Effect of testosterone replacement on measures of mobility in older men with mobility limitation and low testosterone concentrations: secondary analyses of the Testosterone Trials

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Summary

Background The Physical Function Trial (PFT) was one of seven Testosterone Trials (TTrials), the aim of which was to assess the effect of testosterone on mobility, self-reported physical function, falls, and patient global impression-of-change (PGIC) in older men with low testosterone concentrations, self-reported mobility limitation, and walking speed of less than 1·2 m/s. Using data from the PFT and the overall TTrials study population, we also aimed to identify whether the effect of testosterone on mobility differed according to baseline walking speed, mobility limitation, or other participant-level factors.

Methods The TTrials included 790 men aged 65 years or older and with an average of two total testosterone concentrations below 275 ng/dL (9·5 nmol/L), of whom 390 had mobility limitation and a walking speed below 1·2 m/s and were enrolled in the PFT. Participants were assigned (by minimisation method) to 1% testosterone gel or placebo gel daily for 12 months, with participants and study staff masked to intervention allocation. The primary outcome of the PFT was an increase in 6 min walk test (6MWT) distance of 50 m or more. Here we report data for absolute change in 6MWT distance and physical component of Short Form-36 (PF10), and for PGIC and falls. Data are reported for men enrolled in the PFT and those who were not, and for all men in TTrials; data are also reported according to baseline walking speed and mobility limitation. Analyses were done in a modified intention-to-treat population in all patients who were allocated to treatment, had a baseline assessment, and at least one post-intervention assessment. The TTrials are registered with ClinicalTrials.gov, number NCT00799617.

Findings The TTrials took place between April 28, 2011 and June 16, 2014. Of 790 TTrials participants, 395 were allocated to testosterone and 395 to placebo; of the 390 participants enrolled in the PFT, 193 were allocated to testosterone and 197 to placebo. As reported previously, 6MWT distance improved significantly more in the testosterone than in the placebo group among all men in the TTrials, but not in those who were enrolled in the PFT; among TTrials participants not enrolled in the PFT, 6MWT distance improved with a treatment effect of 8·9 m (95% CI 2·2–15·6; p=0·010). As reported previously, PF10 improved more in the testosterone group than in the placebo group in all men in TTrials and in men enrolled in the PFT; among those not enrolled in the PFT, PF10 improved with an effect size of 4·0 (1·5–6·5; p=0·0019). Testosterone-treated men with baseline walking speed of 1·2 m/s or higher had significantly greater improvements in 6MWT distance (treatment effect 14·2 m, 6·5–21·9; p=0·0004) and PF10 (4·9, 2·2–7·7; p=0·0005) than placebo-treated men. Testosterone-treated men reporting mobility limitation showed significantly more improvement in 6MWT distance (7·6 m, 1·0–14·1; p=0·0237) and PF10 (3·6, 1·3–5·9; p=0·0018) than placebo-treated men. Men in the testosterone group were more likely to perceive improvement in their walking ability (PGIC) than men in the placebo group, both for men enrolled in the PFT (effect size 2·21, 1·35–3·63; p=0·0018) and those not enrolled in the PFT (3·01, 1·61–5·63; p=0·0006). Changes in 6MWT distance were significantly associated with changes in testosterone, free testosterone, dihydrotestosterone, and haemoglobin concentrations. Fall frequency during the intervention period was identical in the two treatment groups of the TTrials (103 [27%] of 380 analysed in both groups had at least one fall).

Interpretation Testosterone therapy consistently improved self-reported walking ability, modestly improved 6MWT distance (across all TTtrials participants), but did not affect falls. The effect of testosterone on mobility measures were related to baseline gait speed and self-reported mobility limitation, and changes in testosterone and haemoglobin concentrations.

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See **Comment** page 839

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Research in context

Evidence before this study

The anabolic effects of testosterone on skeletal muscle mass and muscle strength are well recognised, but it is not known whether testosterone improves physical function and mobility or reduces the risk of falls in older men. In 2002 the US National Institute on Aging (NIA) requested that the US Institute of Medicine (IOM) assess the status of clinical research on testosterone therapy in older men, and completed a comprehensive review of the available evidence. The IOM committee concluded that there was insufficient evidence that testosterone treatment of older men with low testosterone was beneficial and recommended that the NIA fund a coordinated set of efficacy trials to identify whether this treatment has any benefits and to fund a larger trial to uncover possible risks only if benefits were found. The NIA followed the IOM's recommendations and funded the Testosterone Trials (TTrials) to determine the efficacy of testosterone treatment in older men with age-related decline in testosterone levels and one or more symptoms or signs of testosterone deficiency. We did a search in March, 2017, for more recent evidence, which was restricted to the English language. A PubMed search was done using the terms "testosterone", "physical function", "anabolic effects of testosterone", "muscle mass", "lean body mass", "muscle strength", "muscle performance", and "falls". A PubMed search of published systematic reviews and meta-analyses was also done on testosterone's effects on lean mass, muscle strength, and physical function. The quality of evidence varied from low to moderate because of the heterogeneity of eligibility criteria, variable testosterone doses and formulations, inclusion of men who were not hypogonadal, small sample sizes of many trials, and use of surrogate endpoints or non-validated outcome measures.

Added value of this study

The TTrials included a set of seven coordinated and overlapping trials; the primary overall results of the TTrials have been reported previously. Here we reported the detailed results of the Physical Function Trial (PFT), which was one of the three main trials. We also describe the effect of testosterone on fall frequency, which had not been studied previously. Additionally, using data from all TTrial participants, we characterised participant characteristics that were related to the treatment response to explain some of the surprising findings of the PFT, namely, that participants with higher gait speed at baseline seemed to show greater improvements in function with testosterone treatment than did those with lower gait speed, contrary to our expectations. The PFT is, to our knowledge, the largest controlled trial to assess the effect of testosterone on physical function and mobility in older men. Unlike previous trials, which often used surrogate endpoints such as lean body mass and muscle performance measures, the TTrials included physical function outcomes that were deemed important to patients and public health. Importantly, the TTrials included men with unequivocally low testosterone concentrations. Through repeated monitoring of testosterone concentrations and masked dose adjustments, we were able to increase and maintain testosterone concentrations in the mid–normal range for healthy young men. Because both self-reported and performance-based measures of physical function have some strengths and some inherent limitations, the TTrials included both categories of outcomes to enable a more comprehensive assessment of physical function and mobility than had been done previously.

Implications of all the available evidence

Testosterone treatment of older men with mobility limitation and unequivocally low testosterone concentrations consistently improves self-reported mobility, but had only a modest effect on walking speed. These findings are important in the context of the substantial pharmaceutical investment in exploring the application of androgens as function-promoting therapies.

