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Potential Protective Effects of Testosterone Therapy on Prostate Cancer

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Abstract

This review article encompasses the historical perspective of androgen deprivation therapy by first reviewing the early research conducted by Huggins and Hodge, followed by a cellular biological discussion of androgen receptors in prostate cancer (PCa) physiology, leading to a subsequent discussion of the risk and potential therapeutic role of testosterone therapy in localized, oligometastatic, and metastatic PCa.

Keywords: testosterone therapy; androgen therapy in prostate cancer; safety of testosterone therapy in prostate cancer; benefit of androgen replacement in prostate cancer

Introduction

Hypogonadism is a constellation of symptoms, including fatigue, low energy state, decreased libido, erectile dysfunction, and low muscle/bone mass, and is a clinical syndrome associated with aging.[1] The overall incidence of male hypogonadism is ~5.6–30% and an estimated 500,000 Americans are reported to have male hypogonadism annually.[1]

Testosterone also decreases with age, with an annual decrease of ~1% in free testosterone levels after the age of 30. Given that hypogonadism is predominantly a disease of the aging man, there is a significant possibility of overlapping diagnosis of prostate cancer (PCa) along with hypogonadism, which can occur at any stage of disease course. PCa currently has >200,000 new cases diagnosed in 2020 alone.[2] The current mainstay for PCa therapy includes active surveillance (AS), radical prostatectomy, local radiation, or systemic therapy, with subsequent adjunct therapies designed to mitigate biochemical recurrence, noted to be as high as 53% who have received radiation, and up to 30% in patients who had undergone surgery.[3]

The initial relationship between PCa and testosterone was first investigated by Huggins and Hodge in the 1940s when serum phosphatases were demonstrated to significantly change with exposure to hormones, including testosterone.[4,5] This was the first established relationship between hormonal effects within an oncological context and set the current paradigm of PCa therapy: targeting testosterone availability to minimize PCa proliferation. However, in 1965, Huggins later on went to propose that hormonal excess might be used for therapeutic

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benefit, a proposal that has now regained renewed significant clinical interest.[6]

Although androgen deprivation has remained the mainstay of advanced PCa therapy, this discovered relationship was made before the advent of prostatic-specific antigen (PSA) measurements and before the availability of reliable serum testosterone measurements, thus limiting its clinical applicability.[7] Nonetheless, the relationship between testosterone and PCa remains complex and highly controversial. Androgens are the initial signal for DNA synthesis; however, extracellular factors and additional gene expression pathways exist within PCa physiology, convoluting therapy targets with regard to PCa.

No conclusive data have been demonstrated that testosterone therapy (TTh) increases PCa risk; however, clinical professional societies, including the Endocrine Society and the American Urological Association, advise against TTh in hypogonadal patients with PCa. In addition, existing clinical guidelines do not address nuances on TTh with respect to clinically localized PCa, locally advanced disease, and metastatic prostatic cancer.

The focus of this chapter is to demonstrate the evolution of the relationship between androgens and PCa, the prostate saturation model, and the potential protective effects of TTh on PCa.

An Overview of the Relationship of Androgens and PCa

Concerning hypogonadism, the relationship between serum androgen and intraprostatic androgen concentration is critical. Testosterone that enters the prostate is converted to dihydrotestosterone (DHT), the most potent androgen within the prostate, through 5-alpha reductase, with an intraprostatic concentration of DHT 10 times greater than serum levels.[3] 5 alpha-reductase functions to maintain prostatic function over a wide range of physiological testosterone levels.[3]

This preservation of prostatic activity is noted to reduce cellular activity when serum physiological androgen levels are very low, known as "castrate levels," and conversely, supraphysiological levels of testosterone result in minimal intracellular changes within the prostate.[3] Prostatic cell growth response extends beyond androgens binding to their respective receptors. Instead, growth response is due to a combined effect from epigenetic factors, growth factors, and negative feedback receptor downregulation, highlighting that serum androgen concentration is a single factor in the multifaceted pathophysiology of PCa development.[3]

To understand the mechanism of androgens in the pathophysiology of PCa, we must first review the dynamic interplay of serum testosterone, androgen receptor fluxes, and its subsequent downstream physiological effects. Testosterone supplementation in patients who are hypogonadal, eugonadal, and supraphysiological manifests differently and precipitates a broad response in androgen receptor response.

