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Clinical Research Article

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Prostate-Specific Antigen Concentrations in Response to Testosterone Treatment of Severely Hypogonadal Men

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Abbreviations: IQR, interquartile range; PSA, prostate-specific antigen.

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Abstract

Context: Clinical guidelines recommend measurement of the serum prostate-specific antigen (PSA) concentration during testosterone treatment of hypogonadal men to determine whether the increase is sufficiently high to warrant urologic referral. Prior studies of the effect of testosterone treatment on PSA concentrations have been conducted in men who were mildly to moderately hypogonadal.
Objective: The objective of this work is to determine the PSA response to testosterone treatment of men who are severely hypogonadal.
Design and Setting: This retrospective cohort study was conducted at a single academic medical center.
Participants: Eighty-five men participated who were severely hypogonadal as a result hypothalamic-pituitary or testicular disease.
Main Outcome Measure: Changes in serum PSA concentrations were measured during testosterone treatment for up to 18 months.
Results: Testosterone treatment increased the median serum testosterone concentration from 36 ng/dL (interquartile range [IQR], 20-91 ng/dL) at baseline to 395 ng/dL (IQR, 266-542 ng/dL) at 6 to 18 months. This treatment resulted in a median increment in PSA above baseline of 0.70 ng/mL (IQR, 0.10-1.85 ng/mL) at 6 to 18 months. Apropos current Endocrine Society clinical guidelines, 31% of the men experienced a PSA increase above baseline greater than 1.4 ng/mL, and 13% reached an absolute PSA concentration of greater than 4.0 ng/mL. Four men were diagnosed with prostate cancer.
Conclusions: The PSA response to testosterone replacement in men who are severely hypogonadal as a result of pituitary or testicular disease is greater than that previously reported in men with mild to moderate hypogonadism. These results suggest the

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magnitude of the PSA response to testosterone replacement is related to the degree of hypogonadism.

Key Words: PSA, testosterone, hypogonadism

Testosterone stimulates the growth and function of the prostate gland, including production of the enzyme prostate-specific antigen (PSA). Testosterone treatment of hypogonadal men has long been known to increase their serum PSA concentrations.

Prostate cancer also causes an increase in the serum PSA concentration [1], so it is common practice to monitor the PSA concentration in a man treated with testosterone to determine whether an increase is within the range expected or sufficiently high to warrant urological referral to evaluate for prostate cancer. Endocrine Society clinical guidelines recommend measuring serum PSA in hypogonadal men older than 50 years 3 and 12 months after initiating testosterone therapy and referring men for urologic evaluation if the serum PSA increases more than 1.4 ng/mL above baseline or to an absolute value of more than 4.0 ng/mL [2]. Neither of these criteria, however, are based on testosterone treatment of hypogonadal men.

Two recent studies did evaluate the effect of testosterone treatment on PSA concentrations in hypogonadal men and found relatively small increases. In the RHYME study, a registry of hypogonadal men, testosterone treatment of 750 men for 1 year increased the mean serum PSA concentration by 0.33 ng/mL [3]. In The Testosterone Trials of men with age-related hypogonadism, testosterone treatment of 395 men for 1 year increased the median serum PSA by 0.20 ng/mL [4]. In both of these studies, the degree of hypogonadism was mild to moderate; the mean baseline testosterone concentration in the RHYME study was 239 ng/dL, and in The Testosterone Trials the mean baseline testosterone concentration was 232 ng/dL.

The United States Food and Drug Administration (FDA) has approved testosterone preparations only for men who have classical hypogonadism due to known pituitary or testicular disease [5]. These men often have much lower serum testosterone concentrations and therefore might have lower baseline PSA concentrations and greater PSA increases in response to testosterone treatment. One study did show that very low endogenous serum testosterone concentrations was associated with very low PSA concentrations [6]. No prior studies, however, have reported the serum PSA responses to testosterone treatment of men who had severe hypogonadism. The goal of this study was to determine the magnitude and range of the increases in the PSA concentration in response to testosterone treatment of men with classical hypogonadism of a severe degree.

1. Materials and Methods

We collected data by retrospective chart review of men seen in Penn Medicine's outpatient endocrinology practice for treatment of severe hypogonadism from 2004 through 2019. The University of Pennsylvania Institutional Review Board approved this study.

