Testosterone Therapy in Men With Prostate Cancer: Scientific and Ethical Considerations

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Abbreviations and Acronyms

AR = androgen receptor
DHT = dihydrotestosterone
LH-RH = luteinizing hormone-releasing hormone
PCa = prostate cancer
PSA = prostate specific antigen
RP = radical prostatectomy
RRP = radical retropubic prostatectomy
T = testosterone

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Purpose: Pertinent literature regarding the potential use of testosterone therapy in men with prostate cancer is reviewed and synthesized.

Materials and Methods: A literature search was performed of English language publications on testosterone administration in men with a known history of prostate cancer and investigation of the effects of androgen concentrations on prostate parameters, especially prostate specific antigen.

Results: The prohibition against the use of testosterone therapy in men with a history of prostate cancer is based on a model that assumes the androgen sensitivity of prostate cancer extends throughout the range of testosterone concentrations. Although it is clear that prostate cancer is exquisitely sensitive to changes in serum testosterone at low concentrations, there is considerable evidence that prostate cancer growth becomes androgen indifferent at higher concentrations. The most likely mechanism for this loss of androgen sensitivity at higher testosterone concentrations is the finite capacity of the androgen receptor to bind androgen. This saturation model explains why serum testosterone appears unrelated to prostate cancer risk in the general population and why testosterone administration in men with metastatic prostate cancer causes rapid progression in castrated but not hormonally intact men. Worrisome features of prostate cancer such as high Gleason score, extracapsular disease and biochemical recurrence after surgery have been reported in association with low but not high testosterone. In 6 uncontrolled studies results of testosterone therapy have been reported after radical prostatectomy, external beam radiation therapy or brachytherapy. In a total of 111 men 2 (1.8%) biochemical recurrences were observed. Anecdotal evidence suggests that testosterone therapy does not necessarily cause increased prostate specific antigen even in men with untreated prostate cancer.

Conclusions: Although no controlled studies have been performed to date to document the safety of testosterone therapy in men with prostate cancer, the limited available evidence suggests that such treatment may not pose an undue risk of prostate cancer recurrence or progression.

Key Words: testosterone, prostatic neoplasms, hypogonadism, androgens

THE use of T therapy in men with PCa is controversial.[1,2] Although there has been a long-standing consensus that T therapy is contraindicated in these men due to the potential for androgenic stimulation causing PCa recurrence or progression, recent evidence suggests that such treatment may not be as risky as once assumed.[3] Indeed several small case series have reported no biochemical recurrence in men following radical

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prostatectomy[4,5] or brachytherapy,[6] and a recent case report noted a decrease in PSA in a man with untreated PCa who received T therapy for 2 years.[7]

The impetus for reconsidering T therapy in men with PCa stems from several factors, one of which is the increasing recognition of the health benefits of T therapy in hypogonadal men, including improvements in energy, vitality, sexual desire, erectile function, body composition and bone mineral density.[8,9] Another impetus is failure to observe a significant increase in PCa associated with T therapy in the general population, as would be predicted by the traditional androgen dependent model of PCa.[1] Finally, there has been pressure from the substantial number of PCa survivors who desire an improved quality of life.

Remarkably no modern controlled studies have investigated the effects of T therapy in men with PCa.[10] This lack of evidence creates a dilemma for the clinician faced with a symptomatic hypogonadal man with a history of PCa. On the one hand, is it reasonable to offer T therapy when tradition and training argue that treatment poses a substantial risk of more rapid PCa growth? On the other hand, is it ethical to deny a beneficial treatment when the risk is theoretical but unproven?

Despite the absence of controlled trials, there is a wealth of scientific and clinical studies regarding the relationship of androgens and PCa that are relevant to this issue. These data are reviewed and synthesized to determine the relative merits of T therapy in men with a history of PCa.

ORIGIN OF THE PROHIBITION AGAINST TESTERONE THERAPY IN MEN WITH PROSTATE CANCER

The original concept that PCa is androgen dependent arose from the work of Huggins and Hodges in 1941, who reported that castration in men with metastatic PCa caused a rapid decrease in the serum marker acid phosphatase and T administration caused an increase in acid phosphatase.[11] In 1967 Prout and Brewer reported that several weeks of T administration resulted in PCa progression or death in 5 of 10 men with recurrent disease after castration.[12] In 1981 Fowler and Whitmore reported that T administration caused an "unfavorable response" in 45 of 52 men with metastatic PCa, most within 30 days.[13] These early observations led to the belief that higher serum T causes more rapid PCa growth and the general consensus that T administration is contraindicated in men with PCa.

CURRENT STATUS OF TESTOSTERONE THERAPY IN MEN WITH PROSTATE CANCER

The androgen dependent model of PCa growth has been reinforced in the modern era by several observations.[10] Androgen deprivation therapy causes reliable and often dramatic decreases in PSA, discontinuation of LH-RH agonist therapy with intermittent therapy causes a several-fold increase in PSA in parallel with increasing serum T and the transient increase in serum T seen with LH-RH agonist therapy, called T flare, has been associated with negative PCa outcomes.[14] These observations have supported ongoing recommendations against T therapy in men with PCa. The Endocrine Society Clinical Guidelines state, "We recommend against starting testosterone therapy in men with breast or prostate cancer," although the low quality of evidence supporting this recommendation was noted.[9] The United States Food and Drug Administration has required manufacturers of T products to include statements in product inserts that androgens are contraindicated in men with known or suspected PCa, without documentation or evidence. No policy statements or clinical guidelines have been published by the American Urological Association regarding T therapy in men with a history of PCa.

Until fairly recently there was little reason to question the traditional prohibition against T therapy in men with PCa or the underlying belief that serum T was a primary driver of PCa growth throughout the range of T concentrations, since T therapy was infrequently prescribed and its benefits were not widely appreciated.[10] However, the increased interest in T therapy during the last 10 to 15 years has sparked a reexamination of the evidence regarding T and PCa, calling into question the traditional view that higher serum T necessarily causes more rapid PCa growth.[3] Thus, a review by the United States Institute of Medicine in 2004 concluded, "In summary, the influence of testosterone on prostate carcinogenesis and other prostate outcomes remains poorly defined. . . ."[15] In addition, a review on the risks of T therapy noted there was "no compelling evidence" that exogenous T increased the risk of PCa.[16]

MECHANISM OF ACTION OF ANDROGENS ON PROSTATE TISSUE

There is no dispute that androgens have an important role in the development and growth of prostate tissue. The mechanism of action of androgens on prostate tissue has been recently reviewed.[17] Briefly T enters the prostate cell where it is largely metabolized in the cytoplasm to DHT by the enzyme 5α-reductase. DHT is the primary