The first relationship between testosterone and prostatic tissue response dates to 1939 and 1940, during which Huggins et al demonstrated that administering testosterone to castrated dogs would increase prostatic secretions and administering estrogen would decrease prostate size.[4] This pivotal discovery was the foundation used to demonstrate that chemical castration through androgen deprivation could lead to cellular process deceleration. This process was biochemically demonstrated through measuring prostatic phosphatase concentrations.[5]

Similarly, Burkhart demonstrated that rising exposure of androgens resulted in a proportional increase in cellular proliferation within prostatic tissue[8] Sheppard et al demonstrated a rise in DNA, RNA, and protein synthesis noted in prostatic tissue after androgen administration.[9] This relationship is what eventually led to the androgen hypothesis, the premise that androgens cause *de novo* PCa or accelerate the growth of latent low-risk PCa.[7] Although the early teachings supported low androgen states as protective and high androgen states as a risk factor for aggressive PCa development, subsequent studies have challenged this notion.[7]

The Advent of the Prostate Saturation Model

As newer findings began questioning the initial androgen hypothesis, the saturation model hypothesis became the new paradigm of understanding androgen homeostasis within the context of PCa. The saturation model posits that at low serum testosterone concentrations, testosterone binds to androgen receptors maximally and beyond this receptor saturation point, any cellular prostatic growth exists independent of serum androgen levels.[7] The relationship of androgen concentration and PCa cellular activity was only relevant at near castrate androgen levels and beyond these levels, cellular activity did not proportionally change with rising androgen levels.[7] This phenomenon was demonstrated *in vivo* when prostatic cell activity was no

longer dependent on androgen levels as early as 1968 by Dr. Coffey et al.[10]

Although the relationship of androgens and prostate activity had been discovered as early as the 1940s and further corroborated in the 1960s, the timing of this relationship was explored further by Lesser and Bruchovsky in 1974, who investigated specific time-dependent prostatic cellular responses to androgen exposure.[11] Lesser and Bruchovsky used prostatic nucleoli as a marker for prostatic proliferation, and demonstrated that DHT administration to castrated rat prostates did not stimulate DNA replication until 4 days after castration, at which point, replication ceased when prostate homeostasis had returned.[11] This study highlights the critical saturation point at which androgens result in DNA proliferation during castrate levels but do not confer significant changes in prostate activity beyond this threshold.

This principle was tested clinically between 1949 and 1967 in which a prospective cohort of patients with metastatic PCa ($n = 52$ patients) was administered exogenous testosterone, and 45 (86.5%) patients experienced an unfavorable response.[12] Interestingly, 25% of patients with symptomatic metastasis (with no prior therapy) and 36% of patients in remission on endocrine therapy had an unfavorable response.[12] Perhaps the most perplexing finding is that 7 of these 52 patients experienced symptomatic benefit from TTh. This study demonstrated the earliest dose-dependent relationships of androgen administration in the setting of PCa and although its findings do not suggest that testosterone is protective, it did open the door for further investigation of the relationship of testosterone and PCa.

The prostate saturation model was expanded by Morgentaler and Traish in 2009 and has allowed for a clinical paradigm shift in the therapeutic and protective role of androgen therapy in PCa.[13] This literature review demonstrated that androgen binding to its receptor within the prostate followed a saturation curve and that DNA proliferation/secretory activity showed the steepest rise in response to androgen exposure at lower levels of testosterone when compared with higher levels of testosterone.[13]

This concept was further expanded by demonstrating that TTh among patients with low-risk PCa did not (1) increase PSA, (2) lead to higher systemic progression, and (3) result in change in prostate size/secretory activity.[13] A later retrospective case series involving two institutions was composed of 13 patients undergoing testosterone replacement therapy for hypogonadism who were also diagnosed with untreated localized prostate.[14] The follow-up period was 2.5 years after initiation of TTh who also underwent confirmatory biopsies without demonstration of cancer progression or concerning rise in PSA.[14] Although this study is limited due to its retrospective nature and lack of control, it further supports the saturation model clinically: PCa growth still occurs at near castrate levels and the addition of exogenous testosterone does not mediate PCa growth.

