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INVITED RESEARCH HIGHLIGHT

Prostate Cancer

Testosterone replacement therapy and the risk of prostate cancer

Daniel Warburton[1], Christopher Hobaugh[1], Grace Wang[1], Haocheng Lin[1], Run Wang[1,2]

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Understanding the role of testosterone replacement therapy (TRT) in the development and progression of prostate cancer is an important concept in treating patients with symptoms of hypogonadism. This article revealed a small number of mostly retrospective, observational studies describing the use of TRT in the general population, in men with prostatic intraepithelial neoplasia (PIN), in men with a history of treated prostate cancer, and in men on active surveillance for prostate cancer. The current literature does not report a statistically significant increase in the development or progression of prostate cancer in men receiving testosterone replacement for symptomatic hypogonadism, and the prostate saturation theory provides a model explaining the basis for these results. The use of TRT in men with a history of prostate cancer is considered experimental, but future results from randomized controlled trials could lead to a change in our current treatment approach.

Since the advent of TRT, supplementation has been utilized to treat secondary effects of hypogonadism including decreased libido, decreased energy level, depressed mood, impairment in cognition, and reduced muscle mass.[1] Concern regarding the effect of testosterone on prostate cancer tumor promotion and progression has led to reservations prescribing such therapy in those individuals with a history of the disease. More recently, however, there has been increased interest and research into testosterone supplementation and its relationship to prostate cancer.

The historical basis for concern originated in 1941 when Huggins and Hodges[2] demonstrated that reducing testosterone to castrate levels caused regression of prostate cancer while administration of exogenous testosterone stimulated its growth. While there is now definitive evidence regarding the effect of castration, the latter finding was based on evidence from one single patient[2] and the validity has been called into question by numerous more recent studies.

TESTOSTERONE REPLACEMENT THERAPY AND NORMAL PROSTATE TISSUE

To appreciate the effect of testosterone on prostate cancer, it is important to understand its influence on normal prostate tissue. In a randomized controlled trial, 44 men aged 44 to 78 years with serum testosterone <300 ng dl^{-1} and symptoms of hypogonadism were randomly assigned to receive 150 mg of testosterone enanthate or placebo. Twelve-core transrectal ultrasound prostate biopsies were performed both at baseline and at 6 months. As expected, there was noted to be an increase in serum testosterone levels to the mid-normal range in those receiving testosterone replacement with no significant change in serum testosterone levels in matched, placebo-treated men. There was not, however, any significant change in median prostate tissue levels of testosterone or dihydrotestosterone in either group.[3]

Similarly, several studies have demonstrated that increasing testosterone to supraphysiologic levels does not increase serum prostate-specific antigen (PSA) significantly. Bhasin *et al.*[4] supplemented 43 healthy men with either 600 mg of testosterone enanthate or placebo for 10 weeks. As secondary endpoints neither PSA nor prostate volume increased, despite serum testosterone levels in excess of 2500 ng dl^{-1}.[4] Cooper *et al.*[5] supplemented 31 healthy men with 100 mg, 250 mg, or 500 mg of testosterone intramuscularly weekly, demonstrating that despite significant increase in free and total serum testosterone in those receiving 250 mg and 500 mg, there was no significant change in PSA or prostate volume.

PROSTATE SATURATION THEORY

A model to describe these findings is the prostate saturation theory. When the level of circulating androgen is below normal, some androgen receptors are inactive, and the secondary downstream effects are decreased. Once androgen receptors within the prostate are saturated, however, increasing testosterone will no longer have an effect. While a distinct value is not known and may vary, the saturation point is thought to occur at low physiologic testosterone levels. This theory is supported by an observational study by Khera *et al.*[6] in which the PSA levels of 451 hypogonadal men who received testosterone replacement were examined. Participants were divided into one of the two groups based on pretreatment testosterone level, either >250 ng dl^{-1}, or <250 ng dl^{-1}. Only the subset of individuals with pretreatment testosterone level <250 ng dl^{-1} had PSA level correlating with free and total testosterone level. In addition, this group was found to have a statistically significant PSA rise after 12 months of testosterone replacement, which did not occur in the group with pretreatment testosterone >250 ng dl^{-1}.[6]

