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Muscular responses to testosterone replacement vary by administration route: a systematic review and meta-analysis

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Abstract

Background Inconsistent fat-free mass (FFM) and muscle strength responses have been reported in randomized clinical trials (RCTs) administering testosterone replacement therapy (TRT) to middle-aged and older men. Our objective was to conduct a meta-analysis to determine whether TRT improves FFM and muscle strength in middle-aged and older men and whether the muscular responses vary by TRT administration route.

Methods Systematic literature searches of MEDLINE/PubMed and the Cochrane Library were conducted from inception through 31 March 2017 to identify double-blind RCTs that compared intramuscular or transdermal TRT vs. placebo and that reported assessments of FFM or upper-extremity or lower-extremity strength. Studies were identified, and data were extracted and validated by three investigators, with disagreement resolved by consensus. Using a random effects model, individual effect sizes (ESs) were determined from 31 RCTs reporting FFM (sample size: n = 1213 TRT, n = 1168 placebo) and 17 reporting upper-extremity or lower-extremity strength (n = 2572 TRT, n = 2523 placebo). Heterogeneity was examined, and sensitivity analyses were performed.

Results When administration routes were collectively assessed, TRT was associated with increases in FFM [ES = 1.20 ± 0.15 (95% CI: 0.91, 1.49)], total body strength [ES = 0.90 ± 0.12 (0.67, 1.14)], lower-extremity strength [ES = 0.77 ± 0.16 (0.45, 1.08)], and upper-extremity strength [ES = 1.13 ± 0.18 (0.78, 1.47)] ($P < 0.001$ for all). When administration routes were evaluated separately, the ES magnitudes were larger and the per cent changes were 3–5 times greater for intramuscular TRT than for transdermal formulations vs. respective placebos, for all outcomes evaluated. Specifically, intramuscular TRT was associated with a 5.7% increase in FFM [ES = 1.49 ± 0.18 (1.13, 1.84)] and 10–13% increases in total body strength [ES = 1.39 ± 0.12 (1.15, 1.63)], lower-extremity strength [ES = 1.39 ± 0.17 (1.07, 1.72)], and upper-extremity strength [ES = 1.37 ± 0.17 (1.03, 1.70)] ($P < 0.001$ for all). In comparison, transdermal TRT was associated with only a 1.7% increase in FFM [ES = 0.98 ± 0.21 (0.58, 1.39)] and only 2–5% increases in total body [ES = 0.55 ± 0.17 (0.22, 0.88)] and upper-extremity strength [ES = 0.97 ± 0.24 (0.50, 1.45)] ($P < 0.001$). Interestingly, transdermal TRT produced no change in lower-extremity strength vs. placebo [ES = 0.26 ± 0.23 (−0.19, 0.70), P = 0.26]. Subanalyses of RCTs limiting enrolment to men ≥60 years of age produced similar results.

Conclusions Intramuscular TRT is more effective than transdermal formulations at increasing LBM and improving muscle strength in middle-aged and older men, particularly in the lower extremities.

Keywords Androgen; Ageing; Muscle; Musculoskeletal; Fat-free mass; Lean mass; Strength

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Introduction

Serum testosterone declines by ~1.2% per year in middle-aged and older men.[1] Across the ageing spectrum, hypogonadism (i.e. serum testosterone <300 ng/dL) is associated with deficits in muscle strength[2] and reduced fat-free mass (FFM),[3] along with a host of other health concerns.[4] These muscular deficits develop gradually and are particularly apparent in lower-extremity muscle groups involved in locomotion and balance,[5] suggesting that impaired physical function accompanies hypogonadism. Several meta-analyses indicate that testosterone replacement therapy (TRT) modestly increases FFM[6,7] and produces small improvements in muscle strength in middle-aged and older men.[8,7] However, these relatively small muscular benefits remain an area of clinical debate, in terms of weighing the risk-to-benefit trade-off and their relevance to improved physical function.[4,9]

Despite the existing evidence, inconsistent FFM and muscle strength responses have been observed in double-blind, placebo-controlled randomized clinical trials (RCTs) administering TRT to middle-aged and older men.[10] For example, several RCTs have reported that transdermal patch-based and gel-based TRT formulations produced small (0.9–1.9 kg) increases in FFM in older men but did not improve muscle function in comparison with placebo[11,12] or resulted in only minor improvements in muscle strength.[13,14] In contrast, other RCTs indicate that older men exhibited relatively larger (3.1–4.2 kg) increases in FFM in response to intramuscular TRT, along with ~10–30% improvements in strength.[15–17] One explanation for these differing responses is that the musculoskeletal benefits of TRT may vary by route of administration (i.e. transdermal vs. intramuscular).[10] Indeed, transdermal and intramuscular TRT administration routes provide different testosterone doses[9] and produce differing pharmacokinetics of androgen elevation,[18,19] which may affect musculoskeletal outcomes. For example, intramuscular TRT formulations produce supraphysiologic testosterone concentrations for several days following injection, with values gradually declining into the physiologic range thereafter.[18,20] In comparison, transdermal TRT formulations produce less robust testosterone elevations[19] that more consistently remain within the physiologic range.[18] The primary objectives of this systematic review and meta-analysis were to determine whether TRT improves FFM and muscle strength in middle-aged and older men and whether the muscular responses to TRT vary by administration route. We hypothesized that intramuscular TRT would produce a greater magnitude of improvement in both FFM and muscle strength than transdermal TRT, when compared with respective placebos, because (i) TRT produces dose-dependent muscular improvement in older men[21] and (ii) intramuscular TRT elevates circulating testosterone to a greater magnitude than transdermal formulations.[19,18]

Methods

Data sources and searches

Our meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (see Online Supplementary Material, *Data* S1). Three authors systematically searched PubMed and the Cochrane Register through 31 March 2017 by using the following search strategy: (testosterone OR androgen) AND (men OR males) AND (clinical trial) AND (sarcopenia OR muscle OR lean mass OR fat-free mass OR strength OR physical performance), and agreed upon eligibility of each study. This strategy was supplemented by manual searches of bibliographies from identified studies. Information from selected trials was extracted and verified in triplicate.

Study selection

Inclusion criteria were pre-defined and included the following: (i) publications in English language-based refereed journals; (ii) double-blind RCTs that compared participants receiving TRT vs. placebo; (iii) participant mean age of ≥45 years in the TRT and placebo groups; (iv) TRT administration via intramuscular or transdermal (patch-based or gel-based) formulations, with method and dose specified, for a minimum of eight continuous weeks; (v) at least one of the following outcome measures reported: total body FFM or upper-extremity or lower-extremity maximal strength; and (vi) sufficient information to allow statistical comparisons among groups reported in the paper or provided by the corresponding authors during a supplemental query. We excluded trials (i) where endogenous testosterone secretion was experimentally suppressed prior to initiation of TRT because these studies did not have a true placebo group; (ii) that administered androgens other than testosterone; (iii) that co-administered drugs that affect muscular outcomes or sex-steroid metabolism, unless treatment arms existed that received only TRT and placebo; and (iv) where exercise was combined with TRT, unless there were clearly delineated groups receiving TRT and placebo without exercise. A minimum duration of eight continuous weeks was selected because FFM and strength improvements are observable within this time frame but may not occur in studies of shorter duration. We checked for study duplication based on authorship, study description, number of participants, and participant characteristics, to ensure that we did not include more than one study reporting the same dataset. When duplication occurred, we used the report containing the most comprehensive data for each outcome.

Data extraction and quality assessment

The primary outcomes were total body FFM and total body strength, which represented a combination of upper-extremity

and lower-extremity strength measures. Secondary outcomes were upper-extremity and lower-extremity strengths. Data were extracted by trial arm and were validated in triplicate. Reviewers used an established tool to evaluate the quality of each trial.[22] The authors were contacted twice by email to ask for additional information if a trial met inclusionary criteria but did not report data in a manner that would allow statistical assessment with our a priori methods. Studies were excluded if useable data could not be obtained with the method in the preceding texts.

Data synthesis and analysis

To account for differences in units of strength measures, we adopted the Hedge's *g*-index[23] to characterize the effect size (ES) of each data point, as shown in the following equation, with small sample size correction:

$$\mathrm{g} = \mathrm{c(m)}\frac{\overline{y}_d - \overline{y}_c}{S_{pooled}}$$

where $\overline{y}_d$ is the average change from baseline measurement of the drug group and $\overline{y}_c$ is the average change from baseline measurement of the control group. S_{pooled} is the pooled within-study standard deviation. c(m) is a correction factor given as follows: $\mathrm{c(m)} = 1 - \frac{3}{4m-9}$, where $m = n_d + n_p$ with n_d and n_p being the sample sizes in the drug and placebo groups at post treatment, respectively. The converted ES and its variance for each study were included in the analysis. Heterogeneity was assessed by using the Q statistic.[23] Our analysis indicated that heterogeneity was significant (<0.05) in all scenarios considered. Thus, a random effects model was fit by using the DerSimonian–Laird approach to account for heterogeneity across studies.[24] Improvement was calculated as $\frac{\overline{y}_{db} - \overline{y}_{cb}}{\overline{y}_{cb}} * 100\%$, where $\overline{y}_{db}$ is the ratio between post treatment and pre-treatment measurements of the drug group and $\overline{y}_{cb}$ is the ratio between post treatment and pre-treatment measurements of the placebo group.