Additional clinical data that supported the saturation model were investigated by Khera et al to retrospectively review kinetics of PSA in hypogonadal men who were on AS for localized PCa. A total of 451 men were surveyed with a median follow-up time of 2.5 years without demonstration of cancer progression.[15] Interestingly, he determined the clinical threshold of 250 ng/dL for testosterone and noted that after 9 months of testosterone replacement, there was no longer a correlation between PSA and testosterone, and thus PSA was a parameter independent of testosterone levels.[15] In contrast, near castrate levels of testosterone noted a tighter relationship between PSA levels and serum androgen levels supporting the saturation model clinically.

This model suggests that prostate tissue proliferation did not change with increased serum testosterone levels due to cellular mechanisms in place to protect the prostate from aberrant growth responses from labile serum androgen concentration changes.[16] The saturation point model is clinically relevant in PCa as the relationship between PCa cell stimulation and serum androgen level is only relevant at near castrate levels of testosterone.[17] This model is also what served as the blueprint for the TRANSFORMER II trial, investigating supraphysiological doses as a target in PCa therapy.

Potential Protective Effects of TTh on PCa—Clinical Studies

The relationship of low endogenous testosterone and increased rates and severity of PCa

Before investigating how testosterone replacement therapy and its impact on PCa development, it is critical to highlight the relationship between serum testosterone and PCa prevalence among hypogonadal and eugonadal men.

The first study to recognize the link between was a study in 1996 by Morgentaler, in which the authors identified PCa in 11 of 77 (14%) men with low serum testosterone, and these patients had a normal digital

rectal examination and PSA <4 ng/mL, which suggested that PSA levels and digital rectal examination alone may not be sensitive in detecting PCa in men with low testosterone and PSA levels may be altered based on a patient's androgen state.[18]

This relationship since then has been examined multiple times for the past 20 years. In 2006, Morgentaler et al examined 345 hypogonadal men with PSA <4 ng/mL and found PCa in 21% of men with testosterone <250 ng/dL compared with 12% of men with testosterone level >250 ng/dL, which was statistically significant. A similar study in 2013, of 206 men with benign prostatic hyperplasia or PCa found that low serum testosterone (defined as <240 ng/dL) was an independent predictor for PCa.[17] A study by Shin et al studied 568 men undergoing prostate biopsy, and on multivariate analysis, the authors found a significantly higher incidence of PCa in patients with testosterone <385 ng/dL (38.9% vs. 29.5%).[19]

Low serum testosterone has also been linked to more aggressive higher-grade PCa. In a retrospective review of 117 patients conducted by Hoffman and Morgentaler in 2000, men with hypogonadal serum testosterone levels (determined as a threshold of ≤300 ng/mL) had a greater percentage of Gleason 8 or higher PCa.[20] In addition, lower free testosterone levels were also associated with higher rates of positive biopsies, both findings were independent of PSA levels.[20] This was one of the earlier clinical studies that concluded low free serum testosterone levels as a parameter for potentially aggressive PCa.

