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Editorial

Can Testosterone Therapy Be a Viable Option for Men Suffering With the Effects From Hypogonadism due to Prostate Cancer Treatment?

M. Kirby *, A. Naranjo †[1], L. Ellis †[1], M. Alaka †[1]

* Editor Trends in Urology and Men's Health and President of the British Society for Sexual Medicine (BSSM), Prostate Cancer UK, Fourth Floor, The Counting House, 53 Tooley St, London SE1 2QN, UK
† Prostate Cancer UK, Fourth Floor, The Counting House, 53 Tooley St, London SE1 2QN, UK

Introduction

Historically, men with a history of prostate cancer have been warned against testosterone therapy (TTh) due to concerns of possible increased risk of cancer progression or recurrence [1]. However, recently there has been increasing interest within the clinical community around whether TTh in men who have undergone treatment for prostate cancer may be safe and reduce the risk of developing diabetes and cardiovascular disease.

Testosterone suppression is used therapeutically for most men having curative radiotherapy, usually for a defined period (6 months–3 years), and after treatment, testosterone may slowly recover to normal levels. However, even men not treated with testosterone suppression can experience waning testosterone levels and symptoms of hypogonadism. Symptoms include loss of sexual desire and erectile dysfunction, fatigue, cognitive problems, loss of bone density, and metabolic syndrome with increased risk of developing cardiovascular disease and diabetes [2,3]. It is thought that TTh after curative treatment can help improve men's sexual function and mitigate other side-effects that can significantly impact their quality of life [1].

That being said, while TTh offers many potential benefits, it is important to note that it is not a one-size-fits-all. Although many men will experience significant improvement to their overall wellbeing, there are some men who may be impacted negatively and experience feelings such as anxiety and/or depression due to the fear of their prostate cancer returning. Thus, men should be encouraged to weigh out the pros of TTh against the potential risks before deciding if the treatment is for them. There is some evidence to suggest natural remedies, such as specific exercise and diet routines have a positive association with increasing testosterone levels and may present an option for the men who do have concerns and may not wish to undergo TTh [4,5].

Some studies have shown that men with localised prostate cancer treated with TTh don't have higher rates of recurrence as proposed by earlier studies [1]. Additionally, there are other studies, such as the TRAVERSE study, which investigated whether TTh in men (aged 45–80) with hypogonadism and no history or risk of prostate cancer, increases the risk of prostate cancer or other adverse prostate events. Findings showed that TTh does not increase incidences of high-grade or any prostate cancer and other prostate events [6]. Similarly, preliminary data from a retrospective study of 12 patients that underwent TTh while on active surveillance confirmed that mpMRI findings were stable in patients without biopsy progression [7].

Indeed, we know that some specialists administer TTh under strict parameters to men who have been definitively treated [1,8]. Further studies support the idea that TTh is beneficial for hypogonadal men treated for prostate cancer or following active surveillance [9–11]. The saturation model proposes the theory that serum testosterone has limited ability to stimulate prostate growth due to a hypothesised saturation point occurring at near-castrate levels, thereby challenging the traditional assumption that increased testosterone universally accelerates prostate cancer.

The model primarily addresses low-to intermediate-risk disease, with limited applicability to advanced or metastatic prostate cancer and provides a framework for understanding why androgen deprivation therapy is effective in advanced prostate cancer, while testosterone therapy in hypogonadal men does not appear to raise cancer risk. It also explains why younger men, despite higher testosterone levels, do not exhibit excessive prostate growth or higher prostate cancer prevalence.

Author for correspondence: A. Naranjo.
E-mail addresses: kirbym@professorkirby.co.uk (M. Kirby), alexandra.naranjo@prostatecanceruk.org (A. Naranjo), lizzie.ellis@prostatecanceruk.org (L. Ellis), marion.alaka@prostatecanceruk.org (M. Alaka).
[1] Equal contribution to authorship.

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Table 1
Guidelines for testosterone therapy in men with prostate cancer

BSSM [13]	
Posttreatment, low risk localised	Offer testosterone therapy to symptomatic men with testosterone deficiency syndrome for treated localised low-risk prostate cancer and without evidence for active disease
Locally advanced prostate cancer	Contraindication to TTh
Posttreatment, metastatic	Contraindication to TTh
AUA [14]	
In-situ prostate cancer patients on active surveillance or previously treated prostate cancer	Negotiated decision based on perceived potential benefit of treatment weighed against the limited knowledge of potential risks
Active surveillance	Limited data. Available literature indicates that patients with and without high-grade prostatic intraepithelial neoplasias who were on testosterone therapy did not experience significant increases in PSA or subsequent cancer diagnosis compared to men not receiving testosterone
Post-radical prostatectomy with favourable pathology and undetectable PSA postoperatively	Testosterone therapy can be considered in these men.
Men treated with radiation therapy (with or without ADT)	Available studies have suggested that after RT, patients do not experience recurrence or progression of prostate cancer
Locally advanced or metastatic disease	Poorly understood and administration of testosterone in these scenarios should ideally be performed under research settings
EAU [15,16]	
Untreated, locally advanced, or metastatic prostate cancer	Absolute contraindications
Active prostate cancer	Contraindicated
Surgically treated for localised prostate cancer and without evidence of active disease	Fully counsel men, emphasising the lack of sufficient safety data on long term follow-up
Low-risk individuals previously treated for prostate cancer	Use of TTh should be fully discussed with patients
Endocrine Society [17]	
Men with prostate cancer, a palpable prostate nodule or induration, prostate-specific antigen >4 ng/mL, prostate-specific antigen >3ng/mL in men at increased risk of prostate cancer	We recommend against starting testosterone
CMAJ [18]	
Localised prostate cancer and no evidence of active disease	We suggest these men receive testosterone therapy (weak recommendation; low-quality evidence)
Metastatic prostate cancer	We recommend against (strong recommendation; moderate to high quality evidence)
Successfully treated	Maybe candidates, require referral to specialist
AFP [19]	
Men with known or suspected prostate cancer	Testosterone therapy is contraindicated
Previously treated (and presumed cured)	Controversial; with little data to guide treatment decisions in this group
EAA [20]	
Treated (radical prostatectomy) low-grade prostate cancer who remained in remission with undetectable PSA for at least 2 years	Possible risks and benefits of testosterone therapy should be discussed with the patient and his oncologist and/or urologist to reach an individually appropriate joint decision on management

