International Urology and Nephrology
https://doi.org/10.1007/s11255-021-02876-w

UROLOGY - REVIEW

Efficacy of testosterone replacement therapy for treating metabolic disturbances in late-onset hypogonadism: a systematic review and meta-analysis

Si Hyun Kim[1] · Jae Joon Park[2] · Ki Hong Kim[1] · Hee Jo Yang[1] · Doo Sang Kim[1] · Chang Ho Lee[1] · Youn Soo Jeon[1] · Sung Ryul Shim[3] · Jae Heon Kim[2]

Received: 6 January 2021 / Accepted: 22 April 2021

Abstract

Purpose Late onset hypogonadism (LOH) is an age-dependent reduction of testosterone associated with alterations of metabolic profile, including glucose control, insulin sensitivity, and lipid profile. The purpose of this study was to investigate the efficacy of testosterone replacement therapy (TRT) for treating metabolic disturbances through a meta-analysis of randomized clinical trials (RCTs).

Methods A systematic review of literature published from 1964 to November, 2019 was performed using the PubMed/Medline, Embase, and Cochrane databases. Among the 1562 articles screened, 17 articles were selected for qualitative analysis and 16 articles ($n=1373$) were included for data synthesis following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA). Criteria for final inclusion were RCTs.

Results Sixteen studies were finally included (TRT group, $n=709$; placebo group, $n=664$). Among the metabolic markers, HbA1C [Mean difference (MD) = − 0.172, 95% CI − 0.329, − 0.015], HOMA IR (MD = − 0.514, 95% CI − 0.863, − 0.165), serum insulin (MD = − 12.622, 95% CI − 19.660, − 5.585), and leptin (MD = − 2.381, 95% CI − 2.952, − 1.810) showed significant improvement after TRT versus placebo. Among the lipid profiles, total cholesterol showed significant improvement (MD = − 0.433, 95% CI − 0.761, − 0.105) after TRT. However, HDL showed a decrease (MD = − 0.069, 95% CI − 0.121, − 0.018) after TRT. Among anthropometric markers, waist circumference showed significant improvement (MD = − 0.1640, 95% CI − 2.857, − 0.423).

Conclusion This study demonstrated greater improvement in metabolic profiles for patients given TRT versus placebo. Further well-designed trials are needed to verify our findings and further elucidate effects of TRT on lipid profiles. This systematic review demonstrates that TRT can exert a net beneficial effect on metabolic profiles.

Keywords Hypogonadism · Hormone replacement therapy · Meta-analysis · Metabolic syndrome · Testosterone

✉ Sung Ryul Shim
ryul01@korea.ac.kr

✉ Jae Heon Kim
piacekjh@hanmail.net

Si Hyun Kim
pigqueen0418@naver.com

Jae Joon Park
115803@schmc.ac.kr

Ki Hong Kim
urokim@schmc.ac.kr

Hee Jo Yang
c78154@schmc.ac.kr

Doo Sang Kim
urokds@schmc.ac.kr

Chang Ho Lee
leech@schmc.ac.kr

Youn Soo Jeon
ysurol@schmc.ac.kr

[1] Department of Urology, Soonchunhyang University Cheonan Hospital, Soonchunhyang University Medical College, Cheonan, Korea

[2] Department of Urology, Soonchunhyang University Seoul Hospital, Soonchunhyang University Medical College, 59 Daesagwan-ro, Yongsan-gu, Seoul 04401, Korea

[3] Department of Preventive Medicine, Korea University College of Medicine, Anamdong 5Ga, Seongbuk-gu, Seoul 136-701, Korea

Published online: 05 June 2021

Introduction

It is well established that testosterone levels will decline with age. An age-related decrease of testosterone level combined with hypogonadal signs and symptoms in the absence of Hypothalamic–Pituitary–Thyroid axis pathology, which is called functional hypogonadism, can increase the risks of cardiovascular disease (CVD), diabetes, dementia, osteoporosis, and loss of libido and fertility [1–3]. Late-onset hypogonadism (LOH) is more prevalent in old age because of its direct relationship with the aging process, which might impair the function or production of sex steroid hormones, including testosterone, follicular stimulating hormone (FSH), luteinizing hormone (LH), and gonadotropin-releasing hormone (GnRH) [2, 4]. Moreover, it is important to note that LOH is often associated with metabolic disturbances, including metabolic syndrome (MS), obesity, type 2 DM, and hyperlipidemia clinically [1, 2]. Although sexual dysfunction is regarded as a typical clinical symptom of androgen deficiency for decreased androgen activity in LOH, commonly combined conditions, such as CVD, dementia, MS, type 2 DM, hyperlipidemia, and osteoporosis should also be considered to maintain a healthy life in old age.

Previous systematic reviews and meta-analyses have shown a favorable effect of testosterone replacement therapy (TRT) on sexual dysfunction. Such finding has encouraged clinicians to expect similar favorable effects of TRT on medical conditions associated with LOH [2, 5]. However, up to date, this conclusion remains controversial. The Food and Drug Administration (FDA) of the US has stated that TRT is approved only for congenital hypogonadism or acquired hypogonadism with brain or testis damage. Currently, there is no evidence that TRT is beneficial or has an additional effect compared to standard care.

The main reason for the US FDA's decision not to recommend clinical use of TRT in non-organic LOH is that there is limited evidence showing that TRT can improve medical conditions. In addition, there might be adverse events from using TRT, including coronary artery disease and thrombosis. Although there is an early warning for cardiovascular risk, including coronary artery disease and thrombosis, the FDA statement has emphasized that the real benefit and safety of TRT should be established and investigated more, which has left room for possible availability of TRT for non-organic use, including CVD, dementia, MS, type 2 DM, hyperlipidemia, and osteoporosis associated with LOH. About the safety issue of TRT, the American Association of Clinical Endocrinologists (AACE) has stated that there is no direct evidence of cardiovascular risk after TRT [6]. Recently, we have also shown that androgen activity is related to a low CVD death rate in a large prospective cohort study [7].

To date, there have been various systematic reviews and meta-analyses about TRT used to treat sexual dysfunction, lower urinary tract symptoms, CVD, DM, and dementia [2, 5, 8]. However, there has been no study about the effect of TRT on metabolic disturbances. Thus, the purpose of this study was to suggest quantitative evidence for the use of TRT on metabolic disturbances.

Materials and methods

We performed this systematic review and meta-analysis according to the standard Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [9]. This study was registered in PROSPERO database (registration number: CRD42020201024).

Data sources and literature search

We screened the MEDLINE and Cochrane Library electronic databases up to November 2019 using Medical Subject Headings and text keywords. Subject headings and text keywords included interventions of TRT and outcomes of metabolic markers (HbA1C, HOMA IR, serum insulin, leptin), lipid profile (TC, TG, HDL, LDL), or anthropometric markers (BW, waist circumference, BMI). We included randomized controlled trials (RCTs) in this analysis. We grouped search terms according to Boolean operators OR and AND. We limited searches to human studies, covering all languages and study types. We adopted the same search strategy for the EMBASE using Emtree (Embase subject headings). Two independent investigators (SR Shim and JH Kim) identified additional studies.

Study selection

Our study inclusion criteria were as follows: (1) interventions included administration of TRT, (2) comparisons specified placebos, (3) outcomes were mean difference (MD, the difference between TRT and placebo) for metabolic markers (HbA1C, HOMA IR, serum insulin, leptin), lipid profile (TC, TG, HDL, LDL), or anthropometric markers (BW, waist circumference, BMI).

For overlapping studies with the same cohort, we selected the latest and most appropriate outcomes through strict discussions among all investigators. Two of us (Shim and Kim) independently screened the titles and abstracts of all articles using predefined inclusion criteria. We examined full-text articles independently (Shim and Kim) to decide whether they met the inclusion criteria. Then we independently extracted data using a data extraction form. Final inclusion articles were chosen after evaluation discussion all investigators. We carefully cross-checked all references and data for

each included study to ensure no overlapping of data and to maintain the integrity of the meta-analysis.