A prospective analysis of 137 males performed by García-Cruz et al in 2012 investigated the clinical relationship between PSA, serum testosterone, and oncological burden. This study examined men with formally diagnosed PCa on transrectal-guided prostate biopsy, and found that lower serum testosterone levels, determined as <346 ng/dL, were associated with higher PSA, higher clinical staging, worse D'Amico progression risk, increased risk of bilateral disease involvement, along with greater tumor burden.[21]

Yet another similarly designed study by Isom-Batz et al examined the pretreatment hormonal status of 326 men who underwent radical prostatectomy and examined biochemical recurrence (defined as documented rise in PSA >0.4 ng/mL after treatment). Although the study found no relationship between PSA and testosterone levels, low testosterone was found to inversely correlate with pathological stage, clinical stage, and biopsy grade.[22]

In fact, given the abundance of data supporting hypogonadism as an independent risk factor for greater tumor burden and more aggressive PCa, additional retrospective reviews have been performed to evaluate whether serum testosterone and PSA can both be incorporated as a clinical diagnostic tool in this patient population. In a study led by Rhoden and Morgentaler, the ratio of serum testosterone and PSA was calculated in hypogonadal men to investigate if there was clinical predictive value in detecting PCa.[23] A retrospective evaluation of 184 hypogonadal men, who had undergone transrectal-guided prostate biopsies, demonstrated that the testosterone to PSA ratio was strongly associated with PCa risk, with 80% sensitivity, and 60% specificity.[23]

Thus, these studies underscore the clinical relevance of the saturation model hypothesis in that low testosterone levels can impact prostate carcinogenesis. Given this physiological phenomenon, the relevance of treating hypogonadism is clinically relevant in the context of PCa and directly argues against previously understood relationships of androgens and PCa. The protective effect of the eugonadal state in the setting of PCa argues that TTh could mitigate risk of PCa and may not yield that controversial risk once previously held.

PCa development in patients on TTh

In the examination of existing literature regarding *de novo* PCa development in the setting of TTh, the hypothesis that androgens are the driving factor behind PCa has been investigated repeatedly with the multiple studies supporting that TTh does not directly result in *de novo* PCa development or increased risk of PCa.

In a retrospective review of patients at two institutions performed by Gerstenbluth et al, 54 men with hypogonadism on testosterone supplementation were monitored with serial serum PSA monitoring, demonstrating that the mean change in PSA was ∼0.96 ng/mL and that 11% (6/54 patients) developed a rise in PSA >4 ng/mL prompting a transrectal ultrasound-guided prostate biopsy, with only one patient demonstrating PCa.[24] The strength of the study included longer term analysis (36 months) to assess how TTh affects serum PSA in which 19 patients starting testosterone had an average pretreatment PSA of 1.07, which subsequently rose to 1.66 ng/mL while on TTh ($p < 0.05$); however, no patient in this subset required a biopsy or received a diagnosis of PCa.[24]

In a prospective review conducted by Yassin and Saad out of Germany, 154 hypogonadal men with a mean age of 56, surveyed for 24 months, were monitored while on TTh with notable findings demonstrating that overall prostate volumes among hypogonadal men were low and that incidence of PCa diagnosis was similar to that of eugonadal men.[25]

In addition, a compelling meta-analysis performed by Shabsigh et al in 2009 that examined 52 trials, including 11 placebo controlled randomized studies, demonstrated the incidence of new PCa diagnosis in hypogonadal men on TTh was comparable with general screening.[26] In addition, this comprehensive meta-analysis also noted there was no established relationship between TTh (specifically, FDA-approved testosterone supplementation) and aberrant rise in PSA levels.[26]

Ultimately, a close review of the existing literature in this meta-analysis concluded that the incidence of PCa detection and overall prevalence were no different between hypogonadal men on supplemental androgen therapy and the general public.[26]

In a prospective cross sectional descriptive study conducted by Yassin and Saad, 553 patients were examined: 42 hypogonadal men receiving TTh, 162 untreated hypogonadal men, and 349 eugonadal men who underwent prostate biopsy.[27] Pathological analysis among the *treated* hypogonadal men demonstrated 16.7% rate of positive prostate biopsy with71% of these patients having a primary Gleason Grade Group (GG) 3 pattern.[27] Conversely, in the arm of *untreated* hypogonadal male patients, a 51% positive prostate biopsy rate was noted, of which 40.5% had primary GG3 pattern, and 60% with greater than GG3 pattern.[27] These results were also observed in staging, with no hypogonadal men undergoing TTh being diagnosed with III or IV PCa at the time of their prostate biopsy. The findings of the article suggest that not only does TTh not have an increased risk of *de novo* PCa development, but it also demonstrates a protective effect against the development of high risk locally aggressive PCa.