A. Study Participants

Penn Medicine's Data Analytics Center identified patients seen by Penn Medicine endocrinology faculty from December 2004 to September 2019, by using International Classification of Diseases codes for hypopituitarism and primary hypogonadism. We reviewed paper charts of identified patients from December 2004 to August 2008, and electronic medical records thereafter. We included men as participants in this study who were age 50 years or older, had severe hypogonadism (baseline early-morning serum testosterone concentration < 175 ng/dL), were treated with a testosterone preparation for at least 3 months, and had testosterone and PSA measurements before and at least once during up to 18 months of testosterone treatment. We excluded men who had been treated with testosterone within 3 months prior to the baseline values or who had a history of prostate cancer.

B. Collection of Study Data

Serum testosterone and PSA were measured in the 2 major US commercial laboratories. PSA was measured by radioimmunoassay, and normal for men older than 50 years was less than 4.0 ng/mL during the entire study period. Testosterone was measured by radioimmunoassay until 2010 and by liquid chromatography/mass spectroscopy/mass spectroscopy afterward. Normal ranges for the 2 laboratories were similar before and after the change in methods and between the 2 laboratories: 280 to 800 ng/dL and 241 to 827 ng/dL. All values recorded as baseline values were obtained immediately before initiating testosterone treatment. Serum testosterone and PSA values were recorded from baseline and from months 1 to 3 and months 6 to 18 of testosterone treatment. Testosterone measurements in men being treated with testosterone esters were made midway between injections. The serum PSA was doubled for the 9 men taking a 5-α reductase

inhibitor to account for the known effect of this category of medication on the serum PSA concentration [7]. All 9 men continued to take the 5-α reductase inhibitor at each time point. Digital rectal examinations were performed prior to testosterone treatment. We recorded if a man was referred to a urologist, if he had a prostate biopsy, and if the biopsy demonstrated prostate cancer during the period of observation.

C. Statistical Analyses

Serum testosterone and PSA values were skewed, so these results are presented as percentiles. Association of PSA with testosterone was estimated using the Spearman correlation coefficient. Stata 16.1 statistical software (Stata Corp) was used for all analyses. A 2-tailed *P* value of less than .05 was considered statistically significant.

2. Results

A. Characteristics of Men at Baseline

Eighty-five severely hypogonadal men met the criteria for inclusion in the analyses. Their characteristics at baseline are presented in Table 1. Their mean age was 64.3 years. Sixty-five (76.4%) were White and 10 (11.8%) African American. Mean body mass index was 30.9 kg/m^2. The majority of men (88.2%) had been treated with transdermal testosterone formulations, mostly gels; the rest with injectable esters. Seventy-nine (92.9%) had secondary hypogonadism as a result of pathologic (organic) causes, including pituitary adenoma, pituitary apoplexy, hypophysitis, craniopharyngioma, and meningioma; the remainder had primary hypogonadism due to bilateral orchidectomy or mumps orchitis. Seventy-two men had never previously been treated with testosterone; of the 13 who had been previously treated, 6 discontinued it more than 6 months before the baseline visit, and 7 discontinued it 3 to 6 months before. By the entry criterion, the men were severely hypogonadal: The median serum testosterone concentration was 36 ng/dL (interquartile range [IQR], 20-91 ng/dL).

B. Increases in Serum Testosterone Concentrations

Testosterone treatment increased median serum total testosterone concentrations from severely hypogonadal (36 ng/dL; IQR, 20-91 ng/dL) at baseline to within the normal range (339 ng/dL; IQR, 175-511 ng/dL at months 1-3; and 395 ng/dL; IQR, 266-542 ng/dL) at months 6-18) (Figure 1).

C. Increases in Serum Prostate-Specific Antigen Concentrations

Testosterone treatment increased median serum PSA concentrations from 0.30 ng/mL (IQR, 0.10-0.85 ng/mL) at baseline to 0.95 ng/mL (IQR, 0.40-2.32 ng/mL) at months 1 to 3 and to 1.20 ng/mL (IQR, 0.50-2.60 ng/mL) at months 6 to 18 (see Figure 1). The median increment in PSA above baseline was 0.35 ng/mL (IQR, 0.10-1.25 ng/mL) at months 1 to 3 and 0.70 ng/mL (IQR, 0.10-1.85 ng/mL) at months 6 to 18 (Table 2). At months 6 to 18, 10% of the men had an increase of 4.30 ng/mL or greater (90th percentile) and 5% of men had an increase of 7.27 ng/mL or greater (95th percentile).