Meta-analysis assessment of outcome findings and statistical analysis

We provided all variables in continuous data. For studies that did not report standard deviations, an estimate of the pooled standard deviation of the two groups was applied. For studies that reported only medians, mean, and variance, we estimated means from the median, range, and sample size [10]. We calculated the MD along with their 95% confidence intervals (Cls) for continuous variables. The random-effects model published by Der Simonian and Laird was used to obtain pooled overall MD and 95% CIs for outcomes [11].

We performed meta-regression analysis for each moderator. To examine potential moderators (number of patients; publication year of > 2010 vs. ≤ 2010), we used a restricted maximum likelihood estimator of the variance of true effects. A two-sided $p \leq 0.05$ that did not contain a null value (MD = 0) within the 95% was considered to be significant. All analyses were performed using R software 3.6.0 (R Foundation for Statistical Computing).

Quality assessment

We evaluated the risk of bias and methodological quality in duplicate using Version 2 of the Cochrane risk-of-bias tool for randomized trials. We assessed the following six parameters: randomization process, deviations from intended interventions, missing outcome data, measurement of outcome, selection of reported result, and overall. We graded each parameter as having a low risk of bias, some concerns or high risk of bias. The quality of the evidence related to the estimation of benefits and disadvantages followed suggestions of the GRADE Working Group.

Assessment of heterogeneity

We evaluated statistical heterogeneity using Cochran's Q test and the I^2 statistic. Either a Cochran's Q statistic of $p < 0.1$ or an I^2 statistic > 50% indicated the existence of significant heterogeneity between studies. However, a non-significant x^2 test result ($p \geq 0.1$) or I^2 statistic (≤ 50%) indicated a lack of evidence for heterogeneity, not necessarily implying homogeneity because there might have been insufficient statistical power to detect heterogeneity. Thus, we used a random-effects model for the analysis.

Assessment of potential publication bias

A funnel plot was used to explain the publication bias based on standard error as the measure of study size and MD as the measure of treatment effect. In the absence of publication bias, studies will be distributed symmetrically about the combined effect size. In addition, we performed a Begg and Mazumdar rank correlation test and Egger linear-regression test for publication biases [12].

Results

Study selection

The initial search identified a total of 1562 articles from electronic databases (PubMed $n = 147$; Cochrane $n = 27$; Embase $n = 1388$). Five studies were excluded because they contained overlapping data or appeared in more than one database. After screening titles and abstracts, 1057 papers were eliminated because they were not related to this topic, including 41 review, conference, or editorial studies. Upon a more detailed review, we found that 138 studies were eligible as randomized controlled studies. Of these, we further excluded 103 studies not focusing on the topic of the present study, including those on AIDS ($n = 8$), osteoporosis ($n = 4$), prostate cancer ($n = 4$), testicular cancer ($n = 2$), other malignancies ($n = 2$), CVD ($n = 12$), chronic kidney disease and hemodialysis ($n = 3$), cognitive disorder ($n = 8$), elderly ($n = 14$), metabolic syndrome ($n = 11$), muscle ($n = 6$), parkinsonism ($n = 2$), pharmacology ($n = 11$), sexual function ($n = 7$), skin, spinal cord injury, puberty, priapism, lupus, lower urinary symptoms, and Klinefelter syndrome ($n = 9$). Finally, 35 studies were about the topic of the present study. However, nineteen studies were excluded because they did not meet the criteria for functional hypogonadism. Finally, we selected 16 studies and added one latest study for the meta-analysis (Fig. 1).

We performed a systematic review of 17 studies [13–29] to assess detailed experimental differences and subject descriptions (Table 1). All studies were randomized placebo-controlled trials conducted in Western countries except for Shigehara [21]. The study duration ranged from 3 to 24 months.

Outcome findings

Basic biological characteristics of subjects are shown in Supplementary Fig. 1. Pooled overall MDs for metabolic markers between TRT vs. placebo group were − 0.172 (95% CI − 0.329, − 0.015) for HbA1C, − 0.514 (95% CI − 0.863, − 0.165) for HOMA IR, − 12.622 (95% CI − 19.660, − 5.585) for serum insulin, and − 2.381 (95% CI − 2.952, − 1.810) for leptin. In fasting plasma glucose (FPG), there was no statistically significant difference in overall analysis. However, in FPG subgroup analysis, the MD for secondary functional hypogonadism without DM was − 0.590 (95%

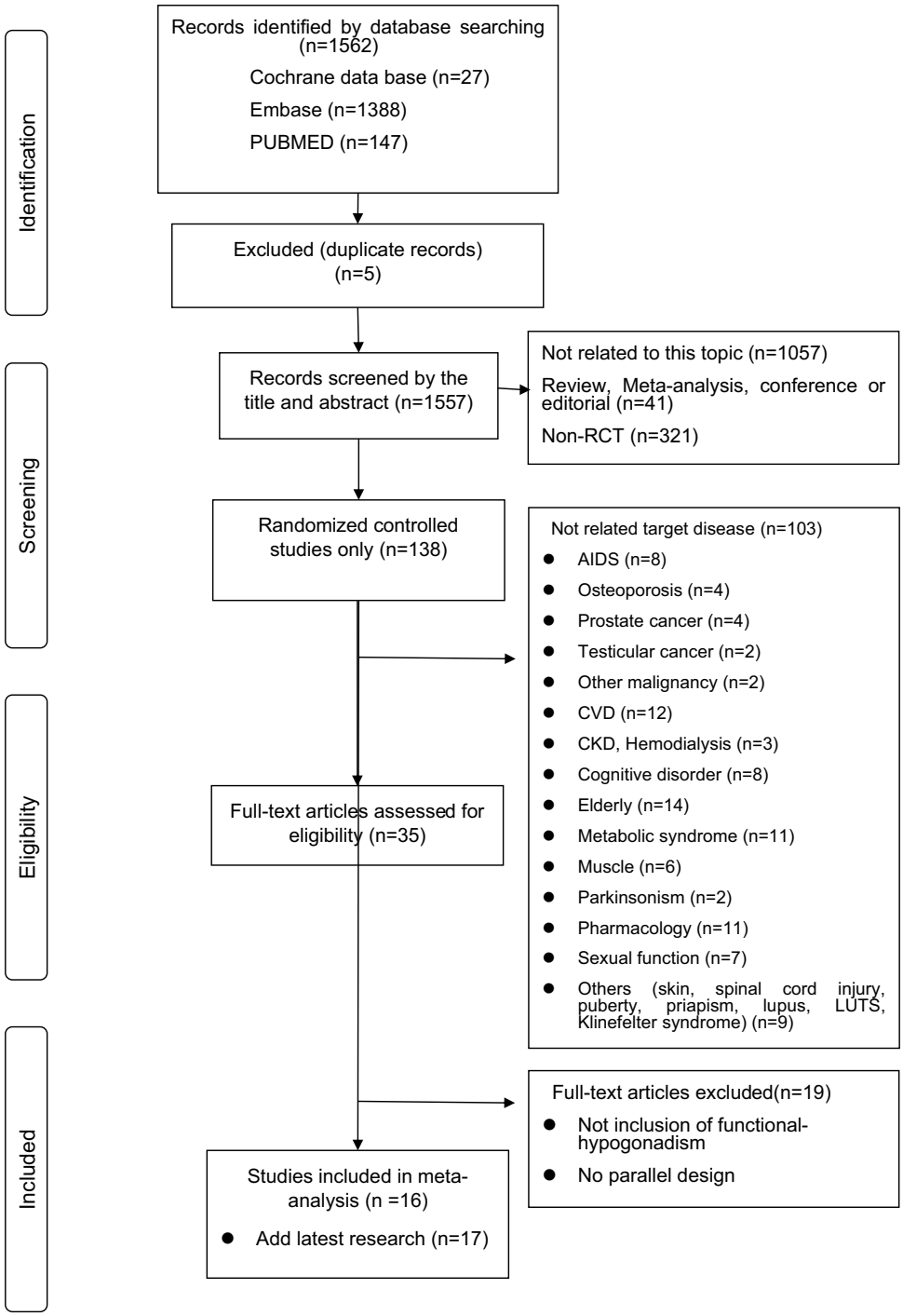

Fig. 1 Flow chart showing study inclusion

CI − 1.140, − 0.040) (Fig. 2). There was no significant difference in MD between adiponectin and hsCRP (Supplementary Fig. 2). The I^2 statistic was 94% for HbA1C, 93% for HOMA IR, 94% for serum insulin, 45% for leptin and 98% for FPG.