A population that has been studied recently to understand the development of *de novo* PCa are patients on AS. Morgentaler et al conducted a retrospective study in 2011, of 13 men on AS for PCa and received TTh for a minimum of 6 months. Twelve men were diagnosed with Gleason 6 on initial biopsy and one with Gleason 7 (3 + 4).[14] Mean duration of TTh after diagnosis of PCa was 23.5 months, and during this follow-up period 54% of patients did not have cancer detected on subsequent biopsy, and none of the 13 patients demonstrated cancer progression.[14]

A study by Kacker et al followed hypogonadal men on AS who were treated for at least 6 months ($n = 28$), as well as men who were not treated ($n = 96$), with mean follow-up of 38.9 months versus 42.4 months, respectively.[28] In the untreated group, 44.7% ($n = 44/96$) developed biopsy progression. In the treated group, 31.8% of men with GG3 disease developed biopsy progression, and 33.3% of men with Gleason 3 + 4 were noted to have increase in tumor volume; however, none of the men in the treated arm were noted to have upgrading beyond Gleason 3 + 4 disease.[28] This study highlights the clinical impact of potentially improving oncological control by adequately treating hypogonadism in patients with concomitant PCa.

Further expanding on existing data regarding hypogonadal men on AS, San Francisco et al studied 154 men followed with AS for PCa of which 35% had disease progression requiring active treatment.[29] Notably, men who progressed were observed to have significantly lower free testosterone levels than those who remained on AS.[29] Furthermore, free testosterone level <0.45 ng/dL was associated with a sevenfold increase in the risk of disease progression with multivariate analysis noting that free testosterone and family history of PCa were independent predictors of disease.[29]

In the study by Wallis et al in 2016, a cohort of >10,000 patients treated with TTh was compared with 28,000 matched controls, with findings that patients on TTh had statistically significant lower risk of developing PCa with a hazard ratio of 0.86.[30] This study also demonstrated that patients with the longest exposure of TTh saw a greater protected effect with a hazard ratio of 0.6, which suggests that long-term testosterone replacement is not only safe but may also be associated with protective effects against development of PCa. It is important to note that this risk reduction was only observed in long-term TTh, as short durations of TTh were not associated with a decreased risk of PCa diagnosis.[30]

Perhaps one of the most compelling studies that exist to date supporting the protective effects of TTh in PCa was conducted by Loeb et al,[31] who led a large nested case–control study using Swedish national cancer registry databases comparing 38,570 men with PCa with 192,838 without PCa, serving as a control. This study

demonstrated that there was no overall increase in risk of PCa in those men who received TTh with an odds ratio of 1.03.[31] Furthermore, there was no significant difference in risk based on duration, type of TTh administered, and timing of treatment between the control group and the group receiving TTh.[31]

In addition, the patients who did receive TTh had higher incidence of favorable PCa noted as early as the first year of TTh initiation and lower rates of aggressive PCa noted after the first year of therapy.[31] This study is strengthened by the quality of the database along with larger number of subjects, allowing for generalizability. Although limited due to inability to randomize, the lack of testosterone levels, and indications for TTh, this larger powered study demonstrates the association of lower risk PCa s among treated hypogonadal men.[31] Interestingly, this study also showed an increase in low-risk and favorable-risk PCa among treated hypogonadal patients, which the study authors attribute to early detection bias.[31]

The plethora of existing data investigating TTh, and the risk of *de novo* PCa development suggests that (1) the risk is comparable with that of eugonadal males who do not receive TTh and (2) TTh has shown protective effects with overall lower rates of higher risk aggressive PCa subtypes. The mechanisms behind these associations are not fully understood, yet they suggest that untreated hypogonadism is not only a detriment to quality of life but could also potentially result in worse oncological outcomes.

