The concept that testosterone (T) promotes the growth of prostate cancer (PCa) was firmly established around the middle of the last century, based initially on animal and human studies entirely appropriate for the post-World War II state-of-the-art. Since then, a great deal of progress has been made in our appreciation of the relationships between T and prostate health. Original concepts have been revised and firmly held opinions have been challenged following clinical observations and discoveries in the fields of biochemistry, genetics, and immunology. More recent developments in the understanding of the interactions between androgens and the androgen receptor and the concept of the prostate being an endocrine organ within the hypothalamus-pituitary-gonadal (HPG) axis domain has shed new insights on the relations and clinical significance of hormones and prostate health.

By a wide margin, urologists treat most men with a current or remote diagnosis of PCa and are consulted and increasingly asked to take primary responsibility for managing those who are also affected by testosterone deficiency (TD). This brings into focus the need to provide a succinct view of the common situations faced by clinicians about the confusing and often controversial issues involving androgens and androgen administration to men. Therefore, following a brief introduction on the fundamentals of T and prostate tissue interactions, we will discuss four scenarios that are of most relevance in clinical practice.

A primer on the prostate and the androgen receptor

A fundamental participant in the translation of androgen action is the androgen receptor (AR), a nuclear transcription factor that binds to androgens and acts through differential DNA targeting and genetic control on the relevant organ systems. The effects of androgens on the prostate gland are unquestionable and, although there has been a significant improvement in our understanding of the cellular and molecular mechanisms, they are not yet fully figured out. In the prostate, T acts mostly as a prohormone. The effective androgen is the more potent dihydrotestosterone (DHT), which is converted from T through the action of 5α-reductase. Different organs have variable amounts of 5α-reductase enzymes 1 and 2. 5α-reductase 2 is more prominent in prostate, external genitalia, and skin, and its deficiency translates into minimal prostate growth and the presence of ambiguous external genitalia in boys who at puberty, however, exhibit the anticipated increase in muscle mass and male habitus. The glandular epithelium and a subset of endothelial cells are the primary androgen target structures within the prostate. DHT acts on the ARs of these tissues to generate a variety of androgen-induced stromal peptide growth factors or andromedins (e.g., prosurvival protein bcl-2, vascular endothelial growth factor) leading to androgen-mediated mitogenic effects and survival signaling. Androgen deprivation, on the other hand, results in insufficient production of andromedins, which in turn, upregulates the production of transforming growth factor β1 (TGF β1) that signals the apoptotic cascade in the secretory compartment of the prostatic epithelium. Understanding the mechanisms of androgen-dependent prostate cells’ growth, differentiation, and death is important because their manipulation has major consequences in the treatment of prostate neoplasms.
Relevant clinical settings

Endogenous T levels and risk of developing PCa

Notwithstanding the lack of convincing evidence, there is a deep-rooted notion among practitioners that androgens play a substantial causal role in the development of PCa. This suspicion is based primarily on four facts:

1. In the presence of profound hypogonadism, at puberty, the gland fails to develop;
2. Experimental evidence in rodents showing that artificially generated hypertestosterone states induce PCa;
3. The spectacular response of most human PCa to surgical or medical castration and the subsequent benefit of more contemporary androgen receptor targeted therapies; and
4. The still controversial yet widely held impression that there is a positive relationship between androgen levels and PCa in humans.

An intuitive hypothesis would suggest that low endogenous T levels prevent or delay the incidence and progression of PCa; this theory was buoyed by the results of cancer-prevention trials, including the PCPT finasteride trial, where PCa was detected in 18% of participants in the treatment group vs. 24% in those receiving placebo. Further support to this observation is given by the finding that a number of men with TD may have subclinical PCa, which manifests itself upon T administration and normalization of androgen levels.

Early reports presented a confusing picture on the association of naturally occurring serum T levels and the incidence of PCa, as illustrated by a quantitative review and two meta-analyses addressing this issue. The review of eight epidemiological studies published by Eaton et al found no significant differences in hormone levels between men developing PCa as compared to those who did not. Shaneyfelt et al concluded from their meta-analysis that men with either serum T or insulin-like growth factor-1 (IGF-1) in the upper quartiles of the population distribution have an approximately two-fold higher risk for developing PCa. The second meta-analysis, by Slater and Oliver, included 25 studies: four showed a positive association between high serum T levels and PCa; in six, high serum T levels were associated with a reduced risk; while in the remaining 15, there was no difference. No wonder there was confusion and controversy on the subject. More recently, additional systematic reviews and meta-analyses have addressed the same topic and a consensus now exists that PCa risk is unrelated to endogenous serum androgen concentrations, and specifically, men with higher endogenous T are at no greater risk than men with lower serum T.

