Efficacy and safety of testosterone replacement therapy in men with hypogonadism: A meta-analysis study of placebo-controlled trials

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Abstract. The purpose of the present meta-analysis was to evaluate the efficacy and safety of testosterone replacement therapy in men with hypogonadism. A search was conducted for appropriate randomized controlled trials and the data from 16 trials were pooled. The intended primary outcome of the present study was to determine the efficacy and safety of testosterone replacement therapy. The current data demonstrated that scores for Aging Male Symptoms (AMS) were significantly reduced following testosterone replacement therapy, with a mean decrease in AMS score of 1.52 [95% confidence interval (CI), 0.72 to 2.32; P=0.0002]. Testosterone replacement therapy increased lean body mass [mean difference (MD), 1.22; 95% CI, 0.33 to 2.11; P=0.007], reduced fat mass in a non-significantly manner (MD, -0.85; 95% CI, -1.74 to 0.04; P=0.06) and significantly reduced total cholesterol (MD, -0.16; 95% CI, -0.29 to -0.03; P=0.01). No significant differences were identified in body weight (MD, 0.09; 95% CI, -1.13 to 1.31; P=0.89), body mass index (MD, 0.10; 95% CI, -0.62 to 0.82; P=0.78) or bone mineral density (MD, -0.01; 95% CI, -0.03 to 0.02; P=0.60). Average prostate volume increased (MD, 1.58; 95% CI, 0.6 to 2.56; P=0.002) following testosterone replacement therapy, but the levels of prostate-specific antigen (PSA) (MD, 0.10; 95% CI, -0.03 to 0.22; P=0.14) and the International Prostate Symptom Scores (MD, 0.01; 95% CI, -0.37 to 0.39; P=0.96) did not change. In conclusion, testosterone replacement therapy improves quality of life, increases lean body mass, significantly decreases total cholesterol, and is well-tolerated and safe for men with hypogonadism who are exhibiting PSA levels of <4 ng/ml.

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Introduction

Hypogonadism is a highly prevalent disease in middle-aged men and is associated with an increased risk of numerous chronic diseases, including metabolic syndrome, osteoporosis and obesity, which significantly affect quality of life (1). Male hypogonadism can chiefly be divided into two forms; these are fetal-onset male hypogonadism and late-onset hypogonadism (LOH). Fetal-onset male hypogonadism is associated with disorders of sexual development or pubertal development (2). Associated with advanced age, LOH is a clinical and biochemical syndrome with characteristic low serum testosterone levels, amongst other symptoms (3). Previous studies have indicated that LOH has a significant effect upon quality of life, and affects the function of multiple organ systems (4,5).

Testosterone replacement treatment (TRT) was first approved in 1972 by the U.S. Food and Drug Administration as a treatment for the symptoms of male hypogonadism; currently, TRT is prescribed for men diagnosed with androgen deficiency to alleviate symptoms and improve quality of life (5). Previous studies that have assessed the impact of TRT on bone mineral density, body weight, bone mass, total lean body mass, metabolic syndrome and Aging Male Symptoms (AMS) over the past decade have been highly inconsistent (6-21); thus, it remains unclear whether testosterone therapy is beneficial with regard to these features in men with hypogonadism. Furthermore, controversy remains over whether TRT is safe for long-term treatment due to the concern that higher serum testosterone presents an increased risk for prostate cancer, which has been a widely accepted hypothesis for ~70 years (22). In the present study, a meta-analysis was performed to evaluate the efficacy and safety of TRT in men with hypogonadism, which may resolve a number of the current controversies in the use of this drug.

Materials and methods

Eligibility criteria. Inclusion criteria were established prior to a literature search, following the guidelines from the Quality of Reporting of Meta-Analyses conference (23). Only placebo-controlled, randomized controlled trials (RCTs) of men with testosterone deficiency that compared TRT-treated with placebo-treated patients were included. All included studies were required to provide treatment of the subjects for at least 6 months. Studies examining TRT therapy for men

with cancer, benign prostatic hyperplasia (BPH) and diabetes were excluded, in addition to studies of men with a severe organic disease, a mental disease diagnosed by a psychiatrist (for instance, major depression currently being treated with antidepressant medication), Parkinson disease or heart failure.

Search strategy. A literature search was performed in December 2014 using the databases of Medline (www.ncbi.nlm.nih.gov/pubmed), Embase (www.elsevier.com/solutions/embase-biomedical-research), Elsevier (www.sciencedirect.com) and the Cochrane Library (www.cochranelibrary.com). The Medline and Embase searches included only a free-text protocol using the term 'testosterone' within the 'Title' and 'Abstract' fields of the records. Furthermore, the search strategy employed the following limitations: Human subjects, English language publications, RCT publication type and publication time between January 2004 and December 2014. Searches of the Cochrane Library used the same free-text protocol using the terms 'testosterone' and 'hypogonadal' within the 'Title' and 'Abstract' fields of the records, applying no limits. All studies published between January 2004 and December 2014 were considered. A total of 1,435 records were initially collated in this study, with 272 records retrieved from the Elsevier database and 1,158 records from the Medline database and Embase. A total of 5 records were retrieved from the Cochrane Library. The records were independently reviewed by 3 authors in order to identify the studies comparing testosterone and control treatments. Furthermore, other, relevant studies cited in the reference lists of the selected studies (Fig. 1) were also evaluated.

Study selection. The quality of the randomized trials was assessed based on methods as follows: Method of randomization, method of blinding, allocation concealment, evidence of selective reporting and incomplete outcome data. Studies that were deemed of high-quality by consensus among study authors (Fig. 2) were included.

