

## UNVEILING THE EFFECT OF TESTOSTERONE THERAPY ON SEXUAL DYSFUNCTION

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### ABSTRACT

Male sexual dysfunction, including ED, PD, and PE, is prevalent, particularly in older men. Research has suggested that hormonal factors, specifically low total testosterone levels, may contribute to these conditions. TTh has been explored as a potential treatment for male sexual dysfunction, but studies have used varying assessment methods. This meta-analysis aimed to provide a comprehensive evaluation by using a consistent assessment tool, the International Index of Erectile Function (IIEF). Methods: Randomized controlled trials (RCTs) comparing TTh with placebo in adult men with sexual dysfunction were included. The primary outcome measure was the IIEF score. Studies were selected through a systematic literature search, and 16 RCTs met the inclusion criteria. Results: 16 studies were deemed from 98 studies was identified. The effect size testosterone therapy (Tth) in overall sexual dysfunction with standardized mean difference (SMD) 1.8, 95% CI 0.31 to 3.43. Impact of testosterone therapy on erectile dysfunction with Mean Difference (MD) 3.07, 95% CI 1.68 to 4.46. P-value 0.0001) ( $p<0.0001$ ). Discussion: Testosterone plays a crucial role in regulating various aspects of male health, including sexual function. TTh has demonstrated positive effects on sexual function, particularly in improving erectile function. The time course of TTh effects suggests that improvements in libido and sexual activity can occur within weeks, while substantial improvements in erectile function may take several months. Additional assessment tools, such as the PDQ-Q4 and DISF-M-II, have also shown positive outcomes with TTh.

**Keywords:** *capital structure, firm size, sales growth, profitability*

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## INTRODUCTION

Male sexual dysfunction encompasses a spectrum of disorders, prominently featuring ailments like erectile dysfunction (ED), Peyronie's disease (PD), and premature ejaculation (PE). These disorders are characterized by compromised sexual functionality. The incidence of male sexual dysfunction rises with advancing age and is notably significant, as over 50% of men aged 40 to 70 report experiencing varying degrees of erectile dysfunction (Anderson, 2022). Evidence indicates that male sexual function is governed by hormonal processes, as evidenced by the correlation between inadequate sexual functioning and total testosterone levels below 8 nmol/L. Moreover, diminished levels of freely circulating testosterone have been linked to signs and symptoms related to androgen deficiency, even among individuals with total testosterone levels within the normal range. Hence, the compromise in male sexual function might stem from reduced levels of circulating androgens (Antonio, 2015).

Prior research has explored the utilization of testosterone replacement therapy (TTH) in men with hypogonadism as a strategy to address male sexual dysfunction. Studies have demonstrated that TTH outperforms placebos in enhancing various aspects of sexual function. However, it's noteworthy that investigations focusing on the impact of testosterone on sexual function exhibit significant diversity in their methodologies, often employing disparate self-reported metrics to gauge the ultimate outcome. To address this challenge, we conducted a meta-analysis in men with testosterone deficiency, employing a consistent assessment tool the International Index of Erectile Function (IIEF) across the studies. The International Index of Erectile Function (IIEF) stands as the most commonly employed and validated instrument for

appraising male sexual function (Ke et al., 2023). It has garnered endorsement both as a principal outcome measure in clinical trials pertaining to erectile dysfunction (ED) and as a means of diagnostically evaluating the severity of ED.

### **Study Criteria**

This meta-analysis applied specific inclusion criteria to select relevant studies for analysis. We only included randomized controlled trials (RCT) comparing the effect of TTh versus placebo and using IIEF as the possible main or secondary outcome were included in the analysis (Lee et al., 2023). Only English-language studies were considered, while non-English studies, duplicates, review articles, and irrelevant publications were excluded from the analysis.

### **Participants Criteria**

The study population included adult men (above 18 years of age) affected by sexual dysfunction, with either normal testosterone levels (eugonadal) or low testosterone levels (hypogonadal).