The pooled overall MD for lipid profiles between TRT and placebo groups was − 0.433 (95% CI − 0.761, − 0.105) in TC, − 0.272 (95% CI − 0.622, 0.077) for TG, − 0.069 (95% CI − 0.121, − 0.018) for HDL, and 0.023 (95% CI − 0.087, 0.132) for LDL. Overall TC and HDL were significantly reduced compared to those in the placebo. However, there was no statistically significant difference in subgroup analysis. (Fig. 3). The I^2 statistic was 99% for TC, 97% for TG, 92% for HDL, and 92% for LDL.

The pooled overall MD for anthropometric markers between TRT and placebo groups was − 0.126 (95% CI − 0.337, 0.086) for BMI, − 0.393 (95% CI − 1.112, 0.327) for BW, − 1.640 (95% CI − 2.857, − 0.423) for waist

Table 1 Characteristics of selected studies for qualitative analysis ($n = 17$)

Publication			Study Period	Western or Asian	Design	TRT indication disease	Inclusion criteria	Number of participants		Mean age (year)		BMI (kg/m^2)		TRT formulation	Testosterone kinds		Study duration	Cut-off for androgen deficiency
Author	Inclusion for meta-analysis	Year						Tx	Placebo	Tx	Placebo	Tx	Placebo		Drug	Dose		
Basu et al. [13]	Yes	2007		Western	Randomized, placebo-controlled, double-blind study	Primary functional hypogonadism	Relative testosterone deficiency	26	29	67	67	27	29	Testosterone patch	Testosterone (Alza, Mountain view)	5 mg/day	24 months	FT < 103 ng/dL and DHEA < 1.57 μg/mL
Magnussen et al. [14]	Yes	2017	April 2012–November 2013	Western	Randomized, placebo-controlled, double-blind trial	Secondary functional hypogonadism with DM	Caucasian men aged 50–70 years, diagnosis of T2DM and stable treatment with metformin	20	19	61	59	30.6	30.8	Gel (daily, 7 times a week, applying to skin)	Testosterone (Testim)	50 mg/day up to 3 weeks, 100 mg/day after 3 weeks	24 weeks	FT < 7.3 nmol/L
Hackett et al. [15]	Yes	2017	September 2008–June 2012	Western	Randomized, placebo-controlled, double-blind multicenter study	Primary functional hypogonadism	Men aged 18–80 years, hypogonadism with symptoms	86	103	61.7	61.5			IM (0, 6, 18, 30 weeks)	Testosterone undecanoate	1000 mg	30 weeks	TT ≤ 12 nmol/L and/or FT ≤ 0.25 nmol/L
Hackett et al. [16]	Yes	2014	September 2008–June 2012	Western	Double-blind, placebo-controlled intervention study	Primary functional hypogonadism	Men aged 18–80 years, hypogonadism with symptoms, T2DM population	27 53	48 48	61.7	61.5			IM (0, 6, 18 weeks)	Testosterone undecanoate	1000 mg	30 weeks	Severe: TT < 8 nmol/L or FT < 0.18 nmol/L Mild: TT 8.1 ~ 12 nmol/L or FT 0.181 ~ 0.25 nmol/L
Magnussen et al. [17]	Yes	2016	April 2012–November 2013	Western	Randomized, placebo-controlled, double-blind trial	Secondary functional hypogonadism with DM	White men, age 50–70 years, T2DM, receiving metformin for > 3 months	20	19	61	59			Gel (daily, 7 times a week, applying to skin)	Testosterone (Testim)	50 mg/day up to 3 weeks, 100 mg/day after 3 weeks	24 weeks	FT < 7.3 nmol/L
Aversa et al. [18]	Yes	2010		Western	Randomized, double-blind, double-dummy study	Secondary functional hypogonadism with DM	Age 50–65 years with metabolic syndrome and/or T2DM, symptomatic hypogonadism	Oral 10 IM 32	10	Oral 57 IM 58	55	Oral 32.5 IM 30.2	31	p.o (2 capsules of 40 mg/twice per day) IM (12 weeks from week 6)	Testosterone undecanoate	160 mg 1000 mg	6 months	TT < 3.20 ng/mL (11 nmol/L) or FT level < 250 pmol/L (10 pg/mL)
Fui et al. [19]	Yes	2016	April 2013–October 2014	Western	Randomized double-blind, parallel, placebo-controlled trial	Primary functional hypogonadism	Aged 18–70 years, obese (BMI ≥ 30 kg/m^2	44	38	54.3	52.8	37.5	37.3	IM (0, 6, and every 10 weeks from week 6)	Testosterone undecanoate	1000 mg	56 weeks	TT < 12 nmol/L
Groti et al. [20]	Yes	2018		Western	Double blind, randomized, placebo-controlled clinical study	Secondary functional hypogonadism with DM	Aged > 35 years, BMI ≥ 30 kg/m^2, treated with oral antidiabetic medications	28	27	60.15		33.34		IM (0, 6, and every 10 weeks from week 6)	Testosterone undecanoate	1000 mg	12 months	TT < 11 nmol/L and/or FT < 220 pmol/L
Shigehara et al. [21]	Yes	2017		Asian	Randomized controlled study	Secondary functional hypogonadism without DM	Waist circumference ≥ 85 cm with HTN, dyslipidemia, DM	32	33	67.0	69.3			IM (every 4 weeks)	Testosterone enanthate	250 mg	12 months	FT < 11.8 pg/mL

Table 1 (continued)

Publication			Study Period	Western or Asian	Design	TRT indication disease	Inclusion criteria	Number of participants		Mean age (year)		BMI (kg/m^2)		TRT formulation	Testosterone kinds		Study duration	Cut-off for androgen deficiency
Author	Inclusion for meta-analysis	Year						Tx	Placebo	Tx	Placebo	Tx	Placebo		Drug	Dose		
Jones et al. [22]	Yes	2011	February 2006–March 2007	Western	Randomized, double-blind, placebo-controlled, multicenter study	Secondary functional hypogonadism with DM	Aged ≥ 40 years, hypogonadism with at least two symptoms, T2DM, metabolic syndrome	108	112	59.9		29.3	29.5	Transdermal (thigh or abdomen) 2% testosterone gel, daily	Testosterone (Tostran)	60 mg	12 months	TT ≤ 11 nmol/L or FT ≤ 255 pmol/L
Simon et al. [23]	Yes	2001		Western	Randomized, double-blinding, placebo-controlled trial	Primary functional hypogonadism	Hypogonadal men	Testosterone 6	6	Testosterone 52.8	55.4	29.9	28.0	Gel	Testosterone	125 mg	3 months	TT ≤ 3.4 ng/mL and < 4.0 ng/mL
								DHT 6		DHT 51.2		27.8				DHT	35 mg	
Heufelder et al. [24]	Yes	2009		Western Western	Single blind, randomized clinical trial	Secondary functional hypogonadism with DM	Hypogonadal men with MetS, T2DM	16	16	57.3	55.9	32.1	32.5	Gel (once daily)	Testosterone (Testogel)	50 mg	52 weeks	TT < 12 nmol/L
Fui et al. [25]	Yes	2017	April 2013–November 2015	Western	Randomized, double-blind, placebo-controlled trial	Secondary functional hypogonadism without DM	Obesity (BMI > 30 kg/m^2)	49	51	54	52.8	37.5	37.3	IM (0, 6, 16, 26, 36, 46 weeks)	Testosterone undecanoate	1000 mg	56 weeks	TT < 12 nmol/L
Hackett et al. [26]	Yes	2014	September 2008–June 2012	Western	Double-blind, placebo-controlled study	Secondary functional hypogonadism with DM	Aged 18–80 years with T2DM	92	98	61.2	62.0	33.0	32.4	IM (0, 6, 18 weeks)	Testosterone undecanoate	1000 mg	30 weeks	TT < 8 nmol/L or FT < 0.18 nmol/L, TT 8.1 ~ 12 nmol/L or FT 0.181 ~ 0.25 nmol/L
Jensen et al. [27]	No	2018	January 2008–September 2009	Western	Single-center, randomized, placebo-controlled, double-blinded study	Secondary functional hypogonadism without DM	Aged 60–78 years with lower bioavailable testosterone, WC > 94 cm	11	13	69	68	29.8	28.4	Gel (once daily)	Testosterone (Testim)	50 mg (100 mg; after three weeks of intervention, FT < 7.3 nmol/L)	3 months	FT < 7.3 nmol/L
Janjgava et al. [28]	No	2014	2010—2013	Western	Randomized in a placebo-controlled study	Secondary functional hypogonadism with DM	T2DM, BMI 27–48 kg/m^2, aged 30–65 years, positive screening questionnaire for androgen deficiency in males	43	42	49.8	49.6	35.65	36.0	IM (once every 3 months)	Testosterone undecanoate	250 mg/mL	6 months	TT < 10.4 nmol/L

