Controversies with testosterone therapy

Mohit Khera, MD
Department of Urology, Baylor College of Medicine, Houston, Texas, USA

KHERA M. Controversies with testosterone therapy. *Can J Urol* 2020;27(Suppl 3):20-23.

Introduction: *Over the past decade, there have been concerns with safety of testosterone therapy (TTh) in hypogonadal men. Several concerns have centered on the use of TTh and its potential link to cardiovascular (CV) events, prostate cancer, and benign prostatic hyperplasia (BPH). There has also been controversy in determining which patients are appropriate candidates for TTh and if lifestyle modification has any role in improving serum testosterone values in hypogonadal men.*

Materials and methods: *A literature review of all articles assessing testosterone and the use of TTh and the association with CV events, prostate cancer, BPH and lifestyle modification was conducted.*

Results: *Majority of patients treated with TTh today are treated off-label. Low serum testosterone levels have been associated with increased CV events. Currently, there is inconclusive evidence to support that TTh increases the risk of CV events. There is an absence of evidence linking TTh to the development of prostate cancer or worsening of BPH symptoms. Finally, lifestyle modification, such as decreasing weight and improving sleep, can improve serum testosterone levels in hypogonadal men.*

Conclusions: *Clinicians prescribing testosterone should be aware of the current controversies associated with TTh. The current literature does not suggest that there is a significant risk with TTh and prostate cancer, worsening of BPH symptoms or CV events. However, more studies, including randomized placebo-controlled trials, are needed. Finally, patients should be counseled appropriately regarding the indications for TTh and the benefits of lifestyle modification prior to initiating TTh.*

Key Words: testosterone therapy, safety, hypogonadal men

Indications for testosterone therapy

In 1981, the FDA issued a class labeling change regarding the indications to treat hypogonadal patients. The label at that time stated "Androgens are indicated for replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone." The label then went on to list certain medical conditions associated with primary and secondary hypogonadism, such as orchitis or pituitary tumor, respectively. Nowhere in the label did it list symptoms, such as erectile dysfunction, low libido, or fatigue, as indications for treatment. However, the label at that time did list "idiopathic" as a one of the potential causes for hypogonadism. Therefore, if a hypogonadal patient did not have a listed medical condition, one could assume that the cause was idiopathic and the patient could be treated on-label. In 2015, the FDA issued a safety announcement stating "The U.S. Food and Drug Administration (FDA) cautions that prescription testosterone products are approved only for men who have low testosterone levels caused by certain medical conditions. The benefit and safety of these medications have not been established for the treatment of low testosterone levels due to aging, even if a man's symptoms seem related to low testosterone." As a result of this announcement, the FDA required that the testosterone label remove the word "idiopathic" under the listed conditions indicated for testosterone therapy (TTh). Thus, hypogonadal patients not having a medical condition known to result in hypogonadism were considered to be treated off-label at this point. Maseroli et al found that roughly 85% of patients being treated with TTh did not have a known medical condition associated with hypogonadism and thus they were being treated off-label.[1] Another concern with the indications for TTh is the use of T as monotherapy to treat erectile dysfunction. Current T guidelines recommend the use of TTh in hypogonadal men who

Address correspondence to Dr. Mohit Khera, Department of Urology, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030 USA

have symptoms such as erectile dysfunction. In fact, Wu et al found that sexual symptoms, such as decreased morning erections, erectile dysfunction and decreased frequency of sexual thoughts, were the most sensitive and specific symptoms for identifying hypogonadal men.[2] However, the American Urological Association (AUA) Erectile Dysfunction (ED) Guidelines do not recommend the use of TTh solely for the treatment of erectile dysfunction.[3] These guidelines recommend that men with ED and testosterone deficiency who are considering ED treatment with a PDE5i should be informed that PDE5i may be more effective if combined with testosterone therapy. The AUA ED Guidelines further state "Men should be advised that testosterone therapy is not an effective mono-therapy for ED. If the man's goal is amelioration of ED symptoms, then he should be counseled regarding the need for ED therapies in addition to testosterone therapy."

Testosterone therapy and cardiovascular risk

For many years it was believed that low serum T levels increased the risk for cardiovascular (CV) events. Numerous prospective studies demonstrated that men with lower serum T levels were more likely to die at an earlier age, mainly due to increased CV events. On the contrary, there have been many published studies demonstrating that TTh may improve the risk factors for cardiovascular disease (CVD), such as obesity and metabolic syndrome. A review article by Morgentaler et al found that of the over 200 articles assessing CV risk with TTh, only four studies suggested that TTh may increase the risk of CV events.[4] Several dozen studies demonstrated beneficial effects of normal T on CV risk and mortality. Low levels of T were associated with increased risk of mortality and CVD. Finally, many studies suggested that severity of CAD was inversely correlated with serum T levels.