Data extraction. The first outcomes of interest were associated with the efficacy of TRT, including the AMS score, body weight (in kg), body mass index (BMI), bone mineral density (in g/cm^2), total lean body mass (in kg), total fat mass (in kg) and total cholesterol (in mg/dl). AMS score was determined based on the responses to the AMS questionnaire (www.aging-males-symptoms-scale.info/documents/question.pdf), which investigated 17 different symptoms. The second outcomes of interest were associated with the safety of TRT, including the prostate-specific antigen (PSA) level (in ng/ml), International Prostate Symptom Scores (IPSS), prostate volume (in ml) and the nature of adverse events (mild to moderate and serious). Data extraction was independently conducted by 2 investigators, and a third reviewer would make a judgment when disagreement arose regarding eligibility, as described previously (24).

Statistical analysis. Statistical analyses were independently performed by 2 authors who were not involved in data extraction. Q-test was used to measure inter-study heterogeneity. I^2 metric was used to quantify heterogeneity, which is independent of the number of studies included in the cumulative analysis. The I^2 values were 0-100%, with higher values denoting a greater

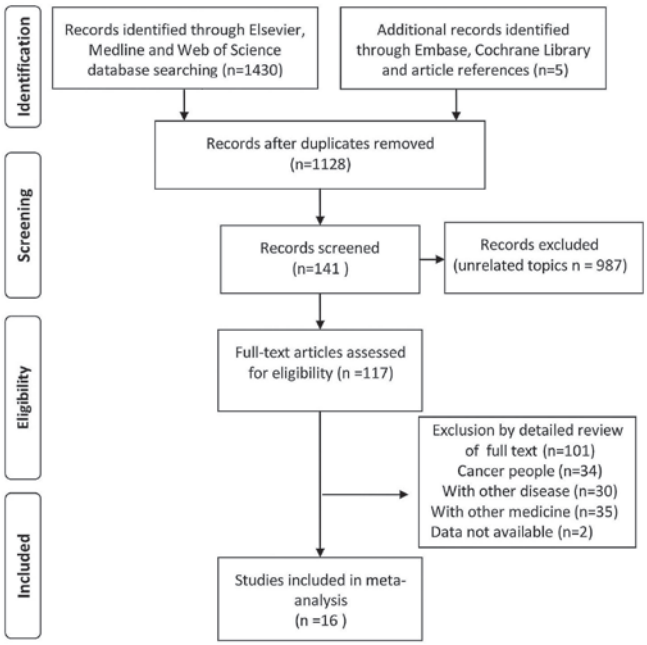

Figure 1. Flowchart of literature searches and results.

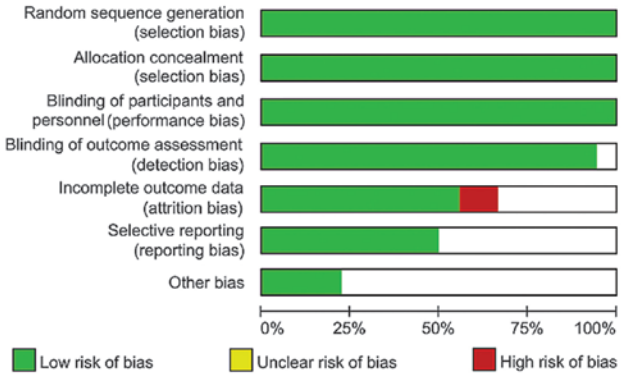

Figure 2. Risk of bias graph. Review authors' judgements regarding each risk of bias item presented as percentages across all included studies.

degree of heterogeneity. I^2<25% reflects a small level of inconsistency, and I^2>50% reflects significant inconsistency. Data were pooled using a fixed-effects model. In studies demonstrating heterogeneity, a sensitivity analysis was conducted in order to establish the cause of heterogeneity. Potential publication bias was identified using a funnel plot, which would suggest a publication bias through asymmetry of the plot. All analyses were performed using RevMan version 5.3 (Cochrane, London, UK). All P-values were calculated using Student's t-test and P<0.05 was considered to indicate a statistically significant difference.

Subgroup and sensitivity analysis. To investigate the causes of heterogeneity, subgroup analyses were made according to the method of administration of testosterone (injection, oral, transdermal) and duration of treatment (6 months vs. >6 months).

Results

Identification of data. A total of 1,435 references were identified in the initial database search. As shown in Table I,

Table I. Study and patient characteristics.

