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Testosterone Replacement Therapy in Patients with Prostate Cancer After Radical Prostatectomy

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Abstract

Purpose—Testosterone replacement therapy in men with prostate cancer is controversial, with concern that testosterone can stimulate cancer growth. We evaluated the safety and efficacy of testosterone in hypogonadal men with prostate cancer treated with radical prostatectomy.

Materials and Methods—We performed a review of 103 hypogonadal men with prostate cancer treated with testosterone after prostatectomy (treatment group) and 49 nonhypogonadal men with cancer treated with prostatectomy (reference group). There were 77 men with low/intermediate (nonhigh) risk cancer and 26 with high risk cancer included in the analysis. All men were treated with transdermal testosterone, and serum hormone, hemoglobin, hematocrit and prostate specific antigen were evaluated for more than 36 months.

Results—Median (IQR) patient age in the treatment group was 61.0 years (55.0–67.0), and initial laboratory results included testosterone 261.0 ng/dl (213.0–302.0), prostate specific antigen 0.004 ng/ml (0.002–0.007), hemoglobin 14.7 gm/dl (13.3–15.5) and hematocrit 45.2% (40.4–46.1). Median followup was 27.5 months, at which time a significant increase in testosterone was observed in the treatment group. A significant increase in prostate specific antigen was observed in the high risk and nonhigh risk treatment groups with no increase in the reference group. Overall 4 and 8 cases of cancer recurrence were observed in treatment and reference groups, respectively.

Conclusions—Thus, testosterone therapy is effective and, while followed by an increase in prostate specific antigen, does not appear to increase cancer recurrence rates, even in men with high risk prostate cancer. However, given the retrospective nature of this and prior studies, testosterone therapy in men with history of prostate cancer should be performed with a vigorous surveillance protocol.

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Keywords

testosterone; hormone replacement therapy; prostatic neoplasms; hypogonadism; prostatectomy

HYPOGONADISM is characterized by low serum testosterone levels and symptoms of androgen deficiency, including a decrease in energy and libido, muscle mass and bone density, as well as impairment in cognition and sexual function, and depressive symptoms.[1] Treatment of hypogonadism with testosterone replacement therapy can mitigate the symptoms and signs of this condition.[1] However, TRT may not be appropriate for all men, particularly those with a history of prostate cancer. This controversy exists in part due to findings that androgens can stimulate CaP growth, an association forged by Huggins and Hodges, who found that castration resulted in regression of metastatic CaP.[2] Subsequent studies found that TRT led to tumor growth and/or recurrence in patients with metastatic or advanced prostate cancer.[3,4] These studies underscore the androgen dependent model of CaP growth, which remains the basis for the avoidance of TRT in men with a history of CaP.[5]

While in vitro data demonstrate that androgens can result in growth of CaP cells, most published clinical studies have failed to associate TRT with CaP recurrence or progression,[6,7] and a 2005 meta-analysis of randomized clinical trials from 1966 to 2004 involving TRT in elderly males showed no difference in CaP rates between TRT and placebo.[8] In fact, only case reports support the growth of CaP in the setting of exogenous androgen.[9] However, in the last 2 decades our understanding of the physiological roles of T has increased, and the relationship between T and energy, vitality, quality of life, sexual desire, erectile function, mental acuity, bone health and cardiovascular disease has become more firmly established.[10,11] Thus, with the growing list of benefits of TRT and lack of clinical evidence supporting the trophic effects of TRT on CaP, the safety of testosterone replacement therapy in the setting of CaP is being reassessed.

Several retrospective studies have evaluated TRT after prostate cancer treatment. In a series of retrospective studies evaluating TRT after brachytherapy, external beam radiation or radical prostatectomy, increases in serum T without corresponding PSA increases were observed with no biochemical recurrence in 105 patients.[12–16] Several other retrospective studies examining the effects of TRT on hypogonadal patients with prostate cancer after RP have shown improvement in hypogonadal symptoms with no BCR.[12–14] We present our single institution experience with TRT in hypogonadal men with prostate cancer treated with RP.

