available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Collaborative Review – Andrology

Testosterone Therapy in Men With Prostate Cancer

Alan L. Kaplan [a,*], *Jim C. Hu* [b], *Abraham Morgentaler* [c], *John P. Mulhall* [d], *Claude C. Schulman* [e], *Francesco Montorsi* [f]

[a] *Department of Urology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA;* [b] *Department of Urology, Weill Cornell Medical College, New York, NY, USA;* [c] *Men's Health Boston, Harvard Medical School, Boston, MA, USA;* [d] *Sexual and Reproductive Medicine Program, Urology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA;* [e] *Clinic E Cavell and University of Brussels, Brussels, Belgium;* [f] *Department of Urology, Universita Vita-Salute San Raffaele, Milan, Italy*

Article info

Article history:
Accepted December 6, 2015

Associate Editor:
Christian Gratzke

Keywords:
Testosterone
Androgens
Testosterone therapy
Prostate cancer
Testosterone deficiency
Saturation mode

Abstract

Context: The use of testosterone therapy in men with prostate cancer was previously contraindicated, although recent data challenge this axiom. Over the past 2 decades, there has been a dramatic paradigm shift in beliefs, attitude, and treatment of testosterone deficiency in men with prostate cancer.
Objective: To summarize and analyze current literature regarding the effect of testosterone replacement in men with prostate cancer.
Evidence acquisition: We conducted a Medline search to identify all publications related to testosterone therapy in both treated and untreated prostate cancer.
Evidence synthesis: The historical notion that increasing testosterone was responsible for prostate cancer growth was based on elegant yet limited studies from the 1940s and anecdotal case reports. Current evidence reveals that high endogenous androgen levels do not increase the risk of a prostate cancer diagnosis. Similarly, testosterone therapy in men with testosterone deficiency does not appear to increase prostate cancer risk or the likelihood of a more aggressive disease at prostate cancer diagnosis. Androgen receptor saturation (the saturation model) appears to account for this phenomenon. Men who received testosterone therapy after treatment for localized prostate cancer do not appear to suffer higher rates of recurrence or worse outcomes; although studies to date are limited. Early reports of men on active surveillance/watchful waiting treated with testosterone have not identified adverse progression events.
Conclusions: An improved understanding of the negative effects of testosterone deficiency on health and health-related quality of life—and the ability of testosterone therapy to mitigate these effects—has triggered a re-evaluation of the role testosterone plays in prostate cancer. An important paradigm shift has occurred within the field, in which testosterone therapy may now be regarded as a viable option for selected men with prostate cancer suffering from testosterone deficiency.
Patient summary: In this article, we review and summarize the existing literature surrounding the use of testosterone therapy in men with prostate cancer. Historically, testosterone was contraindicated in men with a history of prostate cancer. We show that this contraindication is unfounded and, with careful monitoring, its use is safe in that regard.

* Corresponding author. The University of California, Los Angeles, Department of Urology, 10833 Le Conte Avenue, PO Box 951738, Los Angeles, CA 90095, USA. Tel. + 1 202 531 4103.
E-mail address: alkaplan@mednet.ucla.edu (A.L. Kaplan).

http://dx.doi.org/10.1016/j.eururo.2015.12.005
0302-2838/

1. Introduction

Testosterone deficiency (TD; also known as hypogonadism) and prostate cancer are both highly prevalent in older men and may impair overall health and quality of life. Up to 25% of elderly men experience TD [1–3] while the lifetime prevalence of a prostate cancer diagnosis in developed countries approximates 14% [4]. Testosterone therapy is an effective, commonly used treatment for clinically significant testosterone deficiency. Testosterone therapy has been shown to be effective in mitigating the bothersome symptoms and metabolic sequelae of testosterone deficiency [5,6]. Despite strong evidence of benefit, a significant proportion of men with TD (those with concurrent or historical prostate cancer) are frequently denied treatment with exogenous testosterone.

