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Review Article

Testosterone Therapy: Safety, Tolerability of Injectable Androgens and Future Alternatives

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Abstract

In males, testosterone (T) controls several important functions including sperm production, sex drive, muscle mass and fat distribution, bone density and red blood cell production, fat and sugar metabolism as well as mood and cognition. During puberty, luteinizing hormone (LH) and follicle stimulating hormone (FSH) start being produced by gonadotropes of the anterior pituitary gland. FSH is critical for spermatogenesis, while T production is regulated in the testes by LH. The action of T is via the androgen receptor located in the cytoplasm and nucleus of target cells. Starting with the fourth or fifth decade of life total T concentrations begin to decline progressively by approximately 1% per year from an average between 270 and 1070 ng/dL, while bioavailable testosterone is approximately 110–575 ng/dL in men aged 18–69.

Keywords: testosterone; sperm production; sex drive; muscle mass; fat distribution; bone density; red blood cell production; fat and sugar metabolism; mood and cognition

Introduction to Testosterone Preparations for Treatment of Hypogonadism:

In males, testosterone (T) controls several important functions including sperm production, sex drive, muscle mass and fat distribution, bone density and red blood cell production, fat and sugar metabolism as well as mood and cognition. During puberty, luteinizing hormone (LH) and follicle stimulating hormone (FSH) start being produced by gonadotropes of the anterior pituitary gland. FSH is critical for spermatogenesis, while T production is regulated in the testes by LH. The action of T is via the androgen receptor located in the cytoplasm and nucleus of target cells. Starting with the fourth or fifth decade of life total T concentrations begin to decline progressively by approximately 1% per year from an average between 270 and 1070 ng/dL, while bioavailable testosterone is approximately 110–575 ng/dL in men aged 18–69.

Deficiency or absence of this hormone, which could either be of primary (originating in the testes) or secondary (a problem of the hypothalamus or pituitary gland) origin, seen in combination with characteristic symptoms such as impaired libido with loss of sexual function, regression of secondary sex characteristics, low muscle mass or decreased bone density is defined as hypogonadism. Apart from age-related reduction in testosterone concentrations, hypogonadism may also result because of autoimmune or genetic disorders, accidents, infection, prolonged exposure, to heavy metals or alcohol, radiation, tumors and chemotherapy and obesity.

Safety and Tolerability of Long-acting Injectable TU (Testosterone Undecanoate) 1000mg

Since testosterone is an endogenous protein, the pharmaceutically active component is testosterone itself, therefore injectable TU is well tolerated.

Indeed, only minor complications with TU treatment have been reported and these are generally limited to include local irritation at the site of injection, not usually lasting more than 3 days [1]. No patient reports of disrupted treatment due to problems or local discomfort have been reported. In contrast conventional injectable TE often led to mood swings or emotional instability, most likely due to fluctuations in T values after injection and in proximal days before the new injection is due.

Another important consequence of the supraphysiological T levels seen following injections with TE is the elevation of the hematocrit, as reported by independent studies, where patients had received 200 mg of TE every other week [2–4].

Meta-analyses of clinical trials suggest no major adverse effects following TU administration on CVD and PCa and only a minority of patients reported any of the common side-effects of T administration that include gynecomastia and breast tenderness, and acne [5, 6]. With respect to the development of comorbidities, testosterone use has been associated with conditions such as prostate cancer, worsening benign prostatic hyperplasia (BPH), male breast cancer, polycythemia, an increased risk of obstructive sleep apnea (OSA) [7], and cardiovascular disorders (CVD). Indeed, the supposition that patients receiving T replacement therapy have increased the risk of prostate cancer is controversial. In this context, although there is no evidence that testosterone therapy increases the risk of prostate cancer, decades of physicians have been trained with the notion that testosterone is the fuel for prostate cancer as it is known to be driven through the AR. To address this, the incidence of prostate cancer was evaluated in three independent observational studies in more than 1000 hypogonadal men treated with testosterone therapy for up to 17 years [8]. From this cohort only 11 patients received a diagnosed of prostate cancer. Similarly, in a large meta-analysis of 18 prospective studies that included over 3500 men, there was no association between serum androgen levels and the risk of prostate cancer development, for prostate cancer, in a [9].

