Impact of Testosterone Therapy on hypogonadal patients unresponsive to phosphodiesterase-5 inhibitors alone: A systematic review and a meta-analysis

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Research article

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Abstract

Background

Phosphodiesterase-5 inhibitors as the first-line treatment for erectile dysfunction, when patients with hypogonadism fail to respond to phosphodiesterase-5 inhibitors, the beneficial of addition testosterone therapy is a major concern for clinicians. The objective of this study was to collect and summarize the evidence that evaluated the benefit of addition testosterone therapy in hypogonadism fail to respond to phosphodiesterase-5 inhibitors.

Methods

Electronic literature searches of Cochrane Library, PubMed, MEDLINE and EMBASE databases were conducted up to October 2020 and included randomized controlled trials. Specifically, we were looking for papers where Erectile Function Domain Score differences between pre and post-treatment were used as the primary outcome after treatment of testosterone therapy alone, phosphodiesterase-5 inhibitors therapy alone, or a dual treatment of both testosterone therapy and phosphodiesterase-5 inhibitors. Secondary outcomes included the number of phosphodiesterase-5 inhibitors non-responders who subsequently reported a satisfactory treatment of dual treatment with testosterone therapy and phosphodiesterase-5 inhibitors.

Results

A total of 4 studies that met our criteria, consisting of 326 patients. The Erectile Function Domain Score was significantly higher after treatment of testosterone combine with phosphodiesterase-5 inhibitors(4.88[4.18–5.57]), phosphodiesterase-5 inhibitors with placebo(3.15[1.82–4.47]), and testosterone monotherapy (2.04[0.38–3.71]) compared with baseline. Dual treatment with testosterone and phosphodiesterase-5 inhibitors significantly improved Erectile Function Domain Score when compared with testosterone monotherapy (3.16, 95% CI: 1.79–4.53), Of 41.7% patients in the dual treatment group reported an improvement, compared to only 33.0% in phosphodiesterase-5 inhibitors treatment group.

Conclusions

Combination therapy of testosterone and phosphodiesterase-5 inhibitors seems most effective in men with both erectile dysfunction and hypogonadism who initial unrespond to phosphodiesterase-5 inhibitors.

Introduction

In 27.7% of men with erectile dysfunction (ED), total testosterone (T) levels were found to be less than 300ng/dL [1]. Unfortunately, research on the relationship between low testosterone and ED remains inconclusive. In a study conducted on nearly 3,000 men aged between 40–79, results showed that ED was not associated with total T levels in a linear fashion, and the association between ED and free T levels was found to be weak; However, when total T levels (< 8 nmol/L) the relationship between T levels and ED strengthened, and became statistically significant [2]. This suggests that ED should be regarded as a symptom of hypogonadism only when T levels are clearly subnormal.

Phosphodiesterase-5 inhibitors (PDE5-Is) promotes an erectile response through blocking the degradation of cyclic guanosine monophosphate. As a result, the corpus cavernosal smooth muscle relaxes, and this promotes a penile erection following sexual stimulation. PDE5-Is was thus shown to improve erections in up to 70% of patients with ED[3]. Therapeutic efficacy may also improve with dose escalation or when using a low-dose daily dosing strategy. However, alternating between different types of PDE5-Is did not seem to improve treatment efficacy [4, 5]. PDE5-Is have revolutionized ED treatments for patients, but nonetheless have their limitations; *Although PDE5-Is has a good therapeutic effect on most ED patients, patient's existing conditions such as hypertension, dyslipidemia, poor glycemic control, and tobacco use all independently weaken the effect of PDE5-Is* [6]. Interestingly, in a sample of men who failed a trial of PDE5-Is, 40% of them were still able to achieve a long-term satisfactory result after going through a 12 min in-office education and evaluation[4].

Similarly, in men with hypogonadism, it remains unclear whether the addition of TTh improves one's response to PDE5-Is. In Buvat et al.'s study which examined the effects of TTh on PDE5-Is non-responders, they found that the change in Erectile Function Domain Score (EFD) and rate of successful intercourse were nonsignificant within males with a normal T levels at baseline; However, when total T level of < 3 ng/mL at baseline, both EFD change and rate of successful sexual intercourse were significant [7]. Accordingly, a particular combination of TTh and tadalafil, a PDE5-I, significantly improved erectile function in ED patients with hypogonadism, even after treatment cessation [8]. At the

meanwhile, in a Case series study, males with baseline total T levels < 4 ng/mL who unsatisfied with different PDE5-Is treated by TTh, although EFD achieve a statistically significant increase compare with baseline after TTh treatment, 65.6% (21/32) patients were not clinically satisfied with his sexual function[9]. Furthermore, in some hypogonadism patients for whom sildenafil, another PDE5-I, treatment is effective, addition of TTh does not result in better erectile function improvement compared to placebo gel [10].

