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Effects of Testosterone on Benign and Malignant Conditions of the Prostate

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Abstract

Purpose of the review—This review summarizes the current literature regarding the effects of testosterone therapy (TTh) on common disorders of the prostate.

Recent Findings—Testosterone therapy has gained credibility over the last several decades as a potentially safe co-treatment modality for men with benign and malignant prostatic conditions. Our understanding of the effects of testosterone on the prostate continues to evolve with ongoing clinical and basic science research. Findings of these studies have reinvigorated the debate over the effects of testosterone on benign and malignant disorders of the prostate, including BPH, chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), and prostate cancer.

Summary—Despite the burgeoning body of data claiming the safety and efficacy of TTh in common prostatic conditions (including BPH, CP/CPPS, and prostate cancer), diligent monitoring, appropriate patient selection, and informed consent are critical until more definitive studies are performed.

Keywords

Adult; humans; testosterone; sex hormones; benign prostatic hyperplasia; chronic pelvic pain syndrome; chronic prostatitis; prostate cancer; QoL; androgen deprivation; treatment outcome; prostate-specific antigen/serum

Introduction

From 2000 to 2011, global testosterone sales increased 12-fold from \$150 million to \$1.8 billion [1]. This rise in sales is attributable to the rising prevalence of late-onset hypogonadism (LOH) paralleling the expansion of an aging population, increasing medical community awareness of comorbidities associated with hypogonadism and direct-to-

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Compliance with Ethical Standards

Conflict of Interest

Amin S. Herati, Taylor P. Kohn, Peter R. Butler, and Larry I. Lipshultz each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

consumer advertising of the benefits of testosterone therapy (TTh). Nevertheless, the administration of exogenous testosterone has been heavily scrutinized for decades by federal regulatory agencies, including the Food and Drug Administration (FDA), due to its concern that testosterone therapy may increase the risk of benign prostatic hyperplasia (BPH), prostate cancer, cardiovascular and cerebrovascular disease [2].

Many of the concerns regarding TTh's proliferative potential to cause obstructive uropathy and prostate cancer stem from a 1941 study by Huggins and Hodges [3••]. This study examined the impact of castration and androgen replacement in a cohort of men with metastatic prostate cancer. The effects of testosterone injections were assessed in only two men who demonstrated an adverse biochemical response with a rising serum acid phosphatase level following testosterone injection and a subsequent return to baseline acid phosphatase levels following the cessation of testosterone injections. Multiple clinical studies have since emerged that refute the adverse biochemical response observed by Huggins and Hodges and call into question the contributions of serum testosterone concentration on the risk of BPH and prostate cancer [4, 5].

Numerous molecular studies detailing the interactions of the androgens (testosterone and its metabolite dihydrotestosterone [DHT]) with its receptors in the prostate have been performed. It is now widely accepted that testosterone and DHT have a finite ability to stimulate the growth of prostatic epithelial cells due to the high androgen affinity and low capacity of androgen binding sites (saturation reached at low serum testosterone concentrations at roughly castrate serum testosterone levels) [6]. Clinical data contradictory to the work of Huggins and Hodges and research findings at the cellular and molecular level reinvigorated the debate over the effects of testosterone on benign and malignant disorders of the prostate, including BPH, chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), and prostate cancer. This review summarizes the current literature regarding the effects of TTh on these common disorders of the prostate.

Testosterone and BPH

Benign prostatic hyperplasia (BPH) is one of the most common diseases affecting men and an inexorable part of aging. Five-year longitudinal studies of men 40–79 years of age have detected a 1.6% annual rate of prostatic growth across all age groups [7]. Given the dependence of the prostate on testosterone and its metabolites for growth, there have been concerns that TTh may exacerbate prostatic growth and worsen associated lower urinary tract symptoms (LUTS). In 1993, Holmäng et al [8] administered testosterone undecanoate injections to 23 eugonadal middle-aged men and documented a 12% increase in the mean prostate volume after 8 months of therapy without a worsening of LUTS. As a result of these studies implicating a putative link between testosterone and prostatic growth, it is now widely believed that the TTh exacerbates BPH/LUTS. In fact, the American Urological Association (AUA), Endocrine society, and International Society of Andrology continue to recommend against the use of TTh in men with severe BPH and/or significant LUTS [9, 10].