Low testosterone levels linked to worse outcomes postradical prostatectomy for localized PCa

The review of literature will now shift the discussion from *de novo* PCa risk in the TTh patient population to those with established localized PCa diagnoses undergoing curative therapies and emphasize the critical relationship between serum androgen levels in localized PCa.

In a prospective single-institution study led by Lane et al, 501 patients who had undergone a radical prostatectomy were evaluated for risk of biochemical recurrence using a validated nomogram incorporated stage, PSA, margins, and Gleason grade to predict 10-year progression-free survival along with pretreatment serum testosterone level.[32] Notable findings from this study include multivariate analyses demonstrating that low total testosterone was associated with higher rates of Gleason 4–5 PCa pathology; however, there was no statistically significant association between low testosterone levels and biochemical recurrence.[32] As was previously discussed, the higher risk PCas were observed in this untreated hypogonadal population, yet hypogonadal states were not shown to be associated with early cancer progression or overall tumor volume.[32]

An additional single-institution retrospective review, including 103 hypogonadal men with concomitant PCa and 49 eugonadal men with PCa, was evaluated with 77 men of this cohort with low-risk PCa, and the remaining 26 men with high-risk PCa.[32] Men who received TTh before surgery were started within 12 months postprostatectomy and notably, a statistically significant PSA increase was noted. However, the TTh arm had lower biochemical recurrence when compared with the nontreatment arm at 15% when compared with 18–32%.[32] Although a PSA rise was noted in the TTh treatment arm, the lower biochemical recurrence rate in the TTh suggests a possible protective factor; however, limitations from the retrospective nature of the study prevent further generalizability.

In a recent retrospective study conducted by Ahlering et al, postrobotic radical prostatectomy males were evaluated for biochemical recurrence with a total of 850 patients of whom 152 were on TTh.[33] When comparing the TTh arm to the control, the biochemical recurrence rate was 7.2% compared with 12.6%, respectively.[33] Remarkably, further regression analysis notes that TTh was an independent predictor recurrence-free survival, with 54% reduction in biochemical recurrence and delayed time to recurrence by 1.5 years.[33] Of note, both the TTh and control group arms had no difference in patient-reported cardiovascular outcomes, nor were significant PSA rises noted.[33] Perhaps the most clinically exciting of these findings is the delayed time to biochemical recurrence in the TTh arm, again suggesting a possible protective mechanism in post-therapeutic TTh in hypogonadal patients with concomitant PCa.

Interestingly, another study was prospectively conducted by Huynh et al in 2019 investigating low free testosterone and biochemical recurrence after radical prostatectomy. This study included 830 patients status postprostatectomy: 152 were hypogonadal, 410 were eugonadal and matched to serve as a control with findings that noted that low free testosterone was significantly associated with increase Gleason group, worse stage (pT3/T4), and higher rate of biochemical recurrence.[34] This is clinically relevant as free testosterone is biochemically active with respect to prostatic cellular

activity and supports the saturation model that a low androgen state is when PCa is most vulnerable to serum androgen levels.

Additional studies have also investigated using preoperative total testosterone as a clinical predictive tool. In one retrospective study, 107 patients who had undergone laparoscopic radical prostatectomy were classified as hypogonadal (testosterone <300 ng/dL) or eugonadal (testosterone >300 ng/dL), and when comparing age, body mass index, preoperative comorbidities, clinical stage, and preoperative PSA levels, low testosterone was independent risk factor for high Gleason score (>7) and for locally advanced PCa (stage >pT3).[35]

Patients with locally advanced disease (clinical stage T3 or T4), studies have also been performed demonstrating worse clinical stage in those with lower pretreatment testosterone levels. A retrospective review from 2002 investigated 888 patients who had undergone radical prostatectomy with available pre- and post-treatment testosterone levels, demonstrating non-organ confined pathological stage (clinical stage T3 or T4) was associated with lower pretreatment testosterone levels.[36] This indicates an association with hypogonadal states and possibly more aggressive PCa subtypes resulting in locally advanced disease.[36] A similar retrospective study from Japan, including 82 men with clinically localized PCa who underwent radical retropubic prostatectomy pre- and postsurgical testosterone levels, noted that hypogonadal testosterone levels were important predictors of extraprostatic disease and PSA recurrence rates.[37]

Thus, the association of worsening local oncological outcomes and recurrence among hypogonadal patients again underscores the importance of maintaining a eugonadal state and avoiding potential role of the androgen receptor activity at "saturation point." The existing literature also illustrates the potential clinical value of serum total and free testosterone in predicting postoperative outcomes and in guiding closer postoperative surveillance.

