ISSN: 2689-8616

Review Article

Advancements in Journal of Urology and Nephrology

Updated Review on Testosterone & Prostate Health

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Submitted: 2025, Jan 28; **Accepted:** 2025, Feb 21; **Published:** 2025, Feb 28

Citation: Yassin, A., Alzubaidi, R. T., Kamkoum, H., Mahdi, M., Akkad, M. E. et al. (2025). Updated Review on Testosterone & Prostate Health. *Adv J Uro Nephro, 7*(1), 01- 09.

Abstract

With prostate cancer not observed in eunuchs and total androgen suppression by castration an effective first-line treatment for advanced prostate cancer, the dramatic regression seen in tumor symptoms after castration, lead to the theory that high levels of circulating androgens were a risk factor for prostate cancer. This theory however, ignored the effects testosterone variations within a physiologic range could have on early tumor events and since the early 2000s, clinical evidence discounting testosterone as a linear mechanistic cause of prostate cancer growth mounted, with alternative mechanistic hypotheses such as the saturation model being proposed. Together with a growing understanding of the negative health effects and decreased quality of life in men with testosterone deficiency or hypogonadism, a paradigm shift away from testosterone as a prostate cancer inducer occurred allowing clinicians to use testosterone therapy as potential treatment for men with difficult and symptomatic hypogonadism that had been previously treated for prostate cancer. In this review, we contextualize the idea of testosterone as a risk factor for prostate cancer inducement and compile the most current literature about the influence of testosterone and testosterone therapy in prostate cancer.

Keywords: Testosterone, Prostate, Hypogonadism, Luts, Cancer, Quality of Life

1. Introduction

Testosterone has been shown to regulate the metabolism of carbohydrates, lipids and proteins and influence muscle growth and adipogenesis. As the principal circulating androgen in males, it contributes to a variety of physiological processes in different organs and systems such as bone, muscle, fat, brain, peripheral nerves, and genitalia and reproductive system [1,2]. Testosterone deficiency or hypogonadism is therefore a significant medical condition which could have a significant impact on morbidity and overall quality of life with hypogonadism associated with increased incidence of metabolic syndrome, obesity, sexual dysfunction, impaired fertility, increased fatigue and depressive mood, loss of bone and muscle mass, anemia, diabetes, sarcopenia, and increased mortality [3]. Despite being available since the early 1940s, testosterone therapy has been successively met with resistance due to the belief that it may cause or promote prostate cancer growth. In this review, the context of this association is summarized and the risk of testosterone therapy in prostate cancer patients is reviewed in light of the latest literature, in particular, discussing the implications for hypogonadal patients.

2. Testosterone and Prostate Cancer - The History of the Association

The association between testosterone and prostate cancer stems from the landmark reports of Huggins and co-workers. In this initial study, it was reported that the serum marker acid phosphatase was not only dramatically reduced following castration of men with metastatic prostate cancer, but also increased by the administration of testosterone; additionally, a follow-up report further highlighted the clinical benefits of castration against the administration of testosterone allowing for the conclusion that testosterone administration caused "enlarged growth" of prostate cancer [4,5]. In light of such evidence, castration was presented as the first effective treatment for metastatic prostate cancer and the procedure was to rapidly become common practice for advanced disease. Additional reports further corroborated the administration of testosterone in men with prostate cancer led to rapid and poor outcomes [6,7]. The introduction of the anatomic nerve-sparing radical prostatectomy by steered a revolution in the diagnosis and management of prostate cancer, which was followed by the introduction of prostate-specific antigen (PSA) blood test

and, the use of luteinizing-hormone-releasing hormone (LHRH) agonist medications as a replacement for surgical castration [8,9]. Nonetheless, the idea that testosterone was negatively linked with prostate cancer was reinforced by the notions of "testosterone flare", a transient rise of serum testosterone which accompanies LHRH agonists, which was then associated with severe adverse events such as vertebral collapse, paralysis, acute urinary retention and even death; and of the need for "total androgen blockage" by reports that even the smallest amount of residual androgen after orchiectomy could negatively impact survival [10-13].

