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The Effect of Testosterone Replacement Therapy on Prostate-Specific Antigen (PSA) Levels in Men Being Treated for Hypogonadism

A Systematic Review and Meta-Analysis

De-Ying Kang, MD and Hong-Jun Li, PhD

Abstract: Testosterone replacement therapy is used for the treatment of age-related male hypogonadism, and prostate-specific antigen (PSA) is a primary screening tool for prostate cancer. The systematic review and meta-analysis aimed to determine the effect of testosterone replacement therapy on PSA levels.

Medline, *Cochrane Library*, *EMBASE*, and *Google Scholar* databases were searched until February 28, 2014, and inclusion criteria were as follows: randomized controlled trial; intervention group received testosterone/androgen replacement therapy; control group did not receive treatment; and no history of prostate cancer. The primary outcome was change of PSA level between before and after treatment. Secondary outcomes were elevated PSA level after treatment, and the number of patients who developed prostate cancer.

After initially identifying 511 articles, 15 studies with a total of 739 patients that received testosterone replacement and 385 controls were included. The duration of treatment ranged from 3 to 12 months. Patients treated with testosterone tended to have higher PSA levels, and thus a greater change than those that received control treatments (difference in means of PSA levels = 0.154, 95% confidence interval [CI] 0.069 to 0.238, $P < 0.001$). The difference in means of PSA levels were significant higher for patients that received testosterone intramuscularly (IM) than controls (difference in means of PSA levels = 0.271, 95% CI 0.117–0.425, $P = 0.001$). Elevated PSA levels after treatment were similar between patients that received treatment and controls (odds ratio [OR] = 1.02, 95% CI 0.48–2.20, $P = 0.953$). Only 3 studies provided data with respect to the development of prostate cancer, and rates were similar between those that received treatment and controls.

Testosterone replacement therapy does not increase PSA levels in men being treated for hypogonadism, except when it is given IM and even the increase with IM administration is minimal.

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Abbreviations: BPH = benign prostatic hypertrophy, CI = confidence interval, DM = diabetes mellitus, HIV = human immunodeficiency virus, IM = intramuscular, OR = odds ratio, PO = oral/per os, PSA = prostate-specific antigen, RCT = randomized controlled trial.

INTRODUCTION

Testosterone replacement therapy has become widely accepted for treating age-related and other forms of hypogonadism in men, and is associated with improved mood, increased sexual desire and performance, increased muscle mass and bone mineral density, and improved quality of life.[1–6] Prostate cancer is the most commonly diagnosed male cancer, typically in the sixth and seventh decades of life, and the lifetime risk is approximately 16%.[7] Screening for prostate cancer includes measurement of prostate-specific antigen (PSA) level and digital rectal examination.[8] PSA levels are increased in patients with prostate cancer, and a PSA level $\geq$4.0 ng/mL is generally considered elevated and a further evaluation, including a biopsy, is typically performed.[8] PSA is prostate specific, but not prostate cancer specific, and levels can be altered by medications, benign prostatic hypertrophy (BPH), prostatitis, and urologic manipulations.[8]

Reducing androgen levels to the castrate range has been clearly shown to reduce prostate cancer growth.[9] Conversely, based on early reports, the administration of testosterone was believed to promote prostate cancer growth, and was considered contraindicated in men at risk for prostate cancer.[10,11] With the identification of the adverse consequences of low testosterone levels in men with aging, and the benefits of testosterone replacement, the association of prostate cancer and testosterone has been reexamined and current suggests that testosterone replacement is safe with respect to the development of prostate cancer.[1,12–15]

As PSA is a primary screening tool for prostate cancer, and testosterone replacement therapy is being widely used for the treatment of age-related male hypogonadism, the purpose of this systematic review and meta-analysis was to determine the effect of testosterone replacement therapy on PSA levels in men being treated for hypogonadism.

