Andrology

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ANDROLOGY

REVIEW ARTICLE

Testosterone Therapy After Radical Prostatectomy: Insights From a Systematic Review and Meta-Analysis

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Received: 27 December 2025 | **Revised:** 20 May 2026 | **Accepted:** 26 May 2026

Keywords: prostate cancer | radical prostatectomy | testosterone replacement therapy | testosterone therapy

ABSTRACT

Background: The safety of testosterone therapy (TTh) in men with a history of prostate cancer (PCa) remains controversial, particularly after interventions for PCa including radical prostatectomy (RP). Previous meta-analyses have included heterogeneous populations, limiting interpretation.

Objective: To systematically review and meta-analyze the risk of biochemical recurrence (BCR) in hypogonadal men treated with TTh following RP for PCa.

Methods: A systematic search of Medline was conducted from 1969 to July 2025 according to PRISMA and MOOSE guidelines. Studies reporting BCR rates after TTh in men who underwent RP were included. Data were pooled using a random-effects model. Meta-regression explored the associations with age, Gleason score, follow-up, and preoperative prostate specific antigen (PSA).

Results: Seven retrospective studies met the inclusion criteria, encompassing 398 patients (mean age: 63.9 years; mean follow-up: 29.6 months). Overall, the pooled BCR rate in TTh-treated patients was 3.5% (95% CI: 1.5–8.5). No significant association was found between BCR and age, Gleason score, or follow-up duration. In studies with untreated controls, TTh was associated with a significantly lower BCR risk. Limited data suggested improvements in erectile function and quality of life. Funnel plot analysis indicated no publication bias.

Conclusions: TTh after RP appears to be associated with a limited risk of BCR in hypogonadal men with PCa. However, the absence of randomized controlled trials and incomplete reporting of key clinical variables preclude definitive conclusions. Larger, well-designed prospective studies are warranted to confirm these findings and clarify the long-term safety profile of the use of testosterone replacement therapy in this setting.

1 | Introduction

Prostate cancer (PCa) is the most commonly diagnosed cancer among men in more than half of the countries worldwide, with an estimated 1,467,854 new cases and 397,430 deaths in 2022 (https://gco.iarc.fr/today/en/fact-sheets-cancers). Several nonmodifiable and modifiable risk factors have been identified. The former include age, ethnicity, family history, and germline mutations, whereas obesity, smoking, and metabolic derangements are considered the most common modifiable risk factors [1]. The role of the hormonal milieu, and particularly the specific impact of circulating testosterone (T) levels, remains controversial [2, 3]. The Baltimore Longitudinal Study of Aging, a population-based cohort including 781 men with sex steroid measurements obtained prior to a diagnosis of PCa or at their last visit for those without cancer, reported that higher levels of calculated free testosterone (cFT) were associated with up to a two-fold increase in the incidence of high-risk PCa [4]. Using records from all patients admitted to National Health Service (NHS) hospitals and treatment centers in England (Hospital Episode Statistics Admitted Patient Care, HES APC), it was observed that patients with hypogonadism-related conditions—such as Klinefelter's syndrome, testicular hypofunction, and hypopituitarism—have a lower risk of developing PCa [4].

However, despite this evidence, several preclinical and clinical studies have strongly supported the "saturation hypothesis," which proposes that under physiological conditions, androgen receptors in the human prostate are saturated by circulating androgens and are therefore relatively insensitive to further increases in T levels [5]. Accordingly, in a meta-analysis of 18 prospective studies, which included 3,886 men with incidental PCa and 6,438 controls, Roddam et al. were unable to confirm any association between PCa and T levels [6]. Similar findings were reported by Boyle et al. in a more recent meta-analysis, which included 5,623 PCa cases and 14,604 controls, with a mean follow-up of 10 years [7].

Hypogonadism is relatively common in subjects with newly diagnosed PCa with an estimated prevalence up to 31% in the overall population and 16% in low risk patients [8]. Low T in subjects with PCa can further negatively impact quality of life (QoL) contributing to sexual dysfunction and mood disturbances [9, 10]. Supported by data from the Prostate Testing for Cancer and Treatment (ProtecT) study, which demonstrated low rates of progression and mortality among low-risk PCa patients on active surveillance [11], several uncontrolled studies have explored the use of T replacement therapy in hypogonadal men with PCa.

