Testosterone Therapy and Prostate Cancer

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KEYWORDS

• Testosterone • Prostate • Prostate cancer • Androgens • Prostate-specific antigen
• Testosterone deficiency • Hypogonadism

KEY POINTS

- Considerable evidence contradicts the notion that higher testosterone levels are associated with increased risk of developing prostate cancer, or higher grade Gleason score.
- Major changes in prostate-specific antigens are observed when a serum testosterone moves into or out of the castrate range, but are not observed for changes at higher concentrations.
- Testosterone therapy may now be considered for selected men with a history of prostate cancer, provided that informed consent is obtained and close monitoring is performed.

INTRODUCTION

The biological effects of testosterone have been recognized throughout the recorded history of humankind, even before identification of the key biochemical element produced by the testis. With so much debate surrounding the use of testosterone therapy and prostate cancer, the entire background must be clear. The scientific history of testosterone started in 1849 with Arnold Berthold. Through his experiments with rooster castration and subsequent testes transplantation, he linked the physiologic and behavioral changes of castration to a substance secreted by the testes.[1] More interest developed as Dr Charles E. Brown-Séquard made a presentation on the self-administration of *liquid testiculaire* at the Societé de Biologie in June of 1889. He reported that the injection of testicular extracts derived from dogs and guinea pigs resulted in his increased physical strength, mental abilities, and appetite.[2] Scientists around the world continued to experiment with testicular extracts and testicular "transplants" as treatment for the maladies of aging. Finally, testosterone was isolated by David and colleagues[3] in 1935 and synthesized later that year. Both Adolf Butenandt and Leopold Ruzicka were awarded with the Nobel Prize for Chemistry in 1939 for their work.

Initially, there was an early 'honeymoon period' for testosterone therapy after it first became available, shortly after its synthesis.[4] An article from 1940 in the *New England Journal of Medicine* noted improvements in sexual desire and performance, increased strength, and improved sense of well-being in men treated for hypogonadism.[5] This 'honeymoon period' was short lived, as Huggins and Hodges reported in 1941 that castration caused regression of metastatic prostate cancer, and testosterone injections "activated" prostate cancer,[6] based on alterations in the prostate cancer serum marker, acid phosphatase. From that point on, use of testosterone became rare owing to fear of causing prostate cancer in otherwise healthy individuals.

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The Modern Era of Testosterone Therapy

Before the early 1990s, the use of testosterone therapy was rare, and was limited almost exclusively to younger men with severe cases of testosterone deficiency (TD) owing to pituitary tumors, anorchia, or genetic abnormalities such as Klinefelter syndrome. Over the past 20 years there has been a remarkable and steady growth in the use of testosterone therapy. This has occurred as a result of increased physician awareness of TD and the benefits of treatment, together with increased convenience of testosterone formulations.[7] Notable benefits include improved sexual desire and performance, improved energy, increased muscle and bone density, and improved metabolic status, similar to benefits reported at the advent of testosterone use in the 1940s.[5,8] The reinvigorated interest in testosterone therapy has led to a reexamination of traditional assumptions concerning prostate cancer and testosterone.[9] Despite important advances in our understanding of this topic, the use of testosterone therapy continues to be controversial because of prostate cancer fears, and this remains the greatest concern among physicians around the world with regard to the use of testosterone therapy.[10]

The Androgen Hypothesis

Stemming from reports in the 1940s, the androgen hypothesis has come to include the following features: prostate cancer is an androgen-dependent cancer, high testosterone levels contribute to the development of prostate cancer, high testosterone causes rapid growth of prostate cancer, and low testosterone is protective against development of prostate cancer and causes prostate cancer to regress.[1,11–13] Ever since, medical students and physicians have been taught that high testosterone promotes prostate cancer development and there seemed to be no reason to doubt this axiomatic concept.[14] The relationship between testosterone and prostate cancer was classified as “fuel for a fire” or “food for a hungry tumor”.[15] In an international survey published in 2007, as many as 70% of health care providers were concerned about the association of testosterone therapy and prostate cancer.[16] It was not until recently that this conventional wisdom was challenged.

The breakdown of the androgen hypothesis evolved throughout the years, beginning in the early 1990s. Morgentaler and colleagues[17] published a study in which testosterone deficient men with normal prostate-specific antigen (PSA; <4.0 ng/mL) and a normal digital rectal examination underwent a sextant prostate biopsy before initiating testosterone therapy. Interestingly, 11 of the first 77 men had prostate cancer. Compared with the 15.2% prostate cancer rate noted by Thompson and colleagues[18] in the placebo arm of the Prostate Cancer Prevention Trial, this 14.3% rate was shockingly similar. This was the first indication that low testosterone may be a risk factor for prostate cancer, and not protective against prostate cancer and its progression.[14]

Since this revelation, more than 20 population-based longitudinal studies have shown no relationship between prostate cancer and serum testosterone or other androgens.[19] The Endogenous Hormones and Prostate Cancer Collaborative Group published high-level evidence from a metaanalysis consisting of 18 studies that included 3886 men with incident prostate cancer and 6438 controls.[20] The results demonstrated no direct association between endogenous serum androgens and the development of prostate cancer. Additionally, Muller and colleagues[21] analyzed 3255 men in the placebo arm of the reduction by Dutasteride of Prostate Cancer Events trial. Men underwent prostate biopsies at 2 years and 4 years and there was no relationship found between testosterone or dihydrotestosterone levels and prostate cancer risk.

Although high testosterone levels were thought to contribute to the development of prostate cancer, there is a complete lack of compelling evidence in the literature.[22] An extensive review found that men with higher endogenous testosterone or who had undergone testosterone therapy were not at increased risk of prostate cancer.[20] Supraphysiologic doses of testosterone for up to 9 months in healthy men failed to demonstrate a significant increase in PSA or prostate volume.[23,24] The notion that “more testosterone is bad, less testosterone is good” was not necessarily true.

The Saturation Model

However, physicians still recognize that initiation of androgen deprivation causes rapid declines in PSA and that cessation of androgen deprivation causes rapid increases in PSA. Revisiting the landmark work of Huggins and Hodges, the traditional view suggests a continuous relationship between serum testosterone and prostate cancer growth.[15] Studies from Prout and Brewer[25] and Fowler and Whitmore[12] present an alternative possibility. Both papers noted no evidence of progression in men with prostate cancer not treated by androgen deprivation or castration.[12,25] The evidence presents a paradox: how can prostate cancer be so sensitive to androgen deprivation, yet seem to be indifferent to variations in serum androgens under other circumstances?