However, over the last two decades, a growing amount of data have contradicted the notion that TTh hastens prostatic growth and worsens voiding symptoms. During this period,

several randomized, double blind, placebo-controlled or parallel studies in hypogonadal men of varying ages independently found **no** association between TTh and signs or symptoms of BPH. In one study by Sih et al [11] investigating the effects of testosterone cypionate biweekly for 12 months in hypogonadal men with a mean age 65, no significant increase in urinary retention or exacerbation of LUTS occurred compared to placebo. Similarly, no significant differences in PSA levels or LUTS were observed in another randomized, placebo-controlled trial of 44 men with a mean age of 76 years who were randomized to either testosterone or placebo patches and treated for 12 months [12]. In a 2010 double-blind, randomized, placebo-controlled trial by Kenny et al [13], 99 frail men with a mean age of 77.1 years were randomized to receive transdermal TTh or placebo patches. After 12-months of follow-up, no significant differences in urinary retention rates, PSA, and International Prostate Symptoms Score (IPSS) were observed between the two cohorts. In fact, improved IPSS – Quality of Life (QoL) sub-scores were observed in the TTh cohort with a 2.0% improvement in sub-scores compared to a 1.8% deterioration of IPSS-QoL score of the placebo group. In a study examining histopathologic changes associated with TTh, Marks et al [14] assigned 44 men aged 44–78 years to receive 150 mg of testosterone enanthate (TE) or matching placebo intramuscularly in a 2006 randomized, double blind, placebo-controlled study. The investigators found no difference in prostatic testosterone or DHT levels despite a higher serum testosterone concentration among men randomized to the TTh arm. Prostate biopsies were performed at baseline and 6 months in 40 of these men with no difference in prostate histopathology between in the two groups. Moreover, voiding symptoms and urinary flow rates were equivalent between the two arms over the duration of the study. Three very recent double-blind, placebo-controlled studies performed on 732 hypogonadal men each failed to identify a clinically and statistically significant relationship between TTh and LUTS compared to placebo [15–17].

The aforementioned studies have been analyzed in two recent meta-analyses. Cui and Zhang [18] examined 16 randomized controlled (RCT) trials and 1030 men, demonstrating that the duration of TTh (long-term and short-term) does not have an effect on prostate volume or growth. More recently, Kohn et al [19] identified 14 randomized controlled trials encompassing 2029 hypogonadal men. Kohn et al found that TTh, regardless of the route of administration, had no effect on IPSS scores or PSA kinetics. Higher serum testosterone levels among hypogonadal men on TTh also did not associate with IPSS, even if the patients had “mild” or “moderate” IPSS prior to initiating TTh.

Of interest, several trials over the last two decades have also reported that BPH symptoms decrease in men on TTh. In a 2002 study, 207 hypogonadal men 40–83 years old were randomized to receive either 80mg or 120 mg of oral testosterone undecanoate daily. Lower urinary tract symptoms decreased for all participants and prostate volumes decreased in men whose testosterone levels increased [20]. In a 2011 study by Shigehara et al [21], 46 hypogonadal men with mild BPH were assigned either to no treatment or to receive 250 mg of TE intramuscularly every 4 weeks. Patients receiving testosterone had significantly decreased LUTS, increased maximum urinary flow rate, and increased voided volume compared to the control group. A study of 214 male-twins between 25 and 75 years old by Meikle and colleagues [22] found no relationship between high levels of testosterone and

BPH – in fact, in this study, larger prostate sizes were associated with lower serum testosterone and DHT levels. These findings may be attributable to increased prostatic inflammation and fibrosis present in untreated hypogonadal men either directly due to low serum testosterone or indirectly due to comorbid inflammatory conditions, such as obesity and metabolic syndrome (reviewed by Delay and Kohler [23]).

Testosterone and Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS)

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a chronic pain condition that is characterized by pain in the pelvis, perineum, and/or testicles in the absence of other attributable pathology and is often associated with irritative voiding symptoms [24]. This condition can drastically lower the QoL to levels below those of patients with congestive heart disease and diabetes mellitus [25]. While the etiology remains unclear for up to 90% of CP/CPPS cases, several theories have been proposed including a dysregulated immunologic/inflammatory response with elevated cytokine levels (such as IL-10) [26]. Physiologic changes have been identified in the prostates of men with Category IIIA CP/CPPS, including elevated prostatic interstitial tissue pressures resulting in local tissue ischemia and increased sensitivity [27]. Decreased nitric oxide and increased Rho-Rho kinase activity have been suggested as mechanisms for elevations in intraprostatic pressure [28]. Low testosterone creates a systemic inflammatory state, reduces prostatic nitric oxide levels and increases Rho activity, all of which may increase intraprostatic pressures [28–30].