1. Egonadal status was characterized by a total serum testosterone level of  $\geq 12$  nmol/L (or equivalent in ng/ml), as measured on at least two occasions in the early morning hours (i.e., before 10 am), or according to trial specifications.
2. Hypogonadal status, on the other hand, was defined by a low total serum testosterone level of  $<12$  nmol/L (or equivalent in ng/ml), also measured at least twice in the early morning or per trial stipulations.
3. Sexual dysfunction encompassed conditions such as reduced sexual desire, erectile dysfunction, and disorders related to ejaculation or orgasm, individually or in various combinations.
4. Erectile dysfunction was identified as the persistent inability to achieve and maintain an erection sufficient for satisfactory sexual activity.
5. Low sexual desire was characterized based on trial-defined parameters.
6. Ejaculatory disorders encompassed conditions such as delayed ejaculation, reduced ejaculate volume or force, premature ejaculation, anejaculation, painful ejaculation, or according to trial criteria.
7. Orgasmic disorder encompassed conditions like anorgasmia (either primary—never experienced orgasm or secondary previously experienced orgasms), as well as hypoactive orgasm (difficulty in reaching orgasm).

### **Testosterone Therapy (Tth) Criteria**

The experimental intervention employed for both the eugonadal and hypogonadal groups consisted of testosterone therapy (TTh) (Schluessel et al., 2023), utilizing varied forms of testosterone preparations (such as undecanoate, cypionate, etc.), diverse administration routes (such as topical gel, topical cream, injection, sublingual, oral tablet, etc.), and differing treatment durations (in accordance with trial specifications) (Liu et al., 2023). TTh could have been employed alongside concurrent non-testosterone-based therapies, which encompassed PDE-5 inhibitors, alprostadil, prostaglandins, vacuum therapy, and the like, for the purpose of addressing male sexual dysfunction. In comparison, the control intervention encompassed options such as no treatment (i.e., observation) or placebo, as well as any alternative testosterone or non-testosterone-based therapies like PDE-5 inhibitors, alprostadil, vacuum therapy, psychosexual counseling, among others.

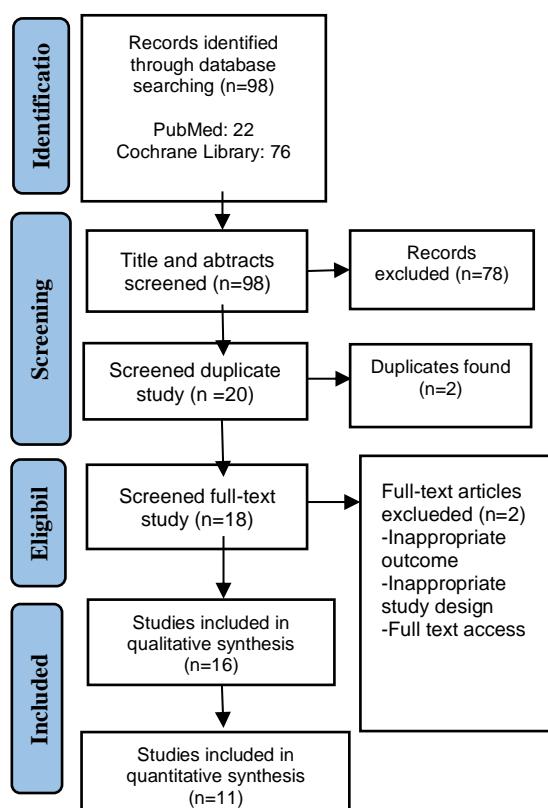
## METHOD

### Literature Search and Study Selection

Following the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), we conducted a comprehensive search encompassing the databases PubMed, MEDLINE, the Cochrane Library, Scopus, Web of Science, and Science Direct up September 2023. The search terms employed were “(Testosterone therapy)” AND “(sexual dysfunction)”. Duplicates and review articles were removed, and the titles and abstracts of the remaining studies were independently screened for eligibility by two authors. To apply the inclusion and exclusion criteria, the same authors read the full text of all selected studies.

