



What are the benefits and harms of testosterone therapy for male sexual dysfunction?—a systematic review

Konstantinos Dimitropoulos¹ · Paolo Verze² · Thomas Van den Broeck³ · Andrea Salonia⁴ · Cathy Yuhong Yuan⁵ · Konstantinos Hatzimouratidis⁶ · Gert Dohle⁷

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Abstract

The role of Testosterone Therapy (TTh) in the management of male sexual dysfunction remains unclear. Objective of the authors was to systematically review the relevant literature assessing the benefits and harms of TTh in men with sexual dysfunction. EMBASE, MEDLINE, Cochrane Systematic Reviews—Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane HTA, DARE, HEED), Google Scholar, WHO international Clinical Trials Registry Platform Search Portal, CINAHL databases and clinicaltrial.gov were searched systematically in March 2015 and an updated search was performed in March 2016. Randomized and non-randomized comparative studies assessing the benefits and harms of TTh in hypogonadal, borderline eugonadal and eugonadal men suffering from sexual dysfunction were included. Risk of bias and confounding assessments were performed. A narrative synthesis was undertaken. Of the 6410 abstracts identified, 36 studies were judged to be eligible for inclusion, including 25 randomized clinical trials (RCTs) and 11 non-randomized comparative studies (NRCs), recruiting a total of 4944 patients. RCTs were judged to have low or unclear risk of bias, while NRCs had high risk of bias and thus, overall quality of evidence was judged to be at least unclear. Based on the evidence mainly provided by the RCTs included in this systematic review, TTh could be considered for men with low or low-normal testosterone levels and problems with their sexual desire, erectile function and satisfaction derived from intercourse and overall sexual life. The exact testosterone formulation, dosage and duration of treatment remain to be clarified, while the safety profile of TTh also remains unclear. TTh could be used with caution in hypogonadal and most probably borderline eugonadal men to manage disorders of sexual desire, erectile function and sexual satisfaction. The overall low-to-moderate evidence quality highlights the need for robust and adequately designed clinical trials.

Introduction

Male sexual dysfunction is a term that encompasses various disorders in sexual function of men that can be classified

into low sexual desire, erectile dysfunction, disorders of orgasm and ejaculation and diminished sexual satisfaction [1]. It has been shown that hormonal mechanisms regulate male sexual function as total testosterone levels <8 nmol/l have been correlated with worse sexual functioning, while low circulating free testosterone concentrations have been associated with androgen-related signs and symptoms even in men with normal total testosterone levels [2–5].

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✉ Konstantinos Dimitropoulos
k.dimitropoulos@nhs.net

¹ Department of Urology, Aberdeen Royal Infirmary, Aberdeen, Scotland, UK

² Department of Urology, University of Naples Federico II, Naples, Italy

³ Department of Urology, University Hospitals Leuven, Leuven, Belgium

⁴ Division of Experimental Oncology/Unit of Urology, URI, IRCCS Ospedale San Raffaele, Milan, Italy

⁵ Department of Medicine, McMaster University, Hamilton, ON, Canada

⁶ Second Department of Urology, Aristotle University of Thessaloniki, Pefka, Thessaloniki, Greece

⁷ Urology Department, Erasmus University Medical Center, Rotterdam, Netherlands

Therefore, impairment of male sexual function could be a result of low circulating androgen levels [6].

Androgen deficiency occurs frequently, as biochemical evidence of low testosterone has been reported in 2.1–12.8% of middle-aged men [7]. However, clinical hypogonadism, a condition characterized by biochemical findings of low testosterone and associated clinical symptoms, has an incidence of 2.1–5.7% in men aged 40–79 years [7]. Depending on the underlying cause, hypogonadism can be classified as primary (due to testicular failure), secondary (due to defects of hypothalamus or pituitary gland) and late-onset or age-related or functional hypogonadism caused by mixed defects of testes, hypothalamus or pituitary. The diagnosis of the latter can be given to middle-aged and older men when there are clinical manifestations of hypogonadism and biochemically proven low serum testosterone levels, but the function of hypothalamic–pituitary–testicular axis remains intact. Its prevalence in community is estimated to be between 2.1 and 12.3% [8] Risk factors for hypogonadism comprise various auto-immune and genetic disorders, diabetes mellitus, chronic obstructive pulmonary disease (COPD), thyroid disorders, obesity, liver cirrhosis, chronic renal failure, haematological disorders, systemic infections (such as human immunodeficiency virus (HIV) infection), previous chemotherapy or radiotherapy for cancer and use of medications [9–11].

