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Testosterone Effects on the Prostate Gland: Review of Pathophysiology and considerations in Prostate Cancer

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Abstract

Testosterone replacement therapy is currently contraindicated in men with a history of prostate cancer. Despite this, new data is emerging in multiple retrospective studies and case reports of testosterone replacement therapy use after treatment for prostate cancer with results that call into question the contraindication. The goal of this paper is to review the association between androgens and the prostate gland physiology and pathology, and analyze the data available concerning the issue of testosterone replacement therapy in men with a history of prostate cancer. We suggest that testosterone replacement therapy may be considered as a reasonable therapeutic option for selected patients with prostate cancer history, but prospective studies are needed to further examine the safety and benefit.

Introduction

Nearly 2.8 million men are living with Prostate cancer (PCa) in the United States [1]. Patients and health care providers remain concerned that testosterone replacement therapy (TRT) may cause or "unmask" PCa. However several studies have shown no meaningful correlation between simultaneous measures of prostate specific antigen (PSA) and serum testosterone among samples of hypogonadal men receiving TRT and untreated eugonadal men [2,3] and observations from three registries of over 1000 hypogonadal men receiving TRT for up to 17 years concluded that TRT does not increase the risk of PCa [4]. For over half a century, testosterone therapy has been contraindicated in men with PCa without regard to the length from diagnosis or severity of disease. With increasing number of men presenting to primary care clinics with symptoms of hypogonadism and growing appreciation of the negative clinical impact of testosterone deficiency, there has been a re-evaluation of the long-held prohibition against TRT in all men with a history of PCa. Huggins and Hodges published the first article in 1941 on the proliferation of PCa cells exposed to hormonal stimulation that became the basis for this contraindication [5].

The androgen hypothesis was proposed over seventy years ago. This was based on a small study that in advanced PCa, the fluctuations in serum acid phosphatase were influenced by androgen supply or withdrawal, and that surgical castration could induce disease regression [5]. This led to the belief that androgens accelerate the growth of neoplastic tissue in the prostate gland or are the cause of newly developed PCa. The use of androgen deprivation therapy in the treatment of advanced PCa has given further validity to this hypothesis in recent years [5,6]. In early studies, increased testosterone levels were associated with the proliferation of PCa cells. Current guidelines contraindicate exogenous testosterone use in patients with a history of PCa [7]. Over seventy years after the study by Huggins and Hodges, the question now is has there been enough evidence to uphold the contraindication for testosterone use in every patient with PCa? This article will review the normal biological relationship of androgens on the cells in the prostate gland, the association between testosterone and PCa, and finally some evidence of treatment of men with previous PCa and the outcomes after TRT.

Biology of Androgens on Prostate Tissue

Formation of the hypothalamic-pituitary-gonadal axis starts to occur around 6 weeks post-conception. Gonadotropins, released at 14 weeks of gestational life from the anterior pituitary, exhibit a stimulatory effect on the Leydig cells of the testes and adrenals where 90% and 10% of testosterone is produced in the body respectively [8]. The peak influence on gonad development does not really occur until at least 20 weeks gestation. Testosterone is thought to play a role in the neonatal period in determining spermatogenic capacity as well as the development of the phallus. At puberty testosterone levels rapidly increase. Longitudinal studies show that after the third decade in life testosterone levels begin to decrease by about 3.2 to 3.5ng/dL per year in healthy men [9,10].

Testosterone's function during puberty includes development of the penis, enlargement of the prostate and seminal vesicles, increasing bone mineral density, and redistribution of body fat and hair. Androgens are essential for prostatic development, growth and function. Testosterone diffuses into the prostate along a concentration gradient. It is reduced to dihydrotestosterone (DHT) by 5α-reductase (5-AR). Prostate tissue has a higher affinity for DHT than testosterone. DHT is also intrinsically about twice as potent as testosterone at stimulating prostate growth [11]. DHT is the main androgen in the prostate gland that controls cell division [12]. The DHT is bound to the androgen receptor in the

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prostatic cells and this complex influences androgen-responsive genes leading to prostate growth and the production of PSA [13]. The prostate gland is about the size of a rice kernel prior to puberty, but it grows rapidly with androgen stimulation to its adult size [14]. In adults, the prostate gland is typically described as walnut shaped; it surrounds the urethra and provides the majority of ejaculatory liquid that accompanies semen.