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From the Department of Evidence based Medicine and Clinical Epidemiology (D-YK), West China Hospital, Sichuan University, Chengdu; and Urological Department of Peking Union Medical College Hospital (PUMCH) (H-JL), Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China.
Correspondence: Hong-Jun Li, Urological Department of Peking Union Medical College Hospital (PUMCH), Peking Union Medical College, Chinese Academy of Medical Sciences, No. 1 Shuaifu, Eastern District, Beijing 100730, China. (e-mail: hongjun63@163.com).
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MATERIALS AND METHODS

Literature Search Strategy

This systematic review and meta-analysis was conducted in accordance with PRISMA guidelines.[16] *Medline*, *Cochrane Library*, *EMBASE*, and *Google Scholar* databases were searched until February 28, 2014, using combinations of the following search terms: testosterone, androgen, prostate cancer, prostatic neoplasms, prostate-specific antigen, PSA, hypogonadism, and gonadal disorders. Reference lists of relevant studies were hand searched. Ethical approval of this study was waived, as systematic review and meta-analyses do not involve patients.

Selection Criteria and Data Extraction

Inclusion criteria were as follows: randomized controlled trial or prospective nonrandomized study; intervention group received testosterone replacement therapy or androgen replacement therapy; control group did not receive testosterone and may have received placebo or conventional treatment; 18 or more years of age; male gender; no history of prostate cancer. Retrospective studies, single-arm studies, those with no numerical data for the outcomes of interest, and letters, comments, case studies, and editorials were excluded. Studies were identified by the search strategy by 2 independent reviewers, and a third reviewer was consulted when disagreement arose.

Data extracted from studies that met the inclusion criteria were the name of the first author, year of publication, study design, demographic data of individuals, dosage and administration of testosterone, and outcomes. Data extraction was performed by 2 independent reviewers, and a third reviewer was consulted for any uncertainties.

Quality Assessment

The methodological quality of each study was assessed using the risk-of-bias assessment tool outlined in the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0)[17] by 2 reviewers, and a third reviewer was consulted for any uncertainties.

Outcome Measures and Data Analysis

The primary outcome measure was the change of PSA level between before and after treatment (PSA_{after} - PSA_{before}). The secondary outcomes were the number of patients with an elevated PSA level after treatment, and the number of patients who developed prostate cancer. Data between groups were compared overall, and by route of administration. For the difference of PSA levels between before and after treatment, the difference in means with 95% confidence interval (CI) between testosterone and control treatments was calculated. A difference in means >0 indicates testosterone is favored, which means that testosterone was associated with a greater change in PSA level than control treatment, whereas a difference in means <0 indicates testosterone was associated with a smaller change in PSA level than control treatment. Odds ratios (OR) with 95% CIs were calculated and compared between testosterone and control treatments. An OR >1 indicates testosterone is associated with a higher percentage of patients with an elevated level than control treatment, whereas an OR <1 indicates testosterone is associated with a lower percentage than control treatment.

A χ^2–based test of homogeneity was performed using Cochran Q statistic and I^2. I^2 indicates the percentage of the total variability in effect estimates among trials because of heterogeneity rather than chance. Random-effects models of analysis were used if heterogeneity was detected ($P < 0.10$, $I^2 > 50\%$). Otherwise, fixed-effects models were used. Pooled difference in means and pooled ORs with corresponding 95% CIs were calculated, and a 2-sided $P < 0.05$ was considered to indicate statistical significance. Sensitivity analysis was carried out for the outcomes using the leave-one-out approach. Publication bias was assessed by constructing a funnel plot and by Egger test. The absence of publication bias is indicated by the data points forming a symmetric funnel-shaped distribution, and a one-tailed significance level >0.05 in Egger test. All analyses were performed using Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ).

RESULTS

Literature Search

A flow diagram of study selection is shown in Figure 1. After initially identifying 511 articles, 430 were excluded and the full texts of 81 were reviewed. Subsequently, 66 were excluded and 15 studies were included in the systematic review and meta-analysis (Table 1).