METHODS

Patient and Serum Variable Selection

A retrospective review of medical records, approved by the institutional review board of Baylor College of Medicine, was performed for hypogonadal men treated with transdermal TRT and a history of CaP treated with RP by 3 surgeons at our institution. Patients without available final pathology data, baseline testosterone or PSA values, or those treated for suspected BCR before TRT initiation were excluded from study and 103 men were included.

Men were grouped into high risk and low/intermediate risk groups (the latter referred to as nonhigh risk). A total of 26 men with high risk CaP were identified as having at least 1 of the pathological characteristics of 1) Gleason score 8 or greater, 2) positive surgical margins or 3) positive lymph nodes after RP (supplementary table 1A, http://jurology.com/). Only patients with 1 or more undetectable PSA after radical prostatectomy were offered TRT after a diagnosis of hypogonadism, which was made after RP based on the presence of hypogonadal symptoms including fatigue, insomnia, weight gain, worsening cognition, decreased libido, and/or worsening erectile function and serum testosterone. Men with symptoms and/or biochemical evidence of hypogonadism and the absence of alternative diagnoses with symptoms overlapping with those of hypogonadism were offered TRT, with baseline T levels ranging from 38 to 513 ng/dl.

While the accepted lower limit of normal serum T is 300 to 375 ng/ml, our clinical experience indicates that men with hypogonadal symptoms, even with serum T levels greater than the lower limit of normal, benefit from TRT. Thus, men with hypogonadal symptoms and serum T levels greater than 300 ng/dl were also treated. Baseline serum hormone, PSA, Hgb and Hct levels were assessed within 3 months of RP, and sequentially every 3 to 6 months after TRT initiation. One patient each received gene therapy before RP, a clinical trial of chemotherapy and ADT, adjuvant radiation therapy for positive surgical margins, adjuvant ADT for Gleason 5 + 4 disease, or ADT plus radiation therapy for positive surgical margins and seminal vesicle involvement for Gleason 4 + 4 disease.

For comparison to this group, 49 men with a history of CaP treated with RP by a single surgeon (BJM) but without hypogonadal symptoms (reference group) were selected. Of these men 34 and 15 had nonhigh risk and high risk CaP, respectively. Patients without available prostate biopsy or final pathology data, or a PSA value within 90 days of RP, were excluded from study (supplementary table 1B). Of note, serum hormone values were not available for patients in the reference group given the absence of hypogonadal symptoms. Men returning for followup after RP were screened for hypogonadism but were not biochemically evaluated if symptoms were absent.

Data Analysis

Baseline serum testosterone, calculated free testosterone, Hgb, Hct, estradiol, sex hormone-binding globulin and PSA levels were evaluated. PSAV was calculated using linear regression of 3 or more serum PSA values obtained during at least a 12-month period. The majority of serum hormone evaluations were performed by the Laboratory for Male Reproductive Research and Testing at Baylor College of Medicine using a chemiluminescent immunoassay on a single Beckman Coulter Access®2 assay system.

Data were analyzed using Microsoft Office Excel® and SPSS®. Statistical comparisons between unpaired values were performed using Mann-Whitney analysis, whereas comparisons between baseline and followup values were performed using Wilcoxon rank sum analysis for paired values, with $p \leq 0.05$ considered statistically significant.

RESULTS

Median followup after TRT initiation was 27.5 months (range 6.2 to 189.3) in the treatment group. In the reference cohort median followup after RP was 16.5 months (range 1.7 to 77.0) (supplementary table 1B). Men in the treatment group were started on TRT after RP with a median interval of 12.3 months (IQR 7.8–16.8). Pretreatment serum hormone and PSA levels for all patients are summarized in table 1 and supplementary table 2 (http://jurology.com/), with no significant differences identified between the high risk and nonhigh risk groups. Initial prostate biopsy median Gleason sums for high risk and nonhigh risk treatment subgroups were 6.0 and 6.0 ($p = 0.09$), respectively (supplementary table 1A). Of note, more T3b tumors were found in the reference group than in the treatment group (12% vs 2%, $p = 0.02$).

