
Testosterone and Prostate Safety

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Abstract

For several decades it has been assumed that higher testosterone (T) leads to greater growth of benign and malignant prostate tissue, but this view has come under greater scrutiny over the last several years. Although there are as yet no large-scale, long-term controlled studies of T therapy to provide a definitive assessment of risk, numerous smaller clinical trials as well as population-based longitudinal studies consistently fail to support the historical idea that T therapy poses an increased risk of prostate cancer or exacerbation of symptoms due to benign prostatic hyperplasia. This lack of prostate risk despite increased serum T appears to be explained by data showing that exogenous T does not raise intraprostatic concentrations of T or dihydrotestosterone, suggesting a saturation model. In contrast, there is mounting evidence that low serum T is associated with greater prostate cancer risk, and more worrisome features of prostate cancer. In conclusion, the available evidence strongly suggests that T therapy is safe for the prostate. Given that the population at risk for T deficiency overlaps with the population at risk for prostate cancer, it is strongly recommended that men undergoing T therapy undergo regular monitoring for prostate cancer. Copyright © 2009 S. Karger AG, Basel

The conventional views protect us from the principal job of thinking.
J.K. Galbraith, Nobel Prize in Economy

One of the greatest impediments to treating men with testosterone (T) therapy is the fear that raising serum T concentrations will result in an increased risk of prostate cancer (PCa) or will convert an occult cancer into a clinical one [1]. This fear stems from the original work by Huggins and Hodges [2], who showed in 1941 that severe lowering of T by castration or estrogen therapy resulted in regression of advanced PCa, and who reported also that T administration caused ‘enhanced growth’ of PCa. This work by Huggins established the androgen dependence of PCa, and later earned him the Nobel Prize.

To this day, androgen deprivation therapy (ADT) remains a mainstay of treatment for men with advanced PCa, with rapid observable reductions in the serum marker, and prostate-specific antigen (PSA). In addition, it is well-recognized that restoration of T concentrations, such as by discontinuation of ADT, results in a rise in PSA in a

substantial number of men. From these two current, clinical observations it is easy to understand why clinicians would be concerned that T therapy might pose an increased risk of PCa. Curiously, clinical experience and scientific research fail to demonstrate an increased risk.

In this chapter, we will review the available evidence regarding the relationship of T and the prostate, with special attention to safety issues regarding PCa. Although there are as yet no large-scale, long-term controlled studies of T therapy to document its safety, there does exist a substantial literature examining this relationship, and providing a rationale for why ADT causes PCa to regress but T therapy does not appear to cause PCa to progress.

T Trials

In the absence of any single large study on T therapy, one must examine the results from smaller studies, many of which have examined PSA changes and PCa detection rates in trials of 12 months to 3.5 years.

One of these was a 12-month study of 371 men on T gel therapy [3]. Over the course of 1 year three cancers were detected, all due to a rise 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 rise 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 T therapy trials. In a review of nine separate T therapy trials involving 579 men and ranging from 3 to 36 months, seven cancers were identified, representing a cancer detection rate of 1.2% [4].

Wang et al. [5] performed one of the longest T therapy 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 PCa, representing a cancer rate of less than 1% per year of treatment.

Finally, PCa rates were investigated among men with and without the prostatic pre-cancerous lesion known as high-grade prostatic intraepithelial neoplasia (PIN). In this 12-month study 75 men with hypogonadism received T therapy, including 55 men with benign pretreatment prostate biopsy, and 20 men with biopsy revealing PIN [6]. 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 to a 25% risk over 3 years in this population, suggesting no significantly increased cancer risk.

One study that examined the effect of T therapy on PSA found that the overall change was mild, and the individual response varied considerably. Among 58 men who underwent T therapy for 1 year, the majority (32 men) demonstrated a mild PSA increase of 0.5 ng/ml or less [4]. 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 >0.5 ng/ml and men whose PSA declined.

To put these studies and their results in perspective, it is important to note that the observed PSA changes in multiple studies of approximately 15–20% 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 [7]. In addition, the annual cancer rate of approximately 1% that shows up repeatedly in T therapy trials compares favorably to cancer detection rates in men undergoing PCa screening [8].

Perhaps most importantly, two studies involving more than 500 men in total have shown that hypogonadal men with PSA of 4.0 ng/ml or less have a biopsy-detectable cancer rate of approximately 14% [9, 10]. If 1 in 7 men with low T has PCA, and if raising T truly caused PCA to grow more rapidly, logic would suggest that T therapy trials should be associated with a much higher rate of PCA.

Longitudinal Studies

The relationship of T and other sex hormones to subsequent development of PCA has been extensively studied in at least 16 population-based longitudinal studies [11–16]. 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.

A total of greater than 430,000 men have been included in these studies, including 1,400 men with PCA, and 4,400 men identified as controls. Not one study has shown a direct correlation between total T levels and PCA. Isolated associations have been reported with some measures and PCA: minor androgens in one [14], calculated free T in another [15], and with quartile analysis of hormone ratios or controlling for multiple variables in a third [16]. None of these positive associations have been supported by later studies. It is worth noting that the largest study of this type actually noted *reduced* PCA risk in men with higher T levels [13].

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 T, on the subsequent risk of development of PCA. Although such studies cannot entirely replace the value of a prospective long-term controlled study of T therapy, 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.