Table 1 (continued)

Publication			Study Period	Western or Asian	Design	TRT indication disease	Inclusion criteria	Number of participants		Mean age (year)		BMI (kg/m^2)		TRT formulation	Testosterone kinds		Study duration	Cut-off for androgen deficiency
Author	Inclusion for meta-analysis	Year						Tx	Placebo	Tx	Placebo	Tx	Placebo		Drug	Dose		
Wittert et al. [29]	No	2021	January 2013–May 2019	Western	Multi-center, double-blind, randomized, placebo-controlled trial	Secondary functional hypogonadism with DM	Men aged 50–74 years with lower total testosterone, Waist circumference ≥ 95 cm, DM	504	503	59.8	59.6	34.8	34.6	IM (0, 6 weeks and then 12-weekly for 2–4 years)	Testosterone undecanoate	1000 mg	2 years	TT < 11 nmol/L

TRT testosterone replacement therapy, *BMI* body mass index, *DM* diabetes mellitus, *T2DM* type 2 diabetes mellitus, *TT* total testosterone, *FT* free testosterone, *DHEA* dehydroepiandrosterone, *HTN* hypertension, *MetS* metabolic syndrome, *IM* intramuscular injection

circumference. In the overall and primary functional hypogonadism group, the waist circumference was significantly reduced. Body weight was decreased only in the primary functional hypogonadism group (Fig. 4). There was no statistically significant difference in total lean body mass or total fat mass (Supplementary Fig. 3). The I^2 statistic was 33% for BMI, 46% for BW, and 85% for waist circumference.

The pooled overall MD for blood pressure between TRT and placebo groups was − 2.271 (95% CI − 5.631, 1.089) for SBP and − 0.763 (95% CI − 2.197, 0.671) for DBP. There was no significant reduction compared to the placebo. However, in the primary functional hypogonadism group, SBP was decreased (Fig. 5). The I^2 statistic was 96% for SBP and 89% for DBP.

Moderator analyses

The meta-regression analysis revealed no significance in the number of patients except for total lean body mass and SBP. However, the publication year (before 2010 for all studies) was significantly associated with elevated MDs of serum insulin, SBP, and DBP (all $p < 0.05$).

Quality assessment

All studies described randomized methods and reasonable ITT analysis. All studies were randomized in allocation sequence and concealed until participants were enrolled and assigned to interventions. There was no baseline difference between intervention groups and non-intervention groups. Blinding method included single-blind in one study and double-blind in all other studies. After we rated each item of the critical appraisal, allocation concealment, blinding method, and detection bias had a moderate grade. A summary of methodological domain assessment for each subject is detailed in Table 1. Seven studies demonstrated the possibility of bias for missing outcome data. Overall, the risk of bias was considered to be low (Supplementary Fig. 4).

Publication bias

We evaluated funnel pictures of all results to detect publication bias. They were distributed symmetrically. After performing additional analysis with the Begg and Mazumdar rank correlation test and Egger linear regression test for publication biases, we found no evidence of publication bias for studies included for this meta-analysis.

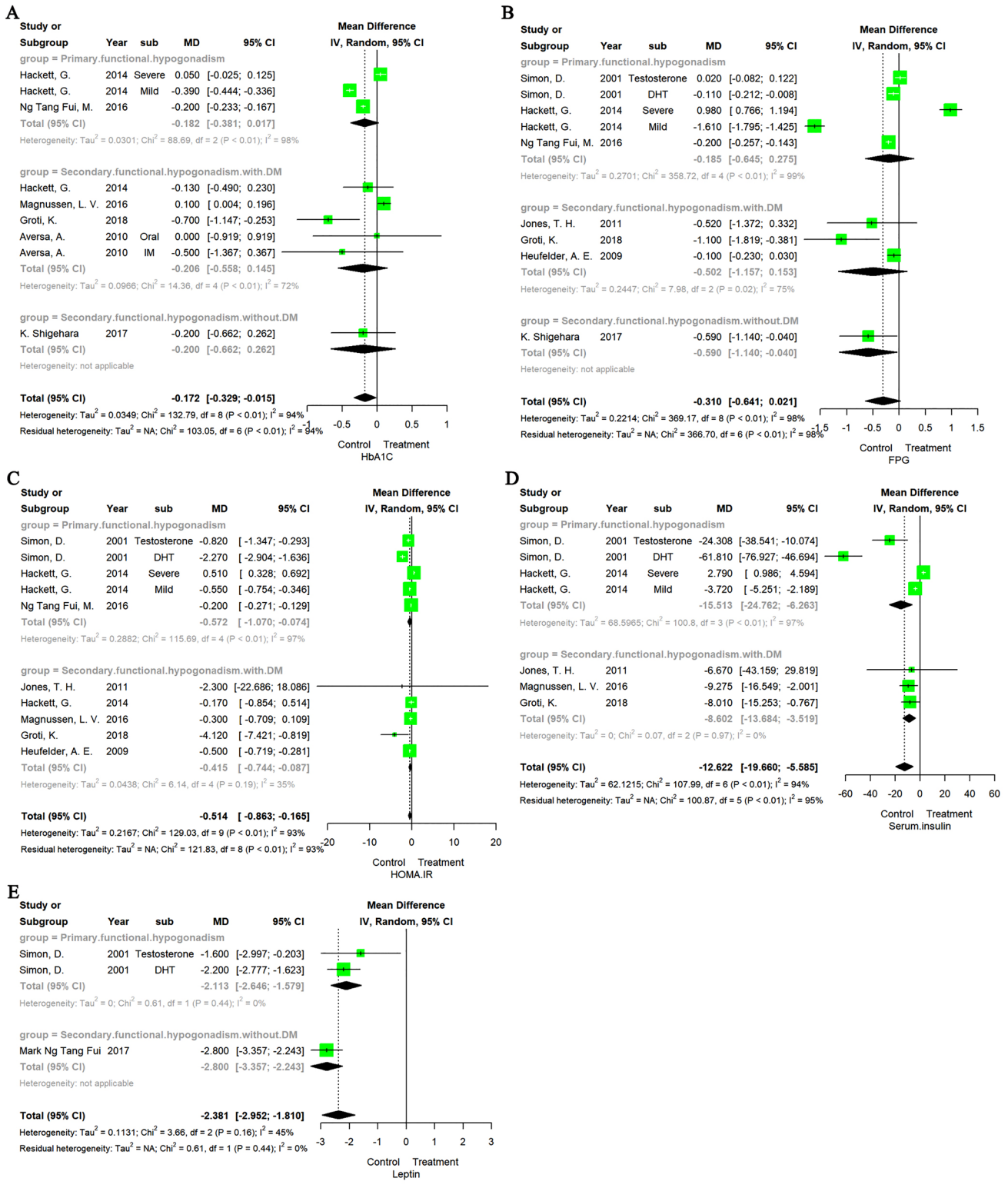

Fig. 2 Changes of metabolic markers after testosterone replacement therapy: **a** HbA1C; **b** FPG; **c** HOMA IR; **d** serum insulin; **e** leptin