Study Characteristics and Quality Assessment

Characteristics of the 15 studies included in the meta-analysis are summarized in Table 1, and outcomes are summarized in Table 2. The number of participants that received testosterone treatment ranged from 5 to 237 (total = 739), and the number of participants in the control groups ranged from 5 to 112 (total = 385). In 6 studies, testosterone was administered transdermally, in 7 intramuscularly (IM), and in 2 orally, and the duration of treatment ranged from 3 to 12 months.

The results of the quality assessment of the included studies are shown in Supplemental Figure 1 (http://links.lww.com/MD/A156). Possible performance bias from inappropriate blinding of participants and personnel might be present in 6 studies, and 1 study did not clearly state the blinding process; thus, 53.3% (8/15) of studies had low performance bias (blinding of participants and personnel), and 40.0% (6/15) of studies had high performance bias.

Outcome Measures

Change of PSA Level

Nine of the 15 studies provided complete data regarding PSA levels before and after treatment (Figure 2). In 4 studies, testosterone was administered transdermally, in 4 IM, and in 1 orally. There was no evidence of heterogeneity among the 9 studies (Q statistic = 6.12, $I^2 = 0\%$, $P = 0.634$); thus, a fixed-effects model was used. Overall, patients treated with testosterone tended to have higher PSA levels after treatment, and thus a greater change than those that received control treatments (difference in means of PSA levels = 0.154, 95% CI 0.069–0.238, $P < 0.001$). The difference in means of PSA levels were significant higher for patients that received testosterone via the IM route than controls (difference in means of PSA levels = 0.271, 95% CI 0.117–0.425, $P = 0$ .001). The difference in means of PSA levels were similar between patients who received testosterone transdermally and controls (difference in means of PSA levels = 0.085, 95% CI: −0.021 to 0.190, $P = 0.116$).

Elevated PSA Level After Treatment

Seven of the 15 studies provided complete data regarding the number of patients with elevated PSA after treatment; however, 2 studies reported zero patients in the control groups,[21,22] and thus the 2 studies were excluded from the analysis because zero cannot be used to calculate an OR (Figure 3). In 2 studies, testosterone was administered transdermally, and in 2 IM. In only 1 study was testosterone given orally,[24] and that study included 3 intervention groups and 1 control group. Because the study found no difference in relevant PSA elevations between the 3 treatment groups, we pooled the data of the 3 intervention groups and compared the pooled data with the control group and obtained an OR. There was no evidence of heterogeneity among the 5 studies (Q statistic = 4.16, $I^2 = 3.72\%$, $P = 0.385$); thus, a fixed-effects model was used. The rates of elevated PSA levels after treatment were similar between patients that received testosterone and controls (OR = 1.02, 95% CI 0.48–2.20, $P = 0.953$). The results were similar when the analysis was performed for testosterone given transdermally and IM.

Development of Prostate Cancer

Only 3 studies provided data with respect to the development of prostate cancer (Table 2). Shigehara et al[21] reported no cases of prostate cancer in the testosterone or control groups with a treatment duration of 12 months. Marks et al[25] reported a prostate cancer rate of 9.5% in the testosterone group as compared with a 21.1% rate in the control group with a treatment duration of 12 months.

Sensitivity Analysis

Sensitivity analyses using the leave-one-out approach indicated the direction and magnitude of the combined estimates did not change markedly with the exclusion of individual studies, indicating that the meta-analysis had good reliability (Supplemental Figure 2, http://links.lww.com/MD/A157, http://links.lww.com/MD/A158).

Publication Bias

Funnel plot symmetry and Egger test indicated there was no publication bias for either PSA level change between before and after treatment or elevated PSA level after treatment (Supplemental Figure 3, http://links.lww.com/MD/A159, http://links.lww.com/MD/A160).

