Chapter 5

Low testosterone levels and decline in physical performance and muscle strength in older men: findings from two prospective cohort studies

published as:

Schaap L.A., Pluijm S.M.F., Deeg D.J.H., Penninx B.W., Nicklas B.J., Lips P., Harris T.B., Newman A.B., Kritchevsky S.B., Cauley J.A., Goodpaster B.H., Tylavsky F.A., Yaffe K., Visser M. Low testosterone levels and decline in physical performance and muscle strength in older men: findings from two prospective cohort studies. Clin Endocrinol (Oxf). 2008 Jan;68(1):42-50. Epub 2007 Jul 30.

Abstract

Objective: Progressive declines in serum levels of testosterone parallel the decline in physical performance and muscle strength in ageing men, although findings are not conclusive. We examined whether levels of testosterone were associated with 3-year decline in physical performance and muscle strength in older men.

Design: Longitudinal data were available for 486 men (mean age 74·9 years, SD 6·4) from the Longitudinal Aging Study Amsterdam (LASA) and 1071 well-functioning men (mean age 73·7 years, SD 2·8) from the Health, Aging and Body Composition (Health ABC) study.

Measurements: Three-year change in physical performance score and grip strength according to categories of total testosterone (TT) and free testosterone (FT) levels.

Results: The mean 3-year change in physical performance was –1·1 (SD 2·7, –13·6%) in LASA and –0·3 (SD 1·5, –2·9%) in Health ABC. The mean 3-year change in grip strength was –9·7 kg (SD 12·2, –13·2%) in LASA and –4·4 kg (SD 11·4, –5·8%) in Health ABC. Low levels of TT were not associated with decline in physical performance or with decline in muscle strength [e.g. mean change in physical performance – 1·09 (SD 0·26) in the lowest quartile (Q1) and –0·88 (0·24) in the highest quartile (Q4) of total testosterone in LASA, and –0·26 (0·07) vs. –0·36 (0·11) in Health ABC]. Similar results were found for FT.

Conclusions: Low levels of TT and FT were neither associated with 3-year decline in physical performance nor with 3-year decline in muscle strength in two independent samples of older men.

Introduction

In men, serum testosterone progressively declines with normal ageing. A substantial proportion of older men (ranging from 20% of 60-year-old to 50% of 80-year-old men) has total testosterone (TT) levels below the normal range for younger men (age 20–45 years).[1] This age-related decline in serum testosterone parallels the decrease in physical performance and decline in muscle strength which may lead to disability, institutionalization and mortality.[2–4]

Previous cross-sectional, observational studies suggest that low serum testosterone levels are associated with low muscle mass, strength and immobility.[5–10] Indeed, we recently showed low levels of bioavailable testosterone to be associated with low muscle strength and poor physical performance in older men.[11] Another study[12] recently demonstrated positive associations between testosterone and physical performance up to a certain threshold, but not above the threshold. This study did not find an association between testosterone and grip strength. To our knowledge, longitudinal studies investigating associations between testosterone and changes in physical performance or strength have not been conducted. Therefore, the temporal relationship between testosterone levels and strength and function is still unclear. In the USA, use of testosterone products increased from 4·7 per 1000 men over 65 years of age in 2001 to 5·6 per 1000 in 2002 (19% increase) and this number is still rising.[13] Despite increasing prescription rates of testosterone supplementation in older men, the possible protective role of testosterone in the decline of muscle strength and physical functioning with ageing is still not clear.

The association between low levels of testosterone and decline in physical performance is of great importance because testosterone supplementation could be used in ageing men to prevent strength loss and physical impairment. It is still unclear whether levels of TT or free testosterone (FT) are prospective determinants of decline in physical performance and/or muscle strength and could potentially be used as early markers for the prevention or treatment of physical impairment.

The aim of this study that used prospective data from two independent cohort studies was to investigate whether low serum TT and FT concentrations in older men are associated with 3-year decline in physical performance and muscle strength.

Methods

Study samples

We analysed baseline and 3-year follow-up data from two independent cohort studies: the Longitudinal Aging Study Amsterdam (LASA) and the Health, Aging and Body Composition (Health ABC) study.

The LASA study is an ongoing cohort study of predictors and consequences of changes in physical, cognitive, emotional and social functioning in older persons.[14] The sampling and data collection procedures and nonresponse have been described in detail elsewhere.[15] The baseline sample consisted of 3107 older men and women (age 55–85 years), drawn from a random, nationally representative, age- and gender-stratified sample. Follow-up measurements were collected every 3 years and mainly comprised medical interviews. Data were collected from face-to-face interviews in the homes of the respondents by specially trained and intensively supervised interviewers.