It took until the 1990s, when topical testosterone formulations were introduced to treat hypogonadism, for the testosterone-dependent model of prostate cancer growth to be questioned [14]. According to this model, higher testosterone concentrations increased the risk of prostate cancer, whereas low testosterone concentrations would have a protective effect. Nevertheless, longitudinal studies did not demonstrate testosterone concentrations to be higher in men with prostate cancer comparatively to non-cancer males. Moreover, reports that hypogonadal men with normal PSA did not have lower cancer rates than the general male population and in fact as many as one in seven who had prostate cancer did not fit the model [15]. Data from clinical trials further showed testosterone therapy to hold a 1% risk of prostate cancer and in 2001, a worldwide consortium concluded that data from 18 different longitudinal studies failed to provide an indication that testosterone, or any other sex hormone, was associated with risk of prostate cancer [15]. In fact, contrasting with the effect of lowering testosterone concentrations in men with prostate cancer, the evidence indicates that changes to testosterone within the physiological range have little or no effect on the prostate (both benign and malign).

This apparent paradox was answered by the idea that prostate cancer growth follows a saturation curve – the so-called Saturation Model [16]. This biphasic model postulates that the sheer prostate cancer response to variations in testosterone levels at castration or near castration range reaches a point of maximal prostate stimulation beyond which further increases produce little or no further effect on the prostate. This model offers a different perspective on Huggins' work since it concerned almost exclusively castrated men [4,5]. Moreover, the fact that men with advanced disease previously castrated responded to testosterone therapy with rapid prostate cancer growth and negative outcomes whereas little negative impact was observed in untreated men was poorly appreciated [6,7].

2.1 Endogenous Serum Testosterone and Prostate Cancer Risk

A plethora of observational studies have reported the association of endogenous (continuous per 1 unit increment or 5 ng/mL increment) total testosterone with prostate cancer demonstrating statistical significance with most of reporting magnitudes of association that were null [17-40]. Conversely, observational studies categorizing endogenous total testosterone as high vs. low and investigated its relationship with prostate cancer showed different results. In these conditions, further analysis reported a reduced-risk of Prostate Cancer (17 out of 25)] than increased-risk of Prostate Cancer (8 out of 25) among men with high concentrations of total testosterone compared to those with low concentrations [20,26,28,30,34,37-39,41-51]. Additionally, reduced-risks findings were more frequent and found to be of statistical significance (11 out of 17) than those of increased-risk findings for prostate cancer (4 out of 8).

2.2 Testosterone Therapy and Prostate Cancer Risk

Meta-analysis of randomized, placebo-controlled studies investigating the association of testosterone therapy and prostate cancer showed an association of reduced risk, albeit an insignificant one [52-55]. Cui analyzed 8 trials grouped into men receiving testosterone therapy for less than 12 months (n = 5) and those receiving treatment between 12 and 36 months (n = 3) [52]. Results showed an insignificant reduction in risk in the first group (summary OR < 12 months = 0.74; 95% CI: 0.25–4.65) whilst the second group showed a null-risk (summary OR12–36 months = 0.99; 95% CI: 0.24–4.02); however, this may be due to the relatively small number of trials analyzed and the low number of prostate cancer cases reported (n = 6). Similarly, Boyle analyzed 11 trials and reported an insignificant reduction of prostate cancer in patients receiving testosterone therapy for less than 12 months (summary OR < 12 months = 0.87; 95% CI: 0.30–2.5) [53].

2.3 Testosterone Therapy in Men Treated for Prostate Cancer

The safety of testosterone therapy with respect to prostate cancer was first reported by Kaufman and Grydon; these case series showed no prostate cancer reoccurrence after radical prostatectomy was undertaken to remove predominantly low-risk prostate cancer with no PSA detectable post surgery nor after a median 24 month follow up period after testosterone therapy commenced [56]. A similar safety profile was reported by Agarwal and Oefelein after review 10 men who had undergone radical prostatectomy for a predominantly intermediate risk of prostate cancer with a median follow-up of 19 months post testosterone treatment starting [57]. Also, in a much larger observation study, Khera observed no significant increase in PSA levels in 57 men treated for 36 months with testosterone after radical prostatectomy (median follow-up 13 months) [58].