DISCUSSION

The results of this meta-analysis showed that testosterone replacement was not associated with an increase in PSA level, although a slight increase was seen when testosterone was given

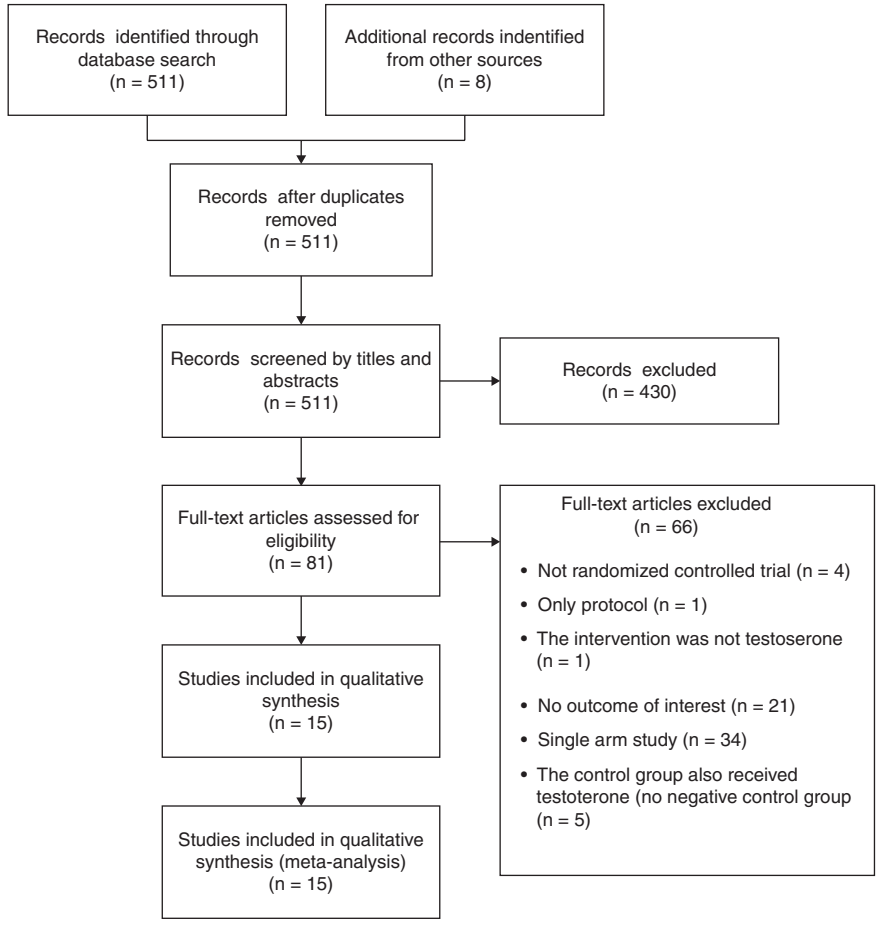

FIGURE 1. Flow diagram of study selection.

