Testosterone Therapy in Men With Untreated Prostate Cancer

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Purpose: A history of prostate cancer has been a longstanding contraindication to the use of testosterone therapy due to the belief that higher serum testosterone causes more rapid prostate cancer growth. Recent evidence has called this paradigm into question. In this study we investigate the effect of testosterone therapy in men with untreated prostate cancer.

Materials and Methods: We report the results of prostate biopsies, serum prostate specific antigen and prostate volume in symptomatic testosterone deficient cases receiving testosterone therapy while undergoing active surveillance for prostate cancer.

Results: A total of 13 symptomatic testosterone deficient men with untreated prostate cancer received testosterone therapy for a median of 2.5 years (range 1.0 to 8.1). Mean age was 58.8 years. Gleason score at initial biopsy was 6 in 12 men and 7 in 1. Mean serum concentration of total testosterone increased from 238 to 664 ng/dl (p < 0.001). Mean prostate specific antigen did not change with testosterone therapy (5.5 ± 6.4 vs 3.6 ± 2.6 ng/ml, p = 0.29). Prostate volume was unchanged. Mean number of followup biopsies was 2. No cancer was found in 54% of followup biopsies. Biopsies in 2 men suggested upgrading, and subsequent biopsies in 1 and radical prostatectomy in another indicated no progression. No local prostate cancer progression or distant disease was observed.

Conclusions: Testosterone therapy in men with untreated prostate cancer was not associated with prostate cancer progression in the short to medium term. These results are consistent with the saturation model, ie maximal prostate cancer growth is achieved at low androgen concentrations. The longstanding prohibition against testosterone therapy in men with untreated or low risk prostate cancer or treated prostate cancer without evidence of metastatic or recurrent disease merits reevaluation.

Key Words: testosterone, prostatic neoplasms, androgens

Testosterone therapy has been shown to have a number of beneficial effects in men with testosterone deficiency, including improvement in symptoms of fatigue, decreased libido and sexual performance.1 However, a major concern has been that increased serum testosterone may cause growth of prostate cancer.2 This concern is based on the observations that androgen deprivation causes PCA regression as reflected by decreased serum PSA, and that normalization of serum T in androgen-deprived men causes an increase in PSA.3 Historically there has been an absolute prohibition against the use of TTh in men with any prior history of PCa.1,3

However, recent literature has called this traditional paradigm into question. A small series of retrospective studies have reported benign outcomes in men who underwent TTh...
following definitive treatment of localized PCa. Of these studies, with a total population of 74 men, were of men with TD who had undergone radical prostatectomy for PCa. None of the participants had biochemical recurrence with followup as long as 12 years. Another study reported no biochemical recurrence in 31 men who underwent TTh for a median of 4.5 years following brachytherapy for localized PCa.

One explanation for the lack of biochemical recurrence is that men were cured of PCa. Another is that a higher serum T concentration does not necessarily lead to greater PCa growth. A global pooled collaborative analysis of 18 longitudinal studies of sex hormones and PCa comprised of 3,886 men with PCa and 6,438 age matched controls found no relationship between endogenous serum androgen concentrations and PCa. In another study intraprostatic T and DHT concentrations were unchanged after 6 months of TTh in men with TD despite large changes in serum T concentrations. A saturation model has been proposed to account for the substantial prostatic changes observed with institution or cessation of androgen deprivation therapy and the relative indifference of prostate tissue to changes in serum T above the near castrate range.

Without large, randomized, long-term studies of TTh in men with TD it remains an unanswered question whether TTh may cause greater PCa growth in this cohort. This question is of particular relevance to the increasing number of men who currently elect active surveillance for newly diagnosed PCa, some of whom are symptomatic from T deficiency and desirous of TTh.

As new data have suggested a less risky relationship between T and PCa than previously assumed, we and others have become more open to the practice of offering TTh to men with a history of PCa. A decrease in PSA was noted in an elderly man who received TTh during PCa surveillance.

