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ORIGINAL ARTICLE

Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis

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Summary

Objectives Ageing in men is associated with a gradual decline in serum testosterone levels and a concomitant loss of muscle mass, accumulation of central adiposity, impaired mobility and increased risk of bone fractures. Whether androgen treatment might be beneficial in these subjects is still under debate. We have carried out a systematic review of randomized controlled trials (RCTs) evaluating the effects of testosterone (T) administration to middle-aged and ageing men on body composition, muscle strength, bone density, markers of bone metabolism and serum lipid profile.

Data source A comprehensive search of all published randomized clinical trials was performed using the MEDLINE, Cochrane Library, EMBASE and *Current Contents* databases.

Review methods Guided by prespecified criteria, software-assisted data abstraction and quality assessed by two independent reviewers, 29 RCTs were found to be eligible. For each investigated variable, we reported the results of pooled estimates of testosterone treatment using the random effect model of meta-analysis. Heterogeneity, reproducibility and consistency of the findings across studies were explored using sensitivity and meta-regression analysis.

Results Overall, 1083 subjects were evaluated, 625 randomized to T, 427 to placebo and 31 to observation (control group). Weighted mean age was 64·5 years (range 49·9–77·6) and mean serum testosterone was 10·9 nmol/l (range 7·8–19). Testosterone treatment produced: (i) a reduction of 1·6 kg (CI: 2·5–0·6) of total body fat, corresponding to −6·2% (CI: 9·2–3·3) variation of initial body fat, (ii) an increase in fat free mass of 1·6 kg (CI: 0·6–2·6), corresponding to +2·7% (CI: 1·1–4·4) increase over baseline and (iii) no change in body weight. The effects of T on muscle strength were heterogeneous, showing a tendency towards improvement only at the leg/knee extension and handgrip of the dominant arm (pooled effect size = 0·3 standard mean difference (SMD), CI: −0·0 to 0·6). Testosterone improved bone mineral density (BMD) at the lumbar spine by +3·7% (CI: 1·0–6·4%) compared to placebo, but not at the femoral neck, and produced a consistent reduction in bone resorption markers (pooled effect size = −0·6 SMD, CI: −1·0 to −0·2). Testosterone also reduced total cholesterol by 0·23 mmol/l (CI: −0·37 to −0·10), especially in men with lower baseline T concentrations, with no change in low density lipoprotein (LDL)-cholesterol. A significant reduction of high density lipoprotein (HDL)-cholesterol was found only in studies with higher mean T-values at baseline (−0·085 mmol/l, CI: −0·017 to −0·003). Sensitivity and meta-regression analysis revealed that the dose/type of T used, in particular the possibility of aromatization, explained the heterogeneity in findings observed on bone density and HDL-cholesterol among studies.

Conclusion The present analysis provides an estimate of the average treatment effects of testosterone therapy in middle-aged men. Our findings are sufficiently strong to justify further interventional studies focused on alternative targets of androgenic treatment carrying more stringent clinical implications, in particular the cardiovascular, metabolic and neurological systems.

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Introduction

Lifestyle, medication, disease and the ageing process itself all contribute to a gradual and progressive decline in serum testosterone levels during life, as a result of a primary testicular and secondary hypothalamo-pituitary dysfunction.[1–5] A certain proportion of middle-aged and elderly men have serum total testosterone concentrations below the reference range for young adult males.[5] Possible consequences of reduced androgen levels include fat mass gain, loss of muscle and bone mass, fatigue, depression, anaemia, poor libido and erectile dysfunction. The clinical features of androgen deficiency in the aging male (ADAM) resemble those of hypogonadism of younger subjects, with a single relevant difference: each of these features can also occur in elderly men with 'normal' androgen levels. For this reason, criticism has been raised towards the observational

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studies linking androgen decline with the frailty of old age, and the ADAM syndrome has not been universally accepted as a true clinical entity. An alternative approach would be to evaluate whether increasing serum testosterone concentration of ageing men to the level found in young adults improves or reverses these symptoms.[6]

Despite much recent interest by physicians, the media and the general population, and the publication of several studies examining the effects of testosterone treatment on body composition,[7–25] strength,[9,11–13,15–17,21,22,24–26] bone density and metabolism[7,9,10,16,22,27–30] and lipid profile,[7–12,14,15,18,21,25,26,31–35] considerable controversy remains concerning the issue of testosterone replacement therapy (TRT) in men over 50. Major concerns have arisen because TRT is not a 'risk-free' treatment and a randomized controlled trial (RCT) to evaluate safety of prolonged TRT is not available, nor is it likely to be in the near future. However, in respect of good clinical practice, prior to development of such a large-scale study, a definitive benefit analysis of TRT has yet to be carried out.[36] Despite a variety of studies showing various effects (from none to dramatic) of TRT on bone, body composition and lipids, a formal rigorous analysis describing what sort of objective changes to expect from T-treatment in middle-aged and ageing men has not yet been carried out. For this reason we have performed a systematic review and meta-analysis on the effects of TRT on body composition and lipid profile based on all the placebo-controlled randomized trials available in the literature. The principal goal was to provide researchers, and physicians facing the decision whether to commence such treatment, with a numerical estimate of the improvement that can be expected following the treatment with available androgen preparations.

In essence, this study sought to address the following questions: 'Does testosterone produce "clinically meaningful"[37] changes in body composition in older men?', 'What are the consequences on the cardiovascular system?', 'Does testosterone produce measurable improvements in bone density?' and, finally, 'Are the effects of androgen treatment different between eugonadal and hypogonadal men' – that is, are these physiological or pharmacological effects? The method we applied to these questions is the type of systematic review of the literature called meta-analysis (for a general review of this topic see[38,39]).

Materials and methods

Data search and selection

A written in-house protocol stating the objectives of the study, the operational definitions, searching methods, inclusion and exclusion criteria, nature of clinically relevant findings, variables of interest, statistical power and period of time covered by the search was submitted to a local consensus panel (three academic board-certified andrologists) and this guided the review process which was started in January 2003 and ended December 2004. Studies were identified by a computerized search of MEDLINE, Cochrane Library, EMBASE and *Current Contents* for the past 30 years (1974–2004), by searching the bibliographies of all retrieved articles and examining references of review articles found during the search to identify additional studies. The search was limited to RCTs published later than 1974, because at that time testosterone assays became widespread and more reliable. The database computerized search used the following key words and MESH terms: 'clinical trial', 'randomized clinical trial', 'fat mass', 'lean mass/muscle/strength', 'bone density/markers', 'serum lipids/cholesterol' and 'testosterone', 'testosterone therapy', 'androgen therapy'. Search was limited to trials performed with testosterone, including T esters, and DHT preparations, independently of delivery. All studies selected for the meta-analysis were randomized; all clinical trials compared one active treatment group with a placebo group, with the exception of three reports[9,10,18] that compared active treatment with a control group (matched and randomized, but not receiving placebo). Interobserver agreement by the two independent reviewers designated to assess eligibility was high, with the exception of two trials where the effects of testosterone *vs.* placebo were evaluated in subjects taking long-term systemic glucocorticoids.[10,22] For these reasons the findings from these studies are highlighted in the figures and tables in italics, and the influence of adding/removing these studies to the overall pooled effect has been evaluated using sensitivity analysis. Trials using human chorionic gonadotrophin (hCG) or clomiphene were not included, nor those using 17-alkylated androgen or oximetholone;[40,41] abstracts were also not included. Table 1 presents important features of each of the 29 published reports identified by the search. In some trials more than one treatment was compared to placebo, in particular some studies combined T with GH or hCG or finasteride; in these trials we selected only the treatment arm in which testosterone alone was given.

