Testosterone Therapy for Men at Risk for or with History of Prostate Cancer

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Opinion statement

Since the early 1940s when Huggins showed that severe reductions in serum testosterone by castration or estrogen therapy caused regression of prostate cancer (PCa), it has been assumed that higher testosterone levels cause enhanced growth of PCa. For this reason, it has been considered taboo to offer testosterone replacement therapy (TRT) to any man with a prior history of PCa, even if all objective evidence suggests he has been cured. The fear has been that higher testosterone levels would "awaken" dormant cells and cause a recurrence. Thus, US Food and Drug Administration–mandated language in all testosterone package inserts states that testosterone is contraindicated in men with a history of, or suspected of having, PCa. Although there is little modern experience with administration of testosterone in men with known history of PCa, there is a varied and extensive literature indicating that TRT does not pose any increased risk of PCa growth in men with or without prior treatment. For instance, the cancer rate in TRT trials is only approximately 1%, similar to detection rates in screening programs, yet biopsy-detectable PCa is found in one of seven hypogonadal men. Moreover, PCa is almost never seen in the peak testosterone years of the early 20s, despite autopsy evidence that men in this age group already harbor microfoci of PCa in substantial numbers. The growing number of PCa survivors who happen to be hypogonadal and request treatment has spurred a change in attitude toward this topic, with increasing numbers of physicians now offering TRT to men who appear cured of their disease. Publications have now reported no prostate-specific antigen (PSA) recurrence with TRT in small numbers of men who had undetectable PSA values after radical prostatectomy. Although still controversial, there appears to be little reason to withhold TRT from men with favorable outcomes after definitive treatment for PCa. Monitoring with PSA and digital rectal examination at regular intervals is recommended.

Introduction

Over the past several years there has been a sea change in attitudes regarding the relationship of testosterone to prostate cancer (PCa), in particular with regard to the possibility of offering testosterone replacement therapy (TRT) to men who appear cured of PCa. Ever since the early 1940s when Huggins and Hodges [1] showed that castration or lowering of testosterone by estrogen administration caused PCa to regress, it has been considered taboo to offer men any form of testosterone supplementation because of concerns that it would cause growth of PCa or recurrence of disease.

This prohibition against TRT in men with a history of PCa reaches to the highest levels of medicine. Product labeling for testosterone formulations includes a contraindication against using testosterone in men with "a history of, or suspicion of, prostate cancer" [2].

Several years ago, the National Institutes of Health temporarily halted testosterone-related research, in part because of prostate safety concerns, until the Institute of Medicine could make recommendations regarding effective and ethical testosterone trials. It has even been suggested that men who only have a family history of PCa not undergo TRT [3].

However, with the increased interest in TRT over the past decade, the relationship of testosterone to PCa has come under greater scrutiny. Surprisingly, multiple reviews have failed to find any compelling evidence supporting the decades-old assumption that higher testosterone levels cause PCa growth [4••,5,6•]. In addition, there is now a growing population of otherwise healthy men who have survived definitive treatment for PCa and who happen to have symptomatic hypogonadism, and are requesting treatment. These events have conspired to create a new environment regarding the use of TRT in men with PCa or at risk for it.

The change in attitudes regarding this issue is manifest by the appearance of publications questioning the relationship of testosterone to PCa [7,8], by several small publications reporting no ill effects of TRT in men who appear cured of PCa [9•,10], and by substantial interest in the topic at medical meetings with lectures addressing this issue.

As a frequent lecturer on the topic of hypogonadism and TRT, I have been impressed with the increasing number of physicians across the country who now indicate their willingness to offer TRT to men who appear cured of PCa. Although many of these physicians have stipulations as to what circumstances would be acceptable before beginning treatment, this is still a major change from just 5 years ago, when it was only a rare physician who would consider offering TRT to any man with a history of PCa, regardless of how many years ago the patient had been initially treated.

Where did this prohibition come from, and does it make sense? Are those offering TRT now incurring serious risks for their patients? Or, has this all been a myth? Might there be a set of circumstances in which TRT may be reasonable, and others in which it should be avoided?

