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Testosterone Therapy in Men on Active Surveillance

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Abstract

In recent decades, although prostate cancer (PCa) mortality has dramatically decreased, addressing the quality of life for PCa survivors has become an area of great interest. This is especially important among men who are enrolled in active surveillance (AS) to manage their PCa. Since men with PCa are likely to experience erectile dysfunction, decreased libido, and loss of lean muscle mass secondary to testosterone deficiency (TD) as a consequence of antitumor therapies or advanced age, testosterone therapy (TTh) is typically the indicated treatment to alleviate the symptoms of TD. However, due to the theoretical causal relationship of increased testosterone levels leading to PCa development, the usage of TTh in men who have been diagnosed with PCa has long been the subject of debate. As there is an increased number of men with PCa who are enrolling in AS for the management of PCa, there needs to be an evaluation of the safety and efficacy of TTh in this cohort. Recently, the previous relationship between TTh and PCa has been challenged, and emerging evidence suggests that TTh may not be directly associated with PCa development or progression. Instead, TTh usage may safely improve the quality of life for those men on AS. This review summarizes and analyzes the latest findings on the use of TTh in men on AS for PCa.

Keywords: testosterone replacement therapy; testosterone therapy; active surveillance; prostate cancer; hypogonadism

Introduction

Testosterone deficiency (TD) is defined by the American Urological Association (AUA) as a serum total testosterone level below 300 ng/dL.[1] The AUA provides additional guidelines that expound on the indication for testosterone therapy (TTh) in TD, including the need for two independent measurements of morning serum testosterone levels taken on separate occasions, the presence of hypogonadal symptoms, and the measurement of confounding hormone levels, namely prolactin and luteinizing hormone.

Serum testosterone levels meeting the criteria for TD have been observed in up to 38.7% of men older than the age of 45.[2] Considering this observation, it is estimated that up to 5.6% of men between the ages of 30 and 79 experience symptomatic TD, with a significant

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increase in prevalence with age.[3] TTh has been utilized to treat individuals with classical TD/hypogonadism and has been demonstrated to promote many health benefits and foster an improved quality of life with enhanced erectile function, increased libido, elevated bone mineral density, and augmented lean body mass.[4]

Further, TTh has demonstrated significant benefit in reducing insulin resistance in obese men and facilitating decreased fat mass and increased skeletal muscle, thereby reducing the risk of sequential type 2 diabetes and metabolic syndrome.[5] Adverse side effects reported with TTh include polycythemia, gynecomastia, and lowered HDL cholesterol.[6]

As TTh usage becomes more widespread, it is important to understand its role in the management of hypogonadal men living with prostate cancer (PCa). PCa is a prevalent malignancy, with an estimated 268,490 new cases expected among American men in 2022.[7] One of the most significant risk factors for PCa is age, with an average age of diagnosis at 66 and an increased risk in aging populations.[8] When PCa is low grade, slowly progressing, and limited locally to the prostate gland, active surveillance (AS) is an accepted treatment option that does not burden patients with the adverse effects of radiation, chemotherapy, or anti-androgen therapies.

Although patients suitable for AS are not considered to be at immediate risk for fulminant PCa, they remain at risk for other ailments of aging men. An additional common affliction of aging males is hypogonadism, with more than 12%, 20%, 30%, and 50% of males experiencing hypogonadism in their fifth, sixth, seventh, and eighth decade of life, respectively.[9] The standard of care for men suffering from hypogonadism is TTh, which subjectively improves their quality of life.

In recent years, there have been vast improvements in PCa treatment outcomes and a notable decrease of around 50% in the rate of PCa mortality, with an associated increase in the number of men on AS.[10] Many of these individuals will live longer but, in turn, may suffer the consequences of hypogonadism or TD, such as erectile dysfunction, loss of lean body mass, decreased libido, and a decrease in quality of life.[11] Subjects in this cohort would likely benefit from TTh. However, its utility cannot be wholeheartedly endorsed without a complete understanding of the risk–benefit profile. In this communication, the available evidence on TTh's safety, efficacy, and potential usage in men on AS is reviewed.