Data abstraction

RCTs were abstracted using computer-assisted data extraction sheets and in-house developed software. For each study included, the following data were abstracted: study reference details, number of subjects, withdrawals and drop-outs, mean and standard deviation (SD) (or standard error (SE)) of baseline and post-treatment groups for all variables related to the outcome of interest (including age), dose and route of administration of all medications used, duration of treatment, prior treatments and discontinuation time, baseline and post-treatment androgen levels and adverse effects. In a few cases, the SD was not reported. If available, the SE was converted to an SD by multiplying it by the square root of the number of patients. Alternatively, the SD was calculated from the raw data points directly or measured in the error bars of a graphic display. When only ranges were provided, SD was obtained by dividing the absolute interval by the square root of the number of patients. Sensitivity analysis was carried out with the exclusion of studies in which SD was calculated, in order to evaluate whether such approach had altered the findings. Percentages of body fat and fat-free mass were converted into absolute values by multiplying them by the body weight. Results on dominant and nondominant arms were recorded separately; when not specified the right arm was included among the dominant and the left among the nondominant. All studies used dual-energy X-ray absorptiometry (DEXA) scans to evaluate bone mineral density (BMD) and both absolute values (g/cm^2) and authors' calculated percentage changes from baseline were abstracted.

Methods of data pooling and analysis

For each study, a treatment-effect size and the 95% confidence interval (CI) for the effect size were calculated using the method of

Table 1. Characteristics of studies selected for analysis

Study	Age (years)	Basal TT*	No.	Regimen	Duration (months)
Amory *et al.*[29]	T: 71 ± 4	T: 9·9 ± 1·6	T: 24	TE 160–200 mg/2-week	36
	P: 71 ± 5	P: 10·5 ± 1·7	P: 24		
Aversa *et al.*[35]	T: 54 ± 2	T: 12·8 ± 2·1	T: 10	tdT 2 × 2·5 mg/day	1
	P: 56 ± 4	P: 13·9 ± 2·1	P: 10	+ Sildenafil 100 mg on demand	
Blackman *et al.*[17]	T: 70 ± 3·2	T: 13·6 ± 3·2	T: 21	TE 100 mg/2-week	6
	P: 70 ± 4·5	P: 14·6 ± 3·3	P: 17		
Boyanov *et al.*[18]	T: 57·5 ± 4·8	T: 9·56 ± 2·3	T: 24	TU 120 mg/day	3
	C: 57·5 ± 4·8	C: 10·7 ± 3·0	C: 24		
Casaburi *et al.*[24]	T: 66·6 ± 7·5	T: 11·0 ± 5·6	T: 12	TE 100 mg/week	2·3
	P: 67·7 ± 8·7	P: 11·0 ± 3·2	P: 12		
Christmas *et al.*[28]	T: 70 ± 0·7	T: 15·6 ± 3·5	T: 19	TE 100 mg/2-week	6
	P: 70 ± 1·1	P: 14·6 ± 4·5	P: 17		
Clague *et al.*[12]	T: 68·1 ± 6·6	T: 11·3 ± 1·7	T: 7	TE 200 mg/2-week	3
	P: 68·1 ± 6·6	P: 11·6 ± 0·9	P: 7		
Crawford et al.[22]	*T: 58·7 ± 20·7*	*T: 13·8 ± 1·7*	*T: 18*	*Testosterone esters*	*12*
	P: 59·9 ± 16	*P: 15·7 ± 2·0*	*P: 16*	*250 mg/2-week*	
Ferrando *et al.*[26]	T: 68 ± 3	T: 12·4 ± 5·3	T: 7	TE 100–400 mg/week	6
	P: 67 ± 3	P: 12·4 ± 5·3	P: 5		
Ferrando *et al.*[19]	T: 68 ± 3	T: 12·4 ± 5·3	T: 7	TE 100–400 mg/week	6
	P: 67 ± 3	P: 12·4 ± 5·3	P: 5		
Kenny *et al.*[16]	T: 76 ± 4	T: 13·5 ± 6·0	T: 24	tdT 2 × 2·5 mg/day	12
	P: 75 ± 5	P: 13·5 ± 3·7	P: 20	+ calcium + Vit.D	
Kenny *et al.*[45]	T: 76 ± 4	T: 13·5 ± 6·0	T: 24	tsT 2 × 2·5 mg/day	12
	P: 75 ± 5	P: 13·5 ± 3·7	P: 20	+ calcium + Vit.D	
Liu *et al.*[23]	T: 67·5 ± 3·3	T: 19·0 ± 0·6	T: 9	Testosterone esters	1
	P: 67·5 ± 3·3	P: 19·0 ± 0·6	P: 8	250–500 mg/week	
Ly *et al.*[15]	T: 71 ± 7	T: 15·0 ± 3·1	T: 17	td DHT 70 mg/day	3
	P: 68 ± 6	P: 12·8 ± 3·1	P: 18		
Marin *et al.*[8]	T: 51·9 ± 2	T: 16·0 ± 4·0	T: 11	TU 80 mg × 2/day	8
	P: 49·9 ± 1·6	P: 16·8 ± 3·5	P: 12		
Meier *et al.*[30]	T: 71·7 ± 7	T: 15·0 ± 3·1	T: 17	td DHT 70 mg/day	3
	P: 68·0 ± 6	P: 12·8 ± 3·0	P: 18		
Morley *et al.*[9]	T: 77·6 ± 2·3	*Only free*	T: 9	TE 200 mg/2-week	3
	C: 76 ± 2·5	*testosterone*	C: 7		
Page *et al.*[25]	T: 71 ± 4	T: 10·0 ± 5·4	T: 33	TE 200 mg/2-week	36
	P: 71 ± 5	P: 9·8 ± 5·4	P: 6		
Park *et al.*[34]	andropause	T: 9·01 ± 2·1	T: 33	TU 160 mg/day	3
	P: 9·38 ± 2·1	P: 6			
Reid et al.[10]	*T: 61 ± 11*	*T: 12·6 ± 3·5*	*T: 15*	*Testosterone esters*	*12*
	C: 61 ± 11	*C: 11·3 ± 5·4*	*C: 15*	*250 mg/month*	
Sih *et al.*[11]	T: 65 ± 7	T: 10·2 ± 3·7	T: 17	TC 200 mg/14–17 days	12
	P: 68 ± 6	P: 8·1 ± 2·7	P: 15		
Simon *et al.*[14]	T: 52·8 ± 4·2	T: 8·3 ± 0·85	T: 6	T gel 125 mg/day	3
	P: 55·4 ± 3·6	P: 9·4 ± 2·5	P: 6		
Snyder *et al.*[13]	T: 73·1 ± 5·8	T: 12·7 ± 2·7	T: 54	tdT 6 mg/day	36
	P: 73 ± 5·9	P: 12·8 ± 2·6	P: 54		
Snyder *et al.*[27]	T: 73·1 ± 5·8	T: 12·7 ± 2·7	T: 54	tdT 6 mg/day	36
	P: 73 ± 5·9	P: 12·8 ± 2·6	P: 54		
Snyder *et al.*[32]	T: 73·1 ± 5·8	T: 12·7 ± 2·7	T: 54	tdT 6 mg/day	36
	P: 73 ± 5·9	P: 12·8 ± 2·6	P: 54		
Steidle *et al.*[20]	T: 56·8 ± 10·6	T: 7·8 ± 2·8	T: 106	T gel 100 mg/day	3
	P: 56·8 ± 10·8	P: 7·5 ± 2·8	P: 99		
Steidle *et al.*[20]	T: 60·5 ± 9·7	T: 8·2 ± 2·8	T: 102	tdT patch 2 × 2·5 mg/day	3
	P: 56·8 ± 10·8	P: 7·5 ± 2·8	P: 99		
Tenover[7]	T: 67·5 ± 5	T: 11·6 ± 1·4	T: 7	TE 100 mg/week	3
	P: 67·5 ± 5	P: 11·6 ± 1·4	P: 6		
Uyanik *et al.*[31]	T: 66·5 ± 6·7	T: 7·7 ± 1·25	T: 17	TU 120 mg/day	2
	P: 67·2 ± 7·6	P: 11·2 ± 3·3	P: 20		
Wittert *et al.*[21]	T: 69 ± 6	T: 17 ± 4·4	T: 39	TU 160 mg/day	12
	P: 68 ± 5	P: 15·6 ± 4·5	P: 37		

