



Effects of testosterone supplement treatment in hypogonadal adult males with T2DM: a meta-analysis and systematic review

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Abstract

Purpose Testosterone supplement treatment (TST) is a classic therapy for hypogonadal men with type 2 diabetes mellitus (T2DM), but the effects of TST in different studies are inconsistent. We conducted this meta-analysis to evaluate the precise role of TST in hypogonadal men with T2DM.

Methods PubMed, Embase, Cochrane Library and Web of Science were searched to identify qualified randomized controlled trials (RCTs). Pooled mean differences (MDs) with 95% confidence intervals (CIs) were calculated to measure the specific effects of TST. Trial sequential analysis was performed to verify the pooled results.

Results A total of eight RCTs were enrolled in our meta-analysis, including 596 hypogonadal participants with T2DM. Compared with comparators, TST can significantly improve glycemic control by reducing homeostatic model assessment of insulin resistance (MD - 0.79, 95% CI - 1.23 to - 0.34), fasting glucose (MD - 0.98, 95% CI - 1.13 to - 0.54), fasting insulin (MD - 2.47, 95% CI - 3.99 to - 0.95) and HbA1c% (MD - 0.45, 95% CI - 0.73 to - 0.16). In addition, TST can result in a decline in cholesterol (MD - 0.29, 95% CI - 0.38 to - 0.19) and triglyceride (MD - 0.37, 95% CI - 0.59 to - 0.15).

Conclusion Our results indicated that TST can improve glycemic control and decrease TC and TG in hypogonadal patients with T2DM. We recommend TST during the anti-diabetic therapy in these patients.

Keywords TST · T2DM · Metabolism · Glucose · Lipid

Jianzhong Zhang, Bin Yang and Wenhui Xiao have contributed equally to this work.

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Introduction

According to Endocrine Society Clinical Practice Guideline in 2010, male hypogonadism was defined as “a clinical syndrome that results from failure of the testis to produce physiological levels of testosterone (androgen deficiency) and a normal number of spermatozoa due to disruption of one or more levels of the hypothalamic–pituitary–testicular axis” [1]. Diagnosis of male hypogonadism requires both the persistent clinical symptoms and androgen deficiency [2]. Hypogonadism can significantly affect patients’ multiple organ functions and quality of life, and has become a great challenge to the world. In men aged between 40–79, the incidence of hypogonadism varied from 2.1 to 5.7%, according to an epidemiological study in America [3]. Many factors were reported associated with male hypogonadism, including obesity, comorbidities and poor health status [2, 4]. Recently, various studies have demonstrated the association between type 2 diabetes mellitus (T2DM) and hypogonadism [5–12]. A meta-analysis in 2010 revealed the association between T2DM and lower total serum testosterone

levels by a multiple regression model adjusting for age and body mass index [13]. The specific mechanism of lower testosterone in T2DM patients is not clear. Any impairment in the hypothalamic–pituitary–testicular axis may lead to lower serum testosterone.

Considering the low testosterone level and clinical symptoms in hypogonadal men, prescriptions for testosterone replacement therapy (TST) have increased significantly in the past few years [2]. TST may present several benefits including growth of muscle mass and strength, increased bone density, improvement in metabolic control, psychological and sexual parameters in hypogonadal patients [14–18]. The effects of TST on hypogonadal patients with T2DM were studied in various trials [19–28], including changes in glycometabolism, lipid parameters, blood pressure, body fat percentages, BMI indexes, the Aging Males' Symptoms (AMS) scale, and International Index of Erectile Function (IIEF) scores. However, some studies demonstrated contradictory results. For instance, with regard to glycometabolism, several studies demonstrated that TST can result in a significant reduction in HOMA-IR [20, 26, 28], FSG [19, 20, 26, 28], FSI [20, 26] and HbA1c% [19, 21, 26, 27] in hypogonadal patients with T2DM. However, the other data did not show significant decrease of these indicators in TST groups.

In terms of lipid parameters, TST was reported associated with decrease in TC [21, 24, 27, 28], TG [26], serum HDL levels [21], serum LDL levels [21], and increase in serum HDL levels [26]. Other studies did not show a significant improvement in lipid metabolism. Meta-analysis as a powerful tool can provide more reliable results than a single study, especially in explaining controversial conclusions. We performed this meta-analysis to evaluate the precise role of TST in hypogonadal men with T2DM.

Materials and methods

This meta-analysis was strictly reported according to the PRISMA (Preferred reporting items for systematic review and meta-analyses) statement [29] (Table S1).

Search strategy and quality assessment

Databases including PubMed, Embase, Cochrane Library and Web of Science were searched to identify qualified trials published up to January 2018. The combination of the following search items was used: “testosterone”, “androgen”, “diabetes mellitus”, “TST”, “TRT”, “hypogonadism” and “randomized controlled trial”. In addition to electronic search original papers, reference lists of the original articles and reviews were evaluated manually to obtain more eligible studies. Besides, if the research results were unclear or

more data were needed, we would contact the corresponding author and participating trialists to get desired information.

Studies involved in this meta-analysis should fulfill the following criteria: (1) English publications; (2) randomized controlled studies; (3) researches associated with the effects of TST in hypogonadal patients with T2DM. To maintain the quality of this meta-analysis, the major exclusion criteria were listed as follows: (1) no clear definitions of the diagnosis of the late-onset hypogonadism and T2DM, population, amount and serving method of testosterone or the outcome assessment; (2) without placebo groups or no treatment groups; (3) insufficient data for estimating a mean difference (MD) with 95% confidence interval (CI); (4) duplicates of previous publication.

Moreover, all included RCTs were evaluated according to the 25-item CONSORT checklists, which focus on reporting how the trials were designed, analyzed, and interpreted (Table S2). The quality of the included RCTs was scored by assessing how many of the 25 items were reported. The number of reported items is positively associated with the quality of a RCT. A research with high quality will report all 25 criteria [30].

