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Published in:
Andrology

DOI:
10.1111/andr.12806

Publication date:
2020

Received: 19 October 2019 | Revised: 16 April 2020 | Accepted: 20 April 2020

DOI: 10.1111/andr.12806

ORIGINAL ARTICLE

ANDROLOGY WILEY

Association between prostate-specific antigen and serum testosterone: A systematic review and meta-analysis

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Abstract

Background: Serum testosterone assays are an important tool in the clinical evaluation of a number of endocrine disorders including male hypogonadism. However, serum testosterone has a limited role in real clinical use due to its inaccuracy. We aimed to assess the association between prostate-specific antigen (PSA) and testosterone as well as the effects of various types of testosterone replacement therapy (TRT) for PSA level.

Methods: Two electronic databases were screened: PubMed (1966 through December 2018) and Cochrane Library (1993 through December 2018). The first strategy compared the overall increase in PSA following testosterone treatment compared with placebo. The second strategy analyzed the overall association between PSA and testosterone among the observational studies.

Results: In the first strategy, 22 articles were included in the final analysis. In the second strategy, 18 studies were included. Testosterone replacement therapy (TRT) showed a significant change in PSA level compared to that in the placebo group (mean difference [MD]: 0.13, 95% CI: 0.01-0.25, P = .04). Compared to placebo, only intramuscular (IM) TRT shows a significant change in PSA level group (MD: 0.16, 95% CI: 0.01-0.30, P = .04), as neither the oral nor topical type showed a significant change in PSA. In the second strategy analysis, there was no overall correlation found between PSA and testosterone (z = 0.04, 95% CI: −0.04 to 0.12, P = .04; r = 0.039). However, in the subgroup of non-BPH (benign prostate hyperplasia), a significant correlation between PSA and testosterone (z = 0.07, 95% CI: 0.01-0.13, P = .009; r = 0.089) was found.

Kim, Noh and Chang authors have contributed equally to this article as co-first authors.

Conclusions: We found that TRT, particularly IM TRT, significantly changed the PSA level compared with the placebo group. Furthermore, there was a significant correlation between PSA and testosterone in patients with non-BPH. According to these findings, we suggest the possibility of PSA as a surrogate marker of testosterone.

KEYWORDS

androgen, testosterone, prostate-specific antigen, meta-analysis

1 | INTRODUCTION

Testosterone deficiency in older men has become a subject of growing concern, as it is related to various chronic diseases such as cardiovascular disease (CVD), dementia, diabetes, metabolic syndrome, and obesity.[1] Testosterone levels gradually decrease with age, and many men over the age of 60 have serum testosterone levels below the lower limit of young adults aged 20-30.[2-4] Moreover, opioids inhibit the function of the entire hypothalamic-pituitary-gonadal axis by binding to opioid receptors in the hypothalamus, thereby causing the hypogonadism.[5] Late-onset hypogonadism may significantly harm quality of life and adversely affect the functioning of multiple organ systems.[6,7] Testosterone replacement therapy (TRT) has come to be widely used to treat age-related and other types of hypogonadism in men, and it has been shown to be associated with improved mood, increased sexual desire and achievement, increased muscle volume and bone mineral density, and improved quality of life.[8] Among the possible route for TRT, injectable, transdermal, buccal, and oral testosterone formulations are available for clinical use in the United States, and other preparations are currently under development as well.[9]

Serum testosterone assays are an important tool in the clinical evaluation of a number of endocrine disorders, such as male hypogonadism, delayed or precocious puberty, and female hyperandrogenism (eg, idiopathic hirsutism, congenital adrenal hyperplasia, polycystic ovarian syndrome, and androgen secreting ovarian or adrenal tumors).[10] Although most testosterone assays have shown feasible sensitivity and reasonable clinical use, they are also relatively inaccurate.[11] Therefore, there is a limitation in that androgen activity can only be evaluated at the testosterone level. Hematocrit has been suggested as a surrogate marker for measurement of testosterone replacement therapy[12]; however, it showed limitation in its clinical use. Thus, a surrogate marker that can complement this is needed.

Prostate-specific antigen (PSA) is a serum glycoprotein originating from normal prostate tissue that is widely used as a tumor marker due to the fact that increased PSA levels directly correlate with the risk of prostate cancer.[9] Still, PSA has been investigated for its potential to represent non-prostate conditions, including obesity, hypertension, diabetes, CVD, and insulin resistance.[13,14] Moreover, a previous study of ours has shown that serum total PSA levels within the reference range are inversely associated with subclinical atherosclerosis and cardiovascular mortality in young and middle-aged Korean men, indicating a possible role of PSA as a predictive marker for subclinical and clinical CVD.[15] Our academic hypothesis was that PSA could reflect androgen activity, including serum testosterone in the normal range of PSA.

Many studies have investigated the relationship between TRT and PSA elevation. PSA has been consistently elevated in several testosterone trials of young and older people, but each increase has been very small (about 0.30-0.43 ng per milliliter).[16] Several meta-analyses have evaluated the effect of testosterone treatment on a rising PSA level.[6,17,18] However, the numbers of studies included in those meta-analyses were not only insufficient, but also resulted in inconsistencies between studies. Moreover, their basis hypothesis was not to investigate the possibility of PSA as a surrogate marker for testosterone but simply to investigate whether TRT is related to prostate cancer risk (increasing PSA condition).

Our study has an academic base that PSA is an AR target gene, and a recent study suggests that PSA might be indicative of AR expression, as PSA expression correlates with the transcription of other AR genes.[19,20] The aim of the present systematic review and meta-analysis was to assess the relationship between PSA and testosterone. In order to validate our hypothesis that PSA could reflect testosterone, we conducted two different methodological processes: a meta-analysis among RCT studies to evaluate the effect of various types of TRT (oral, intramuscular, and topical) on PSA and a weighted proportional meta-analysis of correlation coefficients among observational studies.

2 | MATERIALS AND METHODS

2.1 | Search strategy

Two electronic databases were screened: PubMed (1966 through December 2018) and Cochrane Library (1993 through December 2018). There were two searching strategies used that differed according to their primary outcome. The first strategy compared the overall increase in PSA following testosterone treatment compared with placebo. The subject headings and text keywords included prostate-specific antigen and testosterone. The natural headings included prostate-specific antigen or PSA in the abstract or title, along with testosterone in the abstract or title. The publication type was confined to randomized controlled trials. The searches were limited to human studies and performed for all languages and all study types. The same reference searching strategy was adopted for the EMBASE using Emtree (Embase subject headings).