Treatment

Testosterone and PCa

- Huggins and Hodges [1] showed in 1941 that men with metastatic PCa demonstrated significant reductions in serum acid phosphatase with castration or with estrogen treatment that also lowered serum testosterone. They also administered testosterone for short duration in three men and reported that acid phosphatase levels increased. These two observations formed the basis for the concept that low testosterone levels cause PCa to regress and increasing testosterone levels causes increased growth of PCa. Huggins later won the Nobel Prize for his work demonstrating the hormonal responsiveness of PCa.
- However, other investigators of that era failed to find worrisome progression of PCa in men receiving testosterone administration. Prout and Brewer [11] administered daily injections of testosterone propionate to 26 men, of whom 20 had not been castrated. Although no regression of PCa was noted in any of these men, some did experience beneficial subjective responses, such as increased appetite, decreased bone pain, and an improved sense of well-being. These investigators did not observe any obvious progression of PCa in these men.
- Fowler and Whitmore [12] reported on the experience of testosterone administration in a set of 52 men with a history of bone metastases from PCa treated at the Memorial Sloan-Kettering Cancer Center over a period of 18 years. Only four of these men had not previously undergone castration or estrogen treatment. Of these four, one had an early "unfavorable" response, not otherwise specified, one had a beneficial subjective response, and the remaining two had "unfavorable" responses at 56 and 310 days of testosterone administration. Given the advanced stage of disease of these men, one must consider the possibility that the observed "unfavorable" responses occurred as a result of the natural history of the disease itself.
- In this same report [12], men who had previously undergone androgen ablation with castration or estrogen therapy had a high rate of unfavorable responses with testosterone administration. This is not surprising, because

PCa that responds to testosterone withdrawal is likely to regrow when testosterone is normalized. This group must be distinguished from men who have not undergone treatment to produce severe reductions in serum testosterone.

Testosterone and the risk of PCa

- The concept that higher testosterone represents a risk for PCa growth or subsequent development has been a touchstone of uro-oncology, but the evidence to support this belief has been elusive, and the logic has always been strained. Reviews have failed to find compelling evidence demonstrating a link between higher testosterone levels and PCa. In addition, the concept defies the epidemiology of PCa, rarely occurring during the peak testosterone years of the 20s and 30s, but becoming highly prevalent when men are older and testosterone levels have decreased substantially. Moreover, it is known from autopsy studies that a significant percentage of men in their 20s already harbor microfoci of PCa [13]. If high testosterone caused enhanced PCa growth, one would expect that PCa should be identified more frequently in young men.

Testosterone levels and subsequent risk of PCa

- There are at least 16 longitudinal studies investigating the relationship of endogenous testosterone levels and the subsequent risk of PCa [14,15,16•,17,18]. Not one has shown an association between endogenous levels of total testosterone and subsequent risk of PCa. In these studies, blood is obtained at baseline, men are followed for periods of up to 20 years or longer, and a group of men is identified who have developed PCa in the interim. A control group of an equal or greater number of age-matched individuals who did not develop PCa is then identified. Samples frozen from study entry are then thawed and tested for various hormone levels. Not one of these studies has shown a direct relationship between PCa and total testosterone levels.
- Several of these studies, all of which have explored multiple hormones in addition to testosterone, have identified associations of one or another minor androgen, but none of these has been confirmed by subsequent studies. Two studies have suggested a relationship with testosterone, one with calculated free testosterone [15] and the other by quartile analysis of testosterone ratios to sex hormone–binding globulin (SHBG) and by adjusting simultaneously for four other hormones [19].
- This latter study [19], published in 1996, was derived from the Physicians' Health Study and purported to show for the first time a direct link between testosterone and PCa. In this study, 222 men developed PCa between 1982 and 1992. An age-matched group of 390 men who did not develop PCa served as a control population. The primary findings were that no significant differences were seen in test results between the PCa and non-PCa groups with regard to any of the hormones studied, including total testosterone, estradiol, SHBG, and dihydrotestosterone. There was also no increased risk found for increasing levels of testosterone, or for any other hormone. Among the many additional analyses, a significant association was found for an increasing ratio of testosterone/SHBG, and also for increasing testosterone levels, but only with simultaneous adjustment for four other hormones. Other studies that looked at the testosterone/SHBG ratio failed to confirm this association [16•]. The validity of adjusting for four other variables simultaneously has dubious clinical merit.

- More recently, an analysis of data from the Baltimore Longitudinal Aging Study reported that higher levels of calculated free testosterone were associated with an increased risk of PCa [15]. No association was noted for total testosterone, or for any other hormone. This relationship is suspect for two primary reasons. First, men in the PCa group were significantly older than the men without PCa, and age represents the strongest known risk factor for PCa. Second, men in the cancer group actually had numerically lower mean levels of calculated free testosterone than did men without PCa, raising concerns regarding the validity of quartile analysis. Subsequent studies in larger populations using the same methodology for calculated free testosterone have failed to support this finding [16•].
- In summary, there has been a consistent rejection of the hypothesis that higher testosterone levels lead to increased risk of development of PCa.

Clinical trials

- Although no large long-term TRT trial has yet been performed, available studies reveal a cancer detection rate of 1% [4••]. These studies have included regular prostate-specific antigen (PSA) tests and digital rectal examinations, with biopsy triggered by development of abnormalities. This rate of cancer is similar to that found in prostate screening studies [4••].

Men at high risk for PCa

- A group of 20 hypogonadal men with high-grade prostatic intraepithelial neoplasia (PIN) and 55 hypogonadal men with benign prostate biopsies underwent 12 months of TRT [20•]. One of the men in the PIN group was found to have cancer, with biopsy triggered by development of an abnormal digital rectal examination. This represents a 5% cancer rate in this population and a 1.3% cancer rate for the group as a whole. Because development of frank cancer has been reported to occur within several years in 25% or more of men with PIN [21], these data suggest that TRT did not cause any precipitous progression of cancer in these men.