T, testosterone-treated group; P, placebo-treated group; C, matched control group. No., number of treated subjects; TU, testosterone undecanoate; TE, testosterone enanthate; TC, testosterone cipionate; td T, transdermal testosterone patch; td DHT, transdermal DHT gel; ts T, trans-scrotal testosterone; T gel, transdermal testosterone gel.

Hedges and Olkin.[42] A test for homogeneity was performed on the individual treatment-effect sizes to determine whether they could have arisen from a single population. The conclusion of homogeneity allows the estimation of a single, underlying true treatment-effect size, combining the results of all studies exploring the same variable (overall effect size, EfS). When the outcome of interest was measured using the same scale in every study, effect sizes were expressed as weighted mean differences (WMDs). The pooled effect obtained by WMDs maintains the natural unit of the outcome as reported in each trial and therefore it can be read as the objective result of a 'supertrial' performed on a cumulative population obtained by merging all studies. However, when studies used different scales to measure the effect of treatment, 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). The pooled effect obtained by SMDs is therefore reported in 'units of standard deviations'. This measure reflects how much active treatment affects the distribution of the outcome of interest compared to placebo. As the pooled SMD is not of immediate relevance to the physician, Cohen[43] proposed that we give a common 'user definition' as follows: a small treatment-effect size is considered to be about 0·2 SMD, a medium effect size to be about 0·5 SMD, and a large effect size to be about 0·8 SMD. These guidelines can be used to judge the treatment-effect size of the individual studies as well as the treatment-effect size for all combined studies. Alternatively, the results expressed in SMDs can be multiplied by the SD of a known reference scale to obtain the same dimensional units. In pooling studies, the random-effect model was chosen. The presence of between-studies heterogeneity was quantified using the I^2, that is a measure of the degree of inconsistency across studies, or the among-study variance, denoted τ^2.[44] Subgroup analysis was performed to compare the effect of treatment according to the baseline characteristics of the study population. In the majority of studies inclusion criteria did not allow us to classify studies as performed on hypogonadal or eugonadal subjects. For these reason an operational definition was provided by the reviewers based on the following simple criteria. In each trial, when mean baseline T concentration for both the placebo and the active treatment group were above 10 nmol/l, the study was defined as 'eugonadal' (for men aged > 50 years); on the contrary, if either the placebo or the active treatment group had a mean baseline serum T of < 10 nmol/l, the study was defined as 'hypogonadal'. We acknowledge that there is a consistent degree of uncertainty and heterogeneity in such classification, as well as in the diagnosis of hypogonadism based on serum T specimens measured using different protocols; however, this approach is simple, consistent and reproducible. The test of interaction between groups was used to verify the hypothesis that both groups of studies were similar. A further attempt was made to stratify the studies using three groups rather than two. As the findings were similar, these analyses have been omitted for brevity. When insufficient studies were available in each group, meta-regression analysis was preferred. Between-study heterogeneity was explored using meta-regression analysis to investigate the contribution of studies' characteristics: the reported inclusion criteria for age and gonadal status, the baseline T concentrations (using the mean 0900 h serum total testosterone concentration), patient age (using mean age), the year of publication of the study, the length of study and the kind of preparation used. Meta-regression analysis was performed even if heterogeneity was not a significant issue in the majority of investigated variables. A mixed model with restricted maximum likelihood ratio was used for this purpose.[38] The chance of publication bias was assessed using the funnel plot, Egger's test, Begg's test, the Rosenthal's 'file drawer' method and the trim-and-fill model. All statistical analyses were carried out using Stata Statistical Software, release 8.2SE (Stata Corp., College Station, TX, USA).

Results

Study characteristics

Table 1 summarizes the 29 reports that met all inclusion criteria. Some authors presented the various results of their trial in separate reports, and thus while 29 papers were retrieved, only 24 groups of subjects were studied. Among these, eight had at least one group with an average baseline total testosterone value below 10 nmol/l (throughout the text referred as 'hypogonadal'), and 16 had both groups with testosterone above 10 nmol/l (referred as 'eugonadal'). The articles included in the analysis gave details of 1083 subjects, 625 randomized to T, 427 to placebo and 31 to observation (control group), with a weighted mean age of 64·5 years (range 49·9–77·6 years) and serum testosterone of 10·9 nmol/l (range 7·8–19 nmol/l). The studies varied widely in terms of testosterone preparation, drug delivery and dosing, protocol design, measure of end points, age and gonadal status of enrolled subjects. All studies were randomized and controlled, 26 studies were placebo-controlled,[7,8,11–17,19–32,34,35,45] while three were performed with a control group (matched, randomized, but not receiving placebo).[9,10,18] Only one study was cross-over.[10] Twenty-three trials were double-blinded, two trials were single-blinded (patients only),[9,34] two studies[10,18] and one arm of another trial[20] were open-label, and in one study the blinding was not described.[31] Most of studies were performed in relatively healthy men with few exceptions. One study was performed in men with reduced FEV1 chronic obstructive pulmonary disease (COPD), but no other significant impairments (age range 55–80).[24] Two trials were performed in subjects taking long-term glucocorticoids for respiratory[10] or rheumatic disorders.[22] In the following sections these two studies have been reported separately, highlighted in italics, and included in the overall EfS calculation only if sensitivity analysis revealed that the exclusion of these two trials did not modify the findings substantially. SHBG was measured in 12 out of 29 studies and baseline values were reported to be within the normal range in all studies (mean values: 45·1 ± 14·4 and 43·4 ± 12·7 nmol/l in the active and placebo groups, respectively). A small but significant reduction of SHBG was observed in the T-treated subjects [WMD −4·6 (−7·3 to −1·9) nmol/l].

