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The Effect of Testosterone Replacement on Sexual Function in the Elderly: A Systematic Review and Meta-Analysis

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Purpose: Healthy aging is an important concern in an aging society. Although the causal relationship between hypogonadism and erectile dysfunction in elderly men remains unclear, many physicians have achieved positive results after implementing exogenous testosterone supplementation therapy in patients with normal or slightly low blood testosterone. The purpose of this study was to conduct a systematic review and meta-analysis on whether testosterone replacement therapy (TRT) could improve sexual function in the elderly, as reported recently.

Materials and Methods: As a comprehensive literature search was performed to find articles published in PubMed, Embase, and Cochrane databases by January 2022. The search used keywords of 'aged', 'male', 'sexual behavior', and 'testosterone'. Randomized controlled trials (RCTs) were finally selected. As the main effect variable, results of a questionnaire on sexual function were analyzed and the effects of TRT were compared to those of placebo control.

Results: Five RCT studies were included in this meta-analysis. The overall improvement by mean difference of sexual function for testosterone supplementation was 0.082 (95% CI: -0.049 to 0.213). In subgroup analysis, only intramuscular injection of 1,000 mg testosterone significantly improved sexual function of the elderly (0.229, 95% CI: 0.112 to 0.347). There was no significant difference in sexual function according to testosterone dose in meta-ANOVA (p=0.957). The difference was not statistically significant either in the meta-regression test (p=0.310). Egger's regression coefficient test did not indicate a publication bias (p=0.132).

Conclusions: Although our overall effect size (that is, sexual function effect of TRT) did not show a significant improvement, the direction of improvement in erection and motivation was clearly shown. The injection formulation resulted in a significant sexual function improvement. Since only a few RCTs were included in the analysis, more well-designed prospective studies are needed to have a definite conclusion.

Keywords: Aged; Meta-analysis; Sexual health; Testosterone

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INTRODUCTION

Penile erection is a complex physiological phenomenon. Erectile dysfunction can be caused by several factors. Men over 40 years of age with erectile dysfunction have been found to have normal or low androgen levels in addition to organic or psychogenic causes [1,2]. Sexual function declines with age. This even occurs in healthy men. It has been reported that about 50% of men over the age of 40 have difficulties in sexual intercourse [3]. Although a causal relationship between hypogonadism and erectile dysfunction has not been established [4], it is true that testosterone levels in adult males gradually decrease after age 40 [5]. Although there is still no convincing evidence that testosterone supplementation improves erectile function, the National Institutes of Health (NIH) has suggested that testosterone replacement therapy (TRT) might improve erectile function in some patients with hypogonadism [6].

Because serum testosterone decreases with age, older men have lower testosterone levels than do younger [7,8]. A decrease in testosterone is also associated with a decrease in muscle mass and bone density and an increase in body fat mass, and the effect of testosterone decrease in the elderly is similar to that observed in young men with hypogonadism. Therefore, interest in testosterone replacement in the elderly with low testosterone levels has increased dramatically.

Many physicians have obtained positive results after treating patients with normal or lower-normal testosterone levels using testosterone replacement [4,9]. However, previous studies included a wide range of subjects and sometimes showed contradictory results. Therefore, we conducted a systematic review and meta-analysis on whether TRT could improve sexual function in the elderly as reported recently.

MATERIALS AND METHODS

This systematic review and meta-analysis was registered at PROSPERO (CRD346342). Methods of this study followed the preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [10].

1. Data sources and literature searches

A comprehensive literature search was conducted using Medical Subject Headings (MeSH) terms and text keywords to find articles published in PubMed, Embase, and Cochrane databases by January 2022. Subject headings and text keywords included those related to the population of interest (*i.e.*, elderly men), intervention (testosterone-replacement therapy, TRT), comparison (placebo), and outcomes of individual sexual function (*e.g.*, erection, motivation, desire, and performance) using sexual function measurement questionnaires (*e.g.*, aging males symptoms (AMS) scale, psychosexual daily questionnaire (PDQ), and international index of erectile function [IIEF]). Search terms were classified using Boolean operators (*i.e.*, AND, OR, or NOT). In order to prevent omission in a literature search, we selected TRT as an intervention directly after collecting literature without restrictions on literature-search strategies. We included only randomized controlled trials (RCTs) in this meta-analysis. This search was conducted without restrictions for language. Two independent investigators (HJ Yang and JH Kim) discovered additional studies by manually searching clinical trial databases and reference lists.

2. Study selection

Study inclusion criteria were as follows: (1) interventions included administration of TRT in the elderly men, (2) comparisons with a placebo were specified, and (3) outcomes were mean differences (MDs, the difference between TRT and placebo) for individual sexual function (*e.g.*, erection, motivation, desire, and performance) and sexual function measurement questionnaires (*e.g.*, AMS, PDQ, and IIEF) using an RCT study design. Two investigators (SR Shim and JH Kim) independently analyzed titles and abstracts looked at full-text articles, and then independently extracted data using a data-extraction form. Articles that were finally included in this study were chosen based on inclusion and exclusion criteria followed by an evaluation discussion among all investigators. References and data for each included study were carefully cross-checked to ensure no overlapping data and to maintain integrity of the meta-analysis.

