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# Prostate-Specific Antigen Changes in Hypogonadal Men Treated With Testosterone Replacement

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**ABSTRACT:** Testosterone supplementation is commonly used as a treatment for hypogonadal men with or without erectile dysfunction. The effect of parenteral testosterone replacement therapy on the development or growth of prostate cancer is unclear. We assessed the effect of this treatment on serum prostate-specific antigen (PSA) levels and risk of prostate cancer in hypogonadal men with erectile dysfunction. Criteria for inclusion were a normal pretreatment PSA (<4.0 ng/mL) in conjunction with a normal digital rectal examination (DRE) or a negative pretreatment prostate biopsy for men with either an abnormal DRE or an elevated PSA. Patients received intramuscular injections every 2 to 4 weeks, allowing for dose titration. In this retrospective analysis, 54 hypogonadal men with erectile dysfunction were included, with a mean age of 60.4 years (range 42.0–76.0) and a mean follow-up of 30.2 months (range 2.0–82.0) on testosterone therapy. Mean pretreatment total testosterone level was 1.89 ng/mL (range 0.2–2.92), which increased during treatment to a mean of 9.74 ng/mL (range 1.50–26.30, $P < .001$). Mean pretreatment PSA was 1.86 ng/mL (median 1.01 ng/mL, range 0.0–15.80), which increased to a mean PSA level of 2.82 ng/mL (median 1.56 ng/mL, range 0.0–32.36, $P < .01$) with testosterone treatment. Of the 54 men included in this study, 6 (11.1%) required prostate biopsy while on testosterone therapy because of a rise in serum PSA above 4.0 ng/mL. One patient (1.9%) was diagnosed with prostate cancer. In conclusion, testosterone replacement therapy in men with erectile dysfunction and hypogonadism is associated with a minor PSA elevation, but there does not appear to be a short-term increase in risk for the development of prostate cancer.

Key words: Prostate cancer, impotence, hypogonadism.

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Testosterone supplementation is commonly used as a treatment for hypogonadal men with or without erectile dysfunction. Over the last decade, public attention to the male ''andropause'' and improvements in drug delivery formulations have led to a more widespread use of this form of therapy. However, from a malignancy standpoint, the safety of exogenous testosterone therapy has not been adequately assessed. The discovery of the androgen-dependent growth of prostate cancer revolutionized the field of genitourinary oncology (Huggins and Hodges, 1941). Androgen-ablative techniques induce a temporary remission in most men with advanced prostate cancer, and the addition of exogenous testosterone to men with metastatic cancer can cause the disease to flare (Thompson et al, 1990). It is not surprising that this strong relationship between prostate cancer and androgens raises serious concerns over the treatment of men with testosterone replacement therapy. We evaluated the serum prostate-specific antigen (PSA) changes in a group of hypogonadal men with erectile dysfunction treated with parenteral testosterone replacement.

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## Materials and Methods

We retrospectively reviewed the records of all hypogonadal men with erectile dysfunction started on testosterone replacement therapy from October 1993 to August 1999 at 2 institutions. All patients had a low serum total testosterone level (<3.0 ng/mL) measured by an electrochemiluminescence method (Roche Elecsys 2010, Roche Diagnostics, Basel, Switzerland). For inclusion in this study, patients were required to have had a serum pretreatment PSA level measured within 2 months of starting testosterone replacement and to have had at least 1 PSA measurement during the treatment phase. Total serum PSA was measured by a chemiluminescence method with a 2-site sandwich immunoassay. Inclusion also required either a normal pretreatment PSA level (<4 ng/mL) with a normal digital rectal examination (DRE) or a pretreatment prostate biopsy negative for cancer for patients with an abnormal DRE or an elevated PSA level. Patients were excluded if they were started on finasteride during the treatment period.

Of 82 hypogonadal patients identified, 28 (34.1%) did not meet inclusion criteria. Reasons for exclusion included no recorded PSA level during the testosterone treatment phase in 14 patients, no recorded pretreatment PSA level in 11 patients, no

Table 1. *Characteristics of all hypogonadal men on parenteral testosterone replacement**

| | n = 54 (range) |
|---|---|
| Mean follow-up (mo) | 30.2 (2.0–82.0) |
| Mean age (y) | 60.4 (42.0–76.0) |
| Mean pretreatment total testosterone (ng/mL) | 1.89 (0.20–0.292) |
| Mean total testosterone during treatment (ng/mL) | 9.74 (1.50–26.30) |
| Mean pretreatment PSA (ng/mL) | 1.86 (0.0–15.80) |
| Mean posttreatment PSA (ng/mL) | 2.82 (0.0–23.36) |
| No. patients requiring prostate biopsy | 6 (11.1%) |
| No. patients diagnosed with prostate cancer | 1 (1.9%) |

* PSA indicates prostate-specific antigen.

recorded pretreatment testosterone level in 2 patients, and initiation of finasteride therapy for benign prostatic hyperplasia during testosterone replacement in 1 patient. Overall, 54 (65.9%) men were included in our analysis.