Pooled effect of testosterone on body composition and muscle strength

The single WMD values and the overall pooled estimate of effects for each parameter of body composition are reported in Fig. 1. An average of 9 months of T treatment produced a reduction of 1·6 kg (CI: 2·5–0·6, $P < 0·001$, $I^2 = 0·0\%$; Fig. 1a) in total body fat, which

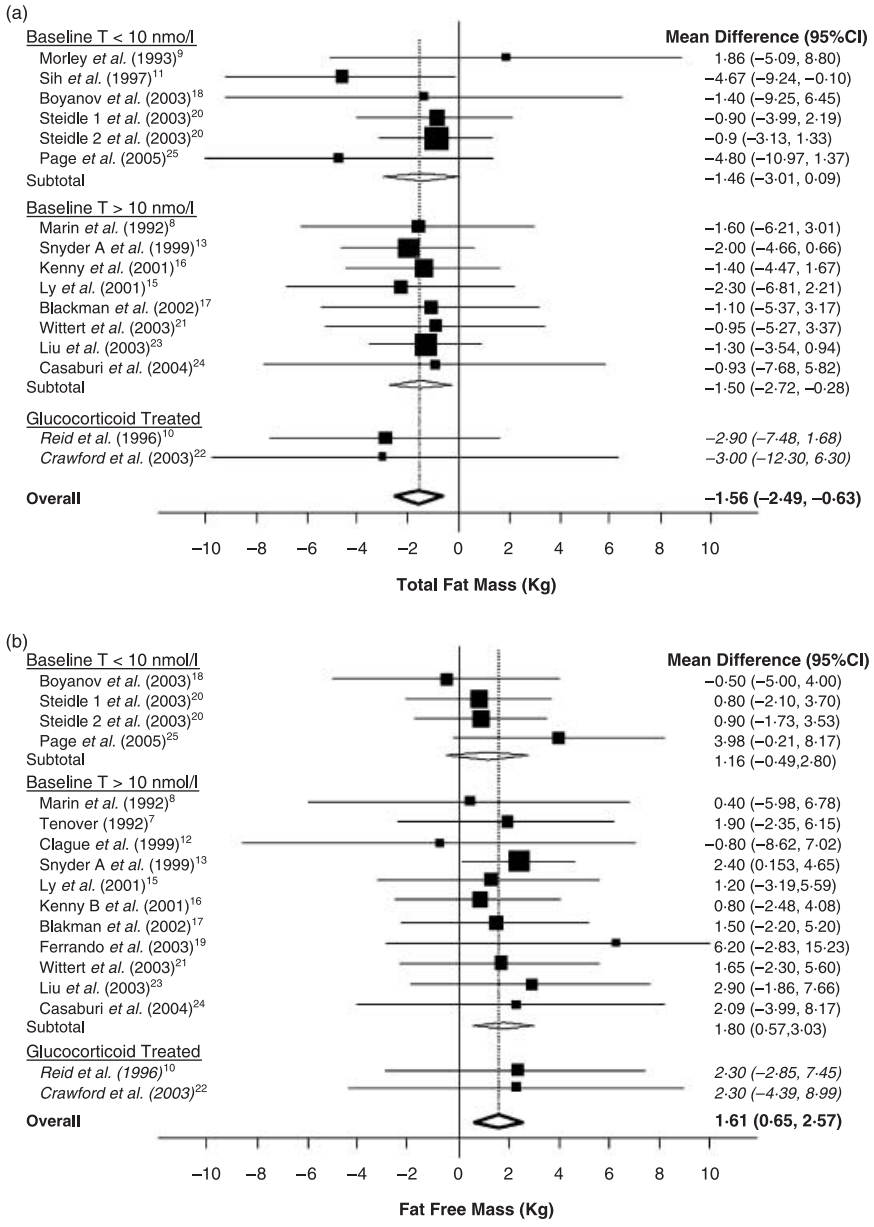


Fig. 1 Effects of testosterone on body composition: (a) total body fat; (b) total fat free mass.

corresponds to –6·2% (9·2–3·3) of initial percentage body fat. The effect in hypogonadal men was –1·46 kg (–3·01 to 0·09, P = ns); the effect in eugonadal men was –1·50 kg (–2·72 to –0·28, $P < 0·05$) and the difference was not statistically significant. Active treatment also produced an increase in fat free mass of +1·6 kg (CI: 0·6–2·6, $P < 0·001$, $I^2 = 0·0\%$), which corresponds to an increase of +2·7% (1·1–4·4) over initial percentage lean body mass (Fig. 1b). Data on fat mass and lean mass were homogeneous (residual heterogeneity $\tau^2 = 0·0$); meta-regression analysis performed for treatment preparation, pretreatment testosterone levels, year of publication, age of subjects, inclusion criteria and study population characteristics failed to reveal any significant contribution. In the majority of studies testosterone produced a small increase in body weight; however, the pooled effect was not statistically significant (EfS = 0·6, CI: –0·9 to 2·2, $P = 0·399$, $I^2 = 0·0\%$).

Data on muscle strength are reported in Fig. 2. Data were analysed separately for dominant and nondominant muscles. When grouped according to outcome, only the dominant knee extension and dominant handgrip showed a tendency towards improvement of testosterone over placebo (EfS = 0·3 SMD, CI: –0·0 to 0·6, $P = 0·06$) (Fig. 2a). No effect could be detected in the nondominant muscles (Fig. 2b). Heterogeneity was not a major concern for either dominant or nondominant lower limb extension and dominant handgrip.

Pooled effect of testosterone on bone density

The effects of testosterone at different skeletal sites are reported in Fig. 3. Mean differences between testosterone and placebo groups are calculated as the difference in the mean of the treatment group.

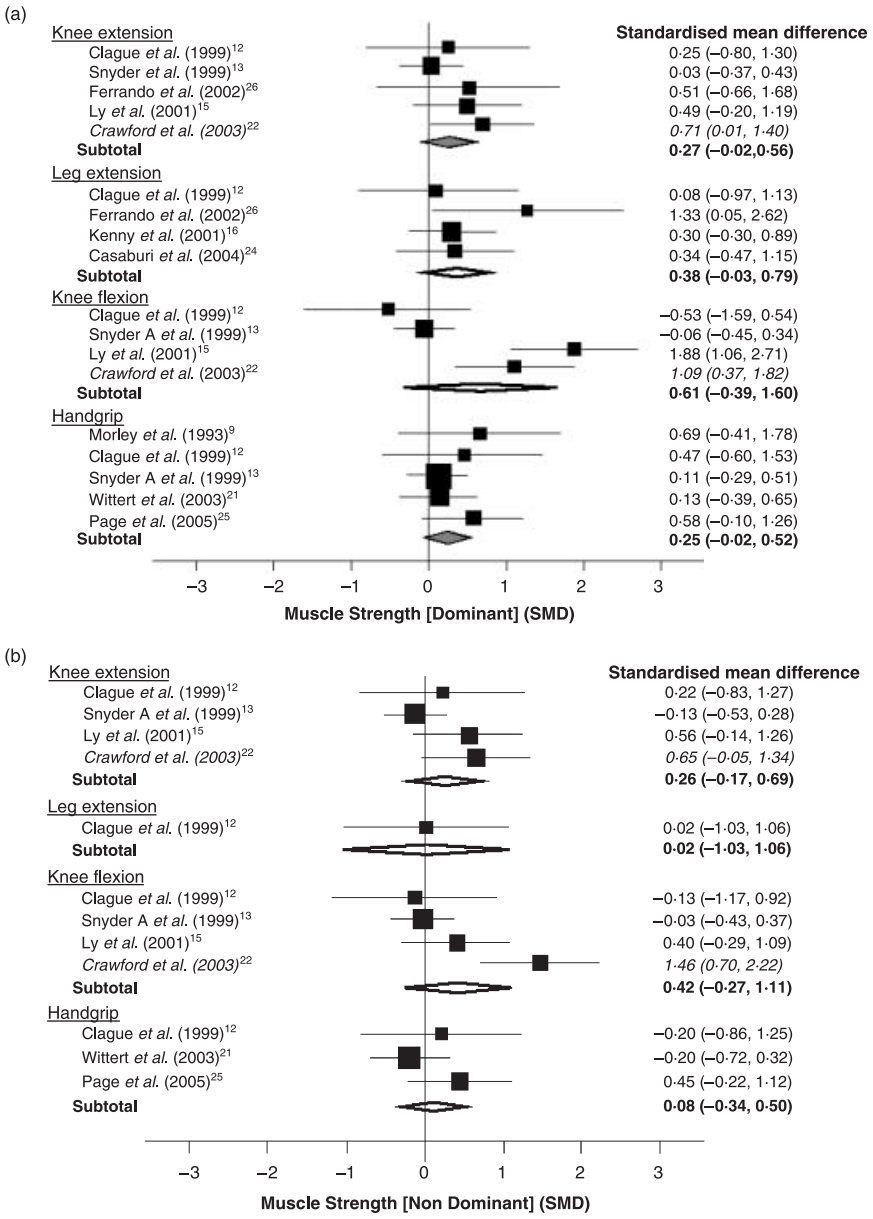


Fig. 2 Effects of testosterone on muscle strength: (a) dominant; (b) nondominant.