A *g*-index statistic was determined for total body FFM and for each muscle strength measure. Effect sizes were coded such that positive numbers reflected increasing FFM or strength and negative values reflected decreasing values in comparison with placebo. For each dependent measure, an ES and the accompanying 95% confidence interval (CI) are reported. Effect sizes of 0.20–0.49 were considered small, 0.50–0.79 medium, 0.80–1.1 large, and ≥1.2 very large.[25]

As noted in the preceding texts, several trials contained multiple upper-extremity and/or lower-extremity strength measures. To examine bias due to lack of independent data points, we conducted sensitivity analyses on total body strength, upper-extremity strength, and lower-extremity strength by combining studies with multiple data points together by using the Mantel–Haenszel method.[26] Specifically, we combined studies with multiple data points as one study, when measurement units were identical. Sensitivity analysis was not performed for FFM because all data points represented individual groups and the units of measurement were consistent among all studies. To assess whether an age effect existed, we also performed subgroup analyses on all eligible RCTs that reported FFM or muscle strength outcomes and limited enrolment to men ≥60 years of age. Analyses were conducted by using the open source statistical software package "metaphor" (v3.1.0).[27]

Results

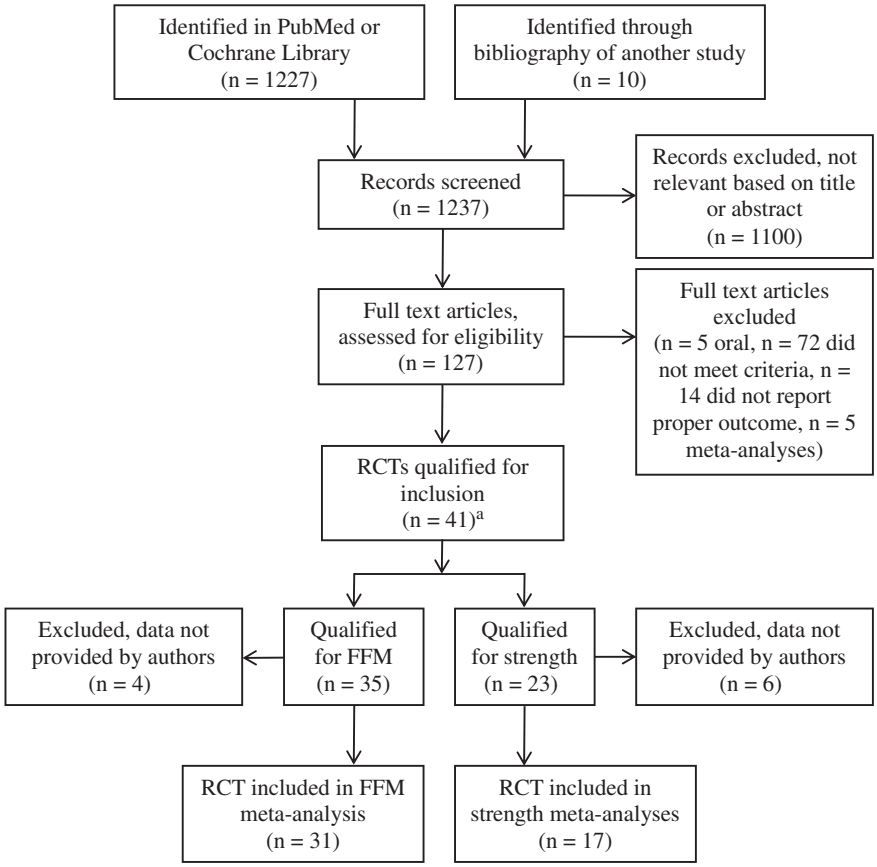
Study selection and characteristics

The initial search yielded 1227 publications, of which 127 were subjected to further scrutiny (Figure 1). From the references of these papers, we identified 10 additional publications that required further review. Of these, 41 unique double-blind, placebo-controlled RCTs met our a priori selection criteria.[28–31,16,32–37,15,38–40,13,41–48,17,49,11,50,51,14,52–59,12,60,61] All eligible studies were randomized, with investigators, providers, and subjects blinded to treatment allocation, and eligibility criteria were specified. Other aspects associated with study quality assessment are reported in Table 1. We included data from 34 of these studies in the primary analysis, of which 15 administered intramuscular TRT and 18 administered transdermal TRT, with study characteristics reported in Table 2. In our subgroup analysis, we included data from 19 of the studies mentioned in the preceding texts that limited enrolment to men ≥60 years of age, of which 9 administered intramuscular TRT[28,31,16,33,35,15,17,49,53] and 10 administered transdermal TRT.[38,40,13,42,44,45,11,50,14,55] We were unable to include the additional seven RCTs that met our selection criteria[56–59,12,60,61] because data were not reported in the necessary format for our a priori statistical design and were not provided by the authors upon query (Table 3).

Fat-free mass

We included 31 transdermal and intramuscular TRT studies (containing 34 ESs) that reported FFM (Figure 2) and obtained a pooled overall treatment ES of 1.20 (95% CI: 0.91–1.49; $P < 0.001$), representing a 3.4% increase in FFM for TRT vs. placebo (Table 4). Secondary analysis of the 15 studies evaluating intramuscular TRT produced an ES of 1.49 (1.13, 1.84; $P < 0.001$), representing a 5.7% FFM increase. Conversely, analysis of 19 studies evaluating transdermal TRT produced an ES of 0.98 (0.58, 1.39; $P < 0.001$), representing only a 1.7% increase in FFM.

Figure 1 Selection process for double-blind, placebo-controlled randomized clinical trials assessing effects of testosterone replacement therapy on fat-free mass and/or muscle strength outcomes in middle-aged and older men.



The discrepancy among total number of qualifying trials (n = 41) and those qualifying for FFM (n = 35) or strength analyses (n = 23) stems from n = 17 trials that qualified for both analyses.

Total body strength

For total body strength, we integrated 17 transdermal and intramuscular TRT studies (containing 100 ESs) that reported lower-extremity (Figure 3) or upper-extremity (Figure 4) strength measures and obtained a pooled overall treatment ES of 0.90 (0.67, 1.14; $P < 0.001$), representing a 6.1% increase in strength vs. placebo (Table 4). Separate analysis of the nine intramuscular TRT studies (containing 44 ESs) resulted in an ES of 1.39 (1.15, 1.63; $P < 0.001$), representing an 11.2% strength improvement. In comparison, analysis of the eight transdermal TRT studies (containing 56 ESs) produced an ES of 0.55 (0.22, 0.88; $P < 0.001$), representing only a 2.1% strength increase.

Lower-extremity strength

For lower-extremity strength, we integrated 17 transdermal and intramuscular TRT studies (containing 62 ESs) and obtained a pooled overall treatment ES of 0.77 (0.45, 1.08; $P < 0.001$), representing a 5% strength increase vs. placebo (Table 4). Separate analysis of 9 intramuscular studies (containing 29 ESs) resulted in an ES of 1.39 (1.07, 1.72; $P < 0.001$), representing a 10.4% increase in strength. Analysis of 9 transdermal TRT studies (containing 33 ESs) produced an ES of 0.26 (−0.19, 0.70; $P = 0.26$), indicating that transdermal TRT did not improve lower-extremity strength.

Upper-extremity strength

For upper-extremity strength, we integrated 12 transdermal and intramuscular TRT studies (containing 38 ESs) and obtained a pooled overall treatment ES of 1.13 (0.78, 1.47; $P < 0.001$), representing a 7.8% strength increase vs. placebo (Table 4). Separate analysis of six intramuscular studies (containing 15 ESs) resulted in an ES of 1.37 (1.03, 1.70; $P < 0.001$), representing a 12.9% increase in strength. In comparison, separate analysis of six transdermal TRT studies (containing 23 ESs) produced an ES of 0.97 (0.50, 1.45; $P < 0.001$), representing only a 4.5% strength improvement.

