Testosterone Therapy Can be Given to Men with No Concern that it will Promote Prostate Cancer Development or Progression

PRO

During my urology training in the 1980s I was taught that 1) high testosterone (T) caused prostate cancer (PCa), 2) PCa never developed in men with low T and 3) T therapy in a man with PCa was like “feeding a hungry tumor” or “pouring gasoline on a fire.” These universally accepted concepts, taught to medical students around the world, must now be recognized as mere lore.

Modern evidence shows that men with high T are at no greater risk for PCa than those with low T. Higher Gleason scores, advanced stage at radical prostatectomy and biochemical recurrences are associated with low T, not high T. Meta-analyses of placebo controlled trials revealed no increased rate of PCa in those receiving T therapy. Men who received T are at no greater risk for advanced or higher grade disease than untreated men. Importantly, there is now high level evidence demonstrating benefits of T therapy for sexuality, physical activity, body composition and mood. Yet we still fear T therapy, choosing old beliefs over a mountain of contradictory evidence. Why?

First, it has the patina of truth. We lower T in men with advanced PCa, and observe marked reductions in PSA. Second, Nobel Prize winner Charles Huggins wrote in 1941 that T injections “activated” PCa. Third, T therapy was so rare until the late 1990s that Huggins’ assertion went unchallenged for half a century, by which time it was accepted as a foundational concept in oncology. Finally, it is exceedingly difficult to change established beliefs, no matter how strong the evidence.

It has been 20 years since we observed that 1 of 7 men (14%) with low T but normal prostate specific antigen (PSA) (less than 4.0 ng/ml) who underwent prostate biopsy had PCa (14%), a risk equal at that time to men with elevated PSA. Clearly, low T was not protective. However, I continued to believe that high endogenous T, or T therapy, was risky until I could find no evidence to support this belief. My eyes were finally opened wide when I discovered that Huggins had based his assertion regarding T activation of PCa on just 1 hormonally intact man treated for only 14 days.

It is fascinating to look back to see how the medical community fabricated a broad, unsupported narrative from a narrow special case, ie PCa regression with androgen deprivation. In the absence of hard data or clinical experience, it seemed logical to assume that raising T must cause PCa growth since lowering T caused regression. However, in healthy volunteers supraphysiological T doses fail to increase PSA or prostate volume. Men who receive T therapy do not demonstrate a greater risk of clinical PCa than those who receive placebo, although 1 in 7 harbors biopsy detectable PCa. This may seem paradoxical but it is easily understood once one recognizes there is a finite ability of androgens to stimulate prostate tissue. Multiple sources of evidence, including cell lines, animals and human clinical data, show that this maximum is reached at low T concentrations of approximately 250 ng/dl in men. This is called the saturation model.

Awareness of the saturation model has changed clinical practice. Many physicians now offer T therapy after radical prostatectomy, radiation therapy or brachytherapy with low biochemical recurrence rates. I now routinely offer T therapy to symptomatic men on active surveillance, with similar progression rates as untreated men. In select cases I have even provided T therapy to men with metastatic disease who declined androgen deprivation, with rewarding symptomatic benefit and without any response indicative of “pouring gasoline on a fire.” The old prohibitions against T therapy are falling aside and the sky has not fallen.

Completing the conceptual revolution, promising results have been reported with high dose T cycled with androgen deprivation (“bipolar” treatment) in men with castrate resistant PCa.

Nearly everything we learned about PCa and T is wrong. Low T is not protective. High T is not risky. T therapy does not increase PCa risk or high grade disease. The only correct observation is that PCa requires androgens for optimal growth and it...
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Given the driver role for androgen receptor (AR) in prostate cancer, we believe that testosterone replacement therapy (TRT) may promote PCa progression and cannot be given without expressing this concern. Until level 1 evidence exists to the contrary, benefit from TRT must be weighed against this risk.

TRT is a reasonable option for symptomatic men with documented low serum testosterone who are at low risk for PCa. Linkage of symptoms, or measurement of T, to the syndrome of hypogonadism is not always clear-cut. Many men with low T are asymptomatic, many men with normal T have symptoms ascribed to hypogonadism and many signs/symptoms of hypogonadism are a normal part of aging. Given these ambiguities, potential benefits of TRT must be weighed against its risks. While this view focuses on risk for PCa, studies also link cardiovascular disease to TRT. Risks of hormone replacement therapy (HRT) in women were missed in smaller outcome studies, resulting in assurance of safety and widespread (and, in retrospect, harmful) prescribing. Real risks were only appreciated after larger, long-term studies. These do not exist for TRT.