Prolonged testosterone exposure, as seen in puberty, or increased levels of circulating testosterone such as seen with TRT, leads to increased expression of 5-AR, particularly the type 1 isoenzyme which is expressed in the prostate [15,16]. Increased 5-AR results in increased conversion of testosterone to DHT, which also leads to stimulation for cell division and prostate development. DHT is a more potent stimulator of prostate growth than testosterone so in theory, the production of DHT promoted by 5-AR leads to prostate enlargement and possible promotion of proto-oncogene activation and PCa development. The stimulus that differentiates normal from malignant prostate tissue growth is not clear. The most consistent effects of testosterone and DHT on the prostate are shown by poorly developed prostates in men with congenital 5-AR deficiency and a reduction in prostate volume and PSA production in men using the medications that inhibit 5-AR, such as finasteride or dutasteride. DHT is proposed to enhance transactivation of androgen receptor genes at their ligand binding domain which stimulates mutations in the androgren receptors. These mutations are rarely found in intitial phases of prostate cancer but are more common in castrate-resistant forms of PCa [17,18].

Testosterone also contributes to prostate function independently of DHT, as luteinizing hormone-releasing hormone agonists (LHRHa) produce greater reductions in prostate volume and PSA than 5-ARIs [15]. In the absence of androgens, for example in pre-pubertal castration or hypopituitarism, benign prostatic hyperplasia (BPH) does not occur. The prevalence of BPH increases from 40% to 90% between the ages of 60 and 90 year-old men despite falling peripheral testosterone levels [19]. It is not clear whether BPH is a risk factor for PCa, both diseases have increased incidence as men age and yet there has been no direct correlation linking BPH to PCa development.

Over the last decade, the androgen hypothesis and the relationship of testosterone to PCa has been more clearly defined. While it has been established that surgical or chemical castration is an essential strategy in the management of advanced PCa, the assertion that testosterone directly causes growth of PCa has been challenged by the saturation model. This shows that maximal androgen-androgen receptor binding occurs at fairly low androgen concentrations in the prostate tissue. Hence, while PSA and prostate tissue are very sensitive to changes in testosterone concentrations at low levels, once androgens have saturated the androgen receptor, increasing testosterone concentrations do not change PSA or prostate tissue growth significantly [15]. The level where the linear correlation ceases between testosterone levels and PCa growth is near the serum testosterone seen in castrate males (about 250ng/dL) [20]. Beyond this, prostate tissue will no longer respond as actively to androgen levels and therefore the risk of PCa does not correlate to rises in testosterone levels above this threshold, as would be observed in non-castrate and eugonadal men.

Prostate Cancer Risks: Not Everything is Related to Hormones

The precise factors responsible for a potential induction of PCa are still not fully understood. Prostate cancer development appears to be a multistep process in which chronic/recurrent inflammation, dietary and inherited factors are thought to be responsible for initiation and promotion of PCa. Proliferative inflammatory atrophy and high grade prostatic intraepithelial neoplasia represent precursors that may progress to latent low grade tumors, which then progress slowly for decades to clinically significant invasive disease [16]. In 2006, a study by Marks showed that even with significant increases in serum testosterone levels with TRT, the level of testosterone in the prostate tissue and gland volume after six months was not significantly different than controls who received placebo [21]. It was also interesting that during the six months, 6 men out of the 40 developed prostate cancer, and 4 in the control group and only 2 receiving TRT.

