THERAPY OF ENDOCRINE DISEASE

Testosterone supplementation and body composition: results from a meta-analysis study

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Abstract

Objective: The role of testosterone (T) in regulating body composition is conflicting. Thus, our goal is to meta-analyse the effects of T supplementation (TS) on body composition and metabolic outcomes.

Methods: All randomized controlled trials (RCTs) comparing the effect of TS on different endpoints were considered.

Results: Overall, 59 trials were included in the study enrolling 3029 and 2049 patients in TS and control groups respectively. TS was associated with any significant modification in body weight, waist circumference and BMI. Conversely, TS was associated with a significant reduction in fat and with an increase in lean mass as well as with a reduction of fasting glycaemia and insulin resistance. The effect on fasting glycaemia was even higher in younger individuals and in those with metabolic diseases. When only RCTs enrolling hypogonadal (total T < 12 mol/l) subjects were considered, a reduction of total cholesterol as well as triglyceride (TGs) levels were also detected. Conversely, an improvement in HDL cholesterol levels as well as in both systolic and diastolic blood pressure was not observed.

Conclusion: Our data suggest that TS is able to improve body composition and glycometabolic profile particularly in younger subjects and in those with metabolic disturbances. Specifically designed studies are urgently needed to confirm this point.

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Introduction

Obesity constitutes a major health problem, and it is a risk factor for cardiovascular (CV) events, type 2 diabetes mellitus (T2DM), certain types of cancer, sleep apnoea, osteoarthritis, and most of all, excess mortality (1, 2, 3, 4, 5).

Considering that obesity is the result of a difference between energy intake and expenditure, lifestyle interventions, aimed at reducing food intake and increasing exercise, are the foundations of obesity care. One systematic review of controlled trials of lifestyle interventions indicates that psychological therapy was associated

with a 2.5% weight loss after 1 year and that a combination of the former with diet and physical exercise almost doubled weight loss (6). However in real life, diet, physical activity, psychological therapies or the combination thereof, over the long term unfortunately, fail (7, 8). Even medical interventions, with the exception of bariatric surgery, have shown limited success, in particular as far as pharmacological treatments are concerned. Numerous anti-obesity drugs have been developed in the last 20 years, but they have often been

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suspended from the market because of poor efficacy and/or insufficient safety. The ideal pharmacological intervention should provide a prompt (during the 1st month) and sustained weight loss (i.e., >5% body weight loss after 3–6 months), without significant adverse effects. This is a difficult goal to achieve because energy balance regulation is redundant and overlaps with the regulation of other vital systems. Meta-analyses of pharmacological interventions demonstrate that available anti-obesity medications, such as orlistat, result in a modest, although clinically significant, weight loss (2.5–5 kg at 1 year) (9, 10). Glucagon-like peptide 1 (GLP1) receptor agonists, such as liraglutide, show an efficacy greater than of orlistat, but average weight loss does not exceed 5% of initial body weight (11). Other drugs, such as lorcaserin and combinations of bupropion–naltrexone or phentermine–topiramate, have not been approved in many countries because of safety concerns. A recent meta-analysis, considering the effects of any behavioural or medical interventions on waist circumference (WC), demonstrates an average reduction of 3 cm in the active arm over placebo (12).

In BMI-matched obese subjects, men have a greater amount of visceral fat than women (13, 14). In men, visceral obesity is the main cause of age-related late-onset

hypogonadism (LOH) (3, 15, 16, 17) and weight loss is the first avenue of its treatment (18). The relative risk of being hypogonadal is increased by a factor of three in overweight individuals and by a factor of six in obese European adults (19). On the other hand, hypogonadism is associated with a substantial increase in fat accumulation, in particular in the visceral stores. Recently, some observational studies in men with LOH reported a substantial weight loss with testosterone supplementation (TS, 17). Hence, the concept of TS as a new anti-obesity medication in men with LOH is growing (17). The anti-obesity activity of TS in hypogonadal men may be effective because, on one hand, it reduces abdominal fat accumulation and, on the other, it improves muscle mass and strength, facilitating adherence to exercise regimens designed to combat obesity (17). In two independent cohorts of hypogonadal obese men observed for up to 6 years, WC decreased by 11.56 cm and weight declined by 17.49 kg (15.04%), after testosterone undecanoate (TU) injections (20). Based on this report, results with TU in LOH-associated obesity seem superior to other lifestyle or medical interventions (see before) and comparable to those obtained with the most invasive therapies, such as bariatric surgery (21). However, randomized controlled trials (RCTs) showing TS-induced weight loss as the

Table 1 Comparisons on available meta-analyses evaluating the relationship between testosterone supplementation (TS), body composition and metabolic outcomes.

	Whitsel et al. (73)	Isidori et al. (74)				Haddad et al. (75)			Fernández- Balsells et al. (76)
		General	Level of baseline TT			General	Level of baseline TT		
			< 10 nM	> 10 nM	Mixed		< 10 nM	Mixed	
Number of trials included	19	29				30			51
Number of patients analyzed	272	1083				1642			2679
Inclusion criteria									
Only hypogonadal included	Yes	No				No			Yes
Mixed population included	No	Yes				Yes			No
Level of baseline TT	< 12 nM								< 10 nM
Outcome analyzed									
Weight	NR		NR	NR	↔		NR	NR	NR
Waist circumference	NR		NR	NR	NR		NR	NR	NR
BMI	NR		NR	NR	NR		NR	NR	NR
Fat mass	NR		↓	↓	↓		NR	NR	NR
Lean mas	NR		↔	↑	↑		NR	NR	NR
Total cholesterol	↓		↓	↔	↔		↔	↓	↔
HDL	↓		↔	↓	↔		↔	↔	↓
LDL	↔		↔	↔	↔		↔	↔	↔
Triglycerides	↔		NR	NR	NR		↔	↔	↔
Diastolic blood pressure	NR		NR	NR	NR		NR	NR	↔
Systolic blood pressure	NR		NR	NR	NR		NR	NR	↔
Fasting glucose	NR		NR	NR	NR		NR	NR	↔
HOMA index	NR		NR	NR	NR		NR	NR	NR
Insulin	NR		NR	NR	NR		NR	NR	NR

