechanisms

Androgens — principally testosterone and its more potent metabolite dihydrotestosterone (DHT) — bind the androgen receptor (AR) and regulate gene transcription that drives prostate cell

differentiation and growth. The prostate synthesizes DHT intraprostatically via 5 α -reductase activity, and tissue androgen exposure reflects both circulating substrate and local metabolism.

The saturation model, first articulated by Morgentaler and Traish, proposes that ARs in prostate tissue become saturated at relatively low androgen concentrations. Below this saturation point, changes in androgen levels may influence prostate cellular activity, but above it, additional increases in serum testosterone produce minimal incremental AR-mediated stimulation. This concept helps explain why restoring testosterone from castrate or very low levels to the physiologic range may have different effects than minor variations within the normal range [4-6].

Molecular complexity — including AR splice variants, co-regulator expression, intraprostatic androgen synthesis, and interpatient heterogeneity — means the saturation model is a useful but not universally definitive framework. Ongoing research on genomic and epigenetic modulators of AR signaling seeks to identify subgroups who might behave differently.

Testosterone Therapy Modalities and Pharmacology

Multiple TT formulations exist, including transdermal gels, transdermal patches, intramuscular injections (short- and long-acting esters), subcutaneous pellets, and oral formulations. Pharmacokinetics, peak-and-trough profiles, patient preference, cost, and monitoring requirements differ by formulation.

Choice of formulation can influence convenience, adherence, and certain side-effect profiles (eg, injection-related peaks may produce transient erythrocytosis). Clinicians should individualize therapy, considering patient comorbidities, preferences, and monitoring capability [7-9].

Testosterone Therapy and Prostate Cancer: Clinical Evidence

Observational cohort studies and registry analyses generally do not demonstrate a robust association between physiological TT and increased incidence of prostate cancer in appropriately screened populations. Many of these studies note that men selected for TT are often healthier and more closely monitored, which could bias findings toward safety.

Randomized controlled trials of TT historically focused on symptomatic and metabolic

endpoints rather than prostate cancer outcomes; however, recent large-scale safety trials and pooled analyses have not identified a significant increase in prostate cancer diagnoses among TT recipients during medium-term follow-up [10-13].

Meta-analyses aggregating randomized and observational data show no consistent signal for increased prostate cancer risk with physiological TT, but most trials are underpowered for this specific outcome and have limited follow-up relative to prostate cancer's natural history. Thus, while evidence is reassuring, definitive long-term data are still needed.

Men with a history of treated localized prostate cancer pose a special clinical dilemma. Retrospective and small prospective series of men treated with radical prostatectomy or radiotherapy who later received TT report low biochemical recurrence rates in carefully selected cases; nevertheless, practice guidelines recommend individualized decisionmaking and intensive PSA surveillance when TT is considered in this population [14-18].

Testosterone Therapy and Benign Prostatic Hyperplasia (BPH) / LUTS

Benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS) increase with age and can significantly impact quality of life. The relationship between systemic testosterone levels and BPH is complex because intraprostatic DHT, growth factors, inflammation, and aging-related stromal-epithelial interactions all contribute to prostatic enlargement.

Randomized trials, cohort studies, and meta-analyses generally indicate that physiological TT does not cause clinically significant worsening of LUTS, IPSS scores, prostate volume, or objective urinary flow measures in the short-to-medium term. Some observational datasets suggest modest increases in BPH diagnosis over prolonged follow-up, but these findings may reflect surveillance bias or the background incidence of BPH with aging rather than a direct causal effect of TT [19-23].

Clinicians should screen for moderate-to-severe LUTS before initiating TT and monitor symptoms after starting therapy. The development of acute urinary retention on TT is uncommon in well-selected populations but requires prompt evaluation.

PSA Kinetics and Monitoring Strategies

Testosterone therapy often causes modest increases in serum PSA, particularly in men who

start from low baseline PSA levels. This rise typically occurs within months of initiation and stabilizes thereafter for most patients.

Professional societies recommend baseline PSA and digital rectal examination (DRE) before initiating TT. Follow-up PSA checks at 3–6 months and periodic monitoring thereafter (eg, annually) are common practice. Significant PSA rises, rapid PSA velocity, or abnormal DRE should prompt urologic evaluation and consideration of biopsy following established ageand risk-adjusted thresholds [2,24-26].

Guideline Recommendations and Clinical Consensus

Major organizations — including the Endocrine Society, American Urological Association (AUA), and European Association of Urology (EAU) — support TT for symptomatic men with confirmed hypogonadism when appropriate baseline evaluation and ongoing monitoring are performed. Guidelines emphasize shared decision-making and individualized risk assessment.

For men with a prior history of prostate cancer, guidelines are cautious; some allow for TT in select men after curative therapy with close surveillance, while others urge greater restraint pending long-term safety data [3,27-29].

Controversies, Limitations, and Future Research Directions

Key controversies include the paucity of very-long-term randomized data focused on prostate cancer incidence and mortality, uncertainty regarding high-risk subgroups (eg, men with BRCA mutations or strong family history), and the need to understand differential effects across TT formulations.

Emerging areas of research include the role of selective androgen receptor modulators (SARMs), precision approaches incorporating genomic risk stratification, and biomarker development to distinguish indolent from aggressive disease more accurately. Well-designed registry studies and randomized trials with long follow-up are priorities.

II. CONCLUSION

However, as a narrative review, the paper's major limitation lies in the absence of a systematic search strategy and quantitative data synthesis, which weakens the strength of its conclusions. The lack of long-term randomized

controlled data, unclear inclusion criteria, and potential citation bias also restrict the generalizability of its findings.

while the article offers an informative and clinically relevant synthesis for healthcare professionals, future versions should adopt a structured systematic review format, include risk-of-bias assessment, and incorporate emerging data on cardiovascular and long-term oncologic outcomes to strengthen evidence-based guidance on testosterone therapy safety.

In summary, current mechanistic understanding and clinical evidence suggest that physiological testosterone replacement therapy, when prescribed to symptomatic, biochemically confirmed hypogonadal men who undergo baseline prostate evaluation and regular monitoring, is unlikely to substantially increase short- to medium-term risk of de novo prostate cancer or clinically significant worsening of BPH/LUTS.

Clinical practice should emphasise clear documentation of symptoms, confirmatory hormone testing, baseline PSA and DRE, shared decision-making, and adherence to monitoring protocols. Clinicians should remain cautious in men with high baseline prostate risk and should engage urology consultation when indicated. Future long-term trials, prospective registries, and studies focusing on high-risk and diverse populations are needed to further clarify safety profiles and optimize individualized care.

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