Chapter 6

Older women and testosterone: the relationship with three-year decline in physical performance and muscle strength

submitted

Abstract

Context: There is growing interest in the role of low testosterone levels on health in women. However, the effects of lower testosterone levels on decline in physical performance or muscle strength in older women have not yet been investigated.

Objective: To investigate the associations between low testosterone levels and three year change in muscle strength and physical performance in a population-based sample of older women.

Design and setting: The Health, Aging, and Body Composition study, an ongoing prospective cohort study, includes 3075 black and white men and women, aged 70-79 years.

Participants: Data were available for 1510 women with baseline levels of total and free testosterone. Physical performance and grip strength were measured at baseline and after three years.

Results: Lower levels of total and free testosterone were not associated with baseline physical performance in analyses of covariance, adjusted for socio-demographic, health and lifestyle factors. However, lower levels of total testosterone were associated with a two times greater three-year decline in physical performance score (mean change -0.16 (SE 0.02) in women with total testosterone levels ≤ 20 ng/dl, compared to a mean change of -0.08 (0.03) in women with levels ≥ 34.7 ng/dl (reference), p=0.01). Lower levels of total and free testosterone were associated with lower baseline grip strength and with greater three-year decline in grip strength in women 73 years or older, but not in younger women.

Conclusions: These data suggest an association between low testosterone levels and greater decline in physical performance and grip strength in older women.

Introduction

Aging is associated with alterations in testosterone (T) concentrations in both men and women. Changes in T levels in women are yet not clearly established, but a recent study suggested that women aged 65-75 have a 50% lower T level compared to young women aged 18-24.[1]

There is growing interest in the role of androgen therapy for women. In post-menopausal women, T has been administered to relieve menopausal symptoms or to enhance sexual function.[2-4] One study demonstrated an increase in fat-free mass in post-menopausal women who were receiving estrogen plus T implants compared to those given estrogen alone.[5] The possible benefits of T supplementation on muscle or mobility function have not been investigated.

The established concern about the impact of hypogonadism in men and the evolving role of androgens in women's health have generated an increased interest in the physiological roles for low levels of testosterone in women. Epidemiological studies in men have shown associations between lower levels of T and low muscle mass, low muscle strength and immobility,[6-9] although these findings are not conclusive. In a recent study from our group, we found that low levels of total and free T were not associated with three-year decline in muscle strength or with three-year decline in physical performance in two independent samples of older men.[10] To our knowledge, the associations between lower T levels and decline in physical performance or muscle strength in older women have not yet been investigated.

The aim of this study is to examine associations between low serum levels of total and free T and physical performance and muscle strength using cross-sectional as well as prospective (three-year change) outcomes in a large sample of older, well-functioning women from the Health, Aging, and Body Composition (Health ABC) study.

Methods

Study sample

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 outcomes in older 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 geographic 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 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 three years, and no plan to move out of the area in the next three years.

Female participants with missing data on total and free T or baseline physical performance or grip strength were excluded from the cross-sectional analyses (74 of 1584 women (4.7%)). There were no significant differences in characteristics between included and excluded women. Women with missing data on three-year change in physical performance or grip strength were additionally excluded from the longitudinal analyses (331 of 1510 women (21.9%)). These excluded women were older, more likely to be black, had more chronic diseases, a lower education level, a lower baseline physical performance score and a lower baseline grip strength compared to women who were included in these analyses (n = 1179). Reasons for loss to follow-up included death (n = 66), refusal or unable to contact the respondent (n = 57) or incomplete data (n = 208).

The study was reviewed and approved by the Institutional Review Boards at the University of Tennessee and the University of Pittsburgh. All participants provided written informed consent before participating in the study.

Physical performance

The Health ABC performance battery was carried out at baseline and at a three-year follow-up visit. Details of the Health ABC performance battery and scoring have been described previously.[11] In brief, this battery includes five repeated chair stands, progressively more-challenging tests of standing balance (semi-tandem, full-tandem, and single leg stands) each held for 30 seconds, a 6 meter walk to determine usual gait speed, and a narrow walk in which participants were instructed to walk between lines of colored tape 20 cm apart at their usual pace. Performance on chair stands was evaluated using a rate of chair stands per second. For the standing balance test, the time of each stand that was held was summed for a maximum of 90 seconds. Gait speed was noted for both walks. Failure on the narrow walk yielded a score of 0 and consisted of stepping on or outside the tape two or more times over 6 meters. Up to three trials were permitted. Performance was divided by the maximum possible

performance for older adults on each test to create ratio scores that were summed for the four tests to obtain a continuous scale ranging from 0 to 4, with a lower score indicating a poorer physical performance. Change in physical performance was calculated as physical performance at three-year follow-up minus baseline physical performance score.

