O′ testosterone, where is thy sting? A Urologist's reflection on testosterone and prostate cancer

Abraham Morgentaler

Blavatnik Faculty Fellow in Health and Longevity, Beth Israel Deaconess Medical Center, Harvard Medical School, USA

eClinicalMedicine
2025;80: 103061

Published Online xxx
https://doi.org/10.1016/j.eclinm.2024.103061

In 1941 Huggins and Hodges reported that castration or administration of estrogen caused a new serum biomarker, acid phosphatase, to decrease in men with metastatic prostate cancer (PCa).[1] This was the first treatment for men with advanced PCa, and androgen deprivation remains the mainstay of treatment for these men to this day. They also reported that testosterone (T) injections caused acid phosphatase to rise and concluded that "Cancer of the prostate is activated by androgen injections." Huggins was awarded the Nobel Prize in Medicine or Physiology in 1966.

For the next 60 years there was a near-complete prohibition against the use of testosterone therapy (TTh) because of the fear that raising serum testosterone would cause *de novo* PCa or cause rapid, aggressive PCa growth.[2]

As a newly minted urologist in 1988 I saw male patients with challenging sexual problems. I was curious about testosterone (T) therapy (TTh) due to my prior research restoring sexual behavior in the castrated male lizard, *Anolis carolinensis,* with intracranial T pellets.[3] I wondered whether men might respond like my lizards. They did! In addition to improvements in libido and erectile function, my patients reported additional non-sexual benefits, like, "My wife likes me again" and "I wake up optimistic about my day."

To avoid the possibility that TTh would trigger rapid growth of an occult PCa, I insisted for years on first performing prostate biopsies. The 14% PCa rate observed in men with low T levels and normal PSA was shocking, since men with low T were supposed to have a vanishingly low risk of PCa.[4] Yet I still believed raising T must be a problem and for years repeated to trainees the same phrases I had been taught: "Giving testosterone is like "pouring gasoline on a fire," and "feeding a hungry tumor."

Yet a wealth of evidence challenges the concept that androgens drive PCa. Higher endogenous testosterone confers no greater risk of developing PCa than lower testosterone.[5] High-grade PCa risk is *reduced* with TTh.[6] Multiple large observational studies reveal no increased PCa rate in men that receive TTh. Several large RCTs found low rates of PCa in the TTh arms, no greater than for placebo.

Arguably the most powerful piece of evidence comes from the recently published TRAVERSE trial, the largest testosterone RCT to date, in which 5246 men with low T were randomized to daily T gel or placebo gel, with a follow-up of 33 months.[7] The trial was originally designed to address the FDA's concern regarding cardiovascular (CV) risk with TTh. The results of this primary study endpoint showed no increased CV risk. The primary prostate safety end point was incidence of high-grade PCa, and any PCa was a secondary end point. The protocol for prostate biopsy was pre-specified, and all biopsy results were centrally adjudicated. A mere 12 total cases were identified in the T group, of which 5 were high-risk. A nearly identical result was obtained in the placebo group, with 11 total cases including 3 high-risk. These results provide conclusive evidence that TTh is not associated with increased PCa risk. The natural history of PCa offers its own serious challenge; men tend to develop PCa when they are older and T levels are low, whereas PCa is exceedingly rare in men in their early twenties when serum T is at its lifetime peak.

Over the course of my professional career, I offered TTh to men with progressively riskier circumstances, first to men at risk for PCa, then to those who appeared cured of PCa, and eventually to men with metastatic disease. This radical departure from standard practices was spurred by compassion for patients suffering from severe reductions in the quality of their lives due to T deficiency, and my repeated observation that TTh in these men failed to cause rapid disease progression.

A 94-year-old scientist with extensive nodal and bony metastases traveled across the country to request TTh. He discontinued standard treatment with androgen deprivation when it left him too weak to leave his home. I warned him TTh could cause such rapid growth of his cancer that he could die in a day or a week. He replied, "I'm 94 years old with metastatic cancer. I'm going to die soon. While I'm alive I'd like to live as well as I can." Within three weeks of beginning TTh he was exercising, corresponding with colleagues, and had regained his appetite. He survived 11 months. His case gave me courage to treat younger men with metastatic PCa, several of whom survived many years on TTh.[8] O′ testosterone, where is thy sting?