Testosterone and PCa

Testosterone, a critical sex hormone, plays an essential role in numerous physiologic mechanisms throughout the human body. The most notable function is developing and supporting the male reproductive system.[12] In the 1940s, testosterone was first associated with the development of prostatic adenocarcinoma, primarily due to Dr. Charles B. Huggins and Dr. Clarence V. Hodges, whose research demonstrated a significant decline of acid phosphatase, an enzyme expressed by the prostate and an early serum marker of PCa, after bilateral castration in men with PCa.[13]

Further, acid phosphatase was observed to increase after the administration of testosterone in men from the same cohort, suggesting the existence of a relationship between testosterone and prostatic acid phosphatase.[13] Investigations into human development demonstrated that the prostate, which is $\sim$1.5 g at birth, undergoes androgen-dependent growth during pubescent years, reaching an average size of 20 g in young adulthood.[14] Further, in hypogonadal men, TTh has been observed to significantly increase the volume of the prostate, lending support to the dogma that testosterone stimulates the growth of prostatic tissue.[15] These findings laid the framework for the utilization of anti-androgen therapy as the initial mainstay of treatment for advanced PCa.[12]

As the understanding of PCa physiology evolved, androgen-deprivation therapy (ADT), also known as medical castration, has played a fundamental role in PCa management. The goal of ADT is to prevent androgens, specifically testosterone and dihydrotestosterone (DHT), from binding to androgen receptors (AR) in prostatic tissue.[16] In androgen-dependent tissue, such as in the prostate, the binding of androgens to the AR initiates translocation of the ligand-receptor complex to the nucleus, ultimately promoting transcription and replication.[16] In recent years, ADT has evolved from bilateral orchiectomy to involve myriad medical agents designed to inhibit AR-androgen bindings, and these modalities are highly effective in treating androgen-sensitive prostatic malignancy.[17]

Although ADT is a critical pillar in the treatment of advanced PCa, recent studies have questioned the association between testosterone and PCa development (Table 1). A landmark collaborative analysis, which compared 3886 men with incident PCa and 6438 controls across 18 independent studies, failed to identify an association between PCa and serum quantities of

Table 1. Summary of Current Studies Regarding the Relationship Between Testosterone Therapy and Prostate Cancer

Author	Year	Study type	Patient No.	Treatment type	Results
Endogenous Hormones and PCa Collaborative Group[18]	2008	Review of 18 prospective studies	3886 men with PCa 6438 controls	Serum sex hormone level analysis	Failed to identify an association between PCa and serum quantities of androgens. Instead, they found an inverse relationship between sex hormone-binding globulin and PCa risk.
Debruyne et al.[19]	2017	Retrospective review	750 hypogonadal men	TTh	The proportion of positive biopsies was nearly identical in men on TTh (37.5%) compared with those not on TTh (37.0%) throughout the study. No differences in PSA levels.
Boyle et al.[20]	2016	Meta-Analysis	5623 cases of PCa 14,604 controls	Endogenous testosterone	An increase in 5 mmol/L testosterone demonstrated a risk of PCa of 0.99 across age and region. No association between elevations in serum testosterone and PCa.
			2213 subjects 1456 controls	Exogenous testosterone via TTh	TTh and PCa had a 0.87 odds ratio, suggesting that PCa and TTh are not associated. There was also a 0.10 ng/mL increase in PSA, suggesting that TTh does not have a modulatory association with PSA.
Muller et al.[21]	2012	Randomized, Controlled Trial	8122 treated and 4073 placebo	Biopsy	Baseline serum testosterone and DHT levels were unrelated to PCa detection or grade.

DHT, dihydrotestosterone; PCa, prostate cancer; PSA, prostate-specific antigen; TTh, testosterone therapy.

androgens such as testosterone, DHT, dehydroepiandrosterone sulfate, and androstenedione.[18] Notably, in this study, an inverse association was observed between concentrations of sex hormone-binding globulin (SHBG) and PCa risk, with a relative risk reduction of 14% (confidence interval [95% CI] = 2–25) when comparing the highest 1/5th to the lowest 1/5th.

These findings from this highly relevant study suggest that serum concentrations of androgens, such as testosterone and DHT, are not associated with PCa development; however, elevations in SHBG, which may result in reduced active testosterone, were associated with a reduced risk of PCa.

Further, in 2016, the Registry of Hypogonadism in Men assessed 999 men with newly diagnosed hypogonadism.[19] From this study, 750 of this cohort underwent TTh, with 23,900 total months of exposure, producing an average increase of 7.1 nmol/L (204.61 ng/L) in testosterone. Among all subjects, 78 prostate biopsies were performed, and TTh-treated subjects had a cancer-positivity rate of 37.5% compared with 37% in the control group.[19] These findings seemingly suggest that testosterone is not directly associated with PCa development.

In 2016, a meta-analysis evaluated the relative risk of PCa with elevated endogenous testosterone, exogenous testosterone via TTh, and prostate-specific antigen (PSA).[20] Beginning with endogenous testosterone, 20 independent studies were assessed with 5623 cases of PCa and 14,604 control subjects with a mean follow-up of 10 years. Subjects with an increase of 5 nmol/L (144.09 ng/L) in serum testosterone demonstrated a summary relative risk for PCa of 0.99 (95% CI 0.96–1.02), with results consistent across subjects' age, region, and follow-up duration.

