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ORIGINAL ARTICLE

Male Endocrinology

Metabolic effects of testosterone replacement therapy on hypogonadal men with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials

Xiang Cai, Ye Tian, Tao Wu, Chen-Xi Cao, Hong Li, Kun-Jie Wang

This systematic review was aimed at assessing the metabolic effects of testosterone replacement therapy (TRT) on hypogonadal men with type 2 diabetes mellitus (T2DM). A literature search was performed using the Cochrane Library, EMBASE and PubMed. Only randomized controlled trials (RCTs) were included in the meta-analysis. Two reviewers retrieved articles and evaluated the study quality using an appropriate scoring method. Outcomes including glucose metabolism, lipid parameters, body fat and blood pressure were pooled using a random effects model and tested for heterogeneity. We used the Cochrane Collaboration's Review Manager 5.2 software for statistical analysis. Five RCTs including 351 participants with a mean follow-up time of 6.5 months were identified that strictly met our eligibility criteria. A meta-analysis of the extractable data showed that testosterone reduced fasting plasma glucose levels (mean difference (MD): –1.10; 95% confidence interval (CI) (–1.88, –0.31)), fasting serum insulin levels (MD: –2.73; 95% CI (–3.62, –1.84)), HbA1c % (MD: –0.87; 95% CI (–1.32, –0.42)) and triglyceride levels (MD: –0.35; 95% CI (–0.62, –0.07)). The testosterone and control groups demonstrated no significant difference for other outcomes. In conclusion, we found that TRT can improve glycemic control and decrease triglyceride levels of hypogonadal men with T2DM. Considering the limited number of participants and the confounding factors in our systematic review; additional large, well-designed RCTs are needed to address the metabolic effects of TRT and its long-term influence on hypogonadal men with T2DM.
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Keywords: humans; hypogonadism; male; testosterone; type 2 diabetes mellitus

INTRODUCTION

Late-onset hypogonadism is a clinical and biochemical syndrome associated with advancing age and characterized by symptoms and deficiency in serum testosterone levels.[1] It is defined by total testosterone <3.2 ng ml^{-1} or 11 nmol l^{-1} and free testosterone <64 pg ml^{-1} or 220 pmol l^{-1} and at least three sexual symptoms.[2] Recently, the association between late-onset hypogonadism and type 2 diabetes mellitus (T2DM) has been demonstrated in numerous studies,[3–11] indicating that up to 40% of men with T2DM have testosterone deficiency, and up to 75% of them have sexual dysfunction, particularly erectile dysfunction.[12,13] Erectile dysfunction occurs as a result of a decline in testosterone levels in aging males.[14] In aging men, total testosterone and free testosterone levels decrease annually owing to defects at all levels of the hypothalamic-pituitary-testicular axis, with a concomitant increase in sex hormone binding globulin.[15] Among diabetic patients, a reduction in sex hormone binding globulin levels induced by insulin resistance leads to a further decline of testosterone levels,[16] including bioavailable and free testosterone.[17] Based on the studies mentioned above, it has been found that T2DM is a risk factor for hypogonadism in aging men.

The aim of testosterone replacement therapy (TRT) is to restore physiological testosterone levels in hypogonadal men in order to improve their health outcomes in clinical conditions. Meta-analyses of randomized trials in older men with low testosterone levels found overall improvements in sexual thoughts, erectile function, intercourse, morning erections and sexual satisfaction with TRT.[18,19] In epidemiological studies, a low bioavailable testosterone concentration was related to decreased lean body mass and muscle strength.[20,21] Some randomized trials have shown that testosterone administration could increase muscle mass and strength, as measured by leg press strength and quadriceps muscle volume.[22–25] Aging men with low testosterone levels are prone to suffer from osteoporosis and fractures.[26,27] A meta-analysis reported a significant increase in lumbar bone mass density in trials that used intramuscular testosterone injections, but not in trials that used transdermal testosterone.[28] Low testosterone levels were consistently associated with chronic depression, which is less severe but with long-lasting symptoms than clinical depression.[29] Some meta-analyses concluded that testosterone may have an antidepressant effect in depressed patients with hypogonadism.[30,31] However, a systematic review that included studies in which testosterone was

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administered to patients with depression who were being treated with antidepressants showed no evidence of additional improvements in depressive symptoms.[32] The inconsistency could be attributed to small sample sizes, short treatment duration, testosterone doses and discrepancy of patient backgrounds.