Introduction

The observation that testosterone administration increases skeletal muscle mass and maximal voluntary muscle strength[1–9] has led to considerable pharmaceutical interest in applying testosterone as an anabolic therapy to improve physical function and reduce the burden of disability in older men with mobility limitation. However, randomised trials of testosterone therapy have not shown consistent improvements in performance-based measures of physical function in older men with functional limitations.[1–16] These trials were limited by their small size and suboptimal statistical power; inclusion of healthy older men without functional limitations; heterogeneity of testosterone doses, on-treatment testosterone concentrations, and outcome ascertainment; and relatively short intervention durations (3–6 months). In 2004, a US Institute of Medicine panel concluded that there was insufficient evidence of a beneficial effect of testosterone replacement on physical function and mobility in older men with functional limitations.[16]

The Testosterone Trials (TTrials) were a set of seven coordinated placebo-controlled trials designed to identify the efficacy of testosterone in improving sexual function, physical function, vitality, and other outcomes in older men with unequivocally low testosterone concentrations and low libido, mobility limitation, low vitality, or a combination of these factors.[17–19] The main findings of the TTrials were reported in 2016.[19]

The Physical Function Trial (PFT) was one of the seven TTrials and was done in participants with a gait speed of less than 1·2 m/s in the 6 min walk test (6MWT) and mobility limitation, defined as self-reported difficulty in walking or climbing stairs. The aim of the trial was to assess the effect of testosterone on mobility

and self-reported physical function. In the primary TTrials analyses,[19] for men who were enrolled in the PFT, 6MWT distance did not improve by at least 50 m significantly more frequently in the testosterone group than in the placebo group (primary outcome). However, in prespecified analyses that included all men in the TTrials, a significant difference between treatment groups in the proportion of men with improved 6MWT distance was identified, showing a benefit in men treated with testosterone.[19] These findings led us to investigate the effects of testosterone in the TTrials participants who were not enrolled in the PFT, and to assess whether the baseline characteristics defining eligibility for the PFT were related to the treatment response.

Therefore, in the present analysis, we report changes in 6MWT distance and physical function component (PF10) of the Medical Outcomes Study Short Form-36 (MOS SF36) among TTrials participants not enrolled in the PFT, and compare these findings with PFT participants and the overall TTrials population. Additionally, we investigate the effect of testosterone on these outcomes in a post-hoc analysis of men enrolled in any of the TTrials whose baseline gait speed was less than 1·2 m/s versus those with baseline gait speed of 1·2 m/s or greater, and in men who reported mobility limitation versus those who did not. Furthermore, we report data for the effects of testosterone on falls and patient global impression-of-change (PGIC) among all TTrials participants.

Finally, because the anabolic effects of testosterone on skeletal muscle are related to testosterone dose and concentrations,[1,2] we also assessed in all TTrials participants whether the changes in 6MWT distance and PF10 were related to changes in total and free testosterone, dihydrotestosterone (DHT), or oestradiol concentrations, while also assessing other participant-level factors that might be associated with the effect of testosterone on these outcome.

Methods

Study design

The TTrials were a set of seven placebo-controlled, double-blind, parallel-group trials done at 12 academic sites in the USA. The study design and the main findings of the TTrials have been reported previously.[17–19] Briefly, participants had to meet eligibility requirements for one or more of the three main trials (covering sexual function, physical function, and vitality). If participants qualified for any of the three main trials, they could participate in one or more of the other trials.[18,19]

The study protocol for the TTrials was approved by the institutional review boards of the University of Pennsylvania and each of the 12 trial sites. All participants provided written informed consent. A data and safety monitoring board reviewed the progress of the study every 6 months until July 15, 2015, with additional quarterly safety reviews.

Participants

TTrials participants were community-dwelling men, aged 65 years or older, with an average of two morning fasting testosterone concentrations below 9·5 nmol/L (275 ng/dL; specifically, <9·5 nmol/L [275 ng/dL] at first screening visit, <10·4 nmol/L [<300 ng/dL] at second screening visit, and <9·5 nmol/L [275 ng/dL] on average), measured by liquid chromatography tandem mass spectrometry (LC-MS/MS) at the Quest Diagnostics Laboratory (San Juan Capistrano, CA, USA). To qualify for the PFT, participants had to have mobility limitation, defined by self-reported difficulty walking 0·25 miles or walking up one flight of stairs, and a 6MWT speed of less than 1·2 m/s.[17] Walking speeds of less than 1·2 m/s have been associated with increased mortality.[20] Our expectation was that men who walked more slowly and perceived mobility problems would be more likely to benefit from testosterone treatment than men with better physical function.

The TTrials exclusion criteria have been described previously;[17] in summary, participants were excluded if they had conditions that could potentially be worsened by testosterone treatment or would preclude assessment of primary or secondary outcomes.

Allocation and masking

All TTrials participants were assigned by means of a minimisation technique to receive testosterone or placebo gel for 1 year.[21] The balancing factors included in the minimisation procedure were participation in the three main trials, trial site, screening testosterone less than or greater than 200 ng/dL, aged up to and including 75 years or older than 75 years, antidepressant use, and phosphodiesterase-5 inhibitor use. An automated computer algorithm assigned the treatment providing optimal balance on the above factors with 80% probability to maintain some randomness to the assignment.

The participants and the study staff were unaware of the intervention allocation, which was known only to the data coordinating centre and the central pharmacy. The testosterone and placebo preparations were similar in look, smell, and feel, and the packaging was identical. When the testosterone dose was adjusted in a participant in the testosterone group, a participant in the placebo group who had made a clinic visit contemporaneously with the participant whose testosterone dose needed to be changed was also asked to change his dose to maintain masking.

Procedures

All TTrials participants initially applied either 5 g of 1% testosterone gel (AndroGel 1%; AbbVie Pharmaceuticals, North Chicago, IL, USA) containing 50 mg testosterone or an equivalent amount of placebo gel daily on the skin. Serum testosterone concentration was measured at months 1, 2, 3, 6, and 9, and dose was adjusted after each

measurement, as necessary, to maintain a testosterone concentration between 500 and 800 ng/dL.[17–19]

At the completion of the trial, serum testosterone, DHT, and oestradiol concentrations were measured using LC-MS/MS and free testosterone was measured using equilibrium dialysis in the Brigham Research Assay Core Laboratory (Boston, MA, USA), as previously described.[19] Hemoglobin was measured as a part of the complete blood count on an automated analyser at Quest Diagnostics Laboratory. All other methods have been described previously.[19]

Outcomes

The primary outcome of the PFT was the proportion of men whose 6MWT distance increased by at least 50 m from baseline. 6MWT distance is a widely used measure of mobility and was selected as the primary outcome because walking is essential for most activities of daily living, walking speed and distance predict clinical outcomes including disability and mortality,[22–24] and estimates of the minimum clinically important difference (MCID; 50 m) were available.[25–27] 6MWT distance was measured at baseline and at months 3, 6, 9, and 12. Secondary outcomes included change in 6MWT distance as a continuous variable and change self-reported physical function, assessed using the PF10 of the MOS SF36.[28] PF10 was selected as the self-reported measure of mobility because this instrument includes several questions about difficulty in walking short and long distances (MCID 8 points). In this analysis, we report 6MWT distance and PF10 score as continuous variables for the whole TTrials population according to baseline walking speed and self-reported mobility limitation, and according to participation or non-participation in the PFT. Because the PF10 was not administered to all participants at baseline, but all participants did complete the SF36 (which includes the PF10) at baseline, in the current analyses we have augmented the PF10 data in previously reported analyses[19] with the score on the PF10 subset of the SF36 for participants who were not administered the PF10 separately at baseline.