## RESULTS AND DISCUSSION

Using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram **Diagram 1**. In this section, we outline the study selection procedure. Initially, a pool of 98 studies was identified from the available literature. Following a thorough examination of the titles and abstracts, 18 articles met the criteria for further evaluation. Subsequently, after conducting a comprehensive assessment of the full-text content, 16 studies were deemed suitable for inclusion in this systematic review and meta-analysis.



**Diagram 1.** Diagram flow of literature search strategy for this systematic review

Androgens are multifaceted hormones with a wide range of effects on metabolism, blood vessels, reproduction, and sexual functions, as supported by multiple academic sources (Kelly, D. M., & Jones, 2013; Kelly, D. M., 2016). Their significance in regulating metabolic processes is particularly noteworthy, carrying clinical implications for conditions such as metabolic syndrome (MetS), obesity, insulin resistance (IR), type 2 diabetes mellitus (T2DM), and alterations in overall body composition and anthropometric parameters. Testosterone (T)

stands as the primary androgen hormone, playing a crucial role either as a precursor for the formation of 5a-dihydrotestosterone (5a-DHT) or through aromatization into estradiol (E2), each with distinct and important physiological functions. It is essential to acknowledge testosterone deficiency (TD), also referred to as 'hypogonadism,' as a medical condition necessitating medical intervention, regardless of its underlying cause, etiology, or the patient's age. Notably, testosterone therapy, which was first introduced as early as the 1940s to address TD, has proven effective in alleviating the signs and symptoms associated with TD, albeit amidst ongoing debates surrounding its utilization in male patients (G. Corona, G. Rastrelli, 2013).

### **Testosterone therapy in overall sexual dysfunction**

In all likelihood, typical males possess an excess of androgens that exceeds the immediate requirements for regular sexual functioning. The sudden and complete cessation of androgens is undeniably linked to a decline in sexual desire and the inability to achieve or sustain an erection. These manifestations are swiftly ameliorated through the administration of a minimal dosage of testosterone (Bancroft, J., & Wu, 1983). In the study conducted by Isidori et al. 2005, it was observed that testosterone therapy (Tth) had a favorable impact on erectile function (EF) in men with average testosterone levels below 10 nmol/l. The effect size, as measured by the standardized mean difference (SMD), was 1.8, with a 95% confidence interval (CI) ranging from 0.31 to 3.43. Subsequently, Bolona et al. 2005 conducted another study where they identified a modest yet statistically significant effect of Tth on EF in men with testosterone levels within the low-normal range. The SMD for this effect was 0.34, with a 95% CI from 0.03 to 0.65. Interestingly, within the subgroup of younger subjects, a more substantial effect of Tth on EF was observed, with an SMD of 1.80 and a 95% CI ranging from 1.0 to 2.7. This highlights the potential influence of aging as a moderator in the responsiveness of erectile dysfunction (ED) to testosterone therapy.

The impact of Testosterone Therapy (TTh) on orgasmic aspects yielded mixed outcomes. Schiavi et al.'s 1997 study (Schiavi, R. C., White, D., Mandeli, J., & Levine, 1997), one of the earliest investigations, demonstrated that TTh enhanced ejaculatory function when compared to non-Treatment (non-T) options. Additionally, two more recent studies by Mitkov et al. in 2013 and Brock et al. in 2016 (Mitkov, Aleksandrova, & Orbetzova, 2013; Brock, G., 2016) found improvements in overall orgasmic function associated with TTh. However, contrasting results were observed in other studies conducted by Buvat et al. in 2011 and Paduch et al. in 2015, where no significant enhancements in orgasmic or ejaculatory parameters were noted with TTh in comparison to non-T treatment (Pignanelli et al., 2023). Notably, in Cavallini et al.'s study, the group receiving TTh exhibited less favorable orgasmic outcomes when compared to the group using carnitines [12]. In this investigation, it was observed that alterations in the overall sexual well-being and the orgasm domain were consistently found to be non-statistically significant within Group 1. Group 1 consisted of 40 patients, with a mean age of 64 years (ranging from 60 to 72), who were administered a daily dose of 160 mg of testosterone undecanoate. Conversely, in Group 2, which comprised 45 patients with an average age of 66 years (ranging from 61 to 73) receiving a combination of 2 g/day of propionyl-L-carnitine and 2 g/day of acetyl-L-carnitine, noteworthy improvements were observed in erectile function and the orgasm domain after 6 months. However, no statistically significant changes were noted in sexual desire and general well-being in this group. Regarding sexual satisfaction, an examination of research outcomes also revealed contradictory findings. Specifically, three studies conducted by Aversa et al. in 2003, Mitkov et al. in 2013, and Paduch et al. in 2015 indicated that Testosterone Therapy (TTh) resulted in enhanced satisfaction with sexual intercourse or overall sexual well-being when compared to non-testosterone treatments (Caruso et al., 2023) (Mitkov, M. D., Aleksandrova, I. Y., & Orbetzova, 2013) (Pignanelli et