The use of testosterone replacement therapy in hypogonadal men and eugonadal men to manage male sexual dysfunction has been investigated previously. Testosterone can be delivered as oral preparation (testosterone undecanoate), intra-muscular injections (testosterone cypionate, undecanoate and enanthate), transdermal preparations, such as skin patches and gels, subdermal depots and sublingual and buccal tablets. Each type of administration has its own advantages and disadvantages in terms of absorption and associated testosterone response, fluctuations of testosterone levels and drug-related adverse events. Because of the lack of comparative studies on different testosterone applications, it is still unclear which type, dose and formulation of testosterone should be used and for how long in men with sexual dysfunction to offer therapeutic benefit with an acceptable safety profile. Moreover, for men suffering from functional hypogonadism, management of possible underlying conditions (such as lifestyle changes e.g. weight loss, management of comorbidities and discontinuation of medications) should be offered as first-line measure, while TTh could be considered as a concomitant form of treatment in selected patients, or after the first-line measures fail [8].

Based on this lack of evidence, the current systematic review was designed to evaluate the benefits and harms of testosterone therapy in hypogonadal and eugonadal men with sexual dysfunction.

Materials and methods

Search strategy, selection of studies and data extraction

The protocol for the review has been published and is available online (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015028029), and the search strategy is outlined in Supplementary 1. In brief, databases including EMBASE, MEDLINE, Cochrane Systematic Reviews—Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane HTA, DARE, HEED), Google Scholar, WHO international Clinical Trials Registry Platform Search Portal, CINAHL databases and clinicaltrial.gov were searched systematically in March 2015 and an updated search was performed in March 2016. Abstract and full-text screening and extraction of data were performed by two reviewers independently (KD and PV). Possible conflicts were resolved by discussion or with an independent arbiter (TVdB). Only English language articles were searched and studies published from 1995 onwards were included. The review was commissioned and undertaken by the 2017 EAU Male Hypogonadism and Male Sexual Dysfunction Panels.

Types of study designs included

All randomized controlled trials [RCTs], quasi-RCTs and non-randomized comparative studies (NRCS) with at least one experimental arm and one control arm were included. Studies with more than two arms were also included. Single-arm case series, case reports, commentaries, reviews, abstract-only studies and editorial commentaries were excluded.

Types of participants included

The study population included adult men (>18 years of age) with sexual dysfunction who were either eugonadal or hypogonadal. Eugonadal status was defined as total serum testosterone ≥ 12 nmol/L (or equivalent in ng/ml) measured at least twice as early morning level (i.e. <10am), or as specified by trialist. Hypogonadal status was defined as low total serum testosterone i.e. <12 nmol/L (or equivalent in ng/ml), measured at least twice as early morning level (i.e. <10am), or as specified by trialist [10]. Sexual dysfunction was defined as either low sexual desire, erectile dysfunction, or ejaculatory or orgasmic disorder or any combinations.

Erectile dysfunction definition included the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance [12] or as defined by trialist, low sexual desire was defined by trialist, ejaculatory disorder was defined by any of the following conditions: delayed ejaculation, decreased volume or force of ejaculation, premature ejaculation, anejaculation, painful

ejaculation or as defined by trialist and orgasmic disorder definition included any of the following conditions: anorgasmia (primary [i.e. never had orgasm] or secondary [has had orgasm previously]), hypoactive orgasm (i.e. difficulty reaching orgasm). Treatment (either previous or concurrent) with non-testosterone based therapy for sexual dysfunction (e.g. PDE-5 inhibitors, alprostadil, vacuum therapy, psychosexual counselling, penile prosthesis, etc.) was allowed. In addition, treatment for underlying condition (e.g. oral anti-diabetics for diabetes, selective serotonin reuptake inhibitors [SSRI] or other anti-depressants for depression) was allowed. Studies that included female-to-male transgender participants were excluded.

Types of interventions included

The experimental intervention for either eugonadal or hypogonadal arm was testosterone therapy (TTh), including different preparations of testosterone (e.g. undecanoate, cypionate, etc.), route of administration (topical gel, topical cream, injection, sublingual, oral tablet, etc.) and/or duration of treatment (as specified by trialist). TTh might have been combined with concurrent non-testosterone based therapy, including PDE-5 inhibitors, alprostadil, prostaglandins, vacuum therapy, etc to treat male sexual dysfunction. The control intervention was no treatment (i.e. observation) or placebo; or any other testosterone or non-testosterone based therapy, including PDE-5 inhibitors, alprostadil, vacuum therapy, psychosexual counselling, etc.

Type of outcome measures included

The primary benefit outcome for patients with low sexual desire and erectile dysfunction was any measure of sexual desire and erectile function (e.g. IIEF, or as defined by trialist) and for patients with ejaculatory or orgasmic disorders was any measure of ejaculatory and orgasmic function, as defined by trialist. The primary harm outcome included adverse effects of treatment (including allergic reactions, skin reactions, elevation of haematocrit, development of prostate cancer, major cardiovascular events, etc.). For all outcomes of potential interest, measures could have been obtained at any time point.

The secondary outcomes were sexual satisfaction for patients with any type of sexual disorders (as defined and measured by IIEF score, or any other measure as defined by trialist) and any additional outcomes judged relevant by the reviewers.