One of the strongest risk factors for PCa is age. There are cases of prostatic intraepithelial neoplasia, a precursor to PCa, in men as young as their twenties suggesting that the initiating events that lead to clinically relevant PCa are likely to occur at a young age [22,23]. However, the incidence of PCa is the lowest during the 2nd and 3rd decades when serum T levels are at their highest. The incidence of PCa rises dramatically in men after the age of 50, even as the testosterone levels are declining [24]. These data indicate that serum testosterone levels do not have a significant role in the development of PCa.

The risk of cancer has not been directly correlated to testosterone exposure such that supra-physiologic and physiologic levels of testosterone were not shown to alter serum PSA, prostate volume or PCa [25-27]. The incidence of PCa is less in individuals with low testosterone levels, for example eunuchs and castrated males, [28-30] but, on the other hand, elevated levels of testosterone are not typically seen in individuals with PCa [31-33]. On the contrary, many studies show that low testosterone levels <250ng/dl are significantly associated with an increased rate of PCa development, higher Gleason scores, more advanced disease, and higher recurrence after radical prostatectomy [34-38]. However it may also be that low pretreatment testosterone levels are a consequence of PCa rather than aggressive PCa being a result of the low testosterone. Several studies have suggested that PCa may result in suppression of testosterone via reduced gonadotropins [39].

Other factors associated with increased risk of PCa include a family history in a close relative, Scandinavian race, African American race in the United States at any age, cigarette smoking, and increased dietary fat intake [40]. Long term prospective studies looking at the incidence with these risk factors are still lacking. A retrospective study, spanning 13 years, found that that African American men developed PCa at a younger age, had higher Gleason scores, and larger palpable tumors [41].

There is increasing evidence that obesity is associated with elevated incidence of aggressive PCa, increased risk of biochemical failure following surgery or radiotherapy, higher frequency of complications following androgen-deprivation therapy, and increased PCa-specific mortality [42]. Obesity is associated with metabolic syndrome, many components of which have been established as risk factors for PCa. A population based study of men in the West Indies followed for nine years showed that men with the largest waist-hip ratio (WHR), which included a waist circumference >99cm, had two-fold increased risk of PCa [43]. Similar findings were seen in subjects from the North Carolina and Louisiana Prostate Project, in which more aggressive PCa was seen in obese subjects as well as normal weight subjects who were African American (OR 1.42, 95% CI 1.00–2.00 and OR 2.69, 95% CI 1.36–5.30, respectively). The most significantly increased risk of aggressive PCa was over three-fold seen in morbidly obese African Americans compared to normal weight Caucasian Americans (OR 3.90, 95% CI1.97–7.75) [44].

Testosterone and Prostate Cancer: History to the link

Prior to the 1940's, the relationship between hormones and PCa was not clear. In the study by Huggins, elevation in acid phosphatase was used as an indicator for PCa recurrence [5]. Nowadays, instead of acid phosphatase, increase in PSA is used as a marker for disease recurrence [45]. Of the three men who received testosterone, all experienced a rise in their acid phosphatase levels after 18 days, but only one had a persistent increase after stopping TRT. This led to the belief that a higher testosterone concentration leads to PCa growth or that "cancer of the prostate is activated by androgen injections"[5].

Currently there are no prospective randomized controlled studies showing a significant relationship between testosterone use and

the development of PCa [46]. In fact a meta-analysis in 2008 with eighteen studies and 3,900 subjects showed there was no significant relationship between circulating hormones and PCa development [47]. Studies have continued to look at the relationship between testosterone as predictor for PCa. Isom-Batz et al. and Lane et al. analyzed pre-operative testosterone levels in men already diagnosed with localized PCa and found that lower levels correlated with advance pathological stage of cancer but not biochemical progression of disease [34,48]. There have been multiple studies (n=13,669 total men) with insignificant or negative associations between PCa risk and any of the endogenous androgen levels [39,49]. The use of androgen deprivation therapy (ADT) as an effective treatment for aggressive metastatic PCa gives another reason for testosterone avoidance in this population. But it does not necessarily mean that an increase in serum testosterone invariably stimulates tumor growth. However the clinical implications of giving the patient a hormone that was meant to be suppressed to a level of less than 50ng/dl seems counterintuitive [50].