Table 1 Quality assessment for double-blind placebo-controlled randomized clinical trials (RCTs) evaluated, using the Delphi criteria[a]

Article	Treatment allocation concealed	Groups similar at baseline[b]	Estimate and variance presented
Agledahl *et al*., 2008[28]	N/R	Yes	Yes
Allan *et al*., 2008[29]	Yes	N/R	Yes
Basaria *et al*., 2010[56]	Yes	Yes/N/R[c]	No
Behre *et al*., 2012[30]	Yes	Yes	Yes
Blackman *et al*., 2002[31]	Yes	Yes/No[e]	Yes
Borst *et al*., 2014[16]	Yes	Yes	Yes
Brockenbrough *et al*., 2006[32]	Yes	N/R	Yes
Caminiti *et al*., 2009[33]	Yes	Yes	Yes
Casaburi *et al*., 2004[34]	N/R	Yes/N/R[c]	Yes
Clague *et al*., 1999[35]	Yes	Yes	Yes
Crawford *et al*., 2003[36]	N/R	Yes/N/R[f]	Yes[g]
Del Fabbro *et al*., 2013[57]	Yes	Yes	No[d]
Dhindsa *et al*., 2016[37]	N/R	Yes	Yes
Dias *et al*., 2016[58]	Yes	Yes	No[d]
Ferrando *et al*., 2002[15]	N/R	Yes	Yes[g]
Frederiksen *et al*., 2012[38]	Yes	Yes	Yes
Gianatti *et al*., 2014[39]	Yes	Yes	Yes[g]
Giannoulis *et al*., 2006[40]	N/R	Yes	Yes
Hildreth *et al*., 2013[13]	Yes	Yes	Yes[g]
Hoyos *et al*., 2012[41]	Yes	Yes	Yes[g]
Katznelson *et al*., 2006[42]	N/R	Yes	Yes
Kenny *et al*., 2001[44]	Yes	Yes	Yes
Kenny *et al*., 2010[43]	Yes	Yes	Yes
Kvorning *et al*., 2013[45]	Yes	N/R	Yes[g]
Magnussen *et al*., 2016[46]	Yes	Yes	Yes
Malkin *et al*., 2005[59]	N/R	Yes	No[d]
Marin *et al*., 1993[47]	N/R	Yes	Yes
Merza *et al*., 2006[48]	Yes	Yes	Yes
Nair *et al*., 2006[12]	Yes	Yes	No[d]
Page *et al*., 2005[17]	Yes	Yes	Yes[g]
Sheffield-Moore *et al*., 2011[49]	N/R	Yes	Yes[g]
Sih *et al*., 1997[60]	N/R	N/R	No[d]
Sinclair *et al*., 2016[61]	Yes	Yes	No[d]
Snyder *et al*., 1999[11]	Yes	Yes	Yes
Srinivas-Shankar *et al*., 2010[50]	Yes	Yes	Yes
Steidle *et al*., 2003[51]	N/R	Yes	Yes
Storer *et al*., 2017[14]	Yes	Yes	Yes[g]
Svartberg *et al*., 2004[52]	N/R	Yes	Yes[g]
Svartberg *et al*., 2008[53]	N/R	Yes	Yes
Tenover *et al*., 1992[54]	N/R	Yes	Yes
Travison *et al*., 2011[55]	Yes	N/R	Yes

N/R, not reported.
[a]All RCTs were randomized, with the investigators, providers, and subjects blinded to treatment allocation, and eligibility criteria were specified.
[b]Baseline characteristics assessed were fat-free mass (FFM) and muscle strength.
[c]N/R for FFM.
[d]Estimate and variance were not reported in the necessary format for statistical analysis in the original article, and data were not provide via author query; the study was excluded from meta-analysis.
[e]Difference in FFM between TRT and placebo groups at baseline.
[f]N/R for strength.
[g]Estimate and variance were not provided in the necessary format for statistical analysis in the original article; these data were obtained via author query.

Sensitivity analysis

We conducted sensitivity analyses to ensure that RCTs containing multiple ESs for upper-extremity and/or lower-extremity strength did not bias our outcomes. Using the Mantel–Haenszel approach,[26] ESs and per cent improvements were similar to the primary/secondary strength outcomes reported in the preceding texts, with intramuscular TRT being associated with the largest ES magnitudes and greatest percentage improvements for all strength outcomes (Table 5).

Subgroup analyses: older men

To evaluate the effects of TRT in older men, we conducted subanalyses of RCTs that limited enrolment to men ≥60 years of age. For FFM, we included 16 transdermal and intramuscular

Table 2 Characteristics of placebo-controlled randomized clinical trials that were included in meta-analyses

Article	Age (years)	Baseline		TRT characteristics			Duration (months)	Reported outcomes	
		T[a]	*N*	Route	Mode	Dose		FFM	Strength
Agledahl *et al.*, 2008[28]	T: 68.9 P: 69.3	T: 245 P: 237	T: 13 P: 13	i.m.	TU	1000 mg 5×/year	12	DEXA	N/A
Allan *et al.*, 2008[29]	T: 62.1 P: 64.5	T: 392 P: 418	T: 31 P: 31	trans	T patch	5 mg/day	12	DEXA	N/A
Behre *et al.*, 2012[30]	T: 61.9 P: 62.1	T: 300 P: 306	T: 183 P: 179	trans	T gel	50–100 mg/day	6	DEXA	N/A
Blackman *et al.*, 2002[31]	T: 70.0 P: 70.0	T: 409 P: 392	T: 21 P: 17	i.m.	TE	100 mg/2 weeks	6	DEXA	N/A
Borst *et al.*, 2014[16]	T: 69.2 P: 70.8	T: 245 P: 264	T: 14 P: 16	i.m.	TE	125 mg/week	12	DEXA	L, U
Brockenbrough *et al.*, 2006[32]	T: 58.9 P: 53.0	T: 219 P: 202	T: 19 P: 21	trans	T gel	100 mg/day	6	DEXA	N/A
Caminiti *et al.*, 2009[33]	T: 71 P: 69	T: 230 P: 210	T: 35 P: 35	i.m.	TU	1000 mg/6 weeks	3	N/A	L
Casaburi *et al.*, 2004[34]	T: 66.6 P: 67.7	T: 302 P: 302	T: 12 P: 12	i.m.	TE	100 mg/week	2.5	DEXA	L
Clague *et al.*, 1999[35]	T: 68.1 P: 65.3	T: 326 P: 335	T: 7 P: 7	i.m.	TE	200 mg/2 weeks	3	N/A	L, U
Crawford *et al.*, 2003[36]	T: 58.7 P: 59.9	T: 398 P: 453	T: 18 P: 16	i.m.	Mixed	200 mg/2 weeks	12	DEXA	L
Dhindsa *et al.*, 2016[37]	T: 54.7 P: 54.5	T: 252 P: 252	T: 22 P: 22	i.m.	TC	250 mg/2 weeks	6	DEXA	N/A
Ferrando *et al.*, 2012[15]	T: 68 P: 67	T: N/R P: N/R	T: 7 P: 5	i.m.	TE	100–400 mg/2 weeks	6	DEXA	L, U
Frederiksen *et al.*, 2011[38]	T: 68 P: 67	T: 361 P: 366	T: 23 P: 23	trans	T gel	50–100 mg/day	6	DEXA	N/A
Gianatti *et al.*, 2014[39]	T: 62 P: 62	T: 251 P: 245	T: 45 P: 43	i.m.	TU	1000 mg 4×/40 weeks	9.25	DEXA	N/A
Giannoulis *et al.*, 2006[40]	T: 70.3 P: 69.5	T: 498 P: 432	T: 23 P: 20	trans	T patch	5 mg/day	6	DEXA	L, U
Hildreth *et al.*, 2013[13]	T: 66.5 P: 66.5	T: 298[b] P: 294	T: 55 P: 28	trans	T gel	25–100 mg/day	12	DEXA	L, U
Hoyos *et al.*, 2012[41]	T: 48 P: 49	T: 381 P: 387	T: 33 P: 34	i.m.	TU	1000 mg/6 weeks	4.5	DEXA	N/A
Katznelson *et al.*, 2006[42]	T: 72 P: 72	T: 392 P: 421	T: 17 P: 17	trans	T patch	5 mg/day	3	DEXA	N/A
Kenny *et al.*, 2001[44]	T: 76 P: 75	T: 389 P: 389	T: 24 P: 20	trans	T patch	5 mg/day	12	DEXA	L
Kenny *et al.*, 2010[43]	T: 77.9 P: 76.3	T: 380 P: 418	T: 69 P: 62	trans	T gel	5 mg/day	12	DEXA	L, U
Kvorning *et al.*, 2013[45]	T: 66.6 P: 67.8	T: 147[c] P: 133[c]	T: 22 P: 23	trans	T gel	50 mg/day	6	N/A	L
Magnussen *et al.*, 2016[46]	T: 61 P: 59	T: 205 P: 271	T: 22 P: 21	trans	T gel	50 mg/day	6	DEXA	N/A
Marin *et al.*, 1993[47]	T: 56.7 P: 58.5	T: 436 P: 447	T: 7 P: 7	trans	T gel	125 mg/day	9	^{40}K	N/A
Merza *et al.*, 2005[48]	T: 63.0 P: 59.7	T: 242 P: 216	T: 20 P: 19	trans	T patch	5 mg/day	6	DEXA	N/A
Page *et al.*, 2005[17]	T: 71 P: 71	T: 286 P: 303	T: 24 P: 24	i.m.	TE	200 mg/2 weeks	36	DEXA	L, U
Sheffield-Moore *et al.*, 2011[49]	T: 73 P: 65	T: 349[b] P: 344	T: 16 P: 8	i.m.	TE	100 mg/week	5	DEXA	L, U
Snyder *et al.*, 1999[11]	T: 73.1 P: 73.0	T: 367 P: 369	T: 54 P: 54	trans	T patch	4–6 mg/day	36	DEXA	L, U
Srinivas-Shankar *et al.*, 2010[50]	T: 73.7 P: 73.9	T: 317 P: 314	T: 130 P: 132	trans	T gel	25–75 mg/day	6	DEXA	L, U
Steidle *et al.*, 2003[51]	T: 58.4 P: 56.8	T: 234[c] P: 228	T: 205 P: 99	trans	T gel	50–100 mg/day	3	DEXA	N/A
Storer *et al.*, 2017[14]	T: 66.6 P: 68.0	T: 307 P: 302	T: 135 P: 121	trans	T gel	50–100 mg/day	36	DEXA	L, U
Svartberg *et al.*, 2004[52]	T: 64.5 P: 67.5	T: 591 P: 623	T: 15 P: 14	i.m.	TE	250 mg/4 weeks	6	DEXA	N/A
Svartberg *et al.*, 2008[53]	T: 69 P: 69	T: 242 P: 237	T: 17 P: 18	i.m.	TU	1000 mg 5×/year	12	DEXA	L, U