Despite these findings, there has traditionally been hesitation to prescribe TRT when prostate cancer is a concern. The causal relationship between the two can be investigated individually in the general

[1]Division of Urology, University of Texas Medical School at Houston, Department of Urology, Houston, Texas, USA; [2]University of Texas MD Anderson Cancer Center, Houston, Texas 77030, USA.
Correspondence: Prof. R Wang (run.wang@uth.tmc.edu)
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population, in men at high risk for prostate cancer, and in those with personal history of the disease. These will each be separately examined.

TESTOSTERONE REPLACEMENT THERAPY AND PROSTATE CANCER

To date, there has been no evidence demonstrating causal effect of TRT on the development of prostate cancer. In a systematic review of the literature assessing for a causality between TRT and prostate cancer, increased PSA, or abnormal digital rectal examination findings, Shabsigh *et al.*[7] identified 11 randomized controlled trials, as well as 29 nonplacebo-controlled studies of men with no prostate cancer history, and four studies of hypogonadal men with history of prostate cancer with pertinent results. Notably, none of the studies reviewed demonstrated an increased risk of a prostate cancer diagnosis or an increased risk of higher Gleason grade in those who did develop the disease.[7]

Men with prostatic intraepithelial neoplasia

A subset of the general population that warrants separate evaluation is those individuals at high risk of a prostate cancer diagnosis. A finding of high-grade PIN on biopsy confers roughly a 20% chance of finding prostate cancer on subsequent biopsy.[8] This, therefore, indicates a higher risk of having prostate cancer than a patient who has undergone a radical prostatectomy (RP) with negative margins and undetectable PSA. While the data are somewhat limited in this population, Rhoden and Morgentaler published a review of 75 patients treated with TRT, 20 of whom were found to have PIN prior to the initiation of therapy. At the conclusion of 12 months of treatment, there was no significant change in PSA in either group, and one of the 20 patients with pretreatment PIN was found to have prostate cancer after biopsy for an abnormal digital rectal exam. Thus, the authors concluded that men with PIN do not have an increased risk of cancer development when treated with testosterone replacement than men without PIN.[9]

Men with treated prostate cancer

Perhaps the most controversial use of TRT is in those individuals with a personal history of prostate cancer. With new research into this practice, however, the paradigm may be changing. Small-scale studies of individuals receiving each prostate cancer treatment modality as well as active surveillance have been performed, with larger randomized control trials underway. In the first examining radiation therapy, Sarosdy[10] followed 31 men receiving TRT for hypogonadism after being treated with prostate brachytherapy. The median time to start replacement therapy was 2 years after treatment and follow-up ranged from 1.5 to 9 years with a median of 5 years. Notably, none of the men stopped testosterone supplementation due to prostate cancer recurrence, and none demonstrated cancer progression.[10] Similarly, small-scale case series have been reported on external beam radiation therapy (EBRT) as primary treatment. Morales reported on five patients treated for hypogonadism after EBRT with a follow-up of 14.5 months. PSA level did transiently rise in one patient; however, none exceeded a PSA of 1.5 ng ml^{-1} to raise concern for biochemical recurrence.[11] More recently, Pastuszak *et al*. reported on 13 hypogonadal men who underwent either EBRT or brachytherapy and subsequently started on TRT. Serum testosterone was noted to increase to statistically significant levels without a significant increase in PSA or prostate cancer recurrence (**Table 1**).[12]