Men in the treatment group had significant increases in serum T levels at almost all followup time points. Only in the high risk subgroup were nonsignificant increases in serum T observed at median followup, likely in part due to the relatively few men with data at that point (supplementary table 2). Increases in free testosterone were observed in the high risk and nonhigh risk groups, as expected in the setting of increasing T. A small increase in estradiol was observed at median followup in all patients, perhaps related to peripheral aromatization, and significant increases in sex hormone-binding globulin were observed in all patients and in the nonhigh risk subgroup starting at 18 to 24 months of followup through more than 36 months. One of the most common side effects of TRT is erythrocytosis, and in our treatment group we observed no significant increases in Hgb or Hct throughout followup.

One of the most significant concerns of TRT in men with a history of CaP is that of CaP growth stimulated by exogenous testosterone. We evaluated PSA in our treatment group over time, and found a small, statistically significant increase in PSA in the high risk and nonhigh risk groups beginning at 18 to 24 months after TRT initiation, suggesting that an overall trend toward increasing PSA does occur in men on TRT (part *A* of figure and supplementary table 2). However, in the reference group we observed no significant increases in PSA (part *B* of figure, table 1).

To better understand whether the observed increase in PSA was indicative of CaP growth, we calculated PSAV in each group (table 2). Median PSAV for all patients in the treatment and reference groups was 0.002 (0.001–0.003) and 0.0002 (−0.001–0.010) ng/ml per year, respectively ($p = 1.00$). There was no difference in PSAV between the treatment and reference high risk subgroups ($p = 0.77$) or between the nonhigh risk subgroups ($p = 0.67$), indicating that neither group had PSA increase at a rate suggestive of BCR based on current recommendations.[17] Biochemical recurrence, as defined by consecutive increasing PSAs and patient referral for salvage radiation therapy, occurred in 4 patients in the treatment group and 8 in the reference group.[18] Notably all recurrences in the treatment and reference cohorts were in high risk patients and comprised 15% (4 men) and 53% (8 men) of those subgroups, respectively ($p = 0.02$). When excluding patients with T3a/3b tumors, high risk treatment and reference group recurrence was limited to 3 and 5 men, respectively ($p = 0.03$). At median followup 1 patient in the high risk treatment group had 2 consecutive PSAs

greater than 0.2 ng/ml, the American Urological Association definition of BCR.[18] Three other high risk patients had suspected recurrence based on consecutive increases in PSA and were referred for salvage radiation therapy. Despite these observations, our median followup remained relatively short in the context of the natural history of CaP, and these data may not be representative of longer term trends.

DISCUSSION

We retrospectively evaluated hypogonadal men with a history of CaP treated with RP, including those with high risk CaP, and compared them to men with a history of CaP treated with RP but without symptoms of, or biochemical evaluation for, hypogonadism. We observed a small but significant increase in PSA in the treatment group but not the reference group, and a lower frequency of BCR in the treatment group. 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 during a comparable followup period.[19–22] Moreover, the recurrence rate was higher in the high risk treatment group than in the high risk reference group, with no men with BCR in the nonhigh risk subgroups.

While a statistically significant increase in PSA was observed in the high risk and nonhigh risk treatment groups, this increase was not supportive of CaP recurrence, with PSAV being lower than an expected PSAV of 0.30 to 0.43 ng/ml per year in hypogonadal men without prostate cancer on TRT, and lower than in men after RP with BCR, in whom PSAV may be between 0.11 and 0.25 ng/ml per month.[17,23,24] It is important to note that more T3b tumors were found in the reference group than the treatment group. However, even after excluding these men, the BCR rate in the high risk treatment group remained lower than in the high risk reference group. In addition, serum hormone data were not available for the reference group, confounding whether the recurrence rate in this group was a chance occurrence or was impacted by the cohort's hormonal milieu.

