Controversies in testosterone supplementation therapy

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Testosterone has now become one of the most widely used medications throughout the world. The rapid growth of the testosterone market in the past 10 years is due to many factors. We currently have a worldwide aging population. In the US, the number of men 65 years old or older is increasing 2–3 times faster than the number of men younger than 65 years. In addition, poor general health and certain medical conditions such as diabetes/metabolic syndrome (MetS), cardiovascular disease (CVD), and osteoporosis have been associated with low serum testosterone levels.\(^1\)\(^-\)\(^3\) There are now fewer concerns regarding the development of prostate cancer (PCa) after testosterone therapy, making it a more attractive treatment option. Finally, the introduction of different forms of testosterone supplementation therapy (TST) with increased promotion, marketing, and direct-to-consumer advertising is also driving market growth. As the demand for TST continues to grow, it is becoming more important for clinicians to understand how to diagnose and treat patients with low testosterone.

There are still several controversies associated with TST. Many clinicians are still concerned about the potential adverse effects of TST on male fertility, CVD, PCa, MetS, and benign prostatic hyperplasia (BPH). The aim of this Asian Journal of Andrology (AJA) special edition on controversies in TST is to carefully examine the literature in each of these topics and offer a better understanding of how TST truly impacts each of these conditions. This special edition also focuses on the diagnosis and management of TST as well as alternative treatment options for androgen deficiency syndrome.

The diagnosis and management of TST can be challenging. For example, there are large variations in laboratory reference ranges and this is compounded by the fact that there are no universally agreed upon cut-offs for total and free testosterone for the diagnosis of hypogonadism.\(^4\)\(^-\)\(^6\) In addition, the signs and symptoms of hypogonadism are nonspecific and serum testosterone levels do not appear to correlate directly with symptoms in all patients.\(^4\) There are now numerous TST options available and deciding on the appropriate treatment option can be challenging. The decision of which TST formulation to use should be based on several factors including cost, compliance, convenience, and efficacy.

An increasingly large number of middle-age men are seeking treatment for androgen deficiency. It is estimated that roughly 3%–8% of men in their reproductive years suffer from hypogonadism.\(^7\) There are several reasons for this including increased anabolic steroid use in younger men, increased use of opioids in younger men and the growing epidemics of diabetes and obesity that are now greatly affecting the younger population.\(^7\) TST can lead to impaired spermatogenesis, and men desiring to initiate a pregnancy in the future should be counseled appropriately before beginning therapy.\(^8\) For patients who are desiring to initiate TST and still preserve their fertility, alternative treatment options should be discussed. In these patients, increasing endogenously serum testosterone levels through stimulation of the hypothalamic-pituitary-gonadal axis is a better option. Treatment options for raising endogenous serum testosterone include the use of clomiphene citrate, anastrozole, and human chorionic gonadotropin. There are many new treatment options currently under development to raise endogenous testosterone and at the same time preserve fertility in young hypogonadal men.

Despite persistent concerns, there are still no convincing data to indicate that TST increases the risk of PCa. However, to date, there are no prospective, controlled studies with adequate sample size and duration to definitively assess the relationship of TST with the risk of PCa. There continues to be a low rate of negative outcomes reported with TST.\(^9\) While further research is required to define the safety of TST in men with a history of PCa, many hypogonadal symptomatic patients are willing to accept the potential risk of PCa recurrence or progression in return for an opportunity to live a happier and fuller life with TST.

For many years, TST has been thought to exacerbate BPH and lower urinary tract symptoms (LUTS). In fact, most of the package inserts of testosterone therapies state that clinicians should monitor patients with BPH for worsening of signs and symptoms, and that elderly patients treated with androgens may be at increased risk for BPH. However, recent data suggest that TST may actually improve BPH/LUTS.\(^10\)\(^-\)\(^11\) The exact mechanism of this improvement is still unknown, but there are several existing theories that have been established. Until more studies are completed, patients should still be counseled on the TST label regarding the risk of urinary retention and worsening LUTS.

There have been several recent observational studies suggesting that the testosterone may increase the risk for CVD.\(^12\)\(^-\)\(^13\) However, the Food and Drug Administration in the US has reviewed these reports and found them to be seriously flawed. TST appears to have a minimal effect on cardiovascular risk factors except for a potential increase in hematocrit. In fact, several studies have found that hypogonadal men initiating TST experience improvements in cardiovascular parameters including reductions in systolic and diastolic blood pressures, reduction in resting heart rate, better endothelial cell function, and reduction in arterial plaque size.\(^2\)

There are still some questions associated with MetS and testosterone. Do low serum testosterone levels cause MetS? Is TST an...
effective treatment for MetS? Low testosterone has been shown to result in elevated fasting insulin, glucose and hemoglobin A1c levels, and possibly to predict the onset of diabetes. TST has been shown to result in significant changes in insulin sensitivity, weight, waist circumference, and hemoglobin A1c levels. The relationship of low testosterone to MetS is often considered to be bidirectional. This relationship is probably not direct, and while there may be an association between testosterone and MetS, causality cannot yet be confirmed.