In this study we report on prostate biopsy and PSA results in a group of symptomatic T deficient men who received TTh while undergoing active surveillance for untreated PCa. The emergence of serial prostate biopsies as a critical component of active surveillance protocols in men with PCa presents a new and unique opportunity to evaluate the effect of TTh on PCa growth.

METHODS

This was a retrospective study of a consecutive series of men who elected surveillance for PCa, and who received TTh for a minimum of 12 months between 2001 and 2009. Patients were evaluated at Men’s Health Boston (Brookline, Massachusetts) and the Urology Department at Baylor Medical College (Houston, Texas). All men were diagnosed with TD based on clinical presentation combined with a single confirmatory blood test result, specifically serum TT less than 350 ng/dl or serum FT less than 15 pg/ml. None presented with clinical depression. FT values were not obtained for all individuals.

Testosterone therapy was individualized to optimize clinical response. T gel was prescribed in doses of 5 to 10 gm daily, injections of testosterone cypionate were administered at 100 to 200 mg every 1 to 2 weeks and testosterone pellets (75 mg) were dosed as 8 to 12 pellets every 3 to 5 months.

Surveillance consisted of PSA and digital rectal examination of the prostate at 3-month intervals, and followup prostate biopsy at yearly intervals. Biopsy results were based on reports generated by the Pathology staff at Beth Israel Deaconess Medical Center in Boston, Massachusetts, and at Baylor Medical College in Houston, Texas. Two biopsy reports were obtained from outside academic institutions in Boston. No central rereview of biopsy specimens was performed. Atypia, high grade prostatic intraepithelial neoplasia or suspicious findings were categorized as negative if no frank cancer was noted.

Blood tests for TT and PSA were performed in-house (Men’s Health Boston) or by medical school laboratory (Baylor), and FT was performed by a national laboratory (Quest Diagnostics) or by the medical school laboratory (Baylor). Prostate volume was determined by transrectal ultrasound performed at the time of prostate biopsy.

Baseline blood test results for hematocrit, SHBG and hormones were obtained before initiation of TTh or on temporary cessation of TTh. Followup values were obtained once therapeutic T values were achieved, generally within 3 months. Baseline PSA refers to the most recent value before the diagnosis of PCa. Records regarding baseline PSA and digital rectal examination were not routinely available for men who initiated TTh before a diagnosis of PCa due to treatment by outside physicians. Institutional review board approval was obtained at Beth Israel Deaconess Medical Center and Baylor Medical College. Statistical analysis was performed using the paired t test (2-tailed) to compare baseline and followup values, with p < 0.05 considered statistically significant.

RESULTS

Baseline characteristics of the study population are shown in table 1. The 13 men were followed for 12 months or longer while receiving TTh after a diagnosis of PCa, with a mean age at PCa diagnosis of 58.8 years (median 62, range 47 to 76). All men had 1 or more symptoms suggestive of TD before the initiation of TTh. Of the men 7 had received TTh for a mean duration of 106 months (range 8 to 302) before PCa diagnosis and 1 of them had a biopsy before initiation of TTh for an increased PSA. The remaining 6 men initiated TTh only after PCa diagnosis. Mean and median duration of TTh following the diagnosis of PCa was 3.1 and 2.5 years, respectively, with a range of 1.0 to 8.1.

A total of 12 men had Gleason score 6 disease on initial biopsy and 1 had Gleason score 7 (3 + 4).
Mean number of cores at initial biopsy was 10.7 (range 6 to 18). A single positive core was found in 11 men and 2 positive cores were found in 2. No core had greater than 30% involvement by cancer.

The mode of TTh was intramuscular injection of testosterone cypionate in 3 men and topical gel in 10. There were 2 men who changed to testosterone pellets late in the study period and 2 added oral agents known to increase serum T (clomiphene citrate, anastrozole) episodically during TTh. Patient number 13 discontinued TTh for 1 year while remaining on anastrozole and then resumed gel therapy.