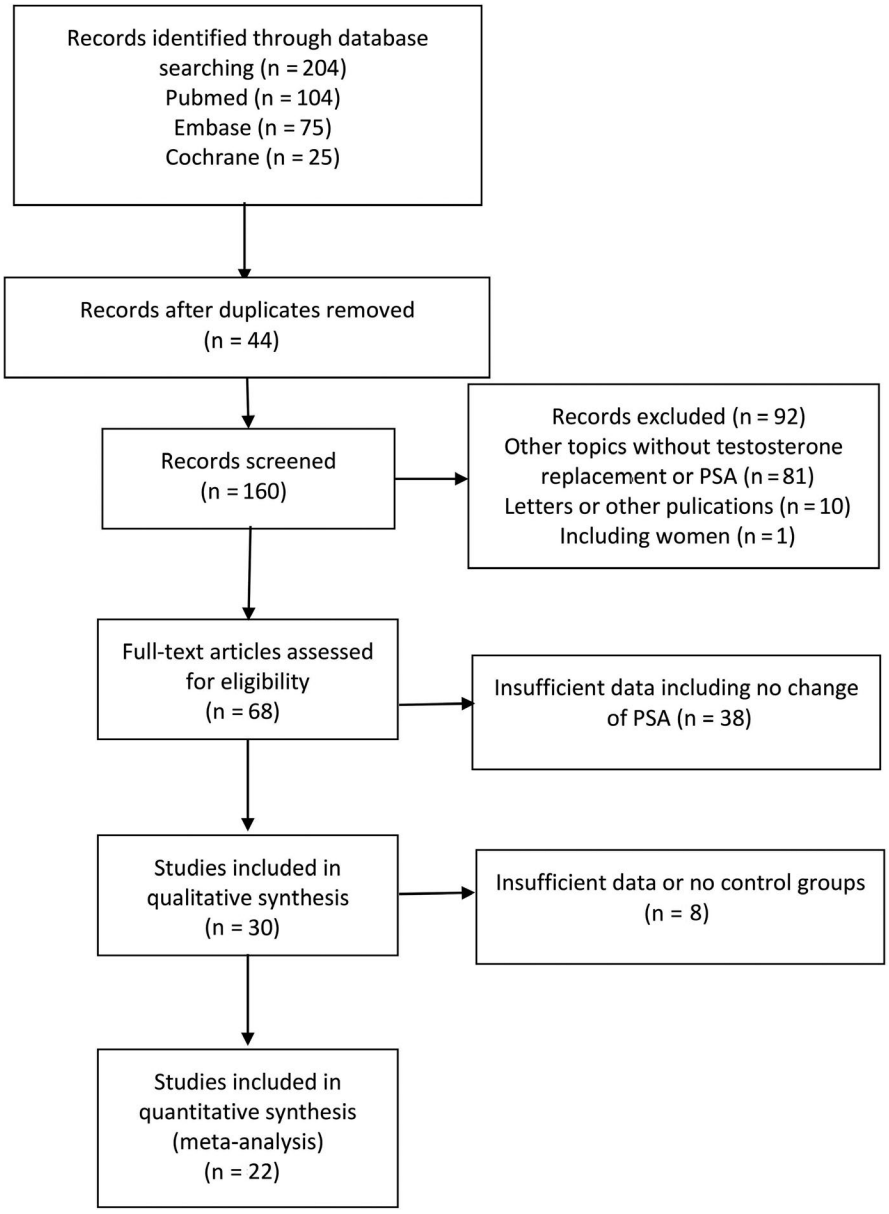

FIGURE 1 Preferred reporting items for systematic reviews and meta-analysis flowchart of first strategy. PSA, prostate-specific antigen

The second strategy analyzed the overall association between PSA and testosterone among the observational studies. The subject headings and text keywords included prostate-specific antigen and testosterone. The natural headings included prostate-specific antigen or PSA in the abstract or title, along with testosterone in the abstract or title. There was no exclusion of publication type except for clinical trials. The searches were limited to human studies and performed for all languages and all study types. The same reference searching strategy was adopted for the EMBASE using Emtree (Embase subject headings).

2.2 | Trial inclusion and exclusion criteria

The study inclusion criteria for the first strategy were as follows: (a) inclusion of any type of testosterone treatment, (b) inclusion of a placebo group, (c) inclusion of information on the PSA level before and after testosterone treatment, (d) exclusion of prostate cancer patients, and (e) randomized controlled trial (RCT) study design. The study inclusion criteria for the second strategy were as follows: (a) inclusion of information on correlation coefficient or coefficient of determination, (b) exclusion of prostate cancer patients, and (c) observational studies. The articles that were ultimately included were determined by evaluation discussions among all investigators, using a point estimation system for each article. The references and data for each included study were carefully cross-checked in order to ensure that no overlapping data were present as well as to maintain the integrity of the meta-analysis.

2.3 | Data extraction

The data were extracted by two independent authors using a predesigned form, and conflicts between them were resolved through

TABLE 1 Characteristics of included studies in first strategy

Study	Study period	Inclusion criteria	Intervention type	Dose	Number	Mean age	SD or range	Baseline PSA (ng/ml)	SD or range	Baseline T (ng/dl)	SD or range
Aversa et al (2003)	1 mo	Arteriogenic erectile dysfunction	T + sildenafil	5 mg dermal	10	54	2	1.4	0.7	369.18	2.1
			Placebo: sildenafil		10	56	4	1.1	0.8	372.07	2.1
Tan et al (2013)	48 wks	T deficiency due to old age	Testosterone undecanoate	1000 mg IM	56	53.1	8.3	0.8	0.57	256.41	2
			placebo		58	53.8	6.9	0.95	0.77	262.75	1.85
Magnussen et al (2016)	24 wks	Type 2 DM patients	Testosterone	50 mg gel	20	61	6	0.7	0.5-1.0 (95% CI)	204.78	6.6-11.9 (IQR)
			Placebo		19	59	6	1	0.6-1.4 (95% CI)	271.12	8.1-12.5 (IQR)
Knapp et al (2008)	16 wks	HIV patients	Testosterone enanthate	300 mg IM	30	43.7	7.4	0.8	0.09	408.00	26
			Placebo		31	42.7	6	0.88	0.14	444.00	25
Kalinchenko et al (2010)	30 wks	Metabolic syndrome patients	Testosterone undecanoate	1000 mg IM	113	51.6	49.8-53.4 (95% CI)	0.8	0.7-0.9 (95% CI)	193.24	6.0-7.4 (95% CI)
			Placebo	0,6,18 wks	71	52.8	50.5-55.0 (95% CI)	0.8	0.7-1.0 (95% CI)	216.32	6.6-8.5 (95% CI)
Fui et al (2016)	56 wks	BMI ≥ 30 kg/m^2 and TT < 12 nmol/L	Testosterone undecanoate	1000 mg IM	49	54.3 (median)	47.3-59.8 (IQR)	0.7	0.5-1.1 (IQR)	236.51	2.5
			Placebo		51	52.8 (median)	47.6-60.1 (IQR)	0.7	0.5-1.2 (IQR)	242.28	2.3
Fui et al (2017)	82 wks	BMI ≥ 30 kg/m^2 and TT < 12 nmol/L	Testosterone undecanoate	1000 mg IM	49	53.2	47.4;59.9 (IQR)	0.72	0.54-1.10 (IQR)	245.16	6.6-10.4 (IQR)
			Placebo		51			0.71	0.48-1.15 (IQR)	242.28	7.1-10.0 (IQR)
Kenny et al (2001)	12 mo	Age ≥ 65	Testosterone	5 mg dermal	24	76	4	2	1.3	389.37	6
			Placebo		20	75	5	1.9	1	389.37	3.7
Cooper et al (1998)	15 wks	Healthy male	Testosterone	100 mg IM/wk	10	28		0.83	0.21(SE)	656.00	45(SE)
				250 mg IM/wk	10			0.83	0.11(SE)	606.00	49(SE)
				500 mg IM/wk	11			0.5	0.06(SE)	647.00	71(SE)

(Continues)

TABLE 1 (Continued)

Study	Study period	Inclusion criteria	Intervention type	Dose	Number	Mean age	SD or range	Baseline PSA (ng/ml)	SD or range	Baseline T (ng/dl)	SD or range
Bhasin et al (2001)	16 wks	Healthy male	Testosterone enanthate plus GnRH agonist	25 mg IM/wk	12	28	5	1	0.2(SE)	593.00	48(SE)
				50 mg IM/wk	12	29	5	0.8	0.1(SE)	566.00	78(SE)
				125 mg IM/wk	12	28	3	0.7	0.1(SE)	553.00	53(SE)
				300 mg IM/wk	12	24	5	0.7	0.1(SE)	653.00	50(SE)
				600 mg IM/wk	13	25	4	0.5	0.1(SE)	632.00	63(SE)
Dobs et al (1999)	20 wks	Hypogonadal male 20 to 65 yrs	Testosterone	2.5 mg dermal	33	44.3	11.1	0.9	0.6	166.00	79
				200 mg IM	33	44.9	11.6	0.9	0.7	182.00	94
Walton et al (2007)	48 wks	Healthy male	MENT(testosterone + etonogestrel)	270 mg/implants	16	32.2	1.2	1.1	0.2		
			Testosterone	600 mg SQ/12 wk				0.8	0.1	651.84	1.9
Wang et al (2000)	90 d	Hypogonadal male	Testosterone	Patch	76		19-68 (range)	0.89	0.1	237.08	0.55
				50 mg/d gel	73			0.88	0.08	237.08	0.53
				100 mg/d gel	78			0.89	0.08	248.05	0.55
Cho et al (2017)	12 wks	Erectile dysfunction with low T (350 ng/dL)	Testosterone	50 mg gel	25	57.9	7.2	1.06	0.7	277.10	66.1
				50 mg gel + exercise	25	60.7	7	1.08	0.76	281.90	54.5
Hackett et al (2014)	30 wks	Healthy male	Testosterone undecanoate	1000 mg IM	27	64	38-83 (range)	1.16	0.22	211.70	0.54
			Placebo (severe group: TT < 8 nmol/L)		48	60	41-74 (range)	1.44	0.2	214.59	0.33
			Testosterone undecanoate	1000 mg IM	53	60	33-76 (range)	2.15	0.65	301.98	0.38
			Placebo (mild group: TT 8 ~ 12 nmol/L)		48	62	33-79 (range)	1.4	0.16	313.52	0.57
Caminiti et al (2009)	3 mo	Elderly male with CHF	Testosterone undecanoate	1000 mg IM	31	71 (median)	67-76 (IQR)	1.4	1.1	230.00	1.8
			Placebo		33	69 (median)	66-74 (IQR)	1.3	0.7	210.00	2.1
Kenny et al (2004)	10 wks	Age ≥ 65 with low T and mild to moderate cognitive impairment	Testosterone enanthate	200 mg IM	6	81	5	0.88	0.71	410.00	112
			Placebo		5	78	3	1.3	0.78	404.00	195

(Continues)

TABLE 1 (Continued)