3. Meta-analysis assessment of outcome findings and statistical analysis

All variables were provided in continuous data. In studies that did not report standard deviation, we applied an estimate of pooled standard deviation of two groups. In studies that reported only a median, we esti-

mated the mean and variance from the median, range, and sample size [11]. We calculated the standard mean difference (SMD) and 95% confidence intervals (CIs) for continuous variables. To obtain pooled overall MD and 95% CIs for outcomes, we used a random-effects model published by DerSimonian and Laird [12]. Each moderator was subjected to a meta-regression analysis for continuous variables (*e.g.*, number of patients and testosterone dose) or a meta-ANOVA for categorical variables (*e.g.*, TRT formulation type, study duration group, and age group). To identify potential moderators, we estimated the variance of true effects using a restricted maximum likelihood (REML) estimator.

A two-sided p-value <0.05 that did not contain a null value (MD=0) within the 95% was considered to be significant. All analyses were conducted using R software 4.1.3 (R Foundation for Statistical Computing).

4. Quality assessment

We evaluated the risk of bias and methodological quality in duplicate using Version 2 of the Cochrane risk-of-bias tool for randomized trials. The following six parameters were assessed: (1) randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of outcome, (5) selection of reported result, and (6) overall. Each parameter was graded as having a low risk of bias, some concerns, or a high risk of bias. The quality of evidence related to estimation of benefits and disadvantages was assessed following suggestions of the GRADE Working Group.

5. Assessment of heterogeneity

Statistical heterogeneity was evaluated using Cochran's Q test and I^2 statistic. Either a Cochran's Q statistic of $p<0.1$ or an I^2 statistic >50% indicated the existence of significant heterogeneity between studies. A non-significant chi-squared test result ($p\geq0.1$) or I^2 statistic ≤50% indicated a lack of evidence for heterogeneity. However, it did not necessarily imply homogeneity because there might have been too little statistical power to detect heterogeneity. Thus, we used a random-effects model of analysis.

6. Assessment of potential publication bias

Funnel plot was prepared for explaining publication bias using standard error as the measure of study size and SMD measures of treatment effect. In the absence of publication bias, studies were distributed symmetrically using combined effect size. Publication biases were also assessed using an Egger linear regression [13].

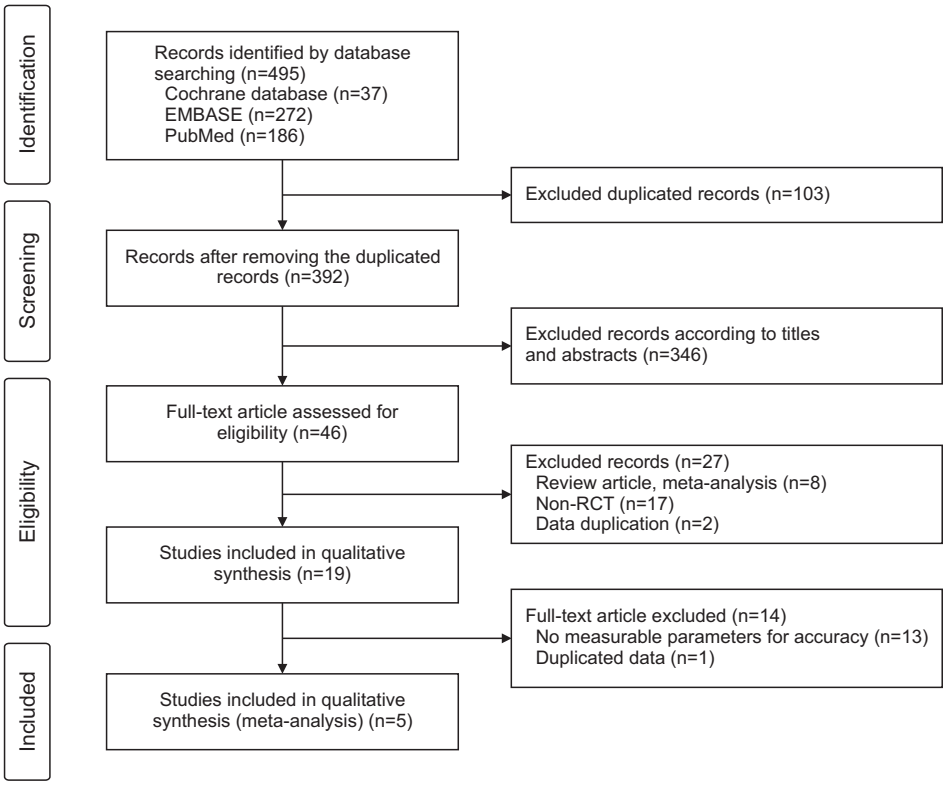

Fig. 1. Flow chart showing study inclusion. RCT: randomized controlled trial.

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RESULTS

1. Study selection

The initial search identified 495 articles from different electronic databases (PubMed, n=186; Cochrane, n=37; Embase, n=272). Of these, 103 that contained overlapping data or appeared in more than one database were excluded. After screening titles and abstracts, 346 studies that were trial registrations or abstracts only were eliminated. Among 46 full-text articles, 27 were further excluded for the following reasons: duplicate records (n=2), review article and meta-analysis (n=8), and non-RCT (n=17). Finally, 19 studies [14-32] met our selection criteria for qualitative analysis and 5 studies [18,22,24,25,29] met our selection criteria for quantitative synthesis (Fig. 1).