NR, not reported; TT, total testosterone.

primary endpoint are still lacking and those reporting it as a secondary outcome are often conflicting: some show weight loss (22, 23), others weight gain (24, 25) and the vast majority a non-significant effect (26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52). Similar information can be obtained by scrutinizing observational and registry studies (53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72).

Meta-analyses are a mainstay of evidence-based medicine, able to overcome marked between-study heterogeneity, useful in addressing questions for which multiple data sources are conflicting or when a variety of reports with low statistical power is available. In fact, pooling data can improve power and provide a convincing result. Surprisingly, meta-analyses investigating

TS- induced weight loss in LOH are lacking. In addition, results from previous meta-analyses on the effects of TS on body composition and other metabolic parameters in LOH are outdated, essentially conflicting ((73, 74, 75, 76, 77), see Table 1). In addition, retrieved and analysed outcomes of interest were different from one meta-analysis to another and the effect of TS on BMI and WC were never reported (see Table 1). Other meta-analyses on the effects of TS on body composition and metabolism were focused on specific LOH subpopulations, such as T2DM (15, 78, 79), metabolic syndrome (MetS) (15, 80), the combination of the two (81), human immunodeficiency virus (HIV) (15, 82, 83) or chronic obstructive pulmonary disease (COPD) (15, 84).

The aim of the present study is to meta-analyse the available evidence on the effects of TS on body weight and

Figure 1

Flow diagram of trial. Unpublished studies were identified through a search of www.clinicaltrials.gov website. N, number; GnRH, gonadotropin-releasing hormone; Gn, gonadotropins.

Table 2 Characteristics of the clinical studies included in the meta-analysis.

Study (arm) (ref.)	Number patients (T/placebo or controls)	Trial duration (months)	Age (years)	Type of population	Baseline total T (nmol/l)	T levels	Dose	Placebo
(27)	11/11	8	59.9	Overweight/ obesity	15.8	Mixed	TU oral 160 mg/day	Yes
(26)	13/13	6	66.7	Elderly men	11.4	Mixed	TE 100 mg/week	Yes
(28)	9/9	9	57.2	Obesity	14.8	Mixed	T gel 125 mg/day	Yes
(29)	8/6	3	76.5	Elderly men	9.4	<12 nM	TE 200 mg/2 weeks	No
(30)	13/0	6	30.2	Healthy	20.7	Eugonadism	TE 200 mg/week	No
(86)	15/0	12	61	Asthma + GC therapy	12.3	Mixed	Mixed ester 250 mg/month	No
(31)	17/15	12	66.4	Elderly men	9.1	<12	TC 200 mg/2 weeks	Yes
(87)	17/17	2	66.9	Elderly men	10.1	Mixed	TU 120 mg/day	Yes
(24)	7/7	3	66.7	Elderly men	11.2	Mixed	TE 200 mg/2 weeks	Yes
(32)	11/10	3	27	Healthy	–	Eugonadism	TE 3.5 mg/kg per 2 weeks	Yes
(88)	13/0	7	34.5	LOH	2.9	<3.6	TU 160 mg/day	No
(88)	15/0	7	31.8	LOH	2.3	<3.6	TE im 250 mg/3 weeks	No
(88)	15/0	7	35.8	LOH	2.7	<3.6	TPEL 1200 mg sub- cutaneous	No
(33)	54/54	36	73.1	Elderly men	12.6	Mixed	T patch 6 mg/day	Yes
(25)	151/0	6	–	LOH	8.4	<10.4	T gel 50–100 mg/day	No
(25)	76/0	6	–	LOH	8.2	<10.4	T patch 10 mg/day	No
(89)	34/33	12	75.5	Elderly men	13.4	Mixed	T patch 5 mg/day	Yes
(90)	6/6	3	54.1	LOH	8.2	<12	T gel 125 mg/die	Yes
(91)	21/17	6.5	70	Elderly men	14	Mixed	TE 100 mg/2 weeks	Yes
(34)	24/24	3	57.5	T2DM, obesity	9.45	Mixed	TU oral 120 mg/day	No
(92)	18/16	12	59.3	Long-term GC therapy	13.7	Mixed	Mixed ester 200 mg/ 2 weeks	Yes
(35)	7/5	6	67.6	Elderly men	12.3	Mixed	TE 200 mg/2–3 weeks	Yes
(36)	17/17	1	67	Elderly men	9.6	Mixed	Mixed ester 250– 500 mg/week	Yes
(93)	140/0	3	57.8	LOH	7.9	≤10.4	T gel 50–100 mg/day	No
(93)	68/0	3	57.9	LOH	7.9	≤10.4	T patch 5 mg/day	No
(94)	33/6	3	–	LOH	8.9	Mixed	TU oral 160 mg/day	Yes
(37)	307/99	3	58	LOH	8.1	<10.4	T gel 50–100 mg/day or T patch 5 mg/day	Yes
(95)	39/37	12	68.5	Elderly men	16.8	Mixed	TU oral 160 mg/day	Yes
(38)	12/12	2.5	67.1	COPD	10.4	Mixed	TE 100 mg/week	Yes
(38)	11/12	2.5	66.1	COPD	11.6	Mixed	Training ± TE 100 mg/week	Yes
(23)	15/14	6.5	65.9	COPD	21.1	Eugonadal	TE 250 mg/4 weeks	Yes
(96)	123/0	42	51.5	LOH	9.2	<10.4	T gel 5, 7.5 or 10 g/day	No
(39)	24/24	36	70.9	Elderly men	9.8	<12	TE 200 mg/2 weeks	Yes
(40)	23/20	6	69.9	Elderly men	17.4	Eugonadal	T patch 5 mg/day	Yes
(97)	27/27	3	64	T2DM	8.7	<12	Mixed ester 200 mg/ 2 weeks	Yes
(98)	17/19	3	72.5	Elderly men	14.4	Mixed	Training ± T patch 5 mg/day	Yes
(98)	17/17	3	72	Elderly men	14.1	Mixed	T patch 5 mg/day	Yes
(99)	30/32	24	66.7	Elderly men	13.2	Mixed	T patch 5 mg/day	Yes
(41)	13/13	3	74.1	Heart failure	14.3	Mixed	Mixed ester 250 mg/ 2 weeks	Yes
(100)	13/13	13	68.9	Elderly men	8.5	<11	TU 1000 mg/12 weeks from week 6	Yes
(42)	31/31	12	63.3	Elderly men	13.5	Mixed	T patch 5 mg/day	Yes
(101)	120/117	6	67.3	Elderly men	10.8	Mixed	TU oral 160 mg/day	Yes
(102)	20/0	7.5	–	LOH	–	<8	TU 1000 mg/6–9 weeks	No
(102)	20/0	7.5	–	LOH	–	<8	TE 250 mg/3 weeks	No
(43)	17/18	13	69	Elderly men	8.4	<11	TU 1000 mg/12 weeks from week 6	Yes