Blood test results are presented in table 2. Mean duration of TTh was 3.1 years (median 2.5). Mean concentrations of TT and FT increased from 238 to 664 ng/dl (p <0.001) and 6.5 to 22.2 pg/ml (p <0.001), respectively. Mean serum LH decreased from 4.0 to 2.1 IU/l (p = 0.04) and mean FSH decreased from 11.9 to 5.3 IU/l (p = 0.002).

**Table 1. Baseline patient characteristics**

<table>
<thead>
<tr>
<th>No. comorbidities:</th>
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<tbody>
<tr>
<td>Hypertension</td>
<td>4</td>
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<tr>
<td>Diabetes</td>
<td>1</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>1</td>
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<tr>
<td>Hypothyroidism</td>
<td>1</td>
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</tbody>
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Mean ng/ml PSA at PCa diagnosis (median) 5.1 (4.0)
Mean ng/dl TT (SD) 238 (116)
Mean ng/dl FT (SD) 6.5 (3.0)
Mean ng/ml prolactin (SD) 9.4 (5.3)
Mean mlU/l thyroid - stimulating hormone (SD) 1.5 (0.9)
Mean pg/ml estradiol (SD) 47.7 (13.0)
Mean nmol/l SHBG (SD) 43.7 (19.9)
Mean IU/l LH (SD) 4.0 (2.1)
Mean IU/l FSH (SD) 11.9 (7.3)
Mean % hematocrit (SD) 43.5 (5.0)

No. symptoms of T deficiency at baseline:
Erectile dysfunction 10
Decreased libido 9
Fatigue/low energy 3
Depressed mood 3

Mean PSA did not change significantly with TTh (see figure). The mean value at initial biopsy was 5.5 ± 6.4 ng/ml (range 0.6 to 24.1) and at most recent biopsy it was 3.6 ± 2.6 ng/ml (range 0.6 to 10.0, p = 0.29). An increase in serum PSA of 0.5 ng/ml or greater with TTh was found in 3 men, while 4 exhibited a PSA decrease of this magnitude with TTh. Prostate volume did not change with TTh and prostate nodules did not develop in any men.

All men underwent at least 1 followup biopsy for a total of 26 followup biopsies. Of these, 14 biopsies (54%) revealed no cancer. No man required additional biopsy for clinical concerns. Two men had followup biopsies suggestive of clinical progression. In 1 man Gleason 7 (3 + 4) disease was reported in 5% of 1 core whereas the initial biopsy revealed low volume Gleason 6 disease. Two subsequent annual biopsies have revealed only low volume Gleason 6 disease and he continues with TTh.

Another patient underwent radical prostatectomy after a followup biopsy showed Gleason score 7 (4 + 3) in 1 of 12 cores with 75% involvement. This occurred 8 years after the original positive biopsy revealed Gleason score 6 in 5% of 1 core. Final pathology revealed Gleason score 6 disease involving 5% of the prostate, with negative margins and nodes. No differences were noted between men who received TTh before or only after a diagnosis of prostate cancer. The 2 cases of possible upgrading previously mentioned included 1 man from each group.

**DISCUSSION**

This study is the first to our knowledge to provide direct evidence regarding the effects of T administration in a group of men with TD with untreated, localized PCa. All 13 men in this series elected active surveillance for PCa, received at least 12 months of TTh for symptoms of TD and underwent 1 or more

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**Table 2. Results of testosterone therapy on blood tests and prostate volume**

