

Two Years of Testosterone Therapy Associated with Decline in Prostate-Specific Antigen in a Man with Untreated Prostate Cancer

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ABSTRACT

Introduction. Testosterone (T) therapy has long been considered contraindicated in men with prostate cancer (PCa). However, the traditional view regarding the relationship of T to PCa has come under new scrutiny, with recent reports suggesting that PCa growth may not be greatly affected by variations in serum T within the near-physiologic range.

Aim. This report details the clinical and prostate-specific antigen (PSA) response of a man with untreated PCa treated with T therapy for 2 years.

Methods. Measurements of serum PSA, total and free T concentrations were obtained at regular intervals at baseline and following initiation of T therapy.

Main Outcome Measure. Serum PSA during T therapy.

Results. An 84-year-old man was seen for symptoms of hypogonadism, with serum total T within the normal range at 400 ng/dL, but with a reduced free T of 7.4 pg/mL (radioimmunoassay [RIA], reference range 10.0–55.0). PSA was 8.5 ng/mL, and 8.1 ng/mL when repeated. Prostate biopsy revealed Gleason 6 cancer in both lobes. He refused treatment for PCa, but requested T therapy, which was initiated with T gel after informed consent regarding possible cancer progression. Serum T increased to a mean value of 699 ng/dL and free T to 17.1 pg/mL. PSA declined to a nadir of 5.2 ng/mL at 10 months, increased slightly to 6.2 ng/mL at 21 months, and then declined to 3.8 ng/mL at 24 months after addition of dutasteride for voiding symptoms. No clinical PCa progression was noted.

Conclusion. A decline in PSA was noted in a man with untreated PCa who received T therapy for 2 years. This case provides support for the notion that PCa growth may not be adversely affected by changes in serum T beyond the castrate or near-castrate range. **Morgentaler A. Two years of testosterone therapy associated with decline in prostate-specific antigen in a man with untreated prostate cancer. J Sex Med **;**:**~**.**

Key Words. Testosterone; Prostate Cancer; Hypogonadism

Introduction

For several decades, there has been general agreement that testosterone (T) therapy is contraindicated in men with a history of, or suspicion of prostate cancer (PCa) due to the fear that higher serum T would lead to cancer recurrence or progression. However, recent publications have failed to find a correlation between PCa and serum T in noncastrated men [1,2], and there are now several studies that have reported no PCa recurrence in men receiving T therapy after definitive treatment of localized PCa [3–5]. Although these latter reports suggest that T therapy may not be as

risky as once believed in men with a prior history of PCa [6]; the biologic effect of T therapy in these men is uncertain since the absence of PCa recurrence may simply reflect complete eradication of the cancer.

This report details the effect of 2 years of T therapy in a man with untreated PCa.

Case Report

This is a case report of an 84-year-old male seen for erectile dysfunction and anorgasmia. Despite his age, he continued to work as an attorney and exercised three times weekly. Treatment with

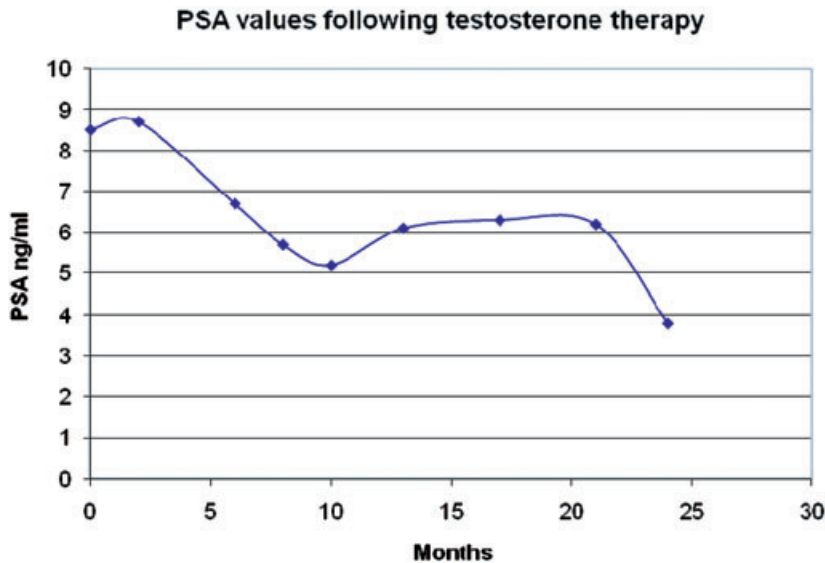


Figure 1 Prostate-specific antigen values at baseline (0 months) and for 24 months of testosterone therapy in an 84-year-old man after diagnosis of prostate cancer, without treatment. Dutasteride was added at month 21, but was discontinued after approximately 1 month.

sildenafil 50 mg had been ineffective. Past medical history was notable only for atrial fibrillation, treated with coumadin. Physical examination revealed normal external genitalia and a moderately enlarged prostate without tenderness or nodularity. Blood tests were notable for total T of 400 ng/dL, but free T was reduced at 7.4 pg/mL (RIA, reference values 10–55 pg/mL). In addition, PSA was elevated at 8.5 ng/mL, and 8.1 ng/mL when repeated. Prostate biopsy revealed Gleason 6 cancer in two of six cores, involving 30% of one core and 5% of the other, at the right and left base, respectively. Prostate volume was 35 cc.