There is similarly limited evidence with regard to testosterone replacement after RP, with all published data obtained in retrospective observational studies (**Table 2**). Agarwal and Oefelein[13] reported that after 19 months on TRT, 10 hypogonadal patients with a history of undergoing a radical retropubic prostatectomy for prostate cancer had no PSA recurrence and had statistically significant improvements in serum total testosterone and hypogonadal symptoms. Similarly, Kaufman and Graydon[14] examined case records of seven hypogonadal men who had undergone curative RP with symptoms of hypogonadism and low serum testosterone levels treated with testosterone replacement. No biochemical or clinical evidence of cancer recurrence was noted. In a much larger case series, Khera *et al*.[15] reviewed the records of 57 men who received TRT following RP. After an average of 36 months following RP, testosterone replacement was initiated and followed for an average of 13 months. Mean testosterone values rose significantly and once again, there was no increase in PSA values and, therefore, no diagnosed biochemical recurrence.[15]

The most robust evidence to date is supplied by a retrospective study by Pastuszak *et al*.[16] of 103 hypogonadal men with prostate cancer treated with testosterone after prostatectomy and 49 nonhypogonadal men with cancer treated with prostatectomy to serve as a control comparison group. For analysis, the subjects were further subdivided into high risk (including those with pathology of Gleason 8 or greater, positive margins, or positive lymph nodes) and nonhigh risk groups. The data were reviewed at a median of 27.5 months on therapy, at which time a significant increase in testosterone was observed in the treatment group, as well as a significant increase in PSA both in the high-risk and nonhigh-risk treatment groups with no increase in the reference group. Four of the patients in the treatment group were found to have cancer recurrence, compared with eight in the control group, although it should be noted that the two groups were not statistically equivalent, with more T3b tumors in the control group. All biochemical recurrences were seen in individuals with high-risk disease.[16]

Men on active surveillance

The final group of individuals who should be evaluated is those undergoing active surveillance or untreated prostate cancer (**Table 3**). Morgentaler *et al*.[17] performed a retrospective study of 13 symptomatic hypogonadal men undergoing active surveillance for prostate cancer while concomitantly receiving TRT. Study participants included 12 men with low volume Gleason 6 (3 + 3) disease and one with low volume Gleason 7 (3 + 4) disease. As was demonstrated in many of the previously described studies, serum testosterone increased significantly with no change in PSA or prostate volume. On subsequent biopsies, there was concern for upstaging in two of these individuals. The first remained on active surveillance and testosterone replacement, with subsequent biopsies demonstrating no progression. The other individual ultimately underwent RP, however, surgical pathology revealed no progression of disease.[17]

FUTURE DIRECTION

While these retrospective observational studies provide somewhat limited evidence, they each suggest that testosterone replacement in symptomatic men with prostate cancer warrants further investigation. Currently, there are several randomized control trials ongoing examining the effect of testosterone replacement in the setting of prostate cancer. While several are in the setting of castrate-resistant or hormone-refractory disease, one trial currently enrolling participants seeks to evaluate the efficacy of TRT in men following RP at improving erectile function. In this interventional phase 0 study, subjects are randomized to an experimental group receiving 5 g of testosterone gel along with 25 mg of sildenafil daily, or a control group receiving

Table 1: TRT after radiation therapy

	Number of patients	Follow-up (month)	Pre-TRT testosterone (ng dl^{-1})	Post-TRT testosterone (ng dl^{-1})	Pre-TRT PSA (ng dl^{-1})	Post-TRT PSA (ng dl^{-1})	Recurrence after TRT (n)
Sarosdy[10]	31	60	188	498	-	All decreased since TRT initiation	0
Morales *et al.*[11]	5	14.5	150	507	0.3	0.47	0
Pastuszak *et al.*[16]	13	29.7	178	368 (P=0.012)	0.3	0.66 (P=0.345)	0