In a meta-analysis of 18 studies including 1,084 patients with a history of the T replacement therapy following definitive local treatment for PCa, Parizi et al. [12] reported a limited rate of biochemical recurrence (BCR). However, this study included a heterogeneous population of patients treated following radical prostatectomy (RP), radiotherapy, brachytherapy, cryotherapy, or high-intensity focused ultrasound, as well as individuals on active surveillance or receiving androgen deprivation therapy (ADT), which represents a crucial limitation for interpretation [12]. The aim of this study is to provide a more homogeneous data analysis by investigating the role of T therapy exclusively in patients who underwent RP. In line with the Sexual and Reproductive Health chapter of the European Association of Urology (EAU) Guidelines [13], the concept of testosterone replacement therapy will be referred to as testosterone therapy (TTh).

2 | Methods

This meta-analysis was performed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Supporting information 1).

The following PICO criteria were used [14]: ***population***: male ≥18-year-old who underwent RP for PCa; ***intervention***: individuals operated for PCa and treated with TTh; ***comparison***: prospective or retrospective analyses from baseline or versus controls; ***outcomes***: rate of BCR.

The protocol of this study (2025 CRD420251129974) was published on the website of the University of York (Centre for Reviews and Dissemination, https://www.crd.york.ac.uk/PROSPERO/view/CRD420251129974).

2.1 | Search Strategy

An extensive Medline, search was performed, including the following key words: ((“testosterone”[Supplementary Concept] OR “testosterone”[All Fields] OR “testosteron”[All Fields] OR “testosterone”[MeSH Terms] OR “testosterones”[All Fields] OR “testosterone s”[All Fields]) AND (“therapeutics”[MeSH Terms] OR “therapeutics”[All Fields] OR “therapies”[All Fields] OR “therapy”[MeSH Subheading] OR “therapy”[All Fields] OR “therapy s”[All Fields] OR “therapies”[All Fields]) AND (“radical”[All Fields] OR “radical s”[All Fields] OR “radicals”[All Fields]) AND (“prostatectomy”[MeSH Terms] OR “prostatectomy”[All Fields] OR “prostatectomies”[All Fields])) AND ((humans[Filter]) AND (male[Filter]) AND (english[Filter])). The search, which accrued data from January first, 1969, up to July 31, 2025, was restricted to English-language articles including human male participants. The identification of relevant studies was performed independently by four of the authors (GR, AM, LB, PC), and conflicts were resolved by a consensus discussion amongst all authors. We did not employ search software but hand-searched the bibliographies of retrieved papers for additional references. The main sources of information were derived from published articles.

2.2 | Study Selection

All prospective and retrospective observational trials reporting data on BCR after TTh in patients treated with RP for PCa were included. Case reports were excluded. Only data from full-text articles were considered, while studies published solely as abstracts were excluded. Similarly, data on TTh in patients with PCa managed with active surveillance or treated with radiation

therapy, brachytherapy, cryotherapy, or high-intensity focused ultrasound were excluded from the analysis (Figure S1).

2.3 | Outcome and Quality Assessment

The primary outcome was the assessment of BCR following TTh. Secondary outcomes included the evaluation of sexual function and QoL after TTh, as well as the risk of BCR in patients treated with TTh compared to untreated controls. Potential determinants of BCR rates were also investigated. The quality of the included studies and risk of bias were assessed using the ROBINS-I tool for observational studies (Table S1) [15].

2.4 | Statistical Analysis

Heterogeneity was assessed using I^2 statistics. Even when low heterogeneity was detected, a random-effect model was applied because the validity of heterogeneity tests can be limited with a small number of component studies. We used funnel plots and the Begg-adjusted rank correlation test to estimate possible publication or disclosure bias [16]. The BCR rate was expressed as the mean percentage with a 95% confidence interval (CI). Meta-regression analyses were performed when indicated. All calculations were conducted using Comprehensive Meta-Analysis software, Version 2 (Biostat, Englewood, NJ, USA). Multivariate analyses were performed using SPSS (Statistical Package for the Social Sciences), Version 25.1 for Windows (IBM Corp., Chicago, IL, USA).

