Published in final edited form as:
Contemp Clin Trials. 2009 March ; 30(2): 133–140. doi:10.1016/j.cct.2008.10.005.

Effects of Testosterone Therapy on Muscle Performance and Physical Function in Older Men with Mobility Limitations (The TOM Trial): Design and Methods

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Abstract

The TOM study is the first, single-site, placebo-controlled, randomized clinical trial designed to comprehensively determine the effects of testosterone administration on muscle strength and physical function in older men with mobility limitations. A total of 252 community dwelling individuals aged 65 and older with low testosterone levels and self-reported limitations in mobility and short physical performance battery (SPPB) score between 4 and 9 will be randomized to receive either placebo or testosterone therapy for 6 months. The primary objective is to determine whether testosterone therapy improves maximal voluntary muscle strength as quantified by the one repetition maximum. Secondary outcomes will include measures of physical function (walking, stair climbing and a lifting and lowering task), habitual physical activity and self-reported disability. The effects of testosterone on affect, fatigue and sense of well being will also be assessed. Unique aspects of the TOM Trial include selection of men with self-reported as well as objectively demonstrable functional limitations, community-based screening and recruitment, adjustment of testosterone dose to ensure serum testosterone levels in the target range while maintaining blinding, and inclusion of a range of self-reported and performance-based physical function measures as outcomes. Clinicaltrials.gov identifier: NCT00240981.

Keywords

testosterone; mobility limitations; physical function; strength; aging; sarcopenia; anabolic therapies

1. Introduction

Limitations in physical function and mobility consequent to advancing age represent a far-reaching public health burden in the United States; a society in which 20% of the population will be 65 years of age or older in 2030. Beyond the sixth decade there is a progressive increase in the measured and perceived difficulty of performing activities such as walking, climbing stairs and lifting objects [1]. Demonstrable limitations in these activities are strongly predictive of falls [2], disability [3], hospitalization [4], quality of life [5] and even mortality [6,7]. The socioeconomic costs of these sequelae and the aging epidemic have

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exposed an unmet need for therapies to improve physical function and mobility in older individuals.

The causality of limitations in physical function and mobility is without doubt complex and multifactorial. A host of age-related chronic conditions and underlying alterations in visual acuity, sensory integration, cognitive function, metabolic homeostasis, cardiovascular fitness and skeletal structure comprise a short-list of plausible contributors. There is also substantial evidence to suggest that the progressive loss in skeletal muscle mass with advancing age, commonly referred to as *sarcopenia*, is an important contributor to limitations in physical function and mobility. This is founded on observations that age-related changes in skeletal muscle mass are paralleled by changes in strength and power [8–10]; two variables associated with performance in measures of mobility such as gait speed, stair climb time or repeated chair rise time [11–13]. Thus, strategies to augment muscle mass may confer improvements upon physical function and mobility by improving muscle strength and power.

In recognition of these observations, there has been a recent surge in the effort to develop function promoting anabolic therapies. At present these interventions include but are not limited to growth hormone secretagogues, myostatin antagonists and selective androgen receptor modulators. In the clinical trial described herein we aim to comprehensively examine the therapeutic potential of the prototypical androgen, testosterone, on muscle strength and physical function in older men with mobility limitations. The gradual but progressive decrease in serum testosterone from age 20 to 80 [14–16] and indisputable evidence that testosterone supplementation increases skeletal muscle mass not only in states of health [17,18], but also disease [19–22] and older age [23–26], have underscored its potential as a function promoting anabolic therapy. Despite the clear anabolic effects of testosterone in older subjects, its administration has not consistently translated into improvements in muscle strength or when studied, physical function or mobility [24,27–33]. In part, these observations may have resulted from fundamental issues related to trial design and methods that have been taken under consideration in the development of the TOM study and are highlighted in this manuscript.

2. Primary research goals

The primary objective of this study is to determine whether testosterone therapy in older men with low testosterone levels and mobility limitations will increase maximal voluntary muscle strength as measured by the 1 repetition maximum. We have selected muscle strength of the lower extremities as our primary outcome measure for sample size determination because of its marked decline with advancing age and its critical importance for physical function and mobility (climbing stairs, getting up from a chair, maintaining balance and avoiding falls). The secondary aim of this study is to test whether testosterone administration mediates improvements in self-reported as well as performance-based measures of physical function, self-reported disability and habitual physical activity. The tertiary aim is to examine whether testosterone administration will reduce fatigue, improve affect and enhance overall sense of well being to a greater extent than placebo.