(*Continues*)

Table 2 (continued)

Article	Age (years)	Baseline		TRT characteristics			Duration (months)	Reported outcomes	
		T[a]	*N*	Route	Mode	Dose		FFM	Strength
Tenover *et al*., 1992[54]	T: 67.5 P: 67.5	T: 335 P: 335	T: 13 P: 13	i.m.	TE	100 mg/week	3	Hydro	N/A
Travison *et al*., 2011[55]	T: 73.8 P: 73.9	T: 251 P: 231	T: 69 P: 69	trans	T gel	50–150 mg/day	6	DEXA	N/A

[a]Testosterone (T) concentrations are ng/dL, rounded to the nearest whole number.
[b]Average T concentration from all groups receiving TRT.
[c]Bioavailable T concentration; total T was not reported. DEXA, dual X-ray absorptiometry; FFM, fat-free mass; Hydro, hydrostatic weighing; i.m., intramuscular; ^{40}K, whole-body potassium-40 measurement; L, lower extremity; Mixed, mixed injectable esters; *N*, number per group; N/A, not assessed; N/R, not reported; P, placebo-treated group; TC, testosterone cypionate; TE, testosterone enanthate; T gel, testosterone gel; TP, testosterone proprionate; T patch, testosterone patch; trans, transdermal; TU, testosterone undecanoate; U, upper extremity.

TRT studies (containing 18 ESs) and obtained a pooled overall treatment ES of 1.36 (95% CI: 0.88, 1.83; $P < 0.001$, Figure 5), representing a 4.2% increase in FFM for TRT vs. placebo (Table 6). Subanalysis of the seven studies administering intramuscular TRT produced an ES of 1.84 (1.12, 2.55; $P < 0.001$), representing a 7.3% FFM increase. In comparison, subanalysis of the nine studies evaluating transdermal TRT produced an ES of 1.04 (0.41, 1.67; $P < 0.001$), representing only a 1.7% increase in FFM. For total body strength, we integrated 14 transdermal and intramuscular TRT studies (containing 93 ESs) that reported lower-extremity (Figure 6) or upper-extremity strength measures (Figure 7) and obtained a pooled overall treatment ES of 0.90 (0.67, 1.14; $P < 0.001$), representing a 6.1% increase in strength vs. placebo. The ESs and percentage increases for intramuscular and for transdermal TRT studies were similar to the primary strength outcomes reported in the preceding texts, with intramuscular TRT being associated with the largest ES magnitudes and greatest per cent improvements (Table 6).

Discussion

The increasing prevalence of TRT[62] is likely to continue, as a result of the increasing geriatric population. Previous meta-analyses of RCTs have reported that TRT positively influences health-related quality of life,[63] bone mineral density,[64,7] body composition,[65,66,7,6] sexual function and libido,[67,7] and several measures of metabolic health in men.[65] However, debate surrounds the potential utility of various TRT formulations in relation to promoting musculoskeletal integrity, muscular strength, and physical function in middle-aged and older men.[9,10] For example, Corona *et al*. reported that parenteral (i.e. intramuscular and transdermal) TRT collectively increased FFM, while oral TRT did not.[65] Tracz *et al*. also reported that intramuscular TRT increased lumbar spine bone mineral density, while transdermal formulations did not.[64] Similarly, meta-analyses have reported that oral TRT[19] and transdermal formulations[68] increase cardiovascular risk, while intramuscular TRT did not. These findings indicate

Table 3 Characteristics of placebo-controlled randomized clinical trials that were excluded from meta-analyses due to inability to acquire data in the format necessary for our a priori statistical design

Article	Age (years)	Baseline		TRT			Duration (months)	Reported outcomes	
		T[a]	*N*	Route	Mode	Dose		FFM	Strength
Basaria *et al*., 2010[56]	T: 74 P: 74	T: 250 P: 236	T: 106 P: 103	trans	T gel	100–150 mg/day	6	DEXA[b]	L, U
Del Fabbro *et al*., 2013[57]	T: 57 P: 63	T: N/R P: N/R	T: 16 P: 13	i.m.	TE	150–200 mg/2 weeks	2.4	DEXA	N/A
Dias *et al*., 2016[58]	T: 72 P: 72	T: 300 P: 304	T: 13 P: 13	trans	T gel	50 mg/day	12	DEXA	N/A
Malkin *et al*., 2006[59]	T: 63.1 P: 64.9	T: 401 P: 349	T: 37 P: 39	trans	T patch	5 mg/day	12	N/A	U
Nair *et al*., 2006[12]	T: 66.2 P: 67.1	T: 357 P: 398	T: 27 P: 31	trans	T patch	5 mg/day	24	DEXA	L, U
Sih *et al*., 1997[60]	T: 65 P: 68	T: 233 P: 294	T: 17 P: 15	i.m.	TC	200 mg/2 weeks	12	N/A	U
Sinclair *et al*., 2016[61]	T: 55.5 P: 54.0	T: 267 P: 262	T: 50 P: 51	i.m.	TU	1000 mg/52 weeks	12	DEXA	U

[a]Testosterone (T) concentrations are ng/dL, rounded to the nearest whole number.
[b]Data were included in meta-analysis, obtained from reference[55]; DEXA, dual X-ray absorptiometry; FFM, fat-free mass; i.m., intramuscular; L, lower extremity; *N*, number per group; N/A, not assessed; N/R, not reported; P, placebo; TC, testosterone cypionate; TE, testosterone enanthate; T gel, testosterone gel; T patch, testosterone patch; trans, transdermal; TU, testosterone undecanoate; U, upper extremity.

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Figure 2 Forest plot for fat-free mass data derived from placebo-controlled randomized clinical trials of middle-aged and older men. Values are the individual and pooled effect sizes listed by testosterone replacement therapy administration route.