The first striking feature of this figure is that nearly all studies reported that the testosterone group behaved better than the placebo group, with only one study showing a null effect.[16] Pooled effects also revealed that the treatment effect was higher at the lumbar spine and femoral neck sites. However, because of high baseline variability of the study population, leading to high pretreatment SD values, the CIs are wide and the pooled effect fails to reach statistical significance. Only a trend towards significance was found at the lumbar spine site (EfS = 0·03 g/cm^2, CI: −0·00 to 0·07, I^2 = 0·0%). Even when combining the effects at the lumbar spine and femoral neck, the pooled WMD only had a borderline significance (EfS = 0·02 g/cm^2, CI: −0·00 to 0·05). As weighted baseline bone density was 1·115 ± 0·088 g/cm^2 at the lumbar spine and 0·864 ± 0·067 g/cm^2 at the femoral neck, the calculated relative increase over placebo would have been of 3% and 2%, respectively (0·03 over 1·11 g/cm^2 and 0·02 over 0·86 g/cm^2). In fact, where available, the effects were also calculated from mean percentage changes during treatment with their respective SDs. This resulted in much smaller CIs and the pooled effects achieved statistical significance. Figure 3b reports the latter calculation for lumbar spine, where testosterone produced a significant increase of +3·7% (CI: 1·0–6·4, $P < 0·01$) in bone density over baseline compared to placebo. However, the effects were not consistent between studies ($\tau^2 = 6·65$), with up to 77·8% of pooled WMDs attributable to heterogeneity. Sensitivity analysis revealed that treatment might play a role in explaining heterogeneity among studies ($P = 0·009$). Meta-regression analysis performed on percentage changes at the lumbar spine and femoral neck revealed a significant effect of treatment preparation used, with the highest effects found with testosterone esters (BMD(%) = 0·98 ± 0·27 × Testosterone Type – 2·24 ± 1·1, $P < 0·001$). Inclusion of the contribution

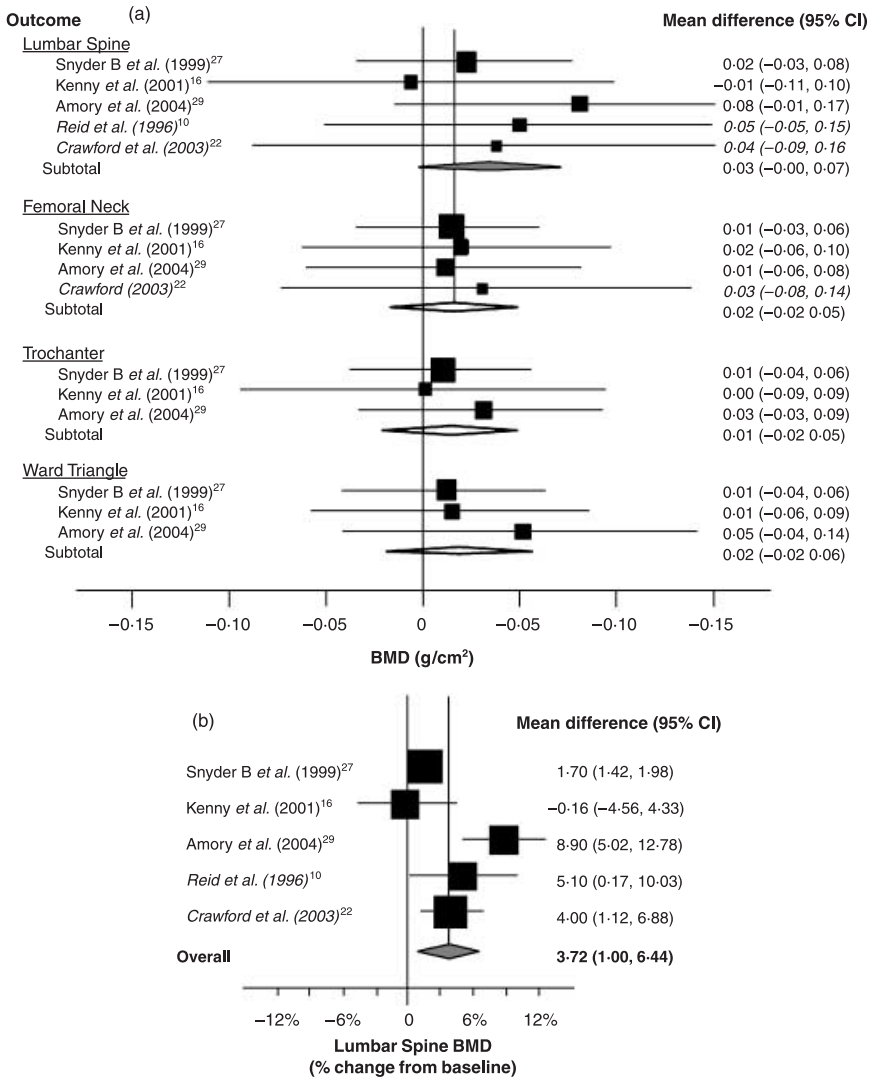


Fig. 3 Effects of testosterone on bone density measured as mean difference on absolute values (a) and reported as percentage change from baseline at lumbar spine (b).

of the testosterone preparation resolved the residual heterogeneity ($\tau^2 = 0$).

Pooled effect of testosterone on bone markers

As few studies reported full data on the same markers, results have been pooled in two major groups: bone formation and resorption markers. Data are therefore reported using the SMD rather than the WMD (Fig. 4). To avoid excessive data, only one marker for each trial was reported. Sensitivity analysis revealed that inclusion of additional markers did not affect in a substantial way the width of the CI of pooled EfS. Overall, testosterone had a moderate effect in reducing bone resorption markers (EfS = −0·6 SMD, CI: −1·0 to −0·2, $P < 0·01$), with no significant effects on bone formation markers. However, the data of bone resorption revealed significant heterogeneity ($I^2 = 60\%$). When analysed separately, the only two markers that showed a statistical reduction during testosterone treatment were the N-telopeptides and the DPD (deoxypyridinoline)/creatinine ratio, with an estimated reduction of 18% and 16% from baseline, respectively ($P < 0·05$).