Data extraction

Two investigators reviewed the identified studies independently to determine whether an individual article could be included. Uncertain data were reassessed and solved by a discussion. All data were recorded in a standardized form and the following basic characteristics from each study were extracted: first author's name, year of publication, country, ethnicity, testosterone cut-off point, diabetes duration, testosterone regimen, medications on comparators, mean age, HbA1c% and total serum testosterone level. The aforementioned data are detailed in Table 1. The primary outcomes were extracted as follows: homeostatic model assessment of insulin resistance (HOMA-IR), fasting plasma glucose (FSG), fasting serum insulin (FSI), HbA1c, total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), body fat, BMI index, systolic and diastolic blood pressure (SBP and DBP), AMS and international index of erectile function (IIEF). The outcomes mentioned above were listed in Table 2.

Trial sequential analysis

Random errors in a meta-analysis can mislead findings [31, 32]. TSA was performed in this meta-analysis to control the risk of random error to obtain a more comprehensive assessment of analyses [33–36]. The cumulative Z-curve was constructed at first. Next, crossing of $Z = 1.96$ ($P = 0.05$) or the monitoring boundaries was assessed. When the cumulative Z-curve crossed by the monitoring boundaries, the

Table 1 Characteristics of the randomized clinical studies included in the meta-analysis

Study	Country	Ethnicity	Study design	Hypogonadism cut-off point	Diabetes duration (years)	Drugs
Dhindsa 2016	USA	Caucasian	RCT	FT < 225 pmol/L	9.4	Deep intramuscular injection testosterone cypionate
Gianatti 2014	Australia	Caucasian	RCT	TT < 12 nmol/L	8.5	Deep intramuscular injection testosterone undecanoate
Hackett 2014	UK	Caucasian	RCT	TT < 12 nmol/L	NM	Deep intramuscular injection testosterone undecanoate
Jones 2011	Multi-countries	Mixed	RCT	TT < 11 nmol/L	NM	Transdermal injection testosterone gel
Gopal 2010	India	Asian	RCT crossover	FT < 225 pmol/L	NM	Deep intramuscular injection testosterone cypionate
Heufelder 2009	Germany	Caucasian	RCT	TT < 11 nmol/L	0.0	Transdermal injection testosterone gel
Kapoor 2006	UK	Caucasian	RCT crossover	TT < 12 nmol/L	NM	Deep intramuscular injection sustanon
Boyanov 2003	Bulgaria	Caucasian	RCT	TT < 15 nmol/L	5.8	Oral testosterone undecanoate

Study	Dose	Comparator	Mean age (years)	Mean BMI	HbA1c%	TT baseline (nmol/L)	Trial duration	TT achieved in TRT group (nmol/L)	RCT quality score
Dhindsa 2016	250 mg per 2 weeks	Placebo	54.6	39.8	7.0	8.8	24 weeks	19.5	20
Gianatti 2014	1000 mg in the 0, 6th and 18th week	Placebo	62	32.4	6.9	8.6	40 weeks	15.3	24
Hackett 2014	1000 mg in the 0, 6th and 18th week	Placebo	61.6	32.7	7.6	9.1	30 weeks	11.2	21
Jones 2011	60 mg per daily	Placebo	59.9	NM	NM	9.4	52 weeks	19.5	21
Gopal 2010	200 mg per 15 days	Placebo	44.2	23.9	7.0	10.2	12 weeks	NM	16
Heufelder 2009	50 mg per daily	No treatment	56.6	32.3	7.5	10.5	52 weeks	15.4	16
Kapoor 2006	200 mg per 2 weeks	Placebo	64	33	7.28	8.5	12 weeks	12.8	17
Boyanov 2003	120 mg per daily	No treatment	57.5	31.0	10.4	10.2	12 weeks	15.5	15

The RCT quality score was calculated by assessing how many of the 25 items were reported. *TT* total testosterone, *NM* not mentioned

result was considered firm. In our study, a power of 80% (20% risk of a type II error) and 5% risk of a type I error was set in TSA. Moreover, 20% relative risk increase was predetermined according to the required information size and 95% CI was provided. The software (TSA, version 0.9; Copenhagen Trial Unit, Copenhagen, Denmark, 2011) was used in the current trial sequential analysis.

Statistical analysis

Data were presented as mean and standard deviation (SD). If only standard error or from the 95% confidence interval of the mean difference (MD) was available, SD value will be transformed. If only median and range were given, a formula described previously was used to estimate mean and SD:

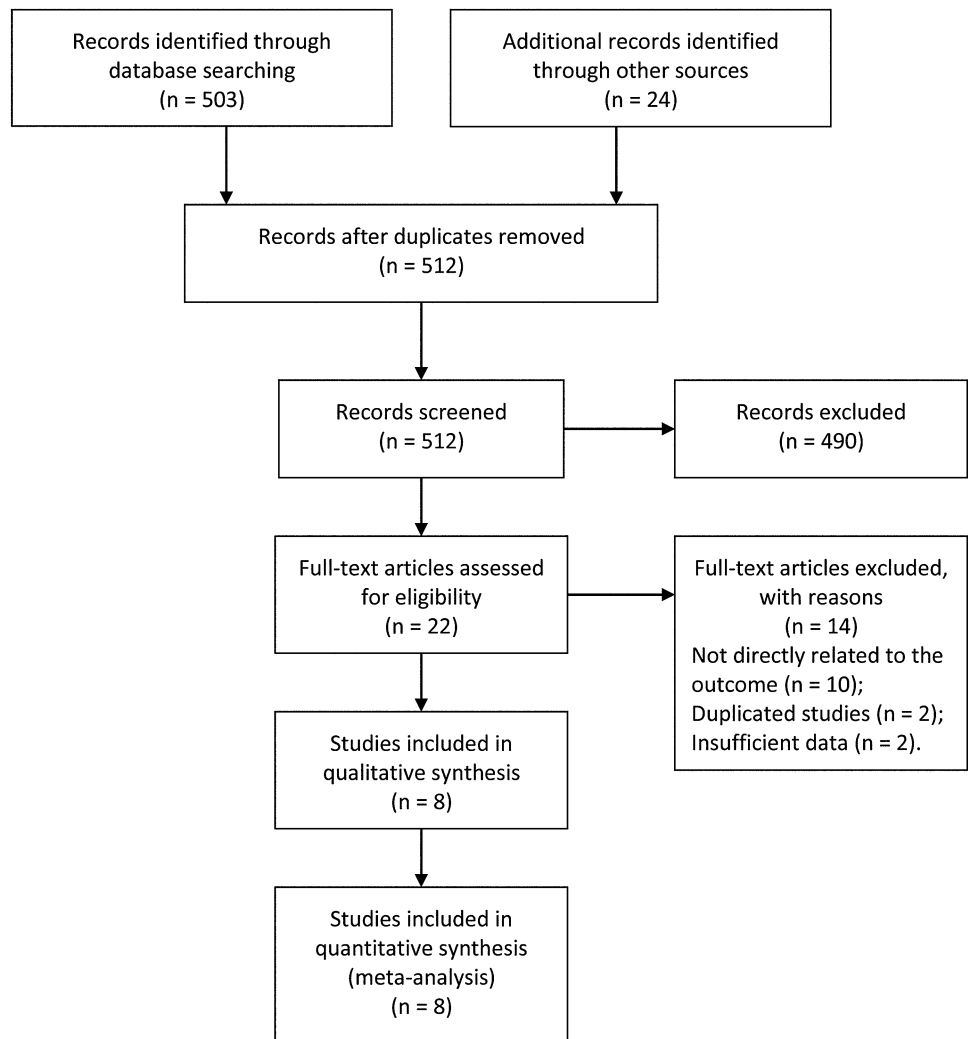
Mean \approx Median; SD \approx Norm IQR = $(P_{75} - P_{25}) * 0.7413$ (IQR: inter-quartile range, P_{75} : 75th percentile, P_{25} : 25th percentile) [37].

Sensitivity analysis was conducted by repeating the meta-analysis while omitting one single study each time. Heterogeneity was assessed by Higgins I^2 statistic and Cochrane Q test. A fixed-effect model was applied if the heterogeneity was not significant ($p > 0.05$ or $I^2 < 50\%$). Otherwise, a random-effect model was utilized. The inverse variance method was applied in a fixed-effect model and the DerSimonian–Laird method was utilized in a random-effect model [38, 39]. Pooled MDs with the corresponding 95% CIs were calculated through above methods. A pooled MD value lower than 0 indicated that TST was associated with decrease of specific parameters, and the result was

Table 2 Endpoints of variables in the randomized controlled trials included in the meta-analysis

Study	Dhindsa 2016	Gianatti 2014	Hackett 2014	Jones 2011	Gopal 2010	Heufelder 2009	Kapoor 2006	Boyakov 2003
Patients (T/C)	20/14	37/30	91/95	68/69	22/22	16/16	24/24	24/24
HOMA-IR (T/C)	2.7±0.5/3.8±0.9	1.8±0.6/2.6±1.4	4.2±2.6/3.9±2.2	NM	5.9±5.3/8.2±10.5	1.5±0.1/2.5±0.1	3.5±0.5/4.6±1.0	NM
FSI (mIU/l) (T/C)	9.9±1.8/13.9±4.0	11.9±5.0/18.4±12.7	NM	18.9±16.4/19.0±15.0	14.5±9.9/16.0±19.3	5.6±0.3/8.4±0.4	11.8±1.8/12.4±2.1	NM
HbA1c(%) (T/C)	7.2±0.9/7.1±1.5	7.1±1.0/7.2±0.7	7.7±1.3/7.5±1.2	6.8±0.4/7.5±0.4	6.3±2.0/6.3±2.7	6.3±0.1/7.1±0.1	NM	8.6±1.0/9.9±1.4
FSG (mmol/L) (T/C)	6.4±0.4/7.3±0.7	7.7±3.0/9.3±2.2	9.5±3.3/9.5±4.0	9.2±3.8/9.6±3.5	8.6±2.7/10.9±3.8	6.1±0.1/6.6±0.2	7.4±0.4/8.7±0.6	6.0±1.3/8.0±2.4
BMI (kg/m ²) (T/C)	38.9±8.1/40.6±8.4	30.9±5.4/33.3±2.7	32.7±5.9/32.3±5.2	32.9±6.5/31.7±5.6	25.7±3.6/22.3±5.1	NM	33.6±0.9/33.0±1.0	30.1±4.7/30.9±4.9
Body fat (%) (T/C)	NM	NM	NM	32.7±6.4/32.9±5.7	NM	NM	32.8±1.1/33.1±1.1	30.1±6.9/32.9±9.0
TC (mmol/L) (T/C)	3.8±0.7/4.0±0.8	3.7±0.8/4.3±1.0	3.9±0.8/4.1±1.1	4.3±1.1/4.5±1.0	4.4±0.9/4.4±1.6	NM	4.8±0.2/5.1±0.2	5.4±1.5/5.6±1.5
HDL (mmol/L) (T/C)	0.85±0.21/1.03±0.31	1.20±0.30/1.10±0.30	1.00±0.27/1.06±0.30	1.09±0.30/1.21±0.27	0.97±0.17/0.87±0.34	1.40±0.10/1.20±0.10	0.97±0.04/1.02±0.04	1.21±0.22/1.18±0.23
LDL (mmol/L) (T/C)	1.99±0.59/2.12±0.72	2.00±0.59/2.10±0.82	2.11±0.69/2.14±0.86	2.49±0.82/2.50±0.70	3.22±0.66/2.91±1.37	NM	2.74±0.18/2.81±0.17	3.60±1.25/3.69±1.30
TG (mmol/L) (T/C)	2.17±1.60/1.94±1.13	1.40±0.74/1.80±1.19	1.90±1.20/2.10±1.30	1.90±1.17/2.19±1.49	1.37±0.43/2.19±1.84	1.80±0.40/2.60±0.40	2.56±0.26/2.76±0.26	1.39±0.73/1.70±0.85
SBP (mmHg) (T/C)	NM	140.0±11.9/140.0±13.3	142.3±19.3/136.3±14.3	138.7±15.2/134.9±16.5	115.3±9.3/118.4±9.8	138.0±1.4/139.0±1.4	127.6±2.8/127.5±2.9	120.0±10.0/122.0±8.0
DBP (mmHg) (T/C)	NM	73.0±7.4/76.0±7.4	78.9±10.1/77.3±8.8	82.8±9.7/80.3±9.8	79.2±2.9/80.0±4.7	80.0±1.0/81.0±1.0	72.6±1.5/72.7±1.7	82.0±4.0/80.0±4.0
AMS (T/C)	NM	28.0±8.9/31.0±11.1	37.1±12.1/37.3±11.1	NM	NM	NM	NM	NM
IEEF-5 score (T/C)	NM	16.0±5.9/19.0±8.2	14.0±10.89/10.5±10.4	NM	NM	NM	NM	NM