More recently, Pastuszak reported on 103 hypogonadal men (26 with high-risk disease) previously treated with radical prostatectomy that underwent testosterone treatment [59]. Whilst a significant increase in PSA levels were observed in the testosterone treatment group (n = 54) (median follow up period of 27.5 months) more true prostate cancer reoccurrences were noted in the control group despite no significant increase in PSA levels (n = 49). With respects to brachytherapy, no biochemical recurrences were reported in 31 men with mostly low-risk prostate cancer treated with brachytherapy with either the Phoenix or American Society for Radiation Oncology recurrence criteria met for any patients during follow-up time (median of 5 years) [60]. Similarly, Balbontin reported that none of the 20 men with predominantly low-risk prostate cancer treated with brachytherapy experienced biochemical recurrence (2.5 years of median follow-up time) with PSA levels decreasing from 0.07 ng/ml to 0.01 ng/ml [61]. The safety of testosterone treatment in 5 men that had

external beam radiation therapy (EBRT) was reported in 2009 [62]. Results showed that whilst a transient increase in PSA levels was observed in one patient, PSA levels stayed below 1.5 ng/ml [62]. Furthermore, Pastuszak reported no significant increase in biochemical markers in 13 men with low and intermediate risk of prostate cancer treated with testosterone therapy after either brachytherapy or EBRT for 30 months [59].

A report by the same group on 98 men receiving testosterone therapy after undergoing radiation treatment (brachytherapy or EBRT) for prostate cancer showed an overall increase in PSA levels from 0.08 to 0.09 mg/ml ($p = .05$) with 6 men meeting either the Phoenix or American Society for Radiation Oncology criteria after a median follow up time of 40.8 months [63]. However, the authors suggest that two of these cases may have been due to a transient increase in PSA levels rather than a true positive. It was noted by the authors that the recurrence rate was lower than previously reported for radiation therapy although it was also noted that no definitive conclusions could be drawn due to limited cohort and retrospective study design.

Using linked, Surveillance, Epidemiology, and End Results-Medicare data, Kaplan identified 149,354 men diagnosed with prostate cancer between 1992 and 2007 with 1181 (0.79%) shown to have undergone testosterone therapy post prostate cancer diagnosis [64]. Using propensity-scoring analysis, results showed no association between the testosterone treatment after prostate cancer diagnosis with overall mortality, cancer-specific mortality, or the subsequent use androgen deprivation therapy. Moreover, they were consistent and independent of cancer stage, grade, and treatment. Time-varying analysis was used in a follow-up study that showed no relationship between the length of testosterone therapy and an increase in either mortality of androgen deprivation therapy [65]. Although in this large population-based studies, outcomes of testosterone use in men with untreated prostate cancer was not the primary outcome, their results are provocative and did not change in respect of prostate cancer treatment type (including active surveillance/watchful waiting) which was statistically controlled for.

2.4 Testosterone Therapy in men Untreated for Prostate Cancer

The risks of testosterone therapy in men diagnosed but untreated for prostate cancer have yet to be investigated by randomized controlled trials. Nevertheless, a study of 19 randomized trials (1966–2004) using the inclusion criteria of testosterone therapy for >90 days in men >45 years old with testosterone deficiency, concluded that no significant difference was found on prostate cancer, PSA >4 ng/mL, and abnormal prostate biopsies rates different between testosterone therapy and the placebo cohort [66]. A systematic review which examined 197 articles covering testosterone therapy further corroborated this data. Studies considering patients with testosterone deficiency, low serum testosterone levels, and a pathological confirmation of prostate cancer being treated with testosterone therapy revealed no evidence of increased risk of prostate cancer as it was diagnosed in 7 out of 542 men (1.3%) receiving testosterone therapy and 5 out of 333 men (1.4%) receiving placebo [67]. Additionally, a multinational patient registry (Registry of Hypogonadism in Men (RHYME), Netherlands) considered baseline and follow-up data on prostate biopsies, PSA, and testosterone levels of 999 treated and untreated, newly diagnosed hypogonadal men, 75% ($n = 750$) of which underwent testosterone therapy. Results showed no significant difference in the number of positive biopsies between men on testosterone (37.5%) and the control group (37.0%). However, our understanding of the safety profile of testosterone therapy in men who are on active surveillance for prostate cancer is less clear. Morgentaler and Rhoden reported 15% of testosterone deficient men with a PSA of 4.0 ng/ml or less had biopsy-detectable prostate cancer; leading to suggestions that in 15% of the cases treating a man with normal PSA levels and testosterone deficiency without undertaking a rule-out biopsy is the equivalent of giving men with prostate cancer testosterone therapy [47]. Similarly, Morgentaler showed no increase in prostate cancer progression events (median follow-up 30 months) in 13 testosterone deficient men on active surveillance for low ($n = 12$) and intermediate risk ($n = 1$) prostate cancer [68]. Further to this, erratic PSA responses were reported in 7 untreated patients, 6 of whom were deemed low risk whilst 1 was considered high risk with a Gleason grade 4+4 disease (no follow-up biopsies were performed and only PSA kinetics was studied); it is worth noting the observations of San Francisco who reported that low free testosterone concentrations were found to be an independent predictor of disease re-classification in a study involving 154 men under active surveillance [69,70].