Pooled effect of testosterone on serum lipid profile

The effects of testosterone on serum total cholesterol were more pronounced in hypogonadal [EfS = −0·42 mmol/l (−16 mg/dl), CI: −0·65 to −0·19, $I^2 = 0\%$], than in eugonadal men (EfS = −0·14, CI: −0·30 to 0·03 mmol/l) (Fig. 5a). Testosterone had no effect on LDL-cholesterol ($P = 0·98$, $I^2 = 70·5\%$) (Fig. 5b). A small but significant reduction in HDL was observed in the group of studies performed in men with higher baseline testosterone concentrations, but the overall effect was not statistically significant (Fig. 5c). The pooled mean difference in eugonadal men was −0·09 mmol/l (−3·3 mg/dl) (CI: −0·17 to −0·00), corresponding to roughly a 4–6% reduction in baseline values. However, some heterogeneity was found with $I^2 = 40\%$ (variation in MD attributable to heterogeneity, $\tau^2 = 7·7$). Sensitivity analysis revealed that treatment preparation may have an effect; in fact, comparing excluded studies on the effects of oxymetholone and other nonaromatizable androgens showed a more profound suppression of HDL than the other preparations [−0·25 mmol/l (−9·8 mg/dl) *vs.* − 0·05 mmol/l (−1·92 mg/dl), $P < 0·05$].

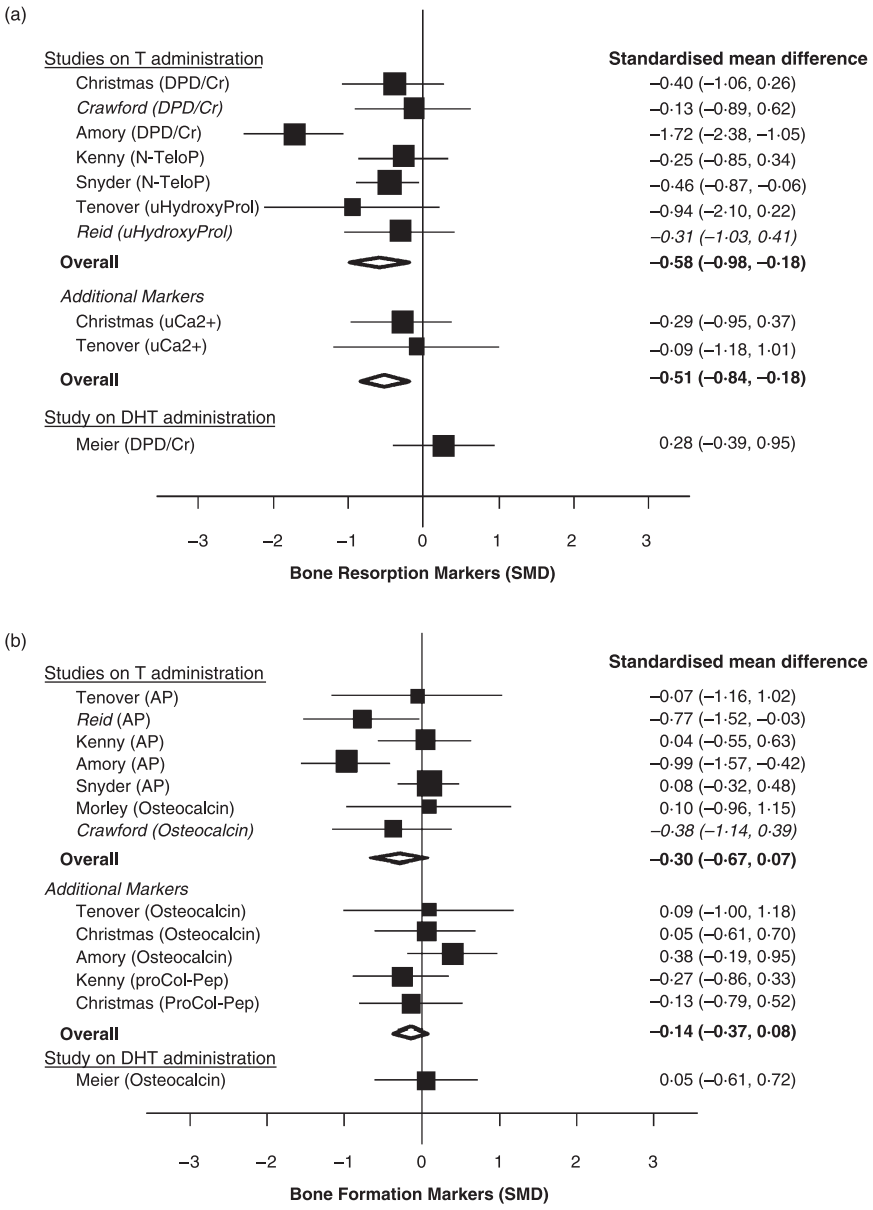


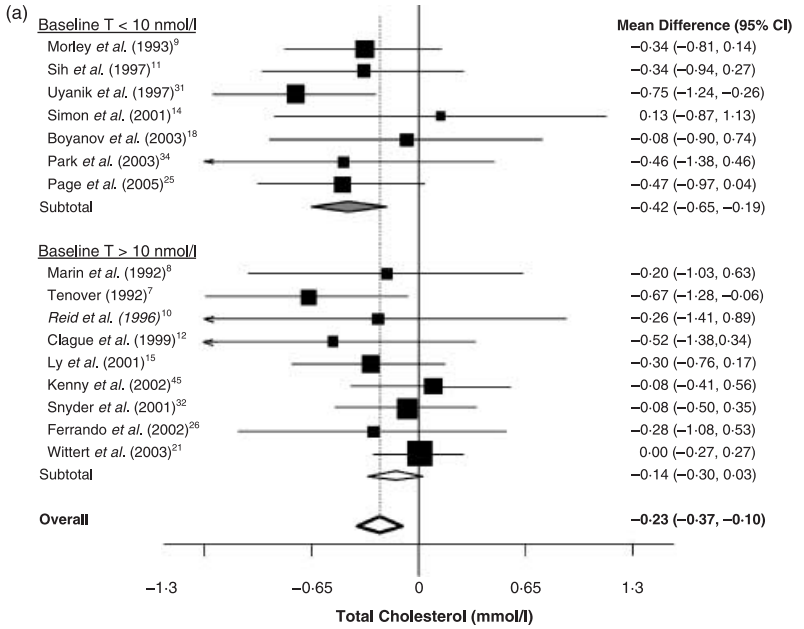
Fig. 4 Effects of testosterone on markers of bone metabolism.