The outcomes were shown as mean±SD. T/C TRT group/comparator group, FSI fasting serum insulin, FSG fasting serum glucose, HDL high-density lipoprotein, LDL low-density lipoprotein, SBP systolic blood pressure, DBP diastolic blood pressure, AMS aging male score, IIEF-5 international index of erectile function 5, NM not mentioned

Fig. 1 Flow diagram of the study selection process

considered significant if the 95% CI did not include 0. Publication bias was evaluated by Egger's linear regression test with a funnel plot. The statistics were analyzed by Stata version 12 (StataCorp LP, College Station, TX, USA).

Results

Characteristics of the enrolled studies

The study selection process was shown in Fig. 1. Finally, a total of eight RCTs including 596 hypogonadal participants with T2DM met the inclusion criteria and were enrolled in our meta-analysis [19–21, 23, 24, 26–28]. Noticeably, hypogonadism was diagnosed according to different norms in these studies and was defined as at least three sexual symptoms and total testosterone (TT) < 11 nmol/L [26, 27] or TT < 12 nmol/L [21, 24, 25, 28] or TT < 15 nmol/L [19] or free testosterone (FT) < 225 pmol/L [20, 23]. The primary testosterone regimen varied from the enrolled studies. Oral

testosterone, testosterone gel by intradermal injection, testosterone by deep intramuscular injection were utilized in one [19], two [26, 27] and five [20, 21, 23, 26, 28] studies, respectively. In addition, testosterone was given at various doses and schedules in these studies. Among the eight RCTs, six trials were double-blind, placebo-controlled studies [20, 21, 23–25, 27, 28], while the other two were single-blind, no treatment controlled studies [19, 26]. Six articles focused on Caucasian [19–21, 24–26, 28], one focused on Asian [23] and the last one is a multi-ethnicity study [27]. The basic characteristics of the involved trials were listed in Table 1.

The effects on glycometabolism

A total of eight studies have reported the glycol-metabolic effects of TST. Among them, three trials demonstrated a reduction in HOMA-IR [20, 26, 28], four showed a decrease in FSG [19, 20, 26, 28], two manifested a decrease in FSI [20, 26] and four reported a decline in HbA1c% [19, 21, 26,

