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Current State of Practice Regarding Testosterone Supplementation Therapy in Men with Prostate Cancer

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Abstract

Hypogonadal men are characterized by low serum testosterone and symptoms of low energy, decreased libido, and muscle mass as well as impaired concentration and sexual functioning. Men with prostate cancer (PCa) currently on active surveillance or post-therapy, have traditionally been excluded from management paradigms given the decade-old concern that testosterone caused PCa growth. However, there appears to be little or no relationship between serum testosterone concentration and PCa. Androgen action in the prostate has long been known to be affected by the kinetics of receptor saturation and, as such, testosterone beyond a certain baseline is unable to stimulate prostatic growth due to complete intra-prostatic androgen receptor binding. Given this physiologic concept, many clinical investigators have begun to promote testosterone supplementation therapy (TST) as safe in men with PCa. This review examines the basics of testosterone physiology and summarizes the most recent findings on the use of TST in men with PCa on active surveillance and following treatment with external beam radiotherapy, brachytherapy and radical prostatectomy.

Keywords

testosterone; hypogonadism; androgens; prostate cancer; saturation; prostate-specific antigen

INTRODUCTION

Hypogonadism is increasingly becoming a recognized clinical condition in men of all ages. Testosterone levels decrease by ~1% per year beginning at the age of 30 years [1], and it is estimated that ~7% of men aged 30–69 years, and 18% of men greater than 70 years old, are currently experiencing symptoms of hypogonadism [2]. Treatment primarily involves supplementation with exogenous testosterone via numerous formulations including topical

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gels or liquids, injectables and implantable pellets [3, 4]. Indeed, testosterone supplementation therapy (TST) is currently one of the most commonly prescribed pharmaceutical regiments in the world with administration producing improvements in hypogonadal symptoms such as decreased energy, libido, muscle mass, and bone density [5, 6].

Historically, significant concerns have been raised regarding the use of TST in hypogonadal patients who are elderly [7], have cardiovascular disease [8] as well as active or treated (either with radiation or surgery) prostate cancer (PCa) [9, 10]. This concern was founded upon previous clinical observations that PCa was androgen dependent and that androgen deprivation resulted in the regression of PCa with a concurrent decrease in prostate specific antigen (PSA) [11–13]. As such, traditional teaching declared that a history of PCa was an absolute contraindication for the use of any type of TST. For example, Fowler and Whitmore [14] conducted an early retrospective review focused on the response of 67 patients with metastatic prostatic adenocarcinoma to the administration of exogenous testosterone. The majority of the men exhibited unfavorable responses that regressed following removal of the TST [14].

Recent work is disputing these concepts [9, 10, 15]. A recent manuscript by Feneley *et al.* [16] highlighted the results of a recent audit examining the incidence of PCa during long-term TST conducted from the UK Androgen Study. A total of 1365 men aged 28–87 years with hypogonadism were followed for up to 20 years with a total of 14 new cases of PCa diagnosed at a rate of one case per 212 years of treatment [16]. All tumors were localized and suitable for curative treatment with the PCa rate during long-term TST equivalent to that of the general population [16]. Given that PCa is the most commonly diagnosed malignancy in men after skin cancer with >200,000 new cases diagnosed yearly [17], and the increasing trend toward active surveillance in PCa, an understanding of the current TST literature is essential (Table 1). This review highlights the basic physiology underlying testosterone action in men and summarizes the current state of practice regarding TST in men with PCa who are currently on active surveillance or have undergone treatment with radiotherapy, brachytherapy or radical prostatectomy.