Table 2 Continued

Study (arm) (ref.)	Number patients (T/placebo or controls)	Trial duration (months)	Age (years)	Type of population	Baseline total T (nmol/l)	T levels	Dose	Placebo
(44)	35/35	3	71	Heart failure	7.9	Mixed	TU 1000 mg/12 weeks from week 6	Yes
(103)	16/16	12	56.6	T2DM	10.4	<12	T gel 50 mg/day	No
(104)	7/6	13	64.8	Stable chronic angina	9.8	<12	TU 1000 mg/12 weeks from week 6	Yes
(105)	32/10	6	57.8	MetS and/or T2DM	10.9	<11	TU 1000 mg/12 weeks from week 6	Yes
(106)	40/10	12	57.2	MetS and/or T2DM	10.1	<11	TU 1000 mg/12 weeks from week 6	Yes
(107)	22/22	3	44.2	T2DM	10.4	Mixed	TC 200 mg/2 weeks	Yes
(45)	113/71	7.5	52.1	MetS	6.7	<12	TU 1000 mg/12 weeks from week 6	Yes
(108)	69/62	12	77.9	frailty, low BMD	13.3	Mixed	T gel 50 mg/day	Yes
(109)	138/136	6	73.8	Elderly frail men	13.8	Mixed	T gel 50 mg/day	Yes
(110)	108/112	12	59.9	MetS and/or T2DM	9.4	Mixed	T gel 60 mg/day	Yes
(111)	130/132	6	73.9	elderly frail men	10.9	Mixed	T gel 50 mg/day	Yes
(46)	8/8	5	69	Elderly men	11.9	Mixed	TE 100 mg/week	Yes
(47)	23/23	6	67.5	Elderly men	12.1	Mixed	T gel 50–100 mg/day	Yes
(48)	33/34	4.5	48.5	Obesity with OSAS	–	Mixed	TU 1000 mg/6 weeks	Yes
(49)	237/79	12	58.7	Elderly men	12.8	Mixed	TU 80–240 mg/day	Yes
(112)	20/18	6	67	Elderly men	–	Mixed	T gel 50–100 mg/day	Yes
(112)	7/9	6	67	Elderly men	–	Mixed	T gel 50–100 mg/day + training	Yes
(50)	97/102	7.5	61.6	T2DM	9.2	Mixed	TU 1000 mg/12 weeks from week 6	Yes
(51)	56/28	12	66	Elderly men	10.3	<12	Training en12 weeks from week	Yes
(51)	55/28	48	66	Elderly men	10.3	<12	T gel 25–100 mg/day	Yes
(113)	60/60	12	–	Elderly men	–	<12	TU 1000 mg/12 weeks from week 6	Yes
(22)	12/12	13.5	56.9	LOH, obesity	8.4	<12	TU 1000 mg/12 weeks from week 6	No
(52)	45/43	10	62	T2DM	8.6	<12	TU 1000 mg/12 weeks from week 6	Yes

TE, testosterone enanthate; TC, testosterone cypionate; BPH, benign prostatic hyperplasia; OSAS, obstructive sleep apnea syndrome; BA, controlled cohort before-and-after comparisons in the same group of patients; CBA, controlled before-and-after study between two or more groups of participants receiving different interventions.

WC, including other parameters concerning body composition and metabolic outcomes.

Methods

This meta-analysis was performed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline (<http://prisma-statement.org/documents/PRISMA%202009%20checklist.pdf>) (85).

An extensive Medline, Embase and Cochrane search was performed including the following words ('testosterone'(MeSH Terms) OR 'testosterone'(All Fields)) AND ('body composition'(MeSH Terms) OR ('body'(All Fields) AND 'composition'(All Fields)) OR 'body composition'(All Fields) AND English(lang) AND 'male'(MeSH Terms)). The search accrued data from January 1, 1969 up to August 31, 2014. In addition, completed but still unpublished RCTs evaluating the effects of TS on different outcomes were identified through a search on the www.clinicaltrials.gov

Table 3 Outcomes of the clinical studies included in the meta-analysis.