Men with low testosterone levels

- If high testosterone is thought to be a risk for PCa growth, then low testosterone should be protective. Sextant biopsy in untreated hypogonadal men with PSA of 4 or less revealed cancer in 11 of 77 men, or 14% [22]. This rate is not dissimilar to the cancer rate of 15% in men with PSA of 4 or less noted by Thompson et al. [23•] in the placebo arm of the Prostate Cancer Prevention Trial.

TRT for men with a history of PCa

- There are several reasons why it has been considered taboo for several decades to offer TRT to a man with a prior history of PCa. PCa is clearly androgen dependent, at least for most initial clinical cancers, and lowering of testosterone to castrate levels causes PCa to regress. Restoration of testosterone to normal levels is associated with recurrence of PCa. Because low testosterone causes PCa to regress, it follows that higher testosterone should cause PCa to grow. Support for this appears to arise from the experience with testosterone flare during initial luteinizing hormone–releasing hormone (LHRH) therapy [24]. Testosterone levels increase for 7 to 10 days,

and this period of time has been associated with increased bone pain and occasional cancer progression, evidenced by urinary retention or vertebral collapse with spinal cord compression [24].

- However, as we have seen, there is no compelling evidence that higher testosterone levels cause PCa to grow, except in cases in which testosterone levels have first been reduced severely. This indicates a saturation effect. This was suggested in 1981 by Fowler and Whitmore [12], after noting that previously untreated men with metastatic PCa failed to demonstrate worrisome early progression with testosterone administration, for periods of up to several months.
- Moreover, it is noteworthy that in the few studies that measured PSA during the flare interval, no PSA increase was seen [25,26], suggesting that any clinical effects may have occurred due to the natural history of the disease itself, or by direct effect of testosterone on bone without necessarily causing tumor progression.
- Because testosterone administration failed to cause observable PCa progression among men with advanced bony metastases, and because an increase in endogenous testosterone during the flare phenomenon failed to cause any increase in PSA among men also with metastatic disease, how can it be considered dangerous to offer TRT to men who have undergone definitive treatment for PCa?
- The easiest population is men with undetectable PSA after radical prostatectomy. If no cancer cells are evident, as suggested by undetectable PSA, then there can be no concern that testosterone administration would cause them to grow. If the concern is that dormant cells might awaken with higher testosterone levels, causing cancer progression, then why do we not see this phenomenon among men with substantial tumor burdens? Although there is little experience in this population, two small studies [9•,10] have been published within the past 2 years, indicating that TRT caused no PSA recurrence in 8 and 10 men, respectively, with undetectable PSA after radical prostatectomy.
- In men after PCa treatment with external beam radiation, brachytherapy, or cryotherapy, there is usually a measurable PSA value, and this value can fluctuate over time, raising anxieties for clinician and patient alike. A literature search fails to identify any published series of TRT administration in these populations. However, the theoretical arguments remain the same. If there is no cancer present, then there should be no concern. Even if cancer is present in small volumes, the evidence suggests that higher testosterone values fail to cause these to progress.

TRT in men at risk for PCa

- Men at risk for PCa consist of those with high-grade PIN, or with increased PSA, with or without prior negative biopsy. As described earlier, TRT in men with PIN failed to cause any obvious increased progression of PCa, and the increase in PSA was similar for men with PIN and without PIN. Men with an elevated PSA are at increased risk of having PCa; however, if a prior biopsy has been done and is negative, there seems little reason to withhold treatment. Most men with increased PSA prove to have negative biopsy results.

TRT in men with untreated PCa or recurrent PCa after treatment

- There is little modern experience of administering TRT to men with known PCa who have not otherwise undergone treatment, or with recurrent PCa. The absence of increased PSA with the flare phenomenon in men with

advanced cancer, or recurrent cancer, provides some reassurance that study of this population may be considered without certain problems. Intermittent LHRH therapy is an example of restoring normal testosterone levels in men with advanced PCa, without evident negative clinical outcomes [27].

Future directions

- The past several years have witnessed a reassessment of the relationship of testosterone and PCa. Although traditionally it has been considered taboo to offer TRT to any man with a history of PCa, regardless of disease status, many clinicians have begun to offer treatment to selected patients. The most common clinical scenario is for the symptomatically hypogonadal man with undetectable PSA after radical prostatectomy. The evidence suggesting a saturation model for PCa and testosterone would suggest that TRT may also be safely offered to others with a history of PCa, or those who may be at risk for PCa. Although there are no direct TRT trials in these populations, historical experience and evidence of PCa behavior under the conditions in which testosterone has been increased support this concept. This area merits further investigation, particularly because there is a growing number of men who may benefit from TRT and a paucity of evidence indicating safety concerns.

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