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Androgen Replacement Therapy After Prostate Cancer Treatment

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Abstract Historically, testosterone supplementation has been avoided in men with a history of prostate cancer because of concern about prostate cancer progression or recurrence. However, recently published data suggest that this concern may not be well founded. The recurring presence of prostate-specific antigen in men with hypogonadism being treated with testosterone after prostatectomy is far less than the expected natural recurrence rate of the disease. There are many theories (including the prostate saturation theory) that may help us understand why testosterone may be safely administered in men with hypogonadism after surgical treatment of prostate cancer. Finally, because patients with hypogonadism already may be at a significant disadvantage in recovering their erectile function after prostatectomy, they perhaps should receive special consideration as candidates for androgen replacement therapy.

Keywords Testosterone · Prostate cancer · Prostatectomy · Hypogonadism · Androgen

Introduction

Historically, testosterone supplementation has been avoided in men with a history of prostate cancer because of the fear that testosterone supplementation may increase the incidence of prostate cancer progression and recurrence [1•]. However, the data to support this theory are not well founded and recently have been challenged by numerous studies [1•, 2, 3]. About 217,730 new cases of prostate cancer were diagnosed in 2010, and about 32,050 men died of the disease [4]. If we assume that 39% of men over the age of 45 years are hypogonadal [5] and that most men being diagnosed and treated for prostate cancer are over the age of 45 years, this results in a significant number of patients with hypogonadism after prostate cancer treatment. Traditionally, these patients have been denied testosterone replacement therapy (TRT).

It is clear that testosterone deficiency can have a negative impact on a man's quality of life, including decreased energy and libido, erectile dysfunction, depression, increased body fat, decreased bone mineral density, and decreased muscle mass [5]. Furthermore, TRT has been shown to reverse the signs and symptoms of hypogonadism [6, 7].

One could argue that men with hypogonadism who have undergone a radical prostatectomy (RP) are much more likely to need testosterone supplementation (or to have lower testosterone levels) than other men with hypogonadism without a history of prostate cancer. After prostate cancer surgery, men are more likely to suffer from depression, erectile dysfunction, decreased sexual performance, and decreased libido. These symptoms are also seen in men with low serum testosterone levels. Thus, hypogonadal men following a prostatectomy may be at an increased risk of suffering from these symptoms, and these symptoms may be alleviated significantly by TRT in these men. A decision to deprive these men of testosterone supplementation should be based on conclusive evidence that giving these men testosterone supplementation would increase the risk of prostate cancer progression and recurrence. This conclusive evidence has not been found.

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Testosterone and Prostate Cancer

While there is strong evidence to indicate that reducing dihydrotestosterone (DHT) levels may decrease the development of prostate cancer [8–10], there is no convincing evidence to show that giving testosterone increases the incidence or recurrence of prostate cancer. The historical concern regarding the use of testosterone in patients with prostate cancer comes from the work of Huggins and Hodges [11] in 1941, which demonstrated that a reduction in testosterone by castration caused metastatic prostate cancer to regress and that administration of exogenous testosterone promoted prostate cancer growth. However, more recent studies question the concern that exogenous testosterone promotes prostate cancer growth [12].

The theory that raising the serum testosterone level of a man with hypogonadism can result in an increased incidence of prostate cancer is not supported by any recent data. Shabsigh et al. [13•] conducted a systematic review of the literature assessing the risk of prostate cancer in men being treated for hypogonadism with TRT. They found 11 placebo-controlled randomized studies, 29 non–placebo-controlled studies of men with no prostate cancer history, and four studies of men with hypogonadism with a history of prostate cancer. Of the studies that met inclusion criteria, none demonstrated that TRT in men with hypogonadism increased the risk of prostate cancer or increased the Gleason grade of cancer detected. Furthermore, TRT did not have a consistent effect on prostate-specific antigen (PSA) levels. Similarly, Calof et al. [14] performed a meta-analysis of 19 placebo-controlled TRT trials in men with hypogonadism and found no higher risk of prostate cancer in men being treated with testosterone than in men receiving a placebo. Finally, Roddam et al. [15] studied sex hormone levels and the risk of developing prostate cancer in 3,886 men with prostate cancer with over 6,438 men without prostate cancer serving as age-matched controls. They found no relationship between the risk of developing prostate cancer and serum concentrations of testosterone, free testosterone, and DHT levels.