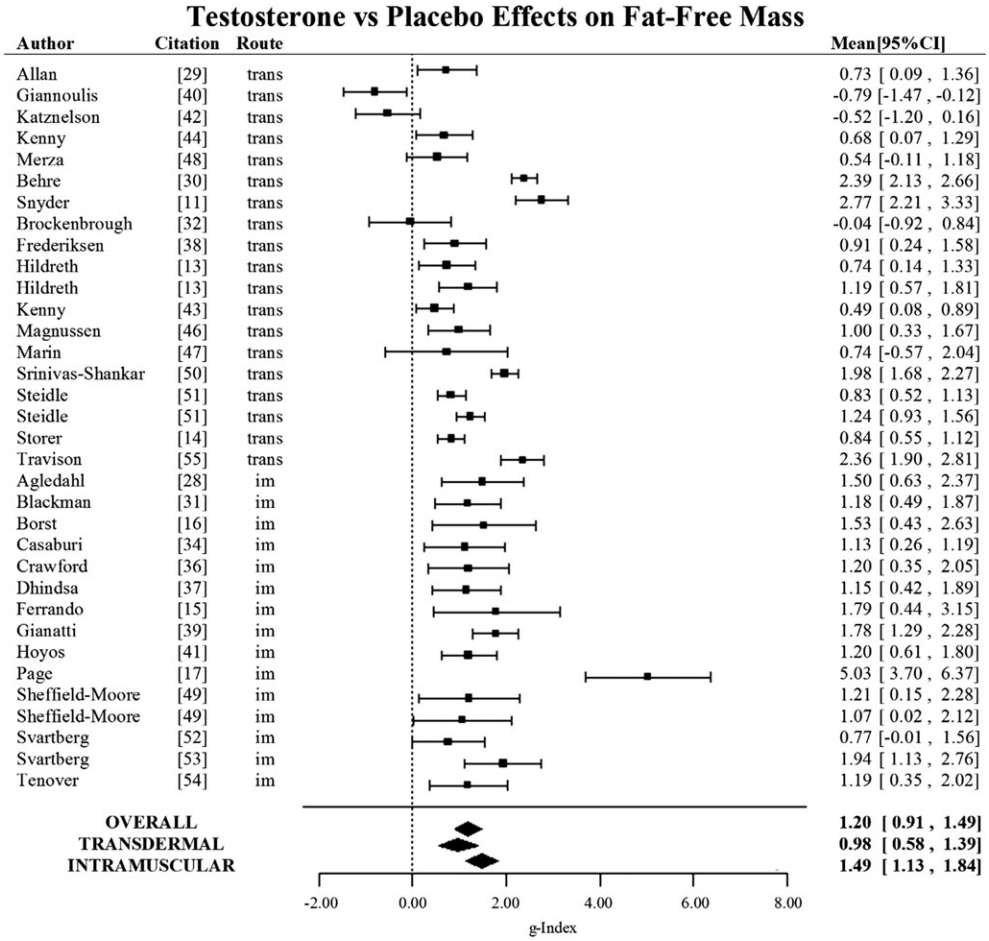
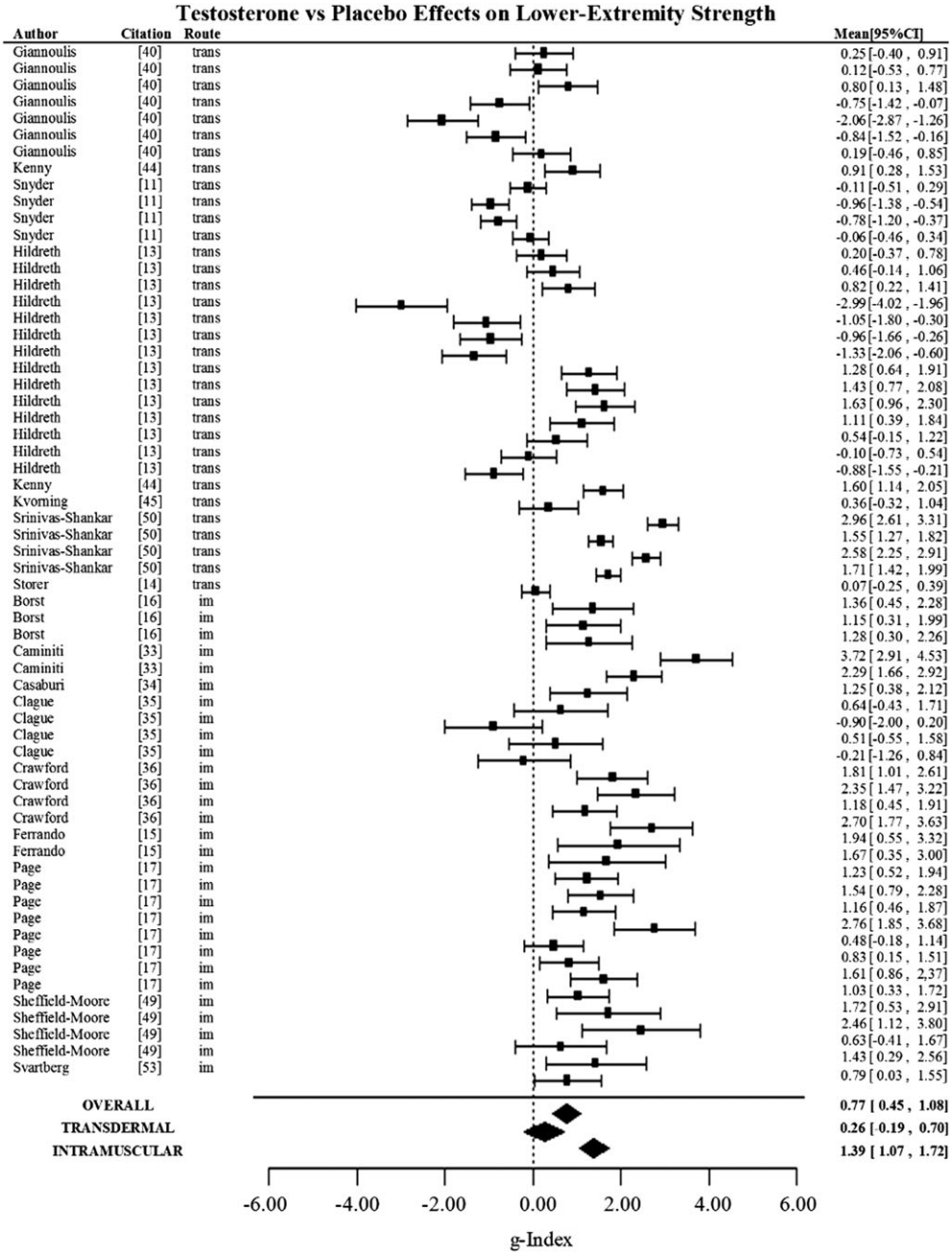


Table 4 Effect sizes and per cent improvement for total body fat-free mass and muscle strength outcomes from placebo-controlled randomized clinical trials of middle-aged and older men

Testosterone replacement therapy (TRT) route	*g*-index (*N*)	Sample size (TRT, placebo)	Effect size	Standard error	95% CI	*P*-value	Improvement (%)
Fat-free mass							
Overall	34	(1213, 1168)	1.200	0.150	(0.910, 1.490)	<0.001	3.4
Intramuscular	15	(242, 230)	1.490	0.180	(1.130, 1.840)	<0.001	5.7
Transdermal	19	(971, 938)	0.980	0.210	(0.580, 1.390)	<0.001	1.7
Total body strength							
Overall	100	(2572, 2523)	0.900	0.120	(0.670, 1.140)	<0.001	6.1
Intramuscular	44	(561, 580)	1.390	0.120	(1.150, 1.630)	<0.001	11.2
Transdermal	56	(2011, 1943)	0.550	0.170	(0.220, 0.880)	<0.001	2.1
Lower-extremity strength							
Overall	62	(1717, 1668)	0.770	0.160	(0.450, 1.080)	<0.001	5.0
Intramuscular	29	(402, 412)	1.390	0.170	(1.070, 1.720)	<0.001	10.4
Transdermal	33	(1315, 1256)	0.260	0.230	(−0.190, 0.700)	0.260	0.3
Upper-extremity strength							
Overall	38	(855, 855)	1.130	0.180	(0.780, 1.470)	<0.001	7.8
Intramuscular	15	(159, 168)	1.370	0.170	(1.030, 1.700)	<0.001	12.9
Transdermal	23	(696, 687)	0.970	0.240	(0.500, 1.450)	<0.001	4.5

Figure 3 Forest plots for lower-extremity muscle strength data derived from placebo-controlled randomized clinical trials of middle-aged and older men. Values are the individual and pooled effect sizes listed by testosterone replacement therapy administration route.



that several risks and benefits associated with TRT may depend largely upon administration route.[10] The present meta-analysis was designed to supplement prior knowledge surrounding the effects of TRT on FFM and muscle strength in middle-aged and older men and to determine the extent to which intramuscular and transdermal TRT administration routes affect these outcomes. Our primary findings indicate that TRT increased total body FFM and total body strength when intramuscular and transdermal TRT routes were examined collectively and separately vs. respective placebos. Improvements in upper-extremity and lower-extremity strength were also observed when TRT administration routes were collectively analysed. However, when evaluated separately, only intramuscular TRT increased lower-extremity strength, with transdermal routes producing no improvement vs. placebo. Interestingly, for all outcomes assessed, the ESs for

Figure 4 Forest plots for upper-extremity muscle strength data derived from placebo-controlled randomized clinical trials of middle-aged and older men. Values are the individual and pooled effect sizes listed by testosterone replacement therapy administration route.