A systematic review and meta-analysis was conducted using five studies covering 2,056 patients. Detailed differences and subject descriptions are shown in Table 1. All studies were randomized controlled placebo trials conducted in Western countries except for Brill et al and Chiang et al [14,22]. The range of mean age was 56.8 to 72.1 years. Study duration ranged from 3 months to 42 months. TRT formulations were testosterone patch, gel, intramuscular (IM), and oral medication (p.o.) and testosterone dosage was 50 mg to 1,000 mg.

2. Outcome findings

For outcome measurements, several different outcome measurements were used for sexual function, including IIEF [22,25,27-30,32], AMS [24], and self-scale [14-16,19,20,23,26,31]. Pooled SMD for overall sexual function assessment between TRT *versus* placebo groups was 0.081 (95% CI: -0.048 to 0.208). The heterogeneity test produced p<0.001. Higgins' I^2 was 85.1%. In subgroup analysis by outcome measures, SMD change compared to the placebo group was 0.341 (95% CI: 0.150 to 0.533) for erection, 0.239 (95% CI: 0.063 to 0.414) for motivation, -0.669 (95% CI: -1.435 to 0.096) for desire, 0.169 (95% CI: 0.009 to 0.328) for performance, 0.237 (95% CI: 0.141 to 0.332) for IIEF, and 0.085 (95% CI: -0.001 to 0.171) in AMS (Fig. 2). Changes of erection, motivation, performance, and IIEF were statistically significant.

To evaluate whether treatment formulation types improved sexual functions, we also conducted subgroup0 0analysis. There were several different formulations, including patch [15], gel [16,18,19,26-29,31], IM

Table 1. Characteristics of selected studies for qualitative synthesis

Reference	Year	West/ Asia	Design	Intervention group	Inclusion criteria Indication disease	Cut-off for androgen deficiency	Use testosterone formula (dosage)	Study duration	Placebo	Outcome (sexual function)
Gomaa et al [14]	2001	Asia	RCT	Polypharmacy *vs.* T	Decreased libido, T: near the normal range	200–350 ng/dL	T 1 mg/d	1 mo	No	Subject scaling (penile response)
Brill et al [15]	2002	West	RCT	T *vs.* growth hormone	Healthy older	200–450 ng/dL	Androderm, 2.5 mg patch ×2 (5 mg/d)	3 mo	No	Frequency of intercourse
McNicholas et al [16]	2003	West	RCT	T gel 50 mg/d (n=68) T gel 100 mg/d (n=72) T patch (n=68)	LOH symptom	≤10.4 nmol/L	Testim gel (50 mg, 100 mg/d, delivering 5–10 mg), patch (5 mg)	3 mo	No	Self-scaling (spontaneous erection, mean/ week)
Tan and Pu [17]	2003	West	RCT	T *vs.* placebo	Alzheimer's disease	<250 ng/dL	T enanthate (IM) 200 mg, q 2 weeks	12 mo	Yes	
Steidle et al [18]	2003	West	RCT	T gel 50 mg (n=99) T gel 100 mg (n=106) T patch (n=102)	≤10.4 nmol/L, LOH symptoms	<250 ng/dL	Testim gel (50 mg/d, 100 mg/d) Androderm patch (5 mg/d)	3 mo	Yes	
Wang et al [19]	2004	West	RCT	T gel 5 g (n=62) T gel 7.5 g (n=22) T gel 10 mg (n=39)	≤10.4 nmol/L, LOH symptoms	≤10.4 nmol/L, LOH symptoms	Androgel (5 g/d, 7.5 g/d, 10 g/d)	42 mo	No	Self-questionnaire