These findings imply no association between elevations in serum testosterone and PCa. In subjects treated with exogenous testosterone via TTh compared with placebo controls, 27 studies were assessed to evaluate TTh and associations with PSA and/or PCa with 2213 subjects receiving TTh and 1456 placebo controls. Eleven studies evaluated PCa, and 26 evaluated PSA. Between TTh and PCa, a summary meta-analysis odds ratio of 0.87 (95% CI 0.30–2.50) was observed, suggesting that TTh is not associated with the development of PCa. Finally, when evaluating the effects of TTh on serum PSA levels, an increase of 0.10 ng/mL (95% CI 0.28–0.48) in PSA was observed with TTh, suggesting that TTh does not have a modulatory association with PSA.

A major investigation, which was designed to evaluate PCa risk reduction with dutasteride, a 5-alpha-reductase inhibitor, assessed 8122 subjects treated with dutasteride and 4073 who received placebo.[21] These subjects, who were between the ages of 50 and 75, had PSA levels <10 ng/mL and had a negative biopsy for PCa within 6 months of onset. Among the placebo group not receiving dutasteride, associations were evaluated between the incidence of PCa and baseline testosterone and DHT serum concentration over a 4-year study period. There were 3255 subjects from the placebo group who abided by the study protocol, and of these, 819 (25.2%) were found to have PCa on biopsy.

Of those with PCa, serum testosterone and DHT were statistically similar and not correlated with Gleason score. No relationship between PCa incidence and serum DHT was observed. In men with normal testosterone concentrations, defined as >10 nmol/L, (>300 ng/L), the baseline testosterone level was not associated with increased risk of PCa; however, in men with reduced baseline testosterone levels, defined as <10 nmol/L, subjects with the lowest baseline testosterone levels had a reduced risk of PCa.

Although the historical paradigm regarding the development of PCa involved androgen stimulation of prostatic tissue, the current literature fails to identify a relationship between testosterone and PCa development (Table 1). In fact, a 2016 investigation by Wallis et al. suggests that TTh may be protective against PCa.[22] In this investigation, health outcomes for 10,311 men treated with TTh were compared with 28,029 controls over a median follow-up of 5.3 years for the treatment group and 5.1 years for the control group. Men in the highest tertile of serum testosterone were observed to have a lower risk of PCa diagnosis, with a hazard ratio of 0.60 (95% CI 0.62–0.73). These findings suggest that TTh is not only not a driver of PCa but may also be associated with a lower risk of developing PCa.

TTh in Men on AS

The reluctance to treat symptomatic hypogonadism in men with PCa can largely trace back to the work of Huggins and Hodges and Huggins in *Studies on Prostatic Cancer I & II*.[13,23] In these landmark studies, it was demonstrated that men with metastatic PCa experienced significant clinical improvement after surgical castration. Further, androgen injection resulted in a rapid rise in serum acid phosphatase, a historical serum marker of PCa, that decreased to baseline after cessation of injections. These researchers concluded that PCa cells are hormone sensitive, and the administration of testosterone may lead to rapid disease progression.

This long-established dogma was challenged in 1996 by Morgentaler et al., who evaluated a cohort of 77 men with low total or free testosterone levels, normal digital rectal exam, and PSA levels of 4.0 ng/mL or less.[24] Prostate biopsy identified PCa in 14% (11/77) of the cohort. The high prevalence of biopsy-detectable PCa in hypogonadal men led to a subsequent study evaluating 345 consecutive hypogonadal men, with PSA levels of 4.0 ng/mL or less, who underwent a prostate biopsy before initiating TTh. Results showed that PCa was detected in 21% of men with testosterone levels of 250 ng/dL or less compared with a 12% detection rate in men with testosterone levels greater than 250 ng/dL ($p = 0.04$).[25]

These findings led to the introduction of the saturation model by Morgentaler and Traish,[26] a concept based on the variable response of PCa cells when exposed to testosterone concentrations that were nonlinear in nature due to fluctuating sensitivity of the AR to either physiologically low or high T concentrations. In 2006, Marks et al. published a randomized, controlled trial evaluating the effects of TTh on prostatic tissue in hypogonadal men, and these results were some of the first supporting the saturation model on a large scale.[27] Forty-four men aged 44 to 78 with testosterone levels below 300 ng/dL (10.4 nmol/L) were randomized and treated with TTh or placebo for 6 months.