Effects of Testosterone on Changes in Prostate-specific Antigen and Benign Prostate Growth

To better understand the risks of testosterone supplementation after prostate cancer treatment, one must understand how testosterone affects prostate tissue growth and changes in PSA. Numerous studies have demonstrated that there is no significant increase in PSA levels upon administration of testosterone [16]. In fact, even raising testosterone to supraphysiologic levels has not resulted in an increase in serum PSA levels. Bhasin et al. [17] administered testosterone enanthate, 600 mg, or placebo weekly for 10 weeks to 43 healthy young men. Although testosterone levels greater than 2,800 ng/dL were seen, there were no significant increases in PSA levels or prostate growth. Similarly, Cooper et al. [18] randomized 31 young healthy men to receive 100, 250, or 500 mg of testosterone via intramuscular injection once a week for 15 weeks. Supraphysiologic serum testosterone levels of 1,138 and 1,994 ng/dL were seen at doses of 250 and 500 mg, respectively. No significant change occurred in the prostate volume or serum PSA levels at any dose of exogenous testosterone.

While previous studies have found no correlation between testosterone levels and PSA [19–21], there are recent data to suggest that PSA levels do rise after testosterone administration, but only in men who are severely hypogonadal. In a study by Khera et al. [22], 461 men followed in a national testosterone registry were divided into patients with baseline testosterone values above and below 250 ng/dL. Patients with baseline serum testosterone levels less than 250 ng/dL were further subdivided into three groups (testosterone levels of <150, 150–200, and >200 ng/dL). At baseline, there was no significant difference in PSA values between patients with serum testosterone values above and below 250 ng/dL (1.05±0.91 vs 1.2±1.2 ng/mL [$P>0.05$]). However, at baseline, there was a significant difference in PSA values between patients with serum testosterone values above and below 200 ng/dL (1.24 vs 0.88 ng/mL, respectively [$P=0.02$]). Furthermore, after 6 months of TRT, there was a significant increase in PSA of 0.32 ng/mL in patients with baseline serum testosterone values less than 250 ng/dL. Patients with baseline serum testosterone values greater than 250 ng/dL did not experience any increase in PSA values after 6 months of TRT (change in PSA $= -0.03 \pm 0.56$). This study is the first to demonstrate correlation between the severity of hypogonadism and changes in PSA values.

Finally, TRT in hypogonadal and eugonadal men has not been shown to significantly increase prostate volumes or worsening of urinary symptoms [18, 21, 23]. Even at supraphysiologic levels of testosterone (>1,138 to 1,994 ng/dL), Cooper et al. [18] found no significant increases in prostate volume.

Prostate Saturation Model

If raising serum testosterone levels does not result in any significant rise in PSA levels, then one may ask how lowering serum testosterone values significantly reduces PSA levels into undetectable ranges. This phenomenon is seen when luteinizing hormone–releasing hormone (LHRH) agonists are given to men with a history of

prostate cancer. The prostate saturation theory offers a likely explanation for these findings. It is known that androgen receptors have a finite ability to bind to androgens [24, 25]. The prostate saturation theory suggests that PSA levels and prostate tissue growth are sensitive to changes in serum testosterone levels only at low levels of serum testosterone [26••] (Fig. 1). As the serum testosterone levels rise, the androgen receptors within the prostate become saturated, at which point PSA levels and prostate growth are no longer sensitive to changes in serum testosterone levels.

A study by Marks et al. [21] on the effect of TRT on prostate tissue in men who had late-onset hypogonadism helps explain the prostate saturation theory. In this randomized, double-blinded, controlled trial, 40 men with hypogonadism were treated with testosterone enanthate, 150 mg, or placebo intramuscularly every 2 weeks. Prostate biopsies were performed at baseline and at the end of 6 months. Serum testosterone increased from 282 to 640 ng/dL in the treated men. In contrast, there was no significant change in testosterone levels within the placebo-treated group (282 to 273 ng/dL). Testosterone and DHT concentrations within the prostate did not change significantly in either group. Treatment-related changes in prostate histology, PSA, tissue biomarkers, gene expression, or cancer incidence or severity were not evident. These data suggest that while 6 months of TRT normalizes serum androgen levels, it appears to have little effect on prostate tissue androgen levels and androgen-dependent cellular functions.

