Testosterone Therapy and Prostate Cancer

Incorporating Low-Level Evidence into Practical Recommendations

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KEYWORDS

• Testosterone therapy • Exogenous androgens • Prostate cancer

KEY POINTS

- For almost 80 years, the use of exogenous androgens was considered an absolute contraindication in men with prostate cancer. Over the last 2 decades additional experience has shown that this view was too rigid and that under specific circumstances some flexibility is warranted.
- Consideration for testosterone therapy for men with prostate cancer should be limited to those with a clinical picture and laboratory confirmation of hypogonadism
- Hypogonadal men successfully treated for prostate cancer are candidates for testosterone therapy. Those on active surveillance and low risk disease are also candidates as long as long as some requirements are met. Recurrent prostate cancer or high risk of recurrence may be candidates under very specific conditions.
- All these patients require close and competent follow with initial and periodic evaluation including pertinent laboratory determinations.

INTRODUCTION

In men's health 2 fields share the characteristics of being both controversial and involving several medical disciplines: testosterone deficiency syndrome (TDS) and prostate cancer (PCa). Although Geriatrics, Endocrinology, Oncology, and Family Medicine could rightly assume some responsibilities in the care of men with TDS and PCa, urologists manage the vast majority of men diagnosis of PCa. Equally, Urology plays a preponderant role in dealing with male hypogonadism.

THE CONTROVERSY

Early in this century, a polemic emerged on the interactions between androgens and PCa development and progression. Former beliefs dating back 8 decades were vigorously questioned and newly refined and increasingly accepted. However, the deeply ingrained concerns about the safety of testosterone (T) administration to men with, or at risk, of PCa remain conspicuous.

ANDROGENS AND PROSTATE CANCER

Shortly after the synthesis of testosterone (T)[1,2] studies established a vital role in the development and function of the prostate. Since then, much progress has been made on the relationships between T and prostate health. Research resulted in the revision of early concepts and firmly held views were challenged following discoveries in the disciplines of biochemistry, genetics, and immunology. Developments in the understanding of the interactions between androgens and the androgen receptor (AR)[3–6] and the concept of the prostate being an endocrine organ within the hypothalamus–pituitary–gonadal axis[7,8] as well as the determination of intracrine steroidogenesis in

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Urol Clin N Am 49 (2022) 573–582
https://doi.org/10.1016/j.ucl.2022.07.002

benign and malignant prostate tissues,[9] translated into a wealth of information on the interrelations and clinical significance of hormones in prostate health. The finding of intricate intraindividual and intratumoral genomic and phenotypic heterogeneity of PCa provided a better understanding of the complexity of this neoplasm and its treatment.[10]

Evolving progress, such as the elucidation of the role of extracellular vesicles capable of transferring functional molecules over significant distances,[11,12] as well as the documentation that androgen deprivation therapy (ADT) alters the gut microbiota resulting in a buildup of bacterial species capable of synthetizing androgens thus promoting the progression of castration resistance PCa (CRPC)[13] have diagnostic and therapeutic repercussions. The identification of dormancy, that PCa uniquely shares with estrogen receptor-positive breast cancer, is in infancy but offers the clarification of poorly defined mechanisms in the evolution of PCa.[14]

THE ANDROGEN RECEPTOR AND THE PROSTATE

An essential player in the translation of androgen action is the AR, a nuclear transcription factor with distinctive molecular features that binds to androgens and acts through differential DNA targeting and genetic control on the relevant organ systems.[15] On binding to the AR in the prostate, T acts mostly as a prohormone. The effective androgen is the more potent dihydrotestosterone (DHT). The variance in the potency of T versus DHT is due to DHT much slower dissociation times, a concept with profound therapeutic implications.[16] The effects of androgens on the prostate are unquestionable although not yet fully characterized.[17] The glandular epithelium is the primary androgen target within the gland. DHT acts on the ARs of these tissues to generate a variety of peptide growth factors leading to mitogenic effects and divergence of survival signaling (apoptosis).[18] Androgen deprivation, results in insufficient production of andromedins that signals the apoptotic cascade in the secretory compartment of the prostatic epithelium.[19] Understanding the mechanisms of androgen-dependent prostate cells growth, differentiation and death are important because their manipulation has major consequences in the management of PCa[20] (discussed in detail in section 5 of this issue).

