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Testosterone Therapy Improves Erectile Function and Libido in Hypogonadal Men

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Abstract

Purpose of Review—Erectile dysfunction (ED) and decreased libido are common complaints in the older male population. Recent studies have elucidated the role testosterone therapy (TTh) can play in men with low testosterone levels. The aim of this review is to provide an overview of these findings and the utility of TTh. We specifically examine the role of TTh on erectile function, co-administration with phosphodiesterase type 5 (PDE5) inhibitors, and libido.

Recent Findings—Recent publications suggest that TTh improves mild ED, though may be less useful in men with more severe ED. In men unresponsive to PDE5 inhibitors and with mild ED, TTh can further improve erectile function. Testosterone therapy has also shown consistent benefit in improving libido in men with low testosterone levels at baseline, with no additional improvements once testosterone levels are normalized.

Summary—The available literature supports a role for TTh in men with low testosterone levels, ED, and low libido, with symptomatic improvement in these men.

MeSH Keywords

Testosterone; Erectile Function; Phosphodiesterase 5 Inhibitors; Hypogonadal men

Introduction

Multiple longitudinal studies have observed that as men age, they experience a decline in total serum testosterone beginning in the third decade of life [1, 2]. By age 70, 30% of men will have low testosterone levels [2]. The symptoms of low testosterone include decreased libido, erectile dysfunction (ED), decreased energy, depressive symptoms, and fatigue [3]. These symptoms can be frustrating to men, and can be at least partially reversed with testosterone therapy (TTh). In this review, we summarize the recent literature examining the relationship between low serum testosterone levels, ED, and decreased libido.

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Search Strategy

To identify articles for this review, the following search terms were used in Medline: “testosterone,” “testosterone replacement therapy,” “erectile dysfunction,” and “libido.” Relevant and recent articles were identified and presented in this review. Articles published within the last 18 months were prioritized in this review.

Testosterone Therapy Improves Symptoms of Mild Erectile Dysfunction

ED affects 1 in 5 men, with this frequency increasing with age and the prevalence of co-morbidities [4, 5]. The National Institute of Health (NIH) defines ED as the “inability to achieve or maintain an erection that is satisfactory for sexual performance” [6]. Subjective erectile function can be assessed using validated questionnaire metrics including the international index of erectile function (IIEF) with the erectile function domain (IIEF-EF) being the most specific for assessing ED. The IIEF-EF consists of 6 questions that inquire about frequency and hardness of erections, ability to penetrate during intercourse, ability to maintain an erection during intercourse, ability to maintain an erection to completion of intercourse, and confidence in a man’s ability to get and maintain an erection [7]. The severity of ED is then classified as mild, mild to moderate, moderate, and severe dysfunction. The IIEF-EF is often used in studies to trend changes in erectile function, with a change of 2 IIEF-EF points being clinically significant for men with mild ED. The minimal clinically important differences (MCID) for moderate and severe ED are a change of 5 and 7 IIEF-EF points, respectively [8].

Erection requires a combination of vascular, neurologic, psychologic, and hormonal factors. Erections are initiated when nitric oxide and other neuroendocrine factors induce relaxation of the smooth muscles of the cavernous arteries and tissues resulting in increased penile blood inflow. As the corpus cavernosum fills with blood, the veins that drain the corpus cavernosum are compressed, resulting in maintained turgidity [9]. This initial release of nitric oxide is mediated in part by testosterone [10]. While evaluating neurologic, vascular, and psychologic factors can be difficult during a clinical visit, a hormonal etiology of ED can easily be assessed by measuring morning serum testosterone levels. The evaluation of testosterone levels in men with ED is recommended by the European Association of Urology guidelines and is indicated in select men with ED per American Urology Association guidelines [11, 12].

Numerous studies have examined the relationship between testosterone levels and erectile function. In cross-sectional studies, men with low testosterone (defined by the US Food and Drug Administration as levels less than 300 ng/dL) have a greater prevalence of ED when compared to men with normal testosterone levels [13–15]. Studies have observed that men who have been placed on androgen deprivation therapy (ADT) for prostate cancer have a dramatic reduction in erectile function with a decrease in testosterone levels [16–18]. Finally, numerous randomized controlled trials (RCTs) have demonstrated that erectile function improves when testosterone is given to men with low testosterone levels [19–24].