Our results support those from several studies on TRT efficacy in patients with a history of CaP treated with RP without increasing risk of BCR or progression. Agarwal and Oefelein evaluated 10 hypogonadal men with organ confined CaP treated with RP and TRT, and found higher T levels and improved hypogonadal symptoms without BCR at 19 months.[13] Kaufman and Graydon evaluated 7 hypogonadal men on TRT after radical prostatectomy in early stage CaP, and found normalization of T levels and symptoms during up to 12 years of followup with no PSA increases or BCR.[14] Khera et al observed no BCR or PSA increases in 57 men after RP with an average of 13 months of TRT.[12] Our study overall supports these findings despite the observed increase in PSA in men on TRT.

While it is premature to postulate that TRT in men with a history of CaP may be protective, the lack of a higher BCR rate in the treatment vs the reference group is interesting and potentially significant. Mechanistically this lack of CaP recurrence despite TRT may be explained via an increase in serum T without changes in residual prostate tissue T levels, as reported by Marks et al in a study of 41 men with symptomatic hypogonadism.[25] The lack of BCR may also implicate the saturation model of androgen receptor binding, which posits that prostate tissue may be sensitive to serum T levels less than 120 ng/dl, whereas above

this level the androgen receptors are saturated and the prostate becomes insensitive to serum T variation.[26] In 31 hypogonadal men followed for 1.5 to 9 years after brachytherapy, Sarosdy found that serum T levels increased with no CaP progression, furthering the dissociation between testosterone replacement therapy and BCR.[15]

Our study is limited by several factors. The retrospective nature of the work limits our findings to this specific population of men. Error may have been introduced by the lack of randomization and patient selection, as well as with the differences between groups, including the higher number of T3b tumors in the reference group and the different median followup periods for the 2 groups. Our study also fundamentally lacked a placebo group to mirror the followup time and hypogonadal state of the TRT group, and our reference group did not have serum T levels evaluated, limiting the diagnosis of hypogonadism and our ability to objectively compare the reference and treatment groups. Furthermore, the time to TRT initiation in the treatment group (12.3 months) was longer than the several weeks needed to reach PSA nadir after RP, constituting a potential treatment delay. However, given concerns that early treatment of men with a history of CaP after RP could result in rapid BCR, our waiting period before TRT initiation was prolonged.[27] Finally, while longer than that of previous studies, our median followup remains short given that many cases of CaP recur 5 or more years after treatment.

While our results do not indicate that treatment of hypogonadism can decrease CaP recurrence rates, they do support the use of TRT in patients with CaP in a monitored setting and argue for longer followup given the significant increase in PSA with time. Thus, clinicians should consider TRT in men with a CaP history after prostatectomy presenting with symptoms of hypogonadism. However, there is no substitute for clinical judgment and close monitoring throughout TRT in these men.

CONCLUSIONS

In hypogonadal men with a history of prostate cancer after RP, TRT results in increases in serum T levels, with a small but significant rise in PSA and a lower BCR rate in treated men compared with age matched reference men without symptomatic evidence of hypogonadism, even in men with a history of CaP bearing high risk features. However, given the retrospective nature of this and prior studies, TRT in men with a history of CaP should be performed with a vigorous surveillance protocol. Furthermore, the global experience with TRT in the setting of CaP remains limited, with fewer than 600 patients evaluated and treated in disparate ways, limiting our ability to draw conclusions regarding the impact of TRT in the setting of CaP, perhaps to be reconciled with further prospective studies, a growing base of treated patients and longer followup.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations and Acronyms

ADT	androgen deprivation therapy
BCR	biochemical recurrence
CaP	prostate cancer
Hct	hematocrit
Hgb	hemoglobin
PSA	prostate specific antigen
PSAV	PSA velocity
RP	radical prostatectomy
T	testosterone
TRT	testosterone replacement therapy