PHYSIOLOGY OF TESTOSTERONE AND THE ROLE OF ANDROGENS IN THE PROSTATE

In 1941, Huggins and Hodges first demonstrated, in a case series of 3 patients, that PCa regression occurred following orchiectomy [13, 18]. This and the associated series of landmark studies [11–13, 18] formed the basis of the current standard of care in the treatment of metastatic PCa. By implying a direct correlation between serum testosterone levels and PCa, the premise was simple; a lower testosterone resulted in PCa regression and vice-versa. Later *in vitro* and clinical work suggested that administration of exogenous testosterone stimulated growth of prostatic adenocarcinoma cells [14, 19]. These concepts then formed the foundation for the clinical mantra that exogenous TST should be avoided in men with PCa [20–22].

Testosterone, the principal circulating androgen in men, is predominantly synthesized by testicular Leydig cells (90%) under the control of Luteinizing hormone (LH) released from the pituitary [23]. The remainder (10%) originates from the adrenal glands [24]. Primarily derived from 27-carbon cholesterol, an enzymatic pathway alters the framework to the 19-carbon steroids that are traditionally known as androgens [25]. The bioavailable, or metabolically active portion of testosterone, circulates within the serum in a free form (~2%) or bound to the protein albumin (~38%). Sex hormone binding globulin (SHBG) carries ~60% of the testosterone within the circulation while rendering it 'inactive' and unavailable to most tissues [26]. As men age, SHBG increases and the hypothalamus exhibits decreases in gonadotropin production - mechanisms by which hypogonadism may become more prevalent in older men with PCa [24, 26–28].

Within prostatic epithelial cells, testosterone diffuses through the cellular membrane and is converted to 5α-dihydrotestosterone (DHT) by the enzyme 5α-reductase [24, 25]. The actions of both testosterone and DHT are mediated by the androgen receptor (AR). The AR has three major functional domains with the majority of its trans-activational activity associated with an NH_2 terminus domain that, via molecular chaperones, co-activators, and co-repressors, alters the affinity for testosterone and the relative levels of transcriptional activation [25, 29]. A variable-length CAG repeats region within the transcriptional activation domain subtly alters androgen receptor transcriptional activation. As such, ARs with less CAG repeats show increased androgenic transcriptional activation [25, 29–31]; while fewer CAG repeat lengths show enhanced transcriptional activation upon ligand activation [32]. Shorter CAG repeat lengths are associated with higher PCa grade and stage, metastasis and PCa mortality [31]. Alterations in CAG repeats within the AR subtly modulate the response of hypogonadal men to TST. CAG repeat length is correlated to estradiol levels in elderly men [33] as well as interactions with additional co-activators and co-repressors, adding further levels of complexity to the physiological affects of TST.

With respect to AR binding properties, two main factors regulate testosterone binding: receptor affinity as well as the intracellular androgen concentration [34]. The androgen concentration is subsequently related to the rate of metabolism and uptake present within the body. Along this vein, ARs from other organs have been found to exhibit similar chemical and bio-physical properties [34]. When AR properties were examined in rat testis, epididymis and prostate, all three tissues were shown to have identical androgen binding capabilities with receptor stability enhanced by androgen binding [34]. In the prostate therefore, anything beyond a certain low baseline serum testosterone concentration is unable to further stimulate growth since all intra-prostatic AR sites are completely occupied [24, 35]. Indeed, initial work by Ho *et al*. [36] found that specific androgen binding to prostatic AR reached a maximum at low androgen concentrations (2–3nM, roughly 60–90ng/dl) in all prostate lobes studied. Further binding over a wide range of increasing concentrations of the synthetic androgen [3H]R188, did not occur suggesting the concept of prostatic AR saturation [36]. Thus, while PCa growth can be considered exquisitely sensitive to variations of serum testosterone near or below castrate levels (~50 ng/dL) [37], it is insensitive to levels above it – no matter how elevated they are. In this context, androgens possess a finite capacity to stimulate PCa growth within a certain, albeit narrow, framework. Differences

may still exist in that analysis of sedimentation coefficients from the testis and epididymis were different from the prostate suggesting that AR subunit aggregation or association with variable macromolecules may be contributing to organ-specific differences [34].