First author, year (ref.)	Country	Sample size, n		Inclusion criteria	Exclusion of PSA levels	Duration of intervention	Dosage and administration method	Main outcomes
		Ex	C					
Amory *et al*, 2004 (8)	USA	24	24	TT<350 ng/dl, Y>65	>4.0 ng/ml	36 months	200 mg TE IM, every 2 weeks	Bone mineral density, prostate volume, PSA
Cavallini *et al*, 2004 (9)	Italy	40	45	FT<6 pg/ml Y>60, with symptoms of androgen decline	>4.0 ng/ml	6 months	TU 160 mg/day, PO	PSA, prostate volume
Page *et al*, 2005 (10)	USA	24	24	TT<350 ng/dl, Y>65	>4.0 ng/ml	36 months	200 mg TE IM, every 2 weeks	Weight, total cholesterol
Marks *et al*, 2006 (11)	USA	21	19	TT< 300 ng/dl, Y=44-78 with symptoms	10.0 ng/ml	6 months	150 mg TE IM, every 2 weeks	IPSS, prostate volume, PSA
Vaughan *et al*, 2007 (12)	USA	24	23	TT<350 ng/dl, Y>65	>4.0 ng/ml	3 years	200 mg TE IM, every 2 weeks	PSA, prostate volume
Emmelot-Vonk *et al*, 2008 (7)	Netherlands	113	110	TT<13.7 nmol/l Y=60-80	Y=60-69, >4.5 µg/l Y>70, >6.5 µg/l	6 months	160 mg/day TU, PO	BMI, body weight, total cholesterol, total lean body mass, total fat mass, IPSS, BMD, adverse event, PSA, prostate volume
Aversa *et al*, 2010 (13)	Italy	40	10	TT<3.0 ng/ml, with metabolic syndrome, Y=45-65	Age-adjusted elevated PSA	24 months	1,000 mg TU IM, every 12 weeks	BMI, total cholesterol
Aversa *et al*, 2010 (14)	Italy	32	10	TT<3.20 ng/ml, with metabolic syndrome, Y=50-65	Age-adjusted elevated PSA	12 months	1,000 mg TU IM, every 12 weeks	BMI, total cholesterol, AMS score, IPSS, prostate volume
Idan *et al*, 2010 (15)	USA	55	55	Healthy, Y>50	>4.0 g/l	24 months	70 mg DHT daily, transdermal	BMI, total cholesterol, prostate volume, IPSS, PSA, mild to moderate adverse event, total lean body mass, BMD
Kalinchenko *et al*, 2010 (16)	Russia	105	65	TT<12.0 nM, with metabolic syndrome, Y=35-70	>4.0 g/l	30 weeks	1,000 mg TU IM, every every 12 weeks	BMI, body weight, total cholesterol, IPSS, prostate volume, PSA
Srinivas-Shankar *et al*, 2010 (17)	New Zealand	130	132	TT<345 ng/dl, presence of frailty, Y>65	>4.0 g/l	6 months	50 mg/day testosterone gel, transdermal	AMS score, total lean body mass, total fat mass, total cholesterol, IPSS, PSA, mild to moderate adverse event, serious adverse event

Table I. Continued.

First author, year (ref.)	Country	Sample size, n		Inclusion criteria	Exclusion of PSA levels	Duration of intervention	Dosage and administration method	Main outcomes
		Ex	C					
Kaufman *et al*, 2011 (18)	USA	234	40	TT<300 ng/dl, Y=18-80	>2.5 g/l	6 months	1.62% testosterone gel, serum total testosterone	Mild-to-moderate adverse event, serious adverse event
Shigehara *et al*, 2011 (19)	Japan	23	23	TT<11.8 pg/ml, with BPH	>2.0 g/l	12 months	250 mg TE IM, every 4 weeks	AMS score, IPSS, PSA
Behre *et al*, 2012 (6)	Germany	183	179	TT<15 nmol/l, Y=50-80 with symptoms of testosterone deficiency	>4.0 g/l	6 months	Hydroalcoholic 1% testosterone gel (50 mg) daily, transdermal	AMS score, BMD, PSA, total lean body mass, total fat mass, bone mass, body weight serious adverse event
Frederiksen *et al*, 2012 (20)	Denmark	20	18	TT<7.3 nmol/l, Y=60-78	>3.0 g/l	6 months	Hydroalcoholic 1% testosterone gel (50 mg) daily, transdermal	BMI, body weight, total cholesterol, total lean body mass, total fat mass, PSA
Ho *et al*, 2012 (21)	Malaysia	60	60	TT>12 nmol/l, Y>40	>4.0 g/l	12 months	1,000 mg TU IM, every 12 weeks	AMS score, serious adverse event, mild to moderate adverse event

Ex, experimental; C, control; PSA, prostate-specific antigen; TT, total testosterone; FT, free testosterone; Y, age in years; TE, testosterone enanthate; IM, intramuscularly; TU, testosterone undecenoate; PO, *per os*; IPSS, International Prostate Symptom Score; AMS, Aging Male Symptom; DHT, dihydrotestosterone; BMI, body mass index; BMD, bone mineral density.

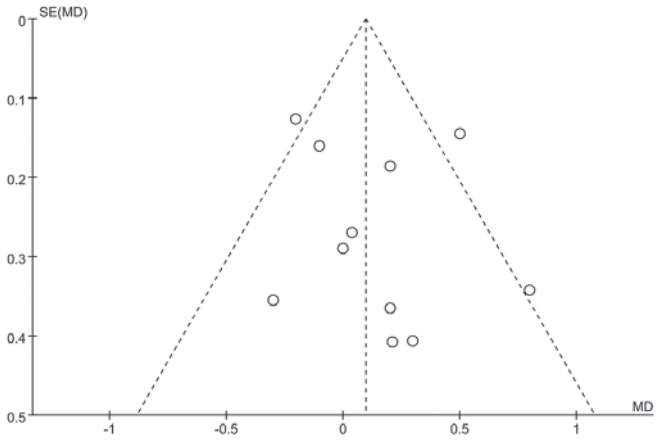

Figure 3. Funnel plot of studies, testing possible publication bias. SE, standard error; MD, mean difference.

through an abstract and full text review, 16 RCTs that met the study criteria were identified. A total of 1,921 patients were randomized across the 16 studies (Table I). All 16 RCTs were double-blinded. A total of 7 RCTs provided treatment for 6 months, with the remainder providing treatment for 1 year. A funnel plot revealed no evidence of publication bias (Fig. 3).

Efficacy

AMS score. A total of 5 RCTs, involving 826 participants (424 in the testosterone group and 402 in the control group), included AMS scores. The present data revealed that the AMS scores improved significantly following TRT. The mean decrease in AMS score was 1.52 (95% CI, 0.72 to 2.32; P=0.0002; Fig. 4A) following TRT. Additional analyses indicated that AMS was significantly improved in short-term studies with transdermal administration (within the same studies), but not in long-term studies with administration via injection. The average decrease in AMS score was 1.74 (95% CI, 0.86 to 2.61; P=0.0001) in short-term and transdermal administration studies, and 0.40 (95% CI, -2.37 to 1.57; P=0.69) in long-term and injection studies.