Study	Study period	Inclusion criteria	Intervention type	Dose	Number	Mean age	SD or range	Baseline PSA (ng/ml)	SD or range	Baseline T (ng/dl)	SD or range
Cavallini et al (2004)	6 mo	Age ≥ 60	Testosterone undecanoate	160 mg po	40	64	60-72 (range)	2	0.7	285.25	1.84
			Carnitine		45	66	61-73 (range)	2.4	0.9	312.36	1.86
			Placebo		45	63	61-74 (range)	1.8	0.8	303.71	2.11
Shamloul et al (2005)	2 mo	Erectile dysfunction	Testosterone undecanoate + sildenafil	120 mg/d	40	58	2.4	1.42	0.5	210.55	1.4
Sih et al (1997)	12 mo	Age ≥ 50	Testosterone cypionate	200 mg biweekly	17	65	7	1	0.2	294.00	26
			Placebo		15	68	6	1.5	0.3	233.00	20
Cherrier et al (2005)	12 wks	Age 50 to 90	Testosterone enanthate + placebo	100 mg IM weekly	20	65	11	1.1	1.3	403.79	8
			T + anastrozole po		19			1.1	0.6	400.91	5.9
			Placebo		21			1.6	1.1	348.99	3.8
Kunelius et al (2002)	6 mo	Age 50 to 70	DHT	125 mg gel	60	58.3	4.8	1.6	1.6	464.36	4.6
			Placebo		60	58.6	5.7	1.5	1.2	458.59	4.5
Sattler et al (2011)	28 wks	Age 65 to 90 with low T	Testosterone + growth hormone	50 or 100 mg gel	56 (body weight change ≥ 1.5 kg)	71	4	1.6	0.9	343.23	3.6
					52 (body weight change < 1.5 kg)	71	4	1.3	0.8	374.95	3
Sheffield-Moore et al (2011)	5 mo	Age 60 to 85	Continuous T	100 mg IM weekly	8	73	8	2.09	1.09	341.00	85
			Monthly cycled T	100 mg IM monthly	8	72	8	1.58	1.04	357.00	103
			Placebo		8	65	3	1.24	1.2	344.00	85
Morales et al (2009)	16 wks	Age 45 to 70	Testosterone undecanoate	80 mg po twice daily	29	59	10.6			902.77	5.4
			DHEA	50 mg	28	60.9	12			902.77	5.4
			Placebo		29	60.2	9.6			856.62	4.4
Wittert et al (2003)	12 mo	Age ≥ 60	Testosterone undecanoate	80 mg po twice daily	39	69	6			490.32	4.4
			Placebo		37	68	5			449.94	4.5

(Continues)

TABLE 1 (Continued)

Study	Study period	Inclusion criteria	Intervention type	Dose	Number	Mean age	SD or range	Baseline PSA (ng/ml)	SD or range	Baseline T (ng/dl)	SD or range
Mathur et al (2009)	12 mo	Age ≥ 20	Testosterone undecanoate	1000 mg IM per 12 wks	7	62.1	5.2	1.6	1	282.66	1.9
			Placebo		6	67.8	7.9	0.9	0.7	291.31	2.8
Mongentaler et al (2014)	6 mo	Age 18 to 80 with low T	Testosterone	20.25/40.5/60.75/ 81 mg gel	234	53.5	9.8	0.9	0.6		118.155
Dias et al (2016)	12 mo	Age ≥ 65 with low T	Testosterone	5 g gel/daily	13	72	1	?	?	300.05	13.4
			Aromatase inhibitor	1 mg	13	70	1	?	?	271.58	12.7
			Placebo		9	72	1	?	?	303.78	16.6

Abbreviations: BMI, body mass index; CHF, chronic heart failure; DHEA, dihydroepiandrosterone; DHT, dihydrotestosterone; DM, diabetes mellitus; GnRH, gonadotropin-releasing hormone; HIV, human immunodeficiency virus; IM, intramuscular; MENT, 7a-methyl-19-nortestosterone; PSA, prostate-specific antigen; SD, standard deviation; SE, standard error; T, testosterone; TT, total testosterone.

consensus. The studies that were ultimately included were agreed upon by all authors. The extracted data included the first author, publication year, study design, treatment arms, number and mean age of patients, type and dose of TRT, inclusion and exclusion criteria, follow-up period, and outcome.

2.4 | Types of interventions and outcomes

For the first strategy, the treatment group received testosterone treatment exposure. The primary outcome was overall change in PSA following testosterone treatment compared with placebo. The secondary outcome was relative change in PSA following testosterone treatment compared with placebo according to each testosterone treatment type. For the second strategy, the overall association between PSA and testosterone was investigated. The secondary outcome included moderator analysis of the BPH groups included in each study.

2.5 | Study quality assessments and quality of evidence

The risk of bias in RCTs was evaluated using the Cochrane Collaboration's tool for assessing risk of bias, including assessments of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other types of bias.[21] The risk of bias in observational studies was assessed using the Newcastle-Ottawa Scale (NOS).[22] The NOS consisted of three main categories of evaluation: selection, comparability, and exposure. Up to nine stars can be assigned to a study, and more than six stars in the final star is considered to reflect high quality.

The quality of the evidence considered in the present study was evaluated based on the Grading of Recommendations, Assessments, Developments, and Evaluation (GRADE).[23] GRADE consists of five criteria, including assessments of the methodology, precision and consistency of results, directness, and risk of publication bias. Based on these five criteria, the certainty of only direct evidence of pairwise meta-analysis was assessed among four levels: high, moderate, low, and very low.

2.6 | Statistical analysis

The analysis of the first strategy included both pairwise and network meta-analysis, while that of the second strategy only included pairwise analysis. A pairwise meta-analysis in RCTs was performed to examine the differences in PSA levels between the TRT and placebo groups. The outcomes were reported as the weighted mean difference (MD) along with the 95% confidence intervals (CIs) and the *P*-value. The pooled MD with 95% CIs shows differences in the

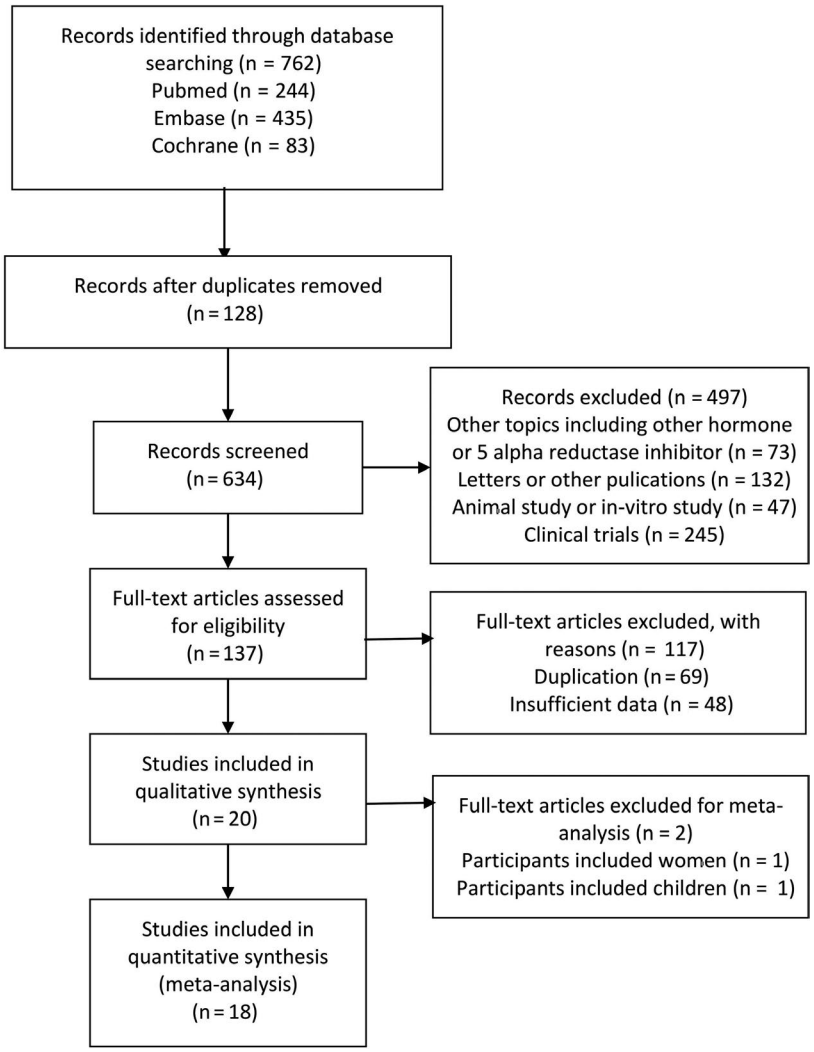

FIGURE 2 Preferred reporting items for systematic reviews and meta-analysis flowchart of second strategy

sizes of the intervention effects. A meta-analysis of observational studies was conducted on the overall association between PSA and intervention. The correlation coefficient between the testosterone and PSA levels was used to estimate the effect size. Since *r* has certain undesirable statistical properties, the correlations were transformed into Fisher's *z* values.[24] The weighted overall effect sizes and 95% CIs indicating the impact of intervention on PSA level were calculated as well. For ease of interpretation, the overall effect sizes were transformed back into r. The statistical heterogeneity between trials was evaluated by Cochran *Q* statistic and I^2 statistic. A *P*-value < 0.05 for the Cochran *Q* statistic or an I^2 statistic > 50% indicates significant heterogeneity.[21] The publication bias was evaluated using the funnel plot and Begg's test.[25,26] Symmetry reversal funnel diagrams and a *P*-value > 0.05 on Begg's test mean no publication.