Patients with T2DM are affected by such metabolic syndromes as glucose intolerance, central obesity, dyslipidemia and hypertension. Some studies have reported an inverse association between testosterone levels and obesity, insulin resistance and dyslipidemia and have also indicated that testosterone therapy could improve glycemic control and dyslipidemia.[33–36] Other contrasting studies in which testosterone was administered to hypogonadal men with T2DM found no effect on glucose or lipid metabolism.[37–39] A meta-analysis of four randomized controlled trials (RCTs) showed that TRT seemed to improve glycemic control as well as fat mass in T2DM subjects with low testosterone levels and sexual dysfunction.[40] However, one of those studies reported data at the midpoint of the study so that some data included in the meta-analysis were not complete, leaving its conclusions in doubt.[36] Therefore, it still remains to be determined whether TRT could improve the glycemic control, central obesity, dyslipidemia and hypertension in hypogonadal men with T2DM.

In our study, we integrated all qualified RCTs available and conducted a meta-analysis of these studies to assess the metabolic effects of TRT on hypogonadal men with T2DM, including glycemic control, insulin resistance, dyslipidemia, obesity and blood pressure.

MATERIALS AND METHODS

Study search strategy

We searched online databases, including the Cochrane Library, EMBASE and PubMed, to identify suitable studies occurring through the end of July of 2013 with no lower date limit. The search was restricted to published English language articles. The search terms used to identify potentially eligible studies in each data base were 'testosterone', 'hypogonadism', 'diabetes mellitus', 'andropause', 'sexual dysfunction', 'testosterone deficiency' and 'androgen deficiency'. We tried to contact all corresponding authors when data were found to be missing.

Identification of articles and data extractions

With 416 articles identified, five studies were retrieved using inclusion criteria that entailed selection of RCT (**Figure 1**).[33–36,39] Only studies that met the following criteria were included: (i) the study compared testosterone with placebo or no treatment and presented quantitative data on outcome parameters, (ii) the study met the criteria for the diagnosis of late onset hypogonadism (total testosterone <3.2 ng ml^{-1} or 11 nmol l^{-1} and free testosterone <64 pg ml^{-1} or 220 pmol l^{-1} and at least three sexual symptoms) and T2DM (fasting plasma glucose over 7.0 at baseline and/or over 11.1 after a 2-h, 75-g oral glucose tolerance test and an elevated level of HbA1c) and (iii) the outcomes of each study included glycemic metabolism, lipid parameters, body composition and blood pressure. Characteristics and outcome variables in individual RCTs are listed using standard forms.

Quality assessment of included studies

The articles were retrieved and assessed for inclusion according to the above criteria by two independent researchers. Dispute between the investigators over inclusion of a study was resolved by discussion. The quality of included studies was assessed by the Cochrane Risk-of-Bias Tool,[41] attributing 1 point to each item (total score range: 0–8).

Data synthesis and data analysis

Meta-analyses were performed for four primary outcomes including glucose metabolism (fasting plasma glucose, fasting serum insulin and HbA1c), lipid parameters (total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol and triglyceride), body fat and blood pressure. Review Manager 5.2 software (The Cochrane Collaboration, Oxford, UK) statistical package was used to generate statistical values. Mean difference (MD) was calculated for continuous variables, and a random effect model was applied because of the limited number of studies. Statistical heterogeneity was assessed using the χ^2 test and was expressed as the I^2 index as described by Higgins and Green. $P < 0.05$ and $I^2 < 50\%$ were considered statistically significant. The CI was established at 95%.

