ORIGINAL ARTICLE

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Low Testosterone, but Not Estradiol, Is Associated With Incident Falls in Older Men: The International MrOS Study

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ABSTRACT

Fracture risk is determined by bone strength and the risk of falls. The relationship between serum sex steroids and bone strength parameters in men is well known, whereas the predictive value of sex steroids for falls is less studied. The aim of this study was to assess the associations between serum testosterone (T) and estradiol (E2) and the likelihood of falls. Older men (aged ≥65 years) from the United States ($n = 1919$), Sweden ($n = 2495$), and Hong Kong ($n = 1469$) participating in the Osteoporotic Fractures in Men Study had baseline T and E2 analyzed by mass spectrometry. Bioavailable (Bio) levels were calculated using mass action equations. Incident falls were ascertained every 4 months during a mean follow-up of 5.7 years. Associations between sex steroids and falls were estimated by generalized estimating equations. Fall rate was highest in the US and lowest in Hong Kong (US 0.50, Sweden 0.31, Hong Kong 0.12 fall reports/person/year). In the combined cohort of 5883 men, total T (odds ratio [OR] per SD increase = 0.88, 95% confidence interval [CI] 0.86–0.91) and BioT (OR = 0.86, 95% CI 0.83–0.88) were associated with incident falls in models adjusted for age and prevalent falls. These associations were only slightly attenuated after simultaneous adjustment for physical performance variables (total T: OR = 0.94, 95% CI 0.91–0.96; BioT: OR = 0.91, 95% CI 0.89–0.94). E2, BioE2, and sex hormone-binding globulin (SHBG) were not significantly associated with falls. Analyses in the individual cohorts showed that both total T and BioT were associated with falls in MrOS US and Sweden. No association was found in MrOS Hong Kong, and this may be attributable to environmental factors rather than ethnic differences because total T and BioT predicted falls in MrOS US Asians. In conclusion, low total T and BioT levels, but not E2 or SHBG, are associated with increased falls in older men. © 2017 The Authors. *Journal of Bone and Mineral Research* Published by Wiley Periodicals, Inc.

KEY WORDS: SEX STEROIDS; FALLS; PHYSICAL PERFORMANCE; GENERAL POPULATION STUDIES; MEN

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Introduction

Fracture risk is determined by both bone strength and the risk of falls. Many studies have investigated the relationship between serum sex steroids and bone strength parameters in men, revealing the importance of estradiol (E2) for trabecular and cortical bone properties.[1] In contrast, epidemiological evidence supporting a role of sex steroids for fall risk in men is limited and inconclusive.

Falls are a major public health concern in the aging population.[2] More than one-third of community-dwelling adults aged 75 years or older experience a fall each year. The likelihood of falling increases with advancing age, and falls are a leading source of injury and disability.[3] Serum levels of testosterone (T), and especially bioavailable (Bio) T, decrease with age in men, whereas serum E2 levels remain mostly unchanged.[4,5] Several epidemiological studies support the relation between this age-related decline in BioT levels and the reduced muscle strength, loss of lean mass, and impaired physical performance/mobility,[6–11] which in turn increase the risk of falls.[12] T therapy in older men with low serum T levels has been shown to increase physical ability and strength in some studies,[13–15] whereas others, including the recent T trial, described no or limited improvement in muscle strength after T treatment.[16–19] Low T levels, expressed as apparent free T concentrations, were associated with an increased likelihood of falls in 792 older men in the MINOS study.[20] The available data to date for incident fall risk are, however, inconsistent. Men with BioT levels in the lowest quartile (<175 ng/dL) had a 40% higher fall risk than those in the highest quartile as shown in 2587 men during a 4-year follow-up in the prospective MrOS US cohort, and this association persisted after adjustment for physical performance.[21] Yet, levels of total T were not associated with incident risk of falls in 623 older men in the LASA study.[7]

For all these studies, radioimmunoassay methods were used to measure serum sex steroid levels. However, these methods have been questioned for their limited accuracy and specificity, especially at lower concentrations.[22–25] No data are available documenting the association between serum sex steroid levels measured by mass spectrometry (MS), considered the gold standard, and the risk of incident falls in men. Therefore, this study prospectively investigated the relation between serum levels of T and E2, assessed by MS, and sex hormone-binding globulin (SHBG) and incident falls in a large population of older men.

Materials and Methods

Study sample

The Osteoporotic Fractures in Men (MrOS) study is an international multicenter, prospective study including older men in the United States ($n = 5994$), Sweden ($n = 3014$), and Hong Kong ($n = 2000$). In this study, associations between serum sex steroids, SHBG, and incident falls were investigated in all three cohorts separately and combined.

The MrOS US study enrolled 5994 community-dwelling men at six academic medical centers.[26,27] Eligible participants were at least 65 years old, could walk without assistance, and had not had bilateral hip replacement surgery. The MrOS US sample analyzed in the present study consists of 70.3% non-Hispanic white men, 11.5% African Americans, 8.8% Asians, and 9.4% other races and ethnicities. The institutional review board at each center approved the study protocol, and written informed consent was obtained from all participants.

The MrOS Sweden cohort consists of three subcohorts from three Swedish cities ($n = 1005$ in Malmö, $n = 1010$ in Gothenburg, and $n = 999$ in Uppsala). Study subjects (men aged 69 to 81 years) were randomly selected using national population registers, contacted, and asked to participate. To be eligible for the study, the subjects had to be able to walk without assistance, provide self-reported data, and sign an informed consent.[28] The study was approved by the ethics committees at the Universities of Gothenburg, Lund, and Uppsala. Informed consent was obtained from all study participants.

The MrOS Hong Kong cohort includes 2000 Chinese men aged 65 years or older who were recruited by advertisements placed in housing estates and community centers for older people. All subjects had to be community dwelling, able to walk without assistance, and not have had bilateral hip replacement. Stratified sampling was adopted to achieve approximately 33% of the participants in each of the three age groups: 65 to 69, 70 to 74, and ≥75 years.[29] The study protocol was