The node-splitting analysis results were considered to indicate no significant inconsistency when 95% CIs of inconsistency factors included zero or when a large probability value was higher than 0.05 for comparison between direct and indirect effects.[27] The relative effects were also evaluated visually using relative effect tables and plots. The probability values are summarized and reported as a rank probability table and plot.

The pairwise meta-analysis was conducted using Review Manager v.5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark, 2008). All of the *P*-values were two-sided, and *P* < .05 was considered to be statistically significant.

3 | RESULTS

3.1 | Systematic review process

3.1.1 | First strategy

A summary of the systematic review process is presented in Figure 1. Literature searches have recognized a total of 204 studies, with 160 remaining after removing duplicates. The titles and abstracts of the 160 remaining articles were reviewed and 92 were excluded according to the inclusion and exclusion criteria. Next, the full text of each of the remaining 68 articles was assessed for final inclusion. Through

TABLE 2 Characteristics of included studies in second strategy

Author	Published year	Studied year	Study type	Group with BPH	Inclusion criteria	Final inclusion for meta-analysis	Age (SD or Range)	BMI (SD or Range)	Number	Baseline PSA (SD or Range) (ng/ml)	Prostate size (SD or Range)
Grober	2008	2001-2007	Retrospective study		Total	Yes					
			Cross-sectional		Eugonadal		53		385	1.6 (0.1-22.8)	
					Hypogonadal		58		229	1.49 (0.1-8.8)	
					Hypogonadal with T		60		229	1.5 (0.1-13.8)	
Shukla	2018	2014	Cross-sectional		Total (>50)	Yes					
					Eugonadal		59.73 (2.59)		116	1.85 (0.73)	
					Hypogonadal		62.48 (3.38)		139	1.96 (0.76)	
Mardanian	2011	2009-2010	Cross-sectional		Total (women)	No					
			Case-control		PCOS		23.38 (4.8)		32	0.19 (0.192)	
					non-PCOS		27.1 (4.9)		32	0.0389 (0.046)	
Schatzl	2000	1998-1999	Cross-sectional	Yes	40 yrs old older and IPSS > 7	Yes	62.8 (10.6)		312	3.1 (3.9)	40.2 (20.9)
Kim	1999		Cross-sectional		Boys	No	(10 ~ 18)		77		
Mustafa	2014	2006-2007	Cross-sectional		50 yrs old older men	Yes	59.19 (12)		179	1.27 (0.88)	
					PSA < 2.5ng/ml		58.44 (12.1)		160	1.05 (0.56)	
					PSA ≥ 2.5ng/ml		66.29 (8.15)		19	3.38 (0.42)	
Roberts	2004	2002	Prospective cohort	Yes	Random selection BPH patients	Yes	60.9 (median)		320	1.3 (median) (IQR 0.7- 2.2)	29.7 (median) (IQR 23.2-40.4)
			Cross-sectional		From Olmsted study						
Rastrelli	2018		Cross-sectional		Clinical hypogonadism men	Yes	51.1 (13.5)	26.8 (4.4)	2622	0.79 (0.51-1.36)	
Jarow	2013		Cross-sectional		Pooled analysis of 7 clinical trials	Yes	54.6 (11)	30 (3.8)	1492	1 (0.8)	
Shin	2016	2009-2014	Retrospective study			Yes	59.82 (12.7)		1221	3.23 (21.14)	
Shim	2018	2010-2011	Cross-sectional	Yes	Aged men with BPH/LUTS	Yes	60.4 (9.6)	24.3 (2.3)	50	1.4 (1.3)	31.1 (8.3)

(Continues)

TABLE 2 (Continued)

Author	Published year	Studied year	Study type	Group with BPH	Inclusion criteria	Final inclusion for meta-analysis	Age (SD or Range)	BMI (SD or Range)	Number	Baseline PSA (SD or Range) (ng/ml)	Prostate size (SD or Range)
Rastrelli	2013		Retrospective cohort		Men with suspected ED	Yes	52.5 (12.4)		2967	0.8 (0.5-1.3)	
			Cross-sectional								
Miner	2011	2008-2010	Prospective cohort		Clinical hypogonadism men	Yes	52.1 (12.3)	31.4 (6.9)	451	1.12 (1.11)	
			Cross-sectional								
Mifsud	2001		Cross-sectional		Total	Yes					
					Fertile				91	0.754 (0.001)	
					Subfertile				112	0.828 (0.06)	
Lee	2014	2011	Cross-sectional		Eugonadal male	Yes	49.0 (median) (IQR 45.0-54.0)	24.8 (median) (IQR 23.3-26.6)	2308	0.71 (median) (IQR 0.50-0.041)	24 (median) (IQR 20.0-28.0)
Ho	2015	2009	Cross-sectional		Men with or without DM	Yes	61.2 (6.8)		186		
					New DM		57 (median) (IQR 11)				
					Previous DM		61 (median) (IQR 9)				
Dhindsa	2008	2006-2007	Cross-sectional		Men with DM	Yes			280		
					Hypogonadal		60.06 (SE 0.92)	35.3 (SE 0.64)	154	0.89 (SE 0.07)	
					Eugonadal		59.78 (SE 0.87)	30.9 (SE 0.47)	126	1.1 (SE 0.08)	
Asiedu	2017		Cross-sectional	Yes	Men with BPH	Yes			30		
Corona	2010	2001-2009	Retrospective cohort		Men with suspected ED	Yes	53.9 (12.4)		2291	0.9 (0.5-1.5)	
			Cross-sectional		Patients without prostate disease		49.6 (12.2)		1421	0.7 (0.5-1.1)	
Tanwar	2015	2009-2013	Retrospective cohort	Yes	Men with BPH	Yes	58.79 (12.7)		1156	3.07 (22.25)	33.72 (21.27)

Abbreviations: BMI, body mass index; BPH, benign prostate hyperplasia; DM, diabetes mellitus; ED, erectile dysfunction; IPSS, International Prostate Symptom Score; IQR, interquartile range; LUTS, lower urinary tract symptoms; PCOS, Polycystic ovarian syndrome; PSA, prostate-specific antigen; SE, standard error.