3. Study Design

3.1 Overview

This is a single-site, placebo-controlled, randomized clinical trial that will enroll a total of 252 community dwelling older men aged 65 and older who have low total (less than 350 ng/dL by liquid chromatography tandem mass spectrometry, LC-MS/MS) or free testosterone (less than 50 pg/mL) levels and who self-report and demonstrate limitations in physical

mobility. Importantly, to operationalize "*mobility limitations*" we will employ two strategies: 1) standardized questions to assess self-reported mobility limitations; and 2) a validated field-based instrument to objectively categorize lower extremity function and mobility. Eligible participants will be randomized to a placebo or testosterone intervention group for 6 months. Unique to this study, steady state testosterone levels will be measured and testosterone dose adjusted to achieve testosterone levels in the mid-to high normal range (500–1000 ng/dL). Subjects will perform laboratory-based measures of muscle performance, physical function and physical activity at baseline and following 3 and 6 months of treatment. In addition, fatigue, affect, sense of well-being, and self-reported function and disability will be assessed by validated questionnaires. All study procedures will be performed at the Boston University Medical Center in Boston, MA. The Clinicaltrials.gov identifier for this study is NCT00240981.

3.2 Eligibility

The eligibility criteria are designed to facilitate the recruitment of community dwelling older men (≥ 65 years of age) that have total testosterone levels measured by LC-MS/MS < 350 ng/dl or free testosterone levels calculated by using law of mass action equation (from total testosterone measured by LC-MS/MS and SHBG levels) < 50 pg/ml, and mobility limitations as defined by 1) self-reported difficulty walking two blocks on a level surface or climbing a flight of stairs, and 2) objective limitations in physical mobility based on their summary score on the Short Physical Performance Battery (SPPB) [34]. Eligible subjects will have summary scores ranging from 4 to 9 on the SPPB as these values represent moderate to mild mobility limitations and strongly predict subsequent disability [3]. Subjects must also be willing to participate in the outcome measures described below. All subjects will provide written informed consent. All study procedures have been approved by the Institutional Review Board of Boston University Medical Center.

3.3 Inclusion Criteria

- Community-dwelling men ≥ 65 years of age
- Self-reported difficulty walking 2 blocks on level ground or a flight of stairs
- A summary score of 4–9 on the SPPB
- Total testosterone by LC-MS/MS ≥ 100 ng/dl and ≤ 350 ng/dl or free testosterone calculated by law of mass action equation < 50 pg/mL
- Willing and able to participate in measures of muscle performance and physical function
- Willing to provide informed consent to be randomized to either the testosterone or placebo treatment group for 6 months

3.4 Exclusion Criteria

- Use of testosterone, dehydroepiandrosterone, androstendione, growth hormone or other androgens in the preceding year
- Prostate or other active cancers, benign prostrate hypertrophy with American Urological Association (AUA)/IPSS lower urinary tract symptom score of > 21, prostate nodule or induration or prostate specific antigen (PSA) > 4 ng/ml
- Neuromuscular, orthopedic or cardiovascular (including unstable angina, New York Heart Association class III or IV congestive heart failure, myocardial infarction within 3 months of study entry, systolic or diastolic blood pressure > 160

and 100 mm Hg, respectively) diseases that would prohibit participation in either the study intervention or outcome measures

- Alanine or aspartate aminotransferase concentrations 3-fold > than the upper limit of normal, creatinine > 2.5 mg/dL, hemoglobin-A1c > 8.5%, or hematocrit > 48%
- Current use of anti-convulsants or glucocorticoids (equivalent to prednisone > 20 mg/day)
- Mini-Mental Status Exam < 24 [35]
- Body Mass Index > 40 kg/m^2
- Excessive alcohol use assessed by AUDIT questionnaire
- Current or recent use of recreational drugs

3.5 Recruitment

The goal of the study is to randomize 252 participants. We anticipate that 30% of the study sample will be comprised of participants from racial or ethnic minorities, including 24% Black or African-Americans and 6% Hispanics. To overcome the notable challenges of recruiting older men for clinical trials and the relatively stringent eligibility criteria (namely, self-reported and objective limitations in physical mobility, low testosterone levels and medical exclusion criteria) and improve the efficiency of the screening process, 3 distinct recruitment strategies will be implemented that utilize a sequential phased screening process.