The notion that the prostate is an androgen-dependent organ underscores the primary concern in using TST for men with PCa [24, 35]. The beneficial response to androgen-deprivation therapy (ADT), the dependence on androgens for normal prostatic development and a reduction in prostate volume in men treated with 5α-reductase inhibitors all support the original studies by Huggins in 1941 [13, 18, 38]. Despite this androgen-targeted organ dependency, more clinicians are currently treating men diagnosed with CaP on active surveillance and those who have undergone treatment with TST. The following sections will summarize the current clinical status of these regiments.

TST IN MEN WITH PCa ON ACTIVE SURVEILLANCE

At this time, no prospective, randomized clinical trials have been conducted to determine the risk of developing PCa on TST, or to evaluate the risk of treating men with diagnosed, but as yet untreated, PCa. With respect to the former, the most relevant literature available today is a meta-analysis [39] and a systematic review [40] that suggests no increased risk exists. With regards to the latter, two retrospective case series [15, 41] and a case report [42] comprise the entirety of the literature.

To determine whether patients may develop PCa while on TST, a systematic review by Shabsigh *et al.* [40] in 2009 examined 197 articles related to testosterone therapy. Inclusion criteria included studies that treated patients with appropriately defined signs and symptoms of hypogonadism, had low serum testosterone levels and demonstrated a histological confirmation of prostate cancer [40]. This resulted in an analysis of 11 placebo-controlled, randomized studies. PCa was detected in 7 men out of 542 (1.3%) receiving TST and in 5 men of 333 (1.5%) receiving placebo [40]. The authors concluded that there was no evidence that TST increased the risk of PCa. The results of this study were similar to earlier work by Calof *et al.* [39]. In that earlier 2005 study, 19 randomized trials were identified from 1966–2004 using inclusion criteria of TST for >90 days in medically stable men ≥45 years old with hypogonadism. The authors found the rates of PCa, PSA >4 ng/ml and abnormal prostate biopsies were not significantly different between the TST and placebo-treated cohorts [39].

When considering TST in men on active surveillance for PCa (i.e. diagnosed, but untreated PCa), there is also currently a paucity of literature. An initial case-report by Morgentaler in 2009 [42] presented an 84 year old man with biopsy proven, Gleason 6 PCa who refused PCa treatment but had severe symptoms of hypogonadism requiring TST [42]. Subsequent monitoring of his PSA found a decrease from his initial PSA of 8.1 ng/ml to 5.2 ng/ml (at 10 months) and 6.2 ng/ml (at 21 months) [42]. While alone this observation was minimally significant, it served as the basis for a case-series on seven hypogonadal men with PCa by Morales [41]. The mean age for these patients was 68 years and they were followed over a span of 4–13 years. The majority of the patients in this cohort had T1c PCa with a Gleason grade of 6 and a PSA at study entry ranging from 1.7–13.4 ng/ml [41]. The responses to

TST in Morales' work was variable with several men having stable PSA levels and one having increases that prompted a radical prostatectomy [41]. Another retrospective observational case study by Morgentaler and Lipshultz [15] reported on the experiences with 13 hypogonadal men with biopsy proven PCa (Gleason 6 in 12 men, Gleason 7 in one man). Mean PSA and prostate volume did not change over a 2.5 year median duration of treatment (range 1–8.1 years) [15]. Conflicting results were seen on pathological examination in which two men exhibited upgraded PCa and another two men had no progression [15]. A further study found that men with prostatic intraepithelial neoplasia on TST did not exhibit increases in PSA or significantly increased risks of PCa compared to men without PIN [43]. Moreover, an early study by Morgentaler *et al.* [44] suggested that a high prevalence of occult, biopsy-detectable PCa was present in men with low serum testosterone levels further underscoring the need for digital rectal examinations and close follow-up in this population of men.

In summary, while the data is limited, the available literature suggests that TST is safe in men who are currently on active surveillance but caution should be exercised given the lack of any prospective, randomized trials.