Muscle strength

Handgrip strength (kg) was measured at baseline and after a three-year follow-up using a hand-held dynamometer (Jamar, TEC, Clifton, NJ, USA). 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.[12] Change in muscle strength was calculated as muscle strength at three-year follow-up minus baseline muscle strength.

Hormones

Serum was obtained after an overnight fast and kept frozen until determination of total T, sex hormone-binding globulin (SHBG) and albumin. Total T and SHBG were measured using IMMULITE®, an automated continuous random-access chemiluminescent immunoassay 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). Total T has a detectable range of 20-1600 ng/dl (0.7-55.5 nmol/l). SHBG has a sensitivity of 0.20 nmol/l with a calibration range up to 180 nmol/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 8.2% for total T, 9.7% for SHBG and 2.0% for albumin.

Free T was calculated according to the method described by Vermeulen et al.,[13] taking the concentrations of total T, SHBG and albumin into account. This method is known to give higher levels of free T compared to directly measured levels of free T.[6,14]

Potential confounders

Potential confounders included age, level of education, study site, race, height (in cross-sectional analyses), BMI, smoking, physical activity, steroid/estrogen use and several chronic

diseases. These confounders are known to be associated with T levels as well as muscle strength and/or physical performance.

Education level was categorized as less than high school, high school graduate, and post-secondary school. BMI was calculated as measured weight (kg)/height $(m)^2$. Smoking status was categorized as never, former and current smoker. Physical activity (outdoor chores, heavy chores, housework, climbing stairs, high and medium intensity exercise, paid work and volunteer work) of the past seven days as well as information on the intensity level at which each activity was assessed by questionnaire. 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.[15] 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 and estrogen use were assessed by asking the respondents whether they used medication prescribed by a doctor. All medications were coded according to the Iowa Drug Information System (IDIS) code.[16] Chronic diseases were assessed by self-report, medication use and clinical data and included pulmonary disease, cardiac disease, diabetes mellitus, arthritis, cerebrovascular diseases, peripheral atherosclerosis and cancer.

Statistical analyses

Descriptive statistics (means ± SD, proportions) were calculated for all variables of interest. Median values with 25^{th} – 75^{th} percentile ranges were reported for variables that were not normally distributed. Because serum levels of total and free T were not normally distributed, analyses were performed using their log (ln) transformed values. Multiple linear regression analyses were used to identify regression coefficients per standard deviation in (ln) T levels for (change in) grip strength and physical performance score. Total T was then categorized into three categories: one category with levels of total T below the detection limit (≤ 20 ng/dl in 49% of the women), a second category with levels greater than 20 ng/dl and below 34.7 ng/dl (based on the median of detectable levels) and a third category with levels of total T of 34.7 ng/dl and higher. Free T levels were categorized into quartiles. The category with the highest level of total or free T was used as the reference group. First, cross-sectional associations between T levels and physical performance and muscle strength were investigated. Analysis of covariance was performed, using physical performance and muscle strength as continuous outcome measures. In a first model, results were adjusted for age, study site, and race. In a second model, results were additionally adjusted for all other potential confounders. We examined whether there was a linear trend across categories of total and free T

by including the categorical variables as an ordinal variable in a multiple linear regression. Second, we performed analysis of covariance to investigate the associations between T levels and three-year change in physical performance and muscle strength. In these analyses, baseline level of physical performance or muscle strength was added as a confounder to all models.

Potential differences in age, race, physical activity and BMI were tested by using age * T, race * T, physical activity * T and BMI * T product terms in additional analyses.