Here we also report data for the prespecified exploratory endpoints of falls and PGIC in all participants in the TTrials. Falls were ascertained every 3 months using a structured questionnaire that asked participants whether they had encountered a fall in the interval period, and if so, whether they had sought medical attention, and whether they had sustained a fracture. The PGIC was ascertained every 3 months using a standardised question that asked if the participants felt their walking ability had improved since the beginning of the intervention using a Likert scale of 1–7 (ranging from "very much worse" to "very much better").

Because the anabolic effects of testosterone on skeletal muscle are related to increase in testosterone concentrations,[12] we also assessed the relation of changes in hormone concentrations (total and free cholesterol, DHT, and oestradiol) with the changes in 6MWT distance and PF10 in all men participating in the TTrials. We also assessed the effect of changes in haemoglobin on changes in 6MWT distance.

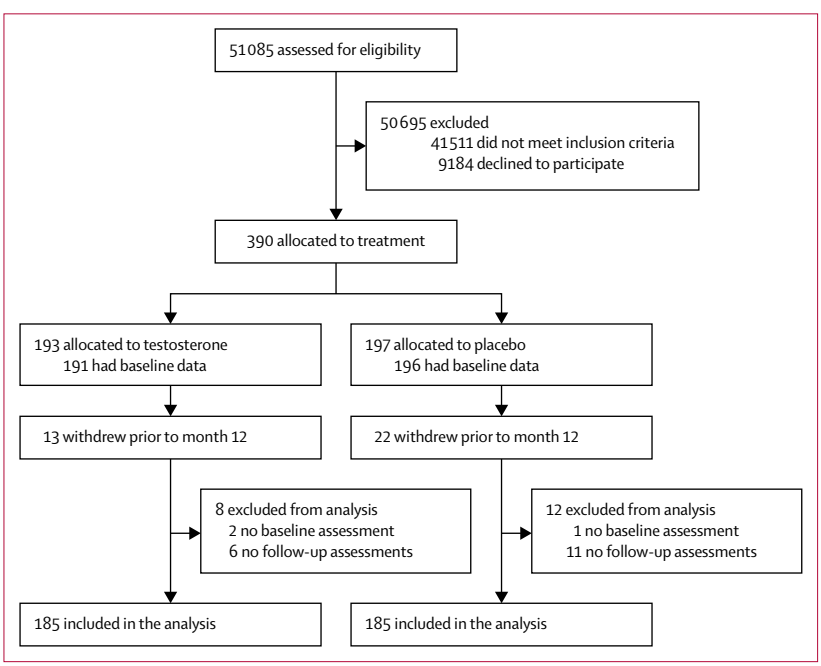

Figure 1: **Trial profile (Physical Function Trial)**

Statistical analysis

The sample size estimate for the PFT was based on the MCID of 50 m, the assumption that 15% of men in the placebo group would increase their walk distance by at least this amount, and the goal of detecting a difference if at least 30% of men in the testosterone group showed such an increase, with 90% power using a two-sided significance level of 0·05 and a repeated measures analysis including all post-baseline assessments. We inflated the sample size by 5% to compensate for the small number of men expected to have no post-baseline values. The sample size target was 175 per treatment group.

In the main analyses of the PFT, we used random-effects models for longitudinal data, which included visit time as a categorical variable and a single main effect for treatment, and included balancing factors and baseline value of the 6MWT distance as fixed-effect covariates. For linear models of continuous outcomes, the treatment effect denoted the average difference in response by treatment group across all visits. For logistic models of binary outcomes, the treatment effect was the log odds ratio of a positive versus negative outcome for testosterone versus placebo participants, averaged over all visits. The association of PGIC with treatment was assessed in a random-effects proportional odds model, adjusted for balancing factors. The extreme responses at each end of the 7-point scale were collapsed after viewing

the results to make a 5-point rather than a 7-point scale to facilitate modelling, since few responses indicated the extreme categories.

We completed hormone analyses (total and free cholesterol, DHT, and oestradiol) using marginal models with parameters estimated using generalised estimating equations (GEEs), including balancing variables and change from baseline of hormone concentrations at each measured timepoint as time-varying covariates and baseline concentration of the hormones and the 6MWT distance. In these models, effects denote the average change in outcome associated with a unit change in hormone concentration. We analysed haemoglobin accounting for change in testosterone concentration, using GEE regression with change in haemoglobin and change in testosterone as time-varying covariates. The association of PGIC with other outcomes was assessed in a mixed-effects model for longitudinal data, considering PGIC as a time-varying covariate and including treatment group, balancing factors for minimisation, and baseline value of the outcome in the model. Tests for treatment interaction with other covariates were performed by adding a term for the interaction to the model.

We investigated whether the baseline characteristics defining eligibility for the PFT were related to the treatment response. Accordingly, we compared the changes in 6MWT distance and PF10 in all men in the TTrials whose baseline gait speed was less than 1·2 m/s versus those with baseline gait speed of at least 1·2 m/s, and in men who reported mobility limitation versus those who did not.

We analysed all participants assigned to treatment with any follow-up data irrespective of their compliance in a prespecified modified intention-to-treat sample, which included all participants assigned to treatment with a baseline assessment and any follow-up data in the group to which they were allocated. We did not adjust the analyses for multiple comparisons as we anticipated that these outcomes would be highly correlated with each other. All analyses were done with SAS version 9.4.

The TTrials are registered with ClinicalTrials.gov, number NCT00799617.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author (SB) and the chief biostatistician (SSE) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Recruitment for the TTrials began on April 28, 2011, and the last participant completed treatment on June 16, 2014. As reported previously,[19] of the 790 men who were enrolled in the TTrials (395 allocated to each treatment group), 390 (49%) were enrolled in the PFT; of those in the PFT, 193 were allocated to the testosterone group and 197 to the placebo group. 35 PFT participants withdrew before month 12, 13 in the testosterone group and 22 in the placebo group (figure 1). The modified intention-to-treat sample included all men who were enrolled and had at least one post-baseline assessment.