Study (arm) (ref.)	Body weight	BMI	WC	Fat mass	Lean mass	Fasting glycemia	HOMA	Total cholesterol	HDL cholesterol	TG	Diastolic blood pressure	Systolic blood pressure
(27)	X	X	X	X	X	X		X	x	x	x	x
(26)	X			X	X			X	x	x		
(28)	X	X	X	X	X	X		X	x	x	x	x
(29)	X			X				X	x			
(30)	X			X	X							
(86)				X	X			X	x	x		
(31)	X	X		X				X				x
(87)		X						X	x			
(24)	X				X			X				
(32)	X		X									
(88)								X	x	x		
(88)*								X	x	x		
(88) [†]								X	x	x		
(33)	X	X		X	X			X	x	x		
(25) [‡]	X			X	X			X	x			
(25) [†]	X			X	X			X	x			
(89)		X		X	X			X	x	x		
(90)						X		X	x	x	x	x
(91)				X	X							
(34)	X	X		X	X	X		X	x	x	x	x
(92)				X	X			X	x	x		
(35)	X				X			X	x			
(36)	X	X		X	X							
(93) [‡]				X	X							
(93) [†]				X	X							
(94)								X				
(37)	X			X	X							
(95)				X	X							
(38)	X			X	X			X	x			
(38) [§]	X			X	X			X	x			
(23)	X			X	X							
(96)	X			X	X			X	x			
(39)	X			X	X			X	x	x		
(40)	X	X				X		X	x	x		x
(97)		X	X	X	X	X	X	X	x	x	x	x
(98) [§]				X	X			X	x	x		
(98)				X	X			X	X	x		
(99)					X	X			X			
(41)	X			X			X					
(100)		X	X	X	X			X	X	x		
(42)	X	X	X	X	X	X	X	X	X	x		
(101)		X		X	X	X	X	X	X	x		
(102)		X						X	X	x		
(102)*		X						X	X	x		
(43)	X	X	X	X	X	X	X	X	X	x		
(44)	X	X				X	X	X	X	x	x	x
(103)			X			X	X		X	x	x	x
(104)		X						X				
(105)		X	X	X	X	X	X	X	X	x	x	x
(106)		X	X	X	X	X	X	X	X	x	x	x
(107)		X	X			X	X	X	X	x	x	
(45)	X	X	X			X	X	X	X	x		
(108)				X	X			X	X	x		
(109)				X	X							
(110)		X	X	X		X	X	X	X	x	x	x
(111)				X	X							
(46)	X	X		X	X	X		X	X	x		
(47)	X	X		X								
(48)	X			X	X	X	X	X	X		x	x
(49)	X			X	X							

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Table 3 Continued

Study (arm) (ref.)	Body weight	BMI	WC	Fat mass	Lean mass	Fasting glycemia	HOMA	Total cholesterol	HDL cholesterol	TG	Diastolic blood pressure	Systolic blood pressure
(112)				X	X							
(112) ^S				X	X							
(50)	X	X	X			X	X	X	X	x	x	x
(51) ^S	X	X		X	X							
(51)	X	X		X	X							
(113)		X	X			X		X	X	x	x	x
(22)	X	X	X	X	X	X	X	X	X	x	x	x
(52)	X	X	X	X	X	X	X	X	X	x	x	x

Data on *T enathathe, [†]T pellet, [‡]T gel, [§]T plus physical activity.

website. The identification of relevant studies was performed independently by two of the authors (VG, GC), and conflicts resolved by the third investigator (AA). We did not employ search software. We hand-searched bibliographies of retrieved papers for additional references. The principal source of information was derived from published articles; if data were missing from the publication, an attempt at retrieval was made through the clinicaltrial.gov website.

Study selection

We included all RCTs both placebo and not placebo controlled, comparing the effect of TS on different endpoints (22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113) (see also Fig. 1 and Tables 2, 3, 4). Observational studies (53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128) or studies not specifically evaluating body composition or glycometabolic outcomes were excluded from the analysis (129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139); see also Fig. 1 and Table 5). Studies using androgens other than TS as well as studies with simultaneous treatment with other hormones and drugs were also excluded, unless there was a clearly defined treatment arm that received only T treatment. In addition, since phosphodiesterase type 5 inhibitors (PDE5is) have been reported to play a possible positive influence on metabolic outcome (140, 141), trials evaluating the effect of TS as an add-on to PDE5is were excluded from the analysis (see also Table 5).

Outcome

The principal outcome of this analysis was the effect of TS, as compared with placebo or control group, on body composition modification including fat and lean mass. Secondary outcomes included several other glycometabolic parameters (Table 3).

Quality assessment

The quality of trials was assessed using the Cochrane criteria ((142); see also Table 4). In particular, the following criteria were evaluated: how the randomization sequence was generated, how allocation was concealed, whether there were important imbalances at baseline, which groups were blinded (patients, caregivers, data collectors, outcome assessors, data analysts), what the loss to follow-up rate was (in the intervention and the control arm), whether the analyses were by intention to treat and how missing outcome data were dealt with. For each study, we also assessed how the population was selected, the duration and route of TS, and the adequacy of study follow-up (143).

Statistical analysis

Heterogeneity was assessed by using I^2 statistics. However, a random-effects model was applied for all analyses, even when low heterogeneity was detected, because the validity of tests of heterogeneity can be limited with a small number of component studies. To estimate possible publication or disclosure bias, we used funnel plots and the Begg adjusted rank correlation test (144, 145). However, because these tests have low statistical power when the number of trials is small, undetected bias may still be present. In addition, since in some trials the

Table 4 Characteristics and outcomes of the randomized clinical trials and observational studies included in the meta-analysis.