Despite the overlapping pathophysiology of low testosterone and CP/CPPS, very few studies have examined the associations between them. In a 2012 prospective case-control study, Byun et al [31] compared 74 Category IIIA CP/CPPS patients to 240 control patients and found slightly higher serum testosterone levels among the CP/CPPS cohort ($4.05\text{ ng/mL} \pm 1.3$ vs $3.97\text{ ng/mL} \pm 1.25$, $p = 0.6$). A more recent propensity-scored matched comparison of Category IIIA CP/CPPS was performed by Lee et al [32] to compare the severity of CP/CPPS symptoms controlling for age, obesity, and metabolic syndrome, between men with serum total testosterone (TT) values $<3.5\text{ ng/mL}$ ($n = 948$) to those above 3.5 ng/mL ($n = 4,740$). Men with low TT values and CP/CPPS exhibited significantly worse total NIH-CPSI scores ($p = 0.003$), including its domains of pain ($p = 0.001$) and QoL ($p = 0.008$). These hypogonadal men were significantly more likely to report moderate to severe prostatitis symptoms and worse LUTS severity than their matched peers, despite non-significant differences in total prostatic volume. Nevertheless, more studies are needed to determine the prevalence of hypogonadism among these patients and determine if TTh has a role in ameliorating the associated voiding symptoms.

Testosterone and Prostate Cancer

Prostate cancer represents the most commonly diagnosed cancer affecting men in the United States and the second most common cause of male cancer-related deaths [33]. While the androgen-responsive growth aspects of the prostate are well recognized and the impact of androgen deprivation on prostate cancer well characterized, the effects of returning hypogonadal men with prostate cancer to a physiologic testosterone level has been more

controversial. For decades, androgen replacement therapy has been considered a contraindication among men with a history of prostate cancer. However, over the last two decades paradigm-changing data has challenged the assertions of Huggins and Hodges [3] and slowly reintroduced TTh in all stages of prostate cancer management from prostate cancer risk reduction in men without prostate cancer to experimental treatments utilizing high-dose TTh in men with castrate-resistant, metastatic prostate cancer.

While a detailed discussion of androgen deprivation therapy for prostate cancer is beyond the scope of this paper, androgen deprivation remains a cornerstone of current prostate cancer treatment. Androgen deprivation is utilized in several clinical scenarios including the management of localized prostate cancer; prostate cancer recurrence following radiation or surgery, in conjunction with radiation or surgery for high-risk but localized prostate cancer; in the initial management of metastatic hormone-naïve prostate cancer; and in the setting of castration resistant prostate cancer [34].

TTh and Prostate Cancer Risk Reduction

5 α -reductase inhibitors (5 α -RIs) have been used as a form of androgen blockade to reduce the risk of prostate cancer. Two landmark studies, the Prostate Cancer Prevention Trial (PCPT) [35] and the Reduction in Dutasteride of Prostate Cancer Events (REDUCE) [36], examined the impact of two 5 α -RIs on the incidence of prostate cancer. By preventing the conversion of testosterone to DHT, 5 α -RIs showed in both studies a statistically significant overall prostate cancer risk reduction of 23–24%. Despite the risk reduction observed with the use of 5 α -RIs, administration of testosterone to supraphysiologic serum levels does not significantly increase the intraprostatic DHT levels. In a recent double-blind, randomized, placebo-controlled trial, 51 healthy eugonadal men were randomized to either receive GnRH antagonist injections and variable transdermal testosterone cream doses (1.25g, 2.5g, 5g, 10g, and 15g) or a placebo injection and placebo transdermal cream [37]. Higher doses of testosterone cream resulted in proportionally higher serum levels of testosterone and DHT and higher intraprostatic testosterone levels; however, intraprostatic DHT levels remained stable after 12 weeks of therapy regardless of the dose administered ($p=0.11$). Moreover, the authors observed stable PSA levels, prostate volumes, and IPSS scores over the 12-week treatment period further supporting the androgen receptor saturation theory. These findings corroborate an earlier study by Marks et al [38] who found similar intraprostatic testosterone and DHT levels after 6 months between hypogonadal men treated with TTh compared to matched, untreated hypogonadal men. While the intraprostatic DHT homeostatic mechanisms are not yet known, homeostasis may be achieved by the reversible conversion of DHT to 5 α -androstane-3 α ,17 β -diol (3 α -diol) by 3 α -hydroxysteroid dehydrogenase (3 α HSD); however, further research is necessary to determine the precise mechanism [39].