In the TTh group, serum testosterone increased from a median of 282 ng/dL (9.8 nmol/L) at baseline to 640 ng/dL (22.2 nmol/L). Testosterone and DHT concentration in the prostate were measured and did not change significantly with TTh. Further, the correlation coefficient between serum and prostatic tissue levels of T and DHT after TTh was 0.35 and 0.01, respectively, with a range of p-values from 0.13 to 0.99 indicating insignificance. Finally, no difference between the treatment group and controls was observed in prostate tissue histology, prostate gene expression, or cancer incidence.

The placebo group experienced no significant change in serum or prostatic androgens. These findings published by Marks et al. suggest that increased concentrations of serum androgens are not correlated with increased prostatic androgen concentration, gene expression, cancer incidence, or biomarkers suggestive of cell proliferation. These findings support the saturation model, whereby the prostatic ARs are saturated at subphysiologic concentrations and ineligible for further stimulation.

It was proposed that maximum AR activity is achieved at low testosterone concentrations whereas saturation results in a reduced AR activity at higher T concentrations. In addition, *in vitro* studies revealed that PCa cells exhibit a dual response to testosterone, whereby cells, which do not proliferate in the absence of testosterone, begin to proliferate after initial testosterone stimulation, plateau with increasing concentration of testosterone, and finally experience a reduction in proliferation after reaching a testosterone

threshold in a phenomenon known as the bipolar testosterone concept.[28,29] Studies have reported that saturation levels of testosterone receptors are at 120 ng/dL *in vitro* and 240 ng/dL *in vivo*.[30,31]

The use of TTh in AS continues to be an area of ongoing investigation. Most studies to date in this cohort have been on a small scale, focusing on the safety of TTh in men on AS for PCa. In 2011, Morgentaler et al. assessed 13 hypogonadal men with PCa on AS while undergoing TTh for a median of 2.5 years.[32] Mean serum testosterone increased from 238 to 664 ng/dL, and no increase in PSA, prostate nodularity, or prostate volume was observed. Moreover, with a mean of two follow-up biopsies per subject, no subject exhibited definitive evidence of PCa progression. In one subject, follow-up biopsy was suggestive for concern of progression from Gleason 6 to Gleason 7 disease.

However, two additional follow-up biopsies returned Gleason 6 pathology. In another subject, radical prostatectomy was performed for concern of progression of Gleason 6 to Gleason 7 disease. However, prostate pathology status postprostatectomy revealed low-volume Gleason 6 disease. The significant findings of this study suggest that TTh utility in hypogonadal men with PCa and on AS is not associated with cancer progression in the short or medium term.

In 2016, Ory et al. evaluated 82 PCa patients with TD who were undergoing TTh for a median of 41 months, measuring PSA, biochemical recurrence, testosterone, and PSA Velocity.[33] Among the subjects, a cohort of 8 were on AS. Within the AS group, median testosterone increased significantly from 5.2 nmol/L (149.97 ng/dL) to 15.5 nmol/L (447.05 ng/dL), median PSA increased significantly from 3.9 to 5.2 ($p = 0.003$), and median PSA velocity was 0.48 ng/mL/year. Among those on AS, no biochemical recurrence or progression of disease was observed. Two subjects from this cohort were withheld further TTh after initial rises in PSA; however, their serum PSA returned to baseline levels after withholding TTh.

The outcomes observed within the AS cohort of this study suggest that TTh can significantly increase serum testosterone without increasing the risk of biochemical recurrence or progression of disease in the short term. Although TTh was associated with a significant increase in PSA, the authors suggest that this rise was a result of the Saturation Model. More specifically, before TTh, the subjects were below the saturation point, and initial TTh stimulated the unsaturated prostatic ARs, producing an expected rise in PSA.

In the largest study to date of men on AS for PCa and receiving TTh, Kacker et al. evaluated 124 patients; among them, 28 patients were treated with TTh for a minimum of 6 months, whereas the rest remained as untreated controls. Subjects from the treatment group experienced a mean increase in testosterone from baseline of 46.9 ng/dL (1.63nmol/L) and a subjective improvement in hypogonadal symptoms. Among the men in the treatment group, 3 (10.7%) had an increase in Gleason score from 3 to 4, and 6 (21.4%) had an increase in tumor volume without a change in Gleason score.

