Chapter 4

The association of sex hormone levels with poor mobility, low muscle strength and incidence of falls among older men and women

Abstract

Objective: The objective of this study was to examine whether low levels of oestradiol and testosterone are associated with impaired mobility, low muscle strength and the incidence of falls in a population-based sample of older men and women.

Design: Cross-sectional population-based study, based on data of the Longitudinal Aging Study Amsterdam (LASA), including 623 men and 663 women, aged 65–88 years.

Measurements: Serum levels of oestradiol, testosterone, albumin and sex hormone-binding globulin (SHBG) were measured. Physical performance, functional limitations and muscle strength were assessed, and a follow-up on falls was performed prospectively within 3 years.

Results: After adjustment for age, level of education, alcohol use, physical activity, chronic disease and body mass index (BMI), men in the highest quartile of the oestradiol/SHBG ratio had significantly higher physical performance scores than men in the lowest quartile (β = 0·103). Serum levels of total testosterone were positively associated with muscle strength (β = 0·085). Calculated bioavailable testosterone levels were positively associated with physical performance and muscle strength (β = 0·128 and 0·109 respectively). No associations of oestradiol levels with mobility were seen in women. Levels of oestradiol and testosterone were not associated with falls.

Conclusions: It can be concluded that low levels of sex hormones were associated with impaired mobility and low muscle strength in men, but not in women. Levels of sex hormones were not associated with the incidence of falls neither in men, nor in women.

Introduction

Falls and decline in mobility are major problems in the elderly. Approximately 30% of the community-dwelling people aged 65 years and older fall at least once per year, and about 15% fall two or more times per year.[1] The incidence of falls increases strongly withage from 30% at age 65 to 50% in those over 80 years of age.[1,2] Falls may result in hip fracture, other fractures, soft tissue injury, or headinjury, and may cause fear of falling and functional decline. More-over, falls are the third cause of chronic disability according to theWorld Health Organization (WHO).[3] Mobility limitations and fractures can lead to disability, institutionalization and death.[4,5]

Serum concentrations of testosterone decrease with age in both sexes, while oestradiol levels in men remain unchanged.[6,7] Serumtestosterone and oestradiol are mainly bound to sex hormone-bindingglobulin (SHBG) and albumin. The free fraction and albumin-boundpart of testosterone and oestradiol are often called bioavailable (non-SHBG-bound) testosterone and oestradiol, and are considered as the fractions that are directly available for the target tissues. It remains to be established whether total, non-SHBG-bound or free sex hormone levels are the best representation of the bioactive concentrations.

The results of some studies suggest that low serum levels of hor-mones, including vitamin D,[8] sex hormones[9] and insulin-like growthfactor (IGF-1),[10] are associated with immobility and an increased risk of falling. One study[9] on the effect of hormone replacement therapy (HRT) reports a protective effect on the risk of falling among early postmenopausal women. In another study,[11] the incidence of falls did not differ between users and nonusers of oe-strogen therapy. It is unclear whether low levels of oestradiol in women are related to a decrease in muscle strength. Studies on the effect of oestrogen therapy on postural balance and muscle strength in women are contradictory. Some studies found a positive effect of oe-strogen therapy on muscle strength and/or balance,[12-14] while others found no effect.[11,15,16]

Accumulating evidence suggests that in ageing men, low serum levels of bioavailable tes-tosterone are associated with low muscle strength,[17,18] thereby increasing the risk of falls. Studies on the effect of testosterone replacement found positive effects on muscle mass and strength.[19-21] However, the association of testosterone with muscle strength and poor mobil-ity is not clear. Until recently, not much attention has been paid to the role of oestradiol in men. One study found that oestradiol levels were not associated with muscle strength and body composition in men.[17]

The Longitudinal Aging Study Amsterdam (LASA), including similar numbers of men and women, is a prospective study in a representative sample of community-dwelling elderly. In this study, levels of oestradiol, testosterone, and a variety of other measures were assessed.