After discussion, the patient declined treatment for his PCa. In addition, the patient requested T therapy for his hypogonadism despite being advised that T therapy was considered contraindicated in men with PCa, and there was a potential risk of disease progression and even death.

Treatment was begun with T gel (Androgel) at 5 g topically daily, and was titrated up to 10 g daily. Two months following prostate biopsy, the patient developed urinary urgency and was treated with 14 days of ciprofloxacin, followed 2 months later by an *E. coli* urinary infection treated successfully with sulfa/trimethoprim. With T therapy, the patient experienced improved erection quality and increased libido, energy, and sense of vigor. Anorgasmia did not resolve. He also uses tadalafil 20 mg, as needed.

Blood tests for total T, free T, and PSA were obtained approximately every 2–3 months over the course of 2 years of treatment. Mean total T concentration was 699 ng/dL and mean free T

17.1 pg/mL. From a baseline PSA of 8.1–8.5 ng/mL, the PSA concentration was 8.7 ng/mL at 2 months, and then declined to 6.7 ng/mL at 6 months, 5.7 ng/mL at 8 months, and 5.2 ng/mL at 10 months (Figure 1). From that point, it increased slightly and was stable at 6.2–6.3 ng/mL for 8 months. At 21 months, dutasteride was added for lower urinary tract symptoms, but was discontinued 1 month later due to the patient's reluctance to take additional medications and a lack of perceived benefit. At 24 months, the PSA was 3.8 ng/mL. Prostate exam remains unchanged, without nodularity or other abnormality. There was no gynecomastia prior to or following T therapy. Hematocrit was within normal limits at all times. The patient has declined follow-up prostate biopsy.

Discussion

This appears to be the first report of T therapy in a man with untreated PCa in the PSA era. The case is noteworthy for what did *not* occur. Despite the presence of multifocal disease and a moderately elevated PSA, 2 years of T therapy did not result in clinical or biochemical progression of PCa. In fact, serum PSA declined during T therapy from a baseline of 8.1–8.5 ng/mL to 6.2–6.3 ng/mL at 21 months (and lower still after addition of dutasteride). It is possible this decline simply reflected resolution of subclinical inflammation, although it is interesting to speculate whether this decline may have resulted directly

from T therapy itself, based on research indicating that T has antiproliferative activity in the prostate [7].

Despite the longstanding prohibition against the use of T therapy in men with a prior history of PCa, there are now at least three publications demonstrating a lack of PCa recurrence with T therapy after definitive PCa treatment. Two articles have reported no PSA recurrence in a total of 17 men, following radical prostatectomy (RRP) in men with undetectable PSA [3,4]. A third study reported that no cancer recurrence was noted in 31 hypogonadal men treated with brachytherapy with a follow-up of approximately 5 years [5]. These small studies suggest that normalization of T in men with definitively treated PCa may not be as risky as once believed.

A number of reports prior to 1982 detail the effects of T administration to men with advanced or metastatic PCa. Although T administration in castrated men produced reliable and rapid PCa progression, T administration in men without prior castration was not associated with evident progression, as determined by clinical course and acid phosphatase [8,9]. In addressing the benign course of noncastrated men with metastatic PCa who received T injections, Fowler and Whitmore postulated that naturally occurring serum T concentrations provided near-maximal stimulation of PCa, and that additional T was thus without effect [8]. That concept is consistent with a saturation model for the relationship of T and PCa [10], which in turn reflects the observation that maximal binding of androgen to the androgen receptor occurs experimentally at very low T concentrations [11]. Marks et al. also reported that intraprostatic androgen concentrations were unchanged when hypogonadal men received 6 months of T injections [12]. This case involving the patient appears to be consistent with this literature.

Although it may seem a departure from standard therapy to provide T therapy to an individual with untreated PCa, it must be acknowledged that a substantial number of men who receive T therapy consistent with established clinical protocols also have PCa, albeit undiagnosed, without evidence that T therapy increases their risk of PCa. In one study, prostate biopsy in 345 men with hypogonadism and PSA ≤ 4.0 ng/mL revealed PCa in 52 men (15%) [13]. Yet the cancer rate among hypogonadal men in T therapy trials is only approximately 1% [14], and a recent meta-analysis has failed to show that hypogonadal men who received T therapy developed PCa at a

greater rate than men who received placebo [15]. If raising T in hypogonadal men reliably caused PCa to grow more rapidly, one would expect to see a high rate of PCa in men undergoing T therapy, given the substantial number of men with occult but biopsy detectable cancer in that population.

One must be extremely cautious in drawing conclusions from a single case, yet this report provides additional evidence that raising serum T in men with modest, naturally occurring T deficiencies does not necessarily precipitate rapid PCa growth. Whereas there is no dispute that optimal growth of PCa requires the presence of androgen, accumulating evidence suggests there is a serum T concentration at which maximal PCa stimulation occurs, and that this saturation point occurs in the near-castrate range [10]. Perhaps the strongest evidence in this regard is the recently published global pooled analysis of 18 longitudinal studies revealing that PCa risk is unrelated to serum androgen concentrations [2]. As the number of men undergoing surveillance for PCa increases, there will be greater demand from patients for treatment of their hypogonadism. A critical re-evaluation of traditional concepts regarding the relationship of T and PCa is warranted.

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