The main concern for TRT and PCa risk is the driver role for T and AR in PCa progression. The AR, like its sibling estrogen receptor (ER), is a ligand activated transcription factor that promotes proliferation and survival in prostate and breast cancer, respectively. Unlike in PCa, which are almost all AR driven, only subgroups of breast cancer are ER driven. Despite this segmentation in breast cancer, large randomized trials demonstrate increased breast cancer mortality in postmenopausal women, as well as increased risk of recurrence/mortality among women given HRT after breast cancer. While similar data do not exist for PCa, given confounders of peak incidence at an older age and long natural history, along with analogous biology, the presence of a similar risk for PCa is plausible and hence a concern.

The AR is an undisputed accelerator of PCa, and the only credentialed therapeutic target. Uninterrupted T stimulated activity of AR over time increases genomic instability and oncogenic alterations. Indeed, one of the most common rearrangements of Ets gene family members results in Ets overexpression downstream of a translocated androgen response element under conditions of ligand activated AR. PCa cells are dependent on ligand activated AR and, despite enormous genomic heterogeneity, almost all PCa cells initially respond to androgen deprivation therapy with life prolonging benefit.

While this T dependence does not mean that TRT will promote PCa, it does imply plausible causality. In particular, considering similarities with breast cancer, there is an onus on TRT proponents to demonstrate safety with regard to PCa risk. There is a plethora of low level evidence from many small trials, and we must consider inability
of underpowered studies to detect small but clinically meaningful harm from a well-intentioned intervention. The influence of industry in biasing this ecosystem is also relevant. HRT in women is an apt cautionary tale, as increased breast cancer and cardiovascular risks required larger studies to be demonstrated. Given that AR is a more dominant driver of PCa than estrogen is in breast cancer, concern is justified for TRT in men.

The AR saturation model attempts to explain the minor impact of TRT in noncastrated men and shifts the risk/benefit balance of TRT, stating that decreases in serum T below a point of maximal AR binding elicit substantial changes in biology but once saturated, additional T produces little stimulation of AR. This view, extrapolated from in vitro binding studies of monolayer cell cultures, is overly simplistic. More than 1,000 mRNA, ncRNA and/or proteins are regulated by the AR in prostate cells to collectively regulate cell cycle, survival, bioenergetics and differentiation, and many are differentially regulated on a time, dose and contextual basis.

The hypothesis that regulation of all of these genes is spatially and temporally saturated by modest levels of T is not supported for several reasons. 1) AR (and other receptors) in in vitro binding assay can be saturated but Vmax is not a valid surrogate for dynamic in vivo systems due to turnover of ligand and receptor, and heterogeneity in diffusion, cell cycle, metabolism etc. PCa is highly heterogeneous, exhibiting adaptive biological complexity in response to its microenvironment and therapeutic stresses. Cancer cells dynamically and heterogeneously change AR mRNA levels or AR protein half-life in response to changes in its environment, and over time as genomic alterations accumulate. 2) Genomic alterations selected under conditions of low ligand can be promiscuously activated by TRT. 3) Nongenomic effects of ligand-AR interaction include cross-talk activation of cell signaling networks, like AKT, MAPK or c-SRC, which are often dysregulated when PTEN or other tumor suppressor genes are deleted. 4) In vivo growth of AR positive PCa xenografts and PDX models are either dependent on or accelerated by exogenous T in eugonadic mice.

Additional clinical observations highlight further the relative roles for T in PCa progression and argue against the saturation model. 5-α Reductase inhibitors, which lower dihydrotestosterone levels, reduce risk of PCa diagnosis and progression in men on active surveillance, and it is plausible that TRT would have the opposite effect. Moreover, why should symptoms and metabolic consequences of hypogonadism, which result from low T stimulated AR activity in benign tissue, not be subject to the saturation theory similar to that proposed for cancer? If TRT does stimulate AR activity above a threshold to alleviate hypogonadism symptoms, why can it not do the same in PCa? If the saturation model were applied to benign tissues, there would be no symptomatic or metabolic benefit to TRT.

TRT is safe and unlikely to affect recurrence in patients with undetectable PSA treated by curative intent, and thus it is reasonable to offer such men TRT if serum T is low and they are symptomatically bothered. Given the aforementioned data, it is plausible that TRT alters the rate of progression in men with detectable PSA after surgery or radiation therapy, or in those on active surveillance. Small studies and meta-analyses report that TRT can increase the rate of rising PSA but, unlike breast cancer, no data tell us whether TRT affects metastasis-free or PCa specific mortality. However, since PSA doubling time does predict shorter time to metastases, increases in PSA in patients with PCa initiating TRT implies plausibility and concern for men with PCa.

All decisions regarding longevity and quality of life involve trade-offs and for some men risks of TRT may be warranted. However, all men should be informed of the possible risks of long-term TRT. Until higher level evidence emerges to disprove this probable causality, it is reasonable and prudent to caution that TRT may promote PCa.

**REFERENCES**


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