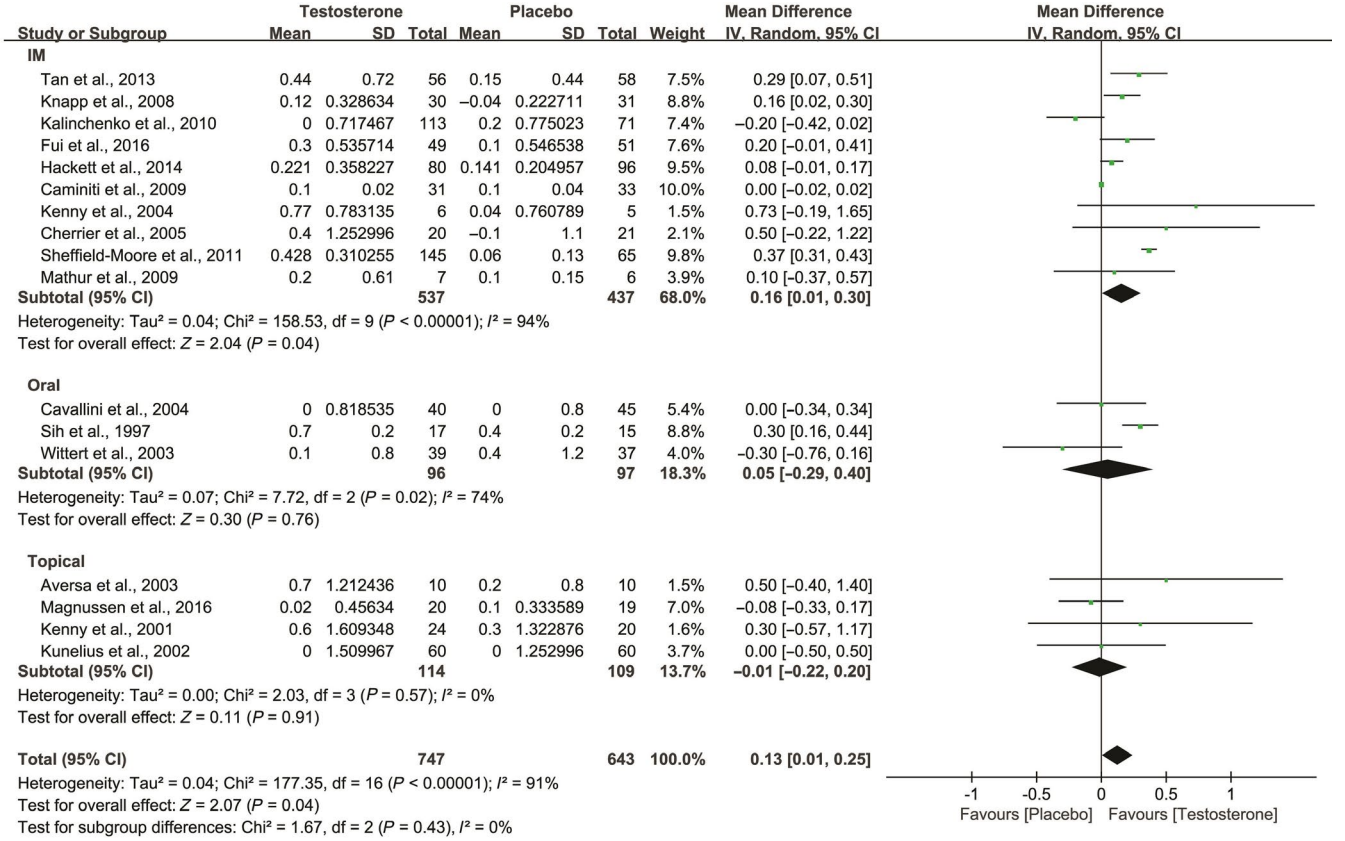

FIGURE 3 Forest plot comparing PSA level change of TRT with placebo. IM, intramuscular; SD, standard deviation; TRT, testosterone replacement therapy

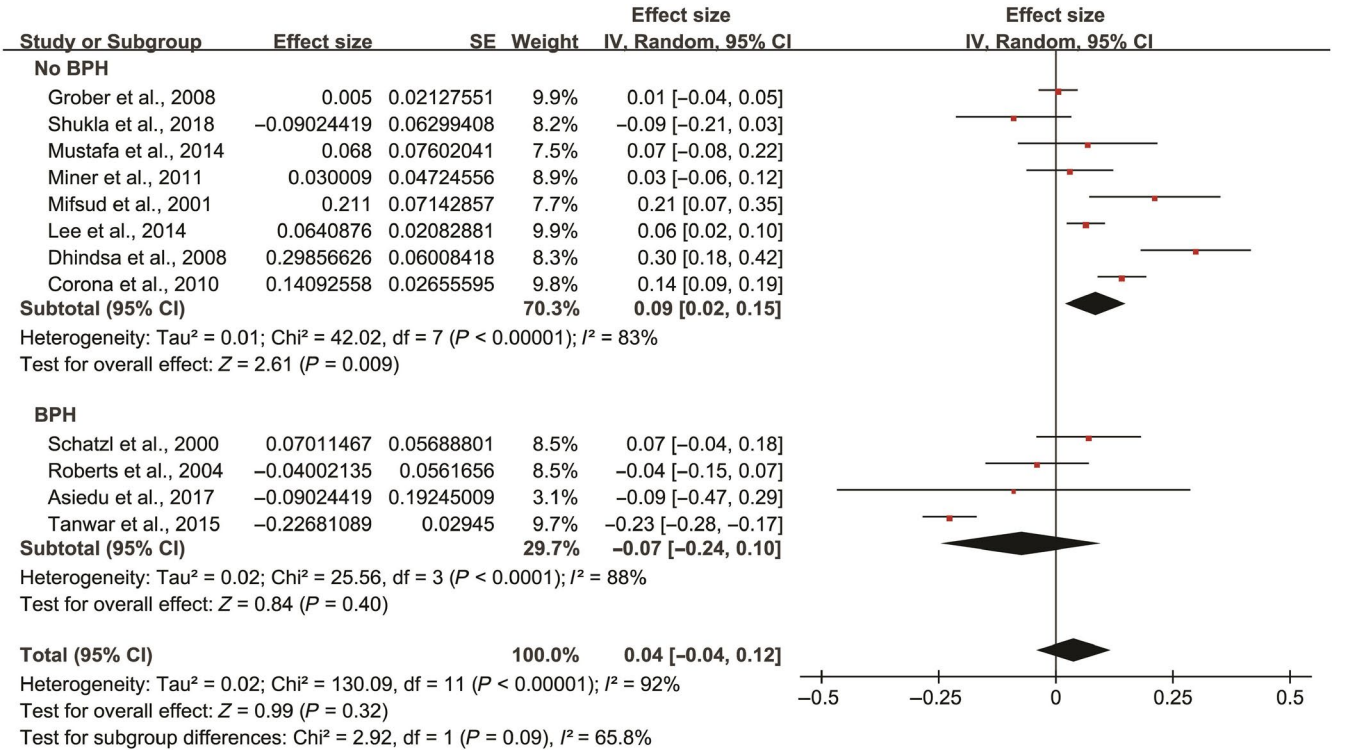

FIGURE 4 Forest plot of studies investigating the relationship between testosterone and PSA. PSA, prostate-specific antigen; SE, standard error

TABLE 3 Summary of prostate-specific antigen level change by type of testosterone replacement therapy

Type of TRT	Number of included study	Number of patient		PSA level change
		Testosterone	Placebo	Mean difference (95% CIs)
IM type	10	537	437	0.16 (0.01-0.30)
Oral type	3	96	97	0.05 (−0.29-0.40)
Topical type	4	114	109	-0.01 (−0.22-0.20)
Combined all type	17	747	643	0.13 (0.01-0.25)

Abbreviations: IM, intramuscular; PSA, prostate-specific antigen; TRT, testosterone replacement therapy.

this process, 29 studies were included in the current meta-analysis. Ultimately, 22 articles were included in the final analysis due to the fact that eight studies had insufficient data or no control groups. Detailed information of each included study, all of which were RCT designs, is presented in Table 1.

3.1.2 | Second strategy

The total process of the systematic review process is presented in Figure 2. We identified a total of 762 studies through literary search, with 634 remaining after deduplication. The titles and abstracts of the 634 related articles were reviewed and 497 were excluded based on the inclusion and exclusion criteria. Following a review of the full text of each of the remaining 137 articles, 20 studies were included in the current meta-analysis. Eighteen articles were ultimately included in the final analysis. Detailed information of each included study is presented in Table 2.

3.2 | Outcomes

3.2.1 | First strategy

Seventeen studies showed that TRT significantly changed the PSA level compared to that of the placebo group (MD: 0.13, 95% CI: 0.01-0.25, P = .04, Figure 3). Heterogeneity among the included studies was observed (P < .00001; I^2 = 91%). Only IM TRT was significantly increase PSA level compared to that of the placebo group (MD: 0.16, 95% CI: 0.01-0.30, P = .04, Figure 3) in subgroup analysis (Figure 4).

3.2.2 | Second strategy

The meta-analysis yielded no correlation between PSA and testosterone (z = 0.04, 95% CI: −0.04 to 0.12, P = .04; r = 0.039), (Table 3). Heterogeneity among the included studies was observed (P < .00001; I^2 = 92%). In the subgroup of no BPH, a significant correlation between PSA and testosterone (z = 0.07, 95% CI: 0.01-0.13, P = .009; r = 0.089) was found.

3.3 | Quality assessment, qualitative risk of bias, and sensitivity analysis

The risk of bias graph and assessment of RCTs are presented in Figures 5 and 6. The results of the quality evaluation of the included observational studies conducted according to the NOS are shown in Table 4. All included observational studies were rated at 6 or higher. The assessment of the quality of the evidence by the GRADE approach is shown in Tables 5 and 6. The certainty was low in the first strategy and very low in the second strategy.