Assessment of risk of bias

The Cochrane risk of bias (RoB) assessment tool for RCTs was used to assess the RoB in the included RCTs [13]. For

RoB in NRCS, a modified Cochrane tool that included additional items to assess confounding bias was used. This was a pragmatic approach informed by the methodological literature pertaining to assessing RoB in NRCSs [14, 15]. A list of the 5 most important potential confounders for harm and benefit outcomes was developed a priori with clinical content experts (EAU 2017 Male Hypogonadism and Male Sexual Dysfunction Guideline Panels). The potential confounding factors included age and relationship status (stable or not) for all sexual disorders patients. Other potential confounding factors were concurrent treatment with PDE-5 inhibitors or other non-testosterone-based therapies, smoking and obesity (all for ED patients). The overall judgement regarding each confounder was based on whether it was measured, if it was balanced across groups, and whether any statistical adjustments were made [16].

Results

Quantity of evidence identified

The study selection process is outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram (Fig. 1). A total of 6410 abstracts were screened, of which 120 full texts were retrieved for further screening. Ultimately, 36 studies met the inclusion criteria, recruiting a total of 4944 patients (2729 from RCTs and 2215 from NRCSs). These included 25 RCTs [17–41] and 11 NRCSs [42–52].

Characteristics of the included studies

Characteristics of RCTs

A total of 25 RCTs were included in the final analysis and their baseline characteristics are presented in Supplementary Table 1. Seventeen RCTs studied hypogonadal patients [18, 19, 23–28, 30, 32–35, 37–40], two studies focused on eugonadal men [17, 41] three studies included borderline eugonadal patients [20–22], two had a mixed set of hypogonadal and eugonadal participants [29, 36] and one study did not clearly mention the eugonadal status of its population [31]. Eighteen RCTs used either T monotherapy or combination therapy of T with other agents vs. observation, placebo or other non-T treatment [17–19, 21–24, 28, 29, 31, 32, 34–36, 38–40]. Seven RCTs compared various forms of T treatment [20, 25–27, 30, 33, 37].

Characteristics of NRCSs

In total, 11 NRCSs were included in the final analysis. Their baseline characteristics are presented in Supplementary