Table 1. Continued 1

Reference	Year	West/ Asia	Design	Intervention group	Inclusion criteria Indication disease	Cut-off for androgen deficiency	Use testosterone formula (dosage)	Study duration	Placebo	Outcome (sexual function)
Gray et al [20]	2005	West	RCT	T IM 20 mg/wk (n=13) 50 mg/wk (n=12) 125 mg/wk (n=12) 300 mg/wk (n=13) 600 mg/wk (n=10)	Under GnRH agonist therapy	Normal T	T enathate (IM) 20, 50, 125, 300, 600 mg, weekly	20 wk	No	Self-questionnaire
Bhasin et al [21]	2005	West	RCT	T IM 20 mg/wk (n=13) 50 mg/wk (n=12) 125 mg/wk (n=12) 300 mg/wk (n=13) 600 mg/wk (n=10)	Under GnRH agonist therapy	Normal T	T enathate (IM) 20, 50, 125 ,300, 600 mg, weekly	20 wk	No	No available data
Chiang et al [22]	2007	Asia	RCT	T gel (n=20) *vs.* placebo (n=20)	Hypogonadal men	<300 ng/dL (or fT <8.7 pg/mL)	1% T alcoholic gel (50 mg/day)	3 mo	Yes	IIEF
Emmelot-Vonk et al [23]	2009	West	RCT	T undecanoate (n=113) *vs.* placebo (n=110)	Hypogonadal men	≤13.7 nmol/L, LOH symptom	T undecanoate (andriol) 40 mg×2	26 wk	Yes	ESF questionnaire (Q1)
Legros et al [24]	2009	West	RCT	T undecanoate 80 mg/d (n=78), 160 mg/d (n=82), 240 mg/d (n=77) *vs.* placebo (n=79)	Hypogonadism	<0.26 nmol/L, LOH symptom	T undecanoate (andriol), 80 mg/d, 160 mg/d, 240 mg/d	12 mo	Yes	AMS scale, total
Hackett et al [25]	2013	West	RCT	T undeconate (n=92) *vs.* placebo (n=98)	T 8.1–12 nmol/L T2DM	≤12 nmol/L (or fT <250 pmol/L)	T undecanoate (Nebido) 1,000 mg	30 wk	Yes	IIEF-erectile function
Sartorius et al [26]	2014	West	RCT	DHT gel (n=37) *vs.* placebo (n=44)	Age >50 y, Healthy volunteers without prostate cancer		DHT (andractim) gel, 70 mg	24 mo	Yes	Brief Male Sexual Inventory
Basaria et al [27]	2015	West	RCT	T gel 1% (n=155) *vs.* placebo (n=151)	Age >60 y, fT <50 pg/mL, total T: 100–400 ng/dL	100–400 ng/dL	T gel 1% (75 mg/d)	36 mo	Yes	IIEF
Cunningham et al [28]	2016	West	RCT	AndroGel 1% (n=234) *vs.* placebo (n=236)	Age ≥65 y with low libido, average T <275 ng/d	Average T <275 ng/dL	AndgoGel 1%, 5 g/day	12 mo	Yes	IIEF- erectile function

Table 1. Continued 2

Reference	Year	West/ Asia	Design	Intervention group	Inclusion criteria Indication disease	Cut-off for androgen deficiency	Use testosterone formula (dosage)	Study duration	Placebo	Outcome (sexual function)
Snyder et al [29]	2016	West	RCT	AndroGel 1% (n=395) *vs.* placebo (n=395)	Age ≥65 y, T <275 ng/dL, LOH symptom	T <275 ng/dL	AndroGel 1% 5g/day	12 mo	Yes	IIEF- erectile function
Hackett et al [30]	2016	West	RCT	T undeconoate (n=107) *vs.* placebo (n=82)	Age: 18–80 y, T2DM	T 8.1–12 nmol/L (or fT 0.18–0.25 nmol/L)	T undecanoate (Nebido) 1,000 mg	30 wk	Yes	IIEF
Stephens-Shields et al [31]	2019	West	RCT		T-Trial participants		T gel, 5 g/d	12 mo	No	PDQ
Narukawa et al [32]	2021	Asia	Cross over study	T only (n=14) *vs.* T+PDE5i (n=12)	LOH symptom	T ≤3 ng/mL (or fT ≤11.8 pg/mL)	T enanthate 250 mg q 3 wk, tadalafil 10 mg QOD	12 wk	No	IIEF-5

AMS: aging males symptoms, DHT: dihydrotestosterone, ESF: eleven questions about sexual functioning, fT: free testosterone, GnRH: gonadotropin-releasing hormone, IIEF: international index of erectile function, IM: intramuscular, LOH: late onset hypogonadism, PDQ: psychosexual daily questionnaire, PDE5i: phosphodiesterase type 5 inhibitor, T: testosterone, T2DM: type 2 diabetes mellitus, RCT: randomized controlled trial.

[17,20,21,25,30,32], and PO [14,23,24]. SMD change compared to the placebo group was 0.072 (95% CI: -0.203 to 0.346) for gel, -0.095 (95% CI: -0.787 to 0.598) for patch, 0.074 (95% CI: -0.016 to 0.164) for p.o., and 0.229 (95% CI: 0.112 to 0.347) for IM injection (Fig. 3). SMD changes were not statistically significant except for IM injection.

1) Moderator analyses

We also considered potential moderating roles of the following variables using meta-regression and meta-ANOVA models: number of patients, testosterone dose, TRT formulation type, study duration group, and age group (Table 2). We did not find any moderating effects of these factors on main treatment effects.

2) Quality assessment

All studies described randomized methods and reasonable intention-to-treat analysis. Most of them were randomized in allocation sequence, which was concealed until participants were enrolled and assigned to interventions. There were three studies [20,31,32] in which blinding methods were conducted as single blind. One study was an open-label study using a different formulation [19]. In one study [20], drop-out occurred as a side effect of the drug in the intervention group. Deviation from the intended intervention bias showed a generally low risk. In one study [31], there was no mention of missing data. There could have been bias because of the missing outcome date. In terms of the risk of bias in measurement of the outcome, one paper was a cross-over study on combined administration of testosterone and tadalafil. It did not describe a placebo placebo. Results might have been affected if tadalafil was administered [32]. In three studies [14,16,17], results of sexual function were briefly described without showing results. Studies with possible bias were excluded from meta-analysis. A summary of methodological domain assessment for each subject is detailed in Table 1. Overall, the risk of bias was considered to be low (Supplement Fig. 1).