While androgen receptors in benign prostate tissue appear to become saturated, one may argue that prostate cancer cells may behave differently and their androgen receptors may not become saturated. However, there are several studies that support the theory that androgen receptors within prostate cancer tissue also may become saturated. In a study by Heracek and colleagues [27], no significant correlation was found between intraprostatic and serum testosterone levels in patients who had benign prostatic hyperplasia (BPH) or prostate cancer. In this study, serum samples were analyzed for testosterone and DHT in 75 patients who had prostate cancer and 51 patients who had BPH. They found significantly higher intraprostatic concentrations of testosterone in men who had prostate cancer as compared with men who had BPH (4.6 vs 3.4 ng/dL, respectively; $P<0.05$). Similarly, higher intraprostatic DHT concentrations were found in patients who had prostate cancer than in men who had BPH (8.9 vs 6.4 ng/dL, respectively; $P=0.01$). There were no differences in serum levels between the two groups of patients. Most importantly, there were no correlations between tissue and serum testosterone and DHT levels in either group of patients. These data suggest the possibility of androgen receptor saturation in prostate cancer tissue, although at higher levels than in benign prostatic tissue. In another study, Tomera and colleagues [28] did not notice any increase in PSA level above baseline in men being treated for metastatic prostate cancer with LHRH agonists alone. The testosterone flare did not result in any increase in PSA or prostate cancer growth despite the mean PSA starting at 500 ng/mL. These data also suggest that androgen receptors in prostate cancer cells may become saturated and higher levels of serum testosterone may not result in any further increase in PSA levels.

The prostate saturation theory helps us understand why raising testosterone levels to supraphysiologic levels does not increase PSA levels or prostate growth. It also explains why reducing serum testosterone to castrate levels results in a significant drop in PSA values. Finally, this theory also explains why greater increases in PSA are seen in patients with severe hypogonadism receiving TRT, and not in mildly hypogonadal or eugonadal patients.

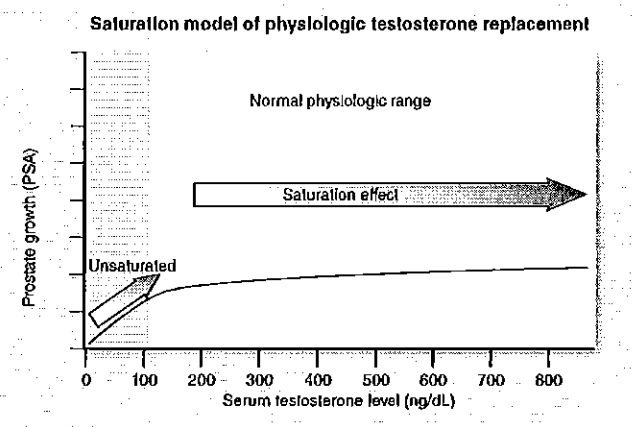

Fig. 1 Prostate saturation model. This model suggests that androgen receptors in the prostate reach a saturation point and that increased prostatic growth or changes in PSA are not seen at higher levels of serum testosterone. PSA—prostate-specific antigen

Testosterone Supplementation After Prostate Cancer

Thus far, there has been a paucity of publications assessing testosterone supplementation in patients after prostatectomy. To date, only three retrospective studies have been published in peer review journals, with a total of 74 patients receiving testosterone after an RP [29–31]. In all three studies, there was not a single recurrence of measureable PSA. Kaufman and Graydon [31] followed seven symptomatic patients with hypogonadism treated with TRT after RP for up to 12 years. These patients experienced symptomatic improvement in

hypogonadal symptoms without any increase in PSA. Agarwal and Oefelein [30] also reported on a small series of 10 patients with hypogonadal symptoms treated with TRT after RP. At a mean follow-up of 19 months, there were no increases in PSA values associated with a significant increase in serum testosterone from 197 to 591 ng/mL. Finally, Khera et al. [31] published a study of 57 patients with hypogonadal symptoms treated with testosterone gels for a mean follow-up of 13 months. While there were no increases in PSA values during TRT, there was a significant improvement in serum testosterone values from 255 to 459 ng/dL.

Another recent study (presented as an abstract) assessed 133 patients with hypogonadism with history of RP who were treated with TRT [32]. Of these patients, 21 were classified as high risk (Gleason score ≥8, positive margins, or node-positive disease). Among high-risk patients, eight patients had a Gleason score of eight or greater, 16 had positive margins, and one patient had a positive lymph node. Patients were given TRT for symptomatic hypogonadism after RP. Serum PSA and testosterone levels were measured every 3 months. There were no PSA recurrences, and there were no statistically significant increases in PSA over the course of treatment. Serum testosterone levels increased from 262 to 418 ng/dL. Due to the high-risk nature of these patients' tumors, one would have expected a higher rate of PSA recurrence due to the natural progression of the disease.