More recently, the progression rates of prostate cancer in testosterone-deficient men on active surveillance were also studied. A retrospective study of 82 hypogonadal men with prostate cancer treated with testosterone therapy found increased PSA levels although no upgrade was made to higher Gleason grade on subsequent biopsies [71]. Similarly, no significant difference in progression rates were observed after a 36 month follow up period between men receiving testosterone therapy ($n = 28$) and a control testosterone deficiency group ($n = 96$) [72]. Whilst, data seem supportive of further research focused on obtaining serum testosterone levels during active surveillance; overall, due to a lack of evidence regarding testosterone therapy in men with untreated prostate cancer caution is advised [72].

2.5 The Concept of Bipolar Androgen Treatment: Can Normalizing Testosterone Levels be Important in Prostate Cancer Control?

It is becoming increasingly clear that testosterone therapy may have a role to play in controlling prostate cancer via optimization of serum androgen concentrations; hypothesized by clinical observations showing low serum testosterone concentrations being associated with higher-grade prostate cancer whilst, prostate cancer in young men with high testosterone concentrations is exceptionally rare [43,73,74]. This is supported by several in vitro studies. Song and Khera observed cells exposed to physiologically normal levels of androgen displayed inhibited growth patterns whilst low androgen adapted LNCaP human prostate cancer

xenografts display inhibited prostate cancer growth under exogenous androgen exposure [75]. Similarly, a study concerning nude mice derived from androgen adapted LNCaP cell lines reported a rapid cancer cell proliferation in the absence of androgen with tumor regression observed upon the implantation of a testosterone pellet resulting in supraphysiological concentrations [76]. Further to this, the use of bipolar androgen therapy (BAT) for the treatment of castrate-resistant prostate cancer (CRPC) was then triggered as in CRPC, the expression of androgen receptor persists despite maximal androgen ablation; on the other hand, androgen receptor-expressing "androgen-sensitive" prostate cancer cells were inhibited by supraphysiological androgen levels [77].

It has been postulated that relicensing of DNA in cells capable of high expression levels of androgen receptor or in those cells that exhibit androgen-induced DNA breakage in rapidly dividing cells are inhibited by high androgen levels [77]. Furthermore, in a low androgen environment, CRPC cells may acquire an adaptive auto regulation mechanism in order to increase androgen receptor expression. The same team suggests that exploiting this androgen receptor up-regulation mechanism through acute supraphysiological androgen followed by acute ablation such as BAT is effective in xenografts [78]. Preliminary clinical observations point towards BAT restoring CRPC cells to androgen-sensitivity to traditional ADT [79]. Although preliminary, this strengthens the argument for a change in perception of the role that androgens play in prostate cancer; raising the possibility of utilizing testosterone as a prostate cancer treatment whilst weakening the orthodoxy of that testosterone therapy in men with no residual disease is clinically risky.

2.6 Testosterone Therapy in Hypogonadal Men: Other Risks?

A recent systematic review and network-meta analysis study [80] compared the benefits and harms of individual testosterone therapy products among hypogonadal men. Results showed not only that testosterone therapy (as a class opposed to placebo) improved quality of life, depression, erectile function, and libido; but also that few differences were found between the treatments. Additionally, no increased risks of major harms were observed. This study builds on previous meta-analyses which reported contradictory findings concerning the risk of adverse events among testosterone therapy users. Whilst increased risk of cardiovascular adverse events among men using testosterone therapy in one meta-analysis a number of other meta-analyses found no increase in the risk of cardiovascular events among users [66,81–86]. The initial Xu et al. meta-analysis considered a broad composite outcome (cardiac disorder, cardiovascular complaints, cardiovascular events, vascular disorders) and has since been criticized for use of a fixed-effects model in which subsequent re-analysis using a random-effects model found no significant increase in the risk of cardiovascular events [84].

