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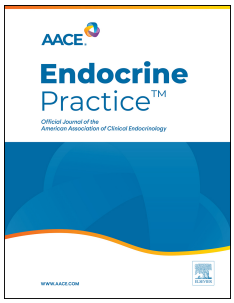

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Robert Benson Jones, Jr., MD, Peter J. Snyder, MD

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Running title: Testosterone after Prostate Cancer

Robert Benson Jones, Jr., MD[1] and Peter J. Snyder, MD[1]

[1]Division of Endocrinology, Diabetes, and Metabolism, Perelman School of Medicine University of Pennsylvania, Philadelphia, PA, USA

Correspondence: Peter J. Snyder, MD

Division of Endocrinology, Diabetes, and Metabolism, Perelman School of Medicine, University of Pennsylvania, 3400 Civic Center Blvd, Philadelphia, PA

Email: pjs@pennmedicine.upenn.edu

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Key Words: prostate cancer, hypogonadism, testosterone

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Robert Benson Jones, Jr., MD[1] and Peter J. Snyder, MD[1]

[1]Division of Endocrinology, Diabetes, and Metabolism, Perelman School of Medicine University of Pennsylvania, Philadelphia, PA, USA

Correspondence: Peter J. Snyder, MD
Division of Endocrinology, Diabetes, and Metabolism, Perelman School of Medicine, University of Pennsylvania, 3400 Civic Center Blvd, Philadelphia, PA
Email: pjs@pennmedicine.upenn.edu
Phone: (215) 898-0208

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ABSTRACT

Objective. The testosterone dependence of metastatic prostate cancer has made physicians reluctant to treat hypogonadal men with testosterone even after treatment of the prostate cancer. Prior studies of testosterone treatment of men with treated prostate cancer have not documented that the men were unequivocally hypogonadal. The goal of the study was to determine if testosterone treatment of men with unequivocal hypogonadism and organ-confined prostate cancer is associated with recurrence of the cancer.

Methods. A computerized search of electronic medical records from 1/1/2005-9/20/2021 identified 269 men who were ≥50 years old and diagnosed with prostate cancer and hypogonadism. We reviewed the individual records of these men and identified those treated by radical prostatectomy and had no evidence of extra-prostatic extension. We then identified men who were hypogonadal prior to the diagnosis of prostate cancer based on at least one morning serum testosterone concentration ≤220 ng/dL, discontinued testosterone treatment when the prostate cancer was diagnosed, resumed testosterone treatment within two years after treatment of the cancer, and were monitored for cancer recurrence, defined by a PSA concentration ≥0.2 ng/mL.

Results. Sixteen men met the inclusion criteria. Their baseline serum testosterone concentrations were 9-185 ng/dL. The median duration of testosterone treatment and monitoring was 5 years (range 1-20 years). None of the 16 men had biochemical recurrence of prostate cancer during this period.

Conclusion. Testosterone treatment of men with unequivocal hypogonadism whose organ-confined prostate cancer is treated by radical prostatectomy may be safe.

Key words: prostate cancer, hypogonadism, testosterone

INTRODUCTION

Testosterone stimulates the normal growth and function of the prostate gland and may also stimulate the growth of prostate cancer. Since the demonstration by Huggins in 1941[1] that surgical castration led to regression of prostate cancer metastases, standard treatment of metastatic prostate cancer has included severely lowering serum testosterone levels, previously by surgical castration and currently by administration of a gonadotropin-releasing hormone analog[2]. Because of this relationship, current clinical guidelines recommend withholding testosterone treatment from hypogonadal men who have prostate cancer that has not been treated successfully[3].