In the past few years, several studies have shown that testosterone levels and erectile function are positively correlated. The recently published Testosterone Trials – a set of RCTs of 790 men with late onset hypogonadism randomly assigned to either testosterone gel or placebo – demonstrated that after 1 year of treatment that men who used testosterone gel had an IIEF-ED score 2.64 points [95% Confidence Interval (CI): 1.06 – 4.02] greater than men who had been assigned to the placebo arm [24]. It is important to note that men enrolled in this study on average had moderate ED, and so this improvement in erectile function was not considered clinically significant.

In early 2017, Corona *et al.* performed meta-analysis of 14 RCTs that studied the effect of TTh on erectile function in men with late onset hypogonadism, and compared pre- and post-IIEF scores [25]. Overall, when compared to placebo, TTh provided only a modest improvement in IIEF-EF, as the mean difference between groups was 2.31 points. The mean change in IIEF-EF, however, was greater when data were stratified by baseline testosterone level. In primary studies using a testosterone threshold <8 nM (231 ng/dL), IIEF-EF increased by 2.95 points, whereas in primary studies with testosterone threshold of <12 nM (346 ng/dL), only a 1.47 point increase in IIEF-EF was observed [25]. Given that a greater improvement in erectile function was observed in studies using a lower testosterone threshold, this supports the theory that once a threshold of “normal” testosterone level is achieved, higher testosterone levels do not further improve erectile function [26]. This definitive study by Corona *et al.* also suggests that TTh may be a useful monotherapy in men with mild ED.

Testosterone Therapy as Adjuvant Therapy with PDE5 Inhibitors

Numerous studies have found that phosphodiesterase type 5 (PDE5) is upregulated in the penis by androgens [27, 28], and when animals are castrated, a decline in both penile nitric oxide and PDE5 levels are seen [28–30]. These early studies support the possibility that men with low testosterone may have a relative deficiency of PDE5, resulting in lower efficacy of PDE5 inhibitors [31]. In a randomized controlled trial by Shabsigh *et al.*, dual treatment with sildenafil and testosterone was more effective than monotherapy with sildenafil for men with testosterone levels <400 ng/dL who had previously failed a trial of PDE5 inhibitors. Men receiving both testosterone and PDE5 inhibitors had an improvement of 4.4 IIEF points from baseline to 4 weeks while those receiving monotherapy only saw an increase of 2.1 IIEF-EF points (p=0.029) [32].

While Buvat *et al.* observed a positive effect in hypogonadal PDE5 inhibitor non-responders, other RCTs have not observed such a positive effect. In a 2012 RCT, Spitzer *et al.* studied 140 men on sildenafil and then randomly assigned them to either receive testosterone or placebo gel. All men had a testosterone level <330 ng/dL or a free testosterone level <50 pg/mL. At 14 weeks, those on dual therapy had an IIEF-EF score 1.01 points higher than those receiving sildenafil plus placebo gel (p=0.36). This study demonstrates that the giving testosterone to men who respond to PDE5 inhibitors may not further improve erectile function after normalization of testosterone levels. However, there is growing evidence supporting the use of testosterone in men with low testosterone and mild ED, especially in those who were previously non-responsive to PDE5 inhibitors [33, 34].

These recent studies suggest that TTh may be most effective as monotherapy in improving erectile function in men with mild ED, but not in men with more severe ED. Early studies have shown that TTh can improve the response to PDE5 inhibitors in non-responders.

Testosterone Therapy and Libido

Libido, or sexual drive, is affected by a multitude of factors, including physiologic ones, such as a defect in the hypothalamic-pituitary access or depression, or environmental ones, such as marital discourse or anxiety [3, 35, 36]. Changes in libido can variably affect individuals, with a wide range of clinical presentations. Longitudinal studies have found that libido declines with increasing male age [35]. When assessing libido, many studies use the sexual desire (SD) domain of the IIEF (IIEF-SD), which asks men to two libido-related questions: “Over the past 4 weeks, how often have you felt sexual desire?” and “Over the past 4 weeks, how would you rate your level of sexual desire?” Like the IIEF-EF domain, the IIEF-SD questions can be used to diagnose mild, mild to moderate, moderate, and severe dysfunction [7]. Other studies have used their own scale, such as the Sexual Arousal, Interest and Drive scale (SAID) – a validated patient reported outcomes measuring 5 scored items, including sexual thought, arousal, as well as interest and drive [37].