The objective of this study was to examine whether low levels of total and bioavailable oestradiol and testosterone were associatedwith impaired mobility, low muscle strength and the incidence of falls in a population-based sample of older men and women.

Methods

Study sample

Data for this study were collected within the LASA, an ongoing interdisciplinary cohort study on predictors and consequences of changes in physical, cognitive, emotional and so-cial functioning in older people.[22] A random sample of men and women, aged 55 and over, stratified by age, sex, urbanization and expected 5 years mortality, was drawn from the population registers of 11 municipalities in three regions of the Netherlands. The design of this study is presented in Figure 1. In total, 3107 subjects were enrolled in the baseline examination (1992/93). In the second data collection (1995/96), 2204 (71% of the original 3107 respondents) completed a main interview. Attrition between the first and second cycle was mainly the result of mortality: 417 of the 3107 (13·4%) respondents died.[23] All inter-views were conducted by specially trained and intensively supervised interviewers (main interview) and nurses (medical interview), and were tape recorded in order to monitor the quality of the data.

The present study was performed in a subgroup of the LASA, including participants who completed a medical interview during the second data collection (1995/96), including health-related questions and a number of physical and cognitive tests,[23] and were aged 65 years and older as of January 1, 1996. Of the 1720 eligible respondents, 1509 (87·7%) took part in the medical interview. These participants were invited to the VU University Medical Centre (VUMC) or a health care centre where blood and urine samples were obtained in the morn-ing after a light (calcium-free) breakfast (n = 1321). Blood was put on ice immediately, and processed within 60 min. Levels of sex hormones, SHBG and albumin were determined in 1285 people. Subsequently, fall data were collected with a fall calendar for 3 years in 1248 of these 1285 subjects. Informed consent was obtained from all participants and the study was approved by the Ethical Review Board of the VUMC.
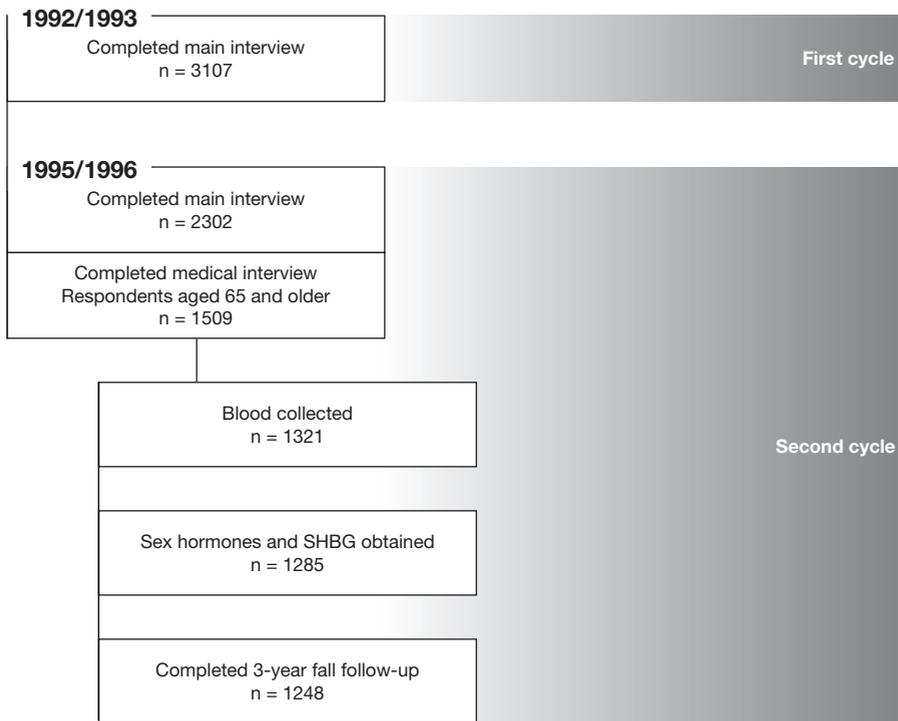
1992/1993