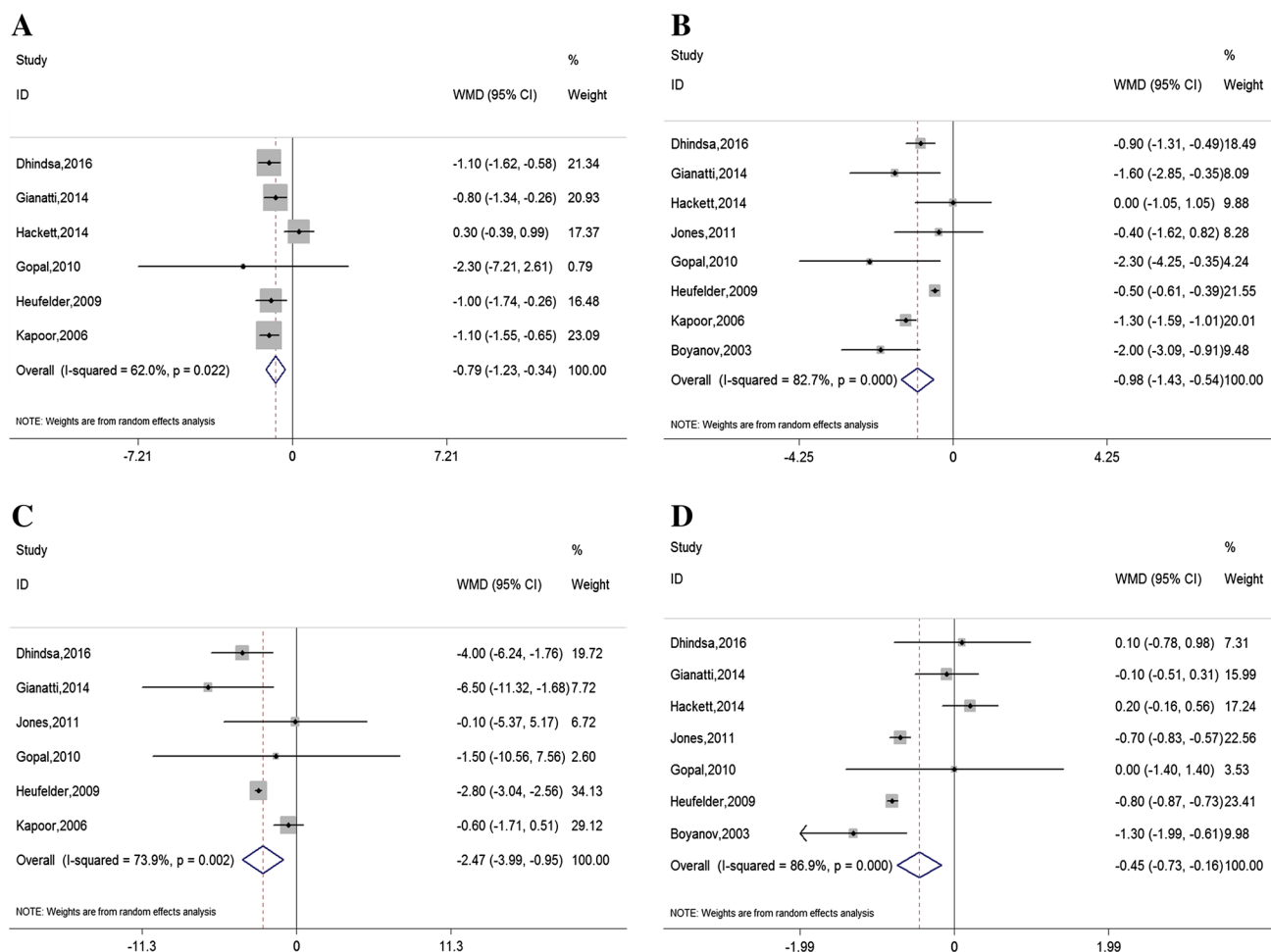


Fig. 2 Forest plots of merged analyses of effects on glycometabolism by TST. **a–d** Indicated forest plots of merged analyses of HOMA-IR, FSG, FSI and HbA1c, respectively

27]. The rest data were not significant between the TST and comparator groups.

Our meta-analyses results showed that, compared with comparators, TST can significantly improve glycemic control, and reduce HOMA-IR (MD: -0.79 , 95% CI: -1.23 to -0.34) (Fig. 2a), FSG (MD: -0.98 , 95% CI: -1.13 to -0.54) (Fig. 2b), FSI (MD: -2.47 , 95% CI: -3.99 to -0.95) (Fig. 2c) and HbA1c% (MD: -0.45 , 95% CI: -0.73 to -0.16) (Fig. 2d).

The effects on lipid parameters

All of the enrolled trials have demonstrated the influence of lipid metabolism by TST. Among the total eight RCTs, four articles have reported a decrease in TC [21, 24, 27, 28], one demonstrated an increase in serum HDL levels and a reduction in serum LDL levels [21], one showed an increase in

serum HDL levels and a decrease in TG [26]. The rest data all showed non-significant changes about lipid parameters.

According to our meta-analyses, TST can result in a decline in TC (MD: -0.29 , 95% CI: -0.38 to -0.19) (Fig. 3a) and TG (MD: -0.37 , 95% CI: -0.59 to -0.15) (Fig. 3b). No significant differences were found in other lipid outcomes including HDL levels (MD: 0.01 , 95% CI: -1.03 to 1.04) (Fig. 3c) and LDL levels (MD: -0.06 , 95% CI: -0.14 to 0.02) (Fig. 3d).

The effects on blood pressure, body fat percentages and BMI indexes

Blood pressure, body fat percentage and BMI indexes were reported in seven [19, 21, 23–28], three [19, 27, 28] and seven [19–21, 23–25, 27, 28] articles, respectively. According to existing trials, our meta-analyses suggested that TST cannot influence systolic (MD 0.13 , 95% CI