3. Publication bias

We prepared funnel plots of all results to detect publication bias. They were distributed asymmetrically. Thus, we performed an additional analysis of Egger linear regression test for publication biases. However, we found no evidence of publication bias in this meta-

Study or subgroup	Measures	Testosterone. dose	Testosterone (n)	Testosterone. mean	Testosterone. SD	Placebo (n)	Placebo. Mean	Placebo. SD	SMD	95% CI
Outcome.g=erection										
Steidle et al [18]	Self.scaling.erection	50 mg	99	0.200	1.500	99	0.000	1.000	0.156	[−0.123; 0.435]
Steidle et al [18]	Self.scaling.erection	100 mg	106	0.600	1.400	99	0.000	1.000	0.489	[0.211; 0.767]
Steidle et al [18]	Self.scaling.erection	T Patch	102	0.400	1.100	99	0.000	1.000	0.379	[0.100; 0.658]
Total (95% CI)									0.341	[0.150; 0.533]
Heterogeneity: Tau^2=0.0085; Chi^2=2.84, df=2 (p=0.24); I^2=30%										
Outcome.g=motivation										
Steidle et al [18]	Self.scaling.motivation	50 mg	99	0.200	1.500	99	0.100	1.200	0.073	[−0.205; 0.352]
Steidle et al [18]	Self.scaling.motivation	100 mg	106	0.600	1.400	99	0.100	1.200	0.381	[0.105; 0.658]
Steidle et al [18]	Self.scaling.motivation	T Patch	102	0.400	1.100	99	0.100	1.200	0.260	[−0.018; 0.538]
Total (95% CI)									0.239	[0.063; 0.414]
Heterogeneity: Tau^2=0.0039; Chi^2=2.39, df=2 (p=0.30); I^2=16%										
Outcome.g=desire										
Steidle et al [18]	Self.scaling.desire	50 mg	99	0.500	1.200	99	2.100	1.400	−1.222	[−1.526; −0.918]
Steidle et al [18]	Self.scaling.desire	100 mg	106	1.000	1.400	99	2.100	1.400	−0.783	[−1.067; −0.498]
Steidle et al [18]	Self.scaling.desire	T Patch	102	0.600	1.200	99	2.100	1.400	−1.147	[−1.446; −0.849]
Snyder et al [29]	DISF.MII.Sexual.desire	50 mg	234	2.600	6.500	236	0.000	5.000	0.448	[0.265; 0.631]
Total (95% CI)									−0.669	[−1.435; 0.096]
Heterogeneity: Tau^2=0.5914; Chi^2=140.87, df=3 (p<0.01); I^2=98%										
Outcome.g=performance										
Steidle et al [18]	Self.scaling.performance	50 mg	99	0.300	1.100	99	0.200	0.900	0.099	[−0.180; 0.378]
Steidle et al [18]	Self.scaling.performance	100 mg	106	0.500	1.200	99	0.200	0.900	0.280	[0.005; 0.556]
Steidle et al [18]	Self.scaling.performance	T Patch	102	0.300	0.700	99	0.200	0.900	0.124	[−0.153; 0.401]
Total (95% CI)									0.169	[0.009; 0.328]
Heterogeneity: Tau^2=0; Chi^2=0.97, df=2 (p=0.61); I^2=0%										
Outcome.g=IIEF										
Chiang et al [22]	IIEF	50 mg	20	5.800	8.479	20	1.200	10.195	0.481	[−0.149; 1.110]
Hackett et al [25]	IIEF.erectile function	1,000 mg	91	0.750	10.388	95	−1.120	10.245	0.181	[−0.108; 0.469]
Hackett et al [25]	IIEF.Intercourse satisfaction	1,000 mg	91	0.510	4.954	95	−0.580	5.013	0.218	[−0.071; 0.506]
Hackett et al [25]	IIEF.sexual desire	1,000 mg	91	0.500	2.201	95	−0.330	2.338	0.364	[0.074; 0.654]
Hackett et al [25]	IIEF.overall satisfaction	1,000 mg	91	0.230	2.694	95	−0.380	3.030	0.212	[−0.077; 0.500]
Hackett et al [25]	IIEF.orgasm	1,000 mg	91	0.000	3.939	95	−0.810	3.971	0.204	[−0.084; 0.492]
Snyder et al [29]	IIEF.EF	50 mg	234	3.100	6.900	236	1.000	6.000	0.324	[0.142; 0.506]
Basaria et al [27]	IIEF	75 mg	133	2.930	23.804	125	1.741	26.706	0.047	[−0.197; 0.291]
Total (95% CI)									0.237	[0.141; 0.332]
Heterogeneity: Tau^2=0; Chi^2=4.77, df=7 (p=0.69); I^2=0%										
Outcome.g=AMS										
Legros et al [24]	AMS	80 mg	78	4.700	10.850	79	4.200	9.906	0.048	[−0.265; 0.361]
Legros et al [24]	AMS.psychological	80 mg	78	1.600	3.897	79	1.500	3.751	0.026	[−0.287; 0.339]
Legros et al [24]	AMS.somatic	80 mg	78	1.900	4.912	79	1.800	4.651	0.021	[−0.292; 0.334]
Legros et al [24]	AMS.sexual	80 mg	78	1.200	3.804	79	1.000	3.804	0.052	[−0.261; 0.365]
Legros et al [24]	AMS.	160 mg	82	5.600	9.557	79	4.200	9.906	0.143	[−0.166; 0.453]
Legros et al [24]	AMS.psychological	160 mg	82	1.300	3.601	79	1.500	3.751	−0.054	[−0.363; 0.255]
Legros et al [24]	AMS.somatic	160 mg	82	1.900	4.133	79	1.800	4.651	0.023	[−0.286; 0.332]
Legros et al [24]	AMS.sexual	160 mg	82	2.300	3.851	79	1.000	3.804	0.338	[0.027; 0.649]
Legros et al [24]	AMS	240 mg	77	5.000	11.008	79	4.200	9.906	0.076	[−0.238; 0.390]
Legros et al [24]	AMS.psychological	240 mg	77	1.400	3.996	79	1.500	3.751	−0.026	[−0.340; 0.288]
Legros et al [24]	AMS.somatic	240 mg	77	2.000	5.011	79	1.800	4.651	0.041	[−0.273; 0.355]
Legros et al [24]	AMS.sexual	240 mg	77	1.800	4.058	79	1.000	3.804	0.202	[−0.112; 0.517]
Hackett et al [25]	AMS	1,000 mg	91	5.190	11.649	95	2.860	11.541	0.200	[−0.088; 0.488]
Total (95% CI)									0.085	[−0.001; 0.171]
Heterogeneity: Tau^2=0; Chi^2=5.71, df=12 (p=0.93); I^2=0%										
Outcome.g=PDQ.Q4										
Snyder et al [29]	PDQ.Q4	50 mg	234	0.200	1.600	229	−0.100	1.400	0.199	[0.016; 0.382]
Total (95% CI)									0.081	[−0.046; 0.208]
Heterogeneity: Tau^2=0.1235; Chi^2=228.40, df=34 (p<0.01); I^2=85%										
Test for subgroup difference: Chi^2=13.92, df=6 (p=0.03)										