3 | Results

3.1 | Descriptive Statistics

Of the 272 articles retrieved, 7 met the inclusion criteria and were analyzed (Table 1 and Figure S1) [17–23]. Overall, 398 patients were included, with a mean age of 63.9 years and a mean follow-up of 29.6 months. All studies retrospectively assessed patient outcomes (Table 1). In most cases, only low- to moderate-risk patients were included, with 84.5% of enrolled patients having a Gleason score < 8. TTh was administered using different formulations, and the definition of BCR varied across studies. Specifically, four trials employed a mixed combination of testosterone preparations, whereas two studies used testosterone gel exclusively. Information regarding the type of testosterone products was unavailable in one of the included trials (Table 1). Finally, three studies compared BCR rates with a control group of patients who did not receive TTh.

3.2 | Biochemical Recurrence

The I^2 in trials assessing BCR rate was 0.0 (p = 0.48). A funnel plot and Begg adjusted rank correlation test (Kendall's τ: 0.0; p = 1.0) suggested no publication bias. TTh was able to significantly increase baseline T levels at follow-up (Figure 1). Overall, 3.5 [5.5;8.5]% BCR rate was observed in subjects treated with TTh (Figure 2). No difference in BCR rates was observed between studies using a prostate specific antigen (PSA) threshold

TABLE 1 | Characteristics of studies included in the meta-analysis.

Author	Study design	Patients *N*	Controls *N*	Duration (months)	Age (years)	PSA levels pre-surgery (ng/mL)	T levels before TTh (nmol/L)	Gleason score < 8 (%)	BCR PSA threshold (ng/mL)	TTh preparation
Kaufman & Graydon 2004 [17]	R	7	—	19.7	62.3	5.24	3.3	100	0.1	mixed
Agarwal et al., 2005 [18]	R	10	.	19	64.3	7.0	6.8	70	0.1	mixed
Khera et al., 2009 [19]	R	57	—	36	64.0	5.58	8.7	93	0.1	T gel
Pastuszak et al., 2013 [20]	R	103	50	27.7	61.0	5.2	8.9	73	0.2	Mixed
Ory et al., 2016 [21]	R	22	—	48	75,5	—	6.6	63.6	0.2	T gel
Ahlering et al., 2020 [22]	R	152	419	40.8	61.4	7.2	—	94.1	0.2	—
Shahine et al., 2021 [23]	R	47	1256	16	59.44	6.29	7.24	98	0.1	Mixed

Note: Quantitative variables are expressed as mean.

Abbreviations: BCR, biochemical recurrence; PSA, prostatic specific antigen; R, retrospective study; T, testosterone; TTh, testosterone therapy.

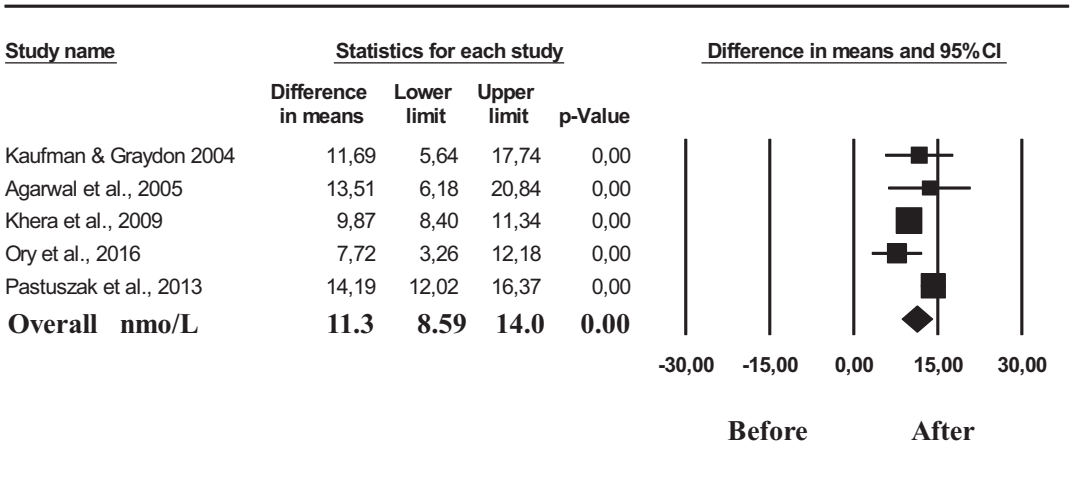

FIGURE 1 | Weighted mean differences (with 95% CI) of circulating testosterone levels before and after testosterone therapy.