It is also pertinent to keep in mind that strong epidemiological evidence exists for a variety of causes influencing the development of PCa independently of sex hormones. They include non-steroid hormones, genetic susceptibility, sexually transmitted agents, diet, and environmental factors. Whether any of these, alone or in combination, work synergistically with sex steroids, has not been conclusively established.

Testosterone therapy (TTh) and prostate health

Men with a clinical picture of hypogonadism and biochemical confirmation of abnormally low T levels are candidates for TTh if no specific contraindications exist. Current evidence suggests that hypogonadal men can receive TTh safely as far as prostate health is concerned. However, regular monitoring during treatment needs to include the recommendations of baseline documentation of a digital rectal examination (DRE) and prostatic-specific antigen (PSA) determination. It is also recommended that these should be repeated every three months during the first year of TTh and yearly thereafter.

It is consistent with current knowledge that re-establishing eugonadism should not impose additional risk of developing PCa. The aim of treatment is to maintain T levels within normal limits. It is not completely clear if a hypergonadic status may be detrimental to prostate health, but it also might translate in significant negative developments in other organ systems (i.e., cardiovascular, respiratory, hematological).

TTh in hypogonadal men successfully treated for PCa

A different situation has evolved in relation to patients with a history of successfully treated PCa. Limited but compelling evidence is accumulating showing that following radical prostatectomy, men with symptomatic hypogonadism can safely receive supplemental T. Smaller but equally encouraging evidence has been presented for similar patients treated with either brachytherapy or external beam radiotherapy. The timing for initiation of T therapy remains undefined but has been vaguely described as, “after a prudent interval.” This, of course, is of little 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, unless there is a strong indication for early salvage or adjuvant therapies. This can be reached fairly early, depending on the pre-surgical levels. The situation is less simple for those who received radiotherapy since undetectable levels might not ever be achieved. For these men, we would consider initiation of T treatment after a persistent PSA nadir has been reached. It could be argued for a potential advantage of early initiation of T supplementation in that an elevation of the PSA may indicate incomplete ablation of the cancer, in which case, additional curative measures may be considered — something akin to a challenge test.
Another intriguing cohort is emerging of younger men treated with combined modality strategies, including androgen deprivation therapy (ADT) plus radiation and who, years after completion of treatment, show no biochemical evidence of recurrence but present with symptomatic TD. In our view, they are candidates for TTh after a thorough explanation of risks and their commitment for close follow-up (vide infra).

**TTh in men with PCa**

Perhaps most controversial in any discussion about prostate health and T is the concept of treating TD to reach physiological T levels in men with untreated PCa. Any such discussion must take into consideration the current understanding of the complexity of the tumor’s biological behavior in relation to gonadal steroids.

We have previously highlighted the complex interaction of T, the AR, and prostate cell growth and survival, which is even more convoluted when considering the concept of androgen-independence. Mechanisms of resistance to ADT can be divided into those that are mediated by the AR (amplified, promiscuous, hypersensitive) and others that bypass the AR completely. However, some preclinical models suggest that AR overexpression represents a therapeutic liability that can be exploited with re-institution of the ligand to promote cell death. Chih-pin et al, working with athymic mice and using xenografts of LNCaP, showed that cells that become rich AR-positive androgen-independent can be reverted by T administration to androgen-dependency. Also, Hatzoglu et al reported a dose-dependent inhibition induced by T in this same human cell line. These basic science studies represent clear examples of the intricate connections between gonadal steroids and the AR in PCa.

Advocates of T administration to men with PCa cite studies going back several decades showing little tumor progression following TTh. Most of those studies, however, did not use TTh alone. We first reported long ago on observations like the now-touted notion of bipolar androgen therapy (BAT) on a group of men with metastatic castration-resistant PCa (CRPC) primed with T prior to receiving intravenous radioactive phosphorus. Most of these men experienced an exacerbation of the cancer, 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 initially suggested the concept of the “saturation model.” Briefly, the concept suggests that changes in T concentrations below the point of maximal AR binding will affect PCa growth. In contrast, once maximal AR binding is reached, the presence of additional androgens produces little further effect.