3.5.1 Recruitment Strategies

- **Strategy 1: Community-based recruiting through the New England Research Institute (NERI).** The NERI has been subcontracted to focus recruitment efforts in communities and at residential facilities (identified through the Boston Housing Authority and Boston Commission on Affairs of the Elderly) in a defined proximity to Boston University Medical Center. In brief, NERI staff will send letters to men 65 years of age or older in the target area based on census tract data. They will then visit the respondents in their homes or at identified sites in the community and provide a study overview followed by one-to-one interactions with potential subjects. These interactions will include: signing an informed consent for pre-screening, collecting demographic and limited medical history information (key inclusion/ exclusion criteria), performing the SPPB and obtaining a blood sample for total testosterone and PSA. Those deemed eligible based on these initial screening tests are referred to Boston University Medical Center for further screening and baseline studies.
- **Strategy 2: Veterans Administration hospital-based recruiting**. In recognition of the large number of older men that receive healthcare at Veterans Administration (VA) hospitals, a collaboration has been developed between the host institution and the affiliated local VA hospital (Jamaica Plain VA Medical Center). The VA site will post study flyers and the primary care physicians will be familiarized with the study inclusion criteria. Interested potential subjects will be referred to the VA clinical research center to provide informed consent for pre-screening and undergo a screening evaluation. Subjects who consent to study participation and meet inclusion/exclusion criteria (including the SPPB and testosterone and PSA levels) will be referred to Boston University Medical Center.
- **Strategy 3: Direct mailings and media campaign.** A Resident List for the City of Boston was obtained with permission from the Boston Election Department to

identify the names and addresses of men age 65 and over who reside in the zip codes of cities within a two mile radius of the Boston University Medical Center. A letter describing the opportunity to participate in a testosterone research study will be sent to these men with a return mailer that contains a form for providing contact information and questions pertaining to demographics, and health and physical mobility. In addition, radio and television advertisements for study participation will be broadcast on local public access channels. Printed recruitment media will be posted in clinics and medical practices in and affiliated with the host institution. Advertisements are also placed in newspapers of the local community at-large as well as in newspapers and newsletters distributed to local seniors and senior interest groups.

3.5.2 Phased Screening Process—In recognition of stringent inclusion/exclusion criteria and the strong likelihood of a high number of screen failures, a multi-phased screening process has been implemented to enhance efficiency.

- **Phase I.** Potential participants will be asked in person (Strategies 1 and 2) or through direct mailing (Strategy 3) the following questions to assess self-reported physical function and mobility:

  "*Do you have difficulty climbing 10 steps without resting*?"

  "*Do you have difficulty walking 2 or 3 blocks on level ground*?"

  If a potential participant responds "Yes" to either of these questions, Phase II is initiated.

- **Phase II.** Eligibility questions will be asked by phone (Strategy 3) or in person (Strategies 1 and 2) related to inclusion and exclusion criteria. If considered eligible, screening will progress to Phase III.

- **Phase III.** The SPPB will be performed in the field (Strategy 1), the VA research center (Strategy 2) or in the Laboratory of Exercise Physiology at Boston University Medical Center (Strategy 3). If the summary score is between 4 and 9, subjects proceed to Phase IV.

- **Phase IV.** Blood will be drawn for determination of testosterone, PSA, complete blood count and chemistry in the field (Strategy 1), VA research center (Strategy 2) or primary research setting (Strategy 3). If the potential participant meets the eligibility criteria a physical examination and graded exercise test (assessing heart rate, blood pressure, ECG, expired gases and ventilatory changes and signs and symptoms with physical exertion), to determine safety of participation in exercise testing, are scheduled at Boston University Medical Center.

3.6 Randomization

Subjects who meet the eligibility criteria and consent to study participation will be randomly assigned in a 1:1 ratio to one of two treatment groups (placebo or testosterone) based on a randomization table that uses a simple blocking scheme and a block size of 6. Subjects will be stratified by age (65–74 and 75–85) prior to randomization.