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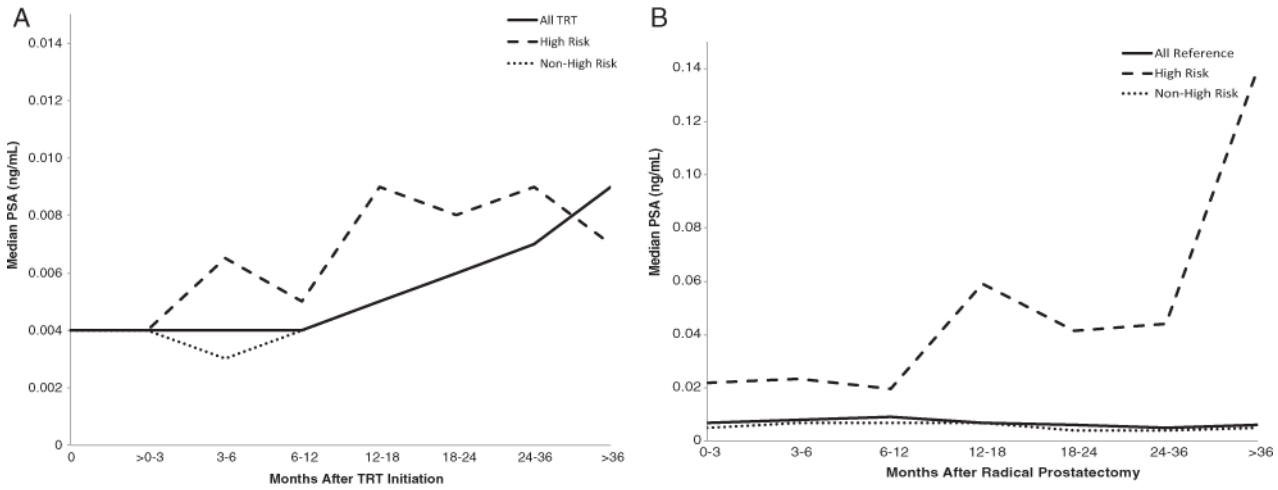

Figure.

Median PSA as function of time after TRT initiation in treatment group (*A*) and after RP in reference group (*B*) for all patients as well as those in high risk and nonhigh risk subgroups.

Table 1

Serum levels for reference group patients after RP and during follow up

	Median ng/ml PSA (IQR) 0–3 Mos	No.	Median ng/ml PSA (IQR) 24–36 Mos	No.	p Value*
All pts	0.007 (0.004–0.016)	50	0.005 (0.002–0.043)	13	0.700
High risk	0.022 (0.007–0.031)	15	0.044 (0.005–0.300)	3	0.593
Nonhigh risk	0.005 (0.003–0.009)	35	0.004 (0.002–0.020)	10	0.475

*Comparisons between followup points and initial 0 to 3-month PSA values.

Table 2

PSA outcomes during followup

	All Pts		High Risk Pts		Nonhigh risk Pts		TRT vs Reference p Value	TRT vs Reference p Value*
Treatment group:								
No. pts	103		26		77			
Median ng/ml/yr PSAV (IQR), No.	0.002	(0.001–0.003), 89	0.002	(0.001–0.011), 22	0.001	(0.001–0.002), 67	1.000	
No. suspected BCR (%)†	4	(4)	4	(15)	0	(0)	0.015	0.03
No. BCR defined as a single PSA greater than 0.2 ng/ml (%)	2	(2)	2	(8)	0	(0)		
No. discontinued TRT for reason other than suspected BCR (%)‡	15	(15)	2	(8)	13	(17)		
Reference group:								
No. pts	50		15		35			
Median ng/ml/yr PSAV (95% CI), No.	0.0002	(−0.001–0.010), 27	0.018	(−0.012–0.106), 10	−0.0003	(−0.001–0.004), 17		
No. suspected BCR (%)†	8	(16)	8	(53)	0	(0)		
No. BCR defined as a single PSA greater than 0.2 ng/ml (%)	5	(10)	5	(33)	0	(0)		

PSA velocity only calculated for patients with 3 or more PSA levels in 1 or more years.

*Suspected recurrence with exclusion of patients with T3a/3b disease.

†Suspected BCR recorded when charted in medical record, if patient was referred to radiation oncologist for increasing PSA and/or if patient underwent salvage therapy for increasing PSA.

‡Included concern for increasing PSA, cardiovascular side effects, increased risk of relapse, cost, no symptomatic improvement, underwent operation or procedure unrelated to CaP, supraphysiological T level, transient ischemic attack or leg pain.