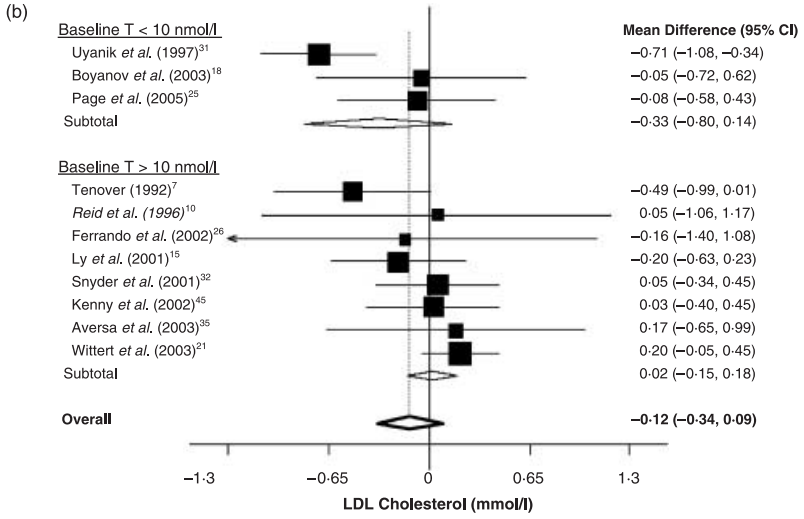
Discussion

The present meta-analysis reveals that androgen therapy in the ageing male determines: (1) a reduction in total body fat mass and an increase in fat free mass; (2) a borderline improvement in BMD accompanied by (3) an overall reduction of bone resorption markers; and (4) a small decrease in total cholesterol and, in men with higher testosterone levels, of HDL-cholesterol. Although few placebo-controlled studies were available on severely hypogonadal men, the magnitude of the effects of testosterone were similar between populations with baseline testosterone above or below 10 nmol/l, whereas the type of testosterone preparation, in particular the possibility of being aromatized, contributed to the effects on bone density and HDL-cholesterol. The findings described here apply to a population of middle-aged and ageing men whose levels span across the most widely accepted cut-off value of 10 nmol/l for the diagnosis of hypogonadism, and therefore simulate well those of the average population of adult males referring to outpatient clinics with signs and symptoms of possible androgen deficiency.[46]

Effects of testosterone on body composition and muscle strength

During the ageing process lipid accumulation can be observed in several tissues such as muscle, vessels and bone marrow, and an increase and redistribution of fat occurs from subcutaneous to visceral deposits.[47–49] The extent and nature of these changes is influenced by multiple factors including genetic, hormonal, metabolic and nutritional factors as well as by physical activity and illness. Healthy hypogonadal men have lower fat-free mass and higher fat mass than





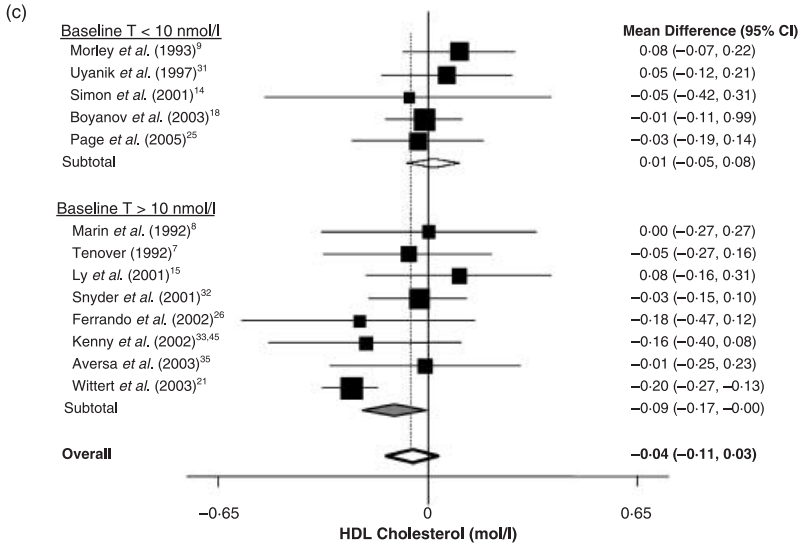


Fig. 5 Effects of testosterone on serum lipid profile: (a) total cholesterol; (b) LDL-cholesterol; (c) HDL-cholesterol. To convert mmol/l to mg/dl divide by 0·02586.

age-matched eugonadal men.[50–52] Several studies reported that increasing testosterone concentrations in older men with low testosterone levels to those of the mid-normal reference range for the healthy young men is associated with a significant increase in lean body mass and a reduction in fat mass,[7–13,15–22,25,53–55] especially at the trunk.[13,40,56]

We reviewed the effects of testosterone on body composition based on the results of available RCTs (Table 1; Fig. 1). In hypogonadal and eugonadal men, pooled increases of +1·6 (0·6–2·6) kg in fat-free mass and decreases of −1·6 (−2·5 to −0·6) kg in fat mass were estimated. The data are homogeneous among studies and no evidence of publication bias was found. We estimated that testosterone-dependent fat mass reduction accounts for a loss of −6·2% of initial body fat, and an increase of +2·7% in initial fat free mass. Although the effects are large and robust, it has been questioned whether these changes in body composition are 'clinically meaningful'.[57] As an increase in intra-abdominal fat is associated with greater mortality for cardiovascular events,[58] it could be argued that testosterone treatment, by reducing fat mass, improves cardiovascular risk. However, no controlled evidence has been found to support this hypothesis and, regardless of the fact that weight loss might be beneficial, testosterone cannot on the basis of the current findings be recommended for weight control in older men. Only recently, an important contribution by Schroeder *et al.* revealed that 17-alkylated androgen may be beneficial for some components of the metabolic syndrome in overweight older men.[41]

Although the results obtained on muscle mass are unequivocal, in either hypogonadal or eugonadal subjects, and seem to be dose dependent,[59] the effects of testosterone on muscle strength are less clear-cut. The majority of studies show a discrepancy between changes in mass and muscle performance.[9,11–13,15–17,21,22,25,26,40] We have shown that androgen treatment may improve the capacity for leg and knee extension and handgrip by an average of two-thirds of a kilogram, roughly corresponding to a 6% increase from baseline. However, despite the homogeneity of the data, the substantial diversity in the methods used to assess muscle function, the difficulty to account for any 'learning effect', familiarity with the equipment and basal 'training status' of subjects render any strong positive or negative conclusion on this issue very difficult to substantiate. Cross-sectional analysis revealed that muscle mass is a positive predictor of bone density in postmenopausal women, probably as the consequence of physical activity plus a direct load on the skeleton.[60] Therefore, an increase in muscle mass may be both directly and indirectly beneficial for bone.