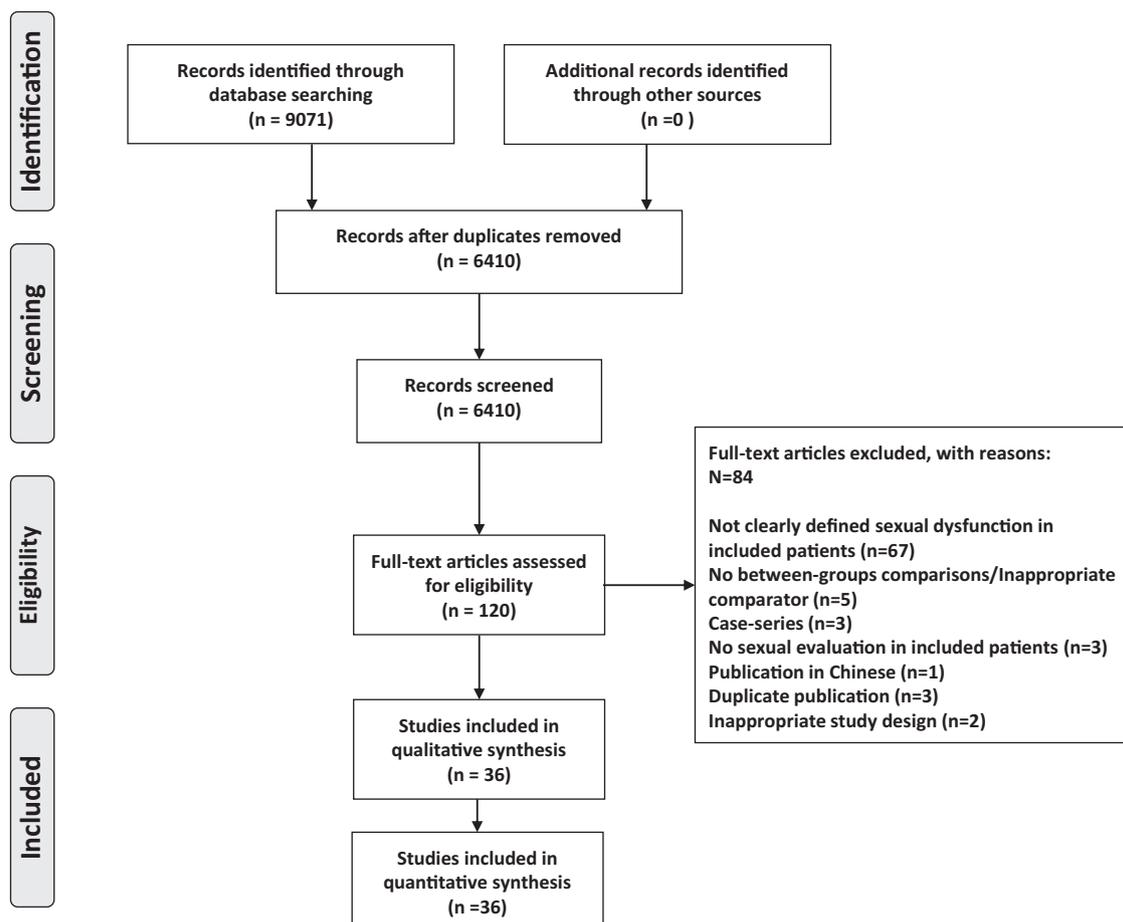


Fig. 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram

Table 1. Eight NRCSs included hypogonadal patients [43–47, 49, 50, 52] while the remaining three studies assessed mixed groups of hypogonadal and eugonadal patients [42, 48, 51]. Five NRCSs used either T monotherapy or combination therapy of T with other agents vs. observation, placebo or other non-T treatment [42, 44, 46–48]. Five NRCSs used as comparators various settings of T monotherapy or combination therapy [43, 45, 49, 50, 52], while 1 NRCS used various comparators that included non-T and T treatments [51].

RoB and confounding assessment of the included studies

The RoB summary and confounder assessment for the 25 RCTs [17–41] and 11 NRCSs [42–52] are presented in Fig. 2. With respect to selection bias, most RCTs had unclear risk. The risks of performance, detection and reporting bias were low, whilst the risk of attrition bias was low-to-unclear. The NRCSs had a high risk of selection, performance, and detection biases. The risks of attrition and reporting bias were unclear. Age as a confounder was considered in almost all of

the studies but not corrected for. Relationship status was considered in half of the studies but not corrected for in all 11 NRCSs. Smoking and obesity status was not considered and corrected for in all studies assessing ED.

Comparing of intervention results

Supplementary Tables 2 and 3 summarize the outcome results for the 25 RCTs [17–41] and 11 NRCSs [42–52], respectively, according to the eugonadal/hypogonadal status of the participants.

Sexual functioning outcomes

Data from RCTs on T vs. non-T treatment Various degrees of improvement in sexual desire following different types of TTh were shown in six studies [19, 21, 22, 36, 38, 40]. No significant differences between the T and comparator groups were revealed by the remaining studies assessing sexual desire parameters [17, 18, 31, 32, 34].

Several studies showed a beneficial effect of TTh on erectile function [19, 21, 22, 24, 29, 36, 38, 40] and erectile