The idea remained dormant for many years but it has been revived and widely promoted in the last decade, both for the treatment of symptomatic TD in men with PCa and for those with CRPC. A small pilot study from Schweizer et al was published in 2015 in which 16 patients with low-volume metastatic CRPC were treated with T and etoposide for three cycles; those with a biochemical response were continued on intermittent testosterone monotherapy while maintaining castrating therapy (BAT). The authors remarked on the promise of the concept and the need for further evaluation in larger studies.

Morgentaler et al published the collective experience of two American institutions (Harvard Medical School and Baylor Medical College) where, in 14 men who received TTh while on active surveillance for PCa, there was no evidence of progression of their malignancy. A common characteristic of these patients was the presence of low-grade disease. Our own experience (Queen’s University) with seven similar men is somewhat discrepant with the one reported by the Harvard/Baylor study: we found that although some did well, there was marked biological variability in the response of these men to T and, most relevant, that the response is unpredictable.

With the re-introduction of the “saturation model,” a wave of relaxation of the long-held concerns regarding exogenous T administration to men with PCa spread in the literature. Such easing of established recommendations from pertinent medical societies remains premature. A more sober attitude is warranted at present. The vast majority of publications on this matter consistently emphasize that not only are more and better studies needed but that evidence for the safety of this approach is equivocal.

Although we favor challenging traditional concepts and entrenched opinions even when they appear unassailable, the challenge must be based on credible evidence that goes beyond speculation based only on in vitro studies, animal models, or limited clinical studies with a woefully short follow-up.

To confront well-established concepts on the use of T in men harboring PCa vigorously and credibly, we need ethically approved, properly sponsored, well-designed, rigidly controlled, and carefully monitored studies. Otherwise, the use of T in these men will be construed as reckless behavior in a field already beleaguered by controversy.

Symptomatic hypogonadal men also harboring clinically significant PCa are uncommon; therefore, we proposed the creation of a global registry for the followup of these men with a straightforward and universally accessible assessment protocol. The protocol included basic reasons as to which hypogonadal men with PCa might be candidates for TTh, a plan for their long-term followup, and standards for initiation and discontinuation of treatment. Initially, norms should exclude cases of high-grade (Gleason sum >8) and metastatic disease. Acceptable participants must be willing and able to adhere to a strict followup (at least quarterly for the first two years and biannually thereafter if they are stable). They should also be willing to discontinue therapy if,
in the judgment of the treating physician, there is evidence of cancer progression. Further investigation of BAT in men with CRPC should be limited to specialized centers with proficiency in the area and volume of candidates to reach meaningful results.

Conclusions

There is increasing evidence that symptomatic hypogonadal men successfully treated for PCa can safely receive TTh under certain circumstances. The issue needs to be addressed from the scientific, medical, ethical, and legal perspectives. The establishment of a global registry would address some of these issues and provide reliable answers in the most expedient manner.

As the validity and universal clinical applicability of the saturation becomes increasingly questioned, the need for persuasive studies acquires an urgent dimension.

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Correspondence: Dr. Alvaro Morales, Department of Urology, Queen’s University, Kingston, ON, Canada; moralesa@queensu.ca

Congratulations, Dr. Luc Valiquette!

Dr. Luc Valiquette was recently awarded the CUA’s Lifetime Achievement Award, which honors outstanding contributions made to Canadian urology and to the CUA.

Dr. Valiquette’s accomplishments in the field of urology are many. In the hospital setting, he served as a member of the Board of Directors (1999–2002) and Chair of Urology (2004–2007) at St. Luc Hospital. At the University of Montreal, he was a member of the Executive Committee (1996–1998); Chair of the Urology Program (1999–2003); and Chair of the Department of Surgery (2007–2015), where he adapted the surgical program to CanMEDS roles and implemented the concept of divisions within the department.

He has also contributed immeasurably to the success of the CUA in various roles: CUASF Treasurer (1996–1998), CUASF Council Chair (1998–2000), CUA Post-Graduate Training Committee member (2004/2005), and finally on the Board of Directors (2004–2008), serving as CUA President in 2006/2007. Dr. Valiquette’s legacy within the CUA includes establishing a central office, restructuring the Office of Education, and founding CUAJ.

Internationally, he has been President of the SIU (2103–2016) and since 2017, has also been President of the International Consultation on Urological Diseases. Closer to home, Dr. Valiquette served as President of the QUA (1993–1995).

He is a world-renowned speaker on stone disease, ED, and incontinence, and a fantastic ambassador for Canadian urology around the world.

The CUA is honored to present him with this accolade!

CUA Awards Committee:
Hassan Razvi (Committee Chair); Chasta Bacsu; Serge Carrier; Marie-Paule Jammal; Andrew MacNeily