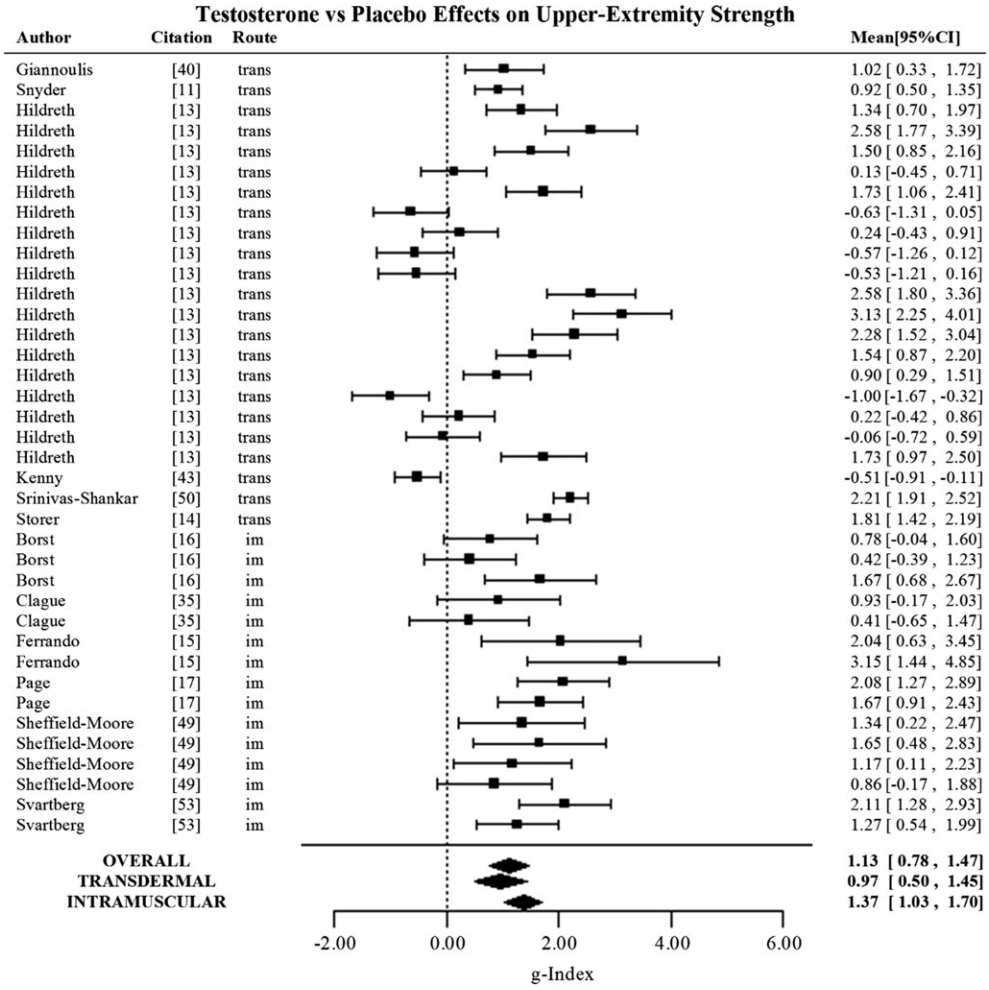


Table 5 Effect sizes and per cent improvement for sensitivity analyses of muscle strength outcomes from placebo-controlled randomized clinical trials of middle-aged and older men

Route	*g*-index (*N*)	Sample size (testosterone replacement therapy, placebo)	Effect size[a]	Standard error	95% CI	*P*-value	Improvement (%)
Total body strength							
Overall	35	(1175, 1126)	1.120	0.190	(0.750, 1.490)	<0.001	6.9
Intramuscular	17	(230, 244)	1.510	0.210	(1.090, 1.930)	<0.001	11.3
Transdermal	18	(945, 882)	0.790	0.270	(0.270, 1.320)	<0.001	2.7
Lower-extremity strength							
Overall	21	(724, 695)	1.090	0.260	(0.580, 1.600)	<0.001	6.3
Intramuscular	10	(154, 161)	1.630	0.310	(1.030, 2.230)	<0.001	10.7
Transdermal	11	(570, 534)	0.650	0.360	(−0.060, 1.360)	0.070	2.4
Upper-extremity strength							
Overall	14	(451, 431)	1.160	0.280	(0.610, 1.720)	<0.001	7.7
Intramuscular	7	(76, 83)	1.310	0.260	(0.800, 1.810)	<0.001	12.1
Transdermal	7	(375, 348)	1.020	0.430	(0.170, 1.870)	0.020	3.2

[a]Strength measures with the same units of measurement from each study were averaged to form a single effect size. Sensitivity analysis was not performed for fat-free mass because all data points represented individual groups with identical units of measurement.

Figure 5 Forest plot for fat-free mass data derived from placebo-controlled randomized clinical trials that limited enrolment to men ≥60 years of age. Values are the individual and pooled effect sizes listed by testosterone replacement therapy administration route.

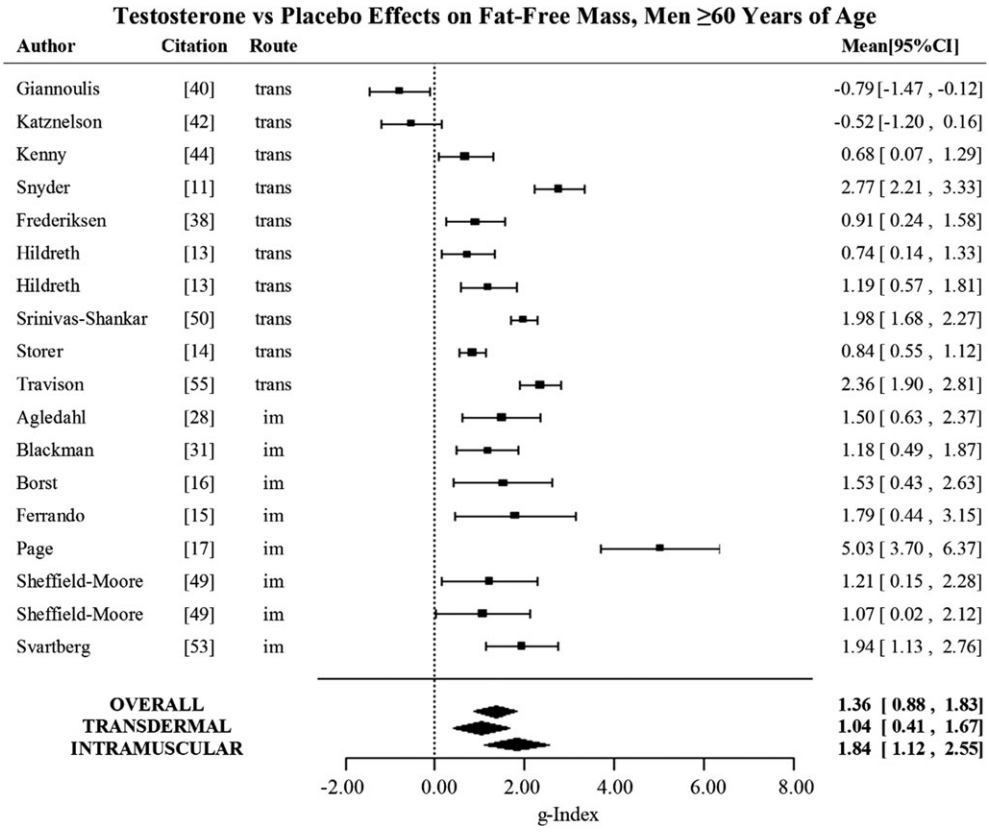
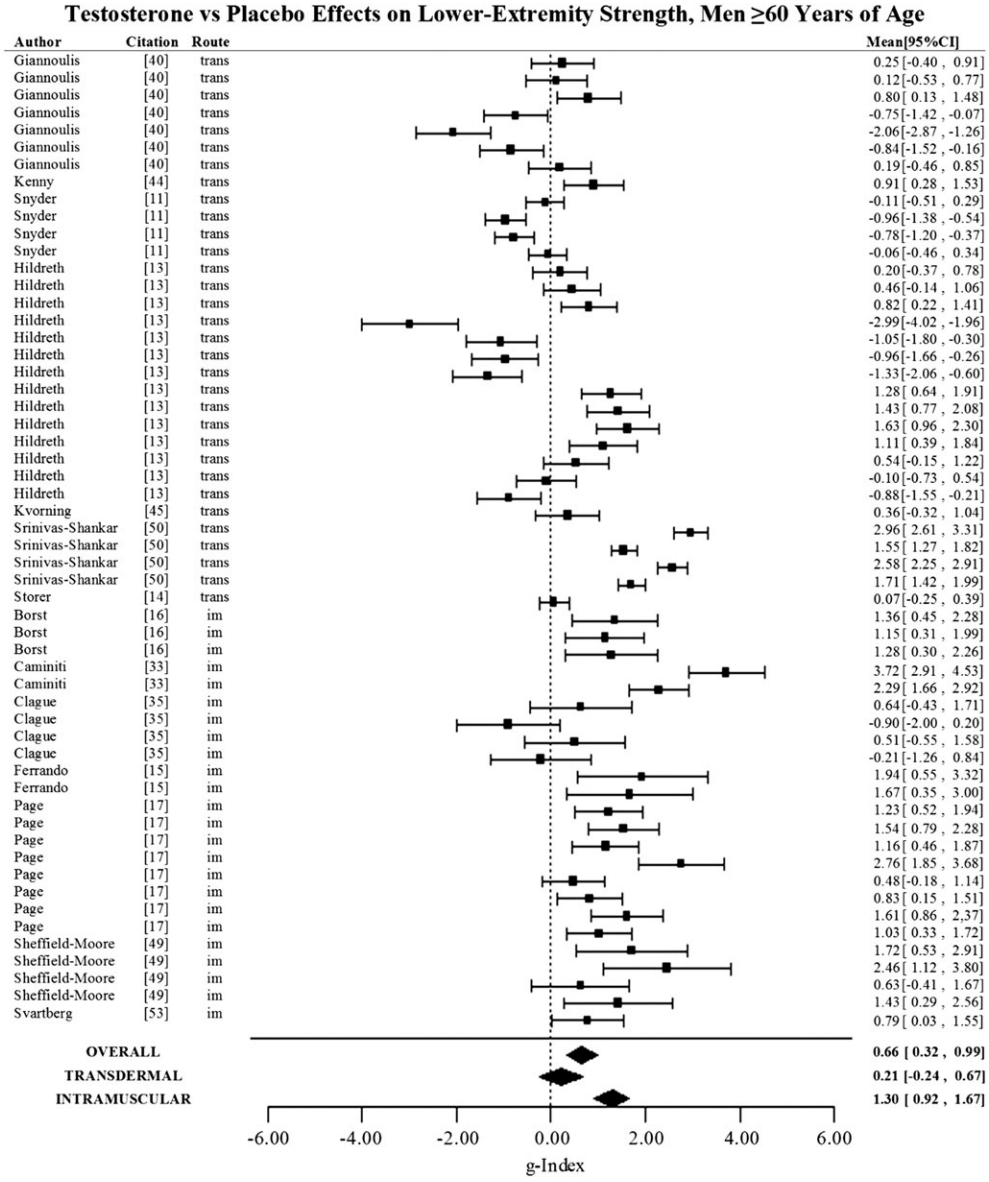