Study (ref.)	Design	Blinding	Drop-out	Intention-to-treat	Eligibility criteria listed
(27)	Parallel	A	A	Yes	Yes
(26)	Cross-over	A	A	Yes	Yes
(28)	Parallel	A	A	Yes	Yes
(29)	NAP	NAP	A	Yes	Yes
(30)	NAP	NAP	NA	Yes	Yes
(86)	NAP	NAP	A	Yes	Yes
(31)	Parallel	NA	A	No	Yes
(87)	Parallel	NA	NA	Yes	Yes
(24)	Parallel	A	A	No	No
(32)	Parallel	A	NA	No	Yes
(88)	NAP	NAP	NA	No	Yes
(88)*	NAP	NAP	NA	No	Yes
(88) [†]	NAP	NAP	NA	No	Yes
(33)	Parallel	A	A	Yes	Yes
(25) [‡]	NAP	NAP	A	No	Yes
(25) [†]	NAP	NAP	A	No	Yes
(89)	Parallel	A	A	Yes	Yes
(90)	Parallel	A	NA	No	Yes
(91)	Parallel	A	A	Yes	Yes
(34)	NAP	NAP	A	Yes	Yes
(92)	Parallel	A	A	Yes	Yes
(35)	Parallel	A	NA	No	Yes
(36)	Cross-over	A	A	Yes	Yes
(93) [‡]	NAP	NAP	A	A	Yes
(93) [†]	NAP	NAP	A	A	Yes
(94)	Parallel	A	A	Yes	Yes
(37)	Parallel	NA	NA	No	Yes
(95)	Parallel	A	A	Yes	Yes
(38)	Parallel	A	A	Yes	Yes
(38) [§]	Parallel	A	A	Yes	Yes
(23)	Parallel	A	A	No	No
(96)	NAP	NAP	NA	Yes	Yes
(39)	Parallel	A	A	Yes	Yes
(40)	Parallel	A	A	Yes	Yes
(97)	Cross-over	A	A	No	Yes
(98) [§]	Parallel	A	A	Yes	Yes
(98)	Parallel	A	A	Yes	Yes
(99)	Parallel	A	NA	Yes	Yes
(41)	Cross-over	A	A	Yes	Yes
(100)	Parallel	A	A	No	Yes
(42)	Parallel	A	A	Yes	Yes
(101)	Parallel	A	A	Yes	Yes
(102)	NAP	NAP	A	Yes	Yes
(102)*	NAP	NAP	A	Yes	Yes
(43)	Parallel	A	A	No	Yes
(44)	Parallel	A	A	No	Yes
(103)	NAP	NAP	A	Yes	Yes
(114)	Parallel	A	NA	Yes	Yes
(105)	Parallel	A	NA	No	Yes
(106)	Parallel	A	NA	No	Yes
(107)	Cross-over	A	NA	No	Yes
(45)	Parallel	A	A	Yes	Yes
(108)	Parallel	A	A	Yes	Yes
(109)	Parallel	NA	A	Yes	Yes
(110)	Parallel	A	NA	Yes	Yes
(111)	Parallel	A	A	Yes	Yes
(46)	Parallel	A	NA	No	Yes
(47)	A	A	A	Yes	Yes
(48)	Parallel	A	A	Yes	Yes
(49)	Parallel	A	A	Yes	Yes
(112)	Parallel	A	NA	Yes	Yes
(112) [§]	Parallel	A	NA	Yes	Yes

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Table 4 Continued

Study (ref.)	Design	Blinding	Drop-out	Intention-to-treat	Eligibility criteria listed
(50)	Parallel	A	A	A	Yes
(51) [§]	Parallel	A	NA	Yes	Yes
(51)	Parallel	A	NA	Yes	Yes
(113)	Parallel	A	A	Yes	Yes
(22)	NAP	NAP	A	A	Yes
(52)	Parallel	A	A	A	Yes

A, adequately described; NA, non-adequately described; NAP, not applicable. Data on *T enanthate, [†]T pellet, [‡]T gel, [§]T plus physical activity.

significance of between group comparisons (*P*) was not reported, the analysis was performed evaluating endpoint values of each parameter in different treatment groups, in a non-paired fashion (non-paired analysis). Considering that most of the studies, which did not describe *P* values, reported non-significant differences across groups, the mean (paired) analysis, which excludes those data, is likely to overestimate the effect of treatments. On the other hand, the non-paired analysis is a very conservative approach, which could underestimate treatment effect. Since body fat mass and lean mass were evaluated through different approaches and expressed in different ways, the mean difference for each study was divided by the pooled estimate of the SD, in order to express the effect size for each study in a common metric, namely the standardized mean difference (SMD). According to Cohen (145), a small treatment-effect size is considered to be about 0.2, a medium effect size to be about 0.5, and a large effect size to be about 0.8. All other data were expressed as weight mean differences. Meta-regression analyses were done in order to test the effects of final T plasma levels on fat and lean mass modification as well as on fasting glycaemia reduction only in placebo-controlled RCTs. Specific sensitivity analyses were also performed to evaluate the effects of the different T preparations on body composition and glycometabolic profile in placebo-controlled RCTs. Multivariate linear regression analysis model, weighing each study for the number of subjects enrolled, was performed in order to verify the effect of TS on fasting glycaemia and HOMA index after the adjustment for differences between the active arm and placebo in total T levels, fat and lean mass at end-point as a well as the mean age of the subjects enrolled and trial duration. In addition, other confounding factors such as BMI and prevalence of diabetes at baseline were considered. All analyses were performed using Comprehensive Meta-analysis Version 2, Biostat (Englewood, NJ, USA). Multivariate analyses were performed on SPSS (Statistical Package for the Social Sciences) for Windows 22.0.