There also have been studies assessing the use of TRT after brachytherapy and radiation therapy in patients with prostate cancer. Sarosdy [33] evaluated TRT in patients with prostate cancer who were treated with brachytherapy. In this study, 31 men were followed for a median of 5 years after starting TRT. Although testosterone levels increased significantly, none of the patients stopped TRT because of cancer recurrence, and none of the patients experienced cancer progression. Morales et al. [2] published a study of five patients with hypogonadism treated with TRT after external beam radiation for prostate cancer. None of the patients in this series developed a biochemical recurrence even up to 27 months after treatment.

Several other abstracts have been presented at national conferences assessing the use of TRT in patients with prostate cancer after treatment with radiation therapy or RP [33–35]. In all three of these studies, there were only two PSA biochemical recurrences. When including all abstracts and publications, to date, there have been a total of 292 patients treated with testosterone after prostate cancer, and the risk of recurrence is less than 1%. This is far less than the expected natural recurrence of the disease. Although most patients with prostate cancer treated with local therapy are cured, about 15% to 40% will experience a biochemical PSA recurrence [36, 37]. The recurrence rates in these series of men being treated with TRT after treatment of prostate cancer are even lower than patients with favorable pathology after RP and not treated with testosterone [38]. Could testosterone supplementation have a protective effect in men with a history of prostate cancer? There are data to suggest that androgens may have a beneficial effect on prostate cancer by promoting a less aggressive phenotype via the androgen receptor [39, 40].

Low Testosterone Levels and Prostate Cancer

There are data to suggest that low levels of testosterone are more likely to be associated with prostate cancer development [19, 41], more aggressive prostate cancer [19], and greater chance of prostate cancer recurrence after radical prostatectomy [42].

Hoffman et al. [19] investigated the relationship of serum free and total testosterone to the clinical and pathological characteristics of prostate cancer. Low free and total testosterone levels were defined as less than 1.5 ng/dL and 300 ng/dL, respectively. These authors retrospectively evaluated 117 patients diagnosed with prostate cancer and found that patients with low serum testosterone had an increased mean percent of positive prostate cancer biopsies compared to patients with normal serum testosterone values (43% vs 22%, respectively [P= 0.013]) and an increased incidence of a biopsy Gleason score of eight or greater (7 of 64 vs 0 of 48, respectively, [P=0.025]).

Yamamoto et al. [43] evaluated 272 patients undergoing RP and correlated their serum testosterone levels with PSA and risk of PSA recurrence. Of the 272 patients, 49 had low (<300 ng/dL) and 223 had normal preoperative testosterone levels. Preoperative serum testosterone levels were an independent and significant predictor of subsequent PSA recurrence along with Gleason score (P=0.006), surgical margin status (P=0.0001), and PSA (P=0.0001). After 5 years, the PSA failure-free survival rate of the patients with low preoperative serum testosterone was significantly worse than that of men with normal serum testosterone (67.8% vs 84.9%, respectively; P=0.035). The investigators concluded that preoperative serum testosterone levels are an independent and significant predictor of PSA failure after RP in patients with clinically localized prostate cancer.

Although there appears to be an association between low testosterone and prostate cancer, one must be careful in assuming causality. There are data to suggest that it may not be low testosterone causing prostate cancer, but rather prostate cancer may be causing the low serum testosterone. This phenomenon can be explained by the fact that after RP, serum testosterone levels have been shown to rise significantly [43, 44]. However, similar studies have demonstrated that there are no changes in serum testoster-

one levels after transurethral resection of the prostate for BPH [44–46]. These data suggest that prostate cancer may exert an inhibitory effect on testosterone synthesis.

Testosterone Replacement Therapy in Men With Active Prostate Cancer

It is well known that the risk of occult prostate cancer in the community is one in seven men [47]. If one assumes that testosterone supplementation promotes prostate cancer growth and progression, then one would assume that the incidence of prostate cancer in men being treated with testosterone supplementation would be higher than that in men not being treated with testosterone supplementation. However, the risk of developing prostate cancer is identical in both of these groups. In fact, it would not be unreasonable to assume that if a clinician were treating 35 men with hypogonadism with testosterone supplementation, he or she could be treating up to five men with active prostate cancer. However, we do not see an increase in the incidence of prostate cancer in these men being treated with testosterone.