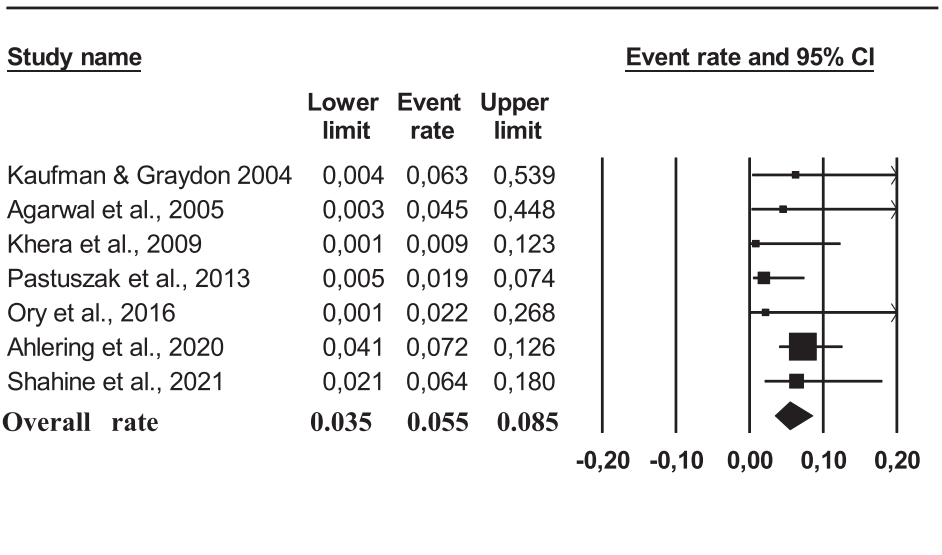

FIGURE 2 | Prostate cancer biochemical recurrence rate (with 95% CI) after testosterone therapy.

TABLE 2 | Slope and intercept estimates derived from meta-regression analysis for various determinants, with prostate cancer biochemical recurrence as the dependent variable.

Paremeter	Slope	Intercept
Age (years)	−0.080[−0.263;0.102]; $p = 0.386$	2.124[−9.134;13.383]; $p = 0.712$
Trial follow-up (months)	0.010[−0.036;0.057]; $p = 0.666$	−3.200[−4.856;−1.544]; $p < 0.0001$
Gleason score < 8 (%)	0.013[−0.040;0.065]; $p = 0.637$	−3.876[−8.163;0.410]; $p = 0.076$
Pre operatory PSA levels (ng/mL)	0.596[−0.054;1.245]; $p = 0.072$	−6.810[−11.187; −2.434]; $p < 0.005$

Abbreviation: PSA, prostatic specific antigen.

of 0.2 ng/mL and those using 0.1 ng/mL (4.0[1.5;11.1]% vs. 4.9[1.9;11.7]%, for 0.2 vs. 0.1 ng/mL, respectively; $Q = 0.045$; $p = 0.831$). Similarly, no difference were observed when trials using T gels were compared to those reporting a different approach (1.4[0.2;9.1]% vs. 4.1[1.9;8.9]%, respectively; $Q = 1.087$, $p = 0.297$). Meta-regression analysis showed that BCR rate was independent of age, trial follow-up, and Gleason score (Table 2). A trend toward a non-statistically significant higher risk associated with elevated preoperative PSA levels was also observed (Table 2).