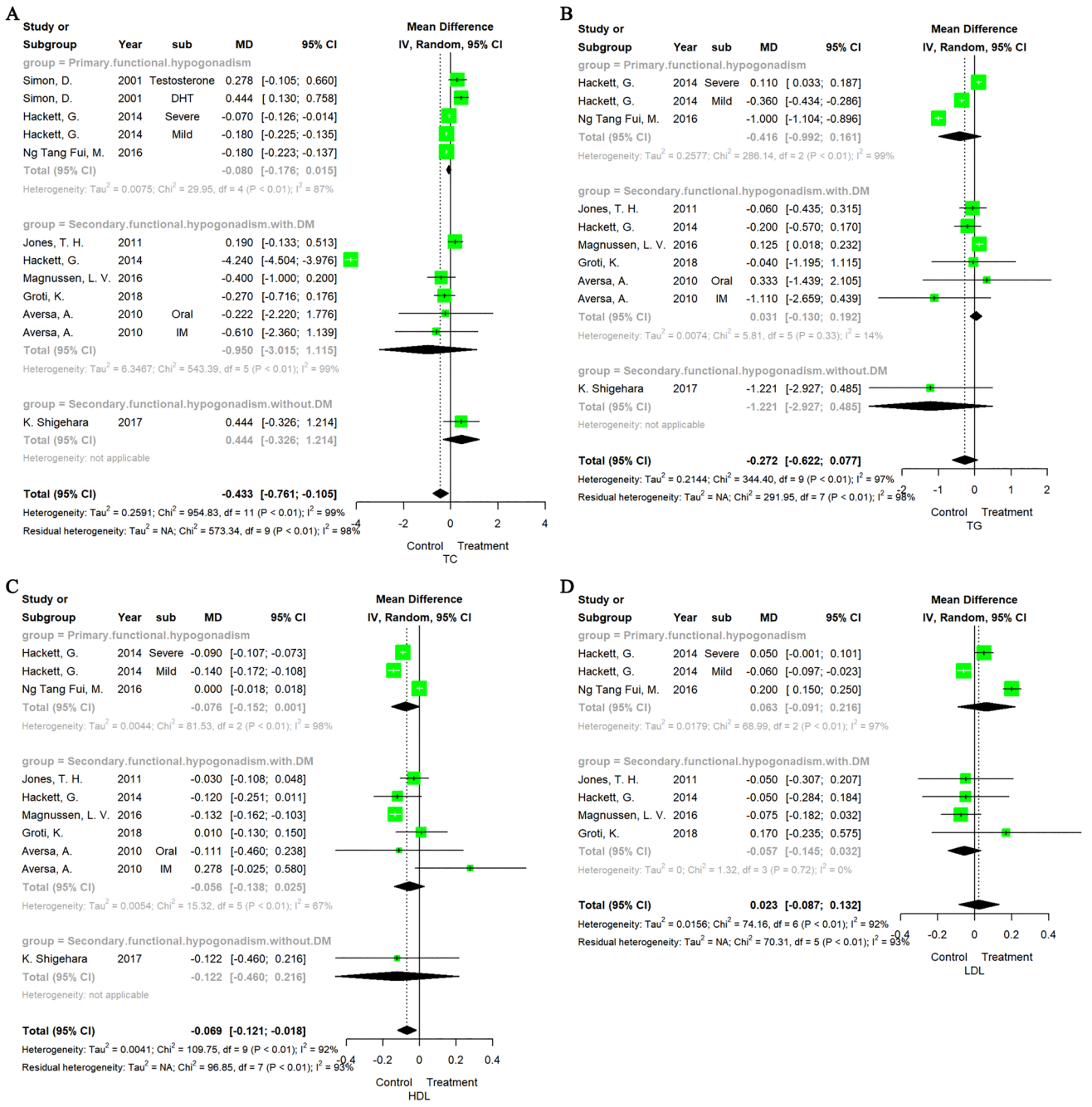

Fig. 3 Changes of lipid profiles after testosterone replacement therapy: **a** total cholesterol; **b** triglyceride; **c** HDL cholesterol; **d** LDL cholesterol

Discussion

There have been several meta-analyses about improvement of erectile dysfunction, CVD risk, and prostate cancer safety among RCTs of TRT. However, there has been no meta-analysis about the efficacy of TRT for treating metabolic disturbances among RCTs. We focused on the possible beneficial effect of TRT on metabolic disturbances, including diabetes, hyperlipidemia, MS, and obesity. As a result, it was found that TRT was efficacious for controlling diabetes, hyperlipidemia, and MS for the first time using meta-analysis among RCTs in LOH.

There are two main reasons that TRT therapy can be useful for treating metabolic disturbances in LOH. First, clinical phenotypes of type 2 DM and LOH are correlated. Although there are well-known genetic or organic etiological factors