Results

Out of 824 retrieved articles, 59 were included in the study (Fig. 1). Among them, 48 were placebo controlled. The characteristics of the retrieved trials (including parameters on trial quality) and type of outcomes considered are reported in Tables 2 and 3. Retrieved studies included 3029 and 2049 subjects in TS and control groups, respectively; mean trial duration was 8.7 months. TS was administered in different doses, formulations and cohorts (Table 2).

The mean age, baseline T and BMI of enrolled patients were 62.0 years, 11.6 nmol/l and 28.6 kg/m² respectively.

T levels

Overall, the use of all T preparations resulted in significantly higher T levels when compared to control group (not shown). However, when only placebo-controlled RCTs were considered, parenteral preparations were associated with the highest T circulating levels at follow up when compared to those observed with oral and transdermal drugs (mean T differences vs placebo 7.69 (6.23; 9.14), 7.57 (5.72; 9.43) vs 2.39 (−0.43; 5.21) nM for parenteral, transdermal and oral preparations respectively; *P* < 0.005 for oral in comparisons to parenteral and transdermal drugs). Conversely, no differences were observed when injectable TU formulation was compared to other parenteral preparations (not shown).

Body composition

Among studies reporting several outcomes, 32 included information on weight (Table 3). Funnel plot and Begg-adjusted rank correlation test suggested no small study effects (Kendall's τ : −0.10; *P* = 0.38). TS was not associated with a reduction of body weight, WC and BMI (Fig. 2 and Supplementary Figure 1, see section on supplementary data given at the end of this article, panels A, B and C).

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Table 5 Studies that met inclusion criteria but did not provide data for meta-analysis.

References	Short summer of the study and main conclusions
(129)	With the aims of comparing the pharmacokinetics and pharmacodynamics of three different formulations of T, 15 hypogonadal men were studied. However, those results were not included in our meta-analysis since the group of participants consisted of not all naïve patients
(130)	The study consisted in evaluating the TRT effects on serum lipids and lipoproteins in 13 hypogonadal men. This work was ruled out given that the patients group was made up of pre-pubertal and post-pubertal men
(131)	Controlled cohort study before and after comparison in the same group of constitutionally delayed puberty boys. TRT (TU 40 mg o.s.) increased fat free mass
(132)	A comparative study aims to verify the pharmacokinetics and bioefficacy of two doses of sublingual T cyclodextrin (2.5 and 5.0 mg; three times per day) with TE (once every 20 days) by i.m. injections over a 2 months study period in 63 hypogonadal men. However, the data could not employ as the group of participants were not all naïve subjects
(133)	The effects of gonadotropin and T therapies on lipids and lipoprotein(a) were studied in 31 hypogonadal males. The data were not considered for our study since the patients were pre-pubertal men
(134)	This study aims to look at the T role in developing insulin resistance and other cardiovascular risks factors in men. The data were not included in the meta analysis as were obtained from a group of subjects affected by puberty delayed
(135)	RCT on the effects of placebo or TE (25, 50, 125, 300 or 600 mg). Data on body composition were provided but the study was excluded since hypogonadism was artificially induced in healthy men by the use of GnRH agonist
(136)	Cross-over RCT of the effects of T patch (50 mg/day) and sildenafil for 8 weeks on sexual function in hypogonadal men with erectile dysfunction. The combined therapy with PDE5 and T or placebo can influence the outcomes of the study
(137)	Observational cohort study before and after study between two groups of participants receiving T (T cypionate 200 mg/3 weeks) or not. There are not data about circulating T both in baseline and at the end of the study. In addition, the data are not complete
(138)	Observational cohort study before and after comparison in the same group of pre-pubertal hypogonadic men. TRT (T undercycle 40 mg o.s.) increased weight and BMI. The data were not considered for our study since the patients were pre-pubertal boys
NCT00957528	RCT on the effects of T (TE100 mg/week) on muscle strength and lean body mass. There are incomplete data and serum T at the start and the end of the study is not reported
(139)	RCT on the effects of placebo, T (gel 1.25, 2.5, 5 or 10 g) and anastrozole (to suppress the conversion of T to estradiol). Data on body composition were provided but the study was excluded since hypogonadism was artificially induced in healthy men by the use of GnRH agonist

Information on fat mass and lean mass were available from 42 and 40 studies, respectively (Table 3). TS was associated with a significant reduction of fat and with an increase of lean mass (Fig. 2, and Supplementary Figure 1, see section on supplementary data given at the end of this article, panels D and E). These effects were confirmed even when only trials using DEXA-derived data were considered (standardized means -0.34 (-0.48 ; -0.20) and 0.55 (0.39 ; 0.72) for fat and lean mass respectively; both $P < 0.0001$). Similar results were observed when only placebo-controlled RCTs were considered (standardized means -0.36 (-0.51 ; -0.20) and 0.57 (0.38 ; 0.75) for fat and lean mass respectively; both $P < 0.0001$) or after excluding those trials enrolling mixed (eugonadal and hypogonadal) populations (standardized means -0.39 (-0.61 ; -0.17) and 0.45 (0.26 ; 0.63) for fat and lean mass, respectively; both $P < 0.0001$).