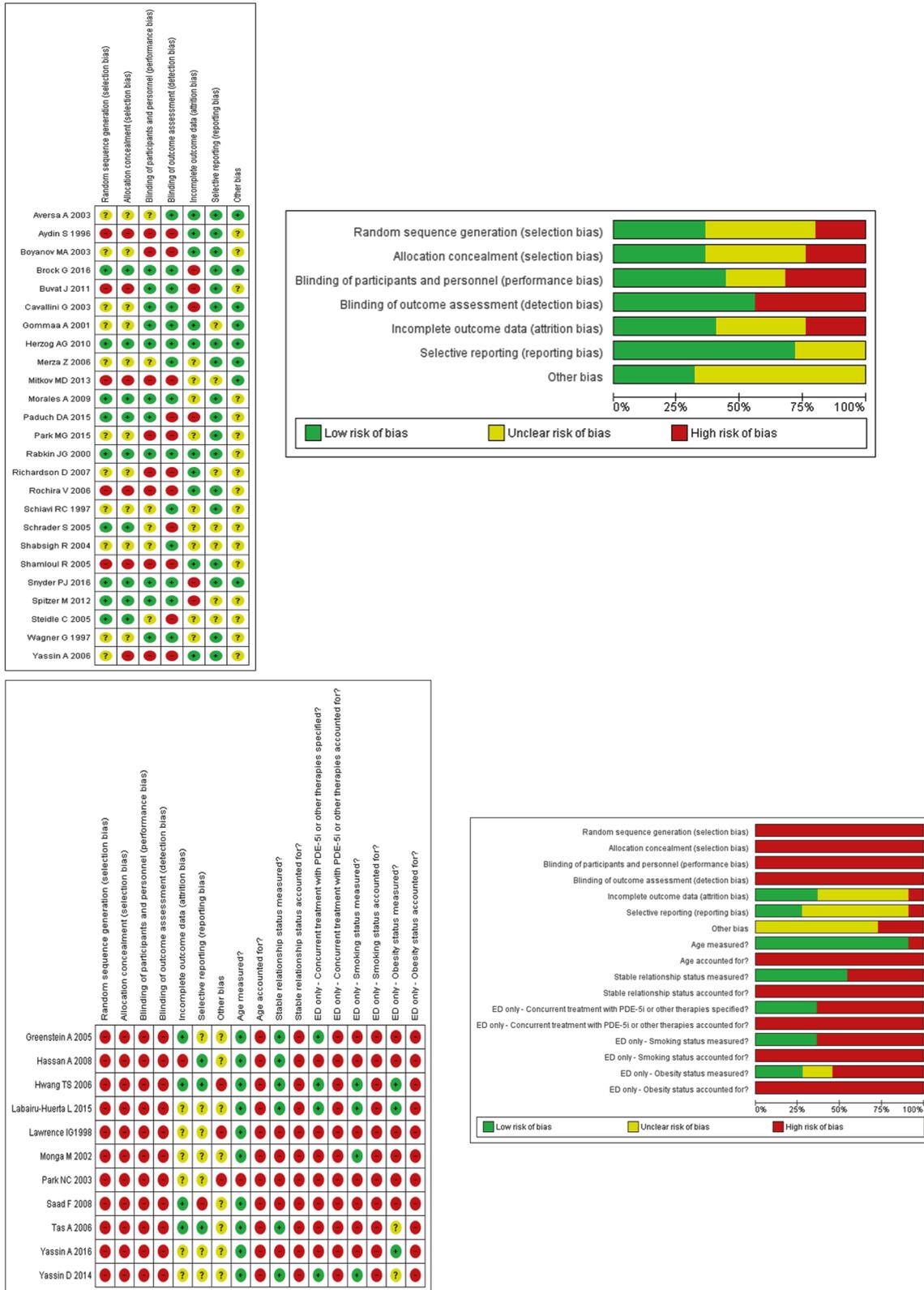


Fig. 2 Risk of bias assessment of randomized clinical trials and non-randomized comparative studies

dysfunction-related quality of life [28] vs. the use of non-T treatment. However, a number of authors reported no TTh effect on erectile function parameters [17, 32, 34, 41], while Cavallini et al. showed worse erectile function parameters in the group of TTh vs. the group that used carnitines [23].

Mixed effects of TTh on orgasmic parameters were revealed, as TTh was shown to improve the ejaculatory function vs. non-T treatment in one study [17], and two other studies [36, 38] showed TTh-related improvement in overall orgasmic function. However, other reports showed no significant improvement in orgasmic or ejaculatory parameters from TTh compared to non-T treatment [34, 39], while in the study of Cavallini et al. the group of TTh had worse orgasmic parameters compared to the group of patients who used carnitines [23].

With regard to sexual satisfaction, analysis of study results once again revealed conflicting findings as TTh led to improvement in satisfaction with sexual intercourse or overall sexual life in three studies vs. non-T treatment [21, 36, 38]. In contrast, three other trials showed no significant improvement from T use in sexual satisfaction vs. the comparator [17, 34, 39], while the carnitines group in Cavallini's study had better sexual satisfaction scores compared to the TTh group [23].

One study revealed an overall improvement in IIEF scores in the group of patients who used a combination of PDE5i and TTh compared to the baseline, but no between-group comparisons were performed [26]. Two other studies did not find any significant improvement in overall sexual function in the TTh groups vs. the comparator ones [32, 34]. No TTh effect on masturbation frequency was shown in the study of Schiavi et al. [17] and no difference in the number of sexual acts between the TTh and non-TTh groups was revealed in the study of Richardson et al. [31]. However, the study of Snyder et al. in hypogonadal men showed significantly higher number of sexual activities in the TTh group compared to the placebo one [40].

Data from RCTs on T vs. other T treatment A study in a group of HIV+patients who used T gel showed significantly higher improvement in sexual desire compared to the group of patients who used another form of T gel [25]. Another trial showed higher improvement in sexual desire in the group of patients who were offered a combination of T cypionate and anastrozole vs. the group that was offered a combination of T cypionate and placebo, however statistical significance was not reported [33]. In the same study, changes in parameters between study groups had no significant difference [33]. No other studies showed significant difference in sexual desire between groups using different T combinations.

Combination treatment of transdermal T, codergocrine mesylate and isosorbite dinitrate led to significantly better parameters in erectile function with satisfactory intercourse

per month compared to T monotherapy [20]. While in the same group of patients, the response in erectile function was better compared to monotherapy, statistical significance was not reported [20]. Two studies conducted in hypogonadal patients with and without HIV infection reported higher degree of improvement in erectile function in the groups of patients who used a specific brand of T gel [25, 27]. While T combination treatment led to higher improvement in erectile function compared to the T monotherapy group, changes in erectile function were not significantly different between study groups [33]. Erectile function was also shown to be better in a study with a group of patients who used a combination of T with tadalafil 5 mg once-a-day vs. the group of T plus tadalafil 10 or 20 mg on demand [37]. No other significant differences were revealed in other studies.

There were no studies that revealed between-group significant results for orgasmic parameters. Two studies showed that hypogonadal patients who used T gel had significantly higher levels of sexual satisfaction in comparison to the patients who used another form of T gel [25, 27]. The combination of T cypionate and anastrozole was shown to lead to higher sexual satisfaction compared to the group of patients who used a combination of T cypionate and placebo, however statistical significance was not reported [33]. No other significant differences in sexual satisfaction were shown in the remaining studies.