Hypogonadism confers an increased risk of developing prostate cancer, higher grade of prostate cancer when detected, and worsens overall cancer-specific survival. In 2006, Morgentaler and Rhoden [40] found a 15.1% prostate cancer prevalence rate among 345 hypogonadal men with a mean age of 58.9 $\pm$ 8.1. Of the 52 patients who were detected to have prostate cancer, 8 had a Gleason score of 7 and 3 had a Gleason score of 8 or higher. Furthermore, men with a total testosterone (TT) level less than 250 ng/dL had a significantly

higher rate of prostate cancer than men with TT levels greater than 250 ng/dL (21.1% vs 12.3%, $p=0.04$). Thirty percent of prostate biopsies in hypogonadal men with a PSA > 2.0 ng/mL were positive for prostate cancer, underscoring the increased risk of prostate cancer in this population. Hoffman et al [41] investigated the relationship between serum testosterone values with clinicopathologic characteristics of prostate cancer in 117 men. Compared to men with normal serum testosterone, men with low serum free testosterone (<1.5 ng/dL) had more frequent positive biopsies, a higher percentage of Gleason biopsy score of 8 or higher; however, this difference was not observed when men were analyzed by low and normal serum total testosterone levels. Finally, Garcia-Cruz et al [42] prospectively analyzed 82 men with high grade prostatic intraepithelial neoplasia (HGPIN) followed over a 2 year period. In this cohort, men with low free and/or low bioavailable testosterone had significantly higher rates of progression from HGPIN to adenocarcinoma of the prostate on repeat biopsy. Thus, the failure to identify an association between disease progression and TTh along with the other studies documenting lower incidence of prostate cancer speak to the potential protective role testosterone in prostate cancer development.

Studies analyzing the association between preoperative testosterone levels and prostate cancer prognosis consistently found better outcomes associated with higher pretreatment testosterone levels. Garcia-Cruz et al [43] prospectively compared the preoperative hormone values of 137 men with Gleason 5+5 with prognostic factors such as PSA, percentage of tumor in the biopsy sample, bilaterality of the tumor, and the D'Amico risk of progression score. Men with lower testosterone values were significantly more likely to have a higher PSA ($p=0.05$), higher clinical staging ($p=0.022$), higher rate of bilateral disease ($p<0.001$) and a higher tumor burden ($p=0.006$). Similarly, when patients were stratified by their D'Amico risk of progression scores, an inverse relationship was observed between mean testosterone values and the D'Amico risk of progression ($p=0.03$). Other studies investigating the risk of testosterone on pretreatment prognostic factors have found a higher positive surgical margin rate [44], higher seminal vesical invasion rate [45], higher risk of patterns 4-5 [46], and higher 5-year PSA recurrence rates [47].

TTh in men with Prostate Cancer on Active Surveillance

Given the large number of men who are diagnosed annually with prostate cancer and the similar growing population of hypogonadal males, several retrospective studies explored the safety of TTh among hypogonadal men with untreated, localized prostate cancer who elected active surveillance (AS). Following an initial case report by Morgentaler [48] describing an 84-year old man with prostate cancer who refused definitive treatment and experienced a declining PSA value over the two-year follow-up period after the initiation of TTh, several small studies examined the impact of TTh on disease progression in the subset of prostate cancer patients on AS. In 2011, Morgentaler et al [49] reported on the short and medium term outcomes of 13 patients with prostate cancer (12 with Gleason 3+3 and one with Gleason 3+4 tumors) and symptomatic hypogonadism treated with testosterone therapy. No change in mean PSA values or prostate volume were observed over a median of 2.5 years of follow-up. More importantly, only two of the 13 patients in this cohort had Gleason score upstaging on re-biopsy and only one underwent radical prostatectomy (RP) with final pathology revealing a Gleason 3+3 pattern with negative margins. In another small series of