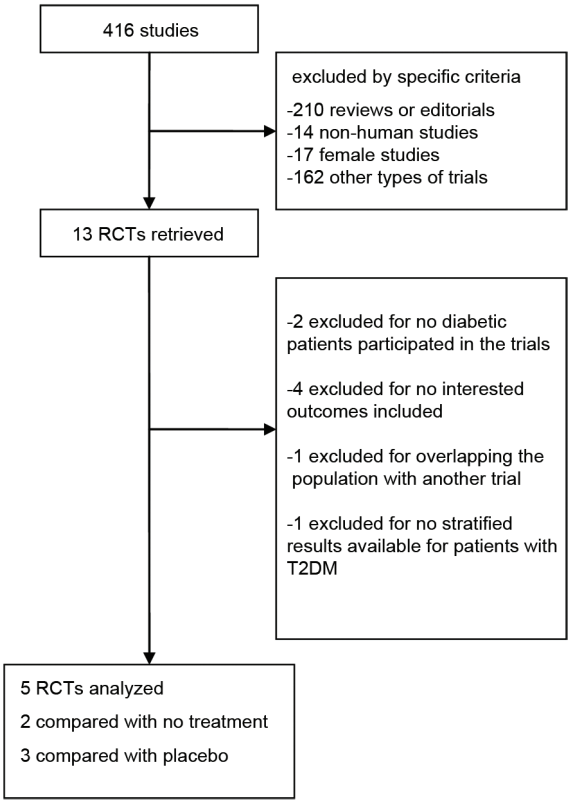

Figure 1: Evidence flow diagram. RCTs: Randomized controlled trials; T2DM: type 2 diabetes mellitus.

RESULTS

Study characteristics

Table 1 represents the study characteristics and methodology for the five studies included in the meta-analysis.[33–36,39] All of these studies were RCTs. Three are double-blind, placebo-controlled trials with two of them being crossover studies,[34,36,39] while the other two studies are open-label and single-blind, no treatment controlled trials.[33,35] Three were performed in Europe,[33–35] one in Asia[39] and the last one is a multicenter study.[36] Three of them lasted 3 months,[33,34,39] and the other two lasted 12 months.[35,36] TRT was administered in different regimens. The outcome variables of each study are listed in **Table 2**, and all the relevant data provided in the trials were converted into mean plus standard deviation (s.d). In all cases of missing or incomplete information, we contacted all the authors of the studies but none could provide any additional data.

Glycemic control and insulin resistance

In total, all five RCTs evaluated fasting plasma glucose levels and HbA1c percentages. Patients who received insulin to treat diabetes were

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

Study	*Boyanov, et al. (2003)*[33]	*Kapoor, et al. (2006)*[34]	*Heufelder, et al. (2009)*[35]	*Gopal, et al. (2010)*[39]	*Jones, et al. (2011)*[36]
Location	Sofia, Bulgaria	Shefield, UK	Munich Germany	Mumbai, India	Multicenter
Design	RCT	RCT crossover	RCT	RCT crossover	RCT
Drugs	O-TU	i.m. Sutanon	T-gel 1%	i.m. TC	T-gel 2%
Dose	120 mg per daily	200 mg per 2 weeks	50 mg per daily	200 mg per 2 weeks	60 mg per daily
Comparator	No treatment	Placebo	No treatment	Placebo	Placebo
Patients (T/C)	24/24	24/24	16/16	22/22	68/69
Age (average, year)	58	64	57	44	60
Baseline testosterone (nmoll^{-1})	NA	8.6	NA	10.2	9.4
Testosterone group (nmoll^{-1})	9.6	8.8	10.5	NA	9.2
Control group (nmoll^{-1})	10.8	8.1	10.4	NA	9.5
Trial duration (month)	3	7	12	7	12
Quality score[a] (failing items)	5 (B, C, D)	7 (B)	6 (B, D)	7 (B)	7 (B)

i.m. sutanon (T-propionate, 30 mg; T-phenyl-propionate, 60 mg; T-isocaproate, 60 mg; T-decanoate, 100 mg ml^{-1}) given by deep intramuscular injection; i.m. TC: testosterone cyponate given by deep intramuscular injection; NA: not available; O-TU: oral testosterone undecanoate; T: testosterone; T/C: testosterone/comparator; T-gel: testosterone gel. [a]Quality items of RCTs according to Cochrane Risk-of-Bias Tool (score range 0–8): A, adequate method of sequence generation; B, blinding of participants performed; C, blinding of personnel performed; D, blinding of assessors performed; E, allocation concealment adequate; F, adequate assessment of each outcome; G, selective outcome reporting avoided; H, intention-to-treat analysis of results.