TABLE 1. Characteristics of the Studies Included in the Meta-Analysis

First author	Study Design	Diagnosis	Testosterone Treatment			Control			Duration	Route
			Number of patients	Age (year)	Dose/Frequency	Number of patients	Age (years)	Type of control		
Kaufman[18]	RCT	Hypogonadal men	170	52.9 ± 9.6	1.62% testosterone gel	26	55.8 ± 10.8	Placebo	6 months	Transdermal
Bauman[19]	Prospective, nonrandomized, placebo controlled	Hypogonadal men with spinal cord injury	11	43 ± 6	Testosterone patch 5 mg/day	11	35 ± 9	Control	12 months	Transdermal
Jones[20]	RCT	Hypogonadal men with type 2 DM and/or metabolic syndrome	108	59.9 ± 9.1	2% testosterone gel; q.d.	112	59.9 ± 9.4	Placebo	12 months	Transdermal
Shigehara[21]	RCT	Hypogonadal men with benign prostate hypertrophy	23	72.0 ± 6.5	Testosterone enanthate 250 mg; every 4 weeks	23	68.9 ± 9.1	Placebo	12 months	IM
Gopal[22]	RCT	Hypogonadal men with type 2 DM	11	44.23 ± 3.29	Testosterone 200 mg; every 15 days	11	NA	Placebo	3 months	IM
Andrade[2]	RCT	Hypogonadal men	17	70.6 ± 6.1	Testosterone cypionate 200 mg; every 3 weeks	14	NA	Hypogonadal males, no testosterone (n = 14) + nonhypogonadal controls (n = 31)	24 weeks	IM
Chiang[23]	RCT	Hypogonadal men	20	Range (20– 75)	1% testosterone gel; q.d.	20	NA	Placebo	3 months	Transdermal
Legros[24]	RCT	Hypogonadal men	78	59.5 ± 6.5	Testosterone undecanoate 80 mg/day	79	58.4 ± 5.5	Placebo	12 months	PO
			82	58.4 ± 5.7	Testosterone undecanoate 80 mg; b.i.d. (160 mg/day)					
			77	58.6 ± 5.7	Testosterone undecanoate 80 mg; TID (240 mg/day)					
Marks[25]	RCT	Hypogonadal men	21	Median 68, Range (44, 78)	Testosterone enanthate 150 mg; every 2 weeks	19	Median 70 Rang (45, 78)	Placebo	6 months	IM
Merza[26]	RCT	Borderline hypogonadal men	20	63 ± 9	Testosterone patch 5 mg/day	19	59.7 ± 10.2	Placebo	6 months	Transdermal
Okun[27]	RCT	Parkinson disease	15	66.7 ± 10.26	Testosterone enanthate 200 mg; every 2 weeks	15	69.9 ± 9.41	Placebo	8 weeks	IM
Park[4]	Prospective, nonrandomized, placebo controlled study	Men with primary hypogonadism or andropause with sexual dysfunction	33	NA	Testosterone undecanoate 80 mg; b.i.d. (160 mg/day)	6	NA	Placebo	3 months	PO
Tan[28]	RCT	Hypogonadal men with Alzheimer disease	5	Mean 72.4 Range (68, 80)	Testosterone enanthate 200 mg; every 2 weeks	5	Mean 68.9, Range (67, 82)	Placebo	12 months	IM
Bhasin[29]	RCT	Hypogonadal men with HIV infection	20	range (18, 60)	Testosterone patch 5 mg/day	21	NA	Placebo	12 weeks	Transdermal
Sih[30]	RCT	Hypogonadal men	17	65 ± 7	Testosterone cypionate 200 mg; every 14–17 days	15	68 ± 6	Placebo	12 months	IM

Data reported as mean ± standard deviation unless otherwise indicated. RCT = randomized controlled trial; DM = diabetes mellitus; HIV = human immunodeficiency virus; IM = intramuscular; PO = oral / per os; NA = not available.

TABLE 2. Clinical Outcomes (PSA Levels and Elevated PSA Concentrations) of Included Studies