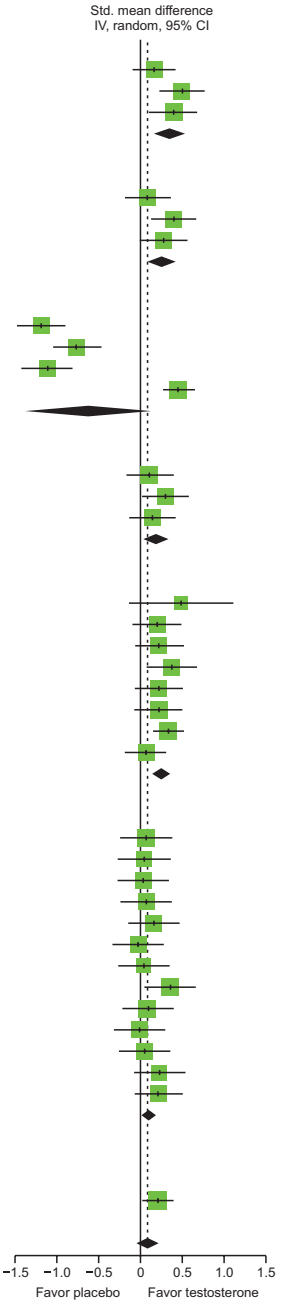

Fig. 2. Overall effect size by outcome. AMS: aging males symptoms, IIEF: international index of erectile function, PDQ: psychosexual daily questionnaire.

analysis (p=0.134).

DISCUSSION

Although many older men are still sexually active, the frequency of sexual intercourse declines with age [33]. Half of sexually active men report at least one sexual discomfort, the most common of which is erectile dysfunction (37%) [33]. Sexual problems in older men are thought to be partly related to hormonal status, with up to 35% of men with erectile dysfunction having hypogonadism [34].

Serum testosterone levels decrease with age. Therefore, older men have lower testosterone levels than younger men [7,8]. Changes in muscle mass, bone density, body fat mass, sexual function, and cognitive function in the elderly are similar to those observed in younger men with hypogonadism [35]. However, many