Patients received intramuscular injections of testosterone cypionate every 2 to 4 weeks. Treatment was initiated at a dose of 200 to 300 mg every 2 to 3 weeks, depending on urologist preference. Dosages were titrated on the basis of subsequent testosterone levels and clinical efficacy. Follow-up was measured from the time testosterone supplementation was initiated to the date of the most recent PSA during therapy. Indications for prostate biopsy while on testosterone replacement included a newly discovered abnormality on a DRE, an elevated PSA greater than or equal to 4 ng/mL, and an elevated PSA velocity (≥0.75 ng/mL/y) (Smith and Catalona, 1994). Prostate biopsy was performed by a transrectal ultrasound guided technique, and at least 4 random core biopsies were taken from each side of the prostate. The pathology reports were reviewed for the presence of prostate cancer, the primary endpoint of the study.

Statistical analysis for comparison of pretreatment and posttreatment PSA levels and testosterone levels was performed with the Wilcoxon signed rank test for nonnormal distributions. The Mann-Whitney *U* test and *t* test were used to compare variables in men requiring prostate biopsy while on testosterone therapy to those not requiring biopsy, with *P* values less than .05 considered significant.

## Results

Mean length of follow-up on testosterone supplementation for the 54 patients was 30.2 months (range 2.0–82.0). Mean age at inception of testosterone therapy was 60.4 years (range 42.0–76.0). Total testosterone levels increased from a pretreatment mean of 1.89 ng/mL (range 0.20–2.92) to a mean of 9.74 ng/mL (range 1.50–26.30) during therapy ($z = -6.24$, $P < .001$). Serum PSA increased on testosterone replacement from a pretreatment mean of 1.86 ng/mL (median 1.00, range 0.0–15.80) to a mean of 2.82 ng/mL (median 1.56, range 0.0–32.36) during therapy ($z = -3.10$, $P < .01$, Table 1). Mean PSA change with therapy was 0.96 ng/mL.

Of the 54 patients, 6 (11.1%) required prostate biopsy. All 6 biopsies were performed because of a rise in serum PSA above 4.0 ng/mL. Overall, prostate cancer was diagnosed in only 1 (1.9%) patient. This patient was a 60-year-old man with a pretreatment PSA of 3.70 ng/mL. After 15 months of testosterone injection therapy, he was found to have a rise in his PSA to 5.90 ng/mL. Subsequently, biopsy was performed, which demonstrated prostate cancer.

The mean pretreatment serum PSA level in the group of 6 patients requiring prostate biopsy during therapy was 5.84 ng/mL (range 0.0–15.80). For the 48 patients not requiring biopsy, mean pretreatment serum PSA level was 1.36 ng/mL (range 0.0–6.23, Table 2). This difference was significant ($P < .01$). There was no significant difference found for age, duration of therapy, or total testosterone levels between the 2 groups ($P > .05$).

A subset analysis was performed to examine the effects of testosterone replacement on the serum PSA of patients with a minimum of 36 months of consecutive treatment. This subset included 19 of the 54 men (35.2%) with a mean follow-up of 58.5 months (range 38.0–82.0). The mean age of the 19 patients at start of therapy was 61.3 years (range 49.0–71.0). Total testosterone levels increased from a pretreatment mean of 1.84 ng/mL (range 0.60–2.60) to a mean of 9.38 ng/mL (range 2.00–22.20) during therapy ($P < .001$). Mean pretreatment PSA was 1.07 ng/mL (range 0.0–2.80) and increased to a mean of 1.66 ng/mL (range 0.0–3.80) on androgen replacement ($P < .05$, Table 3). No patient in this subset required a biopsy, and no patient was diagnosed with prostate cancer.

## Discussion

Exogenous testosterone therapy may unmask an occult adenocarcinoma of the prostate in hypogonadal men (Guinan et al, 1976; Jackson et al, 1989; Loughlin and Richie, 1997; Curran and Bihrle, 1999). One report showed a 29% incidence of occult prostate cancer in a group of men aged 60 years or older with low serum testosterone levels and normal PSA levels (Morgentaler et al, 1996). Moreover, autopsy series show that the overall frequency of latent prostate cancer is between 20% and 40% for men aged 60 to 80 years (Muir et al, 1991). Although many of these undetected cancers probably have limited invasive potential, the addition of exogenous androgen stimulation may theoretically lead to cancer growth and spread.