For this study, data from the first follow-up (1995/1996) were used as a baseline and included male respondents who participated in the medical interviews and were aged 65 years and older as of 1 January 1996 (Figure 1). Respondents who were lost to follow-up between 1992/1993 and 1995/1996 were older, were more often current smokers, were more likely to be cognitively impaired, were to have had depressive symptoms, and were to have had more chronic diseases at baseline compared to respondents with complete follow-up data. Informed consent was obtained from all respondents and the study was approved by the Ethical Review Board of the VU University Medical Center.

The Health ABC study is an ongoing prospective cohort study on the interrelationship of changes in body composition and health conditions on physiological and functional changes in elderly persons. The study sample includes 3075 black and white men and women, aged 70–79 years at baseline. Whites were recruited from a random sample of Medicare beneficiaries residing in zip codes from the metropolitan areas surrounding Pittsburgh, PA, and Memphis, TN. Blacks were recruited from all age-eligible residents in these geographical areas. Potential participants received a mailing, followed by a telephone eligibility screen. Eligibility criteria included age 70–79 years in the recruitment period from March 1997 to July 1998; self-report of no difficulty in walking one quarter of a mile or climbing 10 steps without resting; no difficulty performing basic activities of daily living; no reported use of a cane, walker, crutches or other special equipment to get around; no history of active treatment for cancer in the prior 3 years; and no plan to move out of the area in the next 3 years.

Male participants with baseline data on TT or FT and physical performance or grip

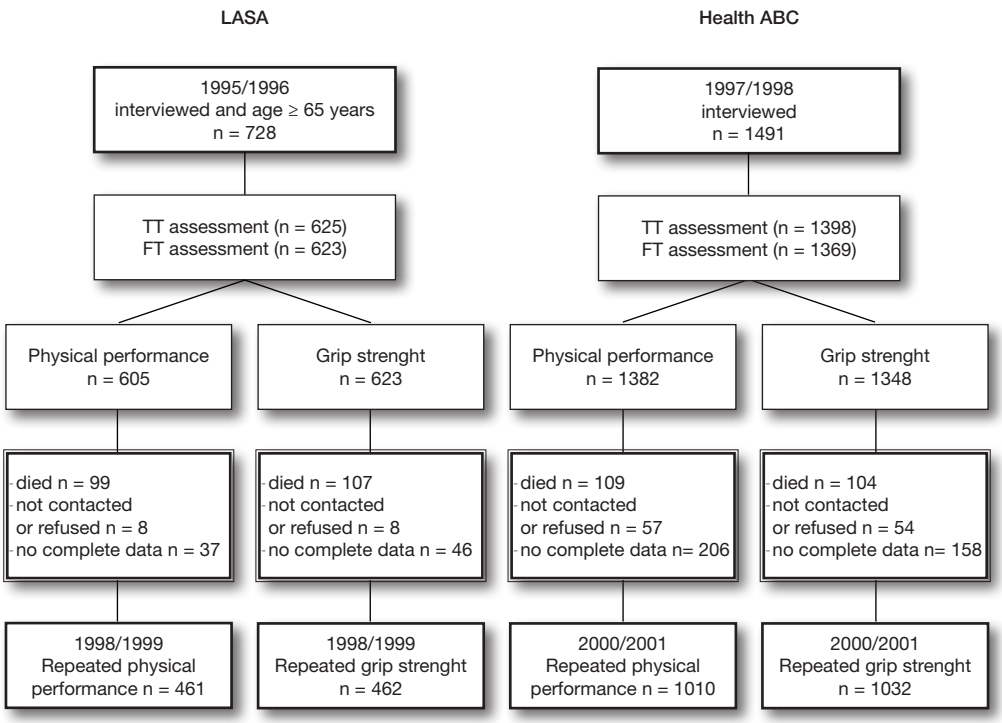

Figure 1

Selection of study participants of the Longitudinal Aging Study Amsterdam (LASA) and Health, Aging and Body Composition (Health ABC) study.

strength were included in this study (Figure 1). Respondents with missing data were older, more likely to be black and to be cognitively impaired, were less educated, had more chronic diseases, had a lower physical performance score and lower grip strength at baseline, compared with other men who were included in the study. The study was reviewed and approved by the Institutional Review Boards at the University of Tennessee and the University of Pittsburgh. All participants provided informed consent before participating in the study.