Results

Baseline characteristics of the study sample stratified by groups of total T levels are shown in Table 1. The baseline mean physical performance score was slightly lower in women with low total T (2.1 (standard deviation (SD) 0.5)) compared to women with intermediate total T levels (>20 to <34.7 ng/dl) and women with high total T levels (≥ 34.7 ng/dl, p = 0.004). Differences in three-year change in physical performance across the three total T groups was borderline significant (p = 0.09). The baseline mean grip strength was lowest (46.7 kg (SD 11.5)) in women with low total T levels, compared to women with intermediate and high total T levels. The mean three-year change was -1.9 kg (SD 7.9) in women with low total T, and -1.2 kg (SD 7.4) and -0.7 (SD 8.4) in women with intermediate and high total T levels (p = 0.11). The Spearman correlation between total and free T was 0.69 (p<0.01).

Continuous analyses

When using multiple linear regression analyses, continuous levels of (ln-transformed) total T were not associated with baseline grip strength or physical performance score and three-year decline in physical performance score (data not shown), but there was an association with three-year decline in grip strength (regression coefficient (B) 1.10, SE 0.45, p = 0.01 for grip strength). Similar results were found for free T (B 0.85, SE 0.33, p = 0.01 for grip strength.

Cross-sectional analyses

The associations between categories of total and free T and baseline physical performance and grip strength are shown in Table 2. No associations were found for total T with physical

Table 1

Female respondent characteristics of the Health ABC study, stratified by categories of total T.

Characteristic	*N*	TT ≤ 20 ng/dl	TT > 20 to <34.7 ng/dl	TT ≥ 34.7 ng/dl	*P* value
Age, yrs	1511	73.5 (2.9)	73.6 (2.9)	73.5 (2.8)	0.82
Education level					
low	353	21.8	25.0	25.0	
intermediate	592	39.3	39.1	39.6	
high	560	38.8	35.9	35.4	0.63
Study site [c]					
Pittsburgh	738	41.4	52.1	56.0	
Memphis	773	58.6	47.9	40.0	<0.001
Race [c]					
black	694	37.0	49.2	59.7	
white	817	63.0	50.8	40.3	<0.001
Smoking [c]					
never	867	56.4	60.4	56.6	
former	145	8.4	11.6	9.9	
current	497	35.2	28.0	33.5	0.10
Physical activity, kcal/wk [b]	1457	4568 [2671-7564]	4512[2626-7311]	4549 [2640-7262]	0.95
Height (m)	1510	1.60 (0.06)	1.59 (0.06)	1.60 (0.06)	0.66
Body Mass Index (kg/m2)	1510	27.0 (5.3)	27.6 (5.1)	29.2 (6.0)	<0.001
Chronic diseases, no. [b]	1511	1 [1-2]	1 [1-2]	1 [1-2]	0.65
Steroid use [c]	1505	3.8	2.6	0.8	0.01
Estrogen use [c]	1505	30.7	18.0	12.0	<0.001
Total testosterone, ng/dl [b]	1511	20 [20-20]	26.2 [23.1-30.1]	50.9 [41.4-67.8]	<0.001
Free testosterone, pg/ml [b]	1494	2.1 [1.4-3.0]	3.0 [2.2-4.0]	6.5 [4.7-9.9]	<0.001
SHBG, nmol/l [b]	1495	73.3 [45.9-126.0]	67.1 [46.7-96.7]	60.4 [41.5-87.0]	<0.001
Albumin, g/l	1510	39.4 (3.1)	39.7 (3.0)	39.6 (3.0)	0.26
Baseline physical performance (range 0-4)	1489	2.1 (0.5)	2.0 (0.5)	2.0 (0.6)	0.004
3-yr change in physical performance [a]	1100	-0.2 (0.4)	-0.1 (0.4)	-0.1 (0.4)	0.09
Baseline grip strength, kg	1417	46.7 (11.5)	46.9 (11.1)	48.2 (12.0)	0.11
3-yr change in grip strength, kg [a]	1090	-1.9 (8.0)	-1.2 (7.4)	-0.7 (8.4)	0.11

Results are presented in mean (SD), unless otherwise indicated; [a] range of change in physical performance from -2.1 to 1.3; range of change in grip strength from -46 to 34 kg; [b] results are presented in median [interquartile range]; [c] results are presented in percentages;

Table 2

Analysis of covariance of serum total and free testosterone concentrations with physical performance and grip strength