seven prostate cancer patients on AS, Morales [50] observed fluctuating PSA responses in men treated with TTh. The fluctuations prompted definitive surgery in one patient, who responded well biochemically to a radical prostatectomy. In 2014, San Francisco et al [51] analyzed what factors increased the risk of progression from AS to definitive treatment in 154 men on AS. Using multivariate regression analysis, the authors found a low free testosterone (<1.5 ng/dL) to associate with a significantly higher risk of progression to definitive treatment ($p = 0.03$). Low free testosterone, particularly values less than 0.45 ng/dL, portended a several-fold increased risk of disease upstaging. While no significant difference was detected using total testosterone threshold values of 250 ng/dL and 300 ng/dL, a threshold value of 346 ng/dL had significant discriminant power with shorter times to definitive treatment for men with total testosterone values less than 346 ng/dL. Most recently, Kacker et al [52] performed the largest retrospective case-control series, which also included men with Gleason 3+4 on AS. Results were favorable for TTh with similar rates of biopsy progression between the two cohorts: 32.1% vs. 43% ($p = 0.28$). Limitations of this study included more extensive biopsy protocols for men not on TTh with 20 core biopsies rather than 12 core biopsies for men on TTh, suggesting possible detection bias. Despite the favorable findings of these studies, appropriate patient selection and supervision are paramount when treating hypogonadal men with active, untreated prostate cancer.

TTh in men after Definitive Prostate Cancer Treatment

Concerns regarding prostate cancer recurrence have historically dissuaded practitioners from supplementing testosterone in hypogonadal men treated by either surgery or radiation. Nevertheless, studies over the last decade have shown that TTh in this population not only ameliorates hypogonadal symptoms and improves quality of life but also does not appear to increase the risk of biochemical recurrence. In 2004, Kaufman and Graydon [53] documented the outcomes of seven men with localized, low to intermediate risk prostate cancer treated with a radical prostatectomy (RP) and TTh post-operatively for hypogonadism. With follow-up ranging from 1 to 12 years, there was no evidence of local recurrence or distant prostate cancer spread in these patients. These findings were corroborated in a case series by Agrawal and Oefelein [54] who also showed no evidence of biochemical recurrence in ten hypogonadal patients with Gleason sums of 6–8 treated with testosterone postoperatively over a median follow-up of 19 months. The largest study examining testosterone replacement in hypogonadal men already treated with RP was performed by Pastuszak et al [55] who compared 103 hypogonadal men treated with TTh to 49 hypogonadal post-prostatectomy men who did not receive TTh. The treatment group consisted of 77 men who had either low or intermediate risk and 26 men with high risk prostate cancer. Patients were followed with serial PSA values assessed every three months after RP with a median follow-up of 27.5 months. Four patients in the treatment cohort experienced recurrence, as defined by consecutively increasing PSA values, compared to eight in the reference group ($p=0.02$), all 12 of whom possessed high risk prostate cancer. While these studies are limited by their small sample sizes and retrospective nature, their findings support the safety of testosterone therapy in post-prostatectomy men.

Evidence suggesting the safety of testosterone therapy after radiation therapy (RT) for low, intermediate, and high risk prostate cancer have also emerged over the last decade. Sarosdy