It has also been observed that testosterone therapy is effective in men with hypogonadism and a history of cardiovascular disease [87] with significant improvements in all cardiometabolic risk factors observed suggesting testosterone therapy as a possible treatment option in the secondary prevention of cardiovascular events in hypogonadal men with a history of cardiovascular disease. Similarly, long-term testosterone therapy in hypogonadal men has been demonstrated to significantly improve urinary and sexual function, as well as quality of life with beneficial sustainable weight loss in hypogonadal men also observed [88-91]. This study is supported by significant and sustained weight loss observed in hypogonadal men irrespective of obesity severity loss over an 8 year period [92]. Finally, a longitudinal study considering more than 350 hypogonadal men supports the association between dynamic patterns of testosterone and prostate cancer development. The study reported that the later that testosterone dropped below 12.1 nmol/l in a man, the less the lifetime risk of prostate cancer in that individual (HR 0.68, 95% CI: 0.57–0.82) [93].

2.7 Is there a Protective role of Testosterone in High-Grade Prostate Cancer?

One intriguing concept that has recently come to light is that incidence and severity of prostate cancer is significantly lower in men receiving TRT, raising the possibility of high-grade prostate cancer protection [94-96]. Analysis of 553 patient biopsies (42 undergoing TRT, 162 untreated hypogonadal and 349 eugonadal men) revealed 16.7% of TRT patients had a positive biopsy with a Gleason score of ≤6 in 71.4% of these patients and >6 in 28.6% in the remaining. Further, a predominant score of 3 and tumor staging of II in 85.7% was observed in this subset of patients. Conversely, in the untreated hypogonadal subset 51.9% showed a positive biopsy with a Gleason score of ≤6 in 40.5% of this subset and a score of >6 in 59.5% the others, further, these patients had a predominant score of 3 (77.4%) and tumor staging of II (41.7%) or III (40.5%). Finally, 37.8% of eugonadal men had a positive biopsy with a Gleason score of ≤6 in 42.4% and >6 in 57.6% of men, a predominant score of 3 (82.6%) and tumor staging of II (44.7%) or III (47.7%) [94]. Further supporting evidence will be required before concrete conclusions can be made; however, if replicated, it represents a paradigm shift in the role of testosterone in prostate cancer and opens up novel options in the treatment of prostate cancer.

3. Conclusion

Our understanding of testosterone influence in prostate cancer has come a long way since higher levels were proposed to be a causal risk. Mounting evidence has shown the relationship to be complex and new ideas such as bipolar androgen treatment have even been proposed to control prostate cancer through normalization of testosterone concentrations. Although not statically significant, meta-analysis of randomized placebo-controlled trials, investigating the use of testosterone therapy and its association with prostate cancer, have reported a reduction in prostate cancer risk [52,53]. Observational studies have also shown the risk to be low for men previously treated with radical prostatectomy or radiotherapy. And, although for men with untreated prostate cancer fewer data are available, reports also suggest that testosterone therapy is safe in men on active surveillance. Congruently, the positive effects of testosterone therapy in the overall quality of life of hypogonadal patients have been extensively described and,

to date, many reports have refuted other health concerns such as increased risk of disease or venous thromboembolism [3]. The data here from a wide range of investigations and analyses thus show the negative view of testosterone therapy as a risk factor for prostate cancer to be ill funded. The need for long-term large-scale placebo-controlled trials to definitively assess the safety of testosterone therapy is still needed; particularly to fully assess its impact on prostate cancer patients untreated for the condition. Indeed, more research is needed in order to truly understand the complex relationship of testosterone and prostate cancer. However, with preliminary research suggesting that testosterone treatment may be useful to help manage the disease it is the time that its negative association with increased prostate cancer risk stops impacting on prospective treatment of hypogonadism men and is recognized, for what it is, an historical misunderstanding.

Acknowledgments

We thank our volunteers Ms. Ayah Alzubaidi and Ms. Dalia Alzubaidi for their precious help in data collection and coordination of tables.

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