Treating Men with Prostate Cancer who are Hypogonadal

The relationship between sex hormones and the development of PCa is complex and is not well established enough to make definite conclusions about its risk for PCa development. The majority of information about TRT in men previously treated for PCa comes from chart reviews, case reports, or open-label studies. In most cases there was no biochemical recurrence of PCa after follow up ranging 1 month to 12 years [2,51-55]. A few studies have resulted in PSA

Table 1: Cases of testosterone replacement therapy and outcomes in men treated for prostate cancer. Treatments varied but overall only 2 of 276 men given testosterone after treatment had biochemical reoccurrence (0.7%).

Reference	Study Design	No. of Subjects	Treatment	Gleason Score (number treated)	Type of TRT (number treated)	Median Follow Up (range)	PCaR	BCR	Summary of Findings
Kaufman 2004 [52]	Retrospective review	7	RRP	6 (n=6) 7 (n=1)	patch (n=3), gel (n=2), IM injection (n=2)	18 mo (6-12 years)	None	No	TRT for the management of hypogonadal symptoms shown to be beneficial and safe, with no evidence of local recurrence. Limitations: short follow up, small number studied
Agarwal P 2005 [51]	Cohort	10	RRP	6 (n=2) 7 (n=7) 8 (n=1)	Topical (n=7), transdermal (n=1), IM (n=2)	19 mo	None	No	Total Testosterone increase significantly (p=0.0002); Quality of life improved significantly (p=0.00005)
Sarosdy 2007 [54]	Observational	31	BRT +/- EBRT +/- ADT	5 (n= 3) 6 (n=19) 7 (n=6) 8/9(n=3)	IM-> later switched to patient preference	30 mo (1.5-9 years)	None	No	TRT may be used with caution and close follow-up is necessary after patients received brachytherapy. There were 3 patients with transient increase in PSA,none was considered significant.
Nabulsi 2008 [55]	Prospective	22	RRP	6-58%* 7-32%	Transdermal	24 mo (14-30 mo)	Yes	1	Only 1/22 (4.5%) patients had a PSA recurrence at 17 months post-RP.
Morales 2009 [58]	Prospective	5	EBRT	6 (n=2) 7 (n=1) 8 (n=2)	Varied ‡	15 mo (6-27 mo)	None	No	One discontinued treatemnt due to headaches, all reported improvement in symptoms of hypogonadism.
Morgentaler 2009 [60]	Case report	1	AS	6	Gel	48 mo	None	No	Decline in PSA seen after TRT for 2 years. No reoccurence of Pca seen.
Khera 2009 [53]	Retrospective	57	RRP	≤6 (N=24) 7 (N=26) ≥8 (N=4)	Gel	13 mo (7-17 mo)	None	No	Testosterone level improved without increase in PSA.
Morales 2011 [62]	Observational	7	AS	6 (n=5) 8 (n=1) 1-NA	IM (n=5) oral (n=1), gel (n=1)	33 mo (6-96 mo)	Yes	1	One patient continued TRT for four years without incident. Another patient has significant rise in PCa with decrease after intermittent discontinuation of therapy. A younger subject had rise in PSA after TRT initiation and underwent biopsy which was positive for PCa (two prior were negative).
Morganteler 2011 [63]	Retrospective	13	AS	6 (n=12) 7 (n=1)	IM (n=3), gel (n=10)¶	30mo (12-97mo)	None	No	7 men had received TRT prior to PCa diagnosis. Two men had biopsies suggestive of disease upgrading but no cancer progression.
Pastuszak 2013 [61]	Retrospective	103	RRP	≤7 (N=77) ≥8 (N=26)	Not specified	27.5	None	No	Overall 15% of patients in the high risk treatment group had suspected BCR, lower than the 18% to 32% recurrence rate for patients not receiving TRT after RP.
Balbontin 2014 [59]	Prospective	20	BRT	5 (n=1) 6 (N=15) 7 (N=3) 8 (N=1)	IM injection	31 mo	None	No	PSA decreased compared to control.
Total		**276**			**Average**	**26.2mo**		**2(0.7%)**	