Various combinations of T led to significant improvements in overall sexual function compared to other T combinations. Combined T treatment led to significantly higher response in overall function vs. T monotherapy [20]. Significantly better results in overall sexual function were also reported in a group of patients who used T and tadalafil 5 mg daily compared to patients who used T and on demand tadalafil 10 or 20 mg [37]. Finally, another trial showed that the combination of T with PDE5i led to significantly better results in overall sexual function compared to baseline, however, no between-group comparisons were made [26].

Data from NRCs on T vs. non-T treatment In general, unclear results were presented by the NRCs comparing TTh vs. non-T treatments. Mixed effects on sexual function were reported by three studies, however authors did not report the level of statistical significance [42, 44, 47]. Two studies showed different degrees of TTh effect on male sexual complaints, but comparisons between the TTh and non-T groups were not performed [46, 51]. Hassan et al. used different types of T and non-T treatments in a population of patients and reported mixed results on the effect of T on male sexual symptoms [48].

Data from NRCs on T vs. other T treatment Different degrees of response in overall and erectile function and

sexual satisfaction with the use of intra-muscular T cypionate and scrotal and non-scrotal Testoderm patches were shown by one study [43]. Three studies used different T treatments and reported mixed effects on male sexual function, however no comparisons between groups were made [45, 51, 52], while another study compared the use of undecanoate T vs. transdermal T and showed higher IIEF scores in the first group, without reporting significance [49]. With respect to the second study of Yassin et al., due to the study design and results presentation, clear outcomes and conclusions cannot be drawn [50].

Adverse events

Data from RCTs on T vs. non-T treatment Various degrees of adverse events were presented by several authors however due to differences among studies general conclusions cannot be drawn. While two studies showed higher rate of elevated haematocrit in the T group vs. the non-T groups [35, 38], the remaining studies either revealed no significant differences between the intervention and comparator groups in various adverse events such as haematocrit elevation, prostate cancer development, skin reactions and others [28, 29, 32, 34, 36] or did not report significance for comparisons [39]. In the study of Snyder et al., while some degree of haemoglobin and PSA elevation was found in the TTh group, the numbers of adverse events referred to the overall study population and no separate report of events that took place in the Sexual Function trial subgroup was available [40].

Data from RCTs on T vs. other T treatment Two studies showed no difference in adverse events between study groups [30, 33]. While in the study of Park et al. the rate of adverse events was higher in the intervention group than the comparator one, authors did not report whether difference was statistically significant [37].

Data from NRCSs on T vs. non-T treatment Various numbers of adverse events were reported in the study of Lawrence et al. for both study groups, but no between-group comparisons were made [42]. With respect to adverse events, in the study of Tas et al. both groups had significant elevations in haematocrit at the end of treatment compared to baseline, but no between-group comparisons were performed [47]. In the study of Park et al., urticaria and acne were reported by the authors in the T group, but adverse events in the placebo group were not reported [44]. Various types and numbers of adverse events were reported in the study of Hassan et al. [48].

Data from NRCSs on T vs. other T treatment In the study of Monga et al., a higher number of complications having to

do with skin reaction was reported in both skin patches groups compared to the T cypionate group, however statistical significance was not reported [43]. No reports on statistical significance were provided for adverse events that included prostate cancer development, major cardiovascular events and elevated haematocrit in the study of Saad et al. [49].

Study results according to T levels

Studies on patients with normal T levels Two RCTs were conducted in men with normal T levels [17, 41]. The use of T led to significant improvement in ejaculation in one of these studies [17], while no other effect on sexual function was revealed.

Studies on patients with low-normal T levels Three RCTs were conducted in 110 patients with low-normal T levels [20–22]. The two RCTs that compared T vs. placebo showed significant improvements in sexual desire and erectile function ([21, 22] while one of them additionally showed significant improvement in sexual satisfaction [21]. Gomaa et al. compared the combination use of T and vasoactive agents vs. monotherapy with T in borderline eugonadal men. The combination treatment led to significant improvement in overall sexual function and higher number of satisfactory intercourses with full erection per month compared to T monotherapy [20].

Studies on patients with low T levels Overall, 17 RCTs and 8 NRCSs studied the effects of T on male sexual function in men with low T levels, although the diverse definitions of hypogonadism were used across all studies [18, 19, 23–28, 30, 32–35, 37–40, 43–47, 49, 50, 52]. The overall number of patients with hypogonadism was 3032 participants (62.3% of all the patients recruited in the studies discussed in this systematic review), while two of the studies conducted in men with hypogonadism [38, 40], represented the largest RCTs of this review (1174 men, 38.7% of all hypogonadal men and 24.1% of all patients discussed in the present review). Erectile function [19, 24, 25, 27, 37, 38, 40, 43], sexual desire [19, 25, 38, 40] and sexual satisfaction [23, 25, 27, 38, 43] were the main domains of male sexual function improved by T use, while the effect of TTh on orgasmic parameters was unclear [23–25, 27]. The study of Snyder et al. also showed higher number of sexual acts in the group of TTh patients [40].

Studies on patients with mixed or unclear T levels Three RCTs and three NRCSs studied the effect of TTh on mixed groups of eugonadal and hypogonadal patients or on men with unclear eugonadal/hypogonadal status [29, 31, 36, 42, 48, 51].