Table 6 Subanalyses' effect sizes and per cent improvement for total body fat-free mass and muscle strength outcomes from randomized clinical trials limiting enrolment to men ≥60 years of age

TRT route	*g*-index (*N*)	Sample size (testosterone replacement therapy, placebo)	Effect size	Standard error	95% CI	*P*-value	Improvement (%)
Fat-free mass							
Overall	18	(574, 555)	1.360	0.240	(0.880, 1.830)	<0.001	4.2
Intramuscular	8	(97, 99)	1.840	0.360	(1.120, 2.550)	<0.001	7.3
Transdermal	10	(477, 456)	1.040	0.320	(0.410, 1.670)	<0.001	1.7
Total body strength							
Overall	93	(2382, 2355)	0.860	0.120	(0.620, 1.110)	<0.001	5.9
Intramuscular	39	(477, 504)	1.330	0.130	(1.070, 1.590)	<0.001	11.3
Transdermal	54	(1905, 1851)	0.550	0.170	(0.220, 0.880)	<0.001	2.0
Lower-extremity strength							
Overall	56	(1580, 1546)	0.660	0.170	(0.320, 0.990)	<0.001	4.5
Intramuscular	24	(318, 336)	1.300	0.190	(0.920, 1.670)	<0.001	10.3
Transdermal	32	(1262, 1210)	0.210	0.230	(−0.240, 0.670)	0.360	0.1
Upper-extremity strength							
Overall	37	(802, 809)	1.170	0.170	(0.840, 1.500)	<0.001	8.1
Intramuscular	15	(159, 168)	1.370	0.170	(1.030, 1.700)	<0.001	12.9
Transdermal	22	(643, 641)	1.040	0.240	(0.580, 1.500)	<0.001	4.8

intramuscular TRT were larger and the percentage improvements were 3–5 times greater than that of transdermal TRT, supporting the contention that intramuscular TRT produces greater muscular benefit than transdermal administration. Similar results persisted when we evaluated RCTs that limited enrolment to men ≥60 years of age, which is the age range most

Figure 6 Forest plot for lower-extremity muscle strength data derived from placebo-controlled randomized clinical trials that limited enrolment to men ≥60 years of age. Values are the individual and pooled effect sizes listed by testosterone replacement therapy administration route.

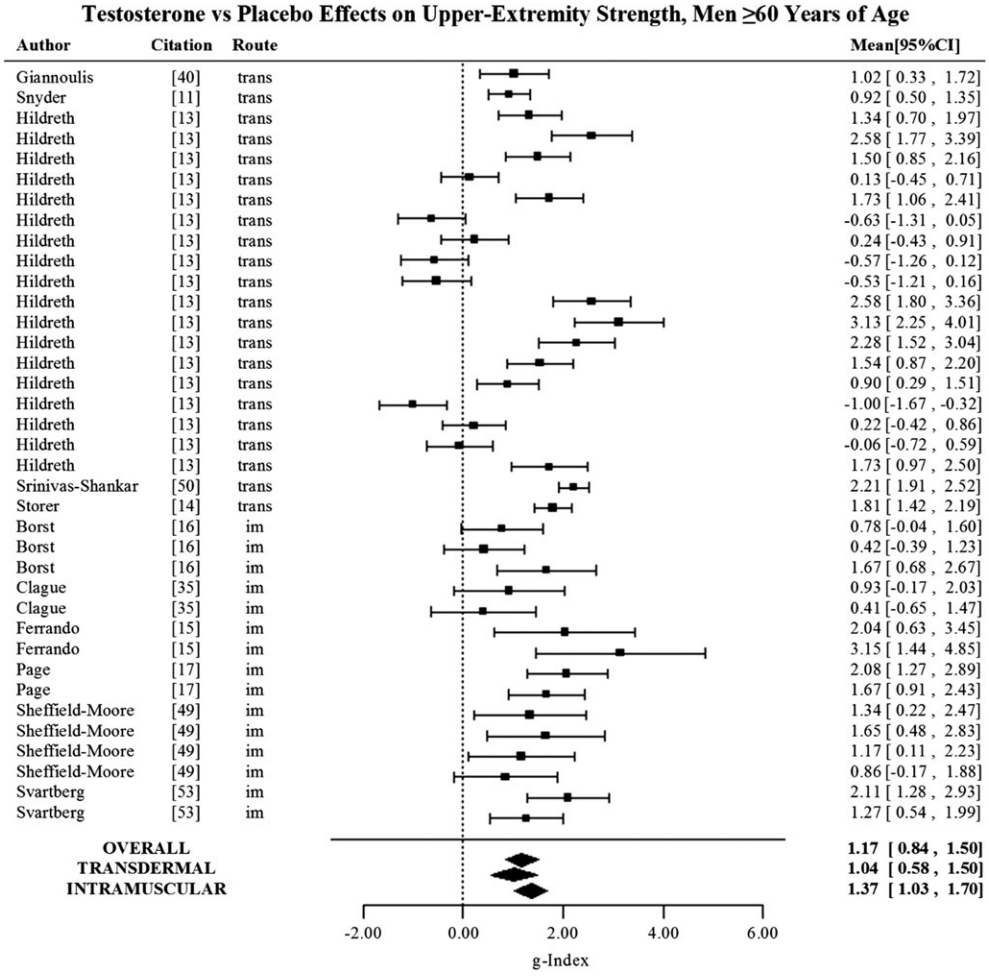


likely to experience hypogonadism,[1] indicating that intramuscular TRT is an effective means to improve FFM and muscle strength in older men.

Comparison with other systematic reviews: FFM

It is generally accepted that TRT increases FFM in middle-aged and older men,[9] although the magnitude of this effect may vary dramatically by administration route.[10] Indeed, previous meta-analyses reported that TRT increased FFM from 1.6 kg (95% CI: 0.6, 2.6)[7] to 3.59 kg (2.38, 4.81)[6] when all administration routes were collectively assessed, a finding that is confirmed with our meta-analysis. Herein, we expand upon these studies by separately evaluating the effects of intramuscular and transdermal TRT on FFM and demonstrate that a much larger magnitude of increase occurs with intramuscular TRT. Specifically, an apparent difference in per cent change from baseline existed among administration routes, with a 5.7% increase in FFM resulting from intramuscular TRT and only a 1.7% increase resulting from transdermal formulations. From a clinical perspective and as an example, this implies that a 90 kg man would experience a 5.1 kg FFM increase with intramuscular TRT, as compared with a

Figure 7 Forest plot for upper-extremity muscle strength data derived from placebo-controlled randomized clinical trials that limited enrolment to men ≥60 years of age. Values are the individual and pooled effect sizes listed by testosterone replacement therapy administration route.