Recently, Morgentaler et al. [48] evaluated the effect of testosterone therapy in men with untreated prostate cancer. This was a retrospective study of 14 men who elected surveillance for prostate cancer and who received TRT for a minimum of 6 months. All men presented with symptoms of testosterone deficiency and a serum total testosterone of less than 350 ng/dL. Monitoring included a PSA and a digital rectal examination of the prostate at 3-month intervals and a follow-up prostate biopsy at yearly intervals. At initial biopsy, 13 men had Gleason scores of six and one man had Gleason score of 7 (3+4). The mean duration of TRT after diagnosis of prostate cancer was 23.5 months (range 9–43 months). The mean follow-up serum testosterone was 661 ng/dL. There was no significant change in PSA before and after initiation of TRT (5.5 vs 3.7 ng/mL, respectively). In addition, there was no change in prostate volume size (45.6±14.5 mL vs 52.4±19.8 mL, respectively; P=0.11). Of the 13 men that had follow-up, two patients had evidence of prostate cancer progression. The first patient was found to have Gleason 7 (3+4) disease in 5% of one core; initial biopsy had revealed low-volume Gleason 6 disease. Two subsequent annual biopsies in this patient revealed only low-volume Gleason 6 disease. The second patient elected to undergo RP after biopsy showed Gleason score 7 (4+3) cancer in one of 12 cores with 75% involvement. However, his final pathology after prostatectomy revealed Gleason 6 disease, involving 5% of the gland, with negative margins and nodes. These two patients appeared to have only mild progression of their disease, which could have occurred naturally without TRT. In the remaining 11 patients under active surveillance, there was no progression of disease after TRT.

Efficacy of Testosterone Replacement Therapy after Prostate Cancer

While all studies thus far have focused on the safety of TRT in patients with prostate cancer, there has been little focus on the efficacy of TRT in these cases [49••]. Men who have undergone an RP are more likely to suffer from erectile dysfunction, decreased sexual performance, depression, and decreased libido than men without a history of RP. Thus, low serum testosterone levels in men after an RP may exacerbate these signs and symptoms.

There are data to suggest that testosterone supplementation can improve sexual desire and sexual performance in men with hypogonadism. Steidle et al. [6] conducted a 90-day randomized placebo-controlled study of 406 men with hypogonadism who received either testosterone gel or placebo. After 90 days of TRT, patients receiving treatment had a significant improvement in sexual motivation, number of sexual encounters, sexual desire, and spontaneous erections. In fact, at 30 days, the number of days with spontaneous erections increased from baseline by 137%. An additional open-label 12-month extension study demonstrated that patients receiving TRT had a 76.6% improvement over patients receiving placebo in regards to sexual performance, defined in terms of average number of days with orgasm, ejaculation, intercourse, masturbation, or erection in response to sexual activity [7].

Recent data suggest that 17.3% of men with hypogonadism have moderately severe or severe (MS/S) depression [50]. Khera et al. [50] found that patients with lower testosterone levels (<250 ng/dL) were more likely to suffer from MS/S depression than patients with testosterone levels of 250 to 299 ng/dL (20.3% vs 13.8%, respectively; P= 0.028). Furthermore, after 6 months of TRT, there was a reduction of almost 66% in the number of patients who suffered from MS/S depression. Thus, TRT should be considered an option for hypogonadal patients suffering from depression.

Clearly, a hypogonadal man after an RP may be at a significant disadvantage in recovering his overall sexual function when compared to a similar eugonadal man. Androgen deprivation is thought to negatively impact erectile function through four major mechanisms [51]. These mechanisms include impairment of nitric oxide synthase release, altered phosphodiesterase type 5 expression and activity, impaired cavernosal nerve function, and contribution to venoocclusive disease in the penis. There also are data to support the theory that early penile rehabilitation after prostatectomy results in overall im-

proved erectile function [52]. Thus, the timing of testosterone supplementation could significantly impact overall post-prostatectomy erectile function rates.

Conclusions

There appears to be inconsistency in the way we currently manage our patients after treatment of prostate cancer. While we are reluctant to raise serum testosterone levels to normal ranges in hypogonadal men, we are comfortable not lowering serum testosterone levels in eugonadal men. We currently do not castrate all eugonadal men after RP. We should be consistent in how we approach patients with eugonadism or hypogonadism after prostate cancer treatment.

It is clear that randomized placebo-controlled studies are needed to assess the safety and efficacy of TRT after prostate cancer. Currently, there is one such randomized placebo-controlled trial underway that is approved by the US Food and Drug Administration (Baylor College of Medicine, Houston, TX [NCT00848497]).

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