Body weight. A total of 5 RCTs, involving 841 participants (445 in the testosterone group and 396 in the control group), included body weight data. No significant difference was identified in body weight between the control and the TRT group; the mean difference between these groups was 0.09 (95% CI, -1.13 to 1.31; P=0.89; Fig. 4B). Subgroup analyses indicated that there was no significant change to body weight during the short-term (MD, 0; 95% CI, -1.25 to 1.26; P=0.99) or the long-term (MD, 1.68; 95% CI, -3.86 to 7.22; P=0.55) studies following TRT. Subgroup analyses also indicated that there were no significant changes to body weight associated with administration via injection (MD, 1.68; 95% CI, -3.86 to 7.22; P=0.55), transdermal administration (MD, -1.01, 95% CI, -2.65 to 0.64; P=0.23) or oral administration (MD, 1.4; 95% CI, -0.53 to 3.33; P=0.38).

BMI. BMI measurements were included in 6 RCTs, involving a total of 633 participants (365 in the testosterone group and 268 in the control group). No significant decrease was reported in BMI following TRT; the mean difference between the two groups was 0.10 (95% CI, -0.62 to 0.82; P=0.78; Fig. 4C). The results of the subgroup analyses revealed a mean increase of 0.17 (95% CI, -0.78 to 1.12; P=0.73) during short-term studies and 0.01 (95% CI, -1.1 to 1.12; P=0.98) during long-term studies. Subgroup analyses also indicated that there were no significant differences in BMI following administration by injection (MD, 0.08; 95% CI, -1.32 to 1.48; P=0.91), transdermal administration (MD, 0.14; 95% CI, -1.38 to 1.66; P=0.86) or oral administration (MD, 0.10; 95% CI, -0.62 to 0.82; P=0.85).

Bone mineral density. A total of 4 RCTs, involving 743 participants (375 in the testosterone group and 368 in the control group), included the bone mineral density (BMD) of patients. TRT did not increase BMD in men with hypogonadism compared with control patients. The mean difference between the two groups was -0.01 (95% CI, -0.03 to 0.02; P=0.60; Fig. 4D). Additional analysis of patients' responses to TRT administered with differing duration and administration methods revealed no statistically significant differences associated with duration of treatment (short-term: MD, -0.01; 95% CI, -0.04 to 0.01; P=0.31; long-term: MD, 0.05; 95% CI, -0.02 to 0.12; P=0.17), or with different administration methods (injection: MD, 0.05; 95% CI, -0.02 to 0.12; P=0.17; transdermal: MD, -0.02; 95% CI, -0.04 to 0.01; P=0.26; and oral: MD, 0.0; 95% CI, -0.05 to 0.05; P=0.60) of TRT treatment.

Total lean body mass. A total of 5 RCTs, involving 985 participants (496 in the testosterone group and 489 in the control group), reported upon total lean body mass. Lean body mass was significantly increased following TRT; the mean difference between the two groups was 1.22 (95% CI, 0.33 to 2.11; P=0.007; Fig. 5A). Additional analysis of patients' response to TRT administered for different durations and via different methods indicated that TRT significantly increased lean body mass during short-term (MD, 1.04; 95% CI, 0.11 to 1.97; P=0.03) and long-term (MD, 3.13; 95% CI, 0.07 to 6.19; P=0.04) treatment. However, no significant difference was identified in total lean body mass amongst the patients administered TRT via injection (MD, 1.7; 95% CI, -0.1 to 3.5; P=0.06) and transdermally (MD, 0.65; 95% CI, -0.58 to 1.88; P=0.30). The included studies did not present any data on oral administration of TRT.

Total fat mass. A total of 5 RCTs, involving 995 participants (503 in the testosterone group and 492 in the control group), reported upon the total fat mass of patients. No statistical difference was identified between the two groups (MD, -0.85; 95% CI, -1.74 to 0.04; P=0.06; Fig. 5B). Subgroup analysis revealed no significant changes in the total fat mass between patients administered TRT transdermally (MD, -0.91; 95% CI, -1.91 to 0.08; P=0.07) and via injection (MD, -0.6; 95% CI, -2.6 to 1.4; P=0.56).

Total cholesterol. A total of 8 RCTs, involving 943 participants (519 in the testosterone group and 424 in the control group), included the total cholesterol levels of patients. TRT decreased total cholesterol in the testosterone group compared with the control patients. The mean difference between the two groups was -0.16 (95% CI, -0.29 to -0.03; P=0.01; Fig. 5C). Subgroup analysis revealed that total cholesterol levels significantly decreased in the long-term group (MD, -0.23; 95% CI, -0.39 to -0.07; P=0.005). However, no significant change in total cholesterol was noted in the short-term group (MD, -0.11; 95% CI, -0.27 to 0.05; P=0.16). Subgroup analysis also