The two intervention groups were similar in baseline characteristics between men in the placebo and testosterone groups in the PFT and in all TTrials (table 1). When men were categorised by baseline gait speed (<1·2 m/s or ≥1·2 m/s) or self-reported mobility limitation, the men allocated to placebo and testosterone

	TTrial participants in the Physical Function Trial		TTrial participants not in the Physical Function Trial	
	Placebo (n=197)	Testosterone (n=193)	Placebo (n=197)	Testosterone (n=201)
Demographics				
Age, years	73·2 (5·9)	73·4 (6·4)	71·4 (5·4)	70·8 (4·6)
Race				
White	168 (85%)	172 (89%)	182 (92%)	176 (88%)
African-American	13 (7%)	10 (5%)	7 (4%)	11 (6%)
Other	16 (8%)	11 (6%)	8 (4%)	14 (7%)
Ethnic origin				
Hispanic	8 (4%)	8 (4%)	2 (1%)	10 (5%)
Non-Hispanic	189 (96%)	184 (95%)	195 (99%)	191 (95%)
Concomitant conditions				
BMI, kg/m^2	31·7 (3·4)	31·5 (3·5)	30·3 (3·6)	30·5 (3·6)
Participant with BMI of more than 30 kg/m^2	135 (69%)	135 (70%)	110 (56%)	116 (58%)
Alcohol use, number of drinks per week	3·5 (5·3)	2·9 (4·1)	3·4 (4·8)	3·1 (4·4)
Smoking				
Current smoker	20 (10%)	19 (10%)	14 (7%)	11 (5%)
Ever smoker	136 (69%)	133 (69%)	132 (67%)	123 (61%)
Diabetes	85 (43%)	81 (42%)	59 (30%)	67 (33%)
Hypertension	145 (74%)	143 (74%)	134 (68%)	143 (71%)
History of myocardial infarction	35 (18%)	28 (15%)	28 (14%)	25 (12%)
History of stroke	11 (6%)	11 (6%)	6 (3%)	5 (2%)
Sleep apnoea	34 (17%)	43 (22%)	42 (21%)	34 (17%)
Sex hormones				
Testosterone, ng/dL	233·4 (64·0)	230·5 (64·3)	238·8 (69·3)	233·0 (62·1)
Free testosterone, pg/mL	63·9 (23·0)	60·5 (21·9)	66·0 (23·8)	63·4 (21·0)
Dihydrotestosterone, ng/dL	20·9 (14·0)	21·6 (12·8)	20·8 (11·9)	20·9 (10·3)
Oestradiol, pg/mL	21·4 (6·5)	20·2 (6·6)	19·5 (6·1)	20·3 (6·8)
Sex hormone binding globulin, nmol/L	29·3 (14·0)	32·3 (16·1)	29·8 (15·5)	30·4 (14·3)
Physical performance				
Gait speed, m/s	1·0 (0·2)	1·0 (0·2)	1·2 (0·2)	1·2 (0·2)
PF10	64·8 (21·3)	65·4 (20·0)	76·9 (18·9)	79·8 (17·4)

Data are mean (SD) or n (%). The PF10 was administered as a separate questionnaire for men in the Physical Function Trial. For men with a missing PF10 score at baseline from the separate questionnaire, the PF10 score taken from the MOS SF36 was used. PF10=physical component domain of the Medical Outcomes Study Short Form-36 (MOS SF36) questionnaire.

Table 1: **Baseline characteristics of TTrial participants included in or not included in the Physical Function Trial**

See Online for appendix

groups were similar in their baseline characteristics (appendix). The men enrolled in the PFT were on average older, had higher BMI, were more likely to have comorbid conditions, and, as expected, had slower gait speed and lower PF10 score than TTrials participants not enrolled in the PFT. Among TTrials participants not enrolled in the PFT, 199 men had baseline gait speed of less than 1·2 m/s (108 in the testosterone group *vs* 91 in the placebo group) and 100 men reported mobility limitation (44 testosterone *vs* 56 placebo; appendix).

Adherence to assigned treatment in men enrolled in the PFT, assessed by weighing the returned bottles and comparing with the expected weight based on the prescribed dose, was high in both the testosterone (mean 97·4%, SD 21·8) and placebo (mean 92·4%, SD 17·4) groups, with fewer than 5% of men with compliance less than 60% and less than 5% with compliance greater than 135% (ie, taking more than the prescribed testosterone dose). As reported previously,[19] the rates of prostate, cardiovascular, and serious adverse events did not differ significantly between groups in all participants in the TTrials.[19]

In men enrolled in the PFT, serum total testosterone concentrations increased from a mean of 8·0 nmol/L (SD 2·2; 230·5 ng/dL, SD 64·3) at baseline to a mean of 17·9 nmol/L (SD 8·8; 516·4 ng/dL, SD 253·6) at 12 months in the testosterone group, but remained unchanged in the placebo group (mean 8·1 nmol/L [SD 2·2; 233·4 ng/mL, SD 64·0] at baseline *vs* 8·0 nmol/L [SD 2·3; 230·3 ng/mL, SD 67·1]). Serum free testosterone, DHT, and oestradiol concentrations also increased in the testosterone group, but did not change in the placebo group (data not shown).

As reported previously,[19] neither the proportion of men increasing their 6MWT distance by more than 50 m (treatment effect 1·42, 95% CI 0·83 to 2·45; p=0·0200), nor the absolute change from baseline in 6MWT distance (treatment effect 4·15 m, 95% CI –2·95 to 11·24; p=0·25) differed significantly between the two intervention groups among men enrolled in the PFT. When data for all TTrials participants were analysed,[19] the proportion of men increasing their 6MWT distance by at least 50 m (treatment effect 1·77, 95% CI 1·21 to 2·58; p=0·0030) and the absolute change in 6MWT distance (treatment