Completed main interview
n = 3107

First cycle

1995/1996

Completed main interview
n = 2302

Completed medical interview
Respondents aged 65 and older
n = 1509

Blood collected
n = 1321

Second cycle

Sex hormones and SHBG obtained
n = 1285

Completed 3-year fall follow-up
n = 1248

Figure 1

Study design

Mobility

Mobility included assessment of physical performance and selfreported functional limitations. The performance tests included a timed walking test (time needed to walk 3 m, turn 180° and walk back as fast as possible), chair stand test (time needed to stand up and sit down five times with arms folded), and tandem stand (ability to stand with one foot placed behind the other for at least 10 s).[24] Those completing the walking test and chair stands were assigned scores of 1–4, corresponding to the quartiles of time needed to complete the test, with the fastest time scored 4. Those who could not complete the test were assigned a score of 0. For the tandem stand, 0 points were given to those who could not perform the tandem stand, 2 points to those who stood less than 10 s, and 4 points to those who stood at least 10 s. The three items were summed to a final score (0–12).[24]

Self-reported functional limitations were assessed with a validated questionnaire concerning the degree of difficulty with the following six activities of daily living: climbing stairs, walking 5 min outdoors without resting, getting up and sitting down in a chair, dressing and undressing oneself, using own or public transportation, and cutting one's own toenails.[25,26] Participants who did not report any difficulty with the activities were given a score of 0; those who had difficulty with all activities were assigned a score of 6.

Muscle strength

Handgrip strength was measured using a strain-gauged dynamometer (Takei TKK 5001, Takei Scientific Instruments Co. Ltd, Tokyo, Japan). Participants were asked to perform two maximum force trials with each hand. For the final scores, the maximum values of the right and the left hand were summed, and divided by two.[25] Handgrip strength has been found to correlate with strength of other muscle groups and is thus a good indicator of overall strength.[27]

Falls

For a period of 3 years, participants were asked to report their falls on a fall calendar every week and to mail the calendar to the research centre every 3 months. Participants were contacted by telephone if they were unable to complete the fall calendar, if the calendar was not returned even after a reminder, or if it was completed incorrectly. A fall was defined as 'an unintentional change in position resulting in coming to rest at a lower level or on the ground'.[26] A 'recurrent faller' was defined as a subject who fell at least two times in 6 months during the 3-year fall follow-up.[28]

Assessment of hormones

Levels of testosterone, 17-beta-oestradiol and SHBG were obtained during the examination in 1995/96 and kept frozen until determination. Testosterone concentrations were measured by radio immunoassay (Coat-A-Count, DPC, Los Angeles, USA), with intra-assay coefficients of variance (CV) of 16% at 1·5 nmol/ l and 7% at 5 nmol/ l, interassay CV was 11% at 2·6 nmol/ l and 7% at 11·5 nmol/ l; oestradiol concentrations were measured by radio immuno-assay (Diasorin Biomedica, Saluggia, Italy), with intra-assay CV of 14% at 30 pmol / l and 7% at 100 pmol/ l, interassay CV was 10% at 70 pmol/ l. SHBG concentrations were measured

by immunoradiometric assay (Orion Diagnostica, Espoo, Finland) with intra-assay CV of 5% at 18 nmol/ l, interassay CV 6% at 10 nmol/ l. The detection limits of testosterone, oestradiol and SHBG were 1 nmol/ l, 18 pmol/ l and 6 nmol/ l, respectively. Levels of testosterone were not measured in women, as they were very low. We used various measures of the levels of bioactive testosterone and oestradiol: total testosterone and total oestradiol, testosterone/ SHBG ratio, oestradiol /SHBG ratio, calculated free testosterone and calculated bioavailable (calculated free testosterone plus albumin-bound) testosterone. Calculated free and bio-available testosterone were determined according to the method described by Vermeulen et al.,[29] taking the concentration of testosterone, oestradiol, SHBG and albumin into account. Calculated free oestradiol and bioavailable oestradiol levels in women could not be deter-mined, as levels of testosterone were not measured in women.