For many years physicians have also been cautious about prescribing testosterone to hypogonadal men who have prostate cancer even when the cancer is not metastatic and has apparently been successfully treated, so these men remain hypogonadal. Yet, men who are eugonadal and have prostate cancer that is not metastatic and are successfully treated for the cancer are allowed to remain eugonadal. This discrepancy has in recent years led some physicians to replace testosterone in hypogonadal men whose prostate cancers are not metastatic and have been successfully treated. Several papers now report the results of monitoring patients for recurrence of prostate cancer after testosterone treatment[4-14]. These reports do not, however, document that the patients were hypogonadal, as judged by unequivocally low early morning testosterone concentrations.

The goal of the present study was to determine if testosterone treatment of men with unequivocal hypogonadism and surgically treated, organ-confined prostate cancer is associated with recurrence of prostate cancer.

METHODS

We collected data by retrospective chart review of men seen in our institution's outpatient practices who had been diagnosed as hypogonadal, diagnosed and treated for prostate cancer, and subsequently treated with testosterone. Our Institutional Review Board exempted this study from review.

Computerized Search

The Penn Medicine Data Analytics Center performed a computerized search of the electronic medical records of patients seen in outpatient clinical encounters by physicians at Penn Medicine from January 1, 2005 to September 20, 2021. The search included men who were assigned International Classification of Diseases codes (ICD9 and ICD10) for hypogonadism and prostate cancer, Current Procedural Terminology (CPT) codes for surgical treatment of prostate cancer, and medication codes for formulations of testosterone. This search identified 269 patients.

Review of Individual Patient Records

The authors then reviewed the individual records of these 269 men. We included in this study men who were age 50 years or older at the time of diagnosis of prostate cancer

and who were hypogonadal based on at least one morning serum testosterone concentration ≤220 ng/dL[15]. We included men who were diagnosed with prostate cancer and treated by radical prostatectomy. We excluded men whose prostate cancer had spread beyond the prostate or were treated with GnRH analogs or by radiation. We included men whose hypogonadism was treated prior to the diagnosis of prostate cancer, who discontinued testosterone when the diagnosis of prostate cancer was made, and then resumed it within two years after radical prostatectomy. Sixteen men met these criteria.

Data Recorded

We recorded the cause of the hypogonadism as primary or secondary based on the serum LH concentration and the specific cause. For the 10 men who had multiple testosterone values available prior to testosterone treatment, we averaged the values for the baseline value. We recorded the PSA value that prompted the prostate biopsy. We reviewed prostate biopsy pathology reports and recorded the total number of cores sampled, the number of cores positive for prostate cancer and the highest Gleason score. We also reviewed the reports from the radical prostatectomies to determine if the cancer extended beyond the margins of the gland. We recorded the duration of testosterone treatment following radical prostatectomy, the final three testosterone concentrations during treatment, and the final PSA concentration during testosterone treatment. The final PSA value was evaluated by comparison to the American College of Urology's PSA criterion for biochemical recurrence after radical prostatectomy, which is ≥0.2 ng/mL, confirmed on repeat measurement[16].

RESULTS

The 16 hypogonadal men who were treated with testosterone following diagnosis and treatment of prostate cancer ranged in age from 51 to 74 years (Table 1). All the men were unequivocally hypogonadal; their morning serum testosterone concentrations ranged from 9 to 185 ng/dL. Importantly, 14 of the 16 men had classical hypogonadism, caused by recognizable pituitary or testicular disease. Eleven of the 14 had a recognizable pituitary cause: pituitary adenoma, hypophysitis, or head trauma. Three men had primary hypogonadism, as indicated by an elevated serum LH concentration. Only two men had idiopathic secondary hypogonadism, based on an unequivocally low testosterone concentration, an LH concentration that was not elevated, and no known cause.

The diagnosis of prostate cancer was made by prostate biopsy. The PSA that preceded the biopsy, the number of positive biopsy cores, and the highest Gleason score from the biopsy are given in Table 1. Treatment of prostate cancer was radical prostatectomy in all the men.