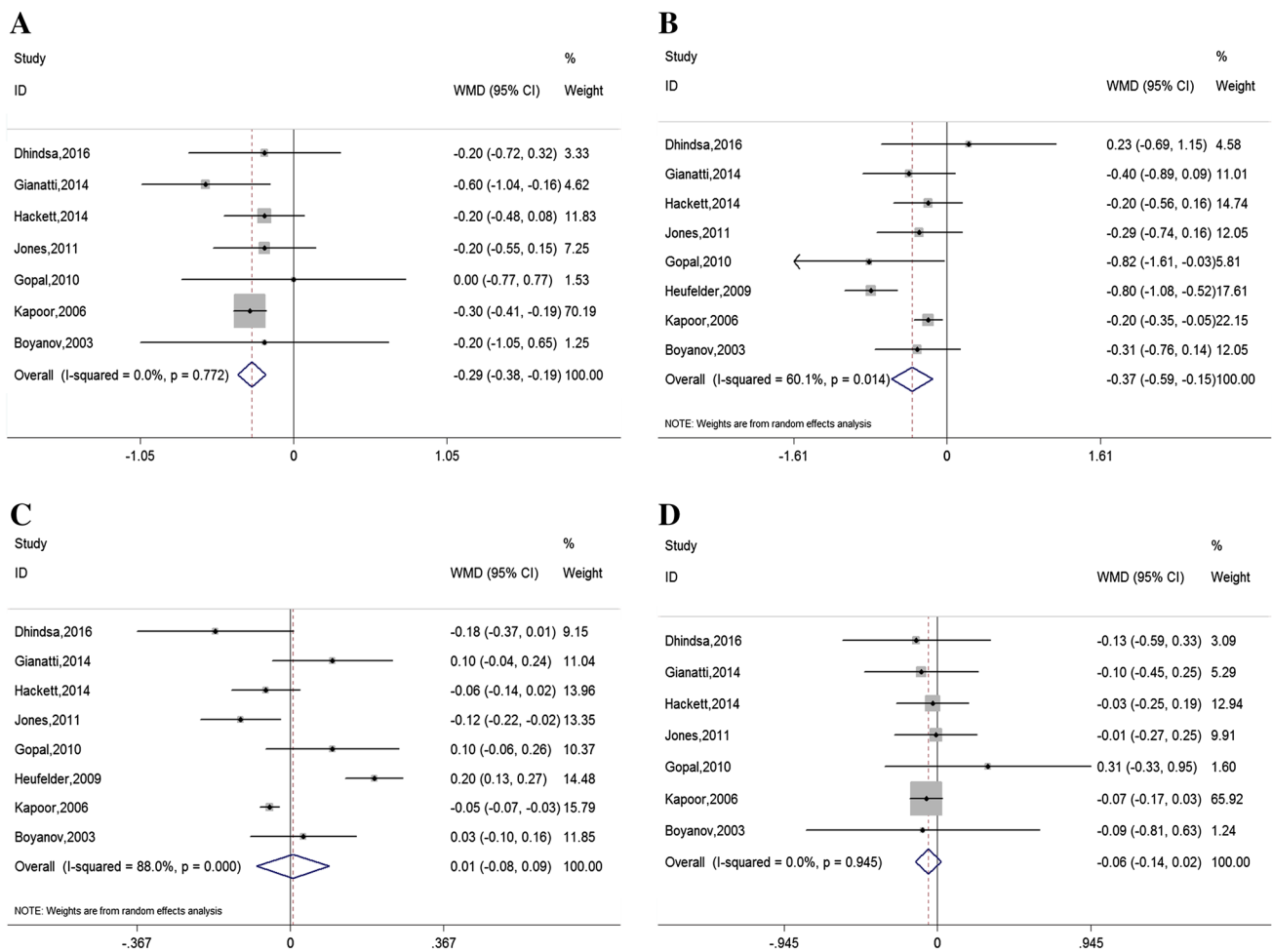


Fig. 3 Forest plots of merged analyses of effects on lipid parameters by TST. **a–d** Indicated forest plots of merged analyses of TC, TG, HDL and LDL, respectively

– 0.53 to 1.80) (Fig. 4a) or diastolic blood pressure (MD 0.01, 95% CI – 1.03 to 1.04) (Fig. 4b), body fat% (MD – 0.33, 95% CI – 0.92 to 0.26) (Fig. 4c) and BMI indexes (MD 0.29, 95% CI – 0.84 to 1.41) (Fig. 4d).

The effects on AMS and IIEF scores

Only two studies reported the AMS and IIEF scores in hypogonadal men with T2DM [22, 24]. Both trials showed a non-significant reduction in AMS in TST groups. For erectile function, two studies showed contradictory results. Hackett et al. demonstrated a significant increase in IIEF scores [24] while Gianatti et al. showed a significant decrease in IIEF scores [22].

Our meta-analyses showed a non-significant decrease in AMS (MD – 1.09, 95% CI – 3.85 to 1.67) and a non-significant increase in IIEF scores (MD 0.31, 95% CI – 6.06

to 6.68). More eligible studies were needed to clarify the effect on sexual function and AMS score.

Adverse events

No differences in adverse events were found between TST and placebo groups. The incidences of serious adverse events in TST groups were 9% [21], 1% [24], 7% [27] in three studies, whereas the other five studies did not report serious adverse events. Cardiovascular-related events were reported in two trials (TST group vs placebo group: 3 vs 3 [21] and 3 vs 7 [27]), and one study showed a trend for cardiovascular events to occur more frequently in the placebo group [27]. Compared with comparators, three studies [20, 21, 27] reported significant increases in hematocrit and one trial [21] reported an increase in PSA after TST.