Assessment of physical performance

In both studies performance tests were carried out at baseline and at a 3-year follow-up visit and included a timed walk test, a repeated chair stands test and a tandem stand using modified protocols.[2] These performance tests are commonly used and a good reliability has been reported in elderly persons.[16–18] In LASA, for the walk test, the participants were asked

to walk 3 m, to turn around and to walk back 3 m as quickly as possible. For the repeated chair stands, participants were asked to fold their arms across their chest and to stand up five times from a chair. For both tests the score ranged from 0 (unable to perform the test) to 4 (fastest quartile of time required doing the test). For the tandem stand, participants attempted to maintain their feet in the tandem stand position (heel of one foot directly in front of the other foot) for 10 s and the score was categorized as (1) unable, (2) 3–9 s, and (3) ≥ 10 s. To convert this to a quantitative score, these three groups received the scores 0, 2 or 4, respectively.

In the Health ABC study, for the walk test, the participants were asked to walk 6 m at their usual pace. For the repeated chair stands, participants were asked to fold their arms across their chest and stand up five times from a chair. For both tests the score ranged from 0 (unable to perform the test) to 4 (fastest quartile of time required doing the test). For the tandem stand, participants attempted to maintain their feet in a semitandem (heel of one foot beside the big toe on the other foot), a tandem stand and a one-legged stand position for 30 s each. Participants were scored 0 if they were unable to hold a side-by-side for 10 s, 1 if they could hold a side-by-side stand for 10 s but were unable to hold a semitandem stand for 10 s, 2 if they held a semitandem stand for 10 s but were unable to hold a full tandem stand for more than 2 s, 3 if they held the full tandem stand for 3–9 s, and 4 if they held the full tandem stand for 10 s.

The scores of the three performance items were summed to a final score (range 0–12), 2 where a lower score indicated a poorer physical performance. Change in physical performance was calculated as physical performance at 3-year follow-up minus baseline physical performance score.

Assessment of muscle strength

In both studies handgrip strength (kg) was measured using a hand-held dynamometer (LASA: Takei TKK 5001, Takei Scientific Instruments Co. Ltd, Tokyo, Japan; Health ABC: Jamar, TEC, Clifton, NJ). All dynamometers were regularly calibrated and checked for any abnormalities. The dynamometer was individually adjusted for hand size, and two trials were performed on each hand. The maximum values of the right and the left hand were summed.[19]

In Health ABC, isokinetic strength of the knee extensors was measured by a Kin-Com 125 AP Dynamometer (Chattanooga, TN) at 60° per second. Participants were familiarized with the testing procedure by performing two practice trials at 50% effort and then completed a maximum of six trials. Start and stop angles were set at 90° and 30°, and from

the first attempt, the torque produced over the entire range was plotted, with the plot of each subsequent attempt overlaid on the previous trails until three similar curves were obtained, with the average maximum strength determined from these three trials. Participants with a systolic blood pressure ≥ 200 mmHg, diastolic blood pressure ≥ 110 mmHg, or who reported a history of cerebral aneurysm or cerebral bleeding, bilateral total knee replacement, or severe bilateral knee pain were excluded from the test, resulting in 1273 men with baseline knee extensor strength measurements. Of the 1273 men, levels of TT or FT were determined in 1208. The coefficient of variation (CV) (repeated testing in 63 participants) for isokinetic knee extensor strength was 10·7%. Three-year follow-up measurements were done in 881 men. Change in muscle strength was calculated as muscle strength at 3-year follow-up minus baseline muscle strength.

Assessment of hormones

In LASA, serum samples were obtained during examination in 1995/1996 and kept frozen until determination of TT, SHBG and albumin Serum TT concentrations were measured by immunoassay (Coat-ACount, Diagnostic Products Corporation, Los Angeles, CA), with a CV of 11% at 2·6 nmol/l and 7% at 11·5 nmol/l. The detection limit was 1 nmol/l. SHBG concentrations were measured by immunoradiometric assay (IRMA, Orion Diagnostica, Espoo, Finland) with a CV of 6% at 10 nmol/l. Albumin concentrations were measured directly after blood collection using an automated analyser (Hitachi 747, Hitachi High-Technologies Co., Tokyo, Japan), obtaining a CV of less than 2%.