By performing a sensitivity analysis on only placebo-controlled RCTs, no relationship between fat and lean mass modification, and final levels of T was detected

at meta-regression analysis (not shown). However, when the data were analysed according to the type of T preparation used, no improvement in body composition (both lean and fat mass modification) was observed in those trials using oral T preparations (SMD $-e-0.61$; 0.04); $P=0.08$ and 1.59 (-0.64 ; 3.83); $P=0.16$ for fat and lean mass respectively). Conversely, the use of both transdermal and parenteral preparations significantly improved body composition with the use of the latter drugs resulting in better outcomes (mean standardized difference -0.67 (-1.01 ; -0.33) vs -0.16 (-0.31 ; -0.01); $Q=7.19$, $P < 0.01$ and 0.61 (0.37 ; 0.85) vs 0.33 (0.18 ; 0.47); $Q=3.80$, $P=0.05$ for fat mass and lean mass, respectively). In addition, among parenteral preparations, injectable TU produced better results when compared to other parenteral formulations (mean standardized difference -0.93 (-1.76 ; -0.09) vs -0.53 (-0.82 ; -0.24); $Q=7.55$, $P=0.023$ and 0.87 (0.62 ; 1.11) vs 0.42 (0.07 ; 0.77); $Q=13.9$, $P=0.001$ for fat mass and lean mass respectively).

Figure 2

Weighted mean differences (with 95% CI) of body weight, WC, BMI, fat and lean mass, fasting glycaemia, HOMA index, total cholesterol, triglycerides, HDL-cholesterol, systolic (SBP) and

diastolic (DBP) blood pressure at end point in studies enclosed in the analysis. *Standardized means were considered.

Glyco-metabolic profile and blood pressure

TS was associated with a reduction of fasting glycaemia and insulin resistance (IR), as detected by HOMA-IR index (Fig. 2, see also [Supplementary Figure 1](#), see section on [supplementary data](#) given at the end of this article, panels F and G). Similar results were observed when only placebo-controlled RCTs were considered (standardized means -0.28 (-0.45 ; -0.12) and -0.72 (-1.11 ; -0.33) for glycaemia and HOMA index respectively; both $P < 0.001$) or after excluding those trials enrolling mixed (eugonadal and hypogonadal) populations (standardized means -0.37 (-0.65 ; -0.09) and -1.27 (-1.84 ; -0.71) for glycaemia and HOMA index, respectively; both $P < 0.01$).

By performing a further sensitivity analysis on only placebo-controlled trials, no relationship between glucose level modification and final levels of T was detected at

meta-regression analysis (not shown). However, when the data were analysed according to the type of T preparation used, no improvement in glucose levels was observed in those trials using oral T preparations (mean difference -0.77 (-1.87 ; 0.33); $P = 0.17$). Conversely, the use of both transdermal and parenteral preparations significantly improved fasting glycaemia with the use of the latter drugs resulting in better outcomes (mean difference -0.48 (-0.64 ; -0.32) vs -0.23 (-0.37 ; -0.10); $Q = 5.95$, $P = 0.015$).

In order to verify whether the glycaemic effects of TS could be associated with a variation in body composition, a multivariate linear regression analysis was performed weighting each study for the number of subjects enrolled, by introducing in the same model, differences between the active arm and placebo in total T levels, fat and lean mass at end-point, age and trial duration as possible predictors

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Table 6 End-point T level modification adjusted relationship between TS-induced glycol-metabolic improvement and body composition changes. Data are derived from a multivariate linear regression model, weighting each study for the number of subjects enrolled, introducing the differences between the active arm and placebo in total T levels and fat and lean mass at end-point as well as age and trial duration as possible predictors of differences in fasting glycaemia and HOMA-IR index.

	Lean mass		Fat mass	
	Adj. R	P	Adj. r	P
HOMA index	0.82	0.001	−0.02	0.43
Fasting glycaemia	0.48	0.001	−0.05	0.27

of differences in fasting glycaemia and HOMA-IR index. The results of this analysis are reported in Table 6. Between-group differences in fasting glycaemia and HOMA-IR index were related to modification in lean but not in fat mass (Table 6). The association with lean mass was confirmed in alternative multivariate regression models when other confounding factors such as BMI (adj $r=0.32$ and 0.35 for fasting glycaemia and HOMA index respectively; both $P<0.0001$) and prevalence of diabetes (adj. $r=0.32$ and 0.46 for fasting glycaemia and HOMA index respectively; both $P<0.0001$) at baseline were considered.

When lipid profile was analysed, no effect of TS on total cholesterol as well as triglyceride levels was observed (Fig. 2, see also Supplementary Figure 1, see section on supplementary data given at the end of this article, panels H and I). However, when only placebo-controlled trials enrolling hypogonadal (TT <12 nmol/l) subjects at baseline were considered, a positive effect of TS on total cholesterol (-0.35 (-0.61 ; -0.08) mM; $P<0.0001$) and triglyceride (-0.22 (-0.37 ; 0.08) mM; $P=0.003$) reduction was observed. Conversely, no effect of TS in HDL cholesterol levels as well as in both systolic and diastolic blood pressure was observed (Fig. 2, and Supplementary Figure 1, see section on supplementary data given at the end of this article, panel L and N). Similar results were observed when only placebo-controlled RCTs were considered (-0.23 (-0.37 ; -0.10) and -0.09 (-0.14 ; -0.03) for total cholesterol and triglycerides respectively; both $P<0.005$) or after excluding those trials enrolling mixed (eugonadal and hypogonadal) populations (-0.28 (-0.44 ; -0.12) and -0.18 (-0.33 ; -0.04) for total cholesterol and triglycerides respectively; both $P<0.05$).

