Testosterone Replacement Therapy and Prostate Risks: Where's the Beef?

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Introduction

It has been over 60 years since Huggins published his landmark work showing that castration caused regression of metastatic prostate cancer, linking forever the issues of prostate cancer and testosterone (T).[1] The recognition that prostate cancer is largely androgen-dependent has resulted in a reluctance, and in some quarters even a strong antipathy, to treat hypogonadal men with testosterone replacement therapy (TRT). After all, castration or pharmacologic lowering of serum T to castrate levels continues to be a mainstay of treatment for advanced prostate cancer to this day. If lowering testosterone makes prostate cancer cells die, then it should follow that raising testosterone should make prostate cancer cells grow.

Nevertheless, there is growing recognition in the medical community that hypogonadism is a significant and treatable condition of men that becomes increasingly common with aging. Moreover, the benefits of TRT have been well documented, including improvement in libido, erectile dysfunction, mood, cognition, lean body mass, and bone density.[2] How then does one reconcile the benefits of TRT in the hypogonadal man with the potential risk that TRT may cause an occult cancer to grow?

Curiously, after all these years of testosterone usage and awareness of the androgen-dependence of prostate cancer, there remains no compelling evidence that TRT does, in fact, represent a true risk for prostate cancer growth. Below, I present a summary of the data regarding TRT and prostate cancer.

Effects of testosterone on the non-malignant prostate

Although the normal prostate has been shown to be androgen-dependent, this does not mean that higher T levels result in greater prostate growth. In hypogonadal men, TRT increases PSA and prostate volume to a modest extent, by approximately 15%.[3] These values rise to the same level as eugonadal men, but no higher.[4] Moreover, exposure of normal men to supraphysiologic serum T concentrations did not result in any measurable increase in PSA at all. Thus, some level of T is necessary for full growth of the prostate, but above that level there appears to be no effect on prostate growth. It is thus incorrect to think of the prostate responding to higher T levels in a dose-response manner.

Case reports

A number of case reports have been published documenting that prostate cancer was diagnosed at some point after initiation of TRT.[5] These reports have been used to support the argument that TRT causes progression of prostate cancer. A recent article described twenty such cases culled from six urology practices.[6] The time between initiation of TRT and diagnosis of prostate cancer was as long as eight years in this report.

These types of reports have merit only if one already believes that TRT increases the risk of prostate cancer, since they show association but not causation. Since prostate cancer is so common, how does one know that TRT had anything at all to do with the subsequent identification of prostate cancer? It is an everyday occurrence for urologists to observe a sudden rise in PSA or a change on digital rectal exam that may trigger a biopsy. Since most of these changes occur without any known precipitating cause, any assertion that TRT caused the prostate change requires some evidence that TRT actually increased the rate of cancer in these men. Without this type of information, case reports or series provide no useful information at all. Indeed, it is even possible that the overall rate of cancer was *decreased* in these same urology practices among men receiving TRT.

Clinical trials with TRT

What do clinical trials actually tell us about the risk of prostate cancer among men receiving TRT? Unfortunately, no large-scale long-term controlled trials have been performed. However, in a 2004 review of prospective TRT clinical trials of 6-36 months, the cancer detection rate was 1%.[3] A similar cancer rate has been observed in retrospective and shorter studies. This cancer detection rate of approximately 1% is very similar to the cancer detection rate in men undergoing prostate screening.

TRT in men at high risk for prostate cancer

A study was performed in which the prostate response to 12 months of TRT was noted in hypogonadal men in whom prostate biopsy revealed high-grade prostatic intraepithelial neoplasia (PIN) compared with hypogonadal men with benign findings on prostate biopsy.[7] Men with PIN represent a high-risk group for subsequent development of prostate cancer, with a cancer rate of 25% at 3 years. In this study, there were 20 men with PIN, and 55 with negative biopsies. At the end of one year, the PSA rise in both groups was the same at 0.3 ng/ml. One cancer was detected in the PIN group (5%), and none in the benign biopsy group. Although one must be cautious in comparing one-year data to three–year data, there clearly was no dramatic rise in prostate cancers in this high-risk group receiving TRT.

Longitudinal studies of endogenous T levels and prostate cancer risk

Longitudinal studies with frozen sera represent one of the more powerful types of studies to investigate the potential etiologic effect of hormone levels on subsequent development of a disease such as prostate cancer. At least 12 such longitudinal population-based studies have been performed looking at the relationship of endogenous T levels (as well as other hormones) to prostate cancer, involving tens of thousands of men.[8-10] Blood samples were drawn at entry, and then men were followed for 10 or more years. At the end of the study, a cohort had developed prostate cancer, and the remainder did not.