In the Health ABC study, serum was obtained after an overnight fast and kept frozen until determination of TT, SHBG and albumins TT and SHBG were measured using IMMULITE®, an automated continuous random-access chemiluminescent immunoassay (CLIA) system (Diagnostic Products Corporation, Los Angeles, CA). Serum albumin concentration was measured by using the bromocresol green method (Vitros; Ortho-Clinical Diagnostics Inc, Rochester, NY). TT has a detectable range of 0·7–55·5 nmol/l. SHBG has a detectable range of 1·0–34·7 pmol/l. Each sample was run in duplicate and an additional 147 'blinded' samples (5%) were collected and included for measurement of each hormone assay to determine assay reproducibility and showed a CV of 10·8% for TT, 9·7% for SHBG and 2·0% for albumins.

In both studies, FT was calculated according to the method described by Vermeulen *et al.*[20] taking the concentrations of TT, SHBG and albumin into account. This method is known to give higher levels of FT compared to directly measured levels of FT.[7,21]

Potential confounders

Potential confounders included age, level of education, study site, race, body mass index (BMI), alcohol use, smoking, physical activity, steroid use, several chronic diseases, cognitive impairment and depressive symptoms. These confounders are known to be associated with testosterone as well as physical performance and/or muscle strength.

In both studies, education level was categorized as less than high school, high school graduate and postsecondary school. BMI was calculated as measured weight (kg)/height (m).[2] Alcohol use was categorized as none, ≤ 7 drinks per week and > 7 drinks per week.[22] Smoking status was categorized as never, former and current smoker.[22] In LASA, physical activity (walking, cycling, housework and exercise) of the past 2 weeks was measured by a validated questionnaire.[23] In Health ABC, physical activity (outdoor chores, heavy chores, housework, climbing stairs, high and medium intensity exercise, paid work and volunteer work) of the past 7 days was assessed by questionnaire as well as information on the intensity level at which each activity was performed. A metabolic equivalent value was assigned to each activity to calculate the number of kcal per week per kg of body weight spent on that activity.[23,24] The scores of all performed activities were summed and multiplied by body weight to create an overall physical activity score in kcal per week.

Steroid use was assessed by asking the respondents whether they had used medication prescribed by a doctor. All medications were coded according to the Anatomic, Therapeutic Chemical classification (ATC-classification for LASA) or the Iowa Drug Information System (IDIS) code (for Health ABC).[25] Chronic diseases were assessed by self-report (and medication use and clinical data in Health ABC) and included pulmonary disease, cardiac disease, diabetes mellitus, arthritis, cerebrovascular diseases, peripheral atherosclerosis and cancer. Cognitive impairment was measured by means of the Mini-Mental State Examination (MMSE) (cut-off ≤ 23 in LASA)[26] or the Teng modified Mini-Mental State Examination (cut-off < 80 in Health ABC).[27] Depressive symptoms were assessed with the Center for Epidemiology Studies-Depression (CES-D) scale (cut-off ≥ 16).[28]

Statistical analyses

Analyses were performed in both studies separately. TT and FT were categorized into four groups, based on both the clinical cut-off level for low testosterone[29] and acceptable numbers of respondents within the three other groups. The category with the highest level of TT or FT was used as the reference group. Analysis of covariance was performed, using absolute change in physical performance score or muscle strength as continuous outcome

Table 1

Respondent characteristics of the Longitudinal Aging Study Amsterdam (LASA) and Health, Aging and Body Composition (Health ABC) study