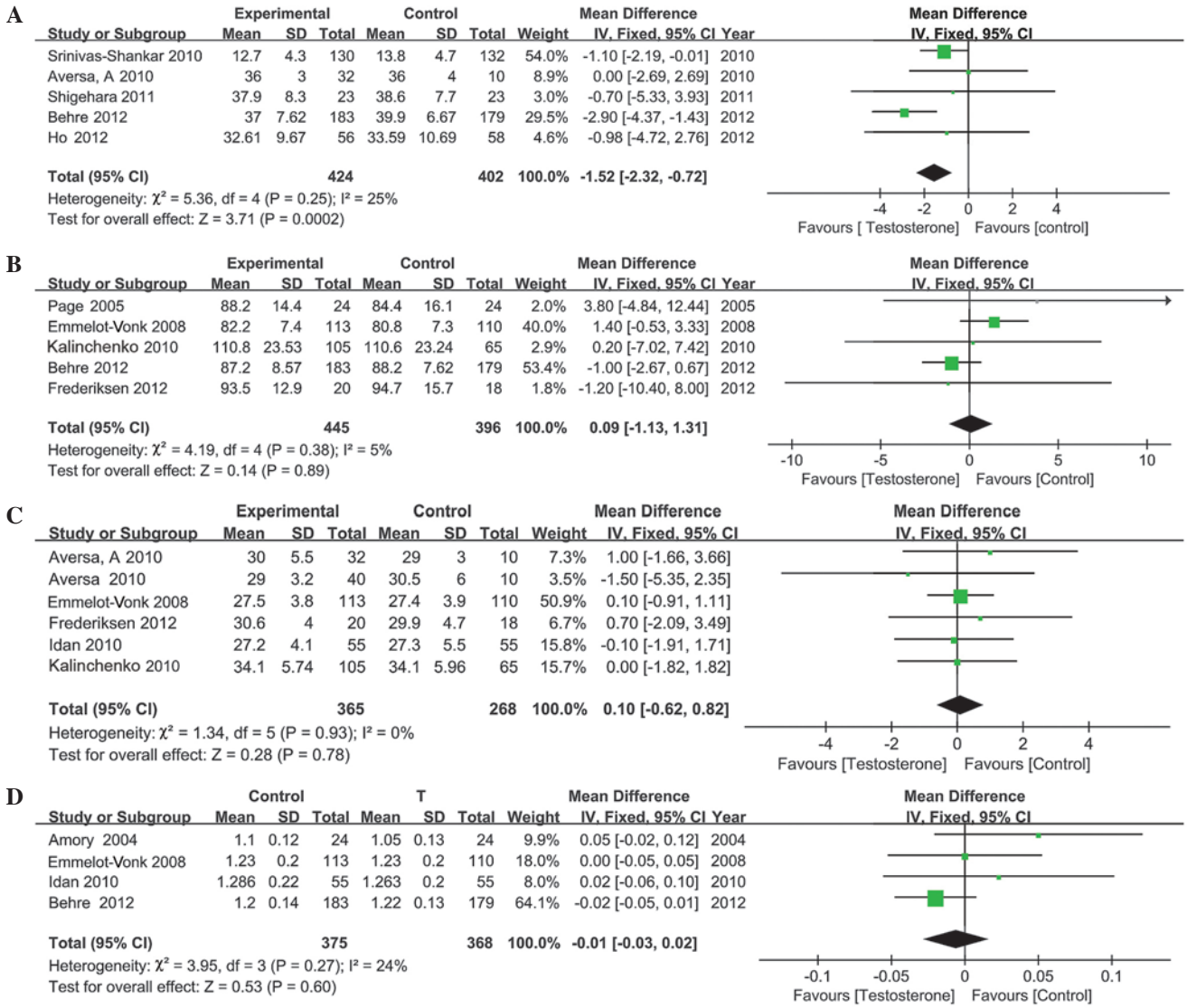

Figure 4. Forest plots revealing differences in the means of a number of variables. Differences in (A) Aging Male Symptom scores; (B) body weight; (C) body mass index; and (D) bone mineral density between experimental and control groups. SD, standard deviation; CI, confidence interval; df, degrees of freedom.

demonstrated that administration by injection (MD, -0.27; 95% CI, -0.5 to -0.04; P=0.02) reduced cholesterol to a greater degree than transdermally-administered (MD, -0.18; 95% CI, -0.37 to 0.01; P=0.07) and orally-administered (MD, 0; 95% CI, -0.26 to 0.26; P=1.00) TRT.

Safety

PSA levels. A total of 11 RCTs, involving 1,392 participants (723 in the testosterone group and 669 in the control group), reported the PSA levels of patients. The present analysis revealed no significant increase in PSA levels following TRT (MD, 0.10; 95% CI, -0.03 to 0.22; P=0.14; Fig. 5D). Subgroup analysis revealed that PSA levels did not increase following long-term TRT (MD, -0.12; 95% CI, -0.32 to 0.07; P=0.21). However, following short term TRT, the PSA levels increased significantly (MD, 0.26; 95% CI, 0.09-0.43; P=0.002) Furthermore, transdermal administration (MD, 0.43; 95% CI, 0.2 to 0.66; P=0.0002) increased PSA levels more than the injection (MD, -0.11; 95% CI, -0.31 to 0.09; P=0.27) or the oral administration (MD, 0.03; 95% CI, -0.21 to 0.27; P=0.81) methods in men with hypogonadism. Following short term TRT, the prostate volume increased significantly (MD, 2.62; 95% CI, 1.42-3.81; P=0.001). Furthermore, the oral administration (MD, 2.61; 95% CI, 1.41-3.8; P=0.0001) resulted in higher increase in prostate volume compared with the injection (MD, -0.5; 95% CI, -2.27 to 1.26; P=0.58) or the transdermal administration (MD, -0.9; 95% CI, -8.17 to 6.37; P=0.81) methods in men with hypogonadism.

IPSS. A total of 7 RCTs, involving 893 participants (479 in the testosterone group and 414 in the control group), provided IPSS. The present analysis indicated that, compared with the control group, TRT did not increase IPSS significantly in the experimental group (MD, 0.01; 95% CI, -0.37 to 0.39; P=0.96; Fig. 6A). Subgroup analysis indicated that there were no significant differences in IPSS in long-term or short-term treatment. Similarly, no significant differences in IPSS were identified within the injection (MD, -0.01; 95% CI, -0.44 to 0.42; P=0.95), transdermal (MD, 0.35; 95% CI, -0.78 to 1.47; P=0.55) or oral (MD, -0.20; 95% CI, -1.43 to 1.03; P=0.96) administration groups.

