



Shifting the Paradigm of Testosterone Replacement Therapy in Prostate Cancer

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Historically, testosterone and prostate cancer have been demonstrated to have a positive association leading providers to forgo testosterone replacement therapy (TRT) in men with concurrent histories of hypogonadism and prostate cancer. This paradigm has been gradually shifting with our evolving understanding of the relationship between testosterone and prostate cancer and the gaining popularity of the saturation model. Newer data suggests improved quality of life for men with hypogonadism after TRT leading to a more tempered view of the effects of this treatment and its risk in prostate cancer. As more reports emerge of TRT in men who have either undergone definitive treatment for prostate cancer or are on active surveillance, some providers see a role for TRT in these patients despite non-consensus in clinical guidelines. It is critical that we examine evidence currently available, while we await more rigorous data to emerge.

Keywords: Androgens; Hypogonadism; Prostate-specific antigen; Prostatic neoplasm; Testosterone

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INTRODUCTION

Testosterone deficiency (TD), or hypogonadism, affects 30% of men aged 40 to 79 years and negatively impacts their overall health and quality of life (QOL) [1]. Based on meta-analysis data, testosterone replacement therapy (TRT) is the treatment of choice for clinically significant TD [2], which is generally accepted as signs and symptoms including reduced libido, gynecomastia, loss of body hair, shrinking testes, low bone density, and/or hot flashes in the presence of low serum testosterone (<300 ng/dL) [3,4]. Exogenous testosterone can be administered by injection, transdermal application, or orally, with variable side effect profiles, but equivocal

efficacy [5]. Administration of TRT has demonstrated variable improvement in sexual function, mood, energy, bone and muscle composition, and overall QOL [6,7]. In addition to TD or late onset hypogonadism (LOH), the aging male population is at an increased risk of prostate cancer, having an estimated lifetime risk of approximately 11.6% [8]. Despite the well documented evidence of its benefits, TRT is a controversial option for men with suspected, known, or historical prostate cancer [9].

Historically, prostate cancer has been a contraindication for TRT in men with LOH [10,11]. Low-powered studies completed in the 1940s demonstrated that men with metastatic prostate cancer had both a clinical and

Received: Dec 20, 2017 **Revised:** Jan 3, 2018 **Accepted:** Jan 5, 2018 **Published online** Mar 22, 2018

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biochemical improvement with androgen deprivation therapy (ADT) and, conversely, testosterone administration accelerated prostate cancer [12]. This work by Huggins earned him the 1966 Nobel Prize in Physiology or Medicine and established that prostate cancer development and growth was directly proportional to androgenic activity in the body. According to the androgen hypothesis, raising serum androgens with administration of exogenous testosterone would promote malignant cell growth and disease progression [12]. This hypothesis subsequently guided treatment of prostate cancer and endorsed the physician concerns regarding TRT in the setting of a prostate cancer diagnosis [13].

Over the past decade, mounting evidence has warranted a reevaluation of these traditional assumptions and has led to a fundamental paradigm shift. The Saturation Model has emerged as a competing theory and is based on the observation that androgens have a limited ability to stimulate prostate cancer growth through the androgen receptor (AR) at serum concentrations below the physiologic range and androgen supplementation beyond the point of androgen-AR binding saturation has little further effect [14]. This would allow for new therapeutic options for TRT in patients with a history of prostate cancer. However, the American Urological Association maintains the stance that current evidence does not provide definitive answers in either direction [15] and many patients who could potentially benefit from TRT are denied treatment [16]. This paper provides clinicians an updated review on TRT and prostate cancer risk with the aim to better inform clinical decision making and thereby improve patient care.

ANDROGEN PHYSIOLOGY IN THE PROSTATE

Large-scale prostate gene expression studies have revealed more than 200 androgen regulated genes, including the well characterized prostate specific antigen (PSA), kallikrein 2, and prostatic acid phosphatase [17]. Lipogenesis, cell cycle regulation, and cell survival pathways have genes known to be androgen regulated [18]. In addition, genes involved in normal prostate function, growth, and survival act through androgen-AR interaction. Dihydrotestosterone (DHT) binds to the nuclear AR in stromal cells of the prostate to stimulate the production and secretion of paracrine growth and

survival factors, which then diffuse from the stroma to the epithelium to influence cell growth and differentiation [19]. Simultaneously, AR-ligand binding in AR-positive luminal cells of the epithelium upregulates the expression of growth factors, such as vascular endothelial growth factor, that cross the basement membrane to affect stromal cells [17,20]. Homeostasis between proliferation and apoptosis is maintained by complex epithelial-stromal signaling with continual cell replacement, but without net growth.