ANDROGENS HOMEOSTASIS AND PROSTATE CANCER RISK

Despite the absence of contemporary evidence, there remains a deep-rooted perception that androgens play a substantial causal role in the development of PCa. This is not surprising considering these known tenets about T and the prostate gland:

- At puberty in the presence of profound hypogonadism, the prostate fails to develop.[21]
- The intuitive hypothesis that low endogenous T levels prevent or delay the incidence and progression of PCa as shown by the results of cancer prevention trials, including finasteride in PCPT.[22]
- Reports on serum T levels associated with PCa diagnosis, including the high prevalence of biopsy detectable prostate cancer (PCa) in men with low testosterone.[23,24]
- The increase in PSA values following androgen stimulation[25]
- The favorable impact of adjuvant ADT with radiotherapy and some early evidence of benefit of neoadjuvant intense ADT in men with high-risk PCa.[26]
- The outstanding, though often temporary, the response of patients to ADT and to the more recently introduced AR targeted therapies in men with advanced disease.[27]

It is, therefore, not surprising that there is a belief among clinicians that low serum T prevents or, delays the development of PCa. By extension, once it has developed, it would progress at a slower rate in a hypogonadal milieu. Reports on the discovery of “occult” PCa shortly after the initiation of TTh further reinforce the concept of a positive correlation between androgens and PCa development and growth.[28,29]

As any other solid tumor, PCa is the result of a chain of genetic and epigenetic mutations resulting in abnormal cell signaling pathways promoting their immortality. For each cancer these mutations define the interactions of the tumor with its immediate microenvironment.[30] For PCa, its relations with the hormonal microenvironment are of crucial importance. Credit must be given to the pioneering work of Huggins, including his prescient observation about bipolar therapy: “In hormone-dependent cancers, the supporting hormones are of cardinal importance in maintaining the life of the malignant cell. This is the principle of cancer control by hormone deprivation. Cancers can also be controlled by supplying large amounts of hormones; this is the principle of hormone interference.”[31] Decades later, Labrie[32] demonstrated that PCa cells are capable of producing potent androgens (T and DHT) from less powerful precursors such as dehydroepiandrosterone (DHEA). It is now clearly established that in addition to the

endocrine processes involving gonadal steroids the intracrine pathways are significant participants in PCa promotion.[33–35]

RELEVANT CLINICAL SITUATIONS

A contributing factor to some of the controversial issues involving the interactions between androgens and PCa stem from the ambiguity of the clinical situations under discussion. There are 3 pertinent clinical situations:

Hypogonadal Men Without the Evidence of Prostate Cancer

It has been determined and broadly accepted that men with a clinical picture of hypogonadism *and* biochemical confirmation of abnormally low T are candidates for TTh.[36] Unfortunately, a significant number of men are reportedly prescribed T without having basic laboratory evaluations[37] and sometimes for flimsy clinical evidence as a cure-all for the infirmities of aging. Guidelines by recognized specialty societies, universally concur[36–38] with the need for baseline investigations. There is no justification for giving T without ruling out potentially serious health issues that may further deteriorate as a consequence T treatment.[39]

Contemporary recommendations, regarding prostate health, are that symptomatic hypogonadal men can safely receive TTh.[36–38,40] Monitoring during treatment includes the requirement of baseline documentation by a digital rectal examination (DRE) as well as a measurement of prostatic specific antigen (PSA). It is also recommended that these should be repeated every 3 months during the first year of TTh and yearly thereafter.

Hypogonadal Men Successfully Treated for Cancer of the Prostate (CaP)

Technically these men would be classified in the previous category, the reality is different and still evolving. There is a significant body of evidence indicating that they are candidates for TTh:

- Still inconclusive but compelling evidence showing that following radical prostatectomy, men with symptomatic hypogonadism can safely receive supplemental T.[41,42]
- Smaller but equally encouraging evidence has been presented for similar patients treated with either brachytherapy[43] or external beam radiotherapy.[44,45]
- Studies supporting these views warn that the findings are hypothesis-generating and require confirmation with multicenter controlled trials.[46]

A paramount concern in this scenario focuses on the timing TTh; it has not been established but has been vaguely described as “after a prudent interval”.[47] This, of course, is of limited help to the clinician. It is our belief (without much evidence to support it) that for those who underwent radical prostatectomy the “prudent interval” is achieved once the PSA is no longer detectable. Consideration must be given to the histopathological information of the surgical specimen (grade group, margins, stage). We advocated for a potential advantage of the early initiation of T supplementation in that an elevation of the PSA may indicate incomplete ablation of cancer, in which case additional curative measures may be considered; something akin to a challenge test[48]. This concept received support at the 2021 AUA meeting whereby Mulhall and colleagues[49] reported on a prospective study of hypogonadal men who had undetectable PSA after radical prostatectomy and were challenged with T administration. Persuasively, those who had an elevation of the PSA following TTh (10%), had detectable disease on imaging.