TRT: testosterone replacement therapy; PSA: prostate-specific antigen

Table 2: TRT after radical prostatectomy

	Number of patients	Follow-up (month)	Pre-TRT testosterone (ng dl^{-1})	Post-TRT testosterone (ng dl^{-1})	Pre-TRT PSA (ng ml^{-1})	Post-TRT PSA (ng ml^{-1})	Recurrence after TRT (n)
Agarwal and Oefelein[13]	10	19	197	591	<0.1	<0.1	0
Kaufman and Graydon[14]	7	24	97	434	<0.1	<0.1	0
Khera *et al.*[15]	57	17	275	440	0.005	0.005	0
Pastuszak *et al.*[16]	103	27.5	261	460	0.004	0.007	4

TRT: testosterone replacement therapy; PSA: prostate-specific antigen

Table 3: TRT in other populations

	Number of patients	Patient population	Follow-up (month)	Pre-TRT testosterone (ng dl^{-1})	Post-TRT testosterone (ng dl^{-1})	Pre-TRT PSA (ng ml^{-1})	Post-TRT PSA (ng ml^{-1})	Progression after TRT (n)
Morgentaler *et al.*[17]	13	Active surveillance, Gleason 6 (12) and 7 (1)	30	238	664 (P<0.001)	5.5±6.4	3.6±2.6 (P=0.29)	0
Rhoden and Morgentaler[9]	20	Patients with PIN on biopsy	12	298	616	1.49±1.1	1.82±1.1 (P>0.05)	1

TRT: testosterone replacement therapy; PSA: prostate-specific antigen; PIN: prostatic intraepithelial neoplasia

5 g of placebo gel and 25 mg of sildenafil daily. Enrollment requires nerve-sparing prostatectomy and undetectable PSA level. Furthermore, individuals will be excluded from the study if they have testosterone level >300 ng dl^{-1}, hemoglobin >18 ng dl^{-1}, preoperative Sexual Health Inventory for Men score <17, positive surgical margins or evidence of residual prostate cancer, clinically suspected advanced disease or evidence of metastatic prostate cancer, or primary Gleason grade >3 or secondary Gleason grade >4. Participants will complete 3 months of testosterone replacement and evaluation will occur at the 6-month time point. To date, no study results have been published.[18]

Over the past 15 years, a significant shift has occurred in the understanding of the relationship between testosterone and prostate cancer. The saturation model suggests that after exceeding low physiologic levels of testosterone, increasing no longer has the potential to stimulate prostate cancer growth, which the limited retrospective evidence supports. With what was previously considered an absolute contraindication to androgen replacement, men with a history of prostate cancer now are receiving consideration for correction of hypogonadism. Such therapy at this juncture is considered experimental, and patients should still be counseled accordingly, but further investigation with randomized control trials may lead to a major revision of the traditional standard.

EDITORIAL COMMENT (BY DR JOHN W DAVIS, DEPARTMENT OF UROLOGY, THE UNIVERSITY OF TEXAS, MD ANDERSON CANCER CENTER, HOUSTON, TEXAS, USA)

In the United States circumstance, it has become common for specialized outpatient clinics staffed by either urologists or other mens' health-related fields to promote the concept of a "Low T Center." Such centers use direct-to-patient advertising methods to encourage self-referral for symptoms of fatigue, low libido, and other symptoms relevant. Consequently, those of us on the prostate cancer screening, detection, and treatment side of the equation encounter an increasing number of patients whose presentation started with an evaluation by a "Low T Center" that led to the detection of an elevated PSA either at baseline, or downstream of initiating testosterone replacement. Therefore, prostate cancer clinicians are increasingly having to factor in TRT into the management of men with elevated PSA and negative biopsy, as well as men treated for prostate cancer. It is common for TRT to be discontinued at the finding of an elevated PSA and certainly at the diagnosis of prostate cancer. If the TRT was working, they will likely want your opinion as to the safety of re-starting it at some point. Warburton *et al.* give us a state-of-the-art highlight of the common situations. At this point, the evidence is strongest that men with elevated PSA and negative biopsy, and post-RP with favorable pathology can re-start, and more data are needed for radiation patients and active surveillance.

COMPETING INTERESTS

All authors declare no competing financial interests.

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