Bipolar androgen therapy and its role in advanced castrate-resistant PCa

Despite the controversy surrounding TTh in the context of advanced PCa, there is a growing body of literature that suggests that using supraphysiological levels of androgens in patients with metastatic castrate-resistant prostate cancer (mCRPC) may be an effective therapeutic strategy to either increase PCa death or reprogram the cells to be more sensitive to antiandrogen therapy. This form of therapy, bipolar androgen therapy (BAT) is still being investigated; however, exemplifies the multifaceted nature of PCa physiology.

Initial studies have noted that high doses of androgens result in DNA damage rather than fuel PCa growth as previously thought, and paradoxically in low androgen states, CRPC cells may autoregulate to increase androgen receptor expression.[38]

Clinically, this translates to the use of androgen therapy as part of the oncological armamentarium and employs the clinicians' ability to use androgens to inhibit DNA repair, downregulate androgen receptor splice variants, and delay the repair of damaged DNA within PCa cells.[38] In other words, supraphysiological testosterone can disrupt cell pathways and induce cellular apoptosis in cancer cells.[38]

This revolutionary discovery has led to the investigation of metastatic castrate-resistant PCa therapy in the TRANSFORMER (Testosterone Revival Abolishes Negative Symptoms, Fosters Objective Response and Modulates Enzalutamide Resistance) trial led by Denmeade et al.[39] The TRANSFORMER trial, was a multi-institutional randomized control trial with crossover conducted during cancer progression comparing BAT with enzalutamide, with the study demonstrating that the BAT to enzalutamide arm had a higher statistically significant progression-free survival at 28.2 months when compared with the enzalutamide to BAT arm at 19.6 months.[39]

The study demonstrates the safety of BAT and raises an exciting physiological concept in which BAT could potentially sensitize mCRPC to existing therapies thereby increasing the efficacy of the drug. Future studies will help elucidate this therapy and this cellular relationship, but preliminary studies have demonstrated that supraphysiological testosterone provides a safe potentially efficacious treatment option in a clinically challenging treatment landscape.

Conclusions

The current landscape of TTh in the setting of PCa has gone through several paradigm shifts from viewing testosterone as potentially dangerous (the proverbial "fuel to the fire") to generally safe, and now to a protective measure and potential therapy.

The prior dogmas of PCa as a hormonally mediated cancer responding to TTh have shifted after the advent of the prostate saturation model noted that prostatic

activity is in response to a myriad of biochemical factors, and androgen levels are only clinically relevant at near castrate and castrate levels.

Clinical corroboration of this model has illustrated that TTh is not only safe but also can protect patients from developing aggressive progressive forms of PCa. This role is ever evolving and requires further exploration as patients could not only have improvements in quality of life but also in oncological outcomes.

Authors' Contributions

A.J., P.K., and M.K. all were involved with article writing. M.K. was responsible for concept design and formatting as well as overseeing article.

Author Disclosure Statement

M.K. is consultant for Abbvie, Clarus, and Acerus, and investigator for TRAVERSE Trial; A.J. and P.K. have no disclosures to report.

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Abbreviations Used

AS = active surveillance
BAT = bipolar androgen therapy
CRPC = castrate-resistant prostate cancer
DHT = dihydrotestosterone
GG = Grade Group
mCRPC = metastatic castrate-resistant prostate cancer
PCa = prostate cancer
PSA = prostatic-specific antigen
TRANSFORMER = Testosterone Revival Abolishes Negative Symptoms, Fosters Objective Response and Modulates Enzalutamide Resistance
TTh = testosterone therapy