Studies comparing BCR in T-treated men and controls showed no significant differences in mean age or baseline Gleason score

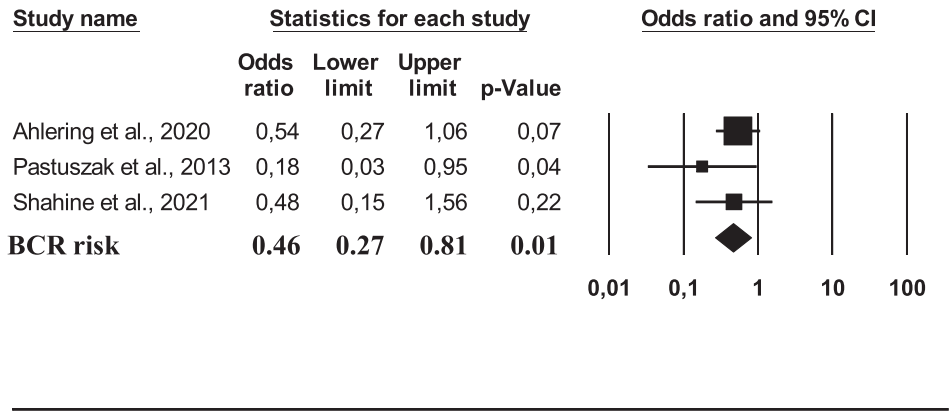

FIGURE 3 | Prostate cancer biochemical recurrence (BCR) risk (with 95% CI) in testosterone treated patients vs. controls.

TABLE 3 | Mean differences (with 95% CI) vs. baseline in different sexual function parameters after testosterone therapy.

Study	IIEF5 score vs. baseline	EPIC score vs. baseline
Shahine et al., 2021 [23]	3.11 [0.49;5,73]; $p = 0.020$	
Agarwal et al., 2005 [18]		11.00 [6.66;15.34]; $p<0.0001$

Abbreviations: EPIC, extended prostate Inventory composite; IIEF, International index of erectile function.

(61.3±0.6 vs. 60.6±1.06 years and 89.7±4.09 vs. 88.4±13.6% for T-treated vs. controls, for mean age and prevalence of Gleason score < 8, respectively; both p = NS). The use of TTh was associated with a significant reduction in BCR rates in T-treated patients compared to controls (Figure 3).

3.3 | Other Outcomes

Data on erectile function and QoL were reported in only one study for each parameter. TTh resulted in a significant improvement in the International Index of Erectile Function-5 (IIEF-5) score and QoL (Table 3).

4 | Discussion

By focusing exclusively on a homogeneous cohort of patients treated with RP for PCa, this study provides evidence that TTh is associated with a limited risk of BCR. Furthermore, when patients receiving TTh were compared with untreated controls, a significant reduction in BCR risk was observed.

The BCR rate observed in the present analysis is notably higher than that reported by Parizi et al. [12] in a previous meta-analysis (up to 2%). However, as previously noted, Parizi et al. [12] included a heterogeneous population of patients treated with both surgical and non-surgical interventions for PCa. In addition, their analysis incorporated data published only as meeting abstracts, often with very limited follow-up, and lacked information on potential selection bias [12]. These differences in population characteristics and follow-up duration may partly account for the four-fold higher BCR risk observed in our study.

Nevertheless, the BCR rate reported here remains lower than that described in a retrospective review of 1,997 patients followed for a median of 5.3 years after RP, where BRC reached up to 15% [24]. Due to limited information on preoperative characteristics in the present dataset, definitive conclusions and direct comparisons between these studies cannot be drawn. It is well established that Gleason grade, positive surgical margins, and pathological stage are major risk factors for BCR [25].

Interestingly, current findings indicate that patients receiving TTh had a lower risk of BCR compared to untreated subjects. It is important to note that preclinical studies have demonstrated that T can exert anti-inflammatory and anti-proliferative effects through activation of epithelial prostate androgen receptors [2, 26–28]. This phenomenon has supported the development of several phase II studies investigating the bipolar androgen therapy, which involves T supplementation in patients with advanced PCa who remain on continuous suppression of endogenous T levels through biochemical or surgical approaches [29–31]. On the other hand, the association between low T, obesity, and metabolic disorders in the general population is well documented [32–37], with similar findings reported during ADT for PCa [38]. It can be speculated that the use of TTh may reduce the risk of long-term metabolic complications, thereby potentially lowering BCR risk. Supporting this hypothesis, Ahlering et al. [22] demonstrated that in patients with PCa, TTh reduced both BCR risk and the incidence of arterial hypertension after a median follow-up of 3.5 years. However, the absence of prospective metabolic outcome data in the studies included in the present meta-analysis prevents definitive conclusions. Furthermore, possible confounding factors related to patient characteristics (e.g., stage, positive surgical margins) cannot be excluded. Similarly, the presence of selection bias—such as preferential

administration of TTh to healthier patients—remains a concern.