Effect modifiers

Age is considered a possible effect modifier in the relationship between sex hormones and falls, grip strength and mobility. It is possible that a stronger association of levels of sex hormones with mobility, grip strength and falls exists in older persons. Older people suffer from muscle deterioration and often have mobility limitations. Furthermore, they have fewer alternative mechanisms for preventing falls than younger people.

Confounders

Potential confounders included age, body mass index (BMI),[30] alcohol use, education,[31] cog-nition,[32] depressive symptoms,[33] chronic diseases[34,35] and physical activity.[31,36] BMI was cal-culated as weight (kg)/height (m)^2. Body weight was measured without clothes and shoes using a calibrated balance beam scale. Height was measured using a stadiometer. Alcohol use was assessed by asking the mean number of glasses of alcohol per week.[37] Education level was assessed by asking the respondent for the highest education level completed, ranging from incomplete elementary school to university education. This was converted into years of education, which ranged from 5 to 18 years. Cognition was assessed with the mini-mental state examination (MMSE) (score range 0–30).[38] Depressive symptoms were measured with the Centre for Epidemiology Studies-Depression (CES-D) scale. The cut-off point for depressive symptoms (CES-D≥16) and impaired cognition (MMSE≤23) were cho-sen at pre-established points.[38,39] Chronic diseases were assessed by self-report during the main interview and included pulmonary disease (asthma or chronic obstructive pulmonary

disease), cardiac disease, diabetes mellitus, arthritis, stroke and peripheral atherosclerosis. The number of chronic diseases was calculated. Physical activity was measured with the LASA physical activity questionnaire (LAPAQ). The LAPAQ is a face-to-face questionnaire that covers the frequency and duration of walking outside, bicycling, gardening, light household activities, heavy household activities, and a maximum of two sport activities during the previous two weeks.[40]

Statistical analysis

T tests, Mann–Whitney tests and χ^2 tests were performed to assess significant differences (P <0·05) in dependent variables between men (n = 623) and women (n = 662). Subjects with low levels of sex hormone were compared with those with high levels of sex hormone, using Student's t tests for continuous variables, Mann–Whitney test for skewed continuous variables, and a χ^2 test for dichotomized variables. The adjusted association between sex hormones and mobility or muscle strength was examined using multiple regression analysis. Associations are expressed as standardized regression coefficients because this measure allows direct comparison of the strengths of the association between different determinants with different outcome measures. The shape of the associations was examined by dividing sex hormone levels into quartiles. The relationship between sex hormones and several fall variables (two or more falls within 6 months; 0 vs. 1 or more falls during 3 years; 0–1 vs. 2 or more falls during three years; 0 –2 falls vs. 3 or more falls during 3 years; 0–3 vs. 4 or more falls during 3 years; 0–4 vs. 5 or more falls during 3 years) was examined using logistic regression analysis. Associations are expressed as odds ratios with a 95% CI. All analyses were stratified by sex.

Table 1

Characteristics of outcome measures in men and women

Outcome measures	N	Male	N	Female	P value*
Physical performance (range 0 –10)†	596	6·46 ± 2·39	631	5·54 ± 2·60	< 0·001
Muscle strength (range 1–136)†	615	71·06 ± 16·58	647	41·98 ± 9·86	< 0·001
Functional limitations (range 0 – 6)‡	616	0 [0 –2]	650	1 [0 –3]	< 0·001
Two or more falls within 6 months§	607	25·5	640	26·6	0·67

*Gender differences in mean values were examined with Student's *t* test and Mann–Whitney test, frequencies with χ^2-test; †results are presented in mean ± standard deviation; ‡results are presented in median [interquartile range]; §results are presented in percentages.