Hence, the question of whether the addition of TTh improves ED when patients with hypogonadism fail to respond to PDE5-Is is a major concern for clinicians. Thus, the present study intends to elucidate the role that TTh plays and its effect on erectile function in PDE5-Is non-responders with hypogonadism.

Materials And Methods

This study was registered at the International prospective register of systematic reviews (PROSPERO registry number: CRD42020215241) and did not involve any human intervention. The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement was adhered to for the reporting of results.

Literature search

A systematic search was conducted within the databases of Pubmed, Cochrane Library, and Google Scholar in order to identify all relevant studies published up till October 2020. Terms and descriptors related to “phosphodiesterase type 5 inhibitors OR sildenafil OR tadalafil,” “testosterone OR testosterone replacement,” and “hypogonadal OR androgen deficiency syndrome,” were combined, with the filter “human”. Studies written in all languages were considered for the current study. The advanced search function was also utilized, where we limited selected article types to clinical studies and randomized controlled trials (RCTs). Trial registries (<http://clinicaltrials.gov> and www.who.int/trialsearch) were also searched. Lastly, to ensure we identified all relevant studies, we also conducted a manual search among the reference lists of articles that were already included at that point in time.

Eligibility Criteria and Selection of Studies

Articles were included if full texts were available, if human participants were enrolled, and if they were primary research papers. We included studies which: 1) assessed the efficacy of a combined treatment consisting of PDE5-Is and TTh in ED patients with low levels of T who were previously non-responsive to initial treatment with PDE5-Is alone 2) included control groups who were treated with PDE5-Is or TTh, with and without placebos. Exclusion criteria included the following: 1) inclusion of patients who treated with PDE5-Is reported satisfactory erections; 2) ED patients with normal T; 3) other therapeutic strategies employed (androgens or antiandrogens) before baseline; 4) studies with missing outcome data. Two authors (Yanhong.Liu and Xiaoyuan.Zhang) assessed all abstracts that were surfaced from the search independently and obtained the full manuscripts of papers identified via the manual search that met the selection criteria. These authors also evaluated the eligibility of the studies and extracted the required data for analysis. Any discrepancies in the selection of articles were solved by mutual agreement among the authors after discussion, and if needed, a third author was included in the discussion.

Data extraction

Two review authors (QW and WXY) independently extracted data from the selected studies, The following study characteristics were identified for each study: 1) study design and population (including the history of non-responders to treatment with different PDE5-Is); 2) T levels, 3) the form and dose of testosterone replacement used; 4) the type and dose of PDE5-Is used; 5) interventions in treatment and control groups; 6) duration of treatment; 7) outcome, specifying the percentage of patients who responded to treatment, if not already otherwise indicated in the inclusion criteria in each study. All included studies were also assessed according to the criteria for nonrandomized studies to evaluate the potential risk of bias.

We specified the primary outcome measure a priori as EFD change of the TTh plus PDE5-Is group compared to the placebo plus PDE5-Is group, and the TTh plus PDE5-Is group compared to the TTh only group. Secondary outcome measures included the number of patients with improved response to treatment with PDE5-Is, pre and post change in EFD for the various groups who underwent treatments of either TTh plus PDE5-Is, TTh or PDE5-Is alone.

Any discrepancies were resolved by discussion, and if needed, consensus was reached by involving a third author (QW).

Sensitivity Analysis and Risk of Bias

Sensitivity analyses were conducted utilizing the leave-one-out approach, and results show that there was no significant change in the direction and magnitude of the combined estimates when individual studies were excluded. Hence, this indicates that the meta-analysis has good reliability. The quality evaluation process was performed using Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane

Collaboration, Copenhagen, Denmark) as shown in Fig. 5. The included articles are all registered RCTs and fulfilled the CONSORT criteria. As there was only a small number of available trials, funnel plot asymmetry tests to evaluate publication bias could not be conducted[11].

Statistical analysis

Statistical analyses were conducted using Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Associations among dichotomous outcomes were assessed using odds ratios (ORs) and their 95% confidence interval (CIs). Associations among continuous variables were assessed using standardized mean difference (SMD) and their 95% CIs. Sensitivity analyses were also conducted by excluding trials with outliers. Next, heterogeneity between trials was quantified using the Q-test or I^2 . A random effect model was utilized because of the limited number of studies[11].