Perhaps of as much concern is the possible causative role of chronic androgen replacement therapy in the development of malignancy from normal prostatic tissue,

Table 2. *Comparison of patients on parenteral testosterone replacement requiring prostate biopsy vs patients not requiring biopsy**

| | Biopsy n = 6 | No Biopsy n = 48 | *P* Value |
|---|---|---|---|
| Mean pretreatment total testosterone level (ng/mL) | 1.97 | 1.88 | NS |
| Mean total testosterone level during treatment (ng/mL) | 9.18 | 9.81 | NS |
| Mean age (y) | 61.7 | 60.2 | NS |
| Mean duration of testosterone therapy (mo) | 14.1 | 32.2 | NS |
| Mean pretreatment PSA (ng/mL) | 5.84 | 1.36 | <.01 |
| Mean posttreatment PSA (ng/mL) | 11.84 | 1.69 | <.01 |

* NS indicates not significant; PSA, prostate-specific antigen.

exemplified by a report of prostate cancer in a 38-year-old bodybuilder who chronically used anabolic steroids over a period of 18 years (Roberts and Essenhigh, 1986). Since eunuchs do not develop prostate cancer, it seems that physiologic amounts of testosterone have at least a permissive role in the development of this malignancy. Nevertheless, prolonged testosterone administration has been shown to induce prostate cancer in a rat model (Noble, 1977) and in a human prostatic epithelial cell line (Wang et al, 2001).

Epidemiologic data also support the possible role of testosterone as a prostatic carcinogen. Caucasian men have a 26 times higher incidence of clinically overt prostate cancer than Chinese men (Yu et al, 1991). This higher risk of prostate cancer is possibly related to differences in androgen metabolism resulting from environmental and dietary factors (Santner et al, 1998).

Despite the theoretical dangers of treating hypogonadal men with testosterone therapy, there are relatively few studies that evaluate the long-term safety of this treatment. The vast majority of prospective and retrospective studies examining this issue report only the short-term effects of testosterone on PSA levels and risk of prostate cancer, with a mean duration of androgen therapy ranging from 2 to 36 months (Tenover, 1992; Holmang et al, 1993; Douglas et al, 1995; Arver et al, 1997; Hajjar et al, 1997; Meikle et al, 1997; Sih et al, 1997; Svetec et al, 1997; Snyder et al, 1999; Guay et al, 2000). Gooren (1994) found no cases of prostate cancer in 33 men between 15 and 62 years of age treated with oral testosterone undecanoate for a minimum of 10 years. However, the majority of patients in this study were under the age of 50 years at start of therapy, and serum PSA changes were not reported. Likewise, Behre et al (1999) evaluated 11 men with a mean age of 35.9 years treated with transscrotal testosterone patches for 7 to 10 years. They found no significant change in PSA levels with treatment, and no patient required prostate biopsy.

Table 3. *Characteristics of hypogonadal men on parenteral testosterone for a minimum of 36 months**

| | n = 19 (range) |
|---|---|
| Mean follow-up (mo) | 58.5 (38.0–82.0) |
| Mean age (y) | 61.3 (49.0–71.0) |
| Mean pretreatment total testosterone (ng/mL) | 1.84 (0.60–2.60) |
| Mean total testosterone during treatment (ng/mL) | 9.38 (2.00–22.20) |
| Mean pretreatment PSA (ng/mL) | 1.07 (0.0–2.80) |
| Mean posttreatment PSA (ng/mL) | 1.66 (0.0–3.80) |
| No. patients requiring prostate biopsy | 0 (0.0%) |
| No. patients diagnosed with prostate cancer | 0 (0.0%) |

* PSA indicates prostate-specific antigen.

The cumulative data from these studies (Table 4) indicate that the unmasking of an occult prostate carcinoma in the immediate period after starting exogenous testosterone is a rare event. However, none of the studies have adequate follow-up in older men to determine if exposing a latent prostate cancer to exogenous testosterone over a relatively longer time frame may induce it into clinically overt cancer. Furthermore, if exogenous testosterone supplementation has a carcinogenic role in the development of cancer from normal tissue, the risk may not become apparent for 5, 10, or even 20 years.