First Author	Route	Treatments	Number of Patients Evaluated (PSA Level Change)	PSA Level (ng/mL) Pre- → Post-Treatment	Number of Patients Evaluated (PSA Level Elevation)*	Number of Patients With Elevated PSA Level	Number of Newly Developed Prostate Cancers
Kaufman[18]	Transdermal	Testosterone	191	NA	191	10 (5.2%)	NA
		Control	28	NA	28	3 (10.7%)	NA
Bauman[19]	Transdermal	Testosterone	11	0.9 (0.7) → 1.1 (0.8)	NA	NA	NA
		Control	11	1.3 (1.0) → 1.3 (0.6)	NA	NA	NA
Jones[20]	Transdermal	Testosterone	88	1.50 (1.80) → 1.41 (1.29)	NA	NA	NA
		Control	92	1.19 (1.18) → 1.18 (1.17)	NA	NA	NA
Shigehara[21]	IM	Testosterone	23	1.055 ± 0.531 → 1.377 ± 0.756	23	1 (4.3%)	0 (0%)
		Control	23	$1.062 \pm 0.531 \rightarrow 1.336 \pm 1.050$	23	0 (0%)	0 (0%)
Gopal[22]	IM	Testosterone	11	NA	11	0 (0%)	NA
		Control	9	NA	9	0 (0%)	NA
Andrade[2]	IM	Testosterone	17	1.29 (0.7) → 1.89 (1.5)	NA	NA	NA
		Control	14	3.26 (3.89) → 2.31 (3.01)	NA	NA	NA
		Healthy control	31	2.38 (4.27) → 2.89 (5.39)	NA	NA	NA
Chiang[23]	Transdermal	Testosterone	20	change: 0.074 (0.208)	NA	NA	NA
		Control	20	change: -0.069 (0.436)	NA	NA	NA
Legros[24]	PO	Testosterone 80 mg/day	78	Pre-treatment all < 4	78	5 (6.5%)	1 (1.3%)
		Testosterone 160 mg/day	82		82	3 (3.8%)	0 (0%)
		Testosterone 240 mg/day	77		77	4 (5.3%)	0 (0%)
		Control	79		79	4 (5.1%)	0 (0%)
Marks[25]	IM	Testosterone	21	change: 0.90 (0.89)	21	NA	2 (9.5%)
		Control	19	change: 0.60 (1.55)	19	NA	4 (21.1%)
Merza[26]	Transdermal	Testosterone	20	NA	20	5 (25%)	NA
		Control	19	NA	19	1 (6%)	NA
Okun[27]	IM	Testosterone	15	NA	15	1 (3.3%)	NA
		Control	15	NA	15	1 (3.3%)	NA
Park[4]	PO	Testosterone	33	0.7 (0.4) → 0.7 (0.4), n = 29	NA	NA	NA
		Control	6	0.6 (0.4) → 0.9 (0.3), n = 6	NA	NA	NA
Tan[28]	IM	Testosterone	5	0.98 → 1.37	NA	NA	NA
		Control	5	NA	NA	NA	NA
Bhasin[29]	Transdermal	Testosterone	14	change: 0.05 ± 0.04	20	0 (0%)	NA
		Control	18	change: -0.01 ± 0.24	21	0 (0%)	NA
Sih[30]	IM	Testosterone	10	change: 0.7 ± 0.2	10	NA	NA
		Control	12	change: 0.4 ± 0.2	12	NA	NA

IM = intramuscular, PO = oral/per os, NA = not available.

* Bhasin[29] used different data sets for evaluating different outcomes. For PSA level, 32 patients were evaluated. For the number of patients with elevated PSA level and the number of patients who developed prostate cancer, 41 patients were evaluated.

IM. Although only 3 of the 15 studies reported the incidence of prostate cancer, there was no difference between the treatment and control groups in the 3 studies.

Early studies suggested that the administration of testosterone could promote prostate cancer growth,[10,11] and later studies showed that reducing androgen levels to the castrate range reduced prostate cancer growth.[9] These data led to the supposition that raising serum testosterone levels with replacement therapy could cause an occult prostate tumor to grow into an aggressive lesion.[13] Current data, however, indicate that variations of testosterone levels within the physiological range have little, if any, impact on prostate cancer growth, a low testosterone level may be associated with a high-risk for developing prostate cancer, and that normal testosterone levels play a protective role against prostate cancer.[13,14,31–33]