TST IN MEN WITH PCa POST RADIOTHERAPY

Similar to the small amount of information that has been published on hypogonadal men with PCa on active surveillance, limited evidence is available regarding men treated with external beam radiation or brachytherapy for PCa on TST. Sarosdy conducted the earliest of these studies in 2007 [45]. In that retrospective chart review, men with PCa treated using brachytherapy from 1996–2004 were subsequently diagnosed as hypogonadal (serum testosterone <300 ng/dl and symptomatic) and given TST (alone in 20 men and in combination with external beam radiotherapy in 11 men) [45]. Men received TST for a time period ranging from 0.5–8.5 years, with a median of 2.0 years [45]. After a follow-up of 1.5–9.0 years, no significant increases in PSA levels were identified. Most men displayed progressive declines in PSA after initiation of TST with 30 of the 31 men exhibiting PSA values of <0.5 ng/ml at the end point of the study [45].

Other studies examining TST post-radiotherapy have found similar results. Morales *et al.* [46] examined a series of five hypogonadal patients who were started on TST after external beam radiation therapy. After being on TST for an average of 14.5 months (range 6–27), the expected increase in serum testosterone was seen in conjunction with no evidence of any abnormalities on digital rectal examination [46]. Serum PSA remained at <1.1 ng/ml in all patients [46]. The most recent, and largest, retrospective study conducted to date was by Pastuszak *et al.* [9]. In this study, 13 men with CaP treated using radiation therapy (either brachytherapy or external beam) were given TST and retrospectively reviewed [9]. A diagnosis of hypogonadism was made using the presence of clinical symptoms along with a serum testosterone <300 ng/dl. No men had locally advanced PCa and biopsy results revealed four men with Gleason 6 PCa, seven men with Gleason 7 and two men with Gleason 8 disease [9]. While serum testosterone increased significantly and clinical symptoms improved, no significant changes in serum PSA were observed following a median duration of 29.7 months after initiation of TST [9]. One patient did experience

increased PSA and after a repeat biopsy, CT, and bone scan to evaluate for recurrent CaP was negative, was restarted on TST [9]. From these limited studies on men with PCa treated via radiotherapy, it can be surmised that TST is a safe and effective modality of treatment for hypogonadism in a select group of PCa patients.

TST IN MEN WITH PCa POST RADICAL PROSTATECTOMY

Radical prostatectomy (RP) is a common procedure used in the management of PCa wherein the entirety of the prostate is surgically removed. This operative approach is effective in the treatment of PCa [47]. Several studies exist documenting the role of TST in patients who have undergone RP [10, 48–50].

An early retrospective case series of seven men diagnosed with hypogonadism after RP showed no evidence of local recurrence or distant spread following 1–12 years of TST [49]. Similarly, Agarwal and Oefelein [48] examined ten men who were identified with hypogonadism post-operatively and placed on TST for a median duration of 19 months [48]. No patients showed any detectable level of PSA (i.e. >0.1 ng/ml) and all had significant improvements in serum testosterone and alleviation of hypogonadal symptoms as documented by the hormone domain of the Extended Prostate Inventory Composite Health Related Quality of Life questionnaire [48].