[56] followed 31 men who had received prostate brachytherapy for low, intermediate and high risk prostate cancer and subsequent TTh for a median of five years. One patient experienced a transient PSA rise after TTh initiation which necessitated TTh cessation as the PSA declined without further intervention. At the conclusion of the study, none of the patients stopped TTh due to possible or confirmed recurrence or progression of their disease. The safety of TTh following brachytherapy was also demonstrated by Balbontin et al [57] who evaluated the clinical and biochemical effects of long-acting testosterone undecanoate injections in a cohort of 20 men with a similar distribution of Gleason scores. The authors observed significantly improved Sexual Health Inventory for Men (SHIM) scores ($p=0.002$) over a median follow-up of 31 months with no prostate cancer progression or recurrence. In a retrospective, multi-institutional study by Pastuszak et al [58], 98 hypogonadal men treated with RT (inclusive of external beam radiation therapy [EBRT], brachytherapy and combined EBRT and brachytherapy) were reviewed over a median follow-up time of 40.8 months. While no significant change in PSA values were observed in RT treated men with low or intermediate risk prostate cancer patient groups, PSA values increased significantly in the high risk group, particularly in those treated with RT without adjuvant androgen deprivation therapy (ADT) prior to initiating TTh. High-risk men who underwent RT and post-operative ADT and subsequent TTh did not have a significant increase in PSA. A total of six men experienced biochemical recurrence (BCR) during the course of this study; four of which had known prostate biopsy and Gleason scores, including two men with intermediate risk and two with high risk prostate cancer. Testosterone therapy was discontinued in three of these patients and restarted in one who had a negative prostate biopsy after his BCR. Based on these studies, TTh appears to be safe for men successfully treated for localized low and intermediate risk prostate cancer with brachytherapy and external beam radiation; however, diligent monitoring and informed consent are necessary until more definitive data are available, particularly in the localized high-risk prostate cancer patients treated with RT.

High-Dose Testosterone and Bipolar Androgen Therapy in men with Castrate-Resistant Prostate Cancer

Androgen deprivation has demonstrable benefits in controlling locally advanced, metastatic prostate cancer and prolonging overall survival; however, a subset of men with advanced disease on ADT will experience biochemical and/or radiographic progression despite androgen blockade, and will develop castration-resistant prostate cancer (CRPC). While the mechanism responsible for the development of castrate resistance is not yet known, molecular studies have identified amplification of high-affinity androgen receptors to compensate for diminished androgen ligand levels, increased levels of enzymes involved in steroidogenesis, production of androgen receptor (AR) mutational variants that are transcriptionally active despite the absence of its ligand, and post-translational modification of the androgen receptor that improve its stability and nuclear localization (reviewed by Wadosky et al [59]). While a direct link between the increased androgen receptor amplification and post-translational modifications, increased levels of steroidogenic enzymes and castrate-resistance has not been discovered, *in vitro* studies have shown the paradoxical effect of tumor growth repression when androgen-independent prostate cancer cell lines (LNCaP) are exposed to high dose testosterone [60]. These findings were recapitulated in two studies, including a murine model by Umekita et al [61], who showed

testosterone propionate (TP) treatment reversed the growth of LNCaP cells xenografts placed subcutaneously into athymic mice, and a subsequent study by Song and Khera [62], who showed LNCaP growth inhibition at testosterone doses starting at concentrations of 4 ng/ml and higher in vitro using a crystal violet mitogenic proliferation assay. These responses are believed to be due to supraphysiologic levels of androgens disrupting the auto-regulatory increase in AR expression by stabilizing ligand-bound AR in the nuclear receptor and inducing double strand DNA breaks at the intronic AR binding sites by creating genotoxic stress and activating endonucleases, such as cytidine deaminase, LINE-1 repeat encoded ORF2 endonucleases, and topoisomerase II beta [63, 64].

In order to exploit the maladaptive AR changes occurring in CRPC cells, high-dose exogenous testosterone and rapid cycling between castrate and supraphysiologic testosterone levels have been utilized to induce apoptosis in CRPC cells. Evidence supporting the potentially therapeutic effect of exogenous testosterone was initially provided in 1967 by Prout et al [4], who documented the impact of TP therapy in 16 prostate cancer patients who had recurred despite bilateral orchiectomy. Although all 16 of these patients experienced disease progression, one patient's response was noteworthy as his general condition and serum alkaline phosphatase levels markedly improved after one month of TP therapy with absence of pain during TP therapy, improved appetite and performance status, and reduction in the size of inguinal lymph nodes from palpable to impalpable nodes. This patient was kept on TP for six months before developing obstructive uropathy requiring transurethral resection of the prostate. Two recent small phase one trials investigated the safety of high-dose exogenous TTh in 25 CRPC patients. Morris et al [65] established the safety of exogenous high-dose testosterone in patients with castration-resistant disease. None of the twelve patients in this study experienced grade three or four toxicities, tumor flare or required opiates for new onset bone pain over a median follow-up time of 84 days (range 23–247 days). While nine of these twelve patients progressed biochemically or radiographically, one patient demonstrated a PSA decline of 50% without radiographic progression and two had less pronounced reductions of PSA (25% and 12% without radiographic progression). In a similar study of 15 patients by Szmulewitz et al [66], prostate cancer patients with disease progression despite ADT and antiandrogen withdrawal were randomized to escalating transdermal testosterone doses of 2.5mg, 5.0mg, or 7.5mg/day. Twelve of the 15 patients in this study progressed with a median time to progression of 9 weeks with no difference between the three doses of transdermal testosterone. In contrast, three patients experienced a decrease in PSA ranging from 16–43% while on treatment and seven experienced stable PSA values for up to 52 weeks before biochemical progression and testosterone discontinuation.