Of the studies included in this meta-analysis, the earliest was performed in 1997 by Sih et al,[30] who studied hypogonadal men with a mean age of 68 years and reported that testosterone supplementation (200 mg testosterone cypionate biweekly for 12 months) improved strength, increased hemoglobin levels, and lowered leptin levels. Andrade et al[2] also treated hypogonadal men with IM testosterone for 6 months and reported an improvement in body composition. Chiang et al[23] and Park et al[4] both reported that testosterone replacement improved quality of life and sexual function in men with testosterone deficiency. In one of the larger studies included in the current analysis, Legros et al[24] examined the effect of oral testosterone undecanoate in men with symptomatic hypogonadism in a multicenter, randomized, double-blind, placebo-controlled trial and found that testosterone replacement did not improve the total Aging Males' Symptom score after 6 months of treatment, except in the sexual symptom subdomain were a modest improvement seen with a dose of 160 mg/day. In other included studies, Bauman et al[19] reported that transdermal testosterone improved lean tissue mass in men with spinal cord injuries, and Merza et al[26] found that transdermal testosterone increased lean body mass and decreased bone absorption in men with borderline hypogonadism. Interestingly, 2 of the included studies examined the effect of testosterone replacement in men with type 2 diabetes mellitus and whereas one[22] found that IM testosterone did not have an effect on insulin resistance or dyslipidemia, the other[20] showed that transdermal replacement

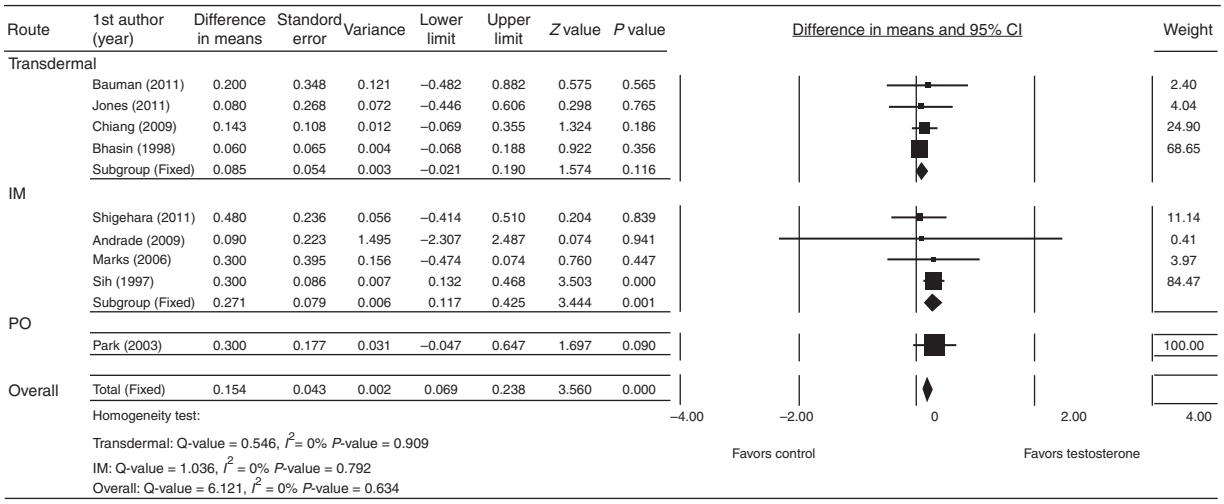

FIGURE 2. Forest plot comparing PSA level change between patients receiving testosterone treatment via transdermal, oral (PO) and intramuscular (IM) routes versus control treatments. CI = confidence interval, Lower limit = lower bound of the 95% CI; Upper limit- = upper bound of the 95% CI.

had a beneficial effect on insulin resistance and lipid levels. Importantly, Marks et al[25] showed that 6 months of IM testosterone enanthate normalized serum testosterone levels and had little effect on prostate tissue androgen levels or function.