Although limited data were available, TTh was associated with improvements in sexual function and QoL. The beneficial effects of TTh on various sexual function parameters are well documented and have been consistently reported in several meta-analyses [39–46]. In line with this finding, the use of ADT in subjects with PCa is associated with more than four-fold increased risk of ED [9]. Beyond the well-known role of T in regulating nitric oxide (NO) formation [47], experimental evidence [48, 49] has also demonstrated that T regulates the expression of phosphodiesterase type 5 (PDE5). A trophic effect of T on penile architecture has been also demonstrated in different animal species [49, 50]. For all the aforementioned reasons, treating hypogonadism can restore impaired erectile dysfunction in both experimental animal models and in the clinical setting. Conversely, T administration to eugonadal individuals is largely ineffective. In line with this, the present data showed that TTh resulted in normalization of circulating testosterone levels. Moreover, the positive effects of T on PDE5 may enhance the efficacy of PDE5 inhibitors and support their use as a rehabilitative tool in patients with PCa, potentially improving overall QoL and reducing the time required to achieve spontaneous erections [51, 52]. Similarly, the beneficial effects of T on general well-being [53], mood [54], and body composition [55, 56] may explain the improvement in QoL reported in at least one study [18] included in the present meta-analysis.

Several limitations must be acknowledged. All included studies were based on retrospective data analyses, which are inherently prone to bias due to incomplete information and potential data loss, potentially compromising the validity of the findings. Furthermore, the type of T formulations varied across studies and only two studies were based on T gels only. In most reports, the Gleason score was below 8. Critical details regarding surgical approach, clinical stage, and the presence of positive surgical margins were frequently unavailable. Nevertheless, meta-regression analysis indicated that BCR rates were independent of Gleason score, although a trend toward increased risk associated with higher preoperative PSA levels was observed. Additional relevant information was limited, including the specific T preparation used, serum T levels, and patient adherence during follow-up. Systematic reviews and meta-analyses are valuable tools for addressing questions where individual studies provide conflicting or low-powered evidence, as data pooling can enhance statistical power and yield more robust conclusions. However, it is important to recognize that aggregating flawed evidence cannot eliminate inherent biases. Despite these limitations, we believe that the present analysis represents a meaningful attempt to provide improved evidence on a narrowly defined clinical question. In conclusion, our analysis suggests that TTh is associated with a limited risk of BCR in hypogonadal men with PCa following RP. Nevertheless, the lack of randomized controlled trials and the limited availability of comprehensive data prevent definitive conclusions. Larger, well-designed prospective studies are urgently needed to clarify this issue.

From a clinical perspective, and in accordance with current scientific guidelines [13, 37], TTh should be considered exclusively for symptomatic hypogonadal patients with low-risk PCa and no evidence of active disease after a minimum of 1 year of follow-up. Treatment decisions should involve shared decision-making, ensuring that patients are fully informed about the limited long-term safety data and the residual uncertainties. Clinicians should closely monitor PSA levels and disease status throughout therapy to mitigate potential risks.

Author Contributions

Acquisition (GR, AM, LB, PC), analysis or interpretation of the data (GC, AM, PC, GR, MM, AS), drafted the paper (GC, PC, AM), or revised it critically (GC, AM, PC, LB, CB, GR, LV, MM, SM, AS).

Funding

No funding support has been collected for this paper.

Disclosures

All authors have nothing to disclose for this paper.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting File1: andr70285-sup-0001-Figure.docx **Supporting File2**: andr70285-sup-0002-File1.doc **Supporting File3**: andr70285-sup-0003-File2.doc **Supporting File4**: andr70285-sup-0004-Table1.docx