1.5 kg FFM increase with transdermal formulations, providing further evidence for the potential utility of intramuscular TRT as means to prevent or reverse sarcopenia and frailty in hypogonadal men.[10] However, our data should be interpreted cautiously given that (i) dual-energy X-ray absorptiometry was used to evaluate FFM in most RCTs included in our meta-analysis (Table 2) and (ii) intracellular and extracellular water are inherently included as components of FFM were assessed via dual-energy X-ray absorptiometry.[69] In this regard, TRT increases extracellular water by ~2 kg in hypogonadal men[70] and peripheral oedema has been observed in small fraction of older men receiving TRT.[56] Other musculoskeletal imaging technologies (e.g. computed tomography, magnetic resonance imaging, or ultrasound) are considered a somewhat more reliable means to directly assess muscle mass because they are not as heavily influenced by extracellular fluid fluctuations,[71,72] although few RCTs have utilized these imaging modalities to assess muscular changes resulting from TRT. Regardless, intramuscular TRT has been shown to increase muscle fibre cross-sectional area in older men, especially when administered at higher doses,[73] demonstrating that testosterone produces direct myotrophic effects independent of fluid change.

Several key differences also exist between our study and previous meta-analyses. For example, other meta-analyses assessing FFM included oral TRT (e.g. testosterone undecanoate, oxandrolone, and/or oxymetholone) or dihydrotestosterone formulations.[65,66,7,6] We excluded RCTs administering dihydrotestosterone or oral TRT because (i) from a clinical standpoint, these formulations are not commonly prescribed in the USA,[62] (ii) Corona *et al*. recently reported that oral TRT did not increase FFM when evaluated separately from other parenteral TRT formulations,[65] and (iii) several RCTs have demonstrated that 5α-reduction of testosterone to dihydrotestosterone does not mediate improvements in FFM or muscular strength resulting from TRT.[16,17,74] Interestingly, our previous meta-analysis reported that transdermal TRT elevated circulating dihydrotestosterone

to a greater magnitude than intramuscular formulations,[10] likely due to the relatively higher 5α-reductase expression in skin vs. skeletal muscle,[75] although the clinical ramifications of these differing dihydrotestosterone elevations remain unknown.

Comparison with other systematic reviews: strength

Our finding that muscular strength improvements varied in middle-aged and older men based on TRT administration route provides evidence that accounts for the contrasting observations reported in several previous RCTs and meta-analyses.[10] For example, some RCTs reported that TRT produced pronounced FFM and strength improvements,[15,49] while others reported very minimal changes in comparison with placebo.[12,11,13,14] Conflicting results are also present among meta-analyses, with Ottenbacher *et al*.[8] reporting that TRT increased upper-extremity and lower-extremity strengths in middle-aged and older men and Isidori *et al*[7] reporting no improvement in knee extension, leg extension, knee flexion, or handgrip strength. In our meta-analysis, muscle strength was quantified as change from baseline, compared with respective placebo, and comprised three strength domains: (i) upper extremity, (ii) lower extremity, and (iii) total body. Across all strength domains, intramuscular TRT yielded higher ESs and per cent changes compared with transdermal TRT. Specifically, within the entire cohort, intramuscular TRT produced a very large and significant ES (ES: 1.39, 10.4% improvement) for lower-extremity strength, while transdermal TRT did not significantly improve this measure. Likewise, we observed a larger ES for upper-extremity strength for intramuscular TRT (ES: 1.37, 12.9% improvement) than for transdermal TRT (ES: 0.97, 4.5% improvement). Similarly, when upper-extremity and lower-extremity strength measures were combined (i.e. total body strength), we observed a very large ES for intramuscular TRT (ES: 1.39, 11.2% improvement) and only a medium ES for transdermal TRT (ES: 0.55, 2.1% improvement). The most likely explanation for the differing strength outcomes reported in our meta-analysis and that of Isidori *et al*.[7] are that we included more data points, despite limiting our selection criteria to double-blind, placebo-controlled RCTs, which was possible because we pooled upper-extremity and lower-extremity strength assessments. Indeed, our results corroborate and update the findings of Ottenbacher *et al*.,[8] which is the only other meta-analysis of placebo-controlled RCTs that evaluated muscle strength responses in men receiving TRT, with the following caveats: (i) we evaluated total body FFM and report a larger magnitude of improvement with intramuscular TRT, providing a physiologic rationale for the larger strength improvements occurring with this administration route; (ii) we did not include studies that administered dihydrotestosterone or oral TRT; and (iii) we report that intramuscular TRT produced similar improvements for upper-extremity and lower-extremity strengths, while Ottenbacher *et al*. reported a higher ES for lower-extremity than for upper-extremity strength, which is likely explained by the larger number of ESs reported in our analysis (100 vs. 38). In addition, we evaluated RCTs that limited enrolment to men $\geq$60 years of age and observed that the magnitude of strength improvements was similar to that occurring in the entire cohort, indicating that the effects of intramuscular TRT on muscle strength persist in older men.

Clinical relevance

The Endocrine Society recommends that the therapeutic target for adult men with classical androgen deficiency is the mid-normal range for healthy, young men (i.e. 400–750 ng/dL), with values assessed 1 week post-injection for intramuscular TRT or on the day of administration for transdermal formulations.[9] To accomplish this, transdermal patch-based TRT preparations typically contain relatively low testosterone doses (35–70 mg T/week), while transdermal gel-based TRT formulations contain much higher doses (350–1000 mg T/week) due to low drug absorption.[76,77] Regardless, transdermal patch-based and gel-based TRT formulations both maintain circulating testosterone in the physiologic range.[19] In comparison, intramuscular TRT typically delivers an intermediate testosterone dose (75–100 mg/week),[9] with differing pharmacokinetics than transdermal formulations, which results in substantially higher circulating testosterone for several days after administration and values that gradually decline into the physiologic range thereafter.[18] It is likely that the larger increase in circulating testosterone resulting from intramuscular TRT at least partially explains the greater FFM and strength improvements occurring with the intramuscular administration route, as TRT-induced improvements in muscle fibre cross-sectional area[73] and muscle strength are dose-dependent in older men.[21] The clinical ramifications of this apparent dose–response effect seem clear, given that muscle quality and physical function are strongly associated[78] and that muscle strength, particularly in the lower extremities, is independently associated with reduced mobility disability[79] and less functional decline in older men.[80]

Limitations

No RCT to date has directly compared muscular responses to different TRT administration routes. Our meta-analysis was designed to compare intramuscular and transdermal TRT vs. respective placebos and to infer differences among administration routes based on ES and per cent change from baseline. We believe this approach is an appropriate surrogate

to a more direct dose–response analysis because (i) intramuscular TRT produces much higher circulating testosterone, on average, than transdermal TRT formulations[19,18]; (ii) the different TRT formulations that we evaluated have vastly different testosterone absorption profiles and pharmacokinetics,[18,20] which limits a direct dose–response comparison; and (iii) several RCTs included in our meta-analysis titrated TRT dose at the individual patient level,[30,15,38,13,11,50,14,55] for which TRT dose and circulating testosterone data are not readily available. In addition, we did not selectively evaluate RCTs that enrolled men with hypogonadism because this would dramatically reduce the number of qualifying studies. However, the TRT and placebo groups from seven intramuscular RCTs and six transdermal RCTs included in our analysis exhibited serum testosterone concentrations within the hypogonadal range. As such, future RCTs comparing muscular responses to intramuscular and transdermal TRT formulations in hypogonadal men are warranted.

Conclusion

In summary, our meta-analysis of double-blind, placebo-controlled RCTs revealed that TRT increased FFM, total body strength, and upper-extremity and lower-extremity strengths when transdermal and intramuscular administration routes were evaluated collectively. Separate analysis of transdermal and intramuscular TRT vs. respective placebos demonstrated that intramuscular TRT leads to larger ESs and 3–5 times greater per cent improvement for all strength and FFM outcomes assessed. This effect was most pronounced for lower-extremity strength, which increased $>$10% with intramuscular TRT and did not improve with transdermal formulations. Similar FFM and muscle strength responses were observed when selectively evaluating RCTs that limited enrolment to men $\geq$60 years of age. These results suggest that intramuscular TRT is more effective than transdermal TRT in terms of preventing sarcopenia and improving muscle strength and physical function in middle-aged and older men.

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Online supplementary material

Additional Supporting Information may be found online in the supporting information tab for this article.

Data S1. PRISMA 2009 Checklist

Conflict of interest

Jared W. Skinner, Dana M. Otzel, Andrew Bowser, Daniel Nargi, Sanjay Agarwal, Mark D. Peterson, Baiming Zou, Stephen E. Borst, and Joshua F. Yarrow declare they have no conflict of interest.

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