	N	Mean (SE) Model 1	*P* value	Mean (SE) Model 2	*P* value
Physical performance score					
Total T (ng/dl)					
≤ 20	734	2.06 (0.02)	0.10	2.05 (0.02)	0.48
> 20 to < 34.7	376	2.05 (0.03)	0.29	2.05 (0.02)	0.63
≥ 34.7 (ref)	379	2.01 (0.03)		2.04 (0.02)	
		P trend	0.08	*P trend*	0.49
FT (pg/ml)					
≤ 1.88	368	2.07 (0.03)	0.02	2.03 (0.03)	0.98
> 1.88 to ≤ 2.90	367	2.09 (0.03)	0.01	2.07 (0.02)	0.27
> 2.90 to ≤ 4.70	371	2.04 (0.03)	0.10	2.08 (0.03)	0.19
> 4.70 (ref)	366	1.98 (0.03)		2.03 (0.03)	
		P trend	0.01	*P trend*	0.94
Grip strength (kg)					
Total T (ng/dl)					
≤ 20	697	46.7 (0.42)	0.04	46.8 (0.40)	0.05
> 20 to < 34.7	362	47.0 (0.57)	0.16	47.4 (0.54)	0.28
≥ 34.7 (ref)	358	48.2 (0.58)		48.2 (0.56)	
		P trend	0.03	*P trend*	0.05
FT (pg/ml)					
≤ 1.88	349	46.7 (0.59)	0.08	46.4 (0.62)	0.04
> 1.88 to ≤ 2.90	349	47.0 (0.58)	0.14	47.2 (0.55)	0.14
> 2.90 to ≤ 4.70	355	46.7 (0.57)	0.06	47.3 (0.56)	0.18
> 4.70 (ref)	347	48.2 (0.59)		48.4 (0.58)	
		P trend	0.06	*P trend*	0.04

Model 1: adjusted for age, site and race;
Model 2: additionally adjusted for education level, physical activity, chronic diseases, height, body mass index, smoking, estrogen use and steroid use. SE=standard error. Multiply total T with 0.0347 to convert to nmol/l, multiply free T with 0.00347 to convert to nmol/l.

performance. Moreover, levels of free T were not associated with physical performance after full adjustment for confounding (model 2).

Lower levels of total T were associated with lower grip strength in model 1 (mean grip strength 46.7 kg (SE 0.42) in women with total T levels ≤ 20 ng/dl compared to a mean grip strength of 48.2 kg (SE 0.58) in women with total T levels ≥ 34.7 ng/dl, p = 0.04). When we adjusted for all other confounders (model 2), the association remained significant (p-value for trend across T groups was 0.05). Lower free T levels were also associated with lower grip strength (mean grip strength 46.4 kg (SE 0.62) in women with free T levels ≤ 1.88 pg/ml compared to a mean grip strength of 48.4 kg (SE 0.58) in women with free T levels > 4.70 pg/ml, p = 0.04, p-value for trend 0.04).

Longitudinal analyses

We then examined the associations of total and free T with three-year change in physical performance and grip strength (Table 3 and Figure 1). Women with low levels of total T showed a 2 times greater decline in physical performance compared to women with high levels of total T (p = 0.01).

Table 3

Analysis of covariance of serum total and free testosterone concentrations with 3-year change in physical performance

	N	Mean (SE) Model 1	*p*-value	Mean (SE) Model 2	*p*-value
Total T (ng/dl)					
≤ 20	532	-0.16 (0.02)	0.03	-0.16 (0.02)	0.01
> 20 to < 34.7	278	-0.14 (0.02)	0.14	-0.15 (0.02)	0.03
≥ 34.7 (ref)	253	-0.09 (0.03)		-0.08 (0.03)	
		P trend	0.03	*P trend*	0.01
FT (pg/ml)					
≤ 1.88	283	-0.13 (0.02)	0.43	-0.15 (0.03)	0.08
> 1.88 to ≤ 2.90	280	-0.13 (0.02)	0.39	-0.14 (0.02)	0.10
> 2.90 to ≤ 4.70	276	-0.19 (0.02)	0.02	-0.18 (0.03)	0.01
> 4.70 (ref)	252	-0.10 (0.03)		-0.08 (0.03)	
		P trend	0.84	*P trend*	0.17

Model 1: adjusted for baseline physical performance score, age, site and race;
Model 2: additionally adjusted for education level, physical activity, chronic diseases, body mass index, smoking, estrogen use and steroid use. SE=standard error. Multiply total T with 0.0347 to convert to nmol/l, multiply free T with 0.00347 to convert to nmol/l.

