

Is it safe to prescribe supplemental testosterone for prostate cancer patients with hypogonadism?

CASE PRESENTATION

A 64-year-old healthy man presented with prostate cancer diagnosed in 2016. The pathology showed Gleason scores 3+3 and 3+4 in multiple cores and the patient underwent an uncomplicated radical prostatectomy. He regained urinary continence; however, he required injection therapy to restore erectile function.

The patient complained of decreased libido and generalized poor performance with his wife, leading to marital distress. Two morning testosterone levels taken a month apart were 178 ng/dL and 155 ng/dL (normal range: 300-1100 ng/dL). PSA levels have remained undetectable.

The patient disclosed a long-standing history of hypogonadism (low testosterone [low T]) and said he had been on testosterone supplementation therapy prior to the radical prostatectomy. The testosterone therapy was effective and he expressed interest in restarting replacement treatment.

Other past medical history includes hypothyroidism and high blood pressure.

PHYSICAL EXAMINATION

Genitourinary

- **Penis:** Normal male phallus with normal urethra. No penile erythema or tenderness. No urethral discharge
- **Scrotum:** No evidence of scrotal rashes or condylomata
- **Testes:** Non-tender with no swelling or masses bilaterally. No hernias or varicoceles. Vas deferens and epididymis palpable and normal bilaterally

Relevant Labs

- **Testosterone levels (morning, 1 month apart):** 178 ng/dL and 155 ng/dL (300-1100 ng/dL)
- **Post prostatectomy PSA:** undetectable

MANAGEMENT

The risks and benefits of testosterone supplementation post prostatectomy were discussed with the patient, including the risk of recurrence of his prostate cancer. The patient was started on AndroGel but ultimately switched to injection therapy for more adequate symptom improvement.

CASE OF THE MONTH

COMMENT

Charles Huggins earned a Nobel Prize in Physiology or Medicine in 1966 for his discoveries concerning the hormonal treatment of prostatic cancer. Today, 80 years after his hallmark publication,¹ androgen deprivation remains frontline treatment for advanced prostate cancer. However, the assertion by Huggins and Hodges that testosterone activates prostate cancer has created considerable confusion for urologists who treat hypogonadism. Many urologists still embrace the theory that the administration of testosterone to a man with existing prostate cancer is like “pouring gasoline on a fire.” How are urologists supposed to decide which prostate cancer patients are safe to treat?

First, it is important to answer this question: Do you always need to treat a low T level? Patients are frequently sent to urologists with low T levels but do not show any signs or symptoms of low T such as decreased sex drive and/or erectile dysfunction. I follow the AUA guideline definition of low T: the observation of 2 morning low T values (T level <300 ng/dL) followed by the signs and symptoms of low T (physical, cognitive, or sexual symptoms) prior to initiating testosterone replacement (Table 1).²

The AUA guideline panel’s “Evaluation and Management of Testosterone Deficiency,”² completed in 2018, guides management of hypogonadism. The panel developed a list of 31 guideline statements that are intended to help the clinician to safely counsel patients with low T levels and treat and follow the condition.

A large percentage of men with prostate cancer, low T levels, and low T symptoms do not receive supplementation because of the potential adverse impact on prostate cancer progression. The AUA guideline panel performed a systematic review that yielded more than 15,000 references, including articles addressing testosterone replacement and prostate cancer for patients on active surveillance or treated via radical prostatectomy or radiation therapy.

The panel agreed that testosterone replacement treatment can be considered for men who have undergone radical prostatectomy and who have undetectable PSA levels and favorable pathology (negative margins and no seminal vesicle or lymph node invasion). Patient selection is key, with caution given regarding high-risk patients, as highlighted in one study that showed increasing PSA values in high-risk post radical prostatectomy men treated with testosterone.³ With regard to radiation therapy, the panel highlighted a study by Balbontin et al.⁴ that reported that men placed on testosterone after

Table 1. Symptoms and Signs Associated with Testosterone Deficiency² (Source: Mulhall JP, Trost LW, Brannigan RE, et al. Evaluation and management of testosterone deficiency: AUA guideline. *J Urol*. 2018;200(2):423-432.)