Based on the four studies suggesting that TTh may increase CV risk, the FDA issued a warning in the testosterone label in 2015 stating "Long term clinical safety trials have not been conducted to assess the cardiovascular outcomes of testosterone replacement therapy in men. To date, epidemiological studies and randomized controlled trials have been inconclusive for determining the risk of major adverse cardiovascular events (MACE), such as non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, with the use of testosterone compared to non-use. Some studies, but not all, have reported an increase risk of MACE in association with the use of testosterone replacement therapy in men." It is important to note that the European Medicines Agency (EMA), which is the equivalent to the FDA in Europe, performed its own review of CV and TTh literature and declined to add any new CV warnings. In 2018, Miner et al conducted a review of all articles since the FDA label change assessing the CV risk associated with TTh.[5] These authors identified 23 studies of which none reported an increase in MACE with TTh. In fact, they found that men whose T normalized with TTh had a reduced risk of MI and death compared with men whose T levels failed to normalize.

The 2018 AUA T Guidelines offered recommendations on counseling hypogonadal patients regarding potential CV risk.[6] These guidelines recommended that clinicians should inform T deficient patients that low T is a risk factor for CV disease. The AUA T Guidelines also recommend prior to initiating treatment, clinicians should counsel patients that at this time, it cannot be stated definitively whether TTh increases or decreases the risk of CV events (e.g., myocardial infarction, stroke, cardiovascular-related death, all-cause mortality). Finally, the AUA T Guideline recommend "Testosterone therapy should not be commenced for a period of 3 to 6 months in patients with a history of CV events. Other testosterone guidelines, such as the Endocrine Guidelines, suggest waiting a minimum of 6 months before initiating TTh after a CV event. The AUA T Guidelines also recommend that prior to initiating TTh, patients at high risk for CV events should be referred for further evaluation.

Currently underway is the largest randomized placebo-controlled trial assessing the use of TTh on MACE, which includes nonfatal MI and nonfatal stroke or death due to CV causes. This study, also known as the TRAVERSE trial, is expected to enroll 6000 participants and is anticipated to be completed by June of 2022.

Testosterone and the prostate

The effects of the TTh on the prostate have been a concern to most clinicians and patients for decades. However, over the past 15 years, this paradigm has shifted. Whereas 15 years ago most clinicians believed that TTh was unsafe to give to men due to the risk of developing prostate cancer,[7] now there are clinical trials using TTh to treat men on active surveillance as well as those with metastatic prostate cancer. In 2003, Rhoden and Morgentaler evaluated the use of TTh in hypogonadal men with a history of high grade prostatic intraepithelial neoplasia (HGPIN).[8] In this study, 20 men had HGPIN and were considered high risk for developing prostate cancer. These authors found that after 1 year of TTh, men with HGPIN did not have a

greater increase in PSA or a significantly increased risk of cancer than men without HGPIN. In 2003, this article was considered controversial as there were concerns of giving TTh to men with HGPIN. Over the next 15 years, there were many studies assessing the use of TTh in men following radical prostatectomy and radiation therapy for prostate cancer.[9-11] While these studies were predominately retrospective in nature and selected for low risk patients, they did not demonstrate an increased risk of prostate cancer recurrence with TTh in these men. Further studies during this time also assessed the use of TTh in men on active surveillance with no increased risk of cancer progression.[11,12]

More recently, there have been studies assessing the use of TTh to treat men with castrate resistant prostate cancer or with low metastatic prostate cancer burden or biochemical PSA recurrence. In 2015, Schweizer et al published a series of 14 men with castrate resistant prostate cancer who were treated with high doses of TTh.[13] These patients received testosterone enanthate 400 mg IM every month for 3 months. Androgen deprivation therapy (ADT) was also continued at this time to suppress endogenous testosterone production, allowing for rapid cycling from supraphysiologic serum T levels to near castrate serum T levels. This rapid cycling was termed bipolar androgen therapy (BAT). The investigators found that BAT was well tolerated and that 50% of patients had a reduction in their PSA, and 50% of patients also had improved radiographic responses. All patients (10 of 10) demonstrated a reduction in PSA after receiving BAT, suggesting that BAT may also restore androgen receptor sensitivity. In a subsequent study by Schweizer et al, the effects of BAT in 29 men with androgen ablation naïve prostate cancer was evaluated.[14] These 29 asymptomatic hormone sensitive prostate cancer patients had either low metastatic prostate cancer burden or non-metastatic disease with a biochemical PSA recurrence. These men received 6 moths of ADT followed by 400 mg of testosterone cypionate IM every 4 weeks for 3 months. The investigators found that 59% of men had a PSA < 4 ng/dl after 18 months (primary endpoint) and that many of these men had significant improvements in quality of life and erectile function.