A significant interaction was found between age and total and free T on change in grip strength (p = 0.007 and p = 0.04, respectively). Figure 1 shows the associations of total and free T levels with decline in grip strength, stratified by two categories: age < 73.4 and age ≥ 73.4 (cut-off based on the mean). There were no significant associations found between total or free T with decline in grip strength in women who were younger than 73.4 years (n = 577). In the older women (≥ 73.4 years, n = 464) however, there was a clear linear trend towards greater loss of grip strength with lower levels of total and free T (p for trend 0.05 and 0.04, respectively).

No interactions were found between T levels and race, physical activity or BMI for any of the associations (p>0.10).

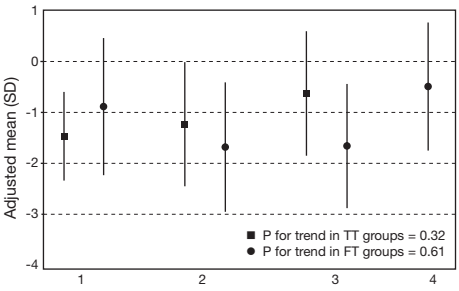

Figure 1A

3-year change in grip strength (kg) in women aged <73.4 years

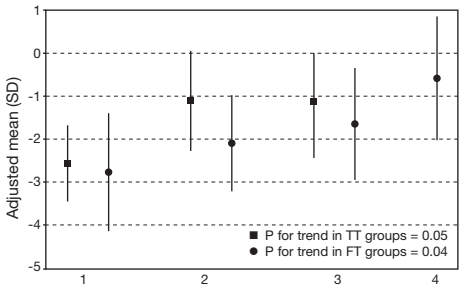

Figure 1B

3-year change in grip strength (kg) in women aged ≥ 73.4 years

Figure 1 A-B

*Analysis of covariance of serum total and free testosterone levels in women aged < 73.4 years (n=578)(A) and in women aged ≥ 73.4 years (n=466)(B) with 3-year change in grip strength according to 3 groups of total testosterone (■) and 4 groups of free testosterone (●). Analyses were adjusted for baseline grip strength, site, race, education level, physical activity, chronic diseases, body mass index, smoking, estrogen use and steroid use. 95% confidence intervals are expressed as a vertical line. * p<0.05.*

1:TT ≤ 20 ng/dl, FT ≤ 1.88 pg/ml;

2:TT >20 and <34.7, FT > 1.88 and ≤ 2.90;

3:TT ≥ 34.7 (ref), FT > 2.90 and ≤ 4.70;

*4: FT > 4.70. Multiply total testosterone with 0.0347 to convert to nmol/l, multiply free testosterone with 0.00347 to convert to nmol/l. P=0.007 for age*total testosterone interaction term, p=0.04 for age*free testosterone interaction term.*

Discussion

To our knowledge, this is the first study that examined the relationship between endogenous T levels and muscle strength and physical performance in older women. We were able to investigate this relationship from both a cross-sectional as well as a prospective vantage in a large sample of older women.

We found that low levels of total and free T were independently associated with lower baseline grip strength in all women under study and with greater three-year decline in grip strength in women aged 73.4 and over. Although we did not find any cross-sectional associations with baseline physical performance, low levels of total T were significantly associated with three-year decline in physical performance score.