Funnel plots for the publication bias of both the first and second analyses demonstrated a certain degree of symmetry (Figures 7 and 8). Furthermore, Begg's tests revealed that there was no

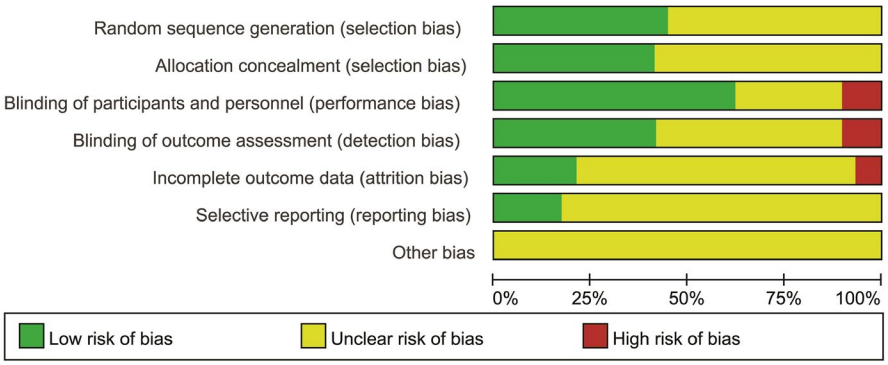

FIGURE 5 Risk of bias graph

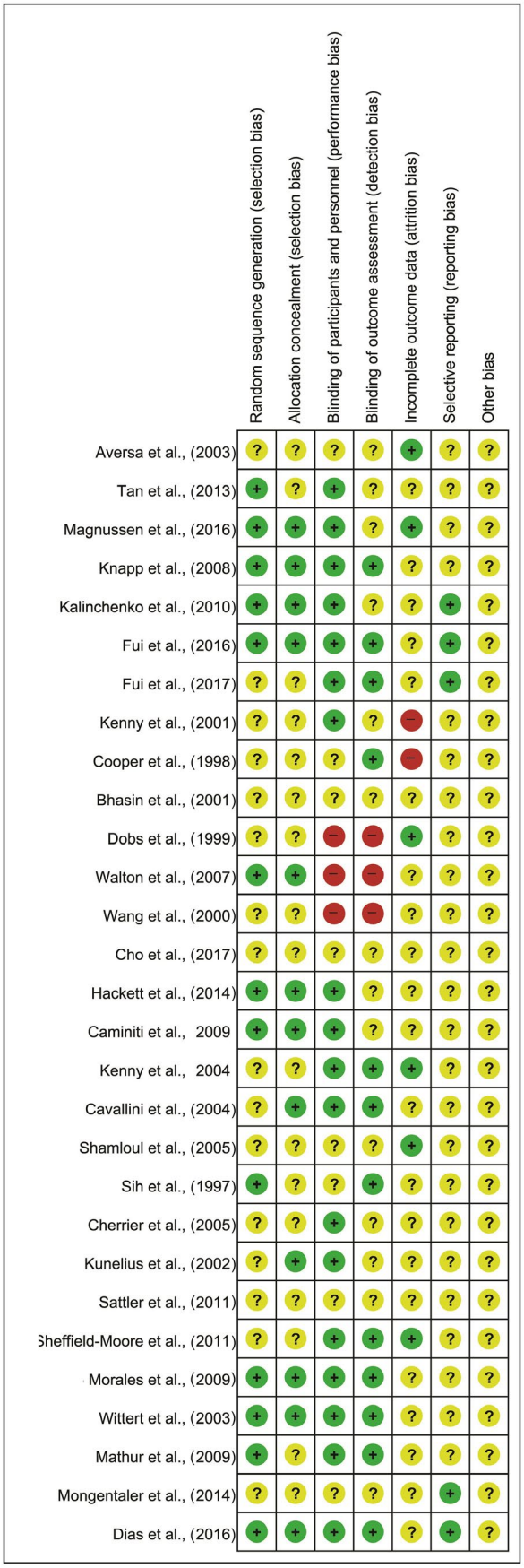

FIGURE 6 Risk of bias assessment. Green plus: low risk of bias, Yellow question: unclear risk of bias, Red minus: high risk of bias

statistical evidence of publication bias in the meta-analysis of either the first strategy ($P = .6786$) or the second strategy ($P = .9934$).

A sensitivity analysis was conducted to evaluate the effect of individual studies on the overall results by removing one study at a time. The meta-analysis results are considered to be statistically reliable due to the fact that there was no significant change in results with the omission of any study.

4 | DISCUSSION

Our study examined the relationship between PSA and testosterone using two different strategies. To date, there have been several meta-analyses investigating the effect of TRT on PSA, but the studies considered did not originally intend to investigate the relationship between PSA and testosterone, but instead intended to investigate the risk of TRT on risk of prostate cancer. This is the first meta-analysis to investigate the relationship between PSA and testosterone to evaluate the possibility of PSA within normal range as a surrogate marker for testosterone. Our study has been investigated based on the fact that PSA is an AR target gene, and a recent study suggests that PSA might be indicative of AR expression, as PSA expression correlates with the transcription of other AR genes. Our study support the previous positive findings from large cohort studies.[28,29]

Our study showed the direct relationship between PSA and testosterone using RCTs, especially by TRT with IM type. This indicates that PSA could also be used to evaluate androgen activity in elderly males. Moreover, this result also reflects that IM type could increase androgen activity more efficiently than the other types. Our study also showed a significant association between PSA and testosterone in groups without symptomatic BPH. Considering the limitation of the routine use of testosterone to check androgen activity due to its diurnal variation and the wide range of its normal value, and additionally considering that there exists a common limitation in those studies that show an association with analyzing circulating sex steroid levels and chronic diseases that provide a valid estimate of the local levels of testosterone, and as bioavailable testosterone does not exist, our study could provide useful information.

Androgen deficiency is commonly related with CVD risk factors, including obesity, hypertension, dyslipidemia, and diabetes.[30] PSA is directly regulated by androgen, and several studies have also shown a possible role of PSA level as a surrogate marker for androgen deficiency.[28,29] Our previous study[15] investigating the association between serum PSA level and subclinical atherosclerosis or CVD mortality was also based on the academic basis suggesting the predictive ability of PSA in reflecting bioactive androgen activity.[29]

The routine clinical use of testosterone assays began about 30 years ago with the development of radioimmunoassays.[31] As a result, there has been remarkable progress in immunoassays for T as well as other hormones.[10] Meanwhile, the assay and evaluation of plasma testosterone raises several problems: (a) Plasma total

TABLE 4 Quality assessment of observational studies by the Newcastle–Ottawa Scale

Study	Selection 1	Selection 2	Selection 3	Selection 4	Comparability A	Comparability B	Exposure 1	Exposure 2	Exposure 3	Scores
Grober (2008)	*	-	-	-	*	-	*	*	*	6
Shukla (2018)	*	*	-	-	*	-	*	*	*	7
Mardanian (2011)	*	*	--	-	*	-	*	*	*	7
Schatz (2000)	*	*	-	-	*	-	*	*	*	7
Kim (1999)	*	-	-	-	*	-	*	*	*	6
Mustafa (2014)	*	-	-	-	*	-	*	*	*	6
Roberts (2004)	*	-	-	-	*	-	*	*	*	6
Rastrelli (2018)	*	*	-	-	*	-	-	*	*	6
Jarow ((2013)	*	-	*	*	*	-	*	*	*	7
Shin (2016)	*	-	-	-	*	*	*	*	*	7
Shim (2018)	*	*	*	-	*	-	*	*	*	8
Rastrelli (2013)	*	-	-	-	*	-	*	*	*	6
Miner (2011)	*	-	-	-	*	-	*	*	*	7
Mifsud (2001)	*	-	-	-	*	-	*	*	*	6
Lee (2014)	*	-	-	-	*	-	*	*	*	6
Ho (2015)	*	-	-	-	*	-	*	*	*	6
Dhindsa (2008)	*	-	-	-	*	-	*	*	*	6
Asiedu (2017)	*	-	-	-	*	-	*	*	*	6
Corona (2010)	*	-	-	-	*	-	*	*	*	6
Tanwar (2015)	*	*	-	-	*	-	*	*	*	7

TABLE 5 Grading of Recommendations, Assessments, Developments, and Evaluation (GRADE) quality assessment of direct evidence of first strategy

Certainty assessment							Number of patients		Effect			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TRT	Placebo	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Change in PSA level												
17	Randomized trials	Serious[a]	Serious[b]	Not serious	Not serious	None	747	643	MD 0.13 higher (0.01 higher to 0.25 higher)		●●◯◯ LOW	Critical
Subgroup: intramuscular type												
10	Randomized trials	Serious[a]	Serious[b]	Not serious	Not serious	None	537	437	MD 0.16 higher (0.01 higher to 0.3 higher)		●●◯◯ LOW	Critical
Subgroup: oral type												
3	Randomized trials	Serious[a]	Serious[b]	Not serious	Serious[c]	None	96	97	MD 0.13 higher (0.29 lower to 0.4 higher)		●◯◯◯ VERY LOW	Important
Subgroup: topical type												
4	Randomized trials	Serious[a]	Not serious	Not serious	Serious[c]	None	114	109	MD 0.13 higher (0.22 lower to 0.2 higher)		●●◯◯ LOW	Important

Abbreviations: CI, confidence interval; HR, hazard ratio; PSA, prostate-specific antigen; TRT, testosterone replacement therapy.