3.7 Outcome Measures

An overview of the primary, secondary and tertiary outcome measures and testing schedule is provided in Table 1. All study personnel are blinded to participants' randomization assignment. A brief description of these measures is provided below.

3.7.1 Primary Study Outcome

- **Muscle Strength.** Maximal voluntary strength is the primary outcome measure in this study. Strength will be quantified by measuring the one repetition maximum (1RM) for the leg press with a Keiser A420 pneumatic resistance machine and integrated software (Keiser Sport, Fresno, CA). The 1RM will also be measured for the chest press and will serve as a secondary outcome. We have recently demonstrated that the reliability of this 1RM testing method is highly reliable (intraclass correlation coefficient (ICC) > 0.983) in older men with mobility limitations [36].

3.7.2 Secondary Study Outcomes

- **50 Meter Walk.** The time to walk 50 m will be measured using a switch mat and infrared timing system T. Subjects will be instructed to walk as fast as possible and allowed to use assistive devices (e.g., canes and walkers) as needed. The 50 m walk measure demonstrates excellent reliability in this cohort (ICC = 0.988) [36].
- **Loaded 50 Meter Walk.** The procedures to measure the time to walk 50 m as fast as possible will be repeated having the subjects carry two canvas tote bags equally weighted with standard Olympic weight plates whose sum is equivalent to 20 percent of their body weight. This measure is highly reliable (ICC = 0.991) in older men with mobility limitations [36].
- **Stair Climb.** The time to ascend a single flight of stairs consisting of 12 steps will be assessed using a switch mat timing system (Lafayette Instrument Company, Lafayette, IN). Subjects will be instructed to climb the stairs as fast as possible and allowed to use the handrail only if needed. This measure demonstrates excellent reliability in the cohort (ICC = 0.992) [36] being studied.
- **Loaded Stair Climb.** The protocol to measure the time to ascend 12 steps as fast as possible will be repeated having the subjects carry two equally weighted canvas tote bags containing standard Olympic weight plates whose sum is equivalent to 20 percent of their body weight. The reliability of this measure is excellent (ICC = 0.978) in older men with mobility limitations [36].
- **Lift and Lower.** As a measure of upper body function, subjects will be instructed to lift a weighted basket equivalent to 15 percent of their body weight from a shelf positioned at standard desk height (78.5 cm) to a shelf positioned at a subject's shoulder height, and then to a shelf positioned at their respective head height, and lower it back down in the reverse sequence as many times as possible in 1 minute. The Lift and Lower measure demonstrates excellent reliability (ICC = 0.947) [36] in this cohort.
- **SPPB.** The SPPB is a composite measure of lower extremity function [34] which includes a 0–4 point categorical scale each for standing balance, 4 meter walk time and repeated chair rise time (5 sit-to-stand sequences). A summary performance score (0–12) is derived from the 3 individual measures.
- **Habitual Physical Activity.** Physical activity will be measured objectively over a 7 day period using ActiGraph GT1M accelerometers (ActiGraph, Pensacola, FL). Physical activity will also be measured by self-report using the Physical Activity Scale for the Elderly.
- **Late-Life Function and Disability Instrument (FDI).** Self-reported function and disability will be measured using the Late-Life FDI, an evaluative outcome instrument for community-dwelling older adults [37,38].

- **Muscle Power.** Muscle power, a product of the velocity multiplied by the force of contraction, will be determined at resistances equivalent to 40–70% of the 1RM for the leg press and chest press using the equipment and software described for capturing strength. In addition, power of the lower extremities will be captured using the Nottingham Leg Rig.
- **Reaction Time.** Reaction time will be measured using an apparatus that simulates driving an automobile. The time that elapses from the onset of the stimulus (a break light), the release of an accelerator pedal and the depression of a break pedal will be recorded.
- **Body Composition and Muscle Volume.** Whole body fat-free and fat mass and appendicular skeletal muscle mass will be quantified by using dual energy X-ray absorptiometry, calibrated by using a soft tissue phantom prior to each measurement. Muscle volume of the thigh muscles will be assessed by magnetic resonance imaging.