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

Study	*Boyanov, et al. (2003)*[33]	*Kapoor, et al. (2006)*[34]	*Heufelder, et al. (2009)*[35]	*Gopal, et al. (2010)*[39]	*Jones, et al. (2011)*[36]
Glucose metabolism					
FPG (T/C, mmol l^{-1})	6.0±1.3/8.0±2.4	7.38±1.8/8.73±3.0	6.1±0.4/6.6±0.8	8.61±2.69/10.92±3.83	9.18±3.75/9.35±3.46
FSI (T/C, mIU l^{-1})	NA	11.76±8.6/12.36±10.4	5.79±1.2/8.67±1.44	14.54±9.86/16.02±19.31	18.85±16.41/19±15.02
HbA1c (T/C, %)	8.6±1.0/9.9±1.4	NA	6.3±0.4/7.1±0.4	6.25±2.05/6.27±2.67	NA
Lipid parameters					
Total cholesterol (T/C, mmol l^{-1})	5.42±1.47/5.55±1.46	4.83±0.98/5.07±0.83	NA	4.43±0.92/4.37±1.56	4.31±1.05/4.52±0.95
HDL cholesterol (T/C, mmol l^{-1})	1.21±0.22/1.18±0.23	0.97±0.2/6.11.02±0.2	NA	0.97±0.17/0.87±0.34	1.09±0.30/1.21±0.27
LDL cholestero (T/C, mmol l^{-1})	3.6±1.25/3.69±1.3	2.74±0.88/2.81±0.83	NA	3.22±0.66/2.91±1.37	2.49±0.82/2.5±0.7
Triglyceride (T/C, mmol l^{-1})	1.39±0.73/1.70±0.85	2.76±1.27/2.56±1.27	NA	1.37±0.43/2.19±1.84	1.9±1.17/2.19±1.49
Body fat (T/C, %)	30.09±6.88/32.86±8.96	32.77±5.4/33.14±5.4	NA	NA	32.69±6.44/32.68±5.71
Blood pressure					
Systolic BP (T/C, mmHg)	120±10/122±8	127.6±13.7/127.5±14.2	NA	115.33±9.32/118.4±9.77	138.7±15.15/134.9±16.49
Diastolic BP (T/C, mmHg)	82±4/80±4	72.7±8.3/72.6±7.3	NA	79.17±2.89/80±40.71	82.8±9.72/80.3±9.80

BP: blood pressure; FPG: fasting plasma glucose; FSI: fasting serum insulin; HDL: high-density lipoprotein; LDL: low-density lipoprotein; NA: not available; T/C: testosterone/comparator; TT: total testosterone. All data are reported as the mean±standard deviation (s.d.).

excluded from the measurements of fasting serum insulin levels. One of the studies did not assess fasting serum insulin,[33] and the HbA1c % endpoint was not provided in studies by Kapoor *et al.* and Jones *et al.*[34,36] Among the five included studies, two showed a reduction in fasting plasma glucose,[33,34] one manifested a decrease in fasting serum insulin[35] and three reported a decline in HbA1c%.[33–35] However, the rest showed no significant difference between the TRT and control groups.