[a]The risk of bias is the highest of the unclear domains.

[b]Significant heterogeneity observed.

[c]The upper and lower limits of 95% CI include both meaningful benefit and harm.

TABLE 6 Grading of Recommendations, Assessments, Developments, and Evaluation (GRADE) quality assessment of direct evidence of second strategy

Certainty assessment							Effect		
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)	Certainty	Importance
Correlation between PSA and testosterone									
12	Observational studies	Not serious	Serious[a]	Not serious	Serious[b]	None	Effect size 0.04 (−0.04 to 0.12)	●◯◯◯ Very Low	Critical
Subgroup: No BPH									
8	Observational studies	Not serious	Serious[a]	Not serious	Not serious	None	Effect size 0.09 (0.02 to 0.15)	●◯◯◯ VERY LOW	Critical
Subgroup: BPH									
4	Observational studies	Not serious	Serious[a]	Not serious	Serious[b]	None	Effect size −0.07 (−0.24 to 0.10)	●◯◯◯ VERY LOW	Important

Abbreviations: BPH, benign prostatic hyperplasia; CI, confidence interval; HR, hazard ratio; PSA, prostate-specific antigen; TRT, testosterone replacement therapy.

[a]Significant heterogeneity observed.

[b]The upper and lower limits of 95% CI include both meaningful benefit and harm.

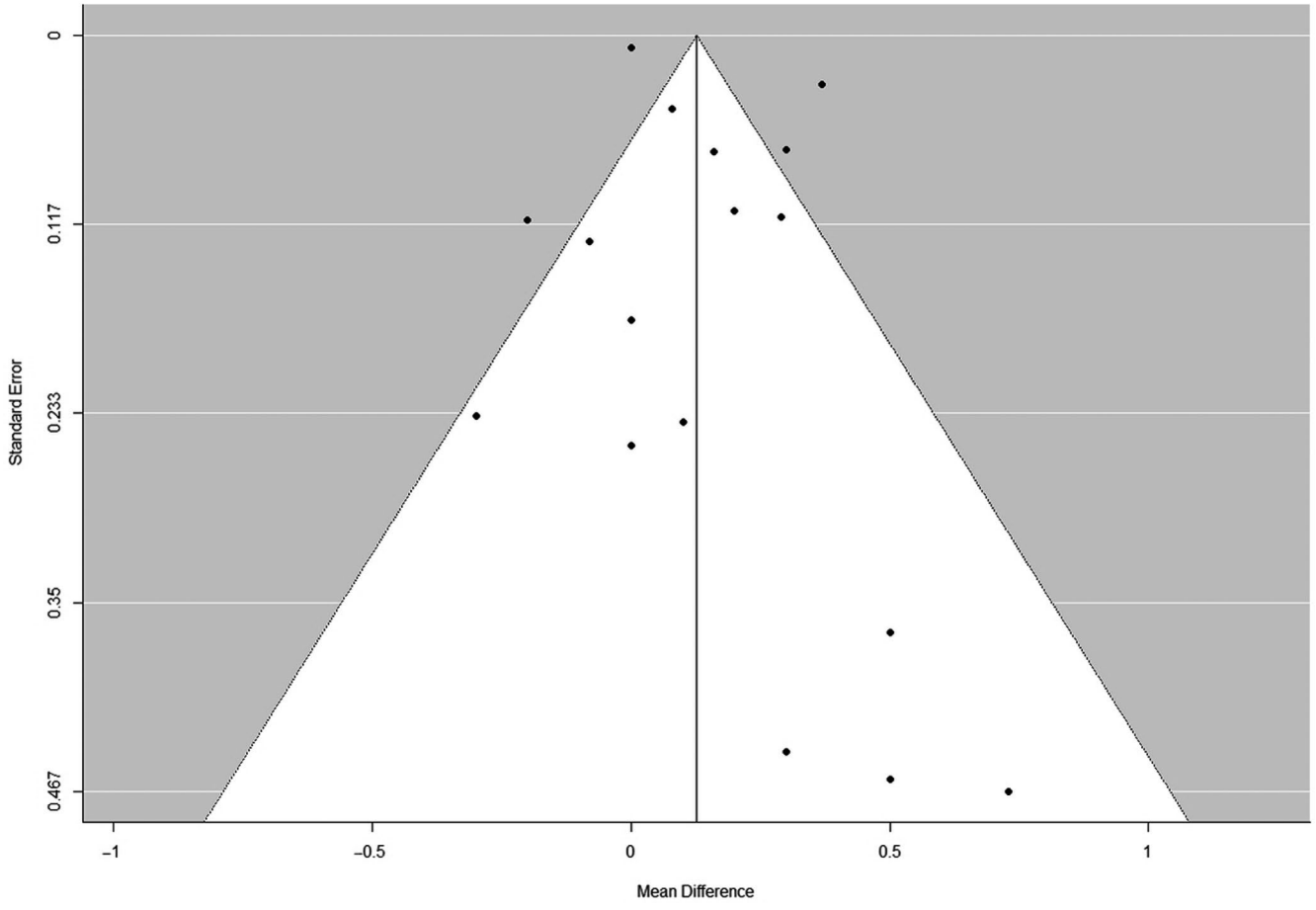

FIGURE 7 Funnel plots for publication bias comparing PSA level change of TRT with placebo

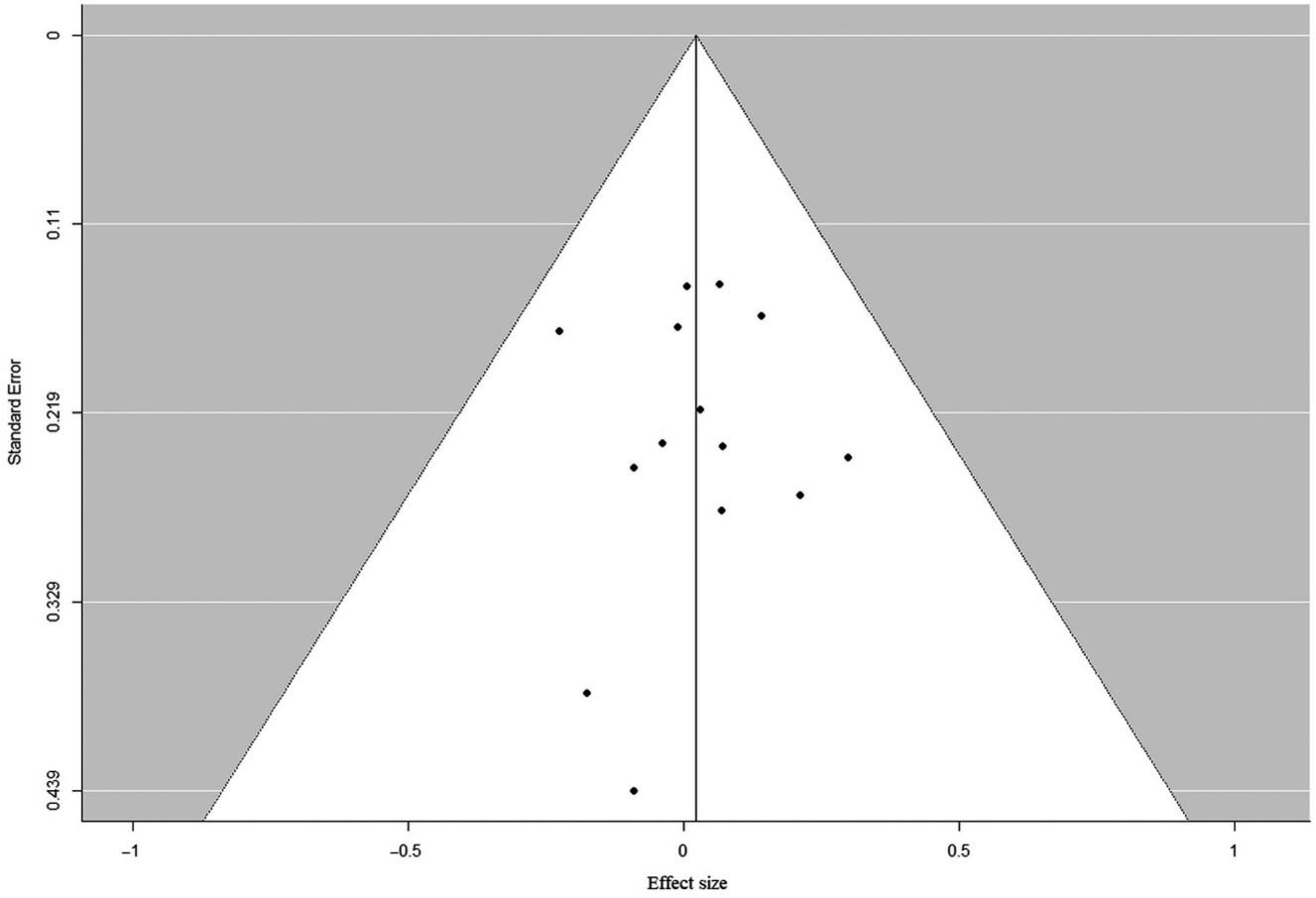

FIGURE 8 Funnel plots for publication bias of studies investigating the relationship between testosterone and PSA