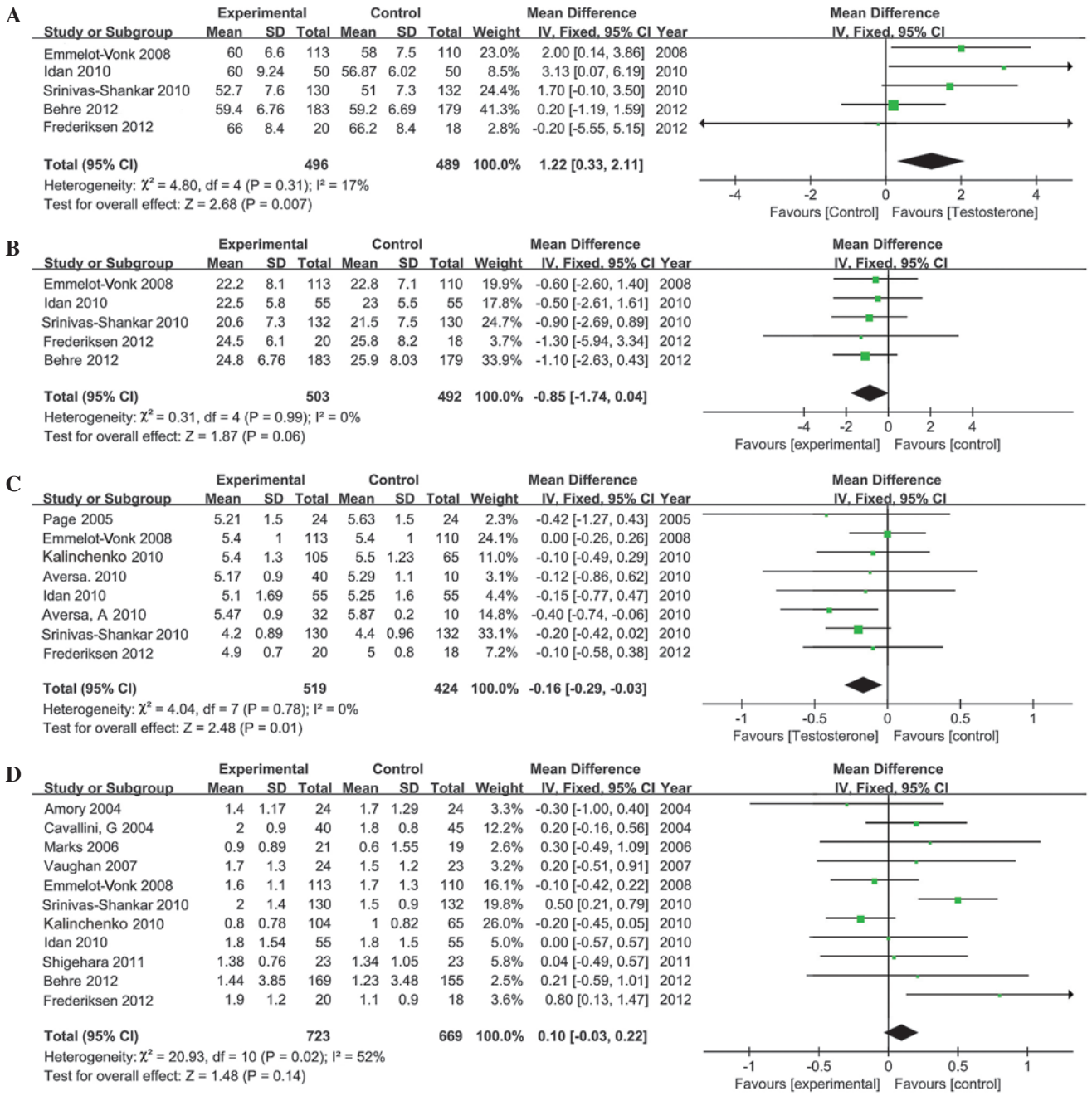

Figure 5. Forest plots revealing differences in the means of a number of variables. Differences in (A) total lean body mass; (B) fat mass; (C) total cholesterol; and (D) prostate-specific antigen levels between experimental and control groups. SD, standard deviation; CI, confidence interval; df, degrees of freedom.

Prostate volume. A total of 8 RCTs, involving 663 participants (355 in the testosterone group and 308 in the control group), included the results of prostate volume. The data revealed that the average increase in prostate volume was 1.58 (95% CI, 0.6 to 2.56; P=0.002; Fig. 6B) following TRT. However, no significant difference in prostate volume was reported following long-term TRT (MD, -0.55; 95% CI, -2.27 to 1.17; P=0.96).

Mild to moderate adverse events. A total of 6 RCTs, involving 1,351 participants (775 in the testosterone group and 576 in the control group), included details of mild to moderate adverse events (Table II). Analysis demonstrated that the frequency of mild to moderate adverse events in the testosterone group was higher than in the control group (MD, 1.58; 95% CI, 1.07 to 2.33; P=0.02; Fig. 6C), particularly in patients undergoing long-term treatment (MD, 3.10; 95% CI, 1.14 to 8.41; P=0.03). However, no significant differences were reported in the number of mild to moderate adverse events in the short-term studies (MD, 1.38; 95% CI, 0.90 to 2.11; P=0.15). Subgroup analyses demonstrated that these adverse events occurred more frequently in the transdermal administration group compared with the other administration groups.

Serious adverse events. Serious adverse events reported in the included studies were: Cancer, mortality, pulmonary embolism, myocardial infarction, heart failure, constrictive pericarditis, elective surgery for intervertebral disc, inguinal hernia repair and deep vein thrombosis.