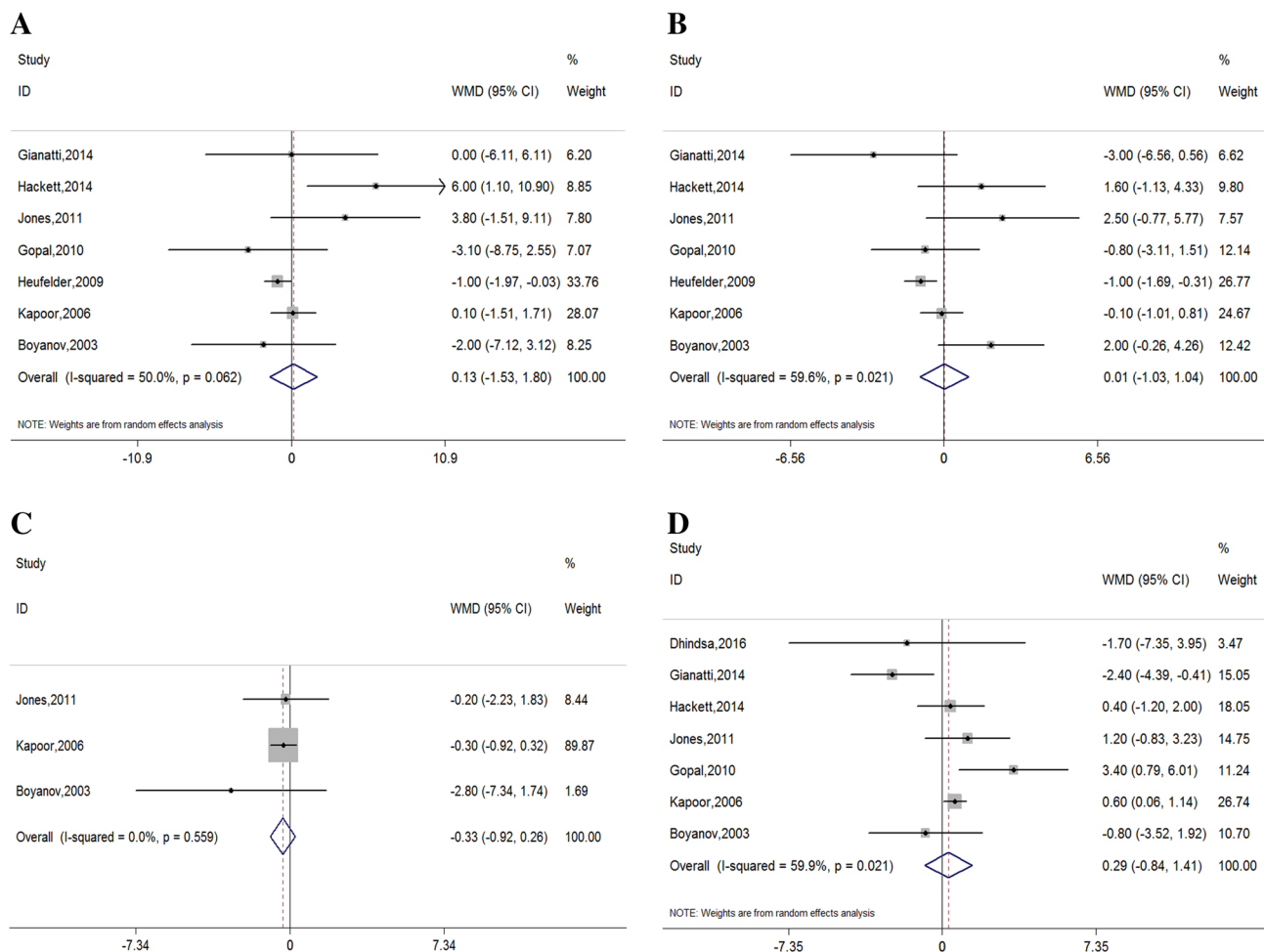


Fig. 4 Forest plots of merged analyses of effects on blood pressure, body fat and BMI indexes by TST. **a-d** Indicated forest plots of merged analyses of SBP, DBP, body fat and BMI, respectively

Trial sequential analysis results

TSA results showed sufficient evidence that TST can reduce HOMA-IR (Fig. 5a), FSG (Fig. 5b), FSI (Fig. 5c), TC (Fig. 5e) and TG (Fig. 5f). However, analysis in HbA1c% showed a negative result (Fig. 5d), suggesting that potential inaccuracy might exist.

Sensitivity analysis

We performed sensitivity analyses to evaluate the influence of individual study on the pooled MDs. Our results demonstrated no alterations in pooled MDs after any study was excluded (Figure S3), indicating that no individual trial could significantly affect the pooled MDs. Accordingly, sensitivity analysis showed that our results were dependable.

Publication bias

Results of Egger’s tests showed no potential publication bias existed in all analyses (HOMA-IR $P=0.452$; FSG $P=0.536$; FSI $P=0.707$; HbA1c $P=0.764$; TC $P=1.000$; TG $P=0.536$; HDL $P=0.711$; LDL $P=0.548$; SBP $P=1.000$; DBP $P=0.764$; body fat $P=0.296$; BMI $P=0.764$). Moreover, evidence of obvious asymmetrical were not found in the funnel plots (Figure S4).

Discussion

A large amount of studies has reported the association between T2DM and hypogonadism. The morbidity of hypogonadism in patients with T2DM is higher than general population, which might be aroused from the activation of the insulin signaling pathway. Meanwhile, after TST, hypogonadal patients showed a marked increase in the expression