testosterone concentrations can vary by more than three steps, depending on age, gender, and the presence of disease; (b) the concentration of total testosterone differs with the time of day; (c) other similar structures and abundant steroids in the circulation can cause analytical interference; (d) only a very small amount of testosterone is not bound to plasma proteins, raising questions about whether total testosterone or free testosterone is the most clinically useful method; (e) the normal range corrected by age and gender using standardized methods is typically insufficient; and (f) there is no universally accepted testosterone calibration standard.[11] In addition, the biological effects of testosterone are known to be interceded by hormonal levels as well as the transcriptional efficiency of the androgen receptor, which shows a relative inter-individual variance.[32] The level of testosterone shows variation in fasting and non-fasting conditions.[33] To date, androgen activity is most extensively predicted by the variable length of a polyglutamine stretch in the N-terminal domain of the receptor. However, this parameter could not be used in real clinical practice due to low cost-effectiveness. It is difficult to evaluate androgenicity solely through testosterone level due to the drawbacks described above. Therefore, we performed a systematic review and meta-analysis to identify the potential of PSA as a surrogate maker of testosterone.

We reported that, in the first strategy, TRT significantly increases the PSA level compared to that of the placebo group. Further, a meta-analysis of observational studies reported that serum testosterone and PSA level were highly correlated in patients without BPH. This inconsistent relationship between testosterone and PSA could be also explained by "saturation model".[34] Corona et al[28] found that PSA is sensitive to serum testosterone level at or below the near-severe hypogonadism, but it is insensitive to serum testosterone level above this concentration. With aging, confounding factors including BPH, prostatitis, or prostate cancer could attenuate this sensitivity, as shown in our study the association between PSA and testosterone was observed in only non-BPH groups.

In our study, among the testosterone replacement therapies, only injection showed the relationship between PSA and testosterone. Hence, it could not be generalized that PSA is directly related with serum testosterone. However, there are differences on the effect to raise serum testosterone according to types of testosterone replacement therapy. Pastusza et al[35] reported that overall, total testosterone and free testosterone levels were significantly higher in men receiving injectable treatment than other types of treatment. We added this content in discussion section.

Dihydrotestosterone (DHT) is the 5α-reduced metabolite of testosterone that is mainly converted from testosterone in target organs such as prostate, skin, and liver.[36] The skin has been recognized as a major site of the androgen metabolism along with the prostate and male genitalia.[37] While both testosterone and DHT can bind to AR, DHT has ten-fold higher affinity to AR than

testosterone.[38] AR, when bound to its ligand (ie, DHT or testosterone), moves from the cytosol to the nucleus and acts as a transcription factor that regulates the expression of target genes such as PSA.[39]

Both PSA and testosterone have circadian rhythms, and there is a temporal relationship of about eight hours between the two rhythms with the highest testosterone levels, compared to those with PSA, suggesting that there might be an inverse relationship between the overall levels of these two compounds.[40] Although PSA could be a good candidate as a marker of bioactive testosterone circulating levels in men, the relationship between serum PSA and testosterone levels is still generally unaccepted: some authors accept a positive correlation[28,41] while others do not.[42,43] The association study between PSA and testosterone dates back to 1992, when Hanash et al reported that prolonged parenteral androgen therapy for one year resulted in the hypersecretion of PSA.[44] The low level of PSA may predict hypogonadism-related symptoms and signs independently of total T levels.[29] Corona et al[28] showed the relationship between testosterone and PSA levels as a scatter plot along with a best fitting regression curve (calculated $R^2 = 0.034$).

The androgen dependency of PSA may be related to the androgen-responsive elements present in the promoter of the PSA gene.[45] The accuracy of low PSA when screening for subjects with potential hypogonadism decreases with age and is less sensitive but more specific in younger individuals due to the fact that androgens regulate PSA levels in a dose-dependent manner in healthy young men.[29,46]

In aged subjects, high PSA may actually have different determinants and may therefore retain less specificity.[47] Morgentaler et al suggested that the human prostate is sensitive to the massive androgen ablation state of castration level but is not susceptible to normal or abnormal (as in late-onset hypogonadism).[34] Therefore, the human prostate androgen receptor is less susceptible to T increases, such as those caused by TRT in the case of mild hypogonadism, as it is "saturated" by the circulating androgens. Based on the "saturation hypothesis",[34] a significant relationship is only obvious in the low testosterone level and is therefore clear in studies assessing TRT in hypogonadal participants,[8,48,49] but not in those evaluating eugonadal subjects.[34,43,50] Meikle et al reported a negative correlation between prostate volume and testosterone levels.[51] Therefore, in patients with BPH, testosterone and PSA may not be significantly correlated due to saturation of androgen receptors. Rastrelli et al suggested that PSA does not increase beyond a certain threshold as a function of increasing total testosterone levels.[29] They suggested threshold of 0.65 ng/mL as the PSA value with the best sensitivity and specificity in detecting severe hypogonadism. This means that men with testosterone values below a threshold are likely to experience a rise in PSA. The low PSA level of diabetic men may be explained by the significantly lower serum testosterone levels in men with type 2 DM, which confirms the direct role of hypogonadism in PSA values that has been reported by many studies.[52-55]

Our study is not devoid of limitations. The duration and dose of TRT of the RCTS in the analysis of the first strategy is very heterogeneous. Moreover, we categorized short-acting injections and depot ones in the same group. The short-acting T injections may be caused sensations of fluctuations in androgen serum concentrations.[56] In addition, the issue of normalization of testosterone after long term follow-up could not be identified in this study. The age range is too broad, and the characteristics of the patients (ie, healthy person, diabetes mellitus, human immunodeficiency virus, chronic heart failure, erectile dysfunction, cognitive impairment, and metabolic syndrome) were very heterogeneous in the inclusion criteria. Although the indicated diseases for TRT and age groups are heterogenous among RCTs, most of the studies have included aged males, which suggests that PSA within normal range could reflect androgen activity not only in young males but also in aged males. The second strategy may suffer from a selection bias due to its inclusion of only retrospective and cross-sectional studies. These limitations may have affected the outcome and made robust recommendations difficult. However, those included number of males among observational studies are a large number, which cannot be ignored. For the general acceptance of PSA as a surrogate marker among males within normal PSA levels and without symptomatic BPH, well-designed multicenter randomized studies are needed. The last limitation is marginally significant observed difference in PSA levels during TRT, which have possibility to reflect low clinical relevance. Considering PSA as a surrogate marker for testosterone during TRT is extremely hard due to the fact that just the intramuscular formulation of testosterone may increase PSA of about 0.01-0.30 ng/ml, which in almost every clinical situation has to be considered as a modification. Although our study showed by the first time that PSA is related with testosterone both from RCTs and observational studies, we could not suggest age-specific PSA as a surrogate marker to predict androgen status. Moreover, without BPH conditions, the correlation showed strong significance. Lastly, our study is not showing the association between free testosterone or sex hormone binding globulin (SHBG) and PSA. About not analyzing free testosterone and SHBG, only few studies included data on free testosterone and SHBG, hence, analyzing free testosterone and SHBG was impossible. Further studies are needed to define absolute cut off value to define PSA as a surrogate marker for androgen activity.

5 | CONCLUSION

We found that TRT significantly changed the PSA level compared to the placebo group, among which IM type was the most effective. Furthermore, there was a significant correlation between PSA and testosterone in patients with BPH. We suggest that PSA within the normal range and without symptomatic BPH may serve as a surrogate marker of testosterone. Well-designed multicenter randomized studies will be needed to increase the quality of evidence.

DECLARATION OF INTERESTS

All authors have nothing to disclose.

ACKNOWLEDGMENTS

This work was supported by Soonchunhyang University Research Fund.

AUTHORS' CONTRIBUTIONS

JHK and SR designed the study. DKK, HYL, JJP, and JHK searched the literature. DKK, HYL, JJP, and JHK extracted the data. MJB analyzed the data. DKK, JWN, and YC interpreted the data. DKK and JHK drafted the manuscript, and all authors critically reviewed the manuscript.

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How to cite this article: Kim DK, Noh J-W, Chang Y, et al. Association between prostate-specific antigen and serum testosterone: A systematic review and meta-analysis. *Andrology*. 2020;8:1194–1213. https://doi.org/10.1111/andr.12806