	LASA		Health ABC	
Characteristics	*N*		*N*	
Age (years)	486	74·9 (6·4)	1071	73·7 (2·8)
Education level				
Low	120	24·7	264	24·7
Intermediate	291	59·9	277	25·9
High	75	15·4	528	49·4
Study site‡				
North-east	141	30·2		
South	208	44·4		
West	119	25·4		
Pittsburgh			538	50·2
Memphis			533	49·8
Race‡				
Black	0	0	350	32·7
White§	493	100	721	67·3
Alcohol use‡				
No drinking	59	12·1	447	41·9
< 1–7 drinks/week	242	49·8	502	47·0
> 7 drinks/week	185	38·1	118	11·1
Smoking‡				
Never	56	11·5	332	31·1
Former	317	65·2	639	59·8
Current	113	23·3	98	9·1
Physical activity (kcal/week)†	459	3056 [1771–5144]	1071	5438 [3064 –9096]
Body mass index (kg/m^2)	482	26·3 (3·3)	1071	27·2 (3·9)
Chronic diseases (N)†	486	1 [0 – 2]	1071	1 [0–1]
Cognitive impaired‡	486	6·8	1070	11·5
Depressive symptoms‡	486	7·0	1062	3·5
Steroid use‡	486	1·9	1070	1·1
Total testosterone (nmol/l)†	486	15·4 [12·3 –18·5]	1071	13·2 [10·4 –16·4]
Free testosterone (nmol/l)†	482	0·28 [0·23 –0·33]	1048	0·21 [0·16–0·26]
SHBG (nmol/l)†	486	40·8 [29·6 –51·4]	1048	50·8 [37·3–66·3]
Albumin (g/l)	486	42·1 (4·3)	1071	40·2 (3·2)
Baseline physical performance (range 0–12)	474	8·1 (2·8)	1063	10·4 (1·3)
3-year change in physical performance*	461	– 1·1 (2·7)	1010	– 0·3 (1·5)
Baseline grip strength (kg)	480	73·4 (16·1)	1043	77·9 (16·1)
3-year change in grip strength (kg)*	462	– 9·7 (12·2)	1032	– 4·5 (11·5)
Baseline knee extensor strength (Nm)			1208	135·5 (34·2)
3-year change in knee extensor strength (Nm)*			881	– 17·2 (27·9)

Results are presented in mean (SD), unless otherwise indicated; *range of change in physical performance within LASA from –9 to 10; within Health ABC from –8 to 6; range of change in grip strength within LASA from –75 to 21 kg; within Health ABC from –92 to 46 kg; range of change in knee extensor strength within Health ABC from –313·7 to 64·1 Nm; †results are presented in median [interquartile range]; ‡results are presented in percentages; §whites within LASA included one Indonesian and one person of a mixed race.

measures. In the first model, results were adjusted for age, study site, race and baseline physical performance or baseline muscle strength, respectively. In the second model, results were additionally adjusted for all other potential confounders. We examined whether there was a linear trend across categories of TT and FT by including the categorical variables as an ordinal variable in a multiple linear regression model. Additionally, we repeated the analysis of covariance using relative change in physical performance score or muscle strength as continuous outcome measures. We also performed linear regression analyses, using TT and FT as continuous variables. We repeated the analyses using an extra category of TT < 8 nmol/l to examine whether men with very low TT have different results and with dichotomized TT and FT (lowest quartile *vs.* other three quartiles). p-values < 0·05 were considered statistically significant. Potential age, race, physical activity and BMI differences in the relationships under study were tested (p < 0·10) using age * testosterone, race * testosterone, physical activity * testosterone and BMI * testosterone product terms in additional analyses.

Table 2

Analysis of covariance of serum total testosterone (TT) concentrations with adjusted absolute change in physical performance score and grip strength (kg) in men

	LASA					Health ABC				
		Model 1		Model 2			Model 1		Model 2	
	N	Mean (SE)	*P*-value	Mean (SE)	*P*-value	*N*	Mean (SE)	*P*-value	Mean (SE)	*P*-value
Change in physical performance score										
< 12 (nmol/l)	98	– 1·07 (0·25)	0·34	– 1·09 (0·26)	0·55	387	– 0·32 (0·07)	0·68	– 0·26 (0·07)	0·50
≥ 12 to < 14	73	– 1·45 (0·29)	0·11	– 1·43 (0·30)	0·15	168	– 0·33 (0·11)	0·70	– 0·31 (0·11)	0·75
≥ 14 to < 18	153	– 1·15 (0·20)	0·33	– 1·15 (0·21)	0·39	288	– 0·21 (0·08)	0·66	– 0·27 (0·08)	0·51
≥ 18 (ref)	120	– 0·86 (0·23)		– 0·88 (0·24)		167	– 0·27 (0·11)		– 0·36 (0·11)	
		P for trend	0·51	*P* for trend	0·55		*P* for trend	0·44	*P* for trend	0·63
Change in grip strength (kg)										
< 12 (nmol/l)	97	– 10·61 (1·22)	0·27	– 10·43 (1·28)	0·40	413	– 4·59 (0·49)	0·48	– 4·42 (0·51)	0·67
≥ 12 to < 14	72	– 9·59 (1·41)	0·65	– 9·09 (1·45)	0·93	172	– 3·84 (0·77)	0·93	– 3·99 (0·77)	0·99
≥ 14 to < 18	152	– 9·84 (0·96)	0·47	– 10·26 (1·00)	0·38	281	– 4·96 (0·60)	0·30	– 5·01 (0·60)	0·31
≥ 18 (ref)	124	– 8·79 (1·07)		– 8·93 (1·14)		166	– 3·94 (0·78)		– 4·01 (0·81)	
		P for trend	0·37	*P* for trend	0·54		*P* for trend	0·80	*P* for trend	0·95