Table 2

Differences between lowest and highest quartiles of levels of oestradiol and testosterone for confounders, sex hormones and outcome measures

Variables	Male						Female		
	Testosterone 1st quartile	Testosterone 4th quartile	P value*	Oestradiol 1st quartile	Oestradiol 4th quartile	P value*	Oestradiol 1st quartile	Oestradiol 4th quartile	P value*
Age (year)	77·3 ± 6·6	74·2 ± 5·9	<0·001	75·5 ± 6·8	76·0 ± 6·3	0·47	74·8 ± 6·2	76·6 ± 6·6	0·01
Alcohol use (glasses/week)†	6 [5–21]	6 [1–21]	0·82	6 [1–20]	6 [1–21]	0·33	0·5 [0–3]	1 [0–6]	0·11
Education in years (range 5–18)	9·3 ± 3·3	10·1 ± 3·3	0·03	9·9 ± 3·7	9·9 ± 3·4	0·85	8·1 ± 3·1	7·7 ± 2·7	0·24
Body mass index	27·4 ± 3·4	24·9 ± 3·4	<0·001	25·2 ± 3·5	26·4 ± 3·1	0·002	25·2 ± 3·8	30·7 ± 5·2	<0·001
Physical activity (min/day)†	105 [49–184]	132 [75–186]	0·03	105 [60–186]	125 [71–176]	0·23	165 [108–225]	169 [109–240]	0·42
Number of chronic diseases†	1 [0–2]	1 [0–2]	0·47	1 [1–2]	1 [0–2]	0·37	1 [0–2]	1 [1–2]	0·05
CES-D score ≥ 16‡	9·0	6·4	0·39	15·1	7·5	0·03	18·1	21·8	0·36
MMSE score ≤ 23‡	20·5	12·8	0·06	20·8	16·4	0·3	13·9	21·8	0·06
Oestradiol, pmol/l	65·4 ± 21·8	89·6 ± 25·9	<0·001	49·4 ± 9·4	110·7 ± 17·0	<0·001	19·1 ± 2·5	50·2 ± 15·7	<0·001
Testosterone, nmol/l	9·6 ± 2·6	21·8 ± 3·0	<0·001	12·9 ± 4·8	18·3 ± 4·8	<0·001	–	–	–
Phys. performance (range 0–10)	6·1 ± 2·5	6·9 ± 2·3	0·008	6·3 ± 2·7	6·5 ± 2·1	0·36	6·0 ± 2·7	4·8 ± 2·4	<0·001
Muscle strength (range 10–136)	67·8 ± 16·3	74·0 ± 15·8	0·001	69·2 ± 15·9	71·3 ± 15·8	0·22	42·4 ± 10·4	40·9 ± 9·4	0·16
Funct. limitations (range 0–6)†	1 [0–2]	0 [0–1]	0·03	1 [0–2]	0 [0–1]	0·003	1 [0–2]	2 [1–4]	<0·001
Two or more falls within 6 months‡	22·7	23·2	0·43	30·3	27·1	0·13	28·6	26·4	0·41

All differences are measured in mean ± standard deviation, unless stated otherwise. *Differences in mean values between highest and lowest quartile were examined with Student's *t* test, in median with Mann–Whitney, in frequencies with χ^2-test. †Results are presented in median [interquartile range]; ‡results are presented in percentages.

First, unadjusted analyses were performed. Second, the potential confounders age, alcohol use, level of education and physical activity were added to the model. Then, the potential confounder BMI was added to the model, and eventually cognition and depression. As no significant change of the beta was seen when cognition and depression were added to the model, these variables were not kept in the model.

Results

This study sample (n = 1285) comprised 623 men and 662 women. Table 1 shows the differences in the dependent variables between men and women. Men scored significantly better on the mobility measures (physical performance and functional limitations) and muscle strength than women (P < 0·001). There was no gender difference in the percentage of subjects with two or more falls in 6 months (P = 0·67).

Table 3

Results of unadjusted and adjusted multiple regression analyses of total levels of serum oestradiol with physical performance, functional limitations and muscle strength in men and women.