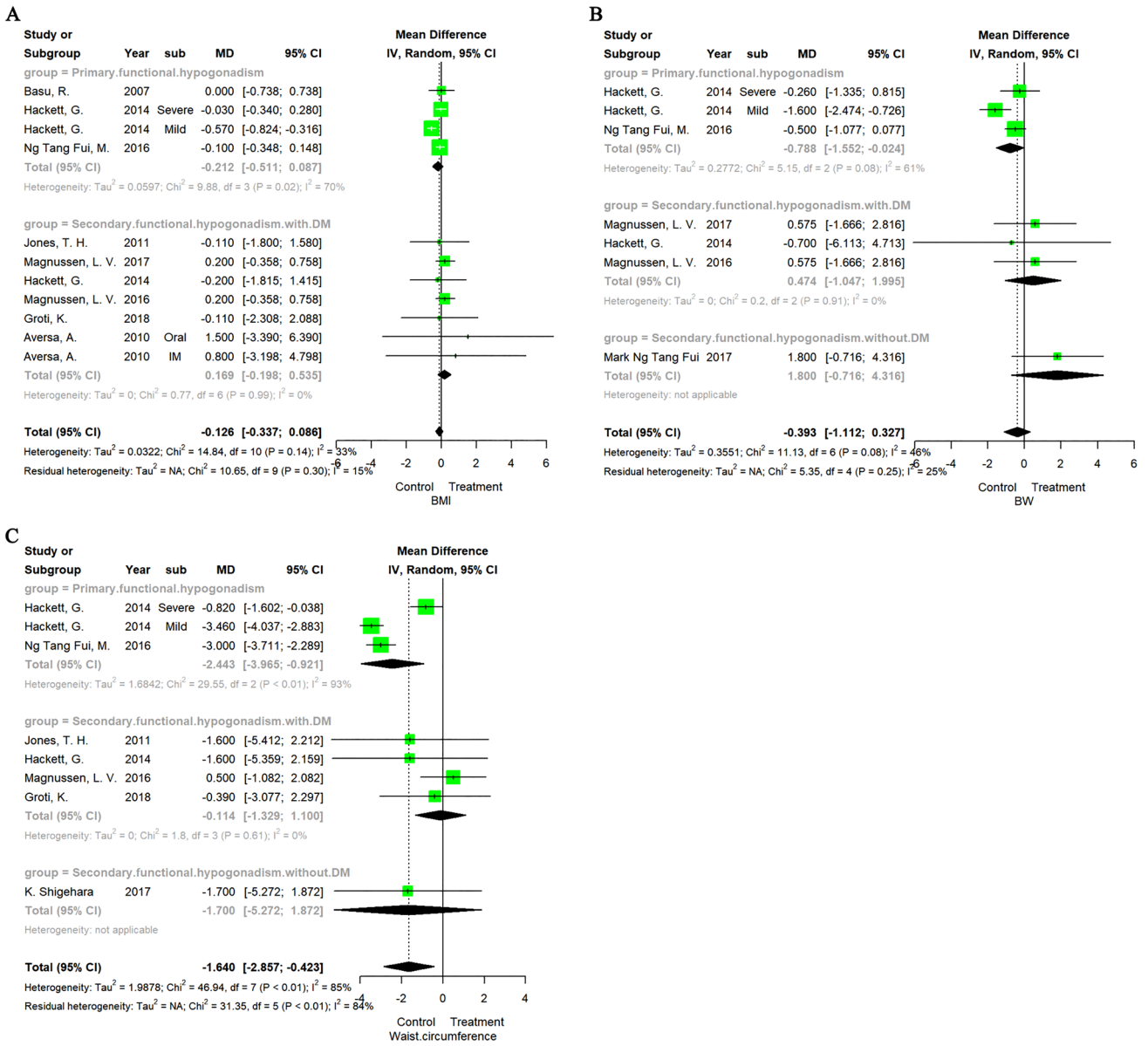

Fig. 4 Changes of anthropometric markers after testosterone replacement therapy: **a** body mass index; **b** body weight; **c** waist circumference

in DM, there is only limited evidence of etiological factors in LOH. Nevertheless, clinical phenotypes include prevalence, clinical association with aging or sexual dysfunction or obesity, and symptom specificity. Both disease conditions are associated with age, sexual dysfunction, and obesity. The prevalence of these two clinical conditions is 2–15%. There is no strong symptom specificity [2, 30].

Second, these two conditions have similar treatment process in that these two conditions could be improved by weight loss or lifestyle change and by a specific therapy [30]. In Type 2 DM, although weight control and life style modification are recommended as the first-line therapy, anti-diabetic medication including metformin is also recommended strongly in newly diagnosed type 2 DM, regardless of front-line therapy or lifestyle modification [2, 5, 30]. The first-line pharmacologic effect on type 2 DM is controversial in terms of clinical efficacy. However, recent RCTs have shown that the use of TRT itself can decrease the proportion of patients with T2DM [29]. A similar strategy could be applied to LOH. Although more RCTs are needed to recommend TRT as a specific therapy in LOH to treat non-organic symptoms, TRT is very hopeful because it has shown efficacy and safety for treating sexual dysfunction based on RCT studies [2]. TRT could be extended to non-organic symptoms including CVD, DM, MS, dementia, and osteoporosis, considering similarities between type 2 DM and LOH [5].

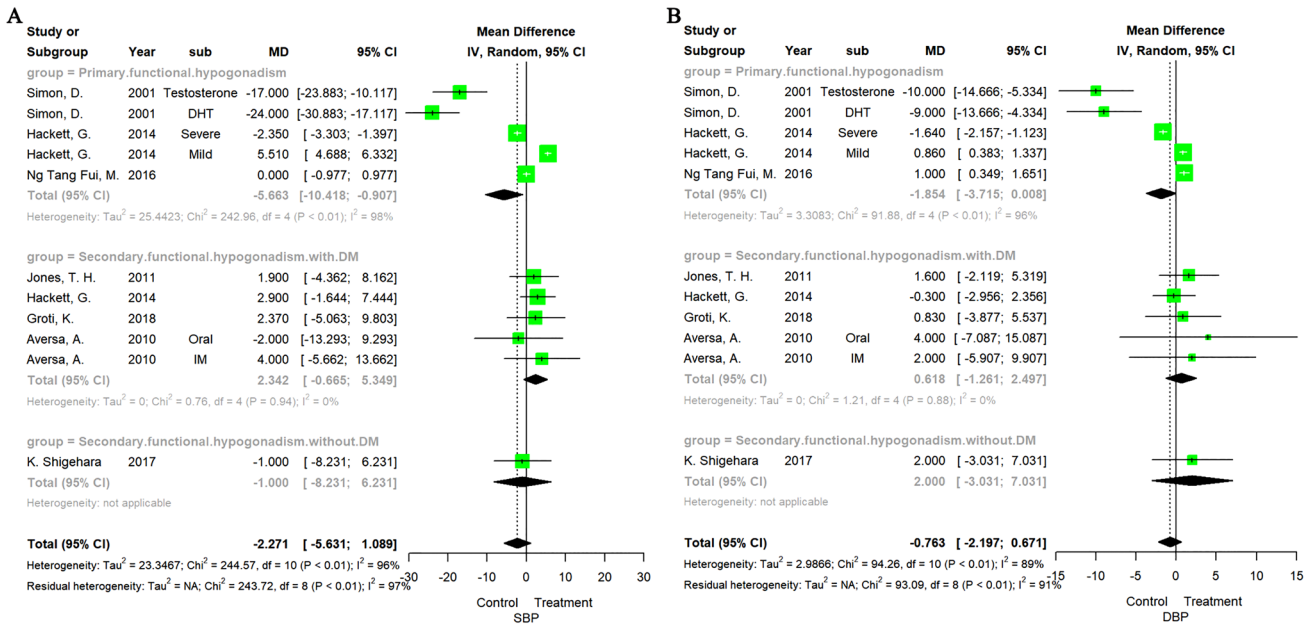

Fig. 5 Changes of blood pressures after testosterone replacement therapy: **a** systolic blood pressure; **b** diastolic blood pressure

Although our study is the first to show the efficacy of TRT for LOH using RCTs, there have been several meta-analyses about this issue using observational studies [31, 32]. These studies have shown that TRT has a favorable effect on body composition and insulin sensitivity [2, 31, 32]. Moreover, there is robust evidence that TRT could be useful not only for organic LOH, but also for non-organic, metabolic LOH [2, 4].

Among robust evidence, studies showing adverse events of androgen deprivation therapy (ADT) in prostate cancer have shown that ADT could negatively affect cardiovascular and metabolic conditions [33]. This reminds us of the importance of androgen and androgen activity in non-organic LOH. Adverse events in body composition after castration (ADT) have already been reported in many animal studies [34]. The mechanism of such adverse effects of ADT could be explained by its direct and indirect effects: direct effect of androgen on beta cells and hepatocytes and indirect effects on body composition changes (increase of adipose tissue, aggravating fatty liver, and loss of muscle volume) [2].

Regarding metabolic markers, Janjgava et al. [28] have shown that TRT could be used with anti-diabetic medication to reduce diabetic complications. In their study, the group with combined treatment using TRT and anti-diabetic medication showed more improvement of HbA1c than the single-treatment group with anti-diabetic medication. Hackett et al. [35] have performed a 4-year metabolic follow-up of results from a BLAST study and found that the TRT group has fewer prescriptions of anti-diabetic medication because of an increase in muscle volume. Magnussen et al. [36] have reported the role of TRT in CVD and metabolic disturbances. Although they failed to show a positive effect of TRT for reducing the CVD risk, TRT still showed a positive effect on metabolic disturbances, including reducing subcutaneous fat, adiponectin, and leptin.

In our study, among metabolic markers, HbA1C, HOMA IR, leptin, and serum insulin showed significant improvement after TRT compared to those in the placebo-treated group. Among anthropometric markers, our study showed a significant improvement in waist circumference after TRT. BMI and body weight also showed some decreases after TRT, although such decreases were not statistically significant. Regarding lipid profiles, total cholesterol showed significant improvement after TRT compared to that in the placebo. Triglyceride also showed improvement, although such improvement was not statistically significant. Interestingly, HDL showed a significant decrease after TRT compared to the placebo. About the role of TRT in HDL, there was limited evidence with inconsistent results. However, it is generally accepted that TRT could affect serum levels of lipids and lipoproteins and that high-dose TRT could decrease HDL and lipoprotein A levels [37].