The overall number of patients included in these studies was 1713 men (35.2% of all patients discussed in the present systematic review). Various results of unclear significance were reported in these studies.

Discussion

Principal findings

The present systematic review screened a total of 36 studies that included nearly 5000 participants with normal, low-normal and low T levels suffering from various degrees and types of MSD. Mixed results on the effects of TTh on male sexual function were found, mainly because of the significant discrepancies across studies with regards to design, definitions and tools used to define and evaluate MSD respectively, type, setting and duration of T and non-T treatment, comparators that were used and pre-set study outcomes of interest.

In terms of quality of evidence, a mixed pattern was again observed depending on the study type. The 25 RCTs [17–41] included in the present systematic review had in general low or unclear RoB based on the relevant assessment performed, while the additional 11 NRCSs [42–52] all had high RoB and thus, the overall quality of evidence was judged to be at least unclear.

Based on data mainly provided by RCTs that compared TTh to placebo or other non-T treatments, the overall impression is that MSD patients could experience some degree of benefit from T use at least in sexual desire, erectile function and sexual satisfaction [19–22, 24, 25, 27, 37, 38, 40]. Although both men with low and low-normal T levels were shown to experience improvement in their sexual parameters, it has to be noted that the number of men with borderline eugonadal status was low (110 patients vs. 3032 men included in trials on hypogonadal patients) and the two largest good-quality RCTs [38, 40] were conducted in hypogonadal men with sexual complaints. Therefore, it is more likely that the current systematic review conclusions apply more to men with low T levels. The effect of TTh on the sexual function of men with normal T levels remains unclear as only two studies in a limited number of MSD patients provided results [17, 41].

Unfortunately, due to the significant differences across studies no additional recommendations could be provided on T formulation, duration of treatment or specific type of population of interest that could get the maximum benefit from T administration. It should also be mentioned that there is a number of studies that presented various degrees of TTh effect on male sexual symptoms without reporting statistical significance or performing between-group comparisons.

The effect of T treatment on orgasm and ejaculation remains unclear as few studies examined this sexual domain and in general presented conflicting results. However, it has to be noted that the largest of these trials showed beneficial effect from T use on orgasmic parameters [38].

Similarly to the sexual parameters, no systematic, consistent and transparent report of adverse events was provided by the vast majority of studies. A small number of trials provided scarce evidence on treatment-associated adverse events that mainly comprised various degrees of haematocrit elevation. No detailed reporting of pre-specified clinically significant adverse events such as prostatic and cardiovascular safety was available. Thus, clear recommendations and warnings about TTh-associated adverse events cannot be provided.

Implications for clinical practice

In a practical setting, since various types and degrees of male sexual disorders can represent clinical manifestations of hypogonadism, its correction with the use of TTh could in theory improve the affected sexual parameters. Unfortunately, due to the unsatisfactory overall quality of evidence of the studies included in the present review, high grade clinical recommendations regarding TTh for MSD in men with low, marginally low or normal testosterone levels cannot be provided.

However, based on the evidence provided mainly by the RCTs included in this SR, TTh could be considered for men with low or low-normal T levels and problems with their sexual desire, erectile function and satisfaction derived from intercourse and sexual life in general [19–22, 24, 25, 27, 37, 38, 40]. The exact testosterone formulation, dosage and mainly duration of treatment remain to be clarified, as due to significant study heterogeneity clear conclusions could not be drawn. Moreover, it should be highlighted that several studies included in this SR did not clearly report whether their cohort of patients suffered from organic (primary or secondary) or functional hypogonadism or whether they enrolled mixed populations of patients and therefore, the overall external validity of the findings could be further limited due to this.

Available literature seems to support the present SR finding that TTh could benefit men with sexual dysfunction. The current recommendations for the diagnosis and treatment of testosterone deficiency from the Fourth International Consultation for Sexual Medicine, encourage TTh for symptomatic men with T levels <12 nmol/l, while for symptomatic men with T levels >12 nmol/l, TTh could be considered based on the clinical presentation [11]. A recent meta-analysis by Corona et al. of RCTs that compared T vs. placebo to treat MSD and used IIEF questionnaire to assess male sexual parameters showed significant improvement in

various aspects of sexual function [53]. In specific, authors stated that TTh could benefit more the patients with more severe forms of T deficiency at baseline and the hypogonadal patients with mild forms of erectile dysfunction, while for more severe cases additional treatments should be required.