Model 1 adjusted for baseline physical performance or grip strength, age, site and race; Model 2 additionally adjusted for education level, physical activity, chronic diseases, cognitive impairment, depressive symptoms, body mass index, alcohol use, smoking and steroid use. SE = standard error. Divide TT by 0·0347 to convert to ng/dl.

Results

Baseline characteristics of respondents from LASA and Health ABC are shown in Table 1. In LASA, the mean 3-year change in physical performance score was –1·1 (SD 2·7, –13·6%). The 3-year change in grip strength was –9·7 kg (SD 12·2, –13·2%). For Health ABC, the mean 3-year changes were –0·3 (SD 1·5, –2·9%) for physical performance and –4·5 kg (SD 11·5, –5·8%) for grip strength, respectively. Three-year change in knee extensor strength was −17·2 Nm (SD 27·9, –12·7%).

The associations between TT and 3-year change in physical performance are shown in Table 2. In LASA as well as Health ABC, no associations were found for TT with change in physical performance. Moreover, levels of FT were unassociated with physical performance in either study (Figure 2). We also examined associations of TT and FT with each individual component of the physical performance and the results were consistent with the results of the physical performance summary score (data not shown). No interactions were found between testosterone levels and age, race, physical activity or BMI for any of the associations.

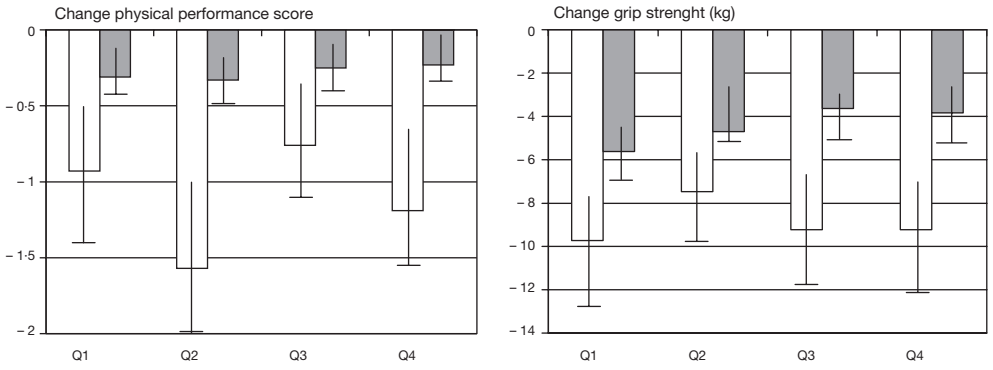

Figure 2

Analysis of covariance of categories of free testosterone (FT) with adjusted absolute change in physical performance (left) and grip strength (right) in men from the Longitudinal Aging Study Amsterdam (LASA, white) and Health, Aging and Body Composition (Health ABC) study (grey). Analyses were

adjusted for baseline physical performance or baseline grip strength, age, site, race, education level, site, physical activity, chronic diseases, cognitive impairment, depressive symptoms, BMI, alcohol use, smoking and steroid use. 95% confidence intervals are expressed as a vertical line.

LASA: Q1 < 0·23; Q2 = 0·23 to < 0·28; Q3 = 0·28 to < 0·33; Q4 = 0·33 nmol/l; p trend 0·96 for change in physical performance; p trend 0·94 for change in grip strength; Health ABC: Q1 < 0·16; Q2 ≥ 0·16 to < 0·21; Q3 ≥ 0·21 to < 0·26; Q4 ≥ 0·26 nmol/l; p trend 0·39 for change in physical performance; p trend 0·06 for change in grip strength. Divide FT by 0·00347 to convert FT to pg/ml.

The associations between TT and FT and grip strength are shown in Table 2 and Figure 2. As with physical performance, we found no associations between levels of TT or FT and change in grip strength in either study.

The associations of TT and FT with 3-year change in knee extensor strength in the Health ABC study are shown in Table 3. Contrary to expectations, lower TT levels tended to be associated with smaller declines in knee extensor strength in Model 2; however, there was no significant trend across the four groups of TT (Table 3). Levels of FT were not associated with change in knee extensor strength (Figure 3).