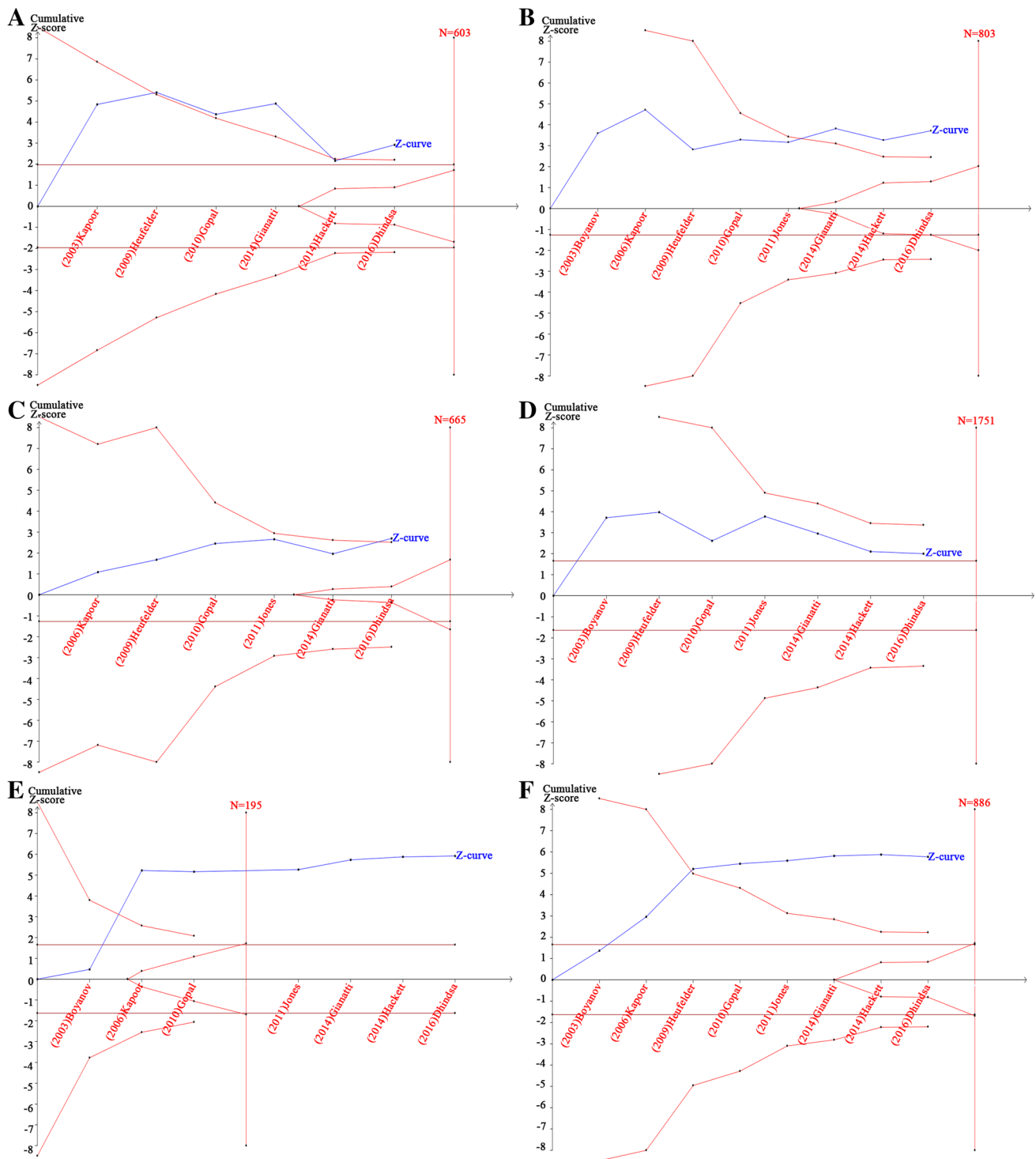


Fig. 5 Trial sequential analysis of the effects of TST. **a–f** Indicated TSA of HOMA-IR, FSG, FSI, HbA1c, TC, TG

of the major genes responsible for glucose transport mediating insulin signaling (IR-b, IRS-1, AKT-2, and GLUT4) [20]. According to the guidelines of European Association of Urology in 2017, TST is recommended for symptomatic hypogonadal men who are not considering parenthood.

There are a number of potential clinical benefits with TST, including improvements in glycemic control, insulin resistance, muscle strength, increased lean mass, libido and erectile function [2, 40–42].

Our results showed that TST can significantly improve glucose control (by reducing HOMA-IR, FSG, FSI and HbA1c), which is consistent with several previous published studies [19–21, 26–28]. Noticeably, although TST can result in significant reduction in HbA1c% in meta-analysis, TSA results suggested potential random errors existed. In addition, a total of six studies calculated HOMA-IR in our meta-analysis. Among them, three used HOMA2 model [21, 25, 26], a more stringent computer-based equation in assessing insulin resistance. The model can better reflect human physiology and accounts for hepatic and peripheral glucose resistance. Subgroup analyses demonstrated that testosterone supplement therapy could decrease HOMA-IR assessed by HOMA1 model (MD – 1.11, 95% CI – 1.44 to – 0.77). However, the effect was not significant in HOMA2 based studies (MD – 0.51, 95% CI – 1.26 to 0.25). Factors which are captured by HOMA2 might be important causes for non-significant decrease in HOMA-IR in TRT groups. More studies were needed to clarify the influence on HbA1c% and HOMA-IR (assessed by HOMA2 model) by TST.

In terms of lipid parameters, TST can decrease the TC and TG levels in serum according to the current meta-analysis. Besides, results of TSA also showed a firm association between TST and reduction of TC and TG. However, although two trials demonstrated increase in serum HDL levels [21, 26] and one study showed a reduction in serum LDL level [21]. Our meta-analysis demonstrated no significant association between TST and changes of these parameters.

Several studies have demonstrated that serum testosterone concentrations are lower in men with poorly controlled T2DM than in healthy men. Unfortunately, little RCTs focused on the effect of TST in poorly controlled T2DM male patients [43]. Trials enrolled in this meta-analysis all had well controlled HbA1c% baselines (ranging from 6.9 to 7.5%), and the effects of TST in men with poorly controlled T2DM are still unknown. Further researches were needed to clarify the role of TST in these patients.

Metabolic syndrome (MetS) is a clustering of several conditions including abdominal (central) obesity, hypertension, elevated FSG, high TG and low HDL levels. The syndrome is associated with an increased risk of developing T2DM and male hypogonadism. An abundance of studies has shown that men with metabolic syndrome (MetS) have lower plasma testosterone levels [44]. Several RCTs and meta-analyses also demonstrated positive metabolic effects of TST on MetS patients, especially combined with hypogonadism [44–47]. Hypogonadal male patients with MetS without established T2DM can also benefit from testosterone treatment by a reduction of insulin resistance [46, 47].

In this meta-analysis, we have several advantages: (1) The sample size is larger than any single study, which made our results convinced. (2) The Egger's tests showed no

publication bias. (3) Sensitivity analyses showed there were no low-quality studies. (4) TSA was conducted for the first time in this study to estimate whether our results were sufficient. In addition, we compared the current meta-analysis with previous meta-analysis by Cai et al. which included five RCTs [48]. The cumulative Z-curve did not cross the trial sequential monitoring boundary and the total size of cases and controls were less than the estimated information size in the previous five RCTs, suggesting potential random errors existed. After including another three RCTs, the cumulative Z-curve crossed the monitoring boundaries, indicating that our results were based on firm evidence.

Despite the overall sufficient statistical evidence generated through this analysis, some limitations should also be emphasized. (1) Most populations included in our analysis were Caucasians, and other ethnicities, for example, the Asian and African will be required in future research to comprehensively evaluate the role of TST in hypogonadal patients with T2DM. (2) Only two or three RCTs analyzed body fat, AMS and IIEF scores, and more RCTs were needed to investigate the effect of TST on sexual function. (3) Adjusted estimates could not be performed in our analysis due to insufficient data for the adjustment by other covariates such as age and lifestyle. (4) In our meta-analysis, primary testosterone regimens were different in various included studies, which might induce potential inaccuracy. (5) Although TSA results showed that TST has a firm improvement in glucose control and reduction in TC and TG, more studies of high quality are required to offer more detailed individual data.

Conclusion

According to our meta-analysis, TST can improve glycemic control, and decrease TC and TG in hypogonadal patients with T2DM. We recommend TST during the anti-diabetic therapy in these patients. In addition, more RCTs of high quality are needed to explore other effects of TRT in hypogonadal men with T2DM.

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Compliance with ethical standards

Conflict of interest Hongjun Li has received research grants from National Natural Science Foundation of China (81370698 and 81671488) and Beijing Natural Science Foundation (Grant No. 7162152).

Research involving Human Participants and/or Animals *Human participants* For this type of study formal consent is not required. *Animals* This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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