<table>
<thead>
<tr>
<th></th>
<th>Mean Baseline (SD)</th>
<th>Mean TTh (SD)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT (ng/dl)</td>
<td>238 (116)</td>
<td>664 (219)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Range</td>
<td>64–413</td>
<td>308–969</td>
<td></td>
</tr>
<tr>
<td>FT (pg/ml)</td>
<td>6.5 (3.0)</td>
<td>22.2 (8.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Range</td>
<td>1.5–10.8</td>
<td>12.7–38.3</td>
<td></td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>43.5 (5.0)</td>
<td>44.1 (1.7)</td>
<td>0.71</td>
</tr>
<tr>
<td>FSH (IU/l)</td>
<td>11.9 (7.3)</td>
<td>5.3 (5.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>LH (IU/l)</td>
<td>4.0 (2.1)</td>
<td>2.1 (2.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>SHBG (nmol/l)</td>
<td>43.7 (19.9)</td>
<td>40.5 (17.1)</td>
<td>0.50</td>
</tr>
<tr>
<td>Estradiol (pg/ml)</td>
<td>47.7 (13.0)</td>
<td>55.6 (19.4)</td>
<td>0.19</td>
</tr>
<tr>
<td>Prostate vol (cc)</td>
<td>51.1 (28.7)</td>
<td>55.1 (28.8)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

For men receiving testosterone injections posttreatment testosterone values were obtained during the latter half of the injection cycle. All others were obtained during treatment with gel alone.

* Statistical significance assessed by 2-tailed t-test for repeated measures with p <0.05 considered significant.
followup biopsies. Median duration of TTh was 2.5 years. All men experienced symptomatic improvement in libido, sexual performance, mood or energy.

None of the men demonstrated definite cancer progression during TTh. Two individuals had apparent disease upgrading that was not confirmed with further followup. Of these cases 1 was based on upgrading to Gleason 7 on a biopsy that returned to Gleason 6 on 2 subsequent followup annual biopsies. In a second case radical prostatectomy was performed for apparent upgrading to Gleason 7 on biopsy yet final pathology revealed only low volume Gleason 6 disease. This case is unlikely to represent true PCa progression.15

These results suggest that TTh in men with TD with localized PCa does not cause cancer progression during 1 to 8 years. These results are notable for what did not occur given the historical belief that T administration causes activation or more rapid growth of PCa.16 No individual experienced incontrovertible changes in PCa volume or grade, or a worrisome increase in PSA. No individual had evidence of metastases, extraprostatic disease or a palpable prostatic nodule. No significant changes in PSA or prostate volume were noted.

These results are contradictory to the traditional belief that higher T necessarily leads to greater PCa growth,17 but are consistent with a substantial literature in which prostate growth, malignant and benign, appears indifferent to serum T from the near physiologic to the supraphysiologic range.11 A global longitudinal study of 3,886 men with PCa and 6,438 age matched controls revealed no association of PCa with total T, free T or DHT.8 A 2004 review concluded that the PCa detection rate in TTh trials was no higher than in the general population,18 and a meta-analysis of 19 TTh trials found no greater PCa risk among men who received TTh vs those who received placebo.19 PCa developed in only 1 of 20 men with prostatic intraepithelial neoplasia after 1 year of TTh.20 Administration of supraphysiologic T doses for 40 weeks resulted in no significant change in PSA or prostate volume,21 and PSA appeared unaffected by physiologic variations in serum T.22

Three studies have been published regarding the use of TTh in men following radical prostatectomy, in a total of 74 men, without PCa recurrence noted.4–6 There was no biochemical recurrence in 31 men who received TTh for a median of 4.5 years following brachytherapy.7 A small study of 5 men who received TTh for a mean of 14 months following external beam radiation therapy also revealed no biochemical recurrence.23

Historical studies suggest that T administration causes rapid PCa growth in androgen deprived men with advanced PCa but not in hormonally intact men.11 Huggins and Hodges provided results of T administration in 2 men, 1 previously castrated,16,17 and erratic acid phosphatase results were noted in the other. Prout and Brewer noted rapid progression or death in 5 of 10 previously castrated men but no progression in another group of 26 men, 20 of whom were intact and 6 who had just undergone castration.24 Fowler and Whitmore noted an unfavorable response in 45 of 52 men with metastatic PCa who underwent T administration.25 However, all but 4 of these men were androgen deprived when they received T. The clinical course of the 4 hormonally intact men was relatively benign, with 3 continuing to receive daily T injections for 52, 55 and 310 days, respectively.