3.7.3 Tertiary Study Outcomes—Sense of well being, affect, and fatigue will be assessed by using the following validated instruments: Psychological Well Being Index [39], Derogatis Affects Balance Scale [40], and the Chalder Fatigue Scale [41], respectively.

3.8 Intervention

3.8.1 Testosterone and Placebo Gel—The study intervention is a daily application of a transdermal gel containing either placebo or 100 mg testosterone (Testim 1%, Auxilium Pharmaceuticals, Norristown, PA) for 6 months (24 weeks). To maintain blinding, all subjects initially receive three tubes of the gel; those assigned to testosterone group receive two active testosterone gel tubes each containing 5 g testosterone gel (50 mg testosterone) plus one tube containing placebo gel, while those assigned to placebo group receive three tubes containing placebo gel. This initial dose of testosterone gel is expected to increase average serum total testosterone concentrations into the mid- to high-normal range in the testosterone treated group. To verify that serum testosterone levels are in the target range, serum testosterone level will be determined two weeks after starting the intervention in a blood sample drawn between 2 and 4 hours after testosterone gel application. If testosterone concentration is < 500 ng/dl, an unblinded physician will increase the testosterone dose to 15 g daily (three 5 g gel tubes daily). If testosterone level is greater than 1000 ng/dL, the unblinded physician will decrease the dose to 5 g gel daily (one 5 g testosterone gel tube plus two placebo tubes). Thus, at all times, all subjects receive three tubes of the gel that are identical in appearance insuring maintenance of masking. The adjustment of the testosterone dose to achieve a mid- to high-normal range (500–1000 ng/dL) is a unique aspect of this trial and a fundamental component in the methods of future clinical trials. This has been neglected in the design of similar and recent studies that failed to induce meaningful changes in testosterone levels and not surprisingly, reported no improvements in muscle strength or physical function and mobility [32,33].

3.8.2 Monitoring, contact mode and frequency—Baseline measures will be completed over a series of 4 visits spanning a 2 week period. Following study initiation and the assessment and adjustment of testosterone dosing at 2-weeks, subjects will be seen bimonthly for safety (detailed below), compliance and overall health assessments. Measures of muscle performance and physical function will also be performed at the study midpoint (3 months) and at the end of the 6-month treatment period. Following termination of the study intervention and completion of the outcome measures, subjects will be seen at a 3 month follow up visit for a final safety assessment.

3.9 Participant Safety

Testosterone gel is an FDA-approved product that has undergone phase I, II, and III studies for the treatment of hypogonadal men [42,43]. Testosterone has not been approved for age-related losses in muscle mass, strength or physical function. Hemoglobin and hematocrit, PSA, and blood chemistries will be monitored at baseline, and then every six weeks throughout the treatment period and at the end of the three month recovery period. Additionally, the subjects will be asked about adverse events and compliance at baseline, during week 2, and every six weeks throughout the treatment period. Physical examinations including prostate digital examination, and AUA/IPSS symptom score will be obtained at baseline and during months 3 and at the end of treatment.

An independent Data and Safety Monitoring Board (DSMB) comprised of individuals with expertise in relevant disciplines and substantial experience in the conduct and oversight of clinical trials has been formed to oversee study progress and participant safety. The DSMB will convene every 6 months and is empowered to discontinue treatment in one or more subjects or halt the study should the occurrence of adverse events so warrant. In addition, the following termination criteria have been established:

- A confirmed increase in serum PSA > 1.4 ng/mL above baseline
- Detection of prostate abnormalities on digital rectal examination
- An AUA symptom index score ≥ 21 or evidence of urinary retention
- Hemoglobin ≥ 180 g/l
- Occurrence of myocardial infarction or stroke

3.10 Statistical Considerations

To test our hypothesis that testosterone administration in older men will improve leg press muscle strength to a greater extent than placebo, we anticipate that 105 participants be needed in each group. This calculation is based on a 0.05 type I error rate, statistical power of 90%, and prior work by our laboratory supporting a testosterone-mediated increase of 245 N (25 kg) in bilateral leg press strength following the 6 month intervention and a standard deviation of the treatment effect of 540 N (55 kg) [23]. This represents a moderate treatment effect size ((f) = 25/55, or 0.45 SD units). Based on these estimates and allowing for a 20% drop out rate in a 6 month time period, we propose to enroll 126 men in each treatment group for a total of 252 participants. No interim efficacy assessment is planned. All analyses will use an intent-to-treat approach; thus all randomized subjects will be used in the primary analysis.