Physical Symptoms and Signs
Reduced energy
Reduced endurance
Diminished work performance
Diminished physical performance
Loss of body hair
Reduced beard growth
Fatigue
Reduced lean muscle mass
Obesity
Cognitive Symptoms and Signs
Depressive symptoms
Cognitive dysfunction
Reduced motivation
Poor concentration
Poor memory
Irritability
Sexual Symptoms and Signs
Reduced sex drive
Reduced erectile function

CASE OF THE MONTH

receiving radiation therapy with or without androgen deprivation therapy did not experience greater rates of recurrence or progression. Last, although data are limited for men on active surveillance, Rhoden and Morgentaler⁵ indicated that these men did not experience any increase in PSA values or incidence of prostate cancer diagnosis when compared to men not receiving testosterone. The panel concluded that although PSA may rise in response to testosterone therapy, the increase is minimal, in the realm of 0.3 to 0.5 ng/mL, an increase that is often seen in the first month of testosterone supplement therapy.⁶

AUA Guideline Statements on Low T and Prostate Cancer

Statement 12: PSA should be measured in men over 40 years of age prior to commencement of testosterone therapy to exclude a prostate cancer diagnosis. (Clinical Principle)

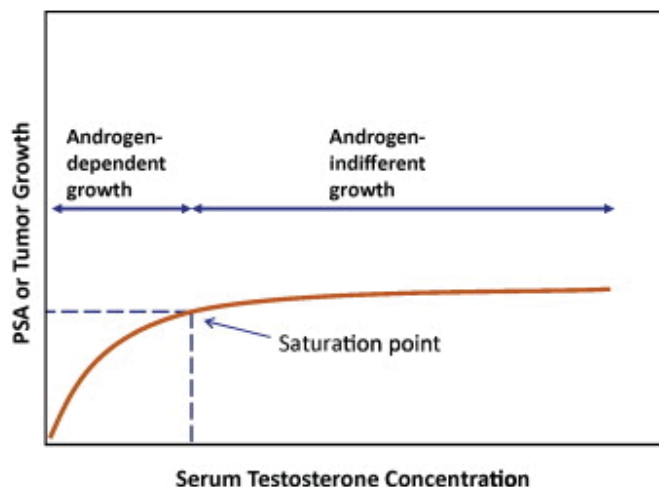
Statement 17: Clinicians should inform patients of the absence of evidence linking testosterone therapy to the development of prostate cancer. (Strong Recommendation: Evidence Level: Grade B)

Statement 18: Patients with testosterone deficiency and a history of prostate cancer should be informed that there is inadequate evidence to quantify the risk-benefit ratio of testosterone therapy. (Expert Opinion)

Saturation Model

The saturation model, as described by Khera et al.,⁷ explains the relationship between prostate tissue sensitivity and changes in serum testosterone. The theory is that at low concentrations of androgens, the prostate is very sensitive to changes in androgen levels and PSA will often increase in response to an increase in the concentration. Once the androgen concentration reaches a saturation point, further administration of higher levels of testosterone does not induce any additional androgen-driven changes in prostate tissue growth (Figure 1).⁷ On the basis of this model, many practitioners who prescribe testosterone for prostate cancer patients feel comfortable knowing the testosterone is most likely not overstimulating prostate tissue.

Figure 1. The saturation model.⁷ (Source: Reprinted from Khera K, Crawford D, Morales A, et al. A new era of testosterone and prostate cancer: from physiology to clinical implications. *Eur Urol*. 2014;65[1]:115-123.)



CASE OF THE MONTH

Take-Home Points

Urologists often find themselves between a rock and a hard place when managing symptomatic hypogonadism in men with prostate cancer on active surveillance or after radical prostatectomy or radiation therapy because of the lack of high-level data to appropriately counsel patients on the risks of recurrence or development of new prostate cancer. Many urologists shy away from treating this population for a multitude of reasons, among them medical-legal ramifications and the need for close follow-up with regular testosterone, CBC, and PSA checks. Even further muddying the waters, the U.S. Food and Drug Administration retains a warning regarding the potential risk of prostate cancer in patients who are prescribed testosterone products. I continue to follow the AUA guideline of informed decision-making, including having the patient sign a comprehensive consent form that outlines all the potential risks of testosterone supplementation.