A wealth of data from various sources including human, animal and PCa cell lines indicates that androgen deprived prostate tissue, malignant and benign, responds rapidly and vigorously to the addition of androgen. However, at higher androgen concentrations prostate tissue appears to become androgen indifferent.11 This biphasic relationship of prostate growth to serum T is consistent with a saturation model in which androgen stimulated growth reaches its limit just beyond the near 100 nmol (approximately 120 ng/dl).29 Another possible mechanism is suggested by the study in which 44 men with TD underwent injections of T or placebo. At 6 months serum T and DHT increased substantially in treated men but intraprostatic concentrations were unchanged from baseline.9 Intraprostatic androgen concentrations decrease proportionally less than serum concentrations after luteinizing hormone-releasing hormone antagonist administration.30 Thus, the intraprostatic hormonal milieu appears to differ significantly from serum, and as yet undetermined regulatory mechanisms may provide some degree of local androgen homeostasis.

The limitations of this study include small population size, and inclusion of men with only low volume and low to moderate grade disease. It is unknown how men with higher grade, or larger volume or metastatic PCa would respond to TTh. The possibility of a causal relationship cannot be excluded.
for men who received TTh before the diagnosis of PCAs. The study is retrospective and uncontrolled. Nonetheless, this study provides for the first time a rigorous and direct assessment of the prostate over time in a group of men with untreated PCAs treated with TTh for durations of 1 year or longer.

CONCLUSIONS
These results are consistent with the saturation model that posits that naturally occurring serum androgen concentrations found in most men with TD at baseline are sufficient to produce maximal androgen mediated PCa growth, and additional availability of T elicits little, if any, additional growth. These results suggest that the longstanding prohibition against offering TTh in symptomatic men with PCa merits reevaluation. Furthermore, these results raise the possibility that the stimulatory effect of hormones on other cancers, such as breast cancer, may also be concentration dependent and subject to a saturation effect.

REFERENCES


EDITORIAL COMMENTS

For more than 60 years it has been widely accepted that T administration causes PCa growth or adds fuel to the fire (reference 16 in article). In this study 13 symptomatic men with TD and untreated PCa received testosterone therapy for a mean of 2.5 years. In this small cohort of men (mean age approximately 59 years) posttreatment biopsies revealed no change in prostate volume or PSA and no definite cancer progression in any man. No cancer was found in 54% of followup biopsies. These results suggest this is a seminal article, requiring further validation and elaboration.

These findings are most consistent with the previously described saturation model (reference 11 in article). The saturation theory suggests that PSA and prostate tissue growth are sensitive to changes in serum testosterone levels only when testosterone serum levels are low and the androgen receptor has unfilled capacity to bind additional androgen. Conversely, at higher serum testosterone levels all androgen receptors are saturated by hormone and any further increases in testosterone have no effect on prostate size or PSA levels. While the saturation theory explains the lack of an observed relationship between testosterone and PSA in eugonadal men, it is unclear if this theory holds true in testosterone deficient cases. Although the number of subjects is small, we now have evidence that this theory may indeed be true in men with untreated PCa and TD. This is a remarkable shift in thinking from only 5 years ago. Perhaps further studies might reveal that treatment of TD may even improve PCa outcomes. Lastly, if T therapy was not associated with disease progression in men with untreated PCa, how concerned must we be about T therapy in men with treated PCa?

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Several publications have suggested that TTh can safely be given after treated prostate cancer in carefully selected patients (references 5, 7 and 23 in article). This study further expands upon this controversial treatment by applying TTh in patients on active surveillance for untreated prostate cancer. Although this approach is feasible, it is experimental at this point and patients should be appropriately cautioned. Nevertheless, it adds to the body of literature that restoration of patients to a eugonadal state may not stimulate prostate cancer growth.

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