Similar to assessing changes in muscle strength, changes from baseline to end-of-treatment in secondary (e.g., 50 m walk time, stair climb time and muscle volume) and tertiary (e.g., well-being and fatigue measures) outcome measures will be compared between the placebo and testosterone-treatment groups by using an analysis of co-variance in which the end of treatment values in the two groups will be compared using baseline values as covariates along with the other relevant pre-determined covariates. Interactions between the treatment groups and these covariates may also be incorporated into the model where clinically justified. All comparisons for primary, secondary and tertiary outcomes will be two-tailed and type I error for all analyses will be 0.05.

4. Discussion

The TOM study is a clinical trial planned to comprehensively examine the potential therapeutic benefits of testosterone administration on prevalent and disabling consequences

of aging, namely, impairments in muscle strength and limitations in physical function and mobility. Unique aspects of the design and methods of this efficacy trial include the targeting of an older cohort with self-reported as well as objectively demonstrable limitations in physical function and mobility, the application of distinct recruitment strategies, the use of highly sensitive and reliable laboratory-based outcome measures, the adjustment of the testosterone intervention to achieve levels in the mid-normal range and a thorough safety assessment regimen. This study will provide a framework from which future clinical trials of anabolic function promoting therapies can be developed.

The TOM study will target older men with low testosterone levels who meet an operational definition of mobility limitations that includes self-reported and objectively demonstrated limitations in physical function and mobility. In contrast to recent trials of replacement therapy in older men that achieved only marginal increases in testosterone levels, this study aims to restore testosterone to the mid- to high-normal range. Given the considerable variability in testosterone levels during replacement therapy, a unique aspect of the methods described here includes adjusting the testosterone dose to achieve the desired increment in circulating levels. Moreover, to our knowledge this is the first clinical trial of testosterone replacement in older individuals with symptomatic functional limitations who also have objective manifestations of age-associated functional limitations. In comparison to previous studies of testosterone administration in older subjects who were higher functioning and community dwelling, the inclusion of individuals with mobility limitations presents a significant recruitment challenge. Thus, we plan to optimize recruitment efficiency by implementing the described multi-faceted and -phased community-based recruitment strategies including on-site community—based screening, fostering a relationship with the local VA hospital, and direct mailings to local residents in the study demographic based on census tract data.

While there is a consensus that testosterone replacement of androgen-deficient men increases fat-free mass, its effects on muscle performance and physical function have been inconsistent across trials. To address this issue, the TOM study will employ a reliable and proven method for measuring dynamic muscle strength that the investigative team has used in older individuals [36] and shown to be androgen-resposnive [23]; the leg press 1RM. The 1RM measure will be administered in accordance with a standardized testing protocol designed to minimize the confounding influence of learning and familiarization effects, provide adequate warm-up, prevent injury and minimize fatigue in order to optimize performance. Measures of physical function are now the principal outcomes to gauge the efficacy of potential anabolic therapies because of their strong predictive ability for hospitalization [4], disability [3] and even mortality [6,7]. To date, studies of testosterone replacement in older men have either excluded objective measures of physical function or suffered methodological shortcomings. In particular, previous studies have not targeted subjects with mobility limitations and the low ceiling of many commonly used measures (e.g., the time to walk a short distance such as 4 or 8m or the timed up-and-go) has prevented the detection of change in response to interventions that may have significantly increased muscle mass and strength in higher functioning community dwelling older individuals. In the TOM study, we hypothesize that more challenging tasks such as walking an intermediate distance and climbing a flight of stairs while carrying a moderate load, and the selected lift and lower measure, will display higher ceilings and therefore better discriminate among subjects of differing abilities and be more sensitive to change. In preliminary studies, these measures were safe, well-tolerated and demonstrated excellent reliability in older individuals [36]. We contend that these metrics have clear relevance to common life tasks that are necessary for maintaining independence such as carrying groceries and performing a variety of household chores.