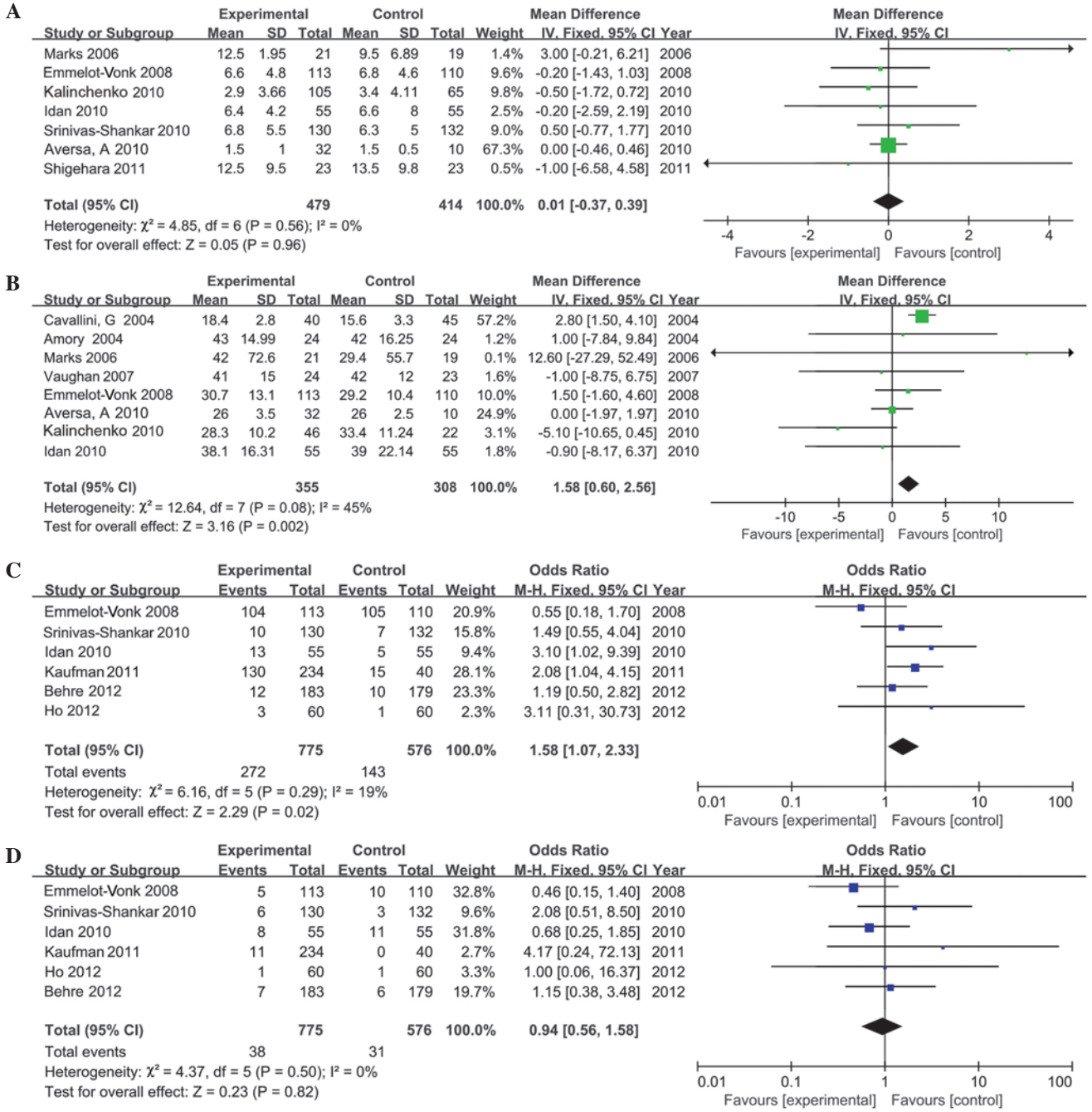

Figure 6. Forest plots revealing differences in the means of a number of variables. Differences in (A) International Prostate Symptom Score; (B) prostate volume; (C) mild to moderate adverse events; and (D) serious adverse events between experimental and control groups. Green squares represent continuous data, while blue squares represent dichotomous data. SD, standard deviation; CI, confidence interval; df, degrees of freedom.

A total of 6 RCTs, involving 1,351 participants (775 in the testosterone group and 576 in the control group), reported upon the number of serious adverse events. TRT did not increase the number of serious adverse events (MD, 0.85; 95% CI, 0.50 to 1.44; P=0.55; Fig. 6D). Similarly, no significant differences were identified upon comparing alternative duration or methods of treatment.

Discussion

Numerous clinical trials have examined the efficacy and safety of TRT for men with testosterone deficiency based on serum levels (6-21); however, paradoxical results have prevented conclusions from being made. A meta-analysis was therefore conducted of 16 RCTs on aging men with primary or secondary hypogonadism to assess the efficacy and safety of TRT. The present analysis indicated that the patients' quality of life improved markedly following TRT, as indicated by decreased AMS scores, which supports the results of previous studies (6,25). However, conflicting data have been reported in studies regarding the efficacy of TRT treatment upon BMD (26). Mittan *et al* (27) reported that using TRT during the post-operative period for patients undergoing hypogonadal pituitary tumor surgery may have beneficial effects on the

Table II. Adverse events.