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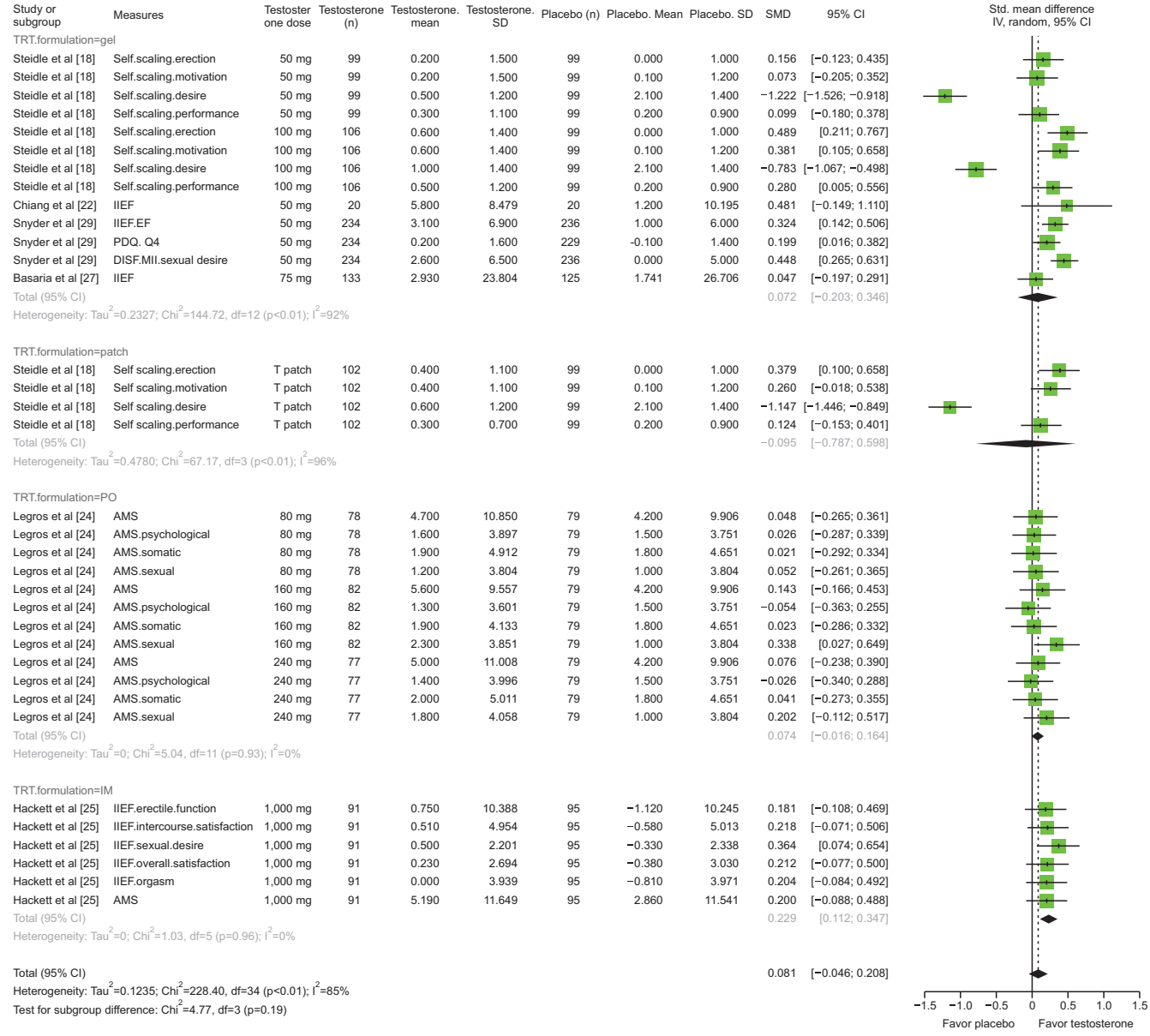

Fig. 3. Overall effect size by TRT formulation. IM: intramuscular, PO: per os, TRT: testosterone replacement therapy.

recent studies have shown that relationships between testosterone replacement and several areas of sexual function in older men might be different from those in younger men. In particular, because of the social status of older men such as the availability of partners, testosterone can modulate motivation without inducing behavioral changes. Steidle et al [18] have reported that sexual desire, sexual motivation, and spontaneous erection are associated with testosterone doses in older men with hypogonadism. However, the association between sexual function (decreased libido, impotence) and testosterone levels is inconsistent across studies. Some studies that did not find a causal relationship suggest that depression and cardiovascular disease known to be common in older men and other chronic conditions, particularly diabetes, might affect sexual function [36,37].

Simultaneously with an increasing proportion of the elderly, interest in treating the elderly with low testosterone levels using testosterone replacement thereby is also increasing dramatically. In older men, testosterone replacement can increase lean body mass, muscle strength, and hemoglobin level, and decreases body and visceral fat [18,38]. The role of testosterone replacement in elderly for sexual function remains controversial. Some studies reporting beneficial effects

Table 2. Associations of moderators with SMD

Variable	*k*	Coefficient (95% CI)	SMD (95% CI)	p-value
No. of total patients	35	0.00 (0.00 to 0.00)	-	0.409[a]
Dose	31	0.00 (0.00 to 0.00)	-	0.295[a]
TRT formulation				0.643[b]
Gel	13	-	0.07 (-0.14 to 0.28)	
Patch	4	-	-0.09 (-0.47 to 0.29)	
p.o.	12	-	0.07 (-0.15 to 0.30)	
IM injection	6	-	0.23 (-0.08 to 0.54)	
Duration (mo)				0.544[b]
<12	19	-	0.04 (-0.13 to 0.22)	
≥12	16	-	0.12 (-0.06 to 0.31)	
Age (y)				0.081[b]
<60	24	-	0.00 (-0.15 to 0.15)	
≥60	10	-	0.24 (0.02 to 0.47)	

Coefficient: regression coefficient, IM: intramuscular, *k*: number of all outcome measures, p.o.: oral medication, SMD: standardized mean difference (Hedges's g), TRT: testosterone replacement therapy, -: not available.
[a]p-values from meta-regression analysis using the restricted maximum likelihood. [b]p-values from meta-ANOVA for categorical moderators.

of testosterone replacement on sexual function have been conducted in young men who have fewer comorbidities that interfere sexual function [4,38]. Results of studies about effects of testosterone replacement on sexual function in elderly men are inconclusive [39,40]. However, a meta-analysis study has reported significant improvements in overall sexual function after testosterone supplementation compared to placebo in men having low or low-normal testosterone levels with erectile dysfunction [41]. These inconsistent results seem to reflect differences in study design. Previous studies had few subjects with various study periods and treatment methods.