These data suggest that if EAU guidelines for prostate screening and monitoring are followed, T therapy should be a safe and effective treatment in hypogonadal men. Furthermore, large scale, randomized, controlled, long-term studies are needed to more completely address the linkage between testosterone levels and prostate cancer.

Increasing evidence suggests that testosterone replacement therapy does not increase lower urinary tract symptoms (LUTS) and is not contraindicated in men diagnosed with BPH. A randomized, double-blind, placebo-controlled trial of 44 hypogonadal men showed that T treatment for 6 months improves serum androgen levels, with little effect on prostate tissue androgen levels, tissue biomarkers, and/or gene expression [7]. An increase in PSA levels and prostate size has indeed been noted in several studies [10, 11], though PSA levels and prostate size remained within the normal range despite a significant increase being observed. This increase in hypogonadal men is associated with subnormal PSA values and small prostate sizes at baseline [12] and is observed with all testosterone preparations. A recent review and meta-analysis concluded that T therapy does not increase PSA levels in men treated for hypogonadism [13].

The association between T treatment and male breast cancer is yet to be fully understood despite the existence of several case reports [14] and one retrospective review [15]. It is postulated that high levels of T may lead to increased aromatization to estrogen, which in turn may stimulate breast tissue growth via estrogen receptors [16]. While, through its erythropoietic function, T leads to an increase in hemoglobin by as much as 5–7% [17], thus exerting a positive effect on men with baseline anemia, it can lead to polycythemia in over 20% of men receiving T treatment [18]. Although complications such as an increased risk of vascular events, including stroke, myocardial infarction, and deep vein thrombosis with possible pulmonary embolus [18] are associated with polycythemia, an observation not yet made in men on T therapy [19]. Similarly, no documented evidence exists of polycythemia in studies using more traditional testosterone esters despite increases of erythropoiesis parameters to eugonadal values [20].

An examination of the literature reveals a wealth of evidence clearly suggesting that low T concentrations are associated with CVD risk and known risk factors for CVD, such as obesity, diabetes, and the metabolic syndrome (MS) [21, 22]. Of 11 longitudinal studies, 9 have demonstrated increased mortality rates in men with low T levels and improved survival in those with higher T [23], while 2 studies showed no effect [24]. In contrast, a recent study by Layton and collaborators investigating the CV safety of testosterone injections, patches, and gels revealed an association between T injections and an increased risk of CV events compared to T gels and patches. However, this study did not assess whether patients met the criteria for use of T and did not assess the safety of T among users compared to non-users [25, 26]. Two studies reporting risks with T gel preparations concluded that there is a significant direct correlation between T therapy and CVD risk [27, 28], although these studies should be interpreted with caution due to their study design limitations [29].

Impact of TU Therapy on Patient-Focused Perspectives

As androgen replacement therapy is normally associated with long-term medical conditions, therapy often extends over many decades, making patient compliance of utmost importance. Prior to TU administration, patients diagnosed with hypogonadism report a significantly reduced QoL, affected by symptoms including low libido, erectile dysfunction, infertility, gynecomastia, hot flashes, or as more non-specific symptoms such as low energy, sleep disturbance, depression or labile mood, impaired cognition, osteoporosis, and loss of muscle mass or increased BMI [23, 30, 31].

Regarding patient compliance and uptake, a major advantage of TU injections is the reduced frequency of visits allowing for reflection on efficacy and safety of TU therapy, when adjustment of the injection interval is required (most often by prolonging to every 13–14 weeks), as compared to almost bi-monthly visits for TE therapy. Furthermore, as TU only requires four injections per year compared to 26 injections per year with TE, there is a greater compliance rate in TU treated patients.