Analysis of covariance using relative change in physical performance score or muscle strength showed similar results compared to the analyses with absolute change in the outcome measures. Linear regression analyses using continuous TT and FT levels did not show associations with 3-year change in physical performance or muscle strength either. Analyses using an extra category of TT < 8 nmol/l (n = 21 in LASA, n = 159 in Health ABC), suggested no associations with physical performance or muscle strength. [LASA: mean change in physical performance of –1·56 (SE 0·60) in the group with TT levels < 8 nmol/l, p = 0·25, mean change in grip strength of –12·60 (SE 2·90), p = 0·25; Health ABC: mean change in physical performance of –0·36 (SE 0·11), p = 0·58, mean change in grip strength of –3·98 (SE 0·82), p = 0·53].

Analyses using dichotomized TT and FT (lowest quartile *vs.* other three quartiles) showed no associations with either physical performance or muscle strength.

		Model 1		Model 2	
	N	Mean (SE)	*P*-value	Mean (SE)	*P*-value
< 12 (nmol/l)	346	– 16·75 (1·20)	0·04	– 16·87 (1·24)	0·10
≥ 12 to < 14	146	– 16·28 (1·86)	0·06	– 16·05 (1·88)	0·09
≥ 14 to < 18	246	– 17·48 (1·43)	0·10	– 17·74 (1·45)	0·21
≥ 18 (ref)	143	– 21·32 (1·88)		– 21·76 (1·95)	
		P for trend	0·07	*P* for trend	0·15

Model 1 adjusted for baseline knee extensor strength, age, site and race; Model 2 additionally adjusted for education level, physical activity, chronic diseases, cognitive impairment, depressive symptoms, body mass index, alcohol use, smoking and steroid use. SE = standard error. Divide TT by 0·0347 to convert to ng/dl.

Table 3

Analysis of covariance of serum total testosterone (TT) concentrations with adjusted absolute change in knee extensor strength (Nm) in men from the Health, Aging and Body Composition (Health ABC) study

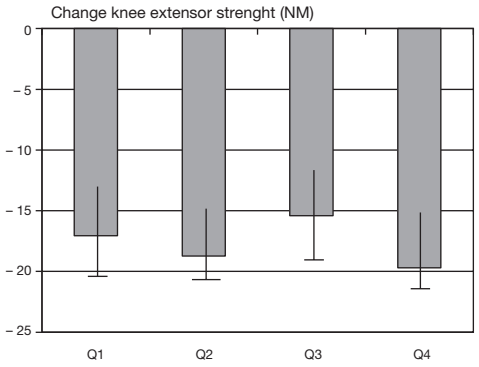

Figure 3

Analysis of covariance of categories of free testosterone (FT) with absolute change in knee extensor strength in men from the Health, Aging, and Body Composition (Health ABC) study. Analyses are adjusted for baseline knee extensor strength, age, site, race, education level, site, physical activity, chronic diseases, cognitive impairment, depressive symptoms, BMI, alcohol use, smoking and steroid use; 95% confidence intervals are expressed as a vertical line; Q1 < 0·16; Q2 ≥ 0·16 to < 0·21; Q3 ≥ 0·21 to < 0·26; Q4 ≥ 0·26 nmol/l; p trend 0·55. Divide FT by 0·00347 to convert FT to pg/ml.

Discussion

To our knowledge, this is the first observational study that examined associations of both TT and FT with physical performance and strength using a prospective design. Our results suggest that low baseline serum levels of endogenous TT and FT in older men are not associated with greater 3-year decline in physical performance and muscle strength. These results were consistent in two independent cohort studies of older men. The Health ABC study is a wellfunctioning sample of older persons, whereas the LASA study is a representative sample of the Dutch elderly population, including frail and less healthy persons. We were able to use objective physical performance and muscle strength tests as outcome measures and we carefully adjusted for confounding.

In this study, grip strength was used as a measure of isometric muscle strength, which is a measure of overall muscle strength. Grip strength has been suggested to be a less valid instrument to determine overall muscle strength, as it might not represent the muscle strength in the lower extremity and mainly measures isometric aspects of muscle strength. Therefore, we repeated the analyses with an isokinetic measure of knee extensor strength as the outcome. The analyses showed that low levels of TT tended to be associated with smaller decline in knee extensor strength, which is opposite to our expectations. This finding is difficult to interpret and might be a statistical artifact.