The median duration of testosterone treatment following treatment of prostate cancer until the end of the observation period was 5 years (range, 1- 20 years). At the end of the observation period, 8 men were using transdermal testosterone as the method of testosterone replacement; 6 men were using injectable testosterone cypionate, and 2 men were using implantable testosterone pellets. Serum testosterone concentrations

during treatment were available for 15 of the 16 men; the averages of the final two (1 man) or three (14 men) values are shown in Table 1.

Serum PSA concentrations during the observation period did not meet the American Urological Association criteria for biochemical recurrence of prostate cancer, ≥0.2 ng/mL, in any of the men[16].

DISCUSSION

This retrospective chart review identified 16 men who had unequivocal hypogonadism and were treated with testosterone following radical prostatectomy for organ-confined prostate cancer. During a median of 5 years of testosterone treatment and monitoring, none exhibited biochemical evidence of recurrence of prostate cancer.

This result is similar in some respects to those in other reports of men with prostate cancer who were treated with testosterone following treatment of the cancer and followed for up to several years. A few studies, like the present, included only men whose prostate cancer was treated by radical prostatectomy and had no evidence of cancer outside of the prostate at the time of radical prostatectomy[4,5,7,12]. These studies also reported no biochemical recurrences of prostate cancer following testosterone treatment in a total of 153 men after median observation periods of 19-41 months. Other studies included men whose prostate cancer was treated by external beam radiation or brachytherapy[6,8,10,12]. Following testosterone treatment, 4 of a total 136

men in these studies had biochemical evidence of recurrence after median observation of 15 months to 5 years. Yet other studies included men who had evidence of spread of the cancer outside of the prostate before testosterone treatment. In these, 59 of 398 men showed biochemical evidence of recurrence after testosterone treatment for median observation periods from 15 months to 3.4 years[9,11,13,14].

Most prior studies, however, did not document that the patients were unequivocally hypogonadal prior to testosterone treatment. Some of the papers did not state the serum testosterone levels prior to testosterone treatment, and in some of those papers that did state the testosterone levels, those levels were not subnormal. In only a few studies were the testosterone values subnormal. In one study of 13 men, the mean serum testosterone level was clearly subnormal, 188 ng/dL[10]. In a study of 7 men, 3 had hypogonadal levels[4], and in a study of 5 men, 4 had hypogonadal levels[8]. None of these reports, however, stated the time of day the blood was drawn, yet normal ranges of testosterone are based on morning values[15]. Testosterone administered to a man who is not actually hypogonadal will not indicate if testosterone treatment of an unequivocally hypogonadal man will stimulate residual prostate cancer growth.

Importantly, no prior reports specified if any of the patients had a known pituitary or testicular cause of hypogonadism, so presumably any man in those studies who did have a low testosterone level prior to treatment had idiopathic, late-onset secondary hypogonadism. The United States Food and Drug Administration has approved testosterone only for men who have known causes of hypogonadism ("classic

hypogonadism") and has specifically excluded from approval idiopathic, late-onset hypogonadism[17].

The study we report here is the first to document that all the patients were hypogonadal based on at least one morning testosterone value. The criterion we used for selecting men as having hypogonadism was <220 ng/dL, based on the model estimate of the fifth percentile for men ages 50-79 years in four cohorts totaling 9054 men[15]. The serum testosterone concentrations of the men in our study before testosterone treatment were 9-185 ng/dL (median, 33 ng/dL). The present study is also the first in which most of men, 14 of the 16, were hypogonadal due to a recognizable pituitary or testicular cause of hypogonadism and therefore meet the FDA criterion for testosterone replacement.

The strengths of this study, in addition to the strict criteria for the diagnosis of hypogonadism in all men and known causes of hypogonadism in most men, include clear documentation of the cancer grade, the extent of surgery and regular monitoring following testosterone treatment for a median duration of 5 years, longer than most prior studies.