Results

A total of 166 studies were identified initially, and after a through selection process as shown in Fig. 1, we initial arrived at a sample of 7 RCTs to be included for analysis, all of which were published between 2004 and 2011[7, 10, 12–16]. However, after a thorough reading of the 7 RCTs, 3 articles were excluded because they did not meet the inclusion criteria. Spitzer et al[10]. only included participants who initial used 100-mg sildenafil reported satisfactory but not unresponsive erections. In trail of Aversa et al[13]. patients with T levels in hypogonadal range were not included. The remaining study conducted by Hackett et al[12]. involved type 2 Diabetes males with hypogonadism, and these patients did not receive any PDE5-Is treatment.

The rest of 4 RCTs encompassed a total of 326 patients, and the follow-up duration ranged between 10 to 13 weeks, with a mean duration of 12 weeks. Two studies [7, 14]used the PDE5-Is + placebo treatment group as their control, whereas the other 2 studies[15, 16] used the TTh as control. As the use of different control groups may influence the results of the analysis, we decided to conduct separate analyses for the 2 different types of control groups. A summary of the trials included are as shown in Table 1.

Table 1
Characteristics of the included studies

Author (year)	Design	Patients	T level	T Form/ does	PDE5-Is Form/ does	Treatment		Trial duration	Outcomes included
						Experiment	Control	(week)	
BuvatI, 2011	RCT	nonresponders to treatment with different PDE5-Is.	Total T < 4 ng/mL or bioavailable T < 1 ng/mL	1% T gel 50 mg (5g/gel) daily	Tadalafil 10 mg once a day	Tadalafil + T	Tadalafil+ Placebo	12	percent of patients responders to treatment ; Erectile function
Yassin 2006	RCT	inadequate response to 100 mg sildenafil.	Total T < 3.4 ng/ml	1% T gel 50 mg (5g/gel) daily	Tadalafil 20 mg twice a week	Tadalafil + T	T	13	Erectile function
Shamloul 2005	RCT	Men failing to respond to sildenafil	Low total T and free T	Oral 120 mg/day Testosterone	Sildenafil 50–100 mg on demand	Sildenafil + T	T	10	Erectile function
Shabsigh 2004	RCT	confirmed lack of response to sildenafil monotherapy	morning serum total T < 4 ng/ml	1% T gel 50 mg (5g/gel) daily	Sildenafil 100 mg on demand	Sildenafil + T	Sildenafil + Placebo	12	percent of patients responders to treatment ; Erectile function

A total of 237 patients were sampled in two studies which compared the effect of TTh plus PDE5-Is group against a control consisting of placebo plus PDE5-Is group. Our results suggest that there was no significant improvement in the EFD of TTh plus PDE5-Is therapy group over the EFD of the PDE5-Is plus placebo group. The pooled SMD for EFD change was 1.20 [(-0.66-3.06), $I^2 = 34$; $p = .21$; Fig. 2]. On the other hand, a total of 89 patients were sampled in rest of two studies comparing the effect of the TTh plus PDE5-Is group against the TTh only group on the

basis of EFD; The TTh plus PDE5-Is group had a pooled SMD for EFD change was 3.16 (95% CI 1.79–4.53, $I^2 = 63$; $p < .00001$; Fig. 2), and had a significantly better improvement in EFD compared to the TTh only group.

Where data pooling was possible in all 4 trials, we examined the EFD change before and after treatment of TTh plus PDE5-Is, and the SMD in improvement from baseline measured with EFD was 4.88 [(4.18–5.57), $I^2 = 0$; $p < .00001$; Fig. 3]. In the placebo and PDE5-Is groups, SMD in improvement from baseline measured with EFD was 3.15 [(1.82–4.47), $I^2 = 0$; $p < .00001$; Fig. 3], and for TTh only group, it was 2.04 [(0.38–3.71), $I^2 = 70$; $p = .02$; Fig. 3].

Two of the included trials [7, 14] which compared between the treatments of TTh plus PDE5-Is group, and placebo plus PDE5-Is therapy reported on the number of patients with improved response to treatment after 8–12 weeks. 47% of patients in the TTh plus PDE5-Is group reported an improvement, compared to only 33.0% in placebo plus PDE5-Is group, the pooled OR was 1.41 (95% CI 0.79–2.54, $I^2 = 0$; $P = 0.25$; Fig. 4). For sensitivity analysis, we then excluded each study to analyze the change in the pooled effect, which was not statistically significant.