al., 2023). In contrast, three separate trials conducted by Schiavi et al. in 1997, Buvat et al. in 2011, and Paduch et al. in 2015 (Schiavi, R. C., White, D., Mandeli, J., & Levine, 1997) (Pignanelli et al., 2023) reported no significant improvement in sexual satisfaction among individuals using testosterone in comparison to the control group.

### Testosterone therapy on erectile dysfunction

The guidelines set forth by the European Association of Urology (EAU) pertaining to male sexual dysfunction have assigned a level of evidence (LE) of 1b (indicating at least one randomized controlled trial) and a grade of recommendation (GR) of B (based on well-conducted but not randomized trials) to emphasize the importance of initially addressing any treatable causes of erectile dysfunction (ED), including hypogonadism (Hatzimouratidis, et al 2010). Similarly, EAU guidelines specifically addressing hypogonadism have assigned an LE of 3 (grounded in well-designed and nonexperimental studies) and a GR of B for considering the use of testosterone in addressing "reduced libido and erectile issues (Ponholzer, A., & Madersbacher, 2009). An additional noteworthy consideration, which has only recently garnered attention, is the time frame for the effects of testosterone (T). This encompasses the duration of treatment required to achieve maximum results. A systematic analysis has revealed that noticeable effects on libido, ejaculation, and sexual activity may manifest within just 2 to 3 weeks, whereas improvements in erectile function (EF) may take up to 6 months to become discernible through the International Index of Erectile Function (IIEF) (Saad, et al, 2011).

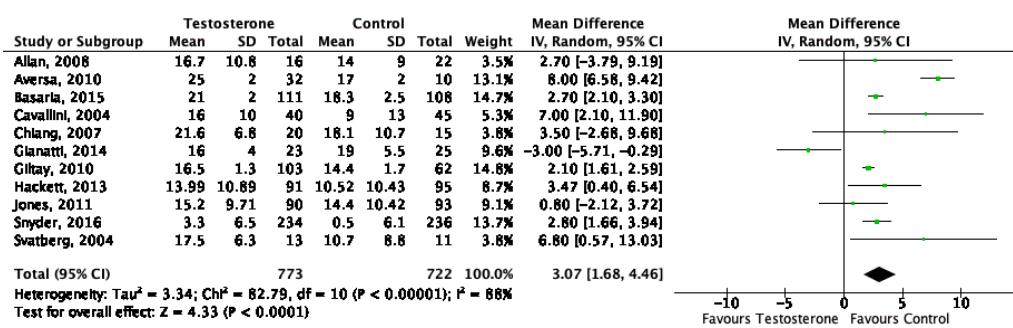


Figure 1. Forest Plot of Testosterone Therapy on Erectile Dysfunction assessed by IIEF