We performed three meta-analyses as part of this review. For fasting plasma glucose, 300 patients were included (151 for TRT and 149 for control), and the random-effect model MD was−1.10 (95% confidence interval (CI) (−1.88, -0.31); P = 0.006) (**Figure 2**). For fasting serum insulin 252 patients were included (127 for TRT and 125 for control), and the random-effect model MD was-2.73 (95% CI (− 3.62, −1.84); P < 0.00001) (**Figure 3**). For HbA1c%, 124 patients were included (62 for TRT and 62 for control), and the random-effect model MD was-0.87 (95% CI (−1.32, -0.42); P = 0.0001) (**Figure 4**). On account of the high heterogeneity (I^2 = 61%) in the pool estimate of fasting plasma glucose, we conducted a subgroup analysis according to different regimens applied in the trials. Consequently, the I^2 dropped to 0 in each subgroups indicating that heterogeneity could be well-explained by the diversity of regimens, and the pool estimates in each subgroups demonstrated a significant decrease in fasting plasma glucose levels.

Lipid parameters

Four studies evaluated lipid parameters,[33,34,36,39] of which two demonstrated a significant decrease in total cholesterol,[34,36] and one reported a decline in HDL and LDL after TRT.[36] Four meta-analyses were carried out to examine the change in total, HDL and LDL cholesterol and triglyceride levels, which included 269 patients (136 for TRT and 133 for control). The pooled estimates showed that triglyceride values declined with the random-effect model MD of −0.35 (95% CI (−0.62, −0.07); P = 0.01) (**Figure 5**). However, no specific difference in cholesterol levels was found between the TRT and control groups.

Obesity and blood pressure

Three of the studies evaluated body fat and blood pressure.[33,34,36] One study found a significant decrease in body fat between TRT

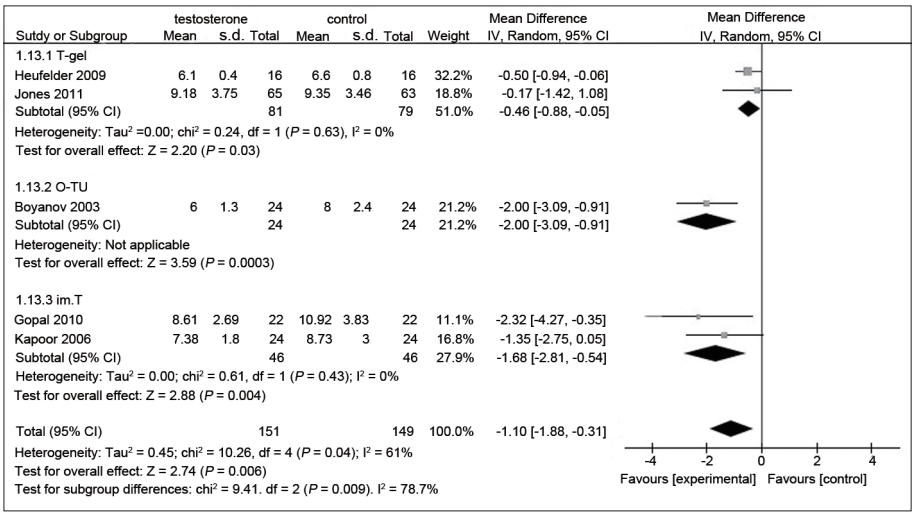

Figure 2: Fasting plasma glucose in testosterone and control groups. CI: confidence Interval; im: intramuscular; IV: intravenous; O-TU: oral tesosterone undecanoate; s.d: standard deviation; T: testosterone.

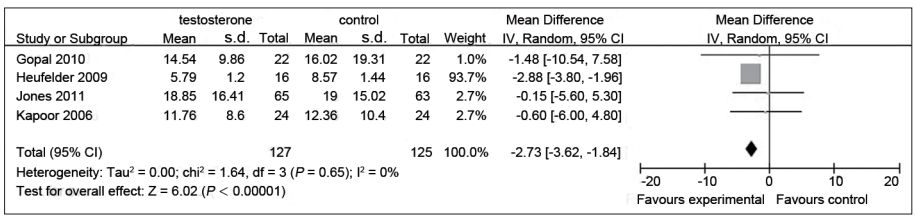

Figure 3: Fasting serum insulin in testosterone and control groups. CI: confidence interval; IV: intravenous; s.d: standard deviation.