Discussion

TTh treatment remains a controversial topic, even after more than 70 years of clinical use, with a significant portion of the research literature providing evidence that TTh does improve sexual symptoms in men with ED. This may be due in part to various testosterone preparations possibly having differing modes of action [17–20]. Previous study have indicated that TTh treatment was ineffective in improving ED when there were high serum levels of estradiol [21]. Clinically, on-demand administration tadalafil was able to reduce serum estradiol levels significantly, but the testosterone/estradiol ratio also rose significantly regardless of whether total or free T rises [22]. Thus, some researchers recommend that clinicians consider starting PDE5-Is therapy during the first consultation for ED, without waiting for confirmation of a normal serum T level [23]. At the same time, a qualitative systematic review concluded that TTh did not show consistent benefits for sexual function [24]. Another systematic review which included 17 RCTs, comprising of a total of 3165 men with hypogonadism indicated that erectile function did not differ significantly between individuals who received the TTh or those who received placebos [25].

Previous meta-analyses also reported that a positive effect of PDE5-Is was further improved with the co-administration of testosterone only in uncontrolled studies, but not in placebo-controlled studies [26]. Our analysis suggests that dual treatment with TTh and PDE5-Is significantly improves EFD when compared to the control group of TTh only. In patients who received dual treatment (TTh and PDE5-Is), there was a higher increase in EFD (4.88 point), but for TTh treatment only it was 2.04 point only. This supports the theory that TTh may facilitate the pharmacological effects of PDE5-Is [27]. The PDE5 gene is expressed less as males age, as well as in men with hypogonadism. Hence, TTh treatment may possibly be able to restore the expression of the PDE5 gene, through regulating its gene expression directly [28]. Accordingly, there was an observed mean increase of 2.3 point in EFD scores for patients with mild ED who were treated with TTh, but not for those with more severe ED. In our meta-analysis, only 2 of the selected articles considered the seriousness of ED. In Shabsigh et al.'s study, 69% of placebo gel control group had mild to moderate ED, while 81% in dual treatment group had mild to moderate ED [14]. In Yassin et al.'s study, 74.3% of the TTh group had mild to moderate ED compared to 67.7% in the dual treatment group [16]. Hence, for men with milder ED, TTh alone may be a possible treatment option [29].

There was also a higher percentage of patients with improved response to treatment after 8–12 weeks for the group receiving treatment of TTh plus PDE5-Is, at 41.7%, compared to 33.0% for the group receiving the placebo plus PDE5-Is. In patients who received dual treatment (TTh and PDE5-Is), there was a higher increase in EFD (4.88 point) when compared with patients who underwent only PDE5-Is treatment (3.15 point), although when PDE5-Is treatment was used as the control group, the change of EFD did not reach statistical difference. This can be attributed to a number of factors. Firstly, ED patients treatment with PDE5-Is increased total T levels by 1.15–1.73 ng/ml [30, 31], significant erectile function improvements were seen only in samples with a lower testosterone threshold, and further increases in testosterone levels do not confer further benefits on erectile function if testosterone threshold has already been hit [32]. So it is unclear whether the additive benefit of TTh was negated by the potentially direct effect of PDE5-Is on serum T levels. Secondly, a meta-analysis of 14 RCTs found that when the testosterone threshold was less than 2.3 nmol/l, EFD increased by 2.95 after TTh, compared to only a 1.47 point increase in EFD when the total T threshold was less than 3.5 nmol/l [33]. Three selected articles described the classification of the total T levels at baseline. In Yassin et al.'s study, total T levels of < 2 ng/mL were observed in 20.6% of the TTh group, and in 17.6% of the dual treatment group [16], while in Shabsigh et al.'s study, total T levels of < 2 ng/mL were observed in 33% of the placebo gel group, compared to only 5% of the dual treatment group [14]. In addition, in Buvat et al.'s study, 28.1% of the sample were bounded by a total T of < 1.45 ng/ml [7]. Most of the included patients with a mild degree of androgen deficiency might possibly weakening the therapeutic effect of TTh, as TTh was more effective in patients with moderate to severe androgen deficiency. It must be noted that imbalances in total T distribution, as well as in ED grading can result in biases in the analyses. Moreover, as a lack of sexual activity also could have caused subclinical hypogonadism, TTh may benefit in ED patients restoring sexual activity and further increase their testosterone levels at a normal range [34].