The increase in PSA exceeded 1.4 ng/mL in 12 men (19%) at months 1 to 3 and in 21 men (31%) at months 6 to 18 (Table 3). Excluding the 4 men whose absolute PSA concentration was greater than 4.0 ng/mL at baseline, an absolute PSA value of greater than 4.0 ng/mL was reached by 3 men (5%) at months 1 to 3 and 9 men (13%) at months 6 to 18.

When the 9 men who were taking 5-α reductase inhibitors were excluded from the analyses, the median increase of PSA above baseline at months 6 to 18, 0.65 ng/mL, was virtually the same as when all men were included, but the 90th and 95th percentile values were somewhat lower: 3.19 ng/mL and 4.30 ng/mL. Also when these 9 men were excluded, the percentage of men whose PSA increases from baseline at months 6 to 18 were more than 1.4 ng/mL

Table 1. Baseline characteristics of men with hypogonadism

Characteristic	
No.	85
Demographics	
Age, y, mean (95% CI)	64.3 (62.4-66.1)
Race, n (%)	
White	65 (76.4)
African American	10 (11.8)
Other	10 (11.8)
BMI, kg/m^2, mean (95% CI)	30.9 (29.6-32.2)
5-α reductase inhibitor use, n (%)	9 (10.6)
Etiology of hypogonadism, n (%)	
Primary hypogonadism	6 (7.1)
Secondary hypogonadism	79 (92.9)
Testosterone treatment formulation, n (%)	
Transdermal	75 (88.2)
Injectable	10 (11.8)
Testosterone, ng/dL, median (IQR)	36 (20-91)
Mean (95% CI)	55 (45-66)
PSA, ng/mL, median (IQR)	0.30 (0.10-0.85)

Abbreviations: BMI, body mass index; IQR, interquartile range; PSA, prostate-specific antigen.

and whose absolute PSA values increased to greater than 4.0 ng/mL changed very little: 27% and 12%, respectively.

The increment in PSA from baseline to months 6 to 18 was weakly associated with the increment in the serum testosterone concentration during the same period: Spearman correlation coefficient equal to 0.216; *P* equal to .077.

D. Prostate Biopsies and Prostate Cancer

Fourteen men were referred for urologic evaluation, all because of an increase in PSA. Of these, 7 had prostate biopsies. All 7 men had increases in PSA of more than 1.4 ng/mL, and 6 reached absolute PSA values greater than 4.0 ng/mL. An additional 8 men met 1 or both criteria for referral but were not referred; we were not able to determine the reasons they were not. We were also not able to determine the reasons biopsies were not performed in the other 7 men who were referred for urologic evaluation.

Three men had prostate biopsies based on their PSA values at months 1 to 3 (Table 3); one was diagnosed as prostate cancer, Gleason score 3 + 4. An additional 4 men had biopsies based on their PSA values at months 6 to 18; 3 were diagnosed as prostate cancer, Gleason scores 3 + 3, 3 + 3, and 3 + 4. Of the 4 men who were diagnosed with prostate cancer, the increases in PSA above baseline and corresponding absolute PSA values at the time of diagnosis were 2.1 ng/mL and 3.0 ng/mL; 4.3 ng/mL and 4.9 ng/mL; 4.2 ng/mL and 5.9 ng/mL; and 7.1 ng/mL and 8.2 ng/mL, respectively. Of the 4 prostate cancers, 3 were confined to the prostate and 1 had perineural invasion.

Table 2. Increases in prostate-specific antigen from baseline following testosterone treatment of severely hypogonadal men

Percentile	PSA increase from baseline, ng/mL	
	Mo 1-3	Mo 6-18
	(n = 62)	(n = 68)
50th	0.35	0.70
75th	1.25	1.85
90th	2.74	4.30
95th	4.22	7.27
Max	8.80	8.90

Abbreviations: Max, maximum; PSA, prostate-specific antigen.