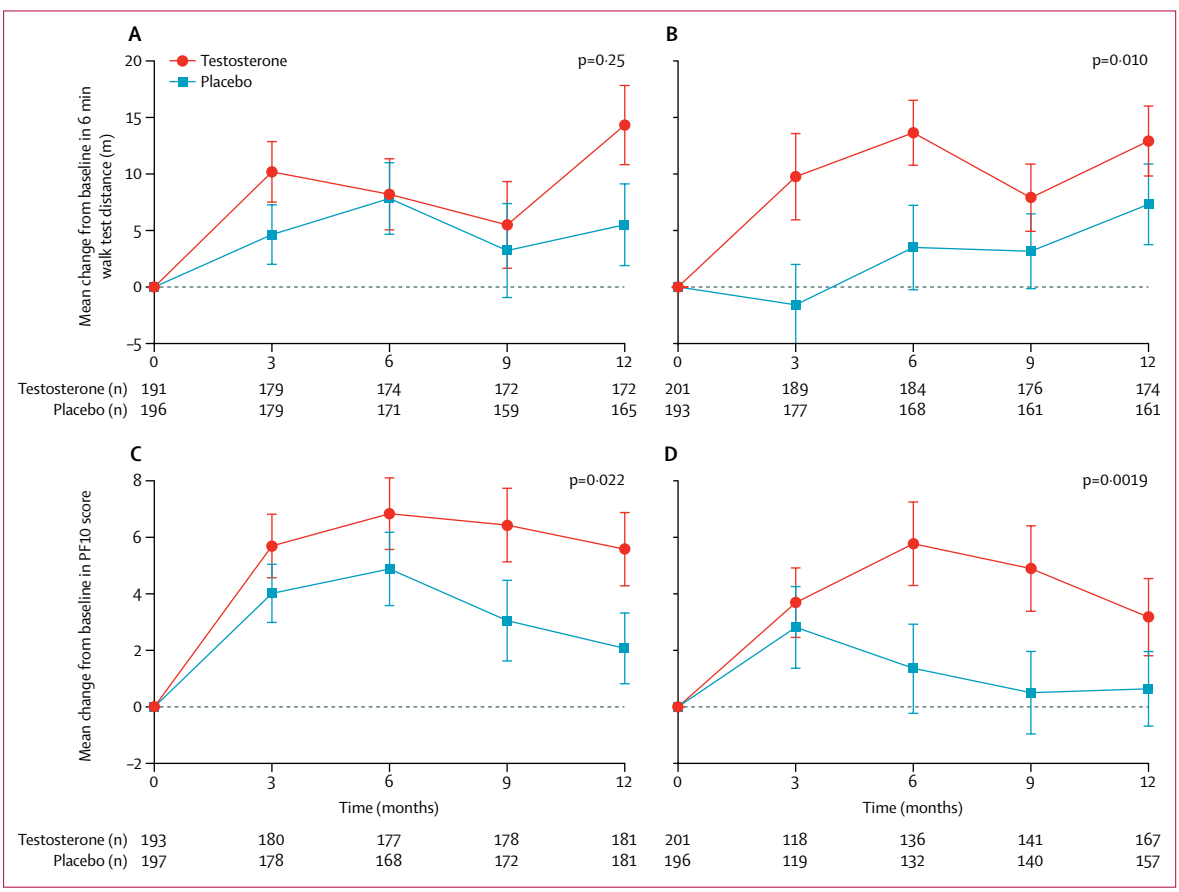

Figure 2: **Change in 6 min walk test distance and PF10 score, by treatment group, stratified by Physical Function Trial enrolment**
Data are means and error bars are 95% CIs. Change in 6 min walk test distance in participants enrolled in the Physical Function Trial (A) and those not enrolled in the Physical Function Trial (B). Change in PF10 in participants enrolled in the Physical Function Trial (C) and those not enrolled in the Physical Function Trial (D). The PF10 was administered as a separate questionnaire for men in the Physical Function Trial. For men with a missing PF10 score at baseline from the separate questionnaire, the PF10 score taken from the MOS SF36 was used. PF10=physical component domain of the Medical Outcomes Study Short Form-36 (MOS SF36) questionnaire.

effect 6·69 m, 1·80 to 11·57; p=0·0074) improved more in testosterone-treated men than in placebo-treated men. Among men not enrolled in the PFT, the proportion of men increasing their 6MWT distance by at least 50 m (treatment effect 2·22, 95% CI 1·26 to 3·91; p=0·0062) and the absolute change in 6MWT distance (treatment effect 8·9 m, 2·2 to 15·6; p=0·010) improved more in testosterone-treated men than in placebo-treated men (figure 2A and B). However, a test for statistical interaction between treatment and enrolment in the PFT with respect to the absolute change in walk distance did not show a significant effect (p=0·33).

Because enrolment in the PFT required men to have baseline 6MWT speed of less than 1·2 m/s plus self-reported mobility difficulty, we assessed whether the treatment response differed depending on baseline 6MWT speed or mobility limitation in all TTrials participants. We also did tests of interaction of treatment with baseline 6MWT speed. Of all men enrolled in the TTrials, those treated with testosterone whose baseline 6MWT speed was at least 1·2 m/s improved their 6MWT distance significantly more than men treated with placebo (treatment effect 14·2 m, 95% CI 6·5–21·9, p=0·0004; figure 3A), whereas men with baseline 6MWT speed of less than 1·2 m/s showed no significant benefit of testosterone (treatment effect 3·5 m, –2·6 to 9·7, p=0·26; figure 3B). The interaction between treatment group and baseline 6MWT speed was significant (p=0·021). Testosterone treatment had a significant effect on 6MWT distance in men with self-reported mobility limitation at baseline (treatment effect 7·6 m, 1·0–14·1, p=0·024; figure 4B), but the effect was not significant in men who did not report mobility limitation (treatment effect 5·9 m, –1·2 to 13·1, p=0·10; figure 4A). The interaction between treatment group and baseline self-reported mobility limitation was not significant (p=0·77).

Of the baseline factors (age, BMI, 6MWT distance, PF10 scores, and testosterone concentrations) that were included as covariates in the primary analysis of men enrolled in the PFT, age, baseline 6MWT distance, and baseline PF10 scores were significantly associated with the change in 6MWT distance; BMI, baseline testosterone