In light of these new publications over the past 15 years, it is not surprising that many clinicians are not as concerned with giving TTh to men with a history of prostate cancer. A study by Millar et al in 2016 sent a survey to urologists regarding their opinion and prescribing patterns on TTh in men on active surveillance for low risk prostate cancer.[15] This survey found that 96% and 84% of urologists believed that it was safe to give TTh to men with a history of a radical prostatectomy and radiation therapy, respectively. In fact, 63% of urologists believed it was safe to give TTh to men on active surveillance. It is important to note that the AUA T guidelines recommend that patients with testosterone deficiency and a history of prostate cancer should be informed that there is inadequate evidence to quantify the risk-benefit ratio of testosterone therapy.[6] However, the AUA T Guidelines do recommend that clinicians should inform patients of the absence of evidence linking testosterone therapy to the development of prostate cancer.

Many urologists are still concerned that TTh will worsen lower urinary symptoms (LUTS). This concern is also fueled by the fact that current package inserts of testosterone products state "Patients with BPH treated with androgens are at an increased risk for worsening of signs and symptoms of BPH." However, currently there is no convincing data to support this claim. In fact, a review article by Delay and Kohler found that long term TTh either had no effect on LUTS or actually improved LUTS over time.[16] Other studies have also found improvements in voided volumes and post-void residuals in men taking TTh.[16] Thus, patients should be counseled appropriately regarding the use of TTh in men with BPH and LUTS.

Testosterone and lifestyle modification

Initial treatment options for many medical conditions include lifestyle modifications. For example, patients presenting with hypertension, hyperlipidemia, or obesity are first encouraged to try lifestyle modification before considering medical therapy. Lifestyle modification as well as varicocelectomy have also been shown to improve serum T levels in hypogonadal men. Camacho et al conducted a longitudinal study of 2736 men assessing changes in weight and testosterone levels.[17] These investigators demonstrated that there is a bi-directional relationship between weight and serum T levels. In this study, men who lost ≥ 15% of their body weight demonstrated a significant increase in free testosterone (FT) (51.8; 95% CI 1.7, 101.9 pmol/l). In addition, those men whose weight increased by ≥ 15% demonstrated a greater decline in FT (-47.1; 95% CI -136.9, 42.7 pmol). In a meta-analysis of 22 studies assessing the effects of weight loss (diet or surgery) on T levels, weight loss through both diet and bariatric surgery were both effective in significantly increasing serum total and free testosterone.[18] A low calorie diet resulted in a 9.8% weight loss with a 83 ng/dL increase in serum T levels. However, bariatric surgery resulted in a 32% weight loss with a 250 ng/dL increase in serum T values. Thus, weight loss seems to be an effective strategy to increasing serum T levels especially if the weight loss can be sustained.

Sleep plays an important role in maintaining normal serum T levels. Greater degrees of nocturnal hypoxia, such as seen with conditions like obstructive sleep apnea (OSA), can result in lower serum T levels due to blunting of LH levels. Improving sleep apnea, either with the use of a CPAP machine, or surgically through uvulopalatopharyngoplasty, has been shown to improve serum T levels.[19] Finally, Leproult et al demonstrated that restricting sleep to 5 hours a night for 8 nights can decrease T levels by 10% to 15%.[20]

Varicocele repair has also been shown to improve serum T values. Sathya et al conducted a prospective study of 200 men who received varicocelectomy or observation.[21] Serum T levels increased on average 80 mg/dL after varicocelectomy. Seventy-eight percent of the patients in the varicocelectomy group normalized their serum T levels compared to 16% in the control group. A meta-analysis by Li et al evaluated 814 patients undergoing varicocele repair.[22] They found that serum T levels increased approximately 100 ng/dL after varicocelectomy. While varicocele repair may increase serum T levels, it appears that this increase is modest, and currently hypogonadism is not an established indication for vaicocelectomy.

Conclusion

Clinicians prescribing testosterone should be aware of the current controversies associated with TTh. Controversies associated with TTh include potential risk of developing prostate cancer and worsening of LUTS. In addition, there are concerns of TTh potentially increasing CV risk. The current literature does not suggest that there is a significant risk with TTh and prostate cancer, LUTS, and CV events. However, more studies, including randomized placebo- controlled trials, are needed. Clinicians prescribing TTh should also be aware that the majority of hypogonadal patients currently being treated with TTh are being treated off-label. Finally, lifestyle modification, such as weight loss and improvement in sleep, as well as varicocelectomy, can improve serum T values. Patients should be counseled appropriately regarding the indications for T therapy and the benefits of lifestyle modification prior to initiating TTh. □