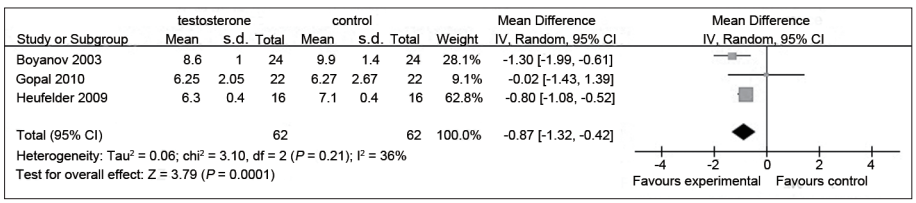

Figure 4: HbA1c% in testosterone and control groups. CI: confidence interval; IV: intravenous; s.d: standard deviation.

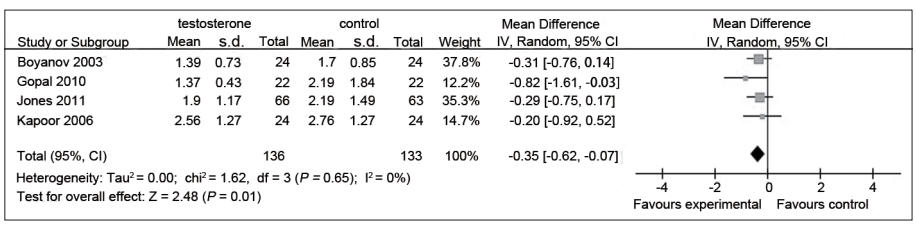

Figure 5: Triglyceride levels in testosterone and control groups. CI: confidence interval; IV: intravenous; s.d: standard deviation.

and control groups.[33] However, our meta-analysis did not identify a statistically significant difference in loss of body fat or blood pressure between the TRT and control groups.

DISCUSSION

Testosterone deficiency has a high prevalence in men with T2DM, and it is also associated with impaired insulin sensitivity, increased percentage body fat, central obesity, dyslipidemia, hypertension and cardiovascular diseases (CVD). Testosterone is converted to estradiol by the actions of aromatase in adipose tissue. Therefore, a reduction of testosterone is inevitable with increased expression of aromatase, which is a result of an increased number of adipocytes in diabetic men. In addition,the normal negative feedback regulation of testosterone depends mainly on its aromatization to estradiol. Thus, a high level of aromatization results in the suppression of testosterone secretion in the wake of progressive hypogonadism.[12] On the other hand, acute withdrawal of TRT in hypogonadal men and in men with prostate cancer who received androgen deprivation therapy is associated with the development of insulin resistance.[42,43] Thus, the vicious circle formed by testosterone deficiency and related

metabolic disorders exerts a detrimental influence on hypogonadal men with T2DM.

TRT was shown to improve glycemic control and insulin resistance in studies by Mårin *et al*. in 1992.[44,45] In the current meta-analysis, our findings that TRT mainly affected glucose metabolism in hypogonadal men with T2DM was consistent with some previous appraisal studies.[33–36] Additionally, our findings elaborated upon previous results, as we utilized more stringent criteria. Insulin resistance as assessed by, which is calculated from the equation (If*Gf/22.5, where If is fasting insulin and Gf is fasting glucose), was definitely improved by TRT after testosterone administration in three studies.[33–35] The benefits of TRT on glucose metabolism can mainly be explained by its influence on the insulin signaling pathway.[12] Insulin stimulates glucose uptake into muscle and adipose tissue via the Glut4 glucose transporter isoform. When insulin activates signaling via the insulin receptor, Glut4 interacts with insulin receptor substrate 1 to initialize intracellular signaling and facilitate glucose transportation into the cell.[46] Decreased expression of Glut4 and insulin receptor substrate 1 have also been reported in diabetic patients.[47] Testosterone was observed to elevate the expression levels and stimulate translocation of Glut4 in cultured skeletal muscle cells and to upregulate Glut4 by activating insulin receptor signaling pathways in neonatal rats.[48] These effects were inhibited by a dihydrotestosterone (DHT) blocker, indicating that glucose uptake may correlate with conversion of testosterone to DHT and activation of the androgen receptor. In the present study, the potential treatment effects of TRT on glucose metabolism were mainly confounded by the allowable use of diabetes-related medications for ethical reasons. Hence, large definitive studies evaluating insulin resistance and HbA1c values in hypogonadal men with uncontrolled diabetes will be necessary in future investigations.