In our study, only testosterone IM formulation significantly improved sexual function. This results might be due to different serum T levels achieved by different testosterone formulations [20]. In addition, the dose-response relationship between testosterone and domains of sexual function might be different in older men from that in younger men. Dose-dependent effects of testosterone on sexual function and spatiotemporal perception in older men were also different from those in younger men [42]. It has been hypothesized that sensitivity of central and peripheral mechanisms regulating sexual function might change with age [20]. The expression of testosterone receptor is low in the penis of older animals [21]. However, whether this alteration of receptor sensitivity also appears in the elderly remains unclear. Also, older men are more sensitive to gonadotropin inhibitory effects of testosterone than younger men [43].

The most worrying part when starting TRT in male hypogonadism is the effect on the cardiovascular system and the prostate. Cardiovascular adverse events were first mentioned in a study by Vigen et al [44]. They said that men who underwent coronary angiography had low serum testosterone levels and that the use of TRT was associated with an increased risk of adverse outcomes. However, recent meta-analyses reported that male hormone-replacement therapy had no effect on the cardiovascular system [45,46]. If a male subject has recently suffered from heart disease, he is recommended to withhold male hormone-replacement therapy [47]. Similar increases in hematocrit and hemoglobin might occur with TRT, which is more pronounced with a high dose of testosterone [18]. Elevated hematocrit was the most frequent dose-limiting side effect, especially in elderly men [48]. A small percentage of treated individuals might show increased hematocrit levels above 55%, which in turn might make them prone to erythrocytosis-related problems. Thus periodic monitoring of hematocrit is recommended [47]. TRT might also have effect on the prostate [49]. Some subjects are diagnosed with prostate cancer after TRT, which is not surprising because older men are at an increased risk of developing prostate cancer with elevated prostate specific antigen (PSA) results in prostate biopsies. In addition, more intensive monitoring of PSA

while taking testosterone might detect more prostate cancer.

The questionnaire is the most used method to evaluate sexual function in patients with sexual dysfunction. It is simple to use and easy to check changes. However, results of a questionnaire are subjective. In addition, the accuracy of the questionnaire might be poor in elderly patients. Studies included in the analysis used several symptom questionnaires. The most frequently used questionnaire was the IIEF [50]. This 15-item self-assessment questionnaire was developed to evaluate erectile function. It is not intended to be used as a measure of overall sexual function. The questionnaire of eleven questions about sexual functioning (ESF) is a validated questionnaire used for evaluating sexual function in the Netherlands [23]. Seven out of 11 questions are similar to those of the IEFF, and five questions of the ESF are described in the IIEF. The ESF is intended to be used as a measure of overall sexual function. In addition, there were cases where AMS and self-made questionnaires were used. Since these questionnaires also have several domains of sexual function, an indirect comparison of sexual function was possible.

This study has several limitations. First, testosterone treatment can affect speech, cognition, and muscle strength in addition to sexual function. Cherrier et al [51] have found improvements in verbal memory during testosterone replacement. Testosterone can functionally alter synaptic transmission to stimulate neuronal growth and survival [52]. Additionally, several studies have found significant biochemical and physical effects (fat mass reduction and lean body-mass gain, and hormone-related improvement in quality of life) when testosterone replacement is used [21,23,53]. Effects of testosterone supplementation on these areas in the elderly require further studies. Second, there are various methods for evaluating sexual function. Most studies used questionnaires to evaluate sexual function changes. However, types of questionnaires differed. Two urology specialists (HJ Yang and JH Kim) assessed sexual function evaluation items by separating areas within the questionnaire and compared changes, not absolute values, of each symptom. Third, evaluation periods were differed. Although a follow-up of three months is a rather short time to show effects of testosterone, some studies have suggested that three months are long enough to find beneficial effects of testosterone supplementation on sexual function [18,54]. Fourth, the target group was not constant, given the nature of a meta-analysis research. Subjects included in this study were elderly patients with blood testosterone levels in the low or low-normal range who had clinical symptoms of hypogonadism.

CONCLUSIONS

In this study, we confirmed that testosterone replacement in elderly patients might not significantly improve their sexual function. Although there are several limitations, TRT can be used as an effort to improve the quality of life of elderly patients. Given the high heterogeneity of studies included in the analysis, well-planned, large-scale studies are needed to draw a definite conclusion.

Conflict of Interest

The authors have nothing to disclose.

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Author Contribution

Conceptualization: HJY, JHK. Data curation: HJY, KHK, DSK. Formal analysis: SRS, JHK. Funding acquisition: JHK. Investigation: HJY, SRS, JHK. Methodology: CHL, YSJ, JHK. Project administration: HJY, SRS, JHK. Resources: HJY, JHK. Software: KHK, DSK, JHK. Supervision: YSJ, SRS, JHK. Validation: CHL, SRS, JHK. Visualization: HJY, JHK. Writing – original draft: JHK, HJY. Writing – review & editing: all authors.

Supplementary Material

Supplementary material can be found *via* https://doi.org/10.5534/wjmh.220171.

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