Several early studies have demonstrated that TTh improves libido [38, 39]. Recently, the Sexual Function sub-trial of the Testosterone Trials examined sexual desire. This placebo-controlled trial included 470 men aged 65 years or older with testosterone levels less than <275 ng/dL [24]. When assessing the impact of TTh on sexual symptoms, the authors used the Derogatis Interview for Sexual Function-Sexual Desire Domain, comprised of 25 scored items, and found that libido improved proportionately with increase in testosterone levels, with an effect size of 0.44 [95% Confidence Interval: 0.32 – 0.56] [40]. Interestingly however, these trials found no threshold below which libido was universally affected for all men in the study.

The results of the largest placebo-controlled multicenter trial assessing the effect of testosterone on sexual function in hypogonadal men (715 men, 18 years of age and older) were published in 2016. Brock *et al.* found that 60 mg of topical testosterone 2% gel applied daily resulted in a significant increase in testosterone levels as well as libido, as measured using the SAID scale after three months of treatment. The study examined a cohort of hypogonadal men with a mean age of 55. Though not placebo-controlled beyond the third month, the open label continuation of the trial for both placebo and active treatment groups showed continued improvement in sexual function at 9 months when on continuous TTh, with no new adverse events [23]. In the group initially treated with placebo, 60% of men achieved normal testosterone levels at the end of the open label study, compared to 66% of the participants on TTh for the duration of the trial. Interestingly, the group that had received placebo before the 3-month time point and later placed on the open-label TTh achieved the same libido improvements as the group that had been on TTh for the entire 9 months. This finding suggests that benefits of TTh on libido plateau after 3 months of therapy. However, the study lacked a true control arm during the open-label portion of the trial, limiting the ability to make this conclusion. Furthermore, a post hoc analysis of the trial’s outcomes after 3 months further revealed that a lower testosterone level at the start of treatment and higher

plasma concentration achieved at the end of treatment were associated with a greater patient reported improvement in libido [41].

The Corona *et al.* meta-analysis also assessed the impact of TTh on libido in hypogonadal men, finding that for 1,269 men across 14 randomized, placebo-controlled trials, the IIEF-SD significantly improved (p=0.001) [25]. These findings suggest that TTh may be more effective in improving sexual desire than in improving erectile function in men with moderate or severe ED. Citing previous studies that had failed to show improvements in libido on therapy, Corona *et al.* highlighted that many of these studies did not specifically examine a population with low testosterone at baseline and that in eugonadal men, TTh may be less beneficial in improving libido.

While TTh can improve libido, it is not without its risks [42]. Due to the wide-spread use of testosterone-related products for seemingly “age-related” symptoms and the potential cardiovascular risk, the FDA has commissioned a large clinical trial to assess the safety of testosterone products [43]. A joint patient-physician decision should be made whether the potential improvement in erectile function, libido, and energy with TTh outweighs the potential side-effects in each individual patient.

Many studies have demonstrated that TTh significantly improves libido in men. Moving forward, large RCTs specifically studying older men for more than a year of treatment are needed to better determine at what testosterone thresholds men demonstrate improvements or decrements in sexual function and desire. Finally, current measures of evaluating libido are either very narrow in their scope or not validated. As such, future work should focus on more clearly defining the impact of TTh on libido.

Conclusion

In men with low testosterone, “normalizing” testosterone levels has multiple benefits, most notably improved libido and improved erectile function when used as monotherapy in men with mild ED. For the latter, TTh is especially promising in hypogonadal men with mild ED who are unresponsive to phosphodiesterase-5 inhibitors. Testosterone therapy may be ineffective in men with moderate and severe ED, as the etiology for these more severe pathologies often include advanced diabetes, radical pelvic surgery, or severe neurologic damage. In these cases, a hormonal factor is often not the primary cause of dysfunction, and thus while TTh should be considered, other treatments are likely to be more effective.

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Key Points

- Testosterone replacement monotherapy can improve erectile function in men with mild ED, but not moderate and severe ED.
- In men with low testosterone who are unresponsive to PDE5 inhibitors, normalization of testosterone levels can improve the response to PDE5 inhibitors.
- Testosterone therapy improves libido in men with low testosterone.