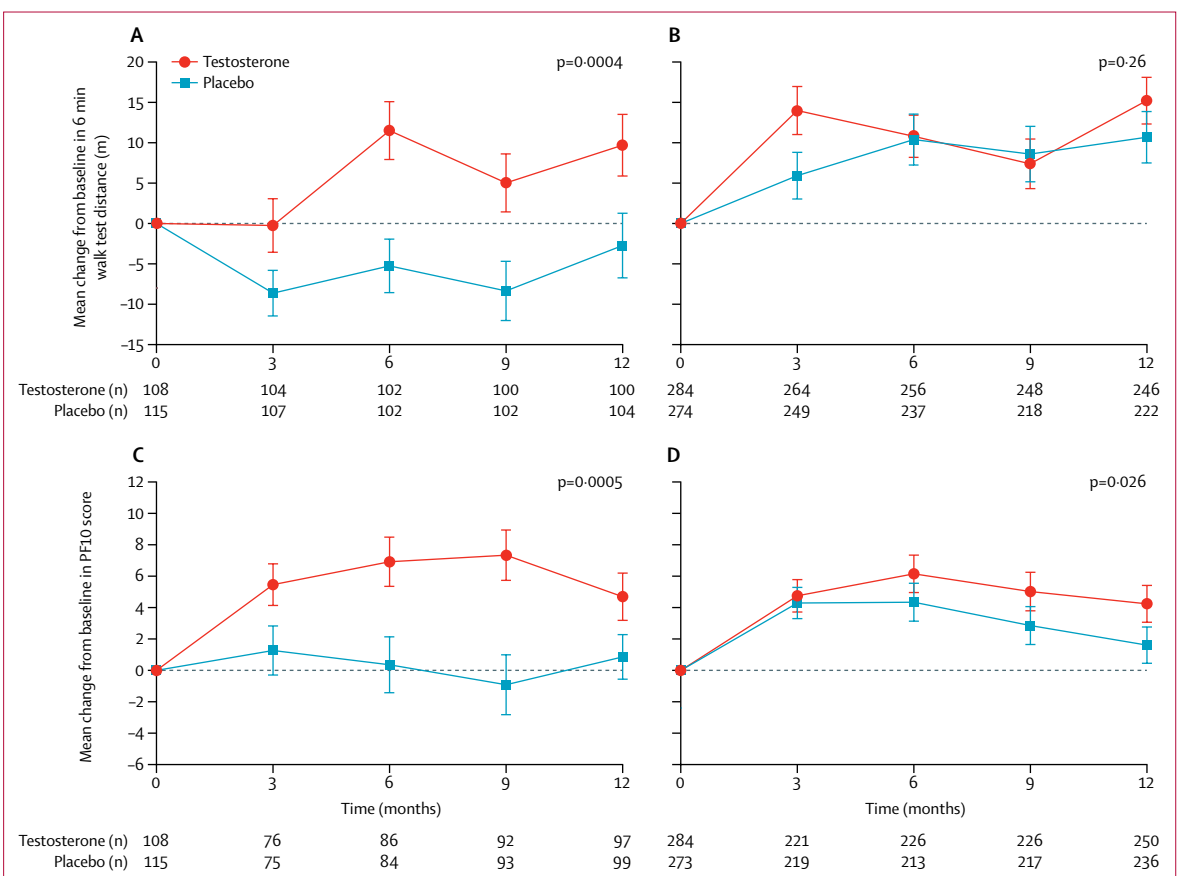

Figure 3: **Change in 6 min walk test distance and PF10 score in TTrials participants, by treatment group, stratified by baseline gait speed**
Data are means and error bars are 95% CIs. Change in 6 min walk test distance in TTrials participants with a baseline gait speed of at least 1·2 m/s (A) and those with a baseline gait speed of less than 1·2 m/s (B). Change in PF10 score in participants with baseline gait speed of at least 1·2 m/s (C) and those with baseline gait speed of less than 1·2 m/s (D). The PF10 was administered as a separate questionnaire for men in the Physical Function Trial. For men with a missing PF10 score at baseline from the separate questionnaire, the PF10 score taken from the MOS SF36 was used. PF10=physical component domain of the Medical Outcomes Study Short Form-36 (MOS SF36) questionnaire.

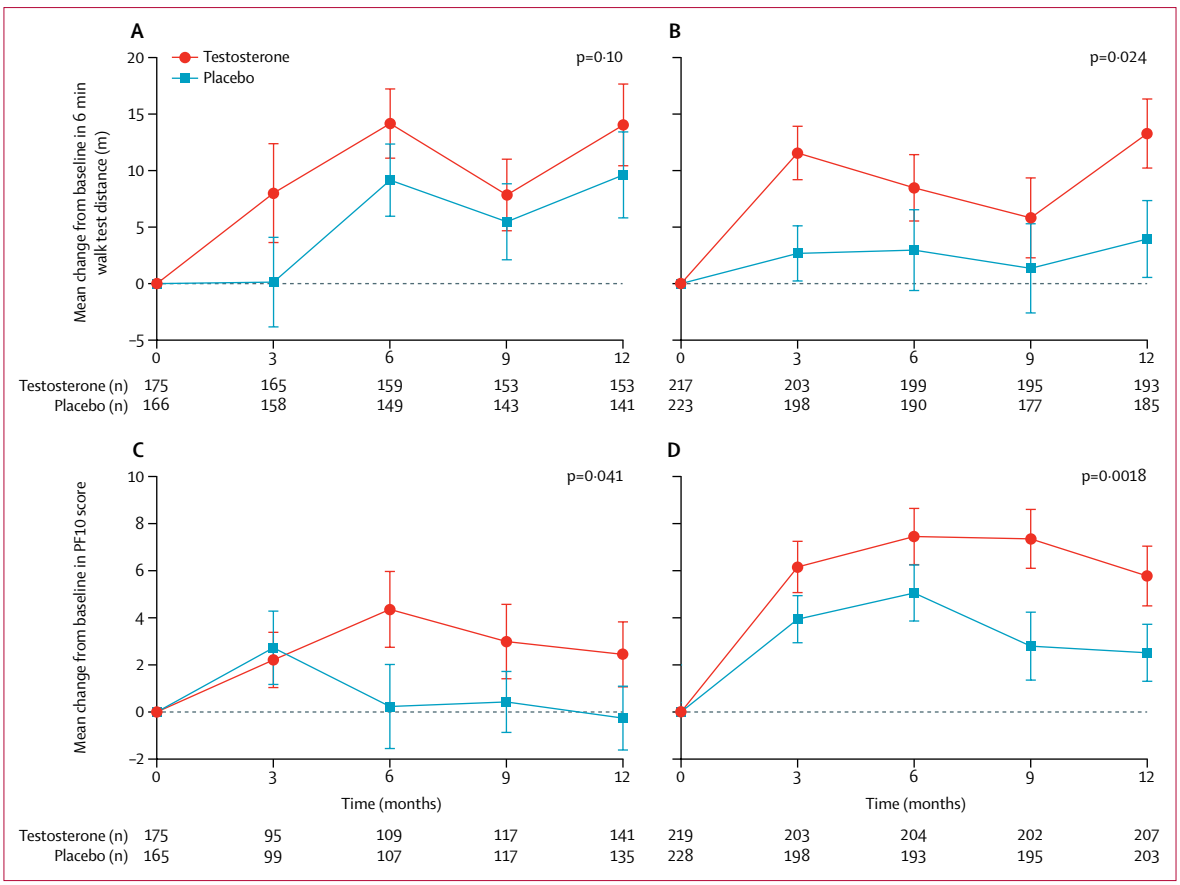

Figure 4: **Change in 6 min walk test distance and PF10 score in TTrials participants, by treatment group, stratified by mobility limitation at baseline**
Data are means and error bars are 95% CIs. Change in 6 min walk test distance in TTrials participants who did not have mobility limitation at baseline (A) and those who had mobility limitation at baseline (B). Change in PF10 score in participants who did not have mobility limitation at baseline (C) and those who had mobility limitation at baseline (D). The PF10 was administered as a separate questionnaire for men in the Physical Function Trial. For men with a missing PF10 score at baseline from the separate questionnaire, the PF10 score taken from the MOS SF36 was used. PF10=physical component domain of the Medical Outcomes Study Short Form-36 (MOS SF36) questionnaire.

concentrations, and the use of antidepressants were not associated with change from baseline in these outcomes (appendix).