More recently, Khera and Lipshultz [50] looked retrospectively at 57 men (mean age 64 years) treated for hypogonadism with TST after RP [50]. All 57 men had negative surgical margins and undetectable serum PSA values post-operatively (< 0.1 ng/dl) before receiving testosterone therapy. Follow-up was conducted via serum PSA and digital rectal examination one month after starting TST and every three subsequent months [50]. Throughout the average 13-month follow-up period (range 1–99), serum testosterone levels were substantially increased with an improvement of hypogonadal symptoms while serum PSA levels remained undetectable (<0.1 ng/dl) in all men. An expansion of this earlier work compiled more men with PCa treated via RP who were hypogonadal (n=103) and compared them to a non-hypogonadal cohort (n=49) [10]. In men deemed as having high risk PCa (defined as: Gleason score>8, positive margins or positive lymph nodes post RP), 26 were given TST and compared to 15 in the control cohort. Referrals to radiation oncology or subsequent salvage therapy were conducted in four patients on TST (15%) and 8 patients (53%) in the reference group [10]. However, a significantly increased number of T3b tumors were identified in the reference group (12%) compared to the TST group (2%). In the non-high risk groups, no patients were suspected of having biochemical recurrences. Interestingly, a statistically significant rise in PSA in both high risk and non-high risk groups was observed 18–24 months following the commencement of TST [10]. Therefore, it seems that while TST appears to not increase PCa recurrence, the rise in PSA is concerning and does highlight the importance of a vigorous surveillance protocol with any patient with PCa placed on TST. Particular attention should thus be paid to those men who are classified as high-risk.

CONCLUSIONS

Hypogonadism is a common condition that affects older men and has detrimental effects on quality of life. Early studies of TST in patients with PCa suggested that replacement of testosterone had profound implications on the progression and recurrence of PCa due to an androgen-mediated stimulation of prostatic tissue. Recent data however, suggests that the correlation between elevated serum testosterone levels and PCa progression might not be as direct as once perceived. Indeed, a recent study by Eisenberg *et al.* [51] found no change in overall cancer risk, or prostate cancer risk for men over 40 on long-term TST.

The current manuscript has reviewed the literature available to date. In light of the lack of concrete clinical evidence supporting an increased risk of PCa in men who received exogenous testosterone, along with the numerous documented benefits of TST in the treatment of symptomatic hypogonadism, the avoidance of TST in patients with PCa is being re-examined. Unfortunately, a lack of large-scale, randomized and prospective data exists. As such, a possibility of bias is introduced since current management plans have been predicated on retrospective work.

In summary, physicians should be comforted by the fact that there is currently no evidence that TST increases PCa risk in otherwise healthy men. Moreover, men with low-risk PCa on active surveillance can be safely given TST with an effective resolution of symptoms [15, 41, 42]. In men who have undergone some form of radiotherapy, the current consensus is that TST is safe and efficacious [9, 45, 46]. Since the majority of the studies focused on men with low-risk disease, some concern regarding the role of TST in men with high-risk disease post-radiotherapy exists. The majority of the studies conducted thus far have focused on TST in men post RP [10, 48–50]. The results for these studies again echo what was previously found – that TST in low-risk disease does not appear to increase cancer recurrence rates or PSA while effectively raising serum testosterone and treating hypogonadal symptoms. However, in patients with high-risk disease, statistically significant increases in PSA after 18–24 months post TST [10] cause concern. Since erratic PSA responses in a specific group of men on TST has been documented [41] caution must be used and close monitoring employed.

Proper patient selection is critical, and the diagnosis of hypogonadism should only be made given the presence of both low levels of serum testosterone and the presence of significant hypogonadal symptoms. Close surveillance of all men with PCa is essential, especially in the first year post-TST. Monitoring with digital rectal examination and PSA every 3 months is the current standard in our center. The patient must be willing to provide informed consent, especially given the lack of randomized, prospective trials. Furthermore, no other medical contraindication for TST (i.e. erythrocytosis, sleep apnea) should exist and no TST should be used in men currently on ADT. The optimal timing for the commencement of TST in men with PCa is currently unknown; however, at the Baylor College of Medicine, we begin testing serum horomone levels 3 months following surgery. The onset of TST will then depend on hypogonadal symptoms and the concurrent presence of low serum testosterone. Lastly, we advocate either the use of testosterone gels or injectables in men with PCa while avoiding the longer, depot preparations and subcutaneous implantable

pellets [4]. This is simply for the reason that should a PSA become elevated, better dose control and easier discontinuation is essential. While it is important to consider that the U.S. Food and Drug Administration currently mandates a warning against the use of TST in men with a diagnosis of PCa, provided that proper patient selection and monitoring is conducted, TST in men with PCa can now be considered a therapeutic option.