Future Alternatives to Injectable Androgens

Given that there is currently no global consensus on the medical approach to T deficiency, and that existing T replacement treatments are surrounded by conflicting efficacy and safety research and clinical reports, it comes as no surprise that alternative approaches to rectifying low T levels are increasing in number. Several decades of research, evaluating the field of selective

estrogen receptor modulators (SERMs) and selective androgen receptor modulators (SARMs), have resulted in the use of clomiphene citrate (CC), an estrogen receptor modulator, in the treatment of male hypogonadism in an off-label capacity [32].

The mechanism of action behind CC involves the disruption of the LH and FSH release from the pituitary gland, thus stimulating the production of T in Leydig cells [33]. An initial study in hypogonadal men, comparing CC, T injections, and T gel, revealed comparable effectiveness with patients reporting similar satisfaction, although increased libido was indicated in the T injection group. While preliminary studies suggest that CC may not only be a suitable alternative to T supplementation and may be advantageous in terms of cost-effectiveness and reduction of side-effects [34] there is a clear need for larger randomized clinical trials to assess its safety and efficacy further, and to ascertain whether CC effectively mitigates the known side-effects of hypogonadism. Alternatively, the discovery of steroidal and non-steroidal SARMs, used in the development of hormonal male contraception, could provide a promising alternative for T therapy.

The identification of an orally bioavailable SARM with the ability to mimic the desired central and peripheral androgenic and anabolic effects of T in a tissue-specific manner and simultaneously avoid the undesirable side-effects, would represent an important step in androgen therapy [35–38].

Many of these compounds are in the early phases of pharmaceutical development with combined research and clinical goals to produce reductions in catabolic consequences of hypogonadism and/or aging to preserve skeletal muscle and bone allowing the individual to maintain functional activities of daily living, reduce fall and fracture risk, and consequent disability. Considering recent guidance [39] on the restriction of exogenous testosterone administration, warranted by observational studies, indicating a potential increased risk of cardiovascular events [40, 41], in hypogonadal and/or aging men SARMs are promising candidates. Indeed, pre-clinical models looking at SARMs have shown a positive elevator ani/bulbocavernosus muscle complex/prostate ratio, demonstrating an improved anabolic/androgenic ratio with limited side-effects [42–44].

Conclusion

All testosterone preparations have, to varying degrees, favorable physical and metabolic effects. In view of its pharmacology, LA-TU presents with significantly improved efficacy and safety when compared to other conventional injectable T preparations (e.g., TE). Its advantages are obvious, from the reduced injection frequency to a significant improvement in side-effects associated with fluctuations of plasma T seen with conventional TE. As of January 2014, the FDA stated they are investigating the potential link between T therapy and several comorbidities, "FDA-approved testosterone treatment increases the risk of stroke, heart attack, or death," but have not yet concluded. Available evidence indicates that TU is largely considered to be safe in most hypogonadal men, with a small inherent risk of adverse events in some high-risk men with multiple comorbidities. T therapy has been associated with occasional modest increases in serum PSA and prostate size, yet within clinical safety limits, and without compelling evidence to support an increased risk of prostate cancer.

Indeed, when given to appropriately selected patients with vigilant monitoring, injectable T can produce improvements in QoL, energy level, libido, muscle mass, cognition, and bone density. Future research should focus on the evaluation of large, multiethnic cohorts of men through prospective trials to better elucidate both risk and hazard ratios of T as it relates to CVD and MS, prostate cancer, LUTS, OSA, erythrocytosis, and other yet-to-be-determined theoretical risks in men both with and without CV risk. In parallel, progress is being made with respect to research looking at the use of SERMs and SARMs, as TU alternatives in the treatment of male hypogonadism. Larger randomized clinical trials are required to determine the proper use, safety, and efficacy of SARMs, but preliminary studies suggest that this is a cost-effective suitable alternative to T supplementation.

For more information on the effect of TTh on different organ systems and/or prevention even in older men, we can refer to the recent published literature in this concern [45-49]. For the question: how long should TTh continue? Data suggests that interruption could cause recurrence in symptoms and signs of hypogonadism. So researchers agree to continue as lifetime treatment such as with Thyroxine or Insulin [50].

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