REFERENCES

1. Huggins C, Hodges CV. Studies on Prostatic Cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Cancer Res.* 1941;1(4):293-297.
2. Mulhall JP, Trost LW, Brannigan RE, Kurtz EG, Redmon JB, Chiles KA, Lightner DJ, Miner MM, Murad MH, Nelson CJ, Platz EA, Ramanathan LV, Lewis RW. Evaluation and management of testosterone deficiency: AUA guideline. *J Urol.* 2018;200(2):423-432.
3. Pastuszak AW, Pearlman AM, Lai WS, Godoy G, Sathymoorthy K, Liu JS, Miles BJ, Lipshultz LI, Khera M. Testosterone replacement therapy in patients with prostate cancer after radical prostatectomy. *J Urol.* 2013;190(2):639-644.
4. Balbontin FG, Moreno SA, Bley E, Chacon R, Silva A, Morgentaler A. Long-acting testosterone injections for treatment of testosterone deficiency after brachytherapy for prostate cancer. *BJU Int.* 2014;114(1):125-130.
5. Rhoden EL and Morgentaler A: Testosterone replacement therapy in hypogonadal men at high risk for prostate cancer: results of 1 year of treatment in men with prostatic intraepithelial neoplasia. *J Urol.* 2003;170(6 Pt 1):2348-2351.
6. Bhattacharya RK, Khera M, Blick G, Kushner H, Miner MM. Testosterone replacement therapy among elderly males: the Testim Registry in the US (TRIUS). *Clin Interv Aging.* 2012;7:321-330.
7. Khera K, Crawford D, Morales A, Salonia A, Morgentaler A. A new era of testosterone and prostate cancer: from physiology to clinical implications. *Eur Urol.* 2014;65(1):115-123.



SETH D. COHEN, MD, MPH

Seth D. Cohen, MD, MPH, is assistant professor of urology at NYU Grossman School of Medicine and director of the NYU Langone Health Sexual Dysfunction Program. He received his medical degree and master of public health degree from Tulane University School of Medicine and School of Public Health and Tropical Medicine in New Orleans and completed his urologic training at Lenox Hill Hospital in New York City. He subsequently completed a fellowship in male sexual dysfunction and prosthetics at the University of California San Diego and Kaiser Permanente in San Diego.

Dr. Cohen has published on surgical techniques for penile prosthetics and has written numerous articles and book chapters on sexual health issues. He has taught courses and lectured nationally and internationally on various sexual dysfunction topics. Dr. Cohen's clinical practice focuses on the workup, diagnosis, and treatment of erectile dysfunction, Peyronie's disease, and hypogonadism. Dr. Cohen also has expertise in minimally invasive benign prostatic hypertrophy (BPH) surgeries such as the UroLift procedure.

Our renowned [urologic specialists](#) have pioneered numerous advances in the surgical and pharmacological treatment of urologic disease.

For questions and/or patient referrals, please contact us by phone or by e-mail.