A previous meta-analysis by the same study group showed beneficial effects of T use on male sexual function of hypogonadal patients [54]. Isidori et al. published a meta-analysis on T treatment for MSD and again found some degree of evidence to support the use of T for MSD [55]. Another meta-analysis by Jain et al. also concluded that TRT could be used in selected groups of patients with erectile dysfunction [56]. In 2007, Bolona et al., in their systematic review and meta-analysis concluded that T use could lead to improvement in erectile function and libido but similarly to the present review findings, a significant inconsistency in results across trials was found [57]. Cunningham et al. reported in detail the findings of the Sexual function Trial following the initial demonstration of TTh effect on the sexual function of older men by Snyder et al. [40, 58]. TTh was shown to consistently improve most types of sexual activity, sexual desire and erectile function in older men with low T levels and low libido. However, this study was not included in the summary of findings table as it fell outside the search window. Moreover, a post-hoc analysis of the Brock et al. study by Wu et al. revealed that higher levels of end-point testosterone were associated with higher rates of improvement in sexual drive but not in erectile function, especially in men with classic (primary or secondary) over non-classic (functional) hypogonadism [59]. In contrast with these findings, two other meta-analyses did not reveal any benefit on male sexual parameters from testosterone use [60, 61].

In terms of treatment-related complications such as prostate cancer or cardiovascular events, due to the limited amount of available data and the lack of systematic reporting of adverse events from the studies included in the present systematic review, the safety profile of TTh remains unclear. Based on the limited information provided by a small number of studies included in the current systematic review, TTh seems to be related to various degrees of haematocrit elevation while its effect on PSA required further clarification, although no cases of prostate cancer were reported. Nevertheless, no clear conclusions could be reached on whether prostatic and cardiovascular safety could be compromised by TTh use. Moreover, it should be highlighted that the external validity of these findings remains limited, as trials had strict inclusion and exclusion criteria for eligible participants.

Therefore, clinicians should carefully select patients who could benefit from TTh based on their previous medical history and must keep a high level of awareness for

potential TTh-related side effects and discontinue its use in case of any safety concerns. Nevertheless, and given the fact that a possible causative relationship between TTh and prostate cancer seems to represent a major concern that prevents a significant proportion of clinical urologists from prescribing TTh to hypogonadal men with testosterone-deficiency-related symptoms [62], it needs to be highlighted that current recommendations report that there is no compelling evidence that TTh can cause prostate cancer or prostate cancer progression [11].

Implications for further research

The obvious lack of good-quality studies investigating the role of TTh in the management of MSD makes the need for an optimized approach in terms of clinical trial design more evident than ever. Standardized definitions that follow the current recommendations should be used to define male sexual disorders and hypogonadism, such as those provided by the International Society for Sexual Medicine (ISSM) and Endocrine Society, respectively [1, 9–11]. Commonly endorsed tools could be used to provide an objective assessment of the male sexual complaints and symptoms of hypogonadism and facilitate the estimation of their response to TTh.

Several validated questionnaires are available nowadays such as the International Index for Erectile Function (IIEF) [63], the Derogatis Sexual Function Inventory (DSFI) [64] and the Brief Male Sexual function Inventory (BSFI) [65] for the assessment of male sexual function, and the Androgen Deficiency in Aging Males (ADAM) [66], the Aging Males' Symptoms Rating Scale (AMS) [67], and the Massachusetts Male Aging Study Questionnaire (MMAS) [68] for the assessment of androgen deficiency symptoms.

Limitations and strengths

Overall, the quality of the evidence obtained from this review was low-to-moderate, mainly because of the few well-designed prospective studies with low RoB. Heterogeneity in study designs, populations, interventions, assessment tools and types of reported outcome measures made meta-analysis inappropriate. Based on that, we could not draw any definitive conclusions on the benefits or harms of T use for MSD, however the general trend observed was that TTh could be used to manage desire, erectile and sexual satisfaction disorders in hypogonadal and most probably borderline eugonadal men.

However, and despite the abovementioned limitations, this review fully presents and discusses the available evidence on TTh use for MSD. Broad inclusion criteria and different definitions of hypogonadal/eugonadal status were used, deviating from the current T threshold of 12 nM for

symptomatic patients. Moreover, this systematic review included both RCTs and NRCs that compared various therapeutic approaches (such as different types of TTh and several combinations of T and non-T treatments) in an attempt to offer the reader a thorough view of the literature. A significant heterogeneity in methods was highlighted which confirms the need for standardized disease definitions, inclusion and exclusion criteria and a core outcome set for future trials. The review was undertaken by a multidisciplinary panel of clinical and methodological experts (EAU 2017 Male Hypogonadism and Male Sexual Dysfunction Guideline Panels) according to PRISMA guidelines.

Conclusion

The current systematic review focused on the benefits and harms of T treatment for MSD in either eugonadal or hypogonadal male patients. Due to the overall unsatisfactory quality of studies, no clear conclusions could be drawn on TTh efficacy and safety and thus, specific recommendations for clinical practice cannot be given.

However, based on the data provided mainly by the RCTs included in this SR, it seems that TTh could indeed benefit hypogonadal and most probably borderline eugonadal men with sexual desire disorders, erectile dysfunction and impaired sexual satisfaction. These findings need to be approached cautiously, mainly due to the limitations having to do with the methodological inconsistency across studies. The need for robust and adequately designed clinical trials on T use for MSD is highlighted for future research, so that definitive results could be reached.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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