References

1. Maseroli E, Corona G, Rastrelli G et al. Prevalence of endocrine and metabolic disorders in subjects with erectile dysfunction: a comparative study. *J Sex Med* 2015;12(4):956-965.
2. Wu FC, Tajar A, Beynon JM et al. Identification of late-onset hypogonadism in middle-aged and elderly men. *N Engl J Med* 2010;363(2):123-135.
3. Burnett AL, Nehra A, Breau RH et al. Erectile dysfunction: AUA guideline. *J Urol* 2018;200(3):633-641.
4. Morgentaler A, Miner MM, Caliber M, Guay AT, Khera M, Traish AM. Testosterone therapy and cardiovascular risk: advances and controversies. *Mayo Clin Proc* 2015;90(2):224-251.
5. Miner M, Morgentaler A, Khera M, Traish AM. The state of testosterone therapy since the FDA's 2015 labelling changes: Indications and cardiovascular risk. *Clin Endocrinol (Oxf)* 2018;89(1):3-10.
6. Mulhall JP, Trost LW, Brannigan RE et al. Evaluation and management of testosterone deficiency: AUA guideline. *J Urol* 2018;200(2):423-432.
7. Gooren LJ, Behre HM, Saad F, Frank A, Schwerdt S. Diagnosing and treating testosterone deficiency in different parts of the world. Results from global market research. *Aging Male* 2007;10(4):173-181.
8. Rhoden EL, Morgentaler A. Testosterone replacement therapy in hypogonadal men at high risk for prostate cancer: results of 1 year of treatment in men with prostatic intraepithelial neoplasia. *J Urol* 2003;170(6 Pt 1):2348-2351.
9. Pastuszak AW, Khanna A, Badhiwala N et al. Testosterone therapy after radiation therapy for low, intermediate and high risk prostate cancer. *J Urol* 2015;194(5):1271-1276.
10. Khera M, Grober ED, Najari B et al. Testosterone replacement therapy following radical prostatectomy. *J Sex Med* 2009;6(4): 1165-1170.
11. Khera M, Crawford D, Morales A, Salonia A, Morgentaler A. A new era of testosterone and prostate cancer: from physiology to clinical implications. *Eur Urol* 2014;65(1):115-123.
12. Morgentaler A, Lipshultz LI, Bennett R, Sweeney M, Avila D Jr, Khera M. Testosterone therapy in men with untreated prostate cancer. *J Urol* 2011;185(4):1256-1260.
13. Schweizer MT, Antonarakis ES, Wang H et al. Effect of bipolar androgen therapy for asymptomatic men with castration-resistant prostate cancer: results from a pilot clinical study. *Sci Transl Med* 2015;7(269):269ra2.
14. Schweizer MT, Wang H, Luber B et al. Bipolar androgen therapy for men with androgen ablation naive prostate cancer: results from the phase II BATMAN study. *Prostate* 2016;76(13):1218-1226.
15. Millar AC, Elterman DS, Goldenberg L, Van Asseldonk B, Curtis A, Jarvi K. A survey of Canadian urologists' opinions and prescribing patterns of testosterone replacement therapy in men on active surveillance for low-risk prostate cancer. *Can Urol Assoc J* 2016;10(5-6):181-184.
16. DeLay KJ, Kohler TS. Testosterone and the prostate: artifacts and truths. *Urol Clin North Am* 2016;43(3):405-412.
17. Camacho EM, Huhtaniemi IT, O'Neill TW et al. Age-associated changes in hypothalamic-pituitary-testicular function in middle-aged and older men are modified by weight change and lifestyle factors: longitudinal results from the European Male Ageing Study. *Eur J Endocrinol* 2013;168(3):445-455.
18. Corona G, Rastrelli G, Monami M et al. Body weight loss reverts obesity-associated hypogonadotropic hypogonadism: a systematic review and meta-analysis. *Eur J Endocrinol* 2013;168(6):829-843.
19. Santamaria JD, Prior JC, Fleetham JA. Reversible reproductive dysfunction in men with obstructive sleep apnoea. *Clin Endocrinol (Oxf)* 1988;28(5):461-470.
20. Leproult R, Van Cauter E. Effect of 1 week of sleep restriction on testosterone levels in young healthy men. *JAMA* 2011;305(21):2173-2174.
21. Vasan SS, Srinivas BV. Does varicocelectomy improve gonadal function in men with hypogonadism and infertility? Analysis of a prospective study. *Int J Endocrinol* 2011;2011:916380.
22. Li F, Yue H, Yamaguchi K et al. Effect of surgical repair on testosterone production in infertile men with varicocele: a meta-analysis. *Int J Urol* 2012;19(2):149-154.