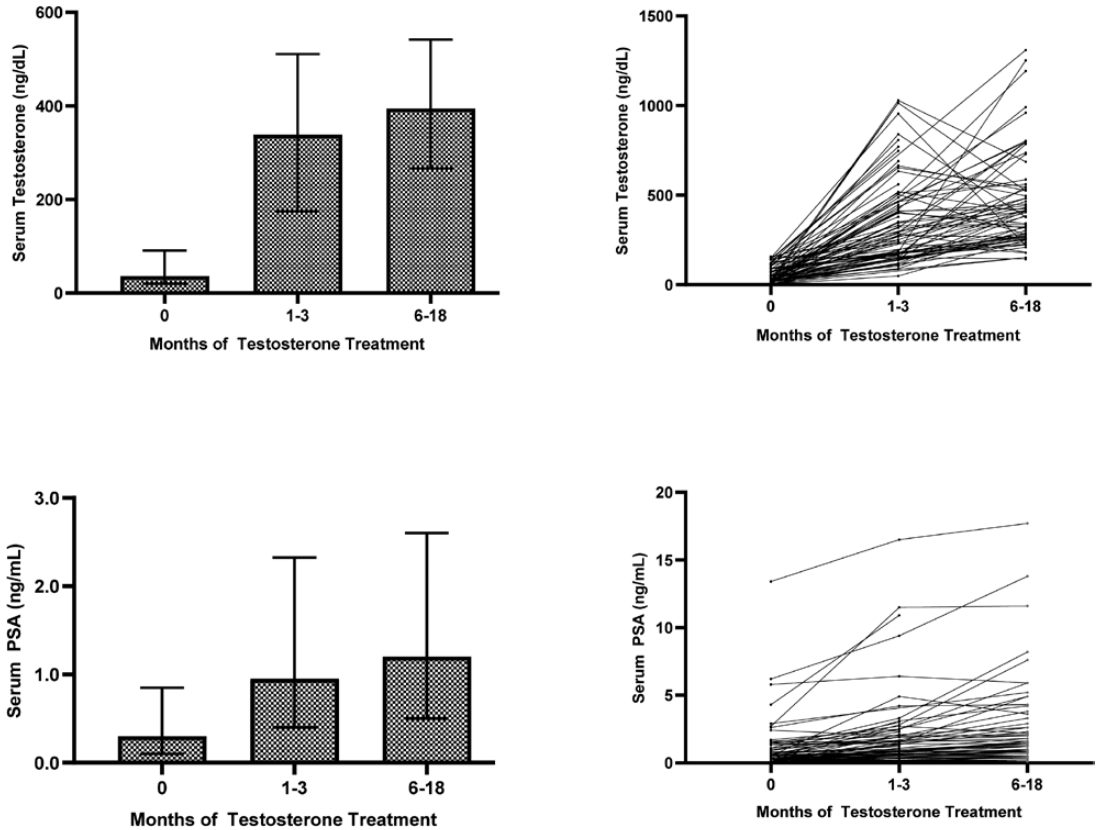

Figure 1. Serum concentrations of testosterone (upper 2 panels) and PSA (lower 2 panels) at months 0 (n = 85), 1-3 (n = 62) and 6-18 (n = 68) when men who had severe hypogonadism were replaced with testosterone. The left two panels show medians and interquartile ranges. The right two panels show individual patient values.

Table 3. Prostate events in severely hypogonadal men treated with testosterone

	Mo 1-3	Mo 6-18
No.	62	68
PSA increase > 1.4 ng/mL, n (%)	12 (19)	21 (31)[a]
Absolute PSA > 4.0 ng/mL, n (%)[b]	3 (5)[c]	9 (13)[c,d]
Prostate biopsy	3	4
Prostate cancer	1	3

Abbreviation: PSA, prostate-specific antigen.
[a]Ten of these 21 men also had increases above baseline greater than 1.4 ng/mL at months 1 to 3.
[b]Excluding the 4 men whose PSA at baseline was greater than 4.0 ng/mL.
[c]All men whose PSA increased to an absolute value greater than 4.0 ng/mL also had a PSA increase above baseline greater than 1.4 ng/mL.
[d]Two of these 9 men also reached absolute PSA values greater than 4.0 ng/mL at months 1 to 3.