Faculty	Specialty	Phone Number/Email
<u>James Borin, MD</u>	Kidney stones, Kidney Cancer, Ureteral Stricture, UPJ obstruction, Endourology, Robotic Renal Surgery, Partial Nephrectomy, Ablation of Renal Tumors, PCNL	646-825-6387 james.borin@nyulangone.org
<u>Benjamin Brucker, MD</u>	Female Pelvic Medicine and Reconstructive Surgery, Pelvic Organ Prolapse-Vaginal and Robotic Surgery, Voiding Dysfunction, Male and Female Incontinence, Benign Prostate Surgery, Neurourology	646-754-2404 benjamin.brucker@nyulangone.org
<u>Seth Cohen, MD</u>	Female Sexual Dysfunction, Male Sexual Dysfunction, General Urology, Benign Disease Prostate, Post-Prostatectomy Incontinence, Erectile Dysfunction, Hypogonadism	646-825-6318 seth.cohen@nyulangone.org
<u>Frederick Gulmi, MD*</u>	Robotic and Minimally Invasive Urology, BPH and Prostatic Diseases, Male and Female Voiding Dysfunction, Kidney Stone Disease, Lasers in Urologic Surgery, and Male Sexual Dysfunction	718-630-8600 frederick.gulmi@nyulangone.org
<u>Mohit Gupta, MD†</u>	Urologic Oncology, Open, Laparoscopic, or Robot-Assisted Approaches to Surgery, Surgical Management of Genitourinary Malignancies including Kidney, Bladder, Prostate, Adrenal, Penile, and Testis Cancers	646-825-6325 Mohit.Gupta2@nyulangone.org
<u>William Huang, MD</u>	Urologic Oncology (Open and Robotic) – for Kidney Cancer (Partial and Complex Radical), Urothelial Cancers (Bladder and Upper Tract), Prostate and Testicular Cancer	646-744-1503 william.huang@nyulangone.org
<u>Grace Hyun, MD</u>	Pediatric Urology including Hydronephrosis, Hypospadias, Varicoceles, Undescended Testicles, Hernias, Vesicoureteral Reflux, Urinary Obstruction, Kidney Stones, Minimally Invasive Procedures, Congenital Anomalies	212-263-6420 grace.hyun@nyulangone.org
<u>Christopher Kelly, MD</u>	Male and Female Voiding Dysfunction, Neurourology, Incontinence, Pelvic Pain, Benign Prostate Disease	646-825-6322 chris.kelly@nyulangone.org
<u>Herbert Lapor, MD</u>	Prostate Cancer: Elevated PSA, 3D MRI/Ultrasound Co-registration Prostate Biopsy, Focal (Ablation) of Prostate Cancer, Open Radical Retropubic Prostatectomy	646-825-6327 herbert.lepor@nyulangone.org
<u>Stacy Loeb, MD, MSc**</u>	Urologic Oncology, Prostate Cancer, Benign Prostatic Disease, Men's Health, General Urology	718-261-9100 stacy.loeb@nyulangone.org
<u>Danil Makarov, MD, MHS***</u>	Benign Prostatic Hyperplasia, Erectile Dysfunction, Urinary Tract Infection, Elevated Prostate-specific Antigen, Testicular Cancer, Bladder Cancer, Prostate Cancer	718-376-1004 danil.makarov@nyulangone.org
<u>Nnenaya Mmonu, MD, MS</u>	Urethral Strictures, Robotic and Open Reconstructive Surgery for Ureteral Obstruction/Stricture, Fistulas, Bladder Neck Obstruction, Penile Prosthesis, Post Prostatectomy and Radiation Urinary Incontinence	646-754-2419 nnenaya.mmonu@nyulangone.org
<u>Bobby Najari, MD</u>	Male Infertility, Vasectomy Reversal, Varicocele, Post-Prostatectomy, Erectile Dysfunction, Male Sexual Health, Hypogonadism, Oncofertility	646-825-6348 bobby.najari@nyulangone.org
<u>Nirit Rosenblum, MD</u>	Female Pelvic Medicine and Reconstructive Surgery, Voiding Dysfunction, Neurourology, Incontinence, Female Sexual Dysfunction, Pelvic Organ Prolapse and Robotic Surgery	646-825-6311 nirit.rosenblum@nyulangone.org
<u>Ellen Shapiro, MD</u>	Pediatric Urology including: Urinary Tract Obstruction (ureteropelvic junction obstruction), Vesicoureteral Reflux, Hypospadias, Undescended Testis, Hernia, Varicocele, and Complex Genitourinary Reconstruction.	646-825-6326 ellen.shapiro@nyulangone.org
<u>Mark Silva, MD*</u>	Kidney stones, PCNL, Kidney Cancer, UPJ obstruction, Endourology, Robotic Renal Surgery, Ablation of Renal Tumors	718-630-8600 mark.silva@nyulangone.org
<u>Gary D. Steinberg, MD</u>	Muscle-Invasive Bladder Cancer, Non-Invasive Bladder Cancer, Radical Cystectomy, Urinary Tract Reconstruction After Bladder Removal Surgery	646-825-6327 gary.steinberg@nyulangone.org
<u>Lauren Stewart, MD</u>	Female Pelvic Medicine and Reconstructive Surgery, Pelvic Organ Prolapse, Incontinence in Women, Female Voiding Dysfunction	646-825-6324 lauren.stewart@nyulangone.org
<u>Samir Taneja, MD</u>	Urologic Oncology – Prostate Cancer (MRI-Guided Biopsy, Robotic Prostatectomy, Focal Therapy, Surveillance), Kidney Cancer (Robotic Partial Nephrectomy, Complex Open Surgery), Urothelial Cancers	646-825-6321 samir.taneja@nyulangone.org
<u>James Wysock, MD, MS</u>	Urologic Oncology – Prostate Cancer, MRI-Guided Biopsy, Kidney and Prostate Cancer Surgery, Robotic Urological Cancer Surgery, Prostate Cancer Image-guided Focal Therapy (Ablation, HIFU), and Testicular Cancer	646-754-2470 james.wysock@nyulangone.org
<u>Lee Zhao, MD</u>	Robotic and Open Reconstructive Surgery for Ureteral Obstruction, Fistulas, Urinary Diversions, Urethral Strictures, Peyronie's Disease, Penile Prosthesis, and Transgender Surgery	646-754-2419 lee.zhao@nyulangone.org
<u>Philip Zhao, MD</u>	Kidney Stone Disease, Upper Tract Urothelial Carcinoma, Ureteral Stricture Disease, and BPH/Benign Prostate Disease	646-754-2434 philip.zhao@nyulangone.org

*at NYU Langone Hospital – Brooklyn ** NYU Langone Ambulatory Care Rego Park ***NYU Langone Levitt Medical †222 East 41st street; NYU Langone Ambulatory Care Bay Ridge, and NYU Langone Levitt Medical