Sensitivity analysis according to population characteristics at baseline in placebo controlled RCTs

No difference in T levels at end point was observed by comparing obese (BMI ≥ 30 kg/m²; $n=11$) and non-obese subjects ($n=21$) at baseline (8.24 (5.64; 10.85) vs 6.84 (5.59; 8.08), $Q=0.91$, $P=0.34$).

TS produced better outcomes in reducing fat mass in hypogonadal (total T <12 nM) subjects at baseline when compared to the rest of the sample (-0.67 (-1.07 ; -0.27) vs -0.23 (-0.38 ; -0.08); $Q=4.12$; $P=0.04$). Conversely, no difference in lean mass between hypogonadal or not hypogonadal patients at baseline was observed (0.54 (0.32; 0.76) vs 0.65 (0.29; 1.01); $Q=0.27$, $P=0.60$).

Furthermore, by comparing the effect of TS in subjects with a metabolic disease ($n=11$) to those evaluating elderly men ($n=10$), the improvement of fasting glycaemia was even higher in the former group when compared to the latter (-0.52 (-0.78 ; -0.25) vs 0.19 (-0.34 ; -0.04) mM; $Q=4.22$, $P=0.03$). Accordingly, the effect of TS was higher in obese subjects (BMI >30 kg/m²) when compared to the rest of the sample (mean difference vs placebo -0.49 (-0.69 ; -0.30) vs -0.25 (-0.38 ; -0.11) mM; $Q=4.13$, $P=0.04$). In addition, a better outcome was also observed in younger individuals (the median age <60 years; -0.52 (-0.65 ; -0.39) vs -0.14 (-0.28 ; 0.01) mM; $Q=14.65$ $P<0.0001$).

Discussion

The present meta-analysis indicates that TS in men – heterogeneous in terms of BMI and metabolic conditions – is associated, in controlled studies, with a small to medium pooled effect size reduction of total fat and an increase in lean mass that is exactly of the same order of magnitude, although in the opposite direction (0.3 and 0.5 SMD respectively). A previous meta-analysis, involving half of the studies scrutinized here (74), reported similar results. The dual, opposite effects of TS on body composition, i.e. an increase in lean mass and a reduction in fat mass, might justify the overall null efficacy of TS on body weight or BMI. Present results are in apparent contrast with several observational studies indicating that TS is associated with a significant weight loss (62, 64, 65, 66, 67, 68, 69) and decrease in BMI (64, 66, 68, 69, 126, 128) and WC (60, 64, 66, 67, 68, 69, 113, 123, 128). RCTs and observational studies obviously differ in study design and patient allocation criteria. However, as far as the effect of TS on obesity is concerned, they also differ in baseline T level and follow-up duration. In particular, in observational studies,

the subjects usually enrolled had more severe hypogonadism and were followed for a longer period. Different patient medication adherence might further contribute to the differences in effects observed. It is important to note that diagnosis of hypogonadism allows only for a short period of placebo-controlled design because the condition is associated with an increased risk of osteoporosis or other metabolic and sexual side effects. Hence, long-term, placebo-controlled studies are scarcely feasible.

TS, even in men with LOH, cannot be considered as a true short-term anti-obesity medication (17), because its effect on body weight is not apparent, at least in the timeframe covered by RCTs.

However, our data showed that TS is not only associated with an improvement in body composition, but also with a more favourable glycometabolic profile. Here we reported a small but significant effect of active treatment on glycaemia and insulin sensitivity, as detected by HOMA-IR index. Similar results were previously reported in selected LOH populations, such as T2DM and MetS (15, 78, 79, 80, 81). It is conceivable that the improvement in glucose metabolism can be ascribed to increased muscle mass or to decreased fat mass. In an experimental model of MetS-associated hypogonadism, obtained by feeding rabbits a high-fat diet, we demonstrated that T administration was able to dramatically reduce visceral adiposity and, in cultured adipocytes, to increase insulin sensitivity and triglyceride metabolism (146). It is interesting to note that the positive associations among T levels, glycaemia and HOMA-IR index were not confirmed in a multivariate model after adjusting for lean, but not fat and mass. This suggests that increased muscle mass is somehow responsible for the more favourable glucose metabolism associated with TS. None of the known anti-obesity medications or surgical interventions improve muscle mass in the way that has been observed with TS.

Positive changes in lipid profile were seen in RCTs considering patients with hypogonadism, but not in eugonadal/mixed subjects. Our results are essentially in agreement with those from some of the previous meta-analyses (73, 74).

The effects of any treatment obviously depend on the characteristics of the subjects receiving that treatment. With respect to its metabolic effects, TS seems to be more effective in younger men and in those with metabolic disturbances. This finding could be of help in defining the population that could benefit most from TS.

Given that in the general European population more than 40 and 25% of obese individuals ($\text{BMI} \geq 30 \text{ kg/m}^2$) have total T below 12 or 10.4 nmol/l, respectively (19),

results of the present meta-analysis are relevant. In fact, TS in these individuals might help them in changing body composition and glucose metabolism. However, the present meta-analysis shows several limitations. In fact, the RCTs scrutinized here were neither specifically designed for weight loss nor had obesity as a selection criterion. In addition, enrolled subjects were not wishing to lose weight. It is possible that motivated, obese, hypogonadal subjects will respond differently to active treatment. Furthermore, it is conceivable that increased muscle mass will allow obese individuals to adhere to structured lifestyle interventions, which include physical activity. All these points should be addressed by dedicated clinical trials.

In conclusion, the present meta-analysis suggests that TS is able to improve body composition and glycometabolic profile particularly in younger subjects and in those with metabolic disturbances even though an overt effect on WC and/or body weight is not apparent. Specifically designed studies are urgently needed to confirm this point.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-15-0262>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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