THE SATURATION MODEL AND ITS PROPOSED MECHANISMS

A new paradigm gaining momentum to replace the traditional testosterone dependent theory has been termed the saturation model [14,21]. According to this model, testosterone and its intracellular metabolite 5 α -DHT are critical for the growth of prostate tissue, but are in excess at physiologic concentrations. The theory maintains that serum testosterone concentration has limited ability to stimulate prostate growth. A hypothesized saturation point occurs at near-castrate levels where the low androgen concentration would be rate-limiting in prostate tissue proliferation [14]. The saturation model is supported by evidence derived from both animal and human studies. In rats, the half-maximal prostate growth occurs at approximately 36 ng/dL, which correlates to near-castrate levels of testosterone [22]. In human prostate tissue, the AR has been reported to become saturated at approximately 120 ng/dL *in vitro*, and 240 ng/dL *in vivo* [23,24]. A 6-month study of TRT in men with LOH revealed that despite administration of exogenous testosterone, which substantially increased serum testosterone, there was no increase in testosterone or DHT within the prostate itself [25]. This has led some to believe that a mechanism of the saturation model could be a lack of prostatic uptake of exogenous testosterone protecting the prostate from large serum androgens changes.

SEX HORMONES AND PROSTATE CANCER RISK

The most definitive data available on the serum testosterone and prostate cancer relationship is from the pooled analysis of 18 prospective trials of 3,886 men with prostate cancer and 6,439 controls [26]. The

Endogenous Hormones and Prostate Cancer Collaborative group analyzed existing worldwide epidemiological data representing over 95% of published data and found no associations between prostate cancer and pre-diagnostic serum levels of free testosterone, total testosterone, DHT, or any other endogenous sex hormones [26].

In 2017, the Registry of Hypogonadism in Men (RHYME) reported their findings from a multi-national patient registry of hypogonadal men [27]. Of the 999 men in the registry, 75% initiated TRT. The major finding was that the proportion of positive biopsies was nearly identical in men on TRT (37.5%) compared to those not on TRT (37.0%) over the course of the 36-month study [27]. These results suggest the safety of TRT in men with newly diagnosed hypogonadism, in whom prostate cancer is still a future risk. Additionally, a 2017 meta-analysis found no increased odds of prostate cancer with use of TRT compared with placebo [5].

EFFECT OF TESTOSTERONE REPLACEMENT THERAPY ON PROSTATE SPECIFIC ANTIGEN

Many studies have attempted to characterize the impact of TRT on PSA level. A retrospective study of 85 patients receiving TRT for hypogonadism reported an increase in free and total testosterone with no significant change in PSA levels over a 2-year period [28]. However, other studies have observed an increase in PSA levels in both healthy and hypogonadal men shortly after initiating TRT. However, this was not found to be associated with any short-term increase in prostate cancer risk [29-31].

TESTOSTERONE REPLACEMENT THERAPY FOLLOWING DEFINITIVE PROSTATE CANCER TREATMENT

A retrospective review on hypogonadal men with prostate cancer resulted in the first published case reports of TRT in 2004. In this series Kaufman and Graydon [32] reported on 7 hypogonadal men with mostly low risk prostate cancer who had undergone curative radical prostatectomy and subsequently had LOH treated with TRT. Although there was variable follow-up, none of these patient had biochemical or

clinical evidence of cancer recurrence at a median of 12-months [32].

Agarwal and Oefelein [33] subsequently reported on ten men with a history of predominantly intermediate risk prostate cancer treated with radical retropubic prostatectomy who developed hypogonadism and initiated TRT. This group had a median follow-up of 19 months during which no PSA recurrences were reported; however, a statistically significant improvement in both total testosterone and hypogonadal symptoms was observed [33]. At a longer median follow-up of 5 years, Sarosdy [34] reported on thirty-one men with primarily low-risk prostate cancer who received TRT after prostate brachytherapy. There were no biochemical recurrences in these patients, and the authors support the use of TRT with caution and close follow-up after prostate brachytherapy [34]. In 2013, Pastuszak et al [35] evaluated 13 men with low and intermediate risk prostate cancer treated with TRT for a median of 30 month after brachytherapy or external beam radiotherapy (EBRT) and found no biochemical recurrences [35].

In 2013, Pastuszak et al [36] compared 103 hypogonadal men with prostate cancer treated with TRT after prostatectomy to 49 untreated eugonadal men after prostatectomy for prostate cancer. The median follow-up period for this cohort was 27.5 months and the median interval from prostatectomy to TRT was just over 1 year. There was a small, but statistically significant increase in PSA in high- and intermediate-risk patients in the TRT group. However, the control group who received no TRT saw more prostate cancer recurrences than the treatment group which had a higher PSA level.

To date, the largest series of men given TRT following brachytherapy or EBRT for prostate cancer is a multi-institutional cohort of 98 patients [37]. This group consisted predominantly of low- or intermediate-risk prostate cancer and had a median follow up of 40.8 months. Six (6.1%) of the men from this 2015 study met criteria for biochemical recurrence during the study period and two of them subsequently required ADT. The authors noted that two of these men may have been experiencing a 'PSA bounce' rather than true biochemical recurrence and the 6% biochemical recurrence rate was still lower than previously published rates among radiation therapy studies. The limited sample size, and retrospective, single-arm cohort design

prevents definitive conclusions from this study [37].