Variables	Male			Female		
	Physical performance (n = 596)	Functional limitations (n = 616)	Muscle strength (n = 615)	Physical performance (n = 631)	Functional limitations (n = 650)	Muscle strength (n = 647)
Unadjusted	β	β	β	β	β	β
Total oestradiol	0·013	−0·044	0·021	−0·150***	0·171***	−0·045
Categories:						
Q1	Reference	Reference	Reference	Reference	Reference	Reference
Q2	0·035	−0·059	0·091	−0·041	0·080	0·006
Q3	0·010	−0·050	0·041	−0·057	0·099*	−0·018
Q4	0·033	−0·076	0·048	−0·190***	0·232***	−0·069
Adjusted†						
Total oestradiol	0·039	−0·056	0·023	−0·054	0·040	−0·051
Categories:						
Q1	Reference	Reference	Reference	Reference	Reference	Reference
Q2	0·002	−0·026	0·035	−0·008	0·030	−0·009
Q3	0·028	−0·054	0·043	0·016	0·016	0·001
Q4	0·045	−0·076	0·031	−0·059	0·062	−0·051

*P < 0·05; *** P < 0·001; Q = quartile; †adjusted for age, alcohol use, education level, physical activity, number of chronic diseases and body mass index.

Table 2 shows differences in potential confounders and dependent variables between the lowest and highest quartiles of levels of oestradiol (in men and women) and testosterone (in men). Men with low levels of testosterone scored significantly lower on physical performance and muscle strength and higher on functional limitations when compared with men with high levels of testosterone. Men with low levels of total testosterone were older, significantly less active, lower educated and had a higher BMI than men with high levels of total testosterone. Men with low levels of oestradiol had significantly more functional limitations, had lower BMI and had more depressive symptoms. Women with low levels of oestradiol had significantly fewer functional limitations, fewer chronic diseases and better physical performance than women with high levels of oestradiol. They were younger and had a lower BMI. Differences in the frequency of those with two or more falls in 6 months were not observed.

The associations between total oestradiol and physical performance, functional limitations and grip strength are shown in Table 3. In men, levels of total oestradiol were not associated with physical performance, functional limitations or muscle strength. In women, unadjusted analysis showed associations of total oestradiol with physical performance and functional limitations. The associations disappeared after adjustment for age, alcohol use, education level, physical activity, chronic disease and BMI. After adjustment, men in the fourth

Variables	Male		
	Physical performance†	Functional limitations†	Muscle strength†
Unadjusted			
Total testosterone	0·144***	−0·091*	0·130**
Categories:			
Q1	Reference	Reference	Reference
Q2	0·050	−0·066	0·097
Q3	0·075	−0·029	0·089
Q4	0·136**	−0·134**	0·166**
Adjusted†			
Total testosterone	0·061	− 0·007	0·085*
Categories:			
Q1	Reference	Reference	Reference
Q2	0·008	−0·030	0·087*
Q3	0·006	0·045	0·066
Q4	0·042	−0·046	0·135**

*P < 0·05; **P < 0·01; ***P < 0·001; Q = quartile. †Adjusted for age, alcohol use, education level, physical activity, number of chronic diseases and body mass index.

Table 4

Results of multiple regression analysis of total levels of serum testosterone with physical performance, functional limitations and muscle strength.

quartile of the oestradiol/SHBG ratio had a significantly better physical performance than men in the first quartile ($\beta = 0{\cdot}103$, data not shown). In women, levels of oestradiol/SHBG were not associated with physical performance, functional limitations or muscle strength.

Table 4 shows the associations of total testosterone with physical performance, functional limitations and muscle strength in men. Levels of total testosterone were associated with physical performance, functional limitations and muscle strength. After adjustment, total testosterone levels were significantly associated with muscle strength. Unadjusted analysis showed that testosterone/SHBG and calculated free testosterone were associated with physical performance, functional limitations and muscle strength (data not shown). After adjustment, testosterone/SHBG and calculated free testosterone were associated with physical performance.

Levels of calculated bioavailable testosterone were positively associated with physical performance, functional limitations and muscle strength (Figure 2). After adjustment, bioavailable testosterone was no longer associated with functional limitations. Men in the highest quartile of bioavailable testosterone had a better performance score and more muscle strength than men in the lowest quartile.