The changes in total and free testosterone and DHT concentrations, but not oestradiol concentrations, were significantly associated with changes in 6MWT distance in the overall TTrials population (effect size for 3·5 nmol/L [100 ng/dL] change in total testosterone: resulted in a 1·0 m change in 6MWT distance, 95% CI 0·4–1·8, p=0·0023; for 69·3 pmol/L [20 pg/mL] change in free testosterone: 0·22 m in 6MWT distance, 0·11–0·37, p=0·0099; for 0·34 nmol/L [10 ng/dL] change in DHT: 0·52 m in 6MWT distance, 0·14–0·9, p=0·0090). The changes in hormone concentrations were not significantly associated with changes in PF10 (data not shown).

The change in haemoglobin concentration was significantly associated with the change in 6MWT distance, even after accounting for the effect of change in total testosterone (effect size 3·8, 95% CI 1·7–6·0, p=0·0009). For each 1·0 g/dL increase in haemoglobin concentration, 6MWT distance improved by an average of 3·8 m. The change in haemoglobin was not significantly associated with change in PF10 (effect size 0·41, –0·51 to 1·3, p=0·38).

As in our previous report,[19] which described an analysis of a somewhat smaller set of PF10 values, self-reported mobility assessed by PF10 improved significantly more in the testosterone group than in the placebo group, both in men enrolled in the PFT (treatment effect 2·8, 95% CI 0·41 to 5·2; p=0·022; figure 2C), and in those who were not enrolled in the PFT (4·0, 1·5 to 6·5; p=0·0019; figure 2D), as well as in all TTrials participants (effect size 3·42, 1·66 to 5·18; p=0·0001). In the analysis of this expanded set of PF10 data used for the present report, the proportion of men with an improvement of 8 or higher in the PF10 score was not significantly higher in testosterone-treated men than in placebo-treated men among participants enrolled in the PFT (treatment effect 1·40, 95% CI 0·95 to 2·06; p=0·089). However, for men not enrolled in the PFT (treatment effect 1·77, 1·06 to 2·95; p=0·028), as well as for all TTrials participants

(treatment effect 1·56, 1·16 to 2·10; p=0·0036), a significantly higher proportion of men treated with testosterone did show this level of improvement. The time-by-treatment interaction was not significant; thus the apparent fluctuations in PF10 scores over time might have been a chance finding. The change in PF10 from baseline in men treated with testosterone was not significantly related to the change in total and free testosterone, DHT, or oestradiol concentrations (data not shown).

PF10 scores improved significantly more in men treated with testosterone than in those treated with placebo, both among men whose baseline 6MWT speed was at least 1·2 m/s (treatment effect 4·9, 95% CI 2·2–7·7, p=0·0005; figure 3C) and in those with a baseline 6MWT speed of less than 1·2 m/s (treatment effect 2·5, 0·29–4·6, p=0·026; figure 3D). Of all participants in the TTrials who reported mobility limitation at baseline, those treated with testosterone improved significantly more than men treated with placebo (treatment effect 3·6, 1·3–5·9, p=0·0018; figure 4D). Testosterone treatment also significantly improved PF10 scores in men who did not report mobility limitation at baseline (treatment effect 2·7, 0·11–5·3, p=0·041; figure 4C), but to a lesser extent.

We asked participants at each visit whether they perceived any changes in their walking ability since the start of the trial using a 7-point scale that was collapsed to a 5-point scale ranging from "very much worse" to "very much better" (PGIC). Men in the testosterone group were significantly more likely to perceive improvement in their walking ability than men in the placebo group, both for men enrolled in the PFT (effect size 2·21, 95% CI 1·35–3·63, p=0·0018) and those not enrolled in the PFT (3·01, 1·61–5·63, p=0·0006). The PGIC in walking ability was positively associated with changes in 6MWT distance as well as in PF10 score (appendix; joint test of no association with for any of the PGIC categories with a change of outcome p<0·0001).

Across all TTrials participants, the number of men with one or more falls (103 in each group), the number of men who reported seeking medical attention for fall-related injury (25 in the testosterone group *vs* 26 in the placebo group), and the number of men with one or more fractures (six in each group) was nearly identical between intervention groups during the intervention period (table 2). The proportion of participants who reported at least one fall in the second year (post-intervention) was also similar in the testosterone group (13%) versus the placebo group (10%).

	Testosterone	Placebo
Year 1*	n=380	n=380
No falls recorded	277 (73%)	277 (73%)
At least one fall recorded	103 (27%)	103 (27%)
Number of falls recorded		
One	73 (19%)	58 (15%)
More than one	30 (8%)	45 (12%)
Sum of all falls	184	202
Number of men seeking medical attention for fall-related injury	25 (7%)	26 (7%)
Number of men with one or more fractures	6 (2%)	6 (2%)
Year 2†	n=351	n=337
No falls recorded	273 (78%)	279 (83%)
At least one fall recorded	78 (22%)	58 (17%)
Number of falls recorded		
One	46 (13%)	34 (10%)
More than one	32 (9%)	24 (7%)
Sum of all falls	161	112

Data are n or n (%) and are for all participants for whom a falls follow-up form was completed. *Intervention period. †Post-intervention period.

Table 2: **Reported falls among all TTrial participants, by treatment group and year**

Discussion

In this analysis of physical function in TTrials participants, testosterone consistently improved self-reported measures of physical function in older men with mobility limitation. Testosterone also seemed to improve 6MWT distance, but the treatment effect was modest and seemed to be related to baseline gait speed, self-reported mobility limitation, and changes in testosterone and haemoglobin concentrations. Testosterone did not reduce fall frequency. Taken together, these findings suggest a small benefit of testosterone on mobility in older men with low testosterone concentrations. The improvement in self-reported mobility and function, measured by the PF10 and the PGIC, was observed in all men treated with testosterone, irrespective of baseline walk speed, although the specific effect on 6MWT distance was greater in men with higher gait speed.

The PFT is one of the largest trials to investigate the effects of testosterone on physical function and had several attributes of good trial design: concealed participant allocation and masked intervention; inclusion of a placebo control; and patient allocation using minimisation balanced on several baseline factors. The TTrials are among the largest trials of testosterone therapy to be completed to date, and the study population consisted of older men with unequivocally low testosterone concentrations, as measured by use of a LC-MS/MS assay certified by the Hormone Standardization Program for Testosterone of the US Centers for Disease Control and Prevention.[19] Unlike many previous trials, which enrolled healthy older men without functional limitations, the PFT enrolled men who not only had self-reported mobility limitation, but also had slow gait speed assessed objectively by the 6MWT. Because patient-reported outcomes as well as laboratory-based physical performance measures each have inherent limitations, the trial included patient-reported outcomes (PF10) as well as performance-based (6MWT speed) measures of mobility; the combined

application of both patient-reported and performance-based measures of mobility provided a more comprehensive assessment of function than either type of measure alone. Additionally, we included a PGIC outcome to corroborate whether the patients perceived their walking speed to have improved.