Until recently, it was considered axiomatic that testosterone therapy was contraindicated in men with prostate cancer. This was based on a strong historical tradition and circumstantial evidence that went unchallenged. The preponderance of data demonstrating the health and quality of life benefits of testosterone therapy has elicited a re-evaluation of classic assumptions regarding the effect of exogenous androgens on the prostate, especially in men with prostate cancer [7,8].

These assumptions date back to the 1940s and can be traced to the work of Charles Huggins. One of only two urologists that have been awarded a Nobel Prize, Huggins and Hodges' work described the role of androgens in prostate cancer progression [9]. Their research in men with metastatic prostate cancer established the androgen hypothesis—that prostate cancer development and growth is directly related to the degree of androgenic activity in the body. Their conclusion that cancer of the prostate is "activated" by androgens gave rise to the belief that raising serum androgens via the administration of exogenous testosterone to men with prostate cancer would necessarily promote malignant cell growth and disease progression [9].

Mounting evidence refuting the androgen hypothesis has emerged over the past decade and there are now numerous published case series indicating lack of apparent cancer progression among men with prostate cancer treated with testosterone therapy [8,10]. Nonetheless, there still remains a major concern among physicians that testosterone therapy may unmask occult prostate cancer in otherwise healthy men with TD, or may cause cancer recurrence or rapid progression in men with known prostate cancer, even after treatment and apparent cure [11]. The objective of this review is to explore these concerns in light of the existing data regarding testosterone and prostate cancer.

2. Evidence acquisition

We conducted a Medline search from 1940 to 2015 to identify all publications related to the use of testosterone in men with prostate cancer, treated or otherwise. We included original studies as well as review articles. Key words used in this search were "prostate cancer", "testosterone", "testosterone replacement", "testosterone therapy", "androgens", "hypogonadism", and "prostate specific antigen."

3. Evidence synthesis

3.1. Historical perspective

In a 1935 study, Kutscher and Wolbergs [12] found that acid phosphatase was present in higher concentrations in human and monkey prostate tissue than any other tissue in the body. This investigative advance allowed Huggins and Hodges [9] to study the effects of hormone manipulation in prostate cancer. It was known at the time that surgical castration would cause regression and clinical improvement of benign prostatic enlargement [13,14]. Huggins and Hodges [9] demonstrated that serum acid phosphatase activity decreased significantly in men with metastatic prostate cancer treated with orchiectomy or with estrogen treatment that was known to reduce testosterone secretion. Additionally, they found that injection of androgen (testosterone propionate) caused an increase of acid phosphatase above preinjection levels, which returned to baseline following cessation of the drug [9]. Huggins and Hodges [9] concluded that: (1) prostate cancer was influenced by androgenic activity in the body, (2) that disseminated prostate cancer is inhibited by androgen elimination, and that (3) prostate cancer is activated by androgen injections [10].

Largely based on these studies, surgical castration (bilateral orchiectomy) became the mainstay of treatment for men with metastatic prostate cancer for decades. Medical castration through androgen deprivation therapy (ADT) has largely supplanted bilateral orchiectomy; although the efficacy of both modalities is undisputed. Prostate specific antigen (PSA) has replaced serum acid phosphatase as the laboratory test of choice in prostate cancer for improved sensitivity and specificity. Men undergoing surgical or medical castration experience dramatic decrease in PSA and, in most cases, clinical disease regression. The positive experiences with ADT, Huggins' Nobel-prize winning work, and some anecdotal case reports, combined to create an axiomatic belief that exogenous androgen is contraindicated in men with prostate cancer. That belief has been largely unchallenged for 7 decades.

3.2. TD

Administration of exogenous androgen had, until recently, relatively few indications. Our emerging understanding of TD, its negative consequences, and the known benefits of testosterone therapy has led to a scientific re-evaluation of the risks of testosterone therapy, including its safety with regard to prostate cancer. Testosterone deficiency is a clinical syndrome consisting of a variety of characteristic symptoms and signs in combination with low serum testosterone concentrations. Symptoms include low libido, erectile dysfunction, reduced morning erections, depressed