We acknowledge that age-related limitations in mobility are complex and multifactorial. By recruiting subjects who report and demonstrate mobility limitations independent of potential cause (e.g., muscle weakness, balance disorders, joint pain), we may undermine the potential salutary effects of testosterone therapy on muscle strength and therefore, physical function. We have recently observed, however, that older subjects with self-reported and objective limitations in mobility demonstrate significantly lower muscle strength than those without [36]. In this initial trial, we are confident that testosterone therapy will increase muscle mass and strength (primary outcome) and propose that this will translate into improvements in physical function (secondary outcomes). Additional trials will need to be performed to establish meaningful improvements in physical function and other health-related outcomes.

In addition to optimizing the methods to detect change in the primary and secondary outcome measures, another distinction of the TOM study is the administration and tailoring of the testosterone dose to restore circulating levels to the mid-normal range. A fundamental shortcoming of two recent trials that studied the effects of testosterone replacement on aspects of strength, physical function and mobility in older men with low testosterone levels was the failure to induce appreciable changes in circulating levels of testosterone [32,33]. These observations underscore the importance of the methods described here that will allow monitoring of testosterone levels during therapy and adjustment of the testosterone dose by an unblinded physician and also insure masking of other study personnel and the participants.

There is significant controversy with respect to the safety of testosterone administration in older individuals. In recognition of these concerns the TOM study will incorporate several measures to minimize the risks to the participant. In particular, this trial will 1) exclude subjects with conditions that might be exacerbated by androgen administration; 2) apply safety measures that will be followed throughout the treatment and follow up period; 3) adhere to termination criteria to guide decisions about treatment discontinuation; 4) monitor testosterone levels in order to maintain the concentrations within the normal range; 5) be overseen by an independent Data Safety Monitoring Board. It should be noted that these monitoring procedures are in compliance with the recommendations of the Endocrine Society's Expert Panel for Testosterone Therapy for Androgen Deficiency Syndromes in Adult Men, and the American College of Physicians/American Society of Internal Medicine Disease Management Module for Male Hypogonadism. Collectively, these steps reflect a committed effort to ensuring the health and safety of study participants.

Conclusions

The prevalence and remarkable socioeconomic costs associated with limitations in physical function and mobility with advancing age have underscored the need to identify function promoting anabolic therapies. Testosterone levels progressively decline into late life and therapeutic replacement augments muscle mass in older individuals; however, its effects on muscle performance and physical function have not been adequately examined. While this trial aims to demonstrate that testosterone safely and effectively promotes gains in muscle strength and physical function in a group of older men with mobility limitations, the design has taken into consideration many of the conceptual and methodological hurdles facing clinical trials of anabolic, function promoting therapies.

Acknowledgments

The authors thank Dr. Wildon Farwell and colleagues at the VA Boston Healthcare System for their efforts to establish the VA investigational site for this study.

Grant Support: NKL was supported in part by NIA K01AG031154. This research is supported by National Institute on Aging (NIA) Grant U01AG01436906 and the Boston Claude A Pepper Older American's Independence Center grant (SB).

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Table 1

Overview of study outcome measures and safety monitoring.

	Baseline	3 Months	6 Months	9 Months
Primary Outcome Measures				
Muscle Strength	X	X	X	
Secondary Outcome Measures				
50 Meter Walk *	X	X	X	
Stair Climb *	X	X	X	
Lift and Lower	X	X	X	
SPPB†	X	X	X	
Physical Activity- Actigraph	X		X	
PASE ‡	X	X	X	
Late-Life FDI #	X		X	
Muscle Power	X	X	X	
Reaction Time	X	X	X	
Body Composition (DEXA)	X	X	X	
Muscle Volume (MRI)	X		X	
Tertiary Outcome Measures				
Psychological Well Being Index	X	X	X	
Derogatis Affects Balance Scale	X	X	X	
Chalder Fatigue Scale	X	X	X	
Safety Assessments				
Physical Examination	X	X	X	X
Blood Analyses [a]	X	X	X	X

* Unloaded and loaded trials

† Short Physical Performance Battery (SPPB)

‡ Physical Activity Scale for the Elderly (PASE)

Late-Life Function and Disability Instrument (FDI)

[a] As described in *3.9 Participant Safety*, blood analyses and determination of adverse events will be performed at 2 weeks and then every 6 weeks for the duration of the study intervention