The situation is more complex for those with low or intermediate PCa who underwent radiotherapy without ADT as undetectable PSA levels might not be attainable. For these men, we would consider the initiation of T treatment after a persistent PSA nadir (>6 months) has been reached.

This cohort demands a close and competent follow-up, particularly in the initial months of TTh. There is no justification to initiate TTh without baseline determinations including T and PSA which are reported not being measured in about 30% of patients in this category in the United States.[50] Monitoring is equally important and frequently ignored.[51]

Hypogonadal Men with Active CaP

Opinions about treating hypogonadism in men undergoing active management of PCa are the most controversial and, the least backed with reliable experimental or clinical information. Despite some anecdotal fulsome views,[52] the use of TTh in men with PCa requires the consideration of the complexity of the tumor’s biological behavior in relation to androgens. Those interactions were described above, but they become vastly more intricate when considering the emergence of androgen independence by PCa.

Processes of resistance to ADT can either be mediated by the AR or by other mechanisms that bypass it (comprehensively reviewed by Crawley and colleagues).[53] In addition, preclinical models suggest that AR overexpression represents a

therapeutic liability that can be exploited with reinstitution of the ligand to promote cell death[54,55] and constitute examples of the intricate connections between androgens and the AR in PCa.

In our estimation, there are 3 distinct cohorts of men with PCa and symptomatic hypogonadism who are potential candidates for TTh but need to be considered separately.

a) Those who have been diagnosed as harboring a localized PCa but whom, for a variety of reasons remain untreated

Treatment options for these men have been detailed in the AUA.ASTRO/SUO guideline.[56] The document, does not contemplate the situation of men who, concomitantly with PCa, endure troublesome hypogonadism. In the absence of more reliable information it is suggested that.

- For those with low-risk diseases, active surveillance (AS) is currently the preferred recommendation. We would add that if a man is on AS and is hypogonadal justifying treatment, he is a potential candidate for TTh if the conditions listed (**Boxes 1** and **2**) are met.
- For those with intermediate- and high-risk disease that chose watchful waiting rather than active management due to personal choice and/or comorbidity, the manifestations of hypogonadism would have to be sufficiently severe and disabling to merit TTh. However, if these unique and relatively uncommon circumstances are present, it is our view that criteria shown in the tables and algorithm should apply.[57] These men should be encouraged to participate in a clinical registry.

b) Recurrent PCa or at high risk of recurrence after treatment with curative intent

This is a challenging cohort as the development of TD in these men may be associated with the initial treatment (radiotherapy, lack of T recovery after adjuvant ADT) or may have pre-existed the finding of PCa. In the majority, hypogonadism is of limited importance as the symptoms may not be necessarily related to their androgen levels but more closely linked to aspects raised by the diagnosis and treatment of the PCa and the worrisome prognosis when facing an initial treatment failure[58,59]

The need for TTh in these men requires exceptional considerations. The indications for it would depend on multiple factors including details of their original tumor and time as its management as well as the plan for the additional treatment of unresolved cancer, one of which would be to establish an even more profound hypogonadal environment aiming at castrate levels of T.[60] It is our perspective that to be considered a candidate for TTh in this situation, the manifestations of hypogonadism should be florid, incapacitating and supported by laboratory confirmation of low serum T,[61] an opinion not universally accepted.[62] Short-acting preparations should be used, particularly in the early phase of T administration, as a prudent approach in case of an exacerbation of the PCa.[63]

c) Those in whom PCa developed resistance to castrate levels of T

Unfortunately, the development of CRPC is a common event in advanced PCa, secondary to multiple mechanisms including the upregulation of the AR from sustained hypogonadism.[9]

For these men, rapid cycling between high and low levels of serum T known as bipolar androgen therapy (BAT) has been investigated with promising results.[64,65] This model is the result of solid empirical observations[66,67] and illustrates the appropriate methodical approach to changing paradigms: well-designed clinical trials such as TRANSFORMER,[68] which are already providing early hopeful answers and others like BAT-RAD starting enrollment in early 2022.[69] Managing patients with the BAT template should be carried out by experienced multi-disciplinary teams under an investigational protocol. Referral to clinical trials for men failing standard chemotherapy or novel androgen target therapies should be encouraged.