Among the control group, 9 (9.4%) men had an increase in Gleason score, and 34 (35.4%) had an increase in tumor volume with no change in Gleason score. Ultimately, the percentage of men with an increase in Gleason score was similar when comparing the treatment group with the control, 10.7% versus 9.4%, respectively, with a lower yet insignificant rate of overall disease progression in the TTh-treated group. Further, there was no significant difference in the negative biopsy rate between the treatment and control groups. The results of this investigation suggest that TTh does not cause rapid progression of PCa in the short term among men undergoing AS, although TTh did produce a reduction in hypogonadal symptoms and an increase in serum testosterone.[34]

Discussion

At present, there remains a paucity of literature to guide clinicians on how to best treat hypogonadal patients on AS for PCa, specifically regarding the utility and safety of TTh. It is recognized that between 12% and 30% of men on AS will experience cancer progression requiring treatment in the short term.[35] The preliminary studies described earlier fail to identify an association of TTh treatment with progression of PCa beyond the progression rate observed in untreated men. These findings suggest that TTh may not place men in this cohort at an unacceptable risk.

Further, a growing body of evidence supports a relationship between hypogonadism and obesity, insulin dysregulation, and diseases such as diabetes mellitus or metabolic syndrome.[5,36,37] This connection is supported by literature identifying the incidence of diabetes mellitus as 39% above the baseline in individuals undergoing ADT for PCa.[38] In addition, recent evidence has demonstrated an inverse association between TTh and both all-cause mortality and cardiovascular events.[22]

These investigations in this cohort suggest that TTh may be utilized to prevent the progression to fulminant diabetes mellitus, facilitate improved lean muscle mass and reduced obesity, and reduce the risk of cardiovascular events and overall mortality.[5,22] Factors such as these must be included in the discourse regarding the risks and benefits of treating hypogonadism in men with active PCa.

Currently, the AUA recommends informing patients on AS that there is inadequate evidence to quantify the risks and benefits of TTh. The perceived benefits of TTh should be considered in light of the limited knowledge of potential risk.[1] In these instances, the patient should be informed that TTh is an area of ongoing study and undergoing TTh is a shared decision based on the potential benefit of treatment.

The TTh for patients who have a history of untreated or treated PCa remains highly debated. More specifically, the established dogma regarding testosterone as a fuel for PCa growth has increasingly been challenged. This is only furthered by ADT remaining the cornerstone of clinical treatment for PCa. Recent studies, however, have failed to identify an association between PCa and serum quantities of androgens, thus supporting the emerging concept that testosterone is not directly related to PCa development.[18,19]

Studies have even gone as far as to reveal that men with existing prostatic lesions do not experience a worsening of their disease or an increase in prostate volume when administered serum androgens; in fact, these studies document that men experienced only the positive effects of TTh.[39]

Although there is evidence that TTh may no longer be linked to the development of PCa, patients need to have a thorough conversation with their providers about the risks and benefits of TTh before making an informed decision about their treatment plan. If a patient does decide to proceed with TTh, the provider must emphasize compliance with monitoring protocols until more definitive evidence of TTh safety emerges. This is critically important for patients on AS or with a history of PCa.

Although men on AS are not considered to be at immediate risk for metastatic PCa, they need to be cautious when seeking out TTh as a solution for the compounding issues that develop with age and PCa treatment, such as hypogonadism. Early studies of men on AS while using TTh fail to observe a correlation between TTh and progression of PCa.[40,41] However, as these studies are limited in statistical power, the possible complications should be discussed with patients on AS who are considering this treatment plan.

Conclusion

In recent years, several investigations have begun to question the entrenched belief of T and DHT uniformly as drivers of PCa. After evaluating the current literature addressing the possible benefits of TTh utility in improving the quality of life of men on AS for PCa, it is evident there may be less risk and more benefit than previously understood. Although there are limited studies regarding TTh for men with hypogonadism and on AS, the results of these early studies are promising, as they have documented little to no association between TTh and PCa progression for this population. Given that an increasing number of men are electing AS as a treatment strategy for PCa, clinicians should consider the importance of PCa management plans and how to optimize quality-of-life measures.

It is hoped that future studies continue to explore and expand investigations on TTh use for men on AS to eliminate the uncertainty regarding a therapy that could potentially improve the quality of life and overall well-being in PCa patients. These studies should also focus on providing information for a risk–benefit analysis that patients may reference when making health care decisions.

Authors' Contributions

Conception and design: W.J.G.H.; Data acquisition and analysis: T.C, J.T., and H.W.; Drafting article: T.C, J.T., H.W., and W.A.; Revising article: W.A., I.V., and W.J.G.H.; Approval: All authors.

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Abbreviations Used

ADT = androgen-deprivation therapy
AR = androgen receptor
AS = active surveillance
AUA = American Urological Association
DHT = dihydrotestosterone
PCa = prostate cancer
PSA = prostate-specific antigen
SHBG = sex hormone-binding globulin
T = testosterone
TD = testosterone deficiency
TTh = testosterone therapy