Testosterone and Prostate Cancer: What are the Risks for Middle-Aged Men?

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Over the last decade there has been a growing awareness of the health benefits of testosterone (T) therapy (TTh) for men with T deficiency, including improved sexual desire and performance, improved mood, increased muscle mass and strength, decreased fat mass, and improved bone mineral density.1 These health benefits are of particular importance for middle-aged men, who generally are still in relatively good health and wish to live with a high quality of life. However, for approximately 70 years there has been a concern that higher serum T represents a risk for prostate cancer (PCa).2 This concern regarding the relationship of T and PCa has been a major hurdle impeding more frequent use of TTh, because many physicians are reluctant to prescribe a beneficial treatment if there is a significant risk of precipitating cancer.

The basis for the historical fear regarding T and PCa stems from the experience that men with advanced PCa demonstrate rapid, dramatic regression of PCa based on serum markers such as prostate-specific antigen (PSA).4 Both treatments had the known effect of lowering serum T, and it was concluded that T caused an “enhanced rate of growth” of PCa. Androgen deprivation has been a mainstay of treatment for advanced PCa since that time. In addition, the investigators reported that T administration in these same men caused immediate PCa “activation” in all the individuals who received it.

However, over the last 10 to 15 years there has been a major reevaluation of the evidence regarding T and PCa. Whereas manipulation of serum T into and out of the castrate range clearly has a major impact on PCa growth, it now appears clear that variations in serum T within the naturally occurring range have minimal, if any effect on PCa.2,3 This change in perspective has important implications for the safety of TTh in middle-aged men. In fact, emerging data suggest that low serum T may be a predictor of high-risk PCa, turning conventional wisdom regarding T and PCa on its head. In this article the author reviews the historical and current evidence regarding the relationship of T and PCa, and discusses implications for TTh for the middle-aged man.

ORIGIN OF THE CONCERN REGARDING TESTOSTERONE AND PROSTATE CANCER

In 1941 Charles Huggins and Clarence Hodges published the first report indicating that castration or treatment with estrogen in men with metastatic PCa caused a decline in the serum marker acid phosphatase.4 Both treatments had the known effect of lowering serum T, and it was concluded that T caused an “enhanced rate of growth” of PCa. Androgen deprivation has been a mainstay of treatment for advanced PCa since that time. In addition, the investigators reported that T administration in these same men caused immediate PCa “activation” in all the individuals who received it.

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KEYWORDS

- Testosterone therapy
- Prostate cancer
- Testosterone
- Androgens
- Testosterone deficiency
metastatic PCa at Memorial Sloan Kettering Cancer Center. Of 52 men who received T, 45 had an “unfavorable” response, most within 30 days. This study led to the widely repeated comment that offering T to a man with PCa was like “pouring gasoline on a fire,” or “feeding a hungry tumor.”

However, reexamination of these historical articles revealed something quite different. In the article by Huggins and Hodges, 3 men were reported to receive T, yet results were only provided for 2 of these men, and 1 of these 2 had already been castrated. Because we know today that an increase in serum T after androgen deprivation causes an increase in prostate markers such as PSA even in men without cancer, we can disqualify this individual from contributing to any general rule about T and PCa. In the end, the landmark article by Huggins and Hodges provides information on only a single man who received T administration without prior androgen deprivation. In this single case, the acid phosphatase results were erratic.

The study by Fowler and Whitmore is even more instructive. Of the 52 men, only 4 were not yet androgen deprived by either castration or estrogen administration. Of these 4 men, 1 had an early unfavorable result, and the other 3 continued to receive daily injections of T for 52, 55, and 310 days, without apparent negative effects. The investigators themselves were so surprised by these results that they postulated that naturally occurring serum T concentrations may be sufficient to produce maximal growth of PCa.

What a reexamination of these and other articles from the pre-PSA era tell us is that T administration in men who were previously androgen deprived resulted in a rapid and near-universal growth in PCa manifestations, whereas T administration in hormonally intact men produced little or no effect. This finding suggests that there is a limit to the ability of androgens to stimulate PCa growth.

LONGITUDINAL STUDIES

The relationship of T and other sex hormones to subsequent development of PCa has been extensively studied, in at least 21 population-based longitudinal studies. In these studies a health history is obtained, and blood samples at baseline are then frozen for the duration of the study, in some cases up to 20 years or longer. At the end of the study men who have developed PCa are identified, and a matched set of men without PCa serve as controls.

Most of these studies surprisingly have shown no influence of serum T or other androgens on PCa risk. A small number have revealed weak associations with minor androgens, or ratios of one hormone to another, and in one case there was an association between quartile levels of free testosterone and PCa risk. However, these results have not been reproducible. It is worth noting that one large study of this type actually noted reduced PCa risk in men with higher T levels.

In 2008 the investigators of 18 of these longitudinal studies pooled their data to form one large data set, creating enough power to examine a variety of questions regarding serum sex hormones and PCa. In contrast to a meta-analysis, this was a single, actual study. With more than 3886 men with PCa and more than 6438 men as age-matched controls, this was one of the largest PCa studies published to date. The results showed no association between any androgens and PCa risk. Men with higher endogenous concentrations of serum T were at no greater risk of developing PCa than men with low levels of serum T.

The importance of these studies is that they provide a sophisticated method of investigation to determine the long-term effects of endogenous hormone levels, especially testosterone, on the subsequent risk of development of PCa. Although such studies cannot entirely replace the value of a prospective long-term controlled study of TTh, they do address the question as to whether high levels of T (or other hormones) predispose men to a greater risk of later development of PCa. On this question, these prospective longitudinal studies provide two uniform and convincing answers: first, that men who develop PCa do not have higher baseline T levels, and second, men with higher T levels are at no greater risk of developing PCa than men with lower T concentrations.

TESTOSTERONE TRIALS

In the absence of any single large study on TTh, one must examine the results from smaller studies. One of these was a 12-month study of 371 men on T gel therapy. Over the course of 1 year 3 cancers were detected, all due to an increase in PSA. One of these increases in PSA was transient and resolved; however, a biopsy was performed and revealed cancer. In this study the mean increase in PSA was 0.4 ng/mL. This increase was noted at 3 months, and PSA remained unchanged over the next 9 months.

Other studies have revealed a similar rate of cancer detection in TTh trials. In a review of 9
separate TTh trials involving 579 men and ranging from 3 to 36 months, 7 cancers were identified, representing a cancer detection rate of 1.2%. Wang and colleagues performed one of the longest TTh trials. In this study 163 men with a mean age of 51 years received T gel for 42 months. Over this time the mean PSA increased from 0.85 ng/mL at baseline to 1.1 ng/mL at 6 months, and then did not change significantly over the next 3 years of the study. Three men were diagnosed with prostate cancer, representing a cancer rate of less than 1% per year of treatment.

Prostate cancer rates were investigated among men with and without the prostatic precancerous lesion known as high-grade prostatic intraepithelial neoplasia (PIN). In this 12-month study 75 men with hypogonadism received TTh, including 55 men with benign pretreatment prostate biopsy, and 20 men with biopsy revealing PIN. A similar 12-month increase in PSA of 0.3 ng/mL was seen in both groups, corresponding to a 15% rise. A single cancer was detected, in the PIN group, representing an overall cancer rate of 1.3%. The 5% cancer rate among men with PIN compares with a 25% risk over 3 years in this population, suggesting no significantly increased cancer risk.

One study that examined the effect of TTh on PSA found that the overall change was mild, and the individual response varied considerably. Among 58 men who underwent TTh for 1 year, the majority (32 men) demonstrated a mild PSA increase of 0.5 ng/mL or less. There were also 14 men with a PSA increase greater than 0.5 ng/mL, but 12 men with a decline in PSA. No apparent differences in age, baseline T concentrations, or baseline PSA were noted between men with a PSA increase of greater than 0.5 ng/mL and men whose PSA declined. In 81 T-deficient men who received TTh, no increase was noted in PSA at 1-year intervals for up to 5 years.

To put these studies and their results in perspective, it is important to be aware that the observed PSA changes in multiple studies of approximately 15% to 20% is not much greater than the 13% increase noted over 1 year in 50- to 60-year-old men participating in the placebo arm of an unrelated study. In addition, the annual cancer rate of approximately 1% that shows up repeatedly in TTh trials compares favorably to cancer detection rates in men undergoing prostate cancer screening.

A meta-analysis of 19 placebo-controlled TTh trials found that men who received T had no greater risk of PCa than men who received placebo. There was also no greater risk of developing a PSA level of more than 4.0 ng/mL. Remarkably, administration of supraphysiologic doses of T for 9 months in healthy men resulted in no increase in prostate volume or PSA.

It is also worthwhile noting that two studies involving more than 400 men in total have shown that T-deficient men with PSA of 4.0 ng/mL or less have a biopsy-detectable cancer rate of 14% to 15%. This result means that 1 in 7 men with normal PSA and low T has PCa. If raising T truly caused PCa to grow more rapidly, one would expect TTh trials to be associated with high rates of cancer. The fact that this does not occur argues strongly that PCa risk is unrelated to serum T concentration.

RESOLVING THE PARADOX

How is it possible that androgen deprivation and its discontinuation can have such a powerful effect on PCa growth, yet so much of the literature fails to demonstrate any effect of T on PCa?

The resolution of this paradox is the recognition that there is a finite ability of androgens to stimulate PCa. This concept has been formalized as the Saturation Model, based on an accumulation of evidence from human trials, animal models, and PCa cell lines.

The key observation in all of these studies is that the prostate demonstrates exquisite sensitivity to changes in androgens at very low concentrations, but little or none at higher concentrations. Thus, a dose-response curve is easily shown in animals and PCa cell lines as androgens are increased; however, there then develops in all cases a plateau, beyond which even logarithmic increases in androgen concentrations elicit no further growth.

One likely mechanism for the Saturation Model is via the androgen receptor (AR), which becomes maximally bound with androgen in human prostate at 4 nmol/L (approximately 120 ng/dL). Because it is the androgen-AR complex that binds to genetic androgen response elements, once the AR has been maximally bound additional androgen is unable to influence cell activities via this mechanism, and serves merely as excess.

An additional mechanism is suggested by the work of Marks and colleagues in which hypogonadal men underwent prostate biopsy and comprehensive evaluation at baseline and after 6 months of injections of T or placebo every 2 weeks. Despite large changes in serum T concentrations, the intraprostatic concentrations of both T and dihydrotestosterone did not change significantly. Furthermore, no changes were noted in expression of androgen-related genes or genes associated with prostatic proliferation. These
results indicate that substantial changes in serum androgen concentrations may occur without being reflected within the prostate, and do not appear to induce biologic changes within prostate tissue.

The Saturation Model explains why manipulating serum T into or out of the castrate range produces large changes in PCa, whereas variations in serum T within the naturally occurring range do not. Once the AR has been maximally bound (ie, saturated), one should expect minimal or no additional prostatic effect from higher serum androgens. Therefore, the one group at some increased risk of androgen-driven PCa stimulation includes men with severely depressed serum T, below the saturation point.

**LOW TESTOSTERONE AND PROSTATE CANCER**

As clinicians have begun to let go of the old belief that raising T would necessarily increase PCa risk, there has been a coincidental recognition that low T may itself represent a risk factor for PCa. There is now emerging data that testosterone deficiency is associated with greater risk of PCa, high Gleason scores, worse stage at presentation, and worse survival.25

A study of 345 men with hypogonadism and PSA levels of 4.0 ng/mL or less found that the group of men in the lowest tertile of total T had more than double the risk of cancer on biopsy compared with men in the highest tertile (odds ratio, 2.15; 95% confidence interval, 1.01–4.55).21 In another study of 326 men who underwent radical prostatectomy, pretreatment T concentrations correlated with the likelihood of organ-confined disease.26 In addition, there is now evidence correlating high Gleason scores with low T.27

Although not all studies have confirmed an association between low T and worrisome aspects of PCa, there is now an accumulation of studies that is certainly provocative. Whereas it was once believed that a long-term placebo-controlled study of TTh would almost certainly show an increase in the risk of PCa, now it must also be considered whether such a study might show a reduction in PCa, particularly high-risk PCa.

**TESTOSTERONE THERAPY AFTER DIAGNOSIS OF PROSTATE CANCER**

The growing number of men who appear to be cured from PCa after definitive therapy has created pressure to consider TTh in those men who are symptomatic for T deficiency. Although this has been a long-standing taboo, clinical experience with TTh together with the scientific evidence suggests this may be far less risky than had previously been assumed. Preliminary results from several small studies suggest that TTh may be used, with caution and in a carefully selected population, after PCa has been successfully treated.

The first of these was a small series of 7 cases in which TTh was provided to symptomatic hypogonadal men who had undergone radical prostatectomy and who had an undetectable postoperative PSA.28 No recurrences were noted in these men despite 1 to 12 years of TTh in these individuals.

A second study reported similar reassuring results in 10 men who had also undergone radical prostatectomy with undetectable PSA.29 Mean total T increased from 197 ng/dL to 591 ng/dL, and symptoms of hypogonadism improved. Most importantly, no PCa recurrences were noted with a median follow-up of 19 months.

A third study reported results in 31 men who received TTh after PCa treatment with brachytherapy.30 In this group the median duration of treatment was 4.5 years with a range of 0.5 to 8.5 years. Total T concentrations rose from a median of 188 ng/dL to 498 ng/dL. No recurrences or PCa progression was noted, and all men remained with PSA less than 1.0 ng/mL at the end of the study.

There are now also reports of TTh in men with untreated PCa undergoing active surveillance. In one of these, an 84-year-old man with bilateral Gleason-6 PCa received 2 years of TTh with no increase in PSA.31

These various reports are consistent with the concept that PCa appears to be largely unaffected by variations in serum T within the naturally occurring range. Whereas not long ago any prior history of PCa was considered a lifelong contraindication to the use of TTh, the evidence no longer supports this notion. Although safety data are still lacking, it may now be reasonable to offer TTh to selected men with a history of PCa, as long as a discussion has taken place advising the patient that there is an unknown degree of risk of PCa progression or recurrence.

**MONITORING FOR PROSTATE CANCER**

Although there is little, if any, compelling evidence that TTh poses an increased risk of prostate cancer, it must also be recognized that there is great overlap between the population at risk for testosterone deficiency and the population at risk for prostate cancer, and it is thus highly recommended that men receiving TTh be monitored at regular intervals for prostate cancer. Monitoring
should consist of PSA determination and digital rectal examination, with biopsy performed for development of an abnormal prostate examination, elevated PSA, or rapid increase in PSA.\(^{18}\)

**SUMMARY**

In the absence of large, controlled prospective trials, it is impossible to definitively determine the safety of TTh in middle-aged men with T deficiency, especially with regard to the risk of PCas. However, there is now a large body of literature over several decades examining the relationship between androgens and PCAs, providing a consistent picture that should provide a moderate degree of comfort to clinicians offering TTh.

Data from humans, animal models, and PCa cell lines indicate that while androgens are critical to the promotion of optimal PCa growth, there is a finite degree of androgen-dependent growth. These data show that the limit to maximal androgen-mediated PCa growth is reached at serum T levels that are well below most naturally occurring serum T concentrations (approximately 120 ng/dL), and that therefore the raising of serum T via TTh is unlikely to affect PCa growth. The single, important exception is the man with severe T deficiency, in whom there remains unmet androgen-driven capacity to stimulate PCa growth.

The field has changed so rapidly that it is no longer unusual to offer TTh to men with a history of treated PCa, and there are even reports of TTh in men undergoing active surveillance with untreated PCa, without evidence of clinical PCa progression. A new consideration is that low T may predispose to a greater risk of PCa, especially high-risk PCa.

The field of androgens and PCa has been turned upside down. With the new perspectives offered by science over the last decade or more, clinicians must balance the proven benefits of TTh against the historical fears regarding PCa that have failed to find evidentiary support.

**REFERENCES**