3. Discussion

Testosterone replacement of 85 men who were severely hypogonadal as a result of pituitary or testicular disease caused relatively large increases in their serum PSA concentrations. After 6 to 18 months of testosterone replacement, the median increment of PSA above baseline was 0.70 ng/mL; 31% of men had increases in PSA of more than 1.4 ng/mL; and 13% of men reached absolute PSA concentrations of more than 4.0 ng/mL.

Prior studies of testosterone treatment reported smaller increases in serum PSA concentrations, but the degree of hypogonadism in these studies was mild to moderate. In a meta-analysis of 15 studies, testosterone treatment was not associated with a significant increase in serum PSA except in men treated with injectable testosterone esters [8]. In another meta-analysis of 26 studies, testosterone treatment also did not increase the serum PSA concentration [9]. The mean baseline serum testosterone concentrations in many of the studies included in both meta-analyses were not subnormal. In the RHYME registry of 750 men whose mean baseline testosterone concentration was 239 ng/dL, testosterone treatment increased the mean serum PSA concentration from 0.68 ng/mL at baseline to 1.01 ng/mL at 12 months [3]. In The Testosterone Trials, which excluded men with known pituitary or testicular disease, testosterone treatment for 1 year of 395 men age 65 years or older, whose mean pretreatment serum testosterone concentration was 232 ng/dL, increased the median serum PSA by 0.20 ng/mL; only 3.6% of the men had increments greater than 1.0 ng/mL, and only 4.4% had absolute concentrations greater than 4.0 ng/mL [4]. No prior studies have examined the effect of testosterone replacement on PSA concentrations in men who are severely hypogonadal.

The results presented here are significant because clinical guidelines for testosterone treatment of hypogonadism recommend monitoring serum PSA concentrations and referring a patient to a urologist for evaluation for possible prostate cancer for specified increments above baseline and absolute PSA concentrations. Endocrine Society clinical guidelines recommend referring men for urologic evaluation if the serum PSA increases more than 1.4 ng/mL above baseline or if the absolute PSA concentration is greater than 4.0 ng/mL [2]. Neither criterion, however, is based on testosterone treatment of hypogonadal men. The criterion of a greater than 1.4 ng/mL-increase is based on the 90% confidence limits of 2 tests performed 3 to 6 months apart in men with benign prostatic hyperplasia in the placebo arm of a finasteride trial [10]. The criterion of an absolute PSA concentration of greater than 4.0 ng/mL is based on prostate cancer detection in eugonadal men [1, 9, 11-13]. Of the severely hypogonadal men reported here, 31% had an increase in PSA of more than 1.4 ng/mL, and 13% reached an absolute PSA value of greater than 4.0 ng/mL. Confirmation of the results presented here by other studies would suggest that future clinical guidelines for the expected PSA response to testosterone replacement reflect the degree of hypogonadism.

A. Strength and Limitations

These findings demonstrate the degree to which serum PSA can be expected to increase in a relatively large number of men who meet the FDA indication for testosterone treatment of classical hypogonadism [5]. Some limitations of this study are the result of its retrospective nature—a review of patients in clinical practice—although that could also make the results more generally applicable to clinical practice. Because the study was retrospective, there was no prespecified protocol for referral for urologic evaluation, which would have influenced the number of biopsies and the diagnosis of prostate cancer. Other limitations are the lack of a control group, lack of data on lower urinary tract symptoms, and incomplete PSA results in about 20% of the men. Because most men in this study were using transdermal testosterone preparations, the results apply primarily to these preparations. This study examined the effect of testosterone treatment on PSA concentrations for up to 18 months, so we do not know the effect afterward.

4. Conclusions

The results presented here demonstrate that the PSA responses to testosterone replacement in men who are severely hypogonadal as a result of hypothalamic-pituitary or testicular causes are greater than previously reported in men with mild to moderate hypogonadism primarily due to normal aging. These results suggest that the magnitude of

the PSA response to testosterone replacement is related to the degree of hypogonadism. These results also suggest that testosterone treatment of severely hypogonadal men often increases PSA above the commonly accepted thresholds for urologic referral.

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Additional Information

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Data Availability: The data sets generated during and/or analyzed during the present study are not publicly available but are available from the corresponding author on reasonable request.

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