Table 5 shows the associations of levels of total oestradiol and testosterone with falls. Unadjusted analysis showed that total oestradiol and total testosterone were not associated with recurrent falling. The oestradiol/SHBG ratio, testosterone/SHBG ratio, free fraction of testosterone and bioavailable testosterone levels were significantly associated with recurrent falling in men, but not in women (data not shown). After adjustments for age, alcohol,
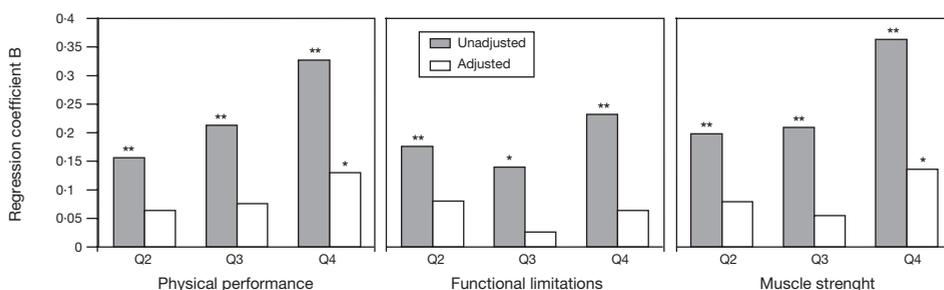

Figure 2

Associations of bioavailable testosterone (quartiles) with physical performance, functional limitations and muscle strength.

**P < 0·001; *P < 0·01; Q = quartile; gray bars represent unadjusted regression coefficients; white bars represent regression coefficients adjusted for age, alcohol use, education level, physical activity, number of chronic diseases and body mass index.

Table 5

Prevalence, adjusted OR and 95% CI for recurrent falling (≥ 2 falls in six months), according to total levels of oestradiol and testosterone, stratified by sex

Variables	Male (n = 608)			Female (n = 640)		
	Fallers (%)	OR unadjusted (95% CI)	OR adjusted† (95% CI)	Fallers (%)	OR unadjusted (95% CI))	OR adjusted† (95% CI)
Total oestradiol in categories:						
Q1	27·1	1·1 (0·7–1·8)	1·0 (0·6 –1·8)	27·1	1·1 (0·7 –1·8)	1·2 (0·7–2·1)
Q2	18·7	0·7 (0·4 –1·0)	0·7 (0·4 –1·1)	20·6	0·8 (0·4 –1·3)	0·8 (0·5 –1·3)
Q3	27·1	1·0 (0·6 –1·6)	1·0 (0·6 –1·6)	27·6	1·1 (0·7–1·9)	1·2 (0·7–1·9)
Q4	27·1	1·0 (ref)	1·0 (ref)	24·7	1·0 (ref)	1·0 (ref)
Total testosterone in categories:						
Q1	21·9	1·0 (0·6 –1·7)	1·0 (0·5 –1·8)			
Q2	25·8	1·1 (0·7–1·9)	1·0 (0·6 –1·8)			
Q3	29·7	1·4 (0·9 –2·4)	1·4 (0·8 –2·4)			
Q4	22·6	1·0 (ref)	1·0 (ref)			

OR = odds ratio; CI = confidence interval. Missing values were replaced with the mean value or median value of the variable. †Adjusted for age, alcohol use, education level, physical activity, number of chronic diseases and body mass index.

education, BMI, chronic disease and physical activity, no associations were observed between levels of serum sex hormones and recurrent fallers among men and women. When the sex hormone levels were divided in quartiles, no trend was seen. Moreover, there were no associations between sex hormone levels and any of the other fall variables (0 vs. 1 or more falls during 3 years; 0–1 vs. 2 or more falls during 3 years; 0–2 falls vs. 3 or more falls during 3 years; 0–3 vs. 4 or more falls during 3 years; 0–4 vs. 5 or more falls during three years) (data not shown).