Although this study presented quantitative results of TRT effects on metabolic disturbance using meta-analysis of RCT studies for the first time, it had several limitations. First, we could not fully explain possible adverse events of TRT. Earlier studies have been concerned about side effects of TRT, including cardiovascular risk and erythrocytosis [4]. About the cardiovascular risk, results are inconsistent. Several cohort studies have shown that TRT could increase CV

risk, including heart attack and cerebrovascular events [38, 39], whereas other studies have shown that low serum testosterone level is associated with increased cardiovascular risk, which could be prevented by TRT [5, 40]. Although our study did not include variable of cardiovascular risk, it did include the variables of blood pressure (SBP and DBP) proved to be not affected by TRT. Second, there was heterogeneity in defining LOH, which might have affected clinical outcomes of TRT. Although most studies used serum testosterone to define LOH, there might be measuring bias because of the difficulty of sampling considering the diurnal variation of testosterone level. Moreover, serum testosterone does not fully represent androgen activity, which could be bioavailable testosterone, sex hormone binding globulin, and AR expression [41]. Although we divided groups into primary functional hypogonadism and secondary functional hypogonadism with DM or without DM, we could not interpret those results from subgroup analysis due to underpowered and insufficient studies included. Third, some studies combining TRT with other interventions were included, which could have a major impact on outcomes [19, 25]. Moreover, the interrelationship between TRT and other interventions was not considered. However, this study was a comprehensive analysis of the relationship between TRT and metabolic markers. Finally, we could not consider the ethnicity variable known to different clinical and pathological phenotypes in type 2 DM and metabolic disturbances [4, 30]. In this study, only one RCT was performed in a non-western region.

Conclusion

Our study showed a positive effect of TRT on metabolic disturbances among RCT trials for the first time. It could provide useful information for clinicians who treat LOH patients. It also gives guidance for individual personalized treatment care of LOH patients. Proper guidance could prevent both overprescribing and passive treatment of TRT. For better shared decision-making, future studies are needed to show the long-term efficacy and safety of TRT for non-organic LOH.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11255-021-02876-w.

Acknowledgements This study was supported by "Soonchunhyang University Research Fund".

Declarations

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Wu FC, Tajar A, Beynon JM, Pye SR, Silman AJ, Finn JD, O'Neill TW, Bartfai G, Casanueva FF, Forti G, Giwercman A, Han TS, Kula K, Lean ME, Pendleton N, Punab M, Boonen S, Vanderschueren D, Labrie F, Huhtaniemi IT, EMAS Group (2010) Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med 363(2):123–135. https://doi.org/10.1056/NEJMoa0911101
2. Corona G, Sforza A, Maggi M (2017) Testosterone replacement therapy: long-term safety and efficacy. World J Mens Health 35(2):65–76. https://doi.org/10.5534/wjmh.2017.35.2.65
3. Corona G, Goulis DG, Huhtaniemi I, Zitzmann M, Toppari J, Forti G, Vanderschueren D, Wu FC (2020) European Academy of Andrology (EAA) guidelines on investigation, treatment and monitoring of functional hypogonadism in males: endorsing organization: European Society of Endocrinology. Andrology 8(5):970–987. https://doi.org/10.1111/andr.12770
4. Ponce OJ, Spencer-Bonilla G, Alvarez-Villalobos N, Serrano V, Singh-Ospina N, Rodriguez-Gutierrez R, Salcido-Montenegro A, Benkhadra R, Prokop LJ, Bhasin S, Brito JP (2018) The efficacy and adverse events of testosterone replacement therapy in hypogonadal men: a systematic review and meta-analysis of randomized, placebo-controlled trials. J Clin Endocrinol Metab 103(5):1745–1754
5. Corona GG, Rastrelli G, Maseroli E, Sforza A, Maggi M (2015) Testosterone replacement therapy and cardiovascular risk: a review. World J Mens Health 33(3):130–142. https://doi.org/10.5534/wjmh.2015.33.3.130
6. Goodman N, Guay A, Dandona P, Dhindsa S, Faiman C, Cunningham GR, ARES Committee (2015) American Association of Clinical Endocrinologists and American College of Endocrinology position statement on the association of testosterone and cardiovascular risk. Endocr Pract 21(9):1066–1073. https://doi.org/10.4158/EP14434.PS
7. Chang Y, Kim JH, Noh JW, Cho YS, Park HJ, Joo KJ, Ryu S (2019) Prostate-specific antigen within the reference range, subclinical coronary atherosclerosis, and cardiovascular mortality. Circ Res 124(10):1492–1504. https://doi.org/10.1161/circresaha.118.313413
8. Corona G, Isidori AM, Buvat J, Aversa A, Rastrelli G, Hackett G, Rochira V, Sforza A, Lenzi A, Mannucci E, Maggi M (2014) Testosterone supplementation and sexual function: a meta-analysis study. J Sex Med 11(6):1577–1592. https://doi.org/10.1111/jsm.12536
9. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6(7):e1000097. https://doi.org/10.1371/journal.pmed.1000097
10. Hozo SP, Djulbegovic B, Hozo I (2005) Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 5:13. https://doi.org/10.1186/1471-2288-5-13
11. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7(3):177–188. https://doi.org/10.1016/0197-2456(86)90046-2
12. Shim SR, Kim S-J (2019) Intervention meta-analysis: application and practice using R software. Epidemiol Health 41:e2019008
13. Basu R, Dalla Man C, Campioni M, Basu A, Nair KS, Jensen MD, Khosla S, Klee G, Toffolo G, Cobelli C, Rizza RA (2007) Effect of 2 years of testosterone replacement on insulin secretion, insulin action, glucose effectiveness, hepatic insulin clearance, and postprandial glucose turnover in elderly men. Diabetes Care 30(8):1972–1978. https://doi.org/10.2337/dc07-0359
14. Magnussen LV, Hvid LG, Hermann AP, Hougaard DM, Gram B, Caserotti P, Andersen MS (2017) Testosterone therapy preserves