The purpose of this AJA special edition on hypogonadism is to address these controversies associated with TST and to increase our understanding of how TST is associated with these aforementioned different conditions. In this special issue, the diagnosis and management of hypogonadism will be first reviewed. Testosterone’s association with CVD and MetS will also be reviewed. Furthermore, this issue will discuss preserving fertility in the hypogonadal patient and alternatives to TST. Finally, this issue will review the effects of testosterone on the prostate including PCa and BPH. It is clear that large, randomized, placebo-controlled trials are needed to provide more definitive data regarding the efficacy and safety of TST in hypogonadal men with these conditions.

REFERENCES
1. Amory JK, Watts NB, Easley KA, Sutton PR, Anawalt BD, et al. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. J Clin Endocrinol Metab 2004; 89: 503–10.
2. Traish AM, Saad F, Feeley RJ, Guay A. The dark side of testosterone deficiency: III. Cardiovascular disease. J Androl 2009; 30: 477–94.
3. Traish AM, Saad F, Guay A. The dark side of testosterone deficiency: IV. Type 2 diabetes and insulin resistance. J Androl 2009; 30: 23–32.
4. Wang C, Nieschlag E, Swerdloff R, Behre HM, Hellstrom WJ, et al. ISSAM, EAU, EAA and ASA recommendations: investigation, treatment and monitoring of late-onset hypogonadism in males. Int J Impot Res 2009; 21: 1–8.
5. Lazarou S, Reyes-Vallejo I, Morgentaler A. Wide variability in laboratory reference values for serum testosterone. J Sex Med 2006; 3: 1085–9.
6. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR, et al. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab 2001; 86: 724–31.
7. Fraser LA, Morrison D, Morley-Forster P, Paul TL, Tokmakejian S, et al. Oral opioids for chronic non-cancer pain: higher prevalence of hypogonadism in men than in women. Exp Clin Endocrinol Diabetes 2009; 117: 38–43.
8. Sun YT, Irby DC, Robertson DM, de Kretser DM. The effects of exogenously administered testosterone on spermatogenesis in intact and hypophysectomized rats. Endocrinology 1989; 125: 1000–10.
9. 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: 115–23.
10. Shigehara K, Sugimoto K, Konaka H, Iijima M, Fukushima M, et al. Androgen replacement therapy contributes to improving lower urinary tract symptoms in patients with hypogonadism and benign prostate hypertrophy: a randomised controlled study. Aging Male 2011; 14: 53–8.
11. Kalinchenko S, Vishnevskiy LE, Koval AN, Mskhalaya GJ, Saad F. Beneficial effects of testosterone administration on symptoms of the lower urinary tract in men with late-onset hypogonadism: a pilot study. Aging Male 2008; 11: 57–61.
12. Finkle WD, Greenland S, Ridgeway GK, Adams JL, Frasco MA, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PLoS One 2014; 9: e85805.
13. Vigen R, O’Donnell CI, Barón AE, Grunwald GK, Maddox TM, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA 2013; 310: 1829–36.
14. McBride JA, Carson CC, Coward RM. Diagnosis and management of testosterone deficiency. Asian J Androl 2015; 10.4103/1008-682X.143317.
15. Hwang K, Minar M. Controversies in testosterone replacement therapy: testosterone and cardiovascular disease. Asian J Androl 2015; 10.4103/1008-682X.146968.
16. Cunningham GR. Testosterone and metabolic syndrome. Asian J Androl 2015; 10.4103/1008-682X.148068.
17. Ramasamy R, Armstrong JM, Lipshultz LI. Preserving fertility in the hypogonadal patient: an update. Asian J Androl 2015; 10.4103/1008-682X.140081.
18. McCullough A. Alternatives to Testosterone replacement: testosterone restoration (TRES). Asian J Androl 2015; 10.4103/1008-682X.143736.
19. Morgentaler A, Conners WP. Testosterone therapy in men with prostate cancer: literature review, clinical experience, and recommendations. Asian J Androl 2015; 10.4103/1008-682X.148067.
20. Jarvis TR, Chughtai B, Kaplan SA. Testosterone and benign prostatic hyperplasia. Asian J Androl 2015; 10.4103/1008-682X.140966.