Discussion

Ageing is associated with a reduction of levels of oestradiol and testosterone in men and women. This may contribute to the greater risk of poor mobility and falls in older people. This study included a large sample of both men and women. To examine our hypothesis, we used both objective tests and self-reports of mobility, and we collected prospective fall data.

The results of this study suggest that low levels of oestradiol and testosterone are associated with impaired mobility and low muscle strength in men, but not in women. We did not observe an independent association between levels of sex hormones and falls.

Studies on the effect of hormone therapy on falls are scarce. While Seeley et al.[11] reported a negative effect, Randell et al.[9] showed a positive effect of oestrogen replacement therapy on falls, but only in early menopausal women, suggesting that falls are particularly related to early menopausal oestrogen deficiency.

We found a positive association of (total, free and bioavailable) testosterone with muscle strength in older men. Our finding that there is an association of testosterone with grip strength confirms the results of other observational studies.[17,18] However, results of testosterone intervention studies are contradicting. Snyder et al.[41] did not observe an improvement in hand grip strength after treatment with testosterone, but others[19,42] found a positive effect of testosterone administration on muscle strength, and on hand grip strength in particular.43 It is difficult to compare these studies on effects of testosterone treatment, because of differences in type of androgen, length of treatment and type of administration (patch or injection).

No adjusted associations could be found of total oestradiol and the oestradiol/SHBG ratio with mobility or muscle strength in older women. Observational studies on the effect of oestradiol on muscle strength are scarce. Two studies did not observe an association between oestradiol and muscle strength.[17,18] Many postmenopausal women have used oestrogen therapy to maintain adequate oestrogen levels crucial for the preservation of bone mass.[44] One study[16] did not find a significant increase in hand grip strength in women using oestrogen, while another study[13] showed that oestrogen therapy resulted in a 15% increase in muscle strength. This increase is relatively small, compared to increases (30%) reported in resistance training studies.[45]

The results in the group of women are opposite to the results we expected. Table 3 shows negative, but nonsignificant, associations of oestradiol levels and oestradiol/SHBG ratio with physical performance and muscle strength. This implies that high serum levels of oestradiol are risk factors for poor physical performance and low muscle strength. Also, according to our results, women with high levels of oestradiol have more functional limitations than women with low levels. Possibly, these results can be explained by the fact that these women have a high body mass index (BMI). As oestradiol after menopause is mainly produced in adipose tissue, women with a high BMI have higher levels of oestradiol. Because BMI is a risk factor of impaired mobility, we believe that this explains the results we found in this study.

Known adverse effects of hormone replacement therapy (HRT) in postmenopausal women include an increased risk of breast cancer and venous thromboembolism.[46] Recently, Hays et al.[47] showed that the effect of HRT on quality of life in postmenopausal women was not clinically meaningful. Because of the severe adverse effects of hormone replacement therapy, and the modest benefits, the use of HRT has declined considerably during the last years. Based on our results, testosterone therapy in men might be useful to prevent agerelated immobility. However, large, long-term studies are needed to prove the beneficial effects and safety.

In this study, we used various measures of bioactive testosterone. According to Van den Beld et al.[17] bioavailable testosterone levels are the best representation of the bioactive testosterone levels. This was confirmed in our study, as the associations of total testosterone, testosterone/SHBG ratio and free testosterone were not as strong as the associations of bioavailable testosterone with mobility and muscle strength.

Our study has several limitations. First, the respondents of this study are a selective group of relatively healthy older men and women, because the frailest respondents of the LASA were not able to visit the hospital or a health care centre. If these nonresponders had lower serum levels of (bioavailable) testosterone and oestradiol, underestimation of the associations might have occurred. Second, an under-report may have occurred in participants during the fall follow-up. The falls were based on self-report, and older persons tend to forget falls.

In conclusion, no association of sex hormones with falls was found. Moreover, in women, no associations were found of oestradiol with mobility and muscle strength. In men, serum total testosterone was positively associated with muscle strength, bioavailable testosterone levels were positively associated with physical performance and muscle strength. The data do not support the use of hormone replacement therapy in women, whereas more studies are needed in men.

Acknowledgements

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