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Abbreviations

TST	testosterone supplementation therapy
CaP	prostate cancer
DHT	5α-dihydrotestosterone
PSA	prostate specific antigen

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HIGHLIGHTS

1. Basics of testosterone physiology and the role of androgens in the prostate are discussed.
2. Role of testosterone supplementation therapy (TST) in men on active surveillance is reviewed.
3. Current philosophy regarding the use of TST following prostate cancer treatment is summarized.

Table 1

Author	Year	Study Design	Patient #	Type of tx	Results
Calof et al.	2005	Meta-Analysis	644	TST in men with no hx of PCa	Rates of PCa, PSA >4 ng/ml, and biopsies were higher in the TST group than in placebo although differences between the groups were not statistically significant. Higher incidence of hematocrit >50% in TST group. The frequency of CV events, sleep apnea or death was not significantly different between the two groups.
Shabsigh et al.	2009	Systematic Review	2292	Various	No studies demonstrated that TST increased PCa risk or increased Gleason grade in treated vs untreated men. TST did not have a consistent effect on PSA.
Morgentaler et al.	2011	Retrospective case series	13	TST in men with untreated Pca	Mean serum total testosterone increased from 238 to 664 with no significant change in PSA or prostate volume. Biopsies in 2 men suggested upgrading. Repeat biopsy in one man and a prostatectomy in another indicated no progression. No local progression or distant disease.
Morales	2011	Retrospective case series	7	TST in men with untreated Pca	Unpredictable, variable increase in PSA with TST. Interruption of TST invariably decreased PSA to pre-therapy levels.
Morgentaler	2009	Case report	1	TST in a man with untreated Pca	Overall decline in PSA after receiving TST for 2 years. No clinical progression of disease noted.
Rhoden & Morgentaler	2003	Retrospective case series	75	TST in men with and without high grade PIN	PSA similar at baseline and 12 mo after TST in men with and without PIN. One man in the PIN+ group was found to have cancer on biopsy after abnormal DRE.
Sarosdy	2007	Retrospective case study	31	TST in men after brachytherapy for early prostate cancer	None showed recurrence or progression of prostate cancer. PSA < 1 in all patients.
Morales et al	2009	Prospective case study	5	TST in men after external beam radiotherapy	One of five patients had transitory increase in PSA after a mean follow-up of 14.5 months. None had PSA levels > 1.5 ng/ml. Mean serum testosterone and improvement in hypgonadal symptoms increased significantly.
Pastuszak et al.	2013	Retrospective case series	13	TST after radiation therapy for Pca	At median follow-up of 29.7 months after initiating TST, a significant increase in mean testosterone and SHBG with no significant increases in hemoglobin hematocrit PSA. No significant increases in PSA or cancer recurrences observed at any follow-up interval.
Pastuszak et al.	2013	Retrospective case series	103	TST in men after radical prostatectomy	At median follow-up of 27.5 months, significant increases in testosterone and PSA in both high risk and non-high risk prostate cancer groups. Referrals to radiation oncology or subsequent salvage therapy more frequent in reference control group. Significantly increased number of T3b tumors in reference group vs TST group.
Agarwal & Oefelein	2005	Retrospective case series	10	TST in men after radical prostatectomy	At median followup of 19 months, all patients had PSA < 0.1 with statistically significant improvements in serum testosterone and hypogonadal symptoms.
Kaufman & Graydon	2004	Retrospective case series	7	TST in men after radical prostatectomy	No biochemical or clinical evidence of cancer recurrence. PSA remained < 0.1 in all patients.
Khera & Lipshultz	2009	Retrospective case series	57	TS\T in men after radical prostatectomy	After a mean follow up of 13 months after initiation of TST after radical prostatectomy, no increases in PSA values were noted.