The data above (Figure 1) examined 11 studies involving a total of 1,020 male participants, the focus of the analysis was to assess the impact of testosterone therapy on the change in the mean International Index of Erectile Function (IIEF) scores in comparison to a control group. The primary result of interest is the Mean Difference (MD) in the change of IIEF scores between the group receiving testosterone therapy and the control group. The MD is calculated to be 3.07, with a 95% confidence interval (CI) ranging from 1.68 to 4.46. This MD value represents the average increase in IIEF scores for individuals who underwent testosterone therapy when compared to those in the control group. Elevated scores on the IIEF are indicative of improved erectile function. There was a high level of heterogeneity observed among the included studies, with an  $I^2$  statistic of 88%. An  $I^2$  of 88% suggests a substantial degree of variation in the study results, indicating that the studies included in the meta-analysis may have differed in important ways, such as patient characteristics. The p-value is reported as less than 0.0001 ( $p < 0.0001$ ). This indicates that the observed difference in mean IIEF scores between the testosterone therapy group and the control group is statistically significant. In other words, the likelihood of observing such a significant difference by chance alone is extremely low. Our meta-analysis suggests that there is a statistically significant improvement in IIEF scores associated with testosterone therapy when compared to a control group. Recent randomized controlled trials (RCT) that included in our meta-analysis by Giltay et al. and Hackett et al. have demonstrated that a statistically significant enhancement in IIEF, albeit as marginal

changes, can be detected at the 6-month mark, with further substantial improvements occurring after 12 months of open-label treatment. Taking these considerations into account, it has been suggested that the time course of testosterone therapy may elucidate some of the negative findings in experimental human studies regarding the relationship between testosterone and sexual thresholds. These studies, often conducted in acute settings spanning weeks, may differ from the time required for penile tissue recovery, which may necessitate several months.

### **Other Assessment Tools**

In our meta-analysis, one of the studies included, which was also the most recent, demonstrated that, when assessing sexual activity using the PDQ-Q4 score over multiple follow-up visits, testosterone treatment yielded a greater increase compared to the placebo. This effect was observed both among men participating in the Sexual Function Trial and among all participants in the testosterone trials. Notably, a stronger elevation in testosterone levels during the treatment period was linked to a more pronounced improvement in the PDQ-Q4 score. However, it's worth mentioning that this response somewhat diminished at the 12-month mark. Furthermore, this study identified that testosterone treatment was associated with increased sexual desire, as indicated by the DISF-M-II, and improved erectile function, which served as the primary outcome in our analysis based on the IIEF. Additionally, individuals in the testosterone group were more likely than those in the placebo group to report an enhancement in their sexual desire since the initiation of the trial.

In a study conducted by Aversa et al. in 2010, which involved hypogonadal men diagnosed with metabolic syndrome, it was observed that after 6 months of oral testosterone undecanoate (TU) treatment, there were no notable improvements in IIEF-5 scores (related to erectile function) or in Aging Males' Symptoms (AMS) scores compared to the baseline measurements. However, when participants crossed over to receive intramuscular (IM) TU treatment, improvements in both IIEF-5 and AMS total scores were observed, with the most significant improvement occurring in the somatic domain of the AMS score. Following 6 months of IM TU treatment, there was an increase in IIEF-5 scores and a decrease in AMS total scores compared to the baseline. Furthermore, these changes became more pronounced over the course of 12 months, with a further significant enhancement in IIEF-5 and AMS scores. Men who switched from oral to IM TU treatment and those who continued with IM TU treatment exhibited significantly better outcomes in both the total and somatic domain scores of the AMS at the 12-month mark. Additionally, individuals in the IM TU group reported improvements in the AMS sexual domain scores at 12 months. These findings were paralleled by significant increases in IIEF-5 and AMS scores, and all components of metabolic syndrome (MS) showed substantial improvement within 6 months, with continued progress observed after 12 months. In conclusion, it can be deduced that the clinical effectiveness of testosterone therapy in this particular population of hypogonadal men with metabolic syndrome is achieved when testosterone levels in the bloodstream reach the medium to medium-high range of normality ( $>5$  ng/ml). However, it's important to note that individual subjective thresholds may vary.

### **CONCLUSION**

Based on our meta-analysis findings, it is evident that testosterone therapy yields a statistically significant enhancement in IIEF scores when contrasted with a control group. Nevertheless, the substantial heterogeneity observed among the studies underscores the necessity for additional research to elucidate the factors contributing to this variability and to enhance treatment approaches for achieving optimal outcomes in individuals with erectile dysfunction.

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