Effects of testosterone on bone density and bone turnover markers

Although many studies identified bone as one of the major targets of TRT, only nine controlled studies have been found that fulfilled the inclusion criteria. On pooling these studies together we found that testosterone improved bone density only at the lumbar spine with an estimated increase of 3·7% (CI: 1·0–6·4) after a minimum of 12–36 months of treatment. All studies demonstrated an increase over placebo, with the exception of one trial,[16] where a null effect was found at the lumbar spine, probably due to the simultaneous calcium supplementation and technical differences (measurement limited to the L1 segment). The effects among studies were widely heterogeneous, and when data were pooled for absolute changes in bone density rather than percentage changes over baseline only a borderline significance was found, suggesting that data are not as robust as those for body composition. The studies by Kenny *et al.*[16,45] and Crawford *et al.*[22] showed null to marginal effects after 12 months of treatment. In longer trials, by Snyder *et al.*[13,27,32] and Amory *et al.*,[29] testosterone patch 6 mg/day and testosterone enanthate 160 mg i.m./2 weekly were, respectively, administered for 36 months to men over 65 years; however, the results are substantially different. In a population with a pretreatment testosterone level of 12·7 ± 2·7 nmol/l, Snyder and colleagues obtained an increase in lumbar BMD of 4·5 ± 0·8% over baseline (final BMD 1·184 ± 0·142 g/cm^2). However, such improvement was not significant when compared to the placebo group, where a 2·5 ± 0·6% increase was also found (the increase of T over P was 1·7 ± 0·3%, Fig. 3b). In the study by Amory *et al.*,[29] a 10% increase in the testosterone-treated subjects and a 0·2 ± 0·8% decrease in the placebo group were found. Even though the on-treatment T concentrations were reported to be similar (21·7 ± 8·6 *vs.* 21·5 ± 1·5 nmol/l), it is likely that the total doses delivered in the two studies are different, blood specimens being collected at nadir in one study (immediately prior to the following injection) and at peak in the other (3–5 h after the application of the patch). By subgrouping subjects according to the pretreatment testosterone concentration, Snyder *et al.* found that it was significantly correlated with the improvement in lumbar BMD, while testosterone levels achieved during treatment were not. However, they also found that in the group with mean pretreatment testosterone of < 10 nmol/l, the increase was of 3·4 ± 1·2%, still much less than that described by Amory *et al.* In the latter study, the effects on BMD reflected the magnitude of increases in serum total testosterone and oestradiol (from 71·5 ± 33·7 to 120·0 ± 20·0 pmol/l, $P < 0·05$) achieved during treatment, rather than pretreatment testosterone concentrations (Table 1). Therefore, it is likely that the discrepancies in the results obtained with testosterone on BMD are largely due to the differences in the delta of increases of serum T and the peak E_2 achieved with different preparations. Using meta-regression analysis we were able to confirm this hypothesis and explain the observed heterogeneity. Clearly, differences in DEXA instruments and protocols used by the two groups of authors may also have played a role. We then analysed whether these effects on BMD were sustained by consistent changes in bone resorption markers. Testosterone treatment significant decreased only N-telopeptides[16,27] and the DPD/creatinine ratio,[22,28,29] which are probably the most sensitive markers of bone resorption,[61] while no changes were found for bone formation markers.[7,10,16,22,27,28,30] In addition, when all markers were grouped in two classes, resorption and formation markers, we found a significant treatment effect only for bone resorption markers, suggesting that this is the principal mode of action of exogenous testosterone in the ageing male. A recent large study evaluating the long-term effects of testosterone treatment showed that BMD continues to increase at the lumbar spine after 18 and 30 months of treatment;[55] however, in the present analysis, because of the small number, it was not possible to group studies according to treatment duration.

Effects of testosterone on serum lipid profile

Exogenous testosterone has been reported to increase the activity of hepatic lipoprotein lipase (LPL), an enzyme involved in HDL catabolism,[62,63] therefore suggesting that testosterone treatment should reduce HDL levels. However, data are controversial.

Our meta-analysis, conducted on RCT trials, revealed a significant decrease in total cholesterol that was more pronounced in the group of hypogonadal men,[9,14] and, on the contrary, a reduction in HDL-cholesterol that was detectable only in studies with higher pretreatment T concentrations. We found that the magnitude of the decrease in HDL-cholesterol was lower in the studies using T esters with respect to other formulations (oral T undecanoate or cypionate and transdermal T). We attribute this to the high serum levels of oestradiol achieved with intramuscular testosterone injection. This is consistent with previous findings by Morley *et al.*[9] and Tenover,[7] who found no change in HDL in men treated with testosterone enanthate, and by Wittert *et al.*, who found a significant decrease in HDL using testosterone undecanoate.[21] In addition, a study on the nonaromatizable oxymetholone revealed profound suppression of HDL levels with a possible increase in LDL-cholesterol.[40] These data confirm that aromatization of exogenous testosterone to oestradiol has clear importance in maintaining HDL-cholesterol concentration in men, counteracting the effects of testosterone on LPL activity.[63]

Limitations and conclusions

Meta-analysis has been used to address questions for which multiple data sources are in conflict or fail to reach a consensus. Meta-analysis is particularly useful when there are a variety of reports with low statistical power; thus, pooling data can improve power and provide a convincing result. In addition, meta-analysis can examine the body of literature as a whole in a way that a single investigation cannot. However, meta-analysis is most likely to provide a convincing answer when the studies are well designed and executed. In the present analysis four major topics of concern were identified. The first is on the differences in the baseline characteristics of the study populations and design. There is a wide distribution of age among eligible studies. In the majority of studies the mean age was between 60 and 80; however, up to one-third of studies enrolled men in their forties or fifties. The effect of treatment may be different in men aged 50 compared to men aged 70; however, this was difficult to prove as other confounding factors (i.e. training and physical activity of subjects) probably have a much greater impact than age on response to treatment. Yet this aspect is seldom assessed in the studies reviewed. The duration of treatment also differed widely among studies. Although the effects may tend to plateau for some variables, for example muscle mass, this may not be true for others, such as bone density, where the effects seems to be sustained.[55] The second concern is whether all relevant reports were included. To overcome this issue, the most comprehensive search was performed and all eligible observations were included. The search was limited to RCTs published in the literature to allow reproducibility (all these articles are easily available). Poor quality reports published in nonpeer-reviewed journals or abstracts were not included. The third concern regards pooling all the results together. Although all reports met the entrance criteria, they otherwise differed in age, size, androgen preparation used, and just about every other characteristic. These differences may suggest that they should not be pooled. However, we were able to demonstrate that heterogeneity was not a concern for many outcomes and, where heterogeneity was found, we were able to demonstrate that was due to discrete aspects that explained with adequate statistical power the differences in effect sizes among trials. Nevertheless, readers are invited not to focus only on the pooled measure but to consider the whole picture reflecting the variation among all included studies.

With respect to the initial purpose of the study – to provide an estimate of what to expect for TRT in elderly men – we found two major limitations. The first is that much information on the effects that testosterone may produce in the ageing male is still missing. Above all, safety data are not available, nor can they be extracted from published results. In addition, efficacy data on other important targets of testosterone, such as the endothelium, the vascular wall, insulin resistance and the brain, which may turn out to be the most relevant in clinical decision making, are not yet available in the form of RCTs (although many preliminary findings have already been published). The second limitation of our meta-analysis is that a large number of data were abstracted from studies with mean baseline T concentration above 10 nmol/l. It is reasonable, but not necessary, to assume that the described effects would be greater if the number of studies on severely hypogonadal subjects ($T < 8$ nmol/l) were larger. In addition, the differences in bioavailable androgen levels at baseline, or during treatment, might not have been accounted for in the current analysis. Regardless of these reservations, we consider that it is no longer a matter of debate as to whether to treat men with very low T levels: there are a large number of studies that, while not placebo-controlled, represent a solid base of evidence for the need to treat these subjects. The aim of the present study is, eventually, to provide an estimate of the changes that could occur in a patient with borderline testosterone levels who is referred to the physician with signs and symptoms of androgen deficiency. Knowledge of expectation is crucial in clinical decision making. On a risk *vs.* benefit analysis, most of the observed findings of testosterone on body composition do not seem to be strong enough to justify its widespread use in ageing males; although large, long-term, nonplacebo-controlled studies achieved more stringent results on bone density and muscle strength than the retrieved RCTs. Our analysis indicates that there is no need for further studies to explore the effects of testosterone on body composition. Instead, we suggest that future trials should focus on more clinically orientated aspects such as fat distribution, insulin resistance and endothelial function. Thus, in addition to the recommendations of the Institute of Medicine, we would add the need for more studies designed primarily to address outcomes with immediate and relevant clinical impact to justify potential interventions for healthy ageing men. Finally, separate mention should be reserved for the studies performed in subjects affected by chronic illness such as HIV infections, end-stage renal disease and autoimmune disorders, where an age-independent reduction in circulating testosterone levels almost invariably occurs. A large body of controlled trials (and ongoing studies) has demonstrated that, in these subjects, the T-induced increase in fat-free mass, muscle strength and number of erythrocytes is reflected in a definite improvement in the

quality of life.[64–70] Disease-related androgen deficiency is a true clinical entity that can occur at any age and always deserve adequate investigation and appropriate treatment.

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