In the past few years, there is an increasing interest in what has been termed 'Female Androgen Insufficiency' (FAI).[17] Main causes of FAI include surgical removal of the ovaries and aging. Symptoms of FAI are fatigue, low energy, sexual dysfunction and a decreased sense of well-being, but also decreased muscle strength and osteoporosis. Diagnosis of FAI is complicated; lab tests for T levels currently in use have been developed for measurement in men who have much higher levels than women, or for measurement in women with high levels of T. This implies that the current assays are less sensitive for measuring low T levels in women. We experienced this problem within our study, as half of the women had total T levels below the detection limit. Therefore, we used sample-specific categories of total and free T in this study. Another problem in diagnosing FAI is the lack of normal reference ranges for T levels in women. So far, few studies have provided values of total T in women within various age ranges.[1,18] In the Cardiovascular Health Study, women in the age range of 65 to 75 years had a mean total T level of 20.5 ng/dl (0.71 nmol/l and free T level of 2.8 pg/ml (9.76 pmol/l), that are comparable with the T levels in our study. Another study also found similar T values in women aged 65 years and older; a mean total T level of 20 ng/dl (0.69 nmol/l) and a mean FT level of 2.8 pg/ml (9.7 pmol/l).[18] However, these values should only be considered as a guideline, since values vary between different types of assays.

T treatment trials in women have mainly looked at the effects on sexual function, which were positive.[2-4] Only few studies examined the effects of T treatment on body composition in women. One small study demonstrated an increase in fat-free mass in post-menopausal women who were receiving estrogen plus T implants compared to those given estrogen alone.[5] Another study in forty post-menopausal women[19] also found improvements in body composition. One recent study, performed in young women (age 19-50 years) with hypopituitarism, demonstrated significant increases in lean body mass and thigh muscle mass with no effect on fat mass after treatment with T.[20] Whether T administration in women results

in increases in muscle strength or performance has never been studied, except in one small study[19] in which increases in lower body muscle strength were found in women receiving estrogen plus T. Based on those results and the results found in the present observational study, it may be worth investigating changes in strength and performance in women participating in T trials.

At present, no T drug has been approved by the Food and Drug Administration (FDA) for treatment in women, because of a lack of knowledge about long-term effects and safety. T treatment in women may increase the risk of cardiovascular disease, breast cancer, liver dysfunction, aggressive behavior and development of facial hair, a deeper voice and acne.[21] Despite these side effects, data from 2003 show that in the US, 21% (approximately 145,000) of all prescriptions for commercially available male T products were written for women.[22]

In women, the ovaries and adrenals produce 50% of T, whereas 50% is contributed by peripheral conversion (in adipose tissue, muscle and skin) of androstenedione into T.[23,24] T acts on multiple tissue and receptor sites, including central nervous system pathways and peripheral sites such as bone, breast, skeletal muscle and adipose tissue. It still remains unknown to what degree T action occurs via aromatization to estrogen. For example, T has direct actions on bone, but T also acts on bone via conversion to estrogen and estrone.[25] In contrast to men, there is a lack of understanding the physiological mechanisms regulating the homeostatic control of T and other androgens in women which warrant further investigation.

This study has several limitations. First, the women in this study were all well-functioning at baseline. This could explain the lack of cross-sectional associations between levels of T and physical performance. We did, however, use the Health ABC performance battery which is designed to minimize ceiling effects and maximize overall dispersion on each performance measure. Second, we measured hormone levels at a single point in time, which may not be representative of a woman's hormone profile over time. However, sex hormone levels are more stable among older (post-menopausal) women compared with pre-menopausal women.[26] In the future, it would be interesting to investigate if changes in T levels are associated with changes in muscle strength and physical performance. Last, a possible relationship between estradiol and muscle strength and performance has been recently suggested.[27] Adjustment for estradiol levels in our study was not possible, because these levels were not measured. However, we were able to adjust for estrogen use in the analyses. Future studies investigating testosterone-related changes in muscle strength and performance should take levels of estradiol into account.

The differences in grip strength and physical performance in women with low levels of T compared to women with higher levels are small. The clinical relevance of these findings

is unknown, since there is no clinical cut-off for T insufficiency in older women. However, because of the increasing interest in T therapy in women and the lack of knowledge about the effects of low T levels in women, the results of this study are important.

In conclusion, we found associations between low levels of total and free T with greater decline in grip strength and physical performance in older women, aged 65 years and older. Other observational studies are needed to confirm our findings and clinical trials with T treatment in older women should include outcomes such as (change in) body composition, muscle strength and physical performance. Furthermore, the development of a sensitive and specific T assay for women is critical for optimal assessment of T action and for the diagnosis of androgen insufficiency and its potential negative effects on health and functioning in (older) women.

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