Pilot studies of bipolar androgen therapy (BAT) also show promising results in the treatment of CRPC. By rapidly cycling from supraphysiologic serum testosterone levels to castrate or near-castrate levels of testosterone, apoptosis is induced in the subset of CRPC cells overexpressing AR as supraphysiologic testosterone levels stabilize the ligand-bound AR nuclear receptor and cause double strand DNA breaks followed by apoptosis of ligand-dependent CRPC cells with low AR levels driven by the low androgen state. The safety and efficacy of BAT was established in an open-label, single-arm pilot study of 16 asymptomatic men with CRPC by Schweizer et al [67] with a median follow-up time of 124.5 days.

During the lead-in phase of the study, patients were treated with BAT and etoposide for three cycles to determine their PSA response to combined BAT and etoposide therapy. Seven of the 14 patients demonstrated a PSA reduction on the combination regimen and continued to the second phase of the study and were treated with BAT only. All seven men eventually exhibited biochemical progression with a median time to progression of 221 days (range 95 – 454 days); however, five of these men continued BAT due to the perceived QoL benefit and absence of radiographic progression. Moreover, BAT monotherapy was well tolerated with rare and low-grade adverse events, including nausea, alopecia and elevated creatinine. These results must be interpreted with caution due to the small sample sizes and lack of randomized, placebo-controlled studies to validate the above findings.

Conclusion

Testosterone therapy has gained credibility over the last several decades as a safe co-treatment modality for men with benign prostate conditions, with mounting evidence supporting safety in men with both treated and untreated prostate cancer. Despite the burgeoning body of data claiming safety and efficacy of TTh in these common prostatic conditions, diligent monitoring, appropriate patient selection, and informed consent are critical until more definitive studies are performed.

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Table

Studies Evaluating the Effects of Testosterone on BPH

Author	Follow up (weeks)	Age (years)		Sample Size		Change in IPSS	
		TrT	Control	TrT	Control	TrT	Control
Randomized Controlled Trials							
Paduch <i>et al.</i> 2015	16	52.7	48.4	30	35	-1.1	0.5
Basaria <i>et al.</i> 2015	26	66.9	68.3	129	119	1.02	0.56
Meuleman <i>et al.</i> 2015	28	58.6	58.4	69	71	-1.33	0.42
Konaka <i>et al.</i> 2015	52	65.7	67.6	120	100	-0.56	0.88
Tan <i>et al.</i> 2013	48	53.1	53.8	56	58	-2.5	-1.6
Behre <i>et al.</i> 2012	28	61.9	62.1	166	155	-0.7	0.6
Shigehara <i>et al.</i> 2011	52	72	68.9	23	23	-3.2	-0.5
Kalinchenko <i>et al.</i> 2010	30	51.6	52.8	104	65	-0.6	-0.5
Srinivas-Shankar <i>et al.</i> 2010	28	73.7	73.9	132	132	-0.2	0.4
Kenny <i>et al.</i> 2010	52	77.9	76.3	53	46	0.1	-0.1
Emmelot-Vonk <i>et al.</i> 2008	28	67.1	67.4	113	110	0.3	0.1
Chiang <i>et al.</i> 2007	14	47.9	56.1	20	17	-1.9	-2
Marks <i>et al.</i> 2006	28	64.5	65.75	20	19	-0.25	-0.5
Kenny <i>et al.</i> 2001	52	76	75	20	24	0.3	1.8
Meta-Analyses							
Kohn <i>et al.</i> 2016	---	63.1	64.4	1044	871	-0.41	0.12
Cui <i>et al.</i> 2013	---	---	---	286	277	Mean Difference = 0.31	