Lack of a control group is a limiting factor in the interpretation of our finding of a relatively small rise in PSA of 0.96 ng/mL over a mean duration of therapy of 30.2 months. It is reasonable to speculate that the growth of prostatic tissue that coincides with aging alone is responsible for a significant portion of this rise in PSA. However, it has been demonstrated that prostate volumes increase in hypogonadal men treated with androgen replacement to sizes comparable to those in eugonadal men (Behre et al, 1994) but revert back to smaller sizes after androgen withdrawal (Meikle et al, 1997). Svetec et al (1997) studied 48 hypogonadal men treated with parenteral testosterone replacement. The mean increase in PSA after initiating testosterone therapy was 0.29 ng/mL, with a mean interval between PSA determinations of 12.8 months. Prostate biopsy was performed in 11 men, but all biopsies were benign. Of interest, PSA velocity was measured in this study, and testosterone supplementation did not alter the PSA velocity beyond established normal levels. In a 36-month randomized study, Snyder et al

Table 4. *Literature review of PSA changes and risk of prostate cancer with testosterone supplementation in hypogonadal men**

| Study (lead author) | No. Treated Patients | Delivery Route | Treatment Duration (mo) | Mean PSA Change (ng/mL) | No. With Cancer |
|---|---|---|---|---|---|
| Tenover (1992) | 13 | IM | 3 | 0.6 | 0 |
| Sih et al (1997) | 10 | IM | 12 | 0.7 | 0 |
| Hajjar et al (1997) | 26 | IM | 24 | 0.49 | 0 |
| Svetec et al (1997) | 48 | IM | 12.8 | 0.29 | 0 |
| Guay et al (2000) | 16 | Patch | 3 | 0.2 | 3 |
| | 25 | IM | 3 | 0.63 | (overall) |
| | 48 | Clomiphene | 3 | 1.0 | |
| Snyder et al (1999) | 54 | Patch | 36 | 0.6 | 1 |
| Present study: all time points | 54 | IM | 30.2 | 0.96 | 1 |
| More than 36 mo only (subset) | 19 | IM | 58.5 | 0.59 | 0 |

* IM indicates intramuscular; PSA, prostate-specific antigen.

(1999) found a small but statistically significant rise in mean PSA of 0.6 ng/mL in the testosterone treatment arm of 54 men. Prostate biopsy was performed in 4 patients, but cancer was diagnosed in only one. The mean serum PSA concentration did not significantly change in the placebo arm.

Although we recognized the drawback of a retrospective design, our study showed that over a mean follow-up of 30.2 months, there did not appear to be an increased risk of prostate cancer. Despite 6 men requiring biopsy, only 1 patient (1.9%) in our series of 54 men on testosterone therapy developed prostate cancer. A more accurate assessment of the number of men with prostate cancer in this series would be obtained by performing prostate biopsy in all patients. It is possible some men harbor significant malignancies undetectable by standard screening with PSA and DRE. Moreover, the relatively small sample size in this study, similar to the other studies in Table 4, limits the ability to detect small increases in the risk of prostate cancer with testosterone replacement therapy. Since no large-scale, prospective studies are planned to evaluate the risk of prostate cancer with testosterone supplementation, we believe studies like this one add valuable information concerning the safety profile of this therapy.

A significant number of men in our analysis discontinued testosterone therapy within 1 year of treatment secondary to poor clinical results or unwillingness to tolerate drug administration. We therefore performed a subset analysis of 19 men on testosterone replacement for at least 36 consecutive months to assess any longer term effects of therapy on serum PSA levels or the development of prostate cancer. In this subset of patients with a mean follow-up of 58.5 months, no patient was diagnosed with prostate cancer. This subset analysis represents one of the longest follow-up evaluations of a significant number of older hypogonadal men on parenteral testosterone supplementation and suggests that there is likely no increased risk of prostate cancer after 4 to 5 years of continuous therapy.

In summary, parenteral testosterone replacement therapy in older hypogonadal men increased the serum PSA level by a mean of 0.96 ng/mL over a mean treatment duration of 30.2 months. Of 54 men, only one was diagnosed with prostate cancer during therapy. Before initiating treatment, a physician should obtain a mandatory serum PSA level and perform a DRE. Serum PSA levels and DREs are then required at frequent intervals during treatment. Any significant increase in PSA above established normal levels during treatment should be evaluated with prostate biopsy and not be attributed to testosterone therapy. Since no large, well-designed studies exist on men treated with testosterone for longer than 3 years, the long-term risk of prostate cancer secondary to testosterone replacement therapy remains to be determined.

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