This study also had important limitations in addition to its retrospective nature. Because we selected men who were treated by radical prostatectomy and whose prostate cancer was confined to the prostate, these results apply only to similar men. The results do not apply to men whose prostate cancer is treated by radical prostatectomy but have evidence of spread of the cancer outside of the prostate. The results also do not apply

to men whose prostate cancer is treated by radiation. The number of men in this study is relatively small, so larger numbers of men need to be evaluated. Five men were observed for less than 3 years.

We report, in summary, that testosterone treatment of 16 men who had well-documented hypogonadism mostly due to recognizable pituitary or testicular disease and whose organ-confined prostate cancer had been successfully treated by radical prostatectomy did not show biochemical evidence of recurrence of the cancer during a median of five years of testosterone treatment and monitoring. Confirmation of these results by other, larger studies would suggest that this treatment is safe for men who meet these criteria.

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Table 1: Hypogonadal men who were treated for prostate cancer and subsequently treated with testosterone.

Subject #	Age (yr)	Etiology of Hypogonadism	PSA pre-biopsy (ng/mL)	Prostate Biopsy		Basal Serum Testosterone (ng/dL)[2]	Treatment Serum Testosterone (ng/dL)[3]	Duration Testosterone Treatment (yr)[4]	Final PSA (ng/mL)[5]
				Positive/total # cores	Gleason score[1]				
1	61	Pituitary adenoma	4.8	4/12	7 (4+3)	<20	273	9	<0.1
2	64	Pituitary adenoma	NA	NA	NA	<20	297	19	<0.04
3	64	Pituitary adenoma	4.9	1/13	7 (3+4)	12	NA	2	<0.1
4	73	Pituitary adenoma	4.6	NA	NA	<20	364	5.5	<0.1
5	69	Pituitary adenoma	4.7	5/13	7 (3+4)	33	662	1.5	<0.05
6	59	Pituitary adenoma	4.1	1/12	7 (3+4)	154	552	5	<0.1
7	74	Pituitary adenoma	15.3	2/12	7 (3+4)	149	726	6	0.12
8	68	Pituitary adenoma	2.4	2/12	9 (4+5)	<20	411	5	<0.6
9	59	Hypophysitis	NA	NA	NA	<20	417	20	<0.1
10	65	Hypophysitis	2.9	1/30	6 (3+3)	9	479	5	<0.1
11	65	Head trauma	1.7	5/13	7 (3+4)	126	460	3	<0.05
12	56	Bilateral orchiectomy	8.7	1/13	6 (3+3)	<20	507	1	<0.1
13	61	Primary hypogonadism	6.4	3/14	7 (3+4)	157	393	1	<0.01
14	51	Primary hypogonadism	5.4	4/13	6 (3+3)	185	268	3	<0.01
15	55	Secondary, idiopathic	5.0	6/22	7 (3+4)	133	314	8	<0.05

16	66	Secondary, idiopathic	9.9	1/12	6 (3+3)	147	251	1	<0.01

[1]Highest Gleason score from the prostate biopsy
[2]Serum testosterone prior to initiation of testosterone treatment
[3]Average of up to three serum testosterone values at the end of the period of treatment and observation
[4]Number of years of testosterone treatment and observation following treatment of prostate cancer
[5]PSA at the end of the period of testosterone treatment and observation

Highlights

- Although prior studies have demonstrated that testosterone treatment of men with treated organ-confined prostate cancer is probably safe, the patients in those studies were not clearly hypogonadal.
- This study is the first to demonstrate that testosterone treatment of men with unequivocal hypogonadism due mostly to pituitary or testicular disease and with treated, organ-confined prostate cancer did not have biochemical recurrence of the prostate cancer when followed for a median duration of five years.
- Confirmation of these results by other studies would suggest that testosterone treatment is safe for men who meet these criteria.

Clinical Relevance

Finding that testosterone treatment of 14 men with unequivocal hypogonadism and treated, organ-confined prostate cancer was not associated with a recurrence of the cancer in a median of five years of observation suggests that this treatment may be safe.