muscle strength and power in aging men with type 2 diabetes-a randomized controlled trial. Andrology 5(5):946–953. https://doi.org/10.1111/andr.12396
15. Hackett G, Cole N, Saghir A, Jones P, Strange RC, Ramachandran S (2017) Testosterone replacement therapy: improved sexual desire and erectile function in men with type 2 diabetes following a 30-week randomized placebo-controlled study. Andrology 5(5):905–913. https://doi.org/10.1111/andr.12399
16. Hackett G, Cole N, Bhartia M, Kennedy D, Raju J, Wilkinson P, Saghir A (2014) The response to testosterone undecanoate in men with type 2 diabetes is dependent on achieving threshold serum levels (the BLAST study). Int J Clin Pract 68(2):203–215. https://doi.org/10.1111/ijcp.12235
17. Magnussen LV, Glintborg D, Hermann P, Hougaard DM, Hojlund K, Andersen M (2016) Effect of testosterone on insulin sensitivity, oxidative metabolism and body composition in aging men with type 2 diabetes on metformin monotherapy. Diabetes Obes Metab 18(10):980–989. https://doi.org/10.1111/dom.12701
18. Aversa A, Bruzziches R, Francomano D, Spera G, Lenzi A (2010) Efficacy and safety of two different testosterone undecanoate formulations in hypogonadal men with metabolic syndrome. J Endocrinol Invest 33(11):776–783. https://doi.org/10.1007/bf03350341
19. Fui MNT, Prendergast LA, Dupuis P, Raval M, Strauss BJ, Zajac JD, Grossmann M (2016) Effects of testosterone treatment on body fat and lean mass in obese men on a hypocaloric diet: a randomised controlled trial. BMC Med. https://doi.org/10.1186/s12916-016-0700-9
20. Groti K, Zuran I, Antonic B, Forsnaric L, Pfeifer M (2018) The impact of testosterone replacement therapy on glycemic control, vascular function, and components of the metabolic syndrome in obese hypogonadal men with type 2 diabetes. Aging Male 21(3):158–169. https://doi.org/10.1080/13685538.2018.1468429
21. Shigehara K, Konaka H, Nohara T, Izumi K, Kitagawa Y, Kadono Y, Iwamoto T, Koh E, Mizokami A, Namiki M (2018) Effects of testosterone replacement therapy on metabolic syndrome among Japanese hypogonadal men: a subanalysis of a prospective randomised controlled trial (EARTH study). Andrologia. https://doi.org/10.1111/and.12815
22. Jones TH, Arver S, Behre HM, Buvat J, Meuleman E, Moncada I, Morales AM, Volterrani M, Yellowlees A, Howell JD, Channer KS (2011) Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study). Diabetes Care 34(4):828–837. https://doi.org/10.2337/dc10-1233
23. Simon D, Charles MA, Lahlou N, Nahoul K, Oppert JM, Gouault-Heilmann M, Lemort N, Thibult N, Joubert E, Balkau B, Eschwege E (2001) Androgen therapy improves insulin sensitivity and decreases leptin level in healthy adult men with low plasma total testosterone: a 3-month randomized placebo-controlled trial. Diabetes Care 24(12):2149–2151
24. Heufelder AE, Saad F, Bunck MC, Gooren L (2009) Fifty-two-week treatment with diet and exercise plus transdermal testosterone reverses the metabolic syndrome and improves glycemic control in men with newly diagnosed type 2 diabetes and subnormal plasma testosterone. J Androl 30(6):726–733. https://doi.org/10.2164/jandrol.108.007005
25. Fui MNT, Hoermann R, Grossmann M (2017) Effect of testosterone treatment on adipokines and gut hormones in obese men on a hypocaloric diet. J Endocr Soc 1(4):302–312. https://doi.org/10.1210/js.2017-00062
26. Hackett G, Cole N, Bhartia M, Kennedy D, Raju J, Wilkinson P (2014) Testosterone replacement therapy improves metabolic parameters in hypogonadal men with type 2 diabetes but not in men with coexisting depression: the BLAST study. J Sex Med 11(3):840–856. https://doi.org/10.1111/jsm.12404
27. Jensen RC, Christensen LL, Nielsen J, Schrøder HD, Kvorning T, Gejl K, Højlund K, Glintborg D, Andersen M (2018) Mitochondria, glycogen, and lipid droplets in skeletal muscle during testosterone treatment and strength training: a randomized, double-blinded, placebo-controlled trial. Andrology 6(4):547–555. https://doi.org/10.1111/andr.12492
28. Janjgava S, Zerekidze T, Uchava L, Giorgadze E, Asatiani K (2014) Influence of testosterone replacement therapy on metabolic disorders in male patients with type 2 diabetes mellitus and androgen deficiency. Eur J Med Res 19:56. https://doi.org/10.1186/s40001-014-0056-6
29. Wittert G, Bracken K, Robledo KP, Grossmann M, Yeap BB, Handelsman DJ, Stuckey B, Conway A, Inder W, McLachlan R, Allan C, Jesudason D, Fui MNT, Hague W, Jenkins A, Daniel M, Gebski V, Keech A (2021) Testosterone treatment to prevent or revert type 2 diabetes in men enrolled in a lifestyle programme (T4DM): a randomised, double-blind, placebo-controlled, 2-year, phase 3b trial. Lancet Diabetes Endocrinol 9(1):32–45. https://doi.org/10.1016/s2213-8587(20)30367-3
30. Rydén L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, Deaton C, Escaned J, Hammes HP, Huikuri H, Marre M, Marx N, Mellbin L, Ostergren J, Patrono C, Seferovic P, Uva MS, Taskinen MR, Tendera M, Tuomilehto J, Valensi P, Zamorano JL, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, De Backer G, Sirnes PA, Ezquerra EA, Avogaro A, Badimon L, Baranova E, Baumgartner H, Betteridge J, Ceriello A, Fagard R, Funck-Brentano C, Gulba DC, Hasdai D, Hoes AW, Kjekshus JK, Knuuti J, Kolh P, Lev E, Mueller C, Neyses L, Nilsson PM, Perk J, Ponikowski P, Reiner Z, Sattar N, Schächinger V, Scheen A, Schirmer H, Strömberg A, Sudzhaeva S, Tamargo JL, Viigimaa M, Vlachopoulos C, Xuereb RG (2013) ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the task force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Eur Heart J 34(39):3035–3087. https://doi.org/10.1093/eurheartj/eht108
31. Corona G, Giagulli VA, Maseroli E, Vignozzi L, Aversa A, Zitzmann M, Saad F, Mannucci E, Maggi M (2016) THERAPY OF ENDOCRINE DISEASE: testosterone supplementation and body composition: results from a meta-analysis study. Eur J Endocrinol 174(3):R99-116. https://doi.org/10.1530/EJE-15-0262
32. Corona G, Maseroli E, Maggi M (2014) Injectable testosterone undecanoate for the treatment of hypogonadism. Expert Opin Pharmacother 15(13):1903–1926. https://doi.org/10.1517/14656566.2014.944896
33. Keating NL, O'Malley AJ, Smith MR (2006) Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol 24(27):4448–4456. https://doi.org/10.1200/JCO.2006.06.2497
34. Harada N (2018) Role of androgens in energy metabolism affecting on body composition, metabolic syndrome, type 2 diabetes, cardiovascular disease, and longevity: lessons from a meta-analysis and rodent studies. Biosci Biotechnol Biochem 82(10):1667–1682. https://doi.org/10.1080/09168451.2018.1490172
35. Hackett G, Cole N, Mulay A, Strange RC, Ramachandran S (2019) Long-term testosterone therapy in type 2 diabetes is associated with reduced mortality without improvement in conventional cardiovascular risk factors. BJU Int 123(3):519–529
36. Magnussen LV, Andersen PE, Diaz A, Ostojic J, Hojlund K, Hougaard DM, Christensen AN, Nielsen TL, Andersen M (2017) MR spectroscopy of hepatic fat and adiponectin and leptin levels

during testosterone therapy in type 2 diabetes: a randomized, double-blinded, placebo-controlled trial. Eur J Endocrinol 177(2):157–168. https://doi.org/10.1530/EJE-17-0071
37. Feingold KR, Brinton EA, Grunfeld C (2000) The effect of endocrine disorders on lipids and lipoproteins. In: Feingold KR, Anawalt B, Boyce A et al (eds) Endotext. MDText.com, Inc, South Dartmouth
38. Finkle WD, Greenland S, Ridgeway GK, Adams JL, Frasco MA, Cook MB, Fraumeni JF Jr, Hoover RN (2014) Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PLoS ONE 9(1):e85805. https://doi.org/10.1371/journal.pone.0085805
39. Lunenfeld B, Mskhalaya G, Zitzmann M, Arver S, Kalinchenko S, Tishova Y, Morgentaler A (2015) Recommendations on the diagnosis, treatment and monitoring of hypogonadism in men. Aging Male 18(1):5–15. https://doi.org/10.3109/13685538.2015.1004049
40. Morgentaler A, Miner MM, Caliber M, Guay AT, Khera M, Traish AM (2015) Testosterone therapy and cardiovascular risk: advances and controversies. Mayo Clin Proc 90(2):224–251. https://doi.org/10.1016/j.mayocp.2014.10.011
41. Kim DK, Noh JW, Chang Y, Lee HY, Park JJ, Ryu S, Kim JHJA (2020) Association between prostate-specific antigen and serum testosterone: a systematic review and meta-analysis. Andrology 8:1194–1213