As far as lipid metabolism was concerned, we found that TRT reduced triglyceride levels between the two groups. Previous studies demonstrated an inconsistent outcome on the correlation between low testosterone and cholesterol levels. Several studies found no obvious link between concentration of serum testosterone and total and LDL cholesterol,[49] while others found that high LDL and triglyceride levels were associated with low testosterone.[50] In addition, an increase in total and LDL cholesterol and triglycerides and a reduction of HDL cholesterol have been observed in patients undergoing androgen ablation.[51–53] TRT has been reported to have a positive effect in the decrease of total and LDL cholesterol levels and triglycerides in hypogonadal men.[34,36] The excess triglycerides and lipids deposited in the body further impair insulin sensitivity, which is related to insulin resistance. In particular, a recent meta-analysis showed that statins could significantly lower testosterone concentrations.[54] It was also found that reduction of LDL cholesterol levels in aging men was greater when TRT was added compared to statin therapy alone.[35] Additional large, well-designed RCTs should be established to investigate this topic.

Apart from the therapeutic benefits of TRT on glycemic control and dyslipidemia, it is also well-known for its benefits in improvement of quality of life, sexual dysfunction, survival, depression, bone density and HIV wasting syndrome.[29] However, TRT remains controversial as a protective metabolic hormone for CVD on account of limited, long-term, placebo-controlled trials and a lack of clear understanding of the related mechanisms. A number of studies have investigated the association between low testosterone levels and CVD, but the outcomes were inconsistent and included some confounding factors. Some studies reported an association between testosterone deficiency and CVD,[55,56] but two meta-analyses demonstrated that low testosterone levels were linked with an increase of all-cause and CVD deaths.[57,58] Moreover, testosterone as a health marker declined as a consequence of obesity, diabetes mellitus and other diseases that increase the risk of death. Epidemiological studies have found a negative relationship between testosterone levels and typical cardiovascular risk markers, such as body mass index, waist circumference, visceral adiposity and carotid intima-media thickness.[59,60] Thus, as a result of confounding factors, it is not apparent whether low testosterone is a cause or consequence of CVD. Four meta-analyses indicated a non-significantly higher risk with testosterone therapy when a composite cardiovascular outcome of the events was considered, but great discrepancies existed in the included trials.[61–64] Testosterone treatment was shown to raise hemoglobin, hematocrit and thromboxane, all of which might give rise to CVD.[63,65] Nevertheless, none of these trials adequately evaluated safety due to confounding factors, mostly differences in baselines and interventions. More research focusing on the safety of TRT in patients suffering from CVD is needed, with less bias and rigid stratification based on age, basic health condition, method of intervention and testosterone and lipoprotein levels.

Several limitations should be recognized in our systematic review. On one hand, three of the included studies in our review did not provide specific information on the methodology used for the testosterone assay,[33,35,39] and one did not show the change in testosterone levels after treatment.[39] Although we made an effort to contact the authors and request the relevant data, no reply was received and thus only published data were available. One the other hand, the RCTs included in this review were performed with a limited number of participants. Hence additional large, well-designed RCTs are needed to address the metabolic effects of TRT and its long-term influence on hypogonadal men with T2DM.

CONCLUSIONS

We found that TRT could improve glycemic control and decrease triglyceride levels of hypogonadal men with T2DM. Considering the limited number of participants and confounding factors in our systematic review, additional large, well-designed RCTs are needed to address the metabolic effects of TRT and its long-term influence on hypogonadal men with T2DM.

AUTHOR CONTRIBUTIONS

KJW and HL provided the original ideas and instructed the writing of this article. XC and YT researched and assessed the literature. YT, TW and CXC extracted the data from each article and drew the tables and figures of the review. XC also wrote the manuscript. All authors read and approved the final manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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