With respect to PSA levels, although not included in the meta-analysis, El-Sakka et al[34] showed no significant change in PSA level after 1 year of testosterone replacement in hypogonadal men with erectile dysfunction, with other studies reporting similar findings.[35,36] Coward et al[37] showed that PSA levels remain stable after administration of testosterone for ≥5 years, and that the incidence of prostate cancer in men receiving replacement therapy was no greater than that of the general population. The contradiction that androgen deprivation can markedly reduce the growth of prostate cancer while administration of testosterone replacement does not affect prostate cancer incidence or growth has been addressed by the saturation model.[14] The model is based on the observation that the prostate is very sensitive to changes in androgens at low concentrations, but exhibits little or no sensitivity to changes at higher androgen concentrations, that is, there is a plateau at which further increases in androgen concentrations elicit no additional response from the prostate.

A primary limitation of this study is the heterogeneity of the studies including the populations examined, testosterone replacement regimes, dosages, and length of therapy, and

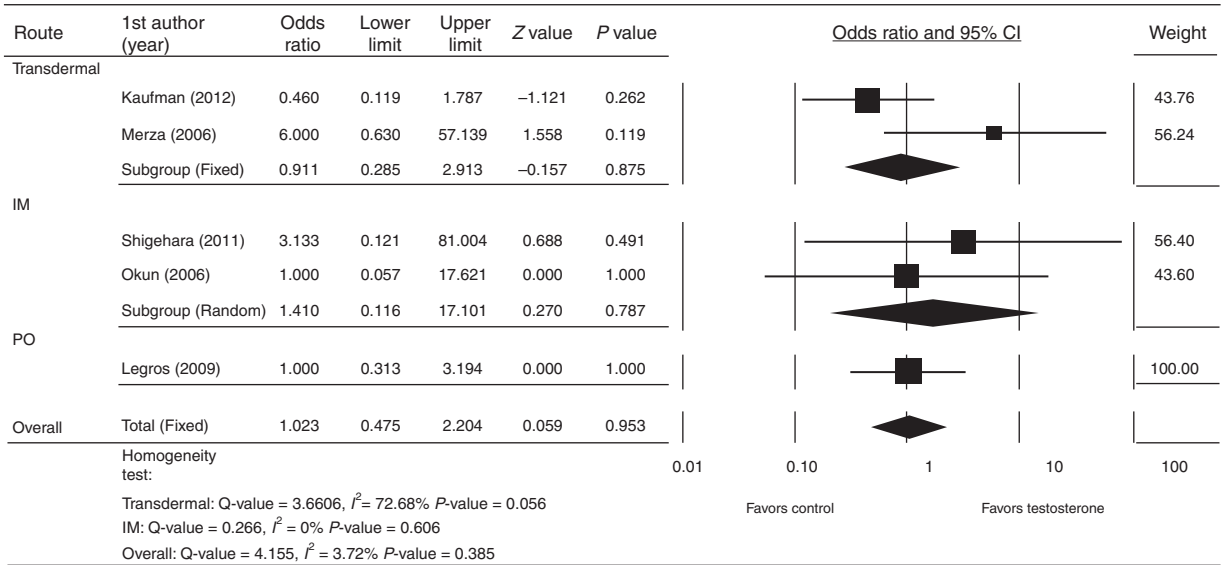

FIGURE 3. Forest plot comparing the number of patients with elevated PSA level after treatment between patients receiving testosterone treatment via transdermal, oral (PO) and intramuscular (IM) routes versus control treatments. CI = confidence interval, Lower limit = lower bound of the 95% CI, Upper limit = upper bound of the 95% CI.

baseline PSA levels. In addition, data in the studies included were not sufficient to estimate the risk of developing prostate cancer.

CONCLUSION

The results of this study indicate that testosterone replacement therapy does not increase PSA levels in men being treated for hypogonadism, except when it is given IM and even the increase with IM administration is minimal. Data of the included studies were not sufficient to evaluate the risk of prostate cancer with testosterone replacement therapy; however, based on evidence in the literature it does not appear that the risk of prostate cancer is affected by testosterone replacement therapy.

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