DISSECTING THE CONTROVERSY: PAST, PRESENT, AND FUTURE

Viewpoints endorsing the administration of exogenous T to hypogonadal men with PCa cite low-level evidence suggesting that little, if any tumor progression occurs following T administration: “in selected cases” providing TTh to men with metastatic disease is not equivalent to “pouring gasoline on a fire”.[70] We first reported[71] on observations in a group of men with CRPC primed with T before receiving intravenous radioactive phosphorus for control of severe bone pain from metastatic disease. Most of these men experienced an exacerbation of related signs and symptoms although a small number (14%) had a temporary remission on T alone. We did not have an explanation for this observation until Fowler and Whitmore[72] suggested the notion of the “saturation model” (SM). Briefly, it proposes that changes in T concentrations below the point of maximal AR binding will enhance PCa growth. In contrast, once maximal AR binding is reached

Box 1
Criteria to consider before initiating TTh in a patient with TD and PCa

- An experienced, qualified, and interested physician
- A patient able and willing to provide informed consent
- An engaged patient committed to a shared-decision making process
- A clinical picture supporting the diagnosis of significant hypogonadism
- Serum T levels supporting the diagnosis of TD
- Absence of spinal metastases with risk of cord compression
- Absence of contraindications for TTh (eg, erythrocytosis, congestive heart failure)
- Favor short-acting T formulations in the early period of treatment
- A priori settlement of benchmarks for the cessation of TTh (eg, PSA velocity/increase $\geq$ 20% within first 3 months)
- Contemplate referral/participation in a clinical trial, registry

the presence of additional androgens results in negligible additional effect.

Their observations shared our finding that the large majority of patients (>80%) receiving T experienced unfavorable responses but also that a prompt regression of these undesirable effects occurs on the withdrawal of T.[73] The intriguing findings remained unexplored for decades but have been revived, expanded and promoted.[74–76]

Morgentaler and colleagues[77] published a collective experience of 2 institutions whereby 13 men who received TTh while on active surveillance for lower risk PCa: not only there was no evidence of progression of their disease and follow-up biopsies were negative for cancer in over half of the patients. Simultaneously, we[66] reported observations in a comparable group of 7 men but our outcomes were different. Although some of them did well, there was marked inconsistency in the response to TTh and the response was unpredictable. The finding of significant inter-individual responses to changes in the hormonal milieu of men with PCa is not surprising considering that multiple genomic, transcriptomic phenotypic, and epigenetic heterogeneity are present not only among individuals but also within the same individual.[10,78] There is also the age differential in the aromatization of T,[79] the diverting kinetics of the 2 isoforms of 5 α-reductase[16] and the changes occurring in the AR signaling pathways during prostate carcinogenesis[80] translating in inconsistencies in the response of PCa to T.

The reintroduction and widespread attention given to the saturation model has the potential to lead to the relaxation of former paradigms regarding the use TTh in men with PCa. However, eschewing more cautious guidelines from professional medical associations[36–38] may be premature for a variety of reasons:

1. The saturation model is not a universally accepted construct. In fact, serious questions have been raised about its validity.[81]
2. Significant limitations of studies supporting it include their retrospective and single-arm design, inadequate power, insufficient follow-up, and the heterogeneity of the baseline characteristics of the participants[82]
3. Despite the number of small positive observational studies there is a paucity of information on crucial clinical endpoints such as metastasis-free survival, or other important progression events in men with PCa receiving TTh.[83]
4. The now well-recognized heterogeneity of PCa may translate into similar heterogeneity in aggressiveness and potential progression as a result of TTh[77,84,85]
5. All previous reports attempting to mitigate concerns about the use of T in men with CaP include specific warnings that the results are preliminary, hypothesis generating, and requiring more investigation to demonstrate efficacy and unequivocal safety[46,86]
6. An extensive systematic search from 1941 to 2019, revealed that TTh is detrimental to patients with advanced PCa (progression rate of at least 38.5%) as well as for those with treated

Box 2
Basic evaluations at onset and during TTh in a hypogonadal man with PCa

- Evaluation of functional response to TTh at 3 and 6 months
- Baseline hematology and biochemistry (serum T, hematocrit, hemoglobin, PSA)
- Imaging for the documentation of loco-regional or metastatic disease depending on the specific oncological scenario
- Follow-up hematology and biochemistry monthly for initial 3 months and every 3 to 6 months thereafter, if stable

high-risk disease successfully treated for (14.4%–57.1%)[87]