BSSM, British Society for Sexual Medicine; TTh, testosterone therapy; EAA, European Academy of Andrology.

Thus, highlighting that TTh may not pose as much of a threat as originally thought when given to carefully evaluated patients [9,12]. Studies have since supported the saturation model, including that by Ory *et al.*, who evaluated 82 hypogonadal men with treated prostate cancer on active surveillance, and found that it supported the idea that TTh is safe in this cohort of men [10]. Kaplan *et al.* also studied the trends of administering TTh among prostate cancer

survivors and found no association between TTh and increased prostate cancer-specific or overall mortality, also supporting the saturation model [8].

Current Evidence and International Medical Organisation's Guidelines

As shown, the guidelines pertaining to testosterone therapy use in hypogonadal men with treated or untreated prostate cancer is shown in Table 1.

Current guidelines affirm that TTh can be offered to symptomatic hypogonadal men who are disease-free following treatment for low-risk prostate cancer, provided they meet certain criteria. Guidelines and studies such as those of Pastuszak *et al.*, 2013, and Pastuszak *et al.*, 2015 provide evidence that testosterone therapy is safe amongst men that have gone radical prostatectomy and radiotherapy and has no association with recurrence or progression [21,22]. Whilst this is promising, it is important to consider that advanced and metastatic prostate cancer are absolute contraindications for TTh. Unfortunately, the guidelines do not specify recommendations specific to men with intermediate or high-risk localised prostate cancer. As these diagnoses differ and may impact the effect of TTh on these men, we recommend that guidelines be more tailored to men according to the risk group of their prostate cancer.

Next Steps

There is an evident unmet need for more research into this area to gain a better understanding of how TTh could affect men treated for prostate cancer and whether this could be a safe option clinically. Coupled with the availability of more effective treatments and longer life expectancy, the treatment of low testosterone levels will become of increasing importance in the future [23].

Prostate Cancer UK has consulted with the clinical community and noted a growing interest in this area. We have found that some trusts are developing their own policies to cover this specific group of patients, with the monitoring of these men being a key aspect of safe treatment [24]. We believe this is a positive step towards the possible utilisation of TTh in appropriate patients.

However, despite the growing evidence, there is still considerable work to be done in this area. Additionally, changing the general clinical mindset around the benefits of TTh will take time and patience, as we still hear anecdotally of worries about the safety of this treatment. We know that prostate cancer mortality rates have decreased by 10% over the last ten years, and so the question of how we help survivors lead more normal lives is now more pertinent than ever [25].

The SPIRIT trial is one such piece of research that could well give a more detailed insight into this area [23]. It is the first randomised control trial, which investigated the efficacy and safety of TTh in prostate cancer survivors with low testosterone levels. However, there are some limitations to note. For instance, this trial only recruited men after prostatectomy (the participants may already have impaired sexual function), the small trial size, and its short duration. If efficacy and short-term safety can be established, then further, more in-depth research via a larger trial can be undertaken in this patient population.

Conclusion

Most guidelines state that metastatic/locally advanced and/or untreated prostate cancer is a contraindication for testosterone therapy. However, several state that specific subgroups of men in the curative/cured setting may be recipients for TTh. Overall, the use of TTh in men with treated prostate cancer remains cautious but positive, with some guidelines affirming that TTh can be offered to symptomatic hypogonadal men who are disease-free following treatment for low-risk prostate cancer, provided they meet certain criteria. In these low-to intermediate-risk patients, the data are reassuring, supporting TTh as a viable option to improve quality of life, including energy, libido, and erectile function. For high-risk patients, some small studies have even shown reduced biochemical recurrence rates, suggesting potential benefits; however, these findings are limited by very small patient numbers and a lack of robust data.

Until more substantial evidence becomes available, clinicians wishing to treat patients with TTh should advise them on the pros and cons of its usage, specifically around the lack of safety data of long-term treatment on the risk of prostate cancer progression or recurrence [26].

Further research could pave the way for new developments in the treatment of men who suffer greatly from the effects of hypogonadism after radical treatment. If found to be safe and effective, as suggested by emerging evidence, for those with a low chance of recurrence, this treatment could be game-changing, allowing more men to manage, or even improve, the impact of low testosterone following prostate cancer treatment, thus improving quality of life and improving survivorship by alleviating hypogonadal symptoms such as fatigue, low mood, and diminished sexual function, thereby enhancing overall quality of life.

Conflict of interest

The authors declare no conflict of interest.

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