FT levels were calculated using the method described by Vermeulen which take levels of TT, SHBG and albumin into account.[20] In Health ABC, we were able to directly measure serum FT concentrations, but it has been suggested that assays to measure FT are not accurate and often give an underestimation of the actual free fraction of T.[7,20] Analyses with the directly measured FT gave similar results as the analyses with calculated FT.

Cross-sectional studies, among which a previous study using LASA data, have shown associations of testosterone with muscle strength and performance.[7,11] Two methodological explanations and possible limitations can be put forward to account for the absence of associations in the present longitudinal study. First, a possible explanation might be the selective loss to follow-up, resulting in healthier samples. Respondents not included in the statistical analyses were older, had a poorer physical performance, were less physically active, were more often smokers, were more likely to be cognitively impaired, were to have had depressive symptoms, and were to have had more chronic diseases, all of which are important determinants of physical decline, compared to respondents with complete follow-up data. These persons, however, did not have lower serum testosterone levels or lower muscle strength at baseline, even after adjustment for age (data not shown). Therefore, it is unlikely that an underestimation of a possible association has occurred. Moreover, these findings suggest that lower testosterone levels are not associated with physical decline, which is in line with the negative findings of this study. It is possible, however, that our findings are sample-specific. Therefore, further studies are needed to confirm our results.

Second, it is possible that persons with extremely low testosterone levels still show a significantly greater decline in physical performance or muscle strength. However, additional analyses using an extra category of TT < 8 nmol/l (n = 21 in LASA, n = 159 in Health ABC), suggested associations with neither physical performance nor muscle strength. Third, it is possible that testosterone only has a short-term effect on muscle or physical performance,[30] which can account for the cross-sectional associations found in previous studies. Another explanation for the absence of associations might be a possible ceiling effect of the physical performance scores. This might account for the Health ABC respondents, as they had no self-reported physical limitations at baseline. The LASA sample, however, includes disabled persons and showed similar results.

Although this study suggests that decline in physical performance and strength is similar in men with high and low levels of testosterone, the magnitude of decline will be greater in men with low baseline physical performance scores and low baseline muscle strength. In the LASA study, we have shown that persons with TT levels in the lowest quartile have a lower baseline performance score compared to persons with TT levels in the highest quartile.[11]

We did not find this in the Health ABC study, in which persons with low and high TT levels have similar baseline performance levels. To examine the magnitude of decline in physical performance and strength we performed additional analyses with relative decline in percentages as outcome measures. We did not find associations with relative decline in physical performance or muscle strength in either study.

Another limitation is the single assessment of TT and FT at baseline. It is possible that changes in TT or FT over time may be associated with changes in physical performance or muscle strength. Two-year changes in directly measured FT, which were available within a subgroup of Health ABC participants, were not associated with 3-year decline in physical performance or muscle strength (data not shown). However, these results should be carefully interpreted because of the suggested lack of reliability of the FT assay as mentioned earlier.

Studies with testosterone administration show inconsistent effects on muscle strength and physical performance.[31–33] A meta-analysis by Isidori *et al*.[34] revealed that the effects of testosterone on muscle strength were heterogeneous, with a tendency towards improvement of dominant leg extension strength and dominant handgrip strength. Another recent meta-analysis by Ottenbacher et al.[35] showed that testosterone therapy shows a small to moderate increase in muscle strength, with larger effects on lower extremity and total body strength than on upper extremity strength measures.

As the testosterone prescription rates in older men continue to increase,[13] it is important to gain insight as to the benefits and risks of testosterone supplementation. Possible risks of testosterone treatment in healthy older men include increased risk of cardiovascular disease and prostate cancer, and an increase in haematocrit levels.[36,37] The balance of the risks and benefits of testosterone therapy needs to be determined in carefully designed, long-term randomized, controlled trials. Until then, testosterone supplementation to improve muscle strength and function in healthy older men should be considered with caution.

In conclusion, low levels of TT and FT were not associated with a greater decline in physical performance or muscle strength in older men in this study. Nevertheless, more research on the benefits and risks of testosterone administration is needed.

Acknowledgements

LASA is supported by the Dutch Ministry of Public Health, Welfare and Sports. The Health ABC study was supported by National Institute on Ageing contracts N01-AG-6–2101, N01-AG-6–2103 and N01-AG-6–2106. This research was supported in part by the Intramural Research programme of the NIH, National Institute on Ageing.

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