Only two types of PDE5-Is (sildenafil, tadalafil) were used in the selected studies, and this may potentially result in a bias, even though previous meta-analyses indicate that there are no significant difference in the efficacy of PDE5-Is relative to each other[3]. A 10–20 mg dosage of tadalafil was associated with greater improvement in the mean proportion of successful sexual intercourse attempts (76.9%) compared to a dosage of 100mg sildenafil (72.2%). On the other hand, the mean change in EFD did not differ between groups[35, 36]. There was no significant dose-response effect when tadalafil was used [37]. The dose of sildenafil used varied among the included studies, where one particular study used 50–100 mg on demand [15] and the other used a dosage of 100 mg on demand [14]. There was only significant improvement in sexual intercourse success and erectile function in using a sildenafil dosage of 50mg when it was compared to a 25mg dose, but there was no difference in the improvements for both 100mf and 50mg doses[38].

In contrast with certain reviews that were published previously, we only included RCTs that enrolled initial PDE5-Is non-responders with hypogonadism. Our study also had several limitations. First, only 2 of the included articles described the classification of baseline T levels and the severity of ED, and the distribution of such participants across the various groups studied was also uneven. Second, the included studies used various cut-off values for the testosterone to determine hypogonadism. Third, the duration of treatment with TTh varied among the included studies and this difference in duration may have affected the outcomes. Therefore, further high-quality research studies need to be conducted to better elucidate the effects of the TTh treatment on patients with hypogonadism who are unresponsive to phosphodiesterase-5 inhibitors alone.

Conclusion

The present meta-analysis and systematic review conducted suggests that the effect of combined TTh and PDE5-Is therapy in males with ED and hypogonadism who are initial unresponsive to PDE5-Is resulted in a significant improvement in erectile function when compared with PDE5-Is and TTh therapy only. Moreover, dual treatment(TTh and PDE5-Is) also associated with greater improvement in proportion of successful sexual intercourse attempts (41.7%) compared to PDE5-Is monotherapy (33.0%). TTh monotherapy conducted for a short period of time in cases of hypogonadism does not seem to more helpful in men who did not respond to initial treatment with PDE5-Is alone. The fact that TTh treatment seems to be more beneficial for men with severe hypogonadism suggests that further research are still needed to clarify whether such a combination therapy may be useful in difficult-to-treat ED patients who do not respond to PDE5-Is.

Abbreviations

PDE5-Is: phosphodiesterase-5 inhibitors; TTh: testosterone therapy; ED: erectile dysfunction; T: testosterone; RCTs: randomized controlled trials; ORs: odds ratios; CIs: confidence interval; SMD: standardized mean difference

Declarations

- Ethics approval and consent to participate

Not applicable

- Consent to publish

Not applicable

- Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

- Competing interests

All authors have read and approved the manuscript. The authors declare that they have no competing interests.

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- Authors' Contributions

QW designed and guided the study; YH L participated in literature search and review, meta-analysis, and interpretation of results; XW Y performed the meta-analysis and helped draft the manuscript.; XY Z analyzed included and excluded studies, helped summarize the collected evidence. All authors read and approved the final manuscript.

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Tables

Table 1 Characteristics of the included studies

Author (year)	Design	Patients	T level	T Form/ does	PDE5-IS Form/ does	Treatment		Trial duration (week)	Outcomes included
						Experiment	Control		
BuvatI, 2011	RCT	nonresponders to treatment with different PDE5-Is.	Total T <4 ng/mL or bioavailable T<1 ng/mL	1% T gel 50 mg (5g/gel) daily	Tadalafil 10 mg once a day	Tadalafil+T	Tadalafil+ Placebo	12	percent of patients responders to treatment ; Erectile function
Yassin 2006	RCT	inadequate response to 100 mg sildenafil.	Total T <3.4 ng/ml	1% T gel 50 mg (5g/gel) daily	Tadalafil 20 mg twice a week	Tadalafil+T	T	13	Erectile function
Shamloul 2005	RCT	Men failing to respond to sildenafil	Low total T and free T	Oral 120 mg/day Testosterone	Sildenafil 50-100 mg on demand	Sildenafil+T	T	10	Erectile function
Shabsigh 2004	RCT	confirmed lack of response to sildenafil monotherapy	morning serum total T<4 ng/ml	1% T gel 50 mg (5g/gel) daily	Sildenafil 100 mg on demand	Sildenafil+T	Sildenafil +Placebo	12	percent of patients responders to treatment ; Erectile function

Figures

Figure 1

Flow chart for the trial identification and selection process.

Figure 2

Subgroup meta-analysis based on control treatment in the selected studies

Figure 3

Subgroup meta-analysis the change of post-treatment and pretreatment in the selected studies.

Figure 4

Forest plot demonstrating relative risk for patients responders to treatment rates when using PDE5-I+T or PDE5-I+P.

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