In a 2014 population-based observational study, Kaplan et al [38] used linked Surveillance, Epidemiology, and End Results-Medicare data to identify 149,354 men diagnosed with prostate cancer and found 1,181 men (0.79%) received exogenous testosterone following their cancer diagnosis. Their analysis determined that TRT in men with a history of prostate cancer was safe, not associated with increased cancer-specific or overall mortality, and did not increase the need for salvage ADT. These results were consistent when classified by cancer stage, grade, and treatment type [38]. In a subsequent analysis, this group examined the duration of TRT exposure on cancer outcomes and found that longer duration of TRT was not associated with an increase in mortality or need for ADT [39]. The group controlled for treatment type, including active surveillance or watchful waiting, and their results remained consistent. Similarly, a cohort study from 2016 looking at TRT in treated and untreated prostate cancer of 82 men found no biochemical recurrence in the men treated with either radical prostatectomy, cryotherapy or high intensity focused ultrasound, no upgrading in the men on active surveillance, and biochemical recurrence in 3 men treated with radiation therapy [40]. The researchers were unable to determine if recurrence was due to TRT or reflected the natural biology of the disease. These findings support the conjecture that TRT may be oncologically safe in hypogonadal men after definitive treatment and advocates its safety for those on active surveillance.

TESTOSTERONE REPLACEMENT THERAPY IN UNTREATED PROSTATE CANCER

Evidence on TRT in men with untreated prostate cancer is sparse and caution must be practiced in this population. In 2006, Morgentaler and Rhoden [41] reported that 15% of hypogonadal men with a PSA of 4.0 ng/mL or less had biopsy-detectable prostate cancer prior to initiation of TRT. According to their estimation, treatment of hypogonadal men with a normal PSA without biopsy equates with offering TRT to men with prostate cancer in 15% of cases. In a 2011 report, 13 symptomatic hypogonadal men with untreated prostate cancer elected active surveillance of prostate cancer and received TRT for treatment of their TD.

Two of these men had follow-up biopsies suggestive of clinical progression that were not confirmed on further follow-up and determined unlikely to represent true prostate cancer progression; otherwise, no local prostate cancer progression or distant disease was observed [42].

In 2011, Morales [43] reported on his experience with TRT in seven patients with symptomatic hypogonadism and untreated prostate cancer. PSA velocity was used as the criterion to discontinue therapy and return to nadir PSA levels allowed re-initiation of TRT. Patient PSA response to testosterone supplementation was variable and unpredictable, but interruption of TRT invariably decreased PSA to pre-therapy levels, implying no clinical significance. In comparison, a study of 154 men on active surveillance found reduction in free testosterone below 0.45 ng/dL to be an independent predictor of disease reclassification (*i.e.*, progression) [44].

A retrospective chart review from 2016 identified 28 men with hypogonadism who underwent TRT while on active surveillance for prostate cancer [45]. Compared to a group of 96 men with untreated hypogonadism on active surveillance, the TRT group conveyed no significant increase in biopsy-proven progression rates. They showed that progression in men on active surveillance was unaffected by TRT over 3 years [45].

CURRENT CONSENSUS RECOMMENDATIONS

Despite consistent evidence suggesting the safety of TRT in men with a history of prostate cancer, there is still controversy over appropriate patient selection, duration of treatment, and triggers to discontinue the therapy. The European Association of Urology uses level 3, grade B evidence to recommend that symptomatic men who have been surgically treated for localized prostate cancer and have no sign of active disease as evident by an undetectable PSA, a normal rectal exam, and an absence of metastatic disease, can be cautiously considered for TRT [46]. This guideline also specifies that patients must have a history of low risk prostate cancer, including a preoperative PSA of less than 10 ng/mL, Gleason score of less than 8, and pathological stage T1–T2. Patients should not be started on TRT until a minimum of one year follow-up from their curative prostate cancer surgery [46]. These guidelines do not comment on the use of TRT in the setting of

active surveillance. These EAU recommendations were agreed upon at the International Consultation for Sexual Medicine in 2015. This group concurs that level one evidence supports that there is no increased risk of prostate cancer or prostate cancer progression with the use of TRT [47]. In addition, they recommend counseling all men over the age of 45 regarding the controversy with TRT and prostate cancer, before initiating therapy [47]. Further prospective studies are required prior to a consensus on TRT for hypogonadal men with active prostate cancer, a history of EBRT, or for patients with surgically treated Gleason 8, PSA greater than 10 ng/mL, or histological variance, such as ductal features.

CONCLUSIONS

Recent academic endeavors have shifted the paradigm of TRT being a contraindication in prostate cancer to becoming a viable option for select patients with symptomatic hypogonadism. Current data suggest that TRT can cautiously be offered to carefully selected men treated with curative intent for low- and intermediate-risk prostate cancer, who have no evidence of disease recurrence. More urologists are becoming comfortable prescribing TRT for these men as well as those on active surveillance for low-risk prostate cancer [48]. Improving QOL in patients is an important aspect of prostate cancer survivorship, and therefore treatment should be considered for men suffering from TD. Further multi-center, randomized, placebo-controlled trials are necessary to make a definitive statement on clinical safety.

Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contribution

Research conceptualization, data acquisition, methodology, and information synthesis: all authors. Participated in the writing, review, editing, and finalization of the review manuscript: all authors.

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