

Testosterone replacement therapy

It is a pleasure to present this introduction to a very special issue of *Translational Andrology and Urology (TAU)* that is focused on “testosterone replacement therapy” (TRT). As editors, we strove to present a current, state-of-the-art and global perspective on this very common and important medical condition. Established national and international experts as well as rising stars were invited to contribute and the response to our invitations to provide manuscripts on this timely subject has been overwhelming and allowed for the inclusion of numerous outstanding original articles, comprehensive review articles, as well as important opinions from many of the world leaders in the area of andrology. The papers in this issue of the *TAU* journal provide insightful updates and perspectives on our current understanding of the epidemiology, pathophysiology and important role of TRT in clinical practice.

Testosterone deficiency is an important diagnosis in the field of men’s health, and clinicians have seen an increasing number of men presenting for evaluation of this condition. An important subgroup includes testosterone deficiency in men with renal failure, as well as men who have undergone kidney transplant surgery. Original research and review articles in this issue address the therapeutic efficacy and safety of TRT in this specific subgroup of hypogonadal men. In addition, we have included an original scientific article describing the improvement of endothelial function that has been documented in men who are receiving TRT.

In 2015, a group of experts met to discuss the treatment of men who present for evaluation of a constellation of factors associated with elements of both primary and secondary hypogonadism. Because this syndrome commonly occurs in men who are middle-aged and older, it was termed adult-onset hypogonadism (AOH). While significant benefits of TRT for patients with AOH have been demonstrated, there are potential risks that can develop with long-term use. A review of this important demographic is aimed at providing a better roadmap for understanding the evaluation and the benefits and risks of TRT in this growing population.

An area of keen interest is how voiding function is affected by TRT. Previous dogma proposed that testosterone therapy worsens the symptoms of benign prostatic hyperplasia (BPH), which led the FDA to place a warning on testosterone products. The important review here within investigates our current understanding of the physiology of testosterone and its relationship with prostatic and lower urinary tract physiology. The review article suggests that not only does TRT not worsen lower urinary tract symptoms (LUTS), but that hypogonadism itself is an important risk factor for LUTS/BPH and TRT may in fact be beneficial for these men.

The primary therapeutic goal of TRT is to restore normal physiologic levels of serum testosterone levels in an attempt to improve symptoms in hypogonadal men. Over the past 70 years, numerous preparations and formulations have been developed for TRT. Included review articles describe and compare currently available FDA-approved testosterone preparations, as well as off-label therapies for TRT. Areas of focus include pharmacology, pharmacokinetics, adverse effects, and specifics related to individual delivery routes.

An important subgroup of men that is addressed in this issue includes those with male factor infertility, those trying to conceive with their partners as well as those with a varicocele. It has been well documented that testosterone has an impact on spermatogenesis, and the specific ramifications of TRT in this population need to be considered prior to the initiation of therapy. The current literature regarding varicocele and its effect on testosterone are reviewed in this issue. Evidence suggests that varicocele repair in hypogonadal men results in elevated levels of total testosterone. Other topics in this review address whether or not men with varicocele are at increased risk for developing low serum testosterone with clinical hypogonadal symptoms over time and whether or not varicocele repair in the eugonadal state reduce the likelihood of later hypogonadism.

An important topic that is reviewed in this issue addresses the role of hormone therapy in the transgender population. Cross-sex hormone therapy has been demonstrated to have positive physical and psychological effects on the transitioning individual. TRT is used in transgender men to induce virilization and suppress feminizing characteristics, while exogenous estrogen is used in transgender women to help feminize patients, and anti-androgens are used as adjuncts to help suppress masculinizing features. This review article discusses the various treatment regimens, health considerations and surveillance protocols, as well as the guidelines utilized to help healthcare providers choose appropriate candidates for hormone therapy.

Perhaps no topic in the TRT controversy has been more divisive in the last few years than the impact of testosterone therapy on cardiovascular disease (CVD). While the research remains inconclusive for the moment, there has been an extensive body of literature focusing on the association of testosterone and TRT with CVD events, including several meta-analyses. The article in

this issue critically reviewed the previous and emerging body of literature on this topic, including original research studies and meta-analyses of epidemiological studies and of randomized controlled trials (RCTs) and suggests that further studies that have the adequate power, epidemiological and clinical data are still required to provide a definitive conclusion on the effect of TRT on the natural history of CVD.

An area of critical interest is how prostate cancer is impacted by TRT and the role of TRT in hypogonadal men diagnosed with prostate cancer. Previously doctrine suggested that testosterone therapy should never be used in this population, as it would certainly worsen the cancer. This important review addresses these concerns and as well as our current scientific understanding of the role of TRT in men with prostate cancer.

As the number of baby-boomers continues to expand, more adult men are presenting to their physician with new symptoms attributed to testosterone deficiency. Subsequently there has been an increasing demand for TRT and the pharmaceutical industry has enthusiastically seized the opportunity to provide therapeutic options for these men. Subsequently, the FDA has taken issue with the surge of the TRT industry for a variety of reasons. The FDA has sent warning letters to pharmaceutical companies regarding misleading or unsubstantiated claims and voiced concerns as to the potential risks to CV health, resulting in increased TRT regulation and significant public impact on the ability to provide TRT in clinical practice. The review articles in this issue address many of the controversies surrounding the indications for therapy and the current evidence and appropriate indications for TRT.

The editors would like to thank all the authors for their lucid, up to date contributions and the timely submission of their manuscripts. Thanks also to Professor Tom F. Lue (Editor-in-Chief, *TAU*) for his kind invitation to edit this special *TAU* journal issue on “TRT”. It has been a distinct pleasure and highly rewarding experience to work with Lucine M. Gao, Science Editor for *TAU*, to shepherd this issue from concept to fruition. Our sincere hope is that readers would find this journal issue on “TRT” both informative and enlightening.



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