The study also had some limitations. The 6MWT speed continued to improve throughout the intervention duration and we do not know whether a longer duration of intervention might have enabled the neuromuscular adaptations needed to translate testosterone-induced muscle mass and strength gains into clinically meaningful functional improvements. We did multiple comparisons without statistical adjustment and some of our findings might be due to chance alone. We assumed the MCID in 6MWT distance to be 50 m, on the basis of information from available epidemiological studies at the time the trial was designed.[25–27] It is possible that in the participants enrolled in the PFT trial, the MCID for 6MWT distance might be lower than this estimate, as suggested by the fact that a greater proportion of men in the testosterone group perceived their walking ability to have improved even though the mean change in 6MWT distance was substantially smaller than 50 m.

Contrary to our expectations, the 6MWT distance improved significantly more with testosterone than with placebo treatment in men who were not enrolled in the PFT (nearly half of whom had a baseline gait speed below 1·2 m/s), but the difference was not significant for those who were enrolled in PFT. We had anticipated that men with clear mobility limitations, both on objective measures and defined by self-report, would be more likely to show benefits of testosterone treatment on measures of physical function. Our analyses show that men with higher baseline gait speed (probably reflecting better physical function at baseline) had significantly greater improvements in their gait speed and PF10 scores with testosterone. The significant interaction between baseline gait speed and treatment group suggests that the effect of baseline gait speed on response to testosterone is likely to be real. It is possible that men with better baseline physical function, compared with those with poor function at baseline, might engage in a higher level of physical activity or might have greater gains in muscle mass, which subsequently contribute to a greater treatment effect; however, physical activity and muscle mass were not measured, which is another limitation of the study.

The men with self-reported mobility limitation showed significant effects of testosterone administration on walking speed and PF10, whereas those who did not report mobility limitation did not show such effects; a test of interaction, however, did not confirm an effect of self-reported mobility limitation on response to testosterone treatment. The PGIC scores indicated a significantly positive effect of testosterone on participant perception of improvement in walking ability overall and separately in men enrolled and not enrolled in the PFT.

The change in haemoglobin was significantly associated with change in 6MWT distance. Some of the improvements in this outcome could be due to the testosterone-induced increase in haemoglobin, but additional direct effects of testosterone on the muscle mitochondrial function, bioenergetics, and aerobic performance could also contribute to the improvement in 6MWT distance.

Although lean body mass and muscle strength were not measured in the trial, testosterone administration has been shown consistently in numerous trials to increase skeletal muscle mass and maximal voluntary strength.[1–11,15,16] Therefore, testosterone would be expected to improve those measures of physical function and mobility that are dependent on lower-extremity strength. The overall treatment effect on 6MWT distance was small, but not dissimilar from that of a physical activity intervention in older adults with mobility limitation.[29] It is possible that the 6MWT, which is more a measure of endurance than of lower-extremity strength, might be less responsive to testosterone than other measures of mobility such as the stair climbing power, which is more strongly associated with lower-extremity strength. Indeed, some trials have shown improvements in stair climbing power and chair stand with testosterone administration.[8,14] Additionally, we aimed to increase testosterone concentrations into the mid-range for healthy men in all the TTrials; it is possible that higher on-treatment testosterone concentrations could result in greater gains in 6MWT distance.

The number of men reporting falls or seeking medical attention for fall-related injuries during the year on treatment was similar in each treatment group. Falls were recorded by self-report and were not adjudicated or ascertained by structured interview; furthermore, serious fall injuries were not ascertained or adjudicated. Although it seems unlikely that testosterone treatment has any substantial effect on falls, further studies using more rigorous ascertainment methods would be needed to identify whether testosterone might have a modest effect on falls.

In summary, testosterone administration in older men with mobility limitation consistently improved self-reported measures of physical function and modestly improved mobility, but did not affect fall frequency. The treatment effect on mobility measures was small and seemed to be related to baseline gait speed and self-reported mobility limitation. These effects might not, by themselves, justify use of testosterone therapy in older men with low testosterone concentrations. Thus, testosterone therapy should probably not be started specifically to improve physical function, although men who are treated with testosterone for other reasons could have some improvement in physical function. It is possible that functional exercise training might augment

the translation of testosterone-induced muscle mass and strength gains into functional improvements, as exercise training has been reported to augment the anabolic effects of testosterone.[30] Further studies of longer duration are needed to identify the clinical meaningfulness of the effects of testosterone on physical function, including use of patient-important outcomes that are more closely aligned with testosterone-induced gains in muscle mass and strength, such as stair climbing speed and chair stand.

Contributors

SBh, SSE, SBa, MP, JAC, KEE, JTF, DCe, AMM, TWS, MEM, GRC, EB-C, PJS, and TMG designed the study. SBh, SSE, TWS, SBa, MP, JAC, KEE, AMM, MEM, GRC, RSS, CW, CEL, EB-C, JPC, DCi, PJS, and TMG implemented the study. SSE, AJS-S, XH, and PP analysed the data. SBh and SSE generated the first draft of the report. All authors reviewed the draft report and provided critical input to the submitted version.

Declaration of interests

SBh reports receiving consulting fees from AbbVie, Novartis, and Regeneron, and grant support from AbbVie, Metro International Biology LLC, Alivegen, Abbott, Novartis, Regeneron, and Transition Therapeutics; he also reports holding pending patent related to an algorithm for free testosterone determination. TMG reports receiving consulting fees from Novartis. PJS reports receiving consulting fees and grant support from AbbVie. GRC reports receiving fees for serving as an adviser to AbbVie, Apricus Biosciences, Clarus Therapeutics, Endo Pharmaceuticals, Ferring Pharmaceuticals, Eli Lilly, Purdue Pharma, and Repros Therapeutics, and grant support from Ardana. AMM reports receiving consulting fees from AbbVie, Aytu, and Eli Lilly, study medication from AbbVie, and grant support from GlaxoSmithKline. RSS reports receiving consulting fees from Clarus Therapeutics, Novartis, and TesoRx, and grant support from Clarus Therapeutics, Eli Lilly, Novartis, and Antares Pharma. CW reports receiving fees for serving on an advisory board from TesoRx and grant support from Clarus Therapeutics, Lipocine, and Antares Pharma. KEE reports receiving fees for serving on a data and safety monitoring board from Merck Sharp & Dohme. JTF reports receiving fees for serving on a data and safety monitoring board from Cara Therapeutics, consulting fees from Analgesic Solutions, Aptynx, Biogen, the Campbell Consortium, Daiichi-Sankyo, Depomed, Evadera, Janssen, Mallinckrodt, Novartis, Pfizer, and Wolter Kluwer Health, and grant support from Pfizer. DCe reports receiving consulting fees from Pfizer and is the president of FACIT.org. MEM reports receiving consulting fees from AbbVie, Eli Lilly, and Pfizer. SBa reports receiving consulting fees from Eli Lilly and grant support from AbbVie. SSE reports receiving grant support from AbbVie. All other authors declare no competing interests.

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