7. There is an ongoing, alarming lack of pertinent detail focused on critical clinical issues to help direct safe utilization of TTh in patients with PCa: (a) baseline patient and cancer characteristics; (b) timing for the onset/discontinuation of TTh; (c) formulations of T to use; (d) standards of follow-up (frequency of assessments and nature of the evaluations (ie, biochemistry, hematology).[78] Little has changed in this regard in the last 2 decades[88]

To tackle time-honored "myths" on the use of T in men *known to have* PCa convincingly, we need ethically approved, properly sponsored, well-designed, rigidly controlled, and carefully monitored studies. Otherwise, the use of T in these men may be construed as reckless in a field already beleaguered by controversy.

The prevalence of hypogonadal men aged 40 to 69 years old who are potential candidates for T administration is projected to reach 481,000 new cases by 2025 in the USA,[89] This, is a vastly larger population than any cohort of men diagnosed with PCa. Thus, there is a very limited number of cases for the conduction of validation studies by single institutions. Registries such as CapSURE[90] are the obvious answer and work appropriately at national levels. There is, however, a large global population of potential candidates that could amplify and solidify the national experiences and that could be reached with a straightforward and universally accessible protocol.[72]

SUMMARY

Current evidence strongly supports that hypogonadal men successfully treated for PCa can safely receive TTh. For those harboring untreated PCa the picture is less clear as this group of men undoubtedly expands due to acceptance of AS as the preferred initial treatment strategy[91] and experience increases with emerging technologies such as MRI and genomic testing,[92–94] prostate-specific membrane antigen PSMA theranostics,[95] and fear of complications or regret of treatment choices.[96]

There is a lack of guiding criteria for the general urologist who should be cautious and embark on it with a great deal of thoughtfulness. For untreated PCa there must be strong valid reasons for not moving forward to curative treatment and an equally strong one for TTh. For the unsuccessfully treated, BAT is a promising oncological option although requires much more prospective study given the ever-changing landscape of CRPC.

Urology should strive for higher levels of evidence, such as clinical registries or other correlative observations from prospective trials, to characterize those clinical scenarios whereby men with TDS and PCa would benefit most from TTh in terms of quality of life. The considerations that we must take into account include the specific baseline patient and cancer characteristics as well as the particular stage in their cancer journey. In addition, we should endeavor to establish the criteria to initiate/discontinue TTh, requirements for follow-up, and T formulations to use. These are essential needs for wide acceptance of the evolving paradigm.

ILLUSTRATIVE CASES

1. A 60-year-old healthy man is referred for a second opinion regarding known TD before his radical prostatectomy for PCa 1 year ago. He was interested in discussing going back on TTh. Initial PSA was 6.6, currently undetectable. Specimen showed Gleason 4 + 3 (Grade Group 2, pT3a, negative margins). He continues with bothersome symptoms of hypogonadism, Total T:267(n = 350–700 ng/dL); Free T:7(n = 9.3–26pg/ml). TTh endorsed with recommendations.
2. A 75 year old with low volume Gleason 3 + 3 (Grade Group 1) CaP on AS. Symptomatic marked hypogonadism leading to TTh. Cumulative moderate increase in PSA with rapid increase 9 years into TTh. T discontinued for 2 years with a subsequent decrease in values. Patient insistent in additional TTh with "excellent grasp" of the issues". Reinitiated TTh with similar results. Patient refused cessation of TTh.
3. A 70-year-old man initially received external beam radiotherapy with 18 months of ADT for high-tier intermediate risk CaP (Grade group 3). PSA nadir at 1.2 ng/mL and steady for 4 years but T never recovered completely (total T: 194 ng/dL). Significant TDS. After extensive shared-decision making process, he decided on TTh with good clinical outcomes and no change in biannual PSA values over 4 years.

CLINICS CARE POINTS

- There is a need for guiding criteria for the general urologist regarding testosterone administration in men with a history of prostate cancer

- Documentation (clinical and biochemical) of hypogonadism is of paramount importance before considering testosterone treatment.
- Strict follow-up is mandatory, particularly in the early stages of testosterone administration.
- Men successfully treated for prostate cancer can safely receive testosterone therapy.
- Hypogonadal men harboring prostate cancer on active surveillance are candidates with specific restrictions.
- Those with intermediate of hig- risk prostate cancer are best managed by specialized centers.
- Participation in clinical trials and registries will help to establish reliable evidence on the safety of testosterone in hypogonadal men.

DISCLOSURE

The authors have nothing to disclose

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