First author, year (ref.)	Discontinued participants, n		Mild to moderate adverse events, n/ total n		Serious adverse events n/ total n	
	Experimental	Control	Experimental	Control	Experimental	Control
Idan *et al*, 2010 (15)	19	14	13/55	5/55	8/55	11/55
Ho *et al*, 2012 (21)	4	2	3/60	1/60	1/60	1/60
Kaufman *et al*, 2011 (18)	66	12	134/234	15/40	5/234	1/40
Emmelot-Vonk *et al*, 2008 (7)	16	14	104/113	105/110	5/113	10/110
Srinivas-Shankar *et al*, 2010 (17)	15	16	10/130	7/132	6/130	3/132
Behre *et al*, 2012 (6)	15	24	12/183	10/179	7/183	6/179

BMD of the spine, but that no significant changes occur in the femoral neck or total femur BMD. The current analysis revealed that TRT had no beneficial effects on BMD in men with hypogonadism without tumors, in contrast with the results of previous studies (28-30). There are three possible reasons for this discrepancy. First, the participants of studies included in the present analysis were selected on the basis of their androgen status, as opposed to their health status or symptoms. The majority of participants in the current study were healthy and had no pre-existing health problems that may have prejudiced results (7). Second, in aging men with low testosterone levels, the effect of TRT on BMD appears to be associated with baseline testosterone levels; testosterone treatment increased BMD only in men whose baseline levels were below the reference range (31). Third, the majority of studies included in the present meta-analysis involved <2 years of TRT, while conventional osteoporosis studies typically extend over a 3-year period. BMD following TRT therefore requires additional study.

The present analysis revealed that, compared with the placebo group, TRT significantly increased lean body mass, which was in accordance with previous studies (25,32). Other previous studies (26,27,32) reported that the weight and fat mass of patients with prostate cancer significantly increased and that their lean mass significantly decreased during androgen deprivation therapy. However, in the present analysis, no improvement was identified in body weight and BMI following TRT. Another previous study demonstrated that body weight and BMI improved significantly in men with hypogonadism also exhibiting type 2 diabetes following TRT (28), suggesting that TRT was more efficacious in improving body weight and BMI in patients with type 2 diabetes.

Clinical trials have examined whether exogenous testosterone administration can decrease serum concentrations of high-density lipoprotein cholesterol (HDL-C) (25). As low HDL-C correlates with an increased risk of cardiovascular disease (CVD), this decrease may contribute to the presumed adverse cardiovascular effects of testosterone. By contrast, a previous study demonstrated that low circulating androgen levels in men are associated with increased risk of CVD and mortality (8), which challenges the assumption that testosterone adversely impacts cardiovascular health in men. However, as there were not enough data to analyze the CVD risk following TRT, additional investigative trials are required to determine whether TRT correlates with altered CVD risk.

Prostate growth is dependent on the presence of testosterone; higher serum testosterone is associated with a larger prostate volume and higher prevalence of BPH. Antiandrogens and orchidectomy decrease the prostate volume in patients with BPH (29,33). Previous evidence has indicated that androgens affect prostate volume and the development of prostate cancer (31). The present analysis revealed that prostate volume increased in the testosterone-treated group compared with the placebo group. However, no statistical differences were identified in PSA levels and IPSS in the testosterone-treated group compared with those in the placebo group. Raynaud *et al* (34) reported that long-term TRT was not associated with significant changes to PSA concentration and PSA velocity or any significant prostate risks. However, Khera *et al* (32) reported that patients with a baseline total testosterone level of <250 ng/dl were more likely to demonstrate increased PSA levels following TRT than those with a baseline total testosterone level of >250 ng/dl, which supports the prostate saturation hypothesis. In the present meta-analysis, the total testosterone of participants was <300 ng/dl, and PSA levels and IPSS did not increase following TRT. However, it cannot be concluded that PSA levels and IPSS did not increase following TRT in patients with a baseline total testosterone level of <50 ng/dl; patients who are severely hypogonadal may experience increased PSA following TRT. The current meta-analysis revealed that prostate volume increased significantly following TRT. The PSA concentration typically demonstrated a greater association with TRT than total prostate volume. The PSA concentration did not increase whilst prostate volume increased significantly; this may be as cell proliferation of the peripheral prostate affected by testosterone is more efficient than the synthesis and secretion of PSA per cell in prostate epithelial cells. This hypothesis conflicts with a previous study reporting that PSA secretion is more rapidly altered by exogenous androgens than prostate growth is (35). The molecular mechanism behind this phenomenon requires additional study.

A novel and unexpected result of the present study was that mild to moderate adverse events associated with TRT occurred at a greater frequency in TRT patients than in the control group, particularly in patients receiving long-term TRT; this was also true of the transdermal administration group. However, the frequency of serious adverse events did not significantly differ between the testosterone and control groups (Table II). A previous meta-analysis (36) demonstrated that TRT was associated with a significantly higher risk of detection of prostate events and adverse events. However, the frequency of cardiovascular events, sleep apnea and mortality did not significantly increase in the present study.

The 16 RCTs (6-21) included in the current meta-analysis were all double-blind, and the quality of the individual studies in the meta-analysis was high (Fig. 6). The results of these analyses may, therefore, be of great importance from a scientific and a clinical standpoint. However, there are a number of limitations to the present analysis, as follows: i) All 16 RCTs included rigorous periodic monitoring of patients and excluded patients at PSA levels of >4 ng/ml, which may be why the meta-analysis failed to detect an increased likelihood of prostate cancer amongst patients receiving TRT; ii) differences in testosterone dosage used and baseline PSA levels were reported, which may explain heterogeneity associated with a number of outcomes; and iii) the adverse events of TRT were analyzed, but not enough data were available to assess specific types of adverse events (for instance, gastrointestinal disorders, psychiatric disorders, infections and infestations, muscle and connective tissue disorders or nervous system disorders) that occur following TRT. Any of the aforementioned factors may affect the results of the meta-analysis.

In conclusion, the present meta-analysis indicated that TRT improved the quality of life, increased lean body mass and significantly decreased total cholesterol. In addition, this treatment is well-tolerated and safe for men with hypogonadism who are exhibiting PSA levels of <4 ng/ml.

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