Skepticism regarding PCa risk with TTh is not new. Numerous studies in the 1980s and 1990s failed to implicate higher serum T as a problem for PCa, and experienced investigators in 1994 argued there was no evidence that TTh was associated with increased PCa

E-mail address: amorgent@yahoo.com.

risk.[9] The testosterone and PCa narrative persists for two main reasons. First, Huggins promoted it for more than a quarter-century. As the greatest PCa authority of his day, he shaped medical opinion via "eminence-based medicine." However, in Huggins' original article he gave T injections to only 3 men, provided results for 2, and one of these was already castrated. His conclusion that T "activated" prostate cancer was therefore based on erratic acid phosphatase results in a single hormonally intact patient who received T injections for only 18 days.[1]

Second, there has been an incorrect assumption that ever-greater androgen concentrations lead to ever-greater PCa growth, whereas it has been shown that the prostate's requirement for androgens appears fully satisfied at a relatively low T concentration of approximately 250 ng/dl, presumably due to saturation of androgen binding to the androgen receptor.[10] Testosterone concentrations above this saturation point do not appear to cause additional prostatic metabolic activity or growth. The evidence fails to provide a basis for restricting TTh in men with PCa, and a modest and reassuring clinical experience-including giving TTh in men with metastatic PCa-argues for a re-evaluation of such restrictions in clinical recommendations and guidelines.

I've learned several lessons from this scientific adventure. Challenge assumptions-even foundational concepts can be wrong. Read primary sources and draw your own conclusions-the greatest scientists have been known to misinterpret their own data. And do not be afraid to try new things in medicine-it is the only way forward for our patients.

Contributors

Conceptualization: Abraham Morgentaler.
Methodology: Abraham Morgentaler.
Writing, Draft and Revisions: Abraham Morgentaler.

Declaration of interests

Abraham Morgentaler reports receiving payments for consulting from Ascend Therapeutics, Besins Healthcare, and Marius Pharmaceuticals; lecture honoraria from Besins Healthcare.

Acknowledgements

No funding was received.

References

1 Huggins C, Hodges CV. Studies on prostatic cancer, I: the effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Cancer Res*. 1941;1:293–297.
2 Nieschlag E, Nieschlag S. Endocrine history: the history of discovery, synthesis and development of testosterone for clinical use. *Eur J Endocrinol*. 2019;180:R201–R212.
3 Morgentaler A, Crews D. Role of the anterior hypothalamus-preoptic area in the regulation of reproductive behavior in the lizard, Anolis carolinensis: implantation studies. *Horm Behav*. 1978;11:61.
4 Morgentaler A, Bruning IIICO, DeWolf WC. Incidence of occult prostate cancer among men with low total or free serum testosterone. *JAMA*. 1996;276:1904–1906.
5 Endogenous Hormones and Prostate Cancer Collaborative Group, Roddam AW, Allen NE, Appleby P, Key TJ. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. *J Natl Cancer Inst*. 2008;100:170–183.
6 Loeb S, Folkvaljon Y, Damber JE, Alukal J, Lambe M, Stattin P. Testosterone replacement therapy and risk of favorable and aggressive prostate cancer. *J Clin Oncol*. 2017;35(13):1430–1436.
7 Bhasin S, Travison TG, Pencina KM, et al. Prostate safety events during testosterone replacement therapy in men with hypogonadism: a randomized clinical trial. *JAMA Netw Open*. 2023;6:e2348692.
8 Morgentaler A, Abello A, Bubley G. Testosterone therapy in men with biochemical recurrence and metastatic prostate cancer: initial observations. *Androgens*. 2021;2(1):121–128.
9 Behre HM, Bohmeyer J, Nischlag E. Prostate volume in testosterone-treated and untreated hypogonadal men in comparison to age-matched normal controls. *Clin Endocrinol*. 1994;40:341–349.
10 Morgentaler A, Traish AM. Shifting the paradigm of testosterone and prostate cancer: the saturation model and the limits of androgen-dependent growth. *Eur Urol*. 2009;55:310–320.