Abbreviations: PCaR: Prostate Cancer Recurrence; BCR: Biochemical Recurrence; MO: Months; TRT: Testosterone Replacement Therapy; PCa: Prostate Cancer; RRP: Radical Retropubic Prostatectomy; BRT: Brachytherapy; AS: Active Surveillance; EBRT: External Beam Radiotherapy; *-actual number not provided; ‡-specific treatment type not provided; NA: Not Available; ¶-4 patients switched from IM to other formulations in middle of study

increases between 4.5% to 60% without progression or recurrence of PCa [55,56]. In a meta-analysis done in 2015, Klap et al. looked at prospective studies analyzing the relationship between testosterone levels and PCa over the last twenty years. The results were varied but overall the conclusion was that the use of exogenous testosterone had "little if any risk"[57]. However, the absolute risk was not zero, so continued observation and monitoring of PSA and digital rectal exams continue to be highly recommended. Yet there is reluctance to prescribe TRT due to the perceived risk of stimulating PCa progression, particularly in survivors of PCa.

Recent reports of men treated with TRT after diagnosis of PCa are summarized in (Table 1) [51-55,58-63]. A total of 276 men followed an average of 26 months showed no sustained increase in PSA or cancer recurrence. Most of the studies are retrospective, or prospective with a small number of subjects. Of the eleven studies, 5 had subjects treated with radical prostatectomy, 3 with brachytherapy, 2 with external beam radiation therapy (EBRT), and 3 with active surveillance. The findings suggest that TRT prescribed for improvement of quality of life had no significant adverse effects. Only 2 patients out of 256 had evidence of biochemical re-occurrence (0.7%). This, in fact, is less than the 1% risk seen in the general population and in men diagnosed with PCa after TRT use. Dupree et al. also advocated for treatment of hypogonadism with TRT in men with history of PCa when the benefits outweigh the risks [64]. Hypogonadism itself has in fact been associated with a higher incidence of PCa at 14% [65], more aggressive Gleason scores [66,67], increased rate of biochemical recurrence and worse 5-year survival rates (67.8% in hypogonadal men vs. 84.9% in eugonadal men) [36,68,69]. Morgentaler asked a very good question in his analysis of the literature available in 2006 "Since prostate cancer is so common, how does one know that TRT had anything at all to do with the subsequent identification of prostate cancer?"[70]. This question is still relevant today.

Conclusion

One in 7 men will be diagnosed with PCa during his lifetime, and PCa is the second leading cause of cancer death in American men, yet most men diagnosed with PCa do not die from it. As life expectancy is increasing, many men with a previous history of treated PCa present with symptoms of hypogonadism associated with low testosterone levels and request TRT. TRT may be associated with decrease in fat mass, increase in lean mass, improvement in bone density and overall health improvements in men with hypogonadism. The use of TRT in men with PCa is controversial, with limited published safety data, but studies in the last decade regarding TRT use after PCa treatment question old beliefs. There is new evidence suggesting that TRT may be considered in selected men with clear indications.

Prospective studies are needed to examine the safety and benefit of TRT in hypogonadal patients in remission from PCa and those treated with active surveillance. Until such data are available, administration of TRT to patients whose initial cancer characteristics were of low risk and who have remained free of cancer for a prudent time may be considered. This should be undertaken cautiously, after a comprehensive discussion of the potential risks and benefits, and under the guidance of an endocrinologist, and either an oncologist or urologist. Before starting treatment, restaging should be considered and a clear surveillance protocol for PCa recurrence should be instituted.

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