Blood samples from these men from years earlier were then compared to see whether testosterone levels differed between these two groups.

Not one of the twelve studies demonstrated a difference in T levels between men who did and did not develop cancer.[3] Moreover, men with higher T levels were shown to have no increased risk of cancer compared to men with lower T levels. Although one study, with data derived from the Physician's Health Study, is frequently cited as demonstrating a relationship between T and prostate cancer, the actual data show no differences in T levels between the cancer group and the non-cancer group.[11] This study did report a difference in the ratio of T to SHBG, which may possibly reflect bioavailable T levels, however no other studies have confirmed this observation.

Although these studies do not address the issue of TRT directly, they do show, repeatedly, uniformly, and powerfully, that higher levels of testosterone are not associated with an increased risk of prostate cancer.

What about men with low T?

If one believes that high T is worrisome for prostate cancer, then it should follow that low testosterone would be protective against the development of prostate cancer. Is this correct?

Prostate biopsies performed in hypogonadal men prior to TRT revealed cancer in 11 of 77 men (14%) with normal DRE and PSA of 4.0 ng/ml or less.[12] A more recent evaluation of 345 hypogonadal men revealed a similar cancer detection rate of 15% for men with PSA of 4.0 or less.[13] Moreover, men with severely reduced T levels had significantly higher CaP rates of 20%. Finally, the combination of low T and PSA of 2.0 ng/ml or higher was particularly worrisome, with a cancer rate of 30%. These results raise the possibility that there may actually be some degree of increased risk of prostate cancer associated with low testosterone. But certainly these data argue against the concept that low T is in any way protective for prostate cancer.

Not only does low T not seem to protect against prostate cancer, but there is some evidence that low T may also be associated with high grade cancers,[14] higher stage at diagnosis, and worse clinical outcomes.

The disparity between the rate of cancer detection in TRT trials (1%) and biopsy-detectable cancer in hypogonadal men (14%) would seem to suggest that existing cancers do not grow with TRT. If occult prostate cancer truly grew with higher T levels, one should expect that roughly 14% of men in clinical TRT trials, or one out of seven, would demonstrate changes in PSA or DRE that would prove to be cancer. However, the cancer rate in TRT trials appears to be no different than baseline levels.

The paradox of testosterone and prostate cancer

As summarized above, a review of the literature clearly fails to show any compelling evidence that higher T, either endogenous or via TRT, increases the risk of prostate cancer. Yet there is little question that lowering T to castrate levels has a beneficial effect on CaP, causing most cancer cells to die. Why then doesn't higher T cause prostate cancer growth, and represent a demonstrable risk for men with occult cancer? This apparent paradox is best explained by the fact that TRT in hypogonadal men is not the opposite of chemical castration. Whereas castration lowers T levels to exceedingly low levels, most men receiving TRT already have substantial, albeit reduced, levels of circulating T. It seems likely that even in a hypogonadal man there would be adequate circulating T levels for any existing prostate cancer to satisfy its metabolic requirements.

The other part of the explanation is that our concept of how testosterone affects prostate growth is overly simplistic. We tend to think of this relationship as a dose-response curve, with higher T levels leading to greater prostate growth. Yet most biologic systems reach a plateau as concentrations of a particular growth factor increase, and the same is likely to hold true for T and prostate cancer. Higher serum concentrations of T do not seem to provide any added spur to growth.

Conclusions

Despite multiple attempts to show that higher T levels lead to an increased risk of CaP, there remains no compelling scientific evidence to support this hypothesis. Physicians should take this into account as they consider TRT for hypogonadal men. Nevertheless, current concerns regarding hormones and cancer make it mandatory that men receiving TRT undergo regular prostate monitoring with PSA and DRE, two or three times within the first year, and then at least annually thereafter. Biopsy should be performed prior to initiation of TRT for any man who has an abnormal PSA or DRE at baseline, or who develops a significant change in these parameters during the course of treatment. This recommendation, of course, applies to all men, regardless of whether they are receiving TRT.

As clinicians, it is our duty to take into account the whole person, and to make treatment decisions based on an evaluation of risks and benefits. With appropriate medical monitoring, TRT appears to be safe for the prostate, and can be an effective treatment for many hypogonadal men.

Although the final chapter regarding the potential risk of TRT for prostate cancer is yet to be written, it should be recognized that as of now there exists no compelling evidence supporting the long-held belief that TRT increases prostate cancer risk. In this age of evidence-based medicine, we should apply the same rigorous standards to assertions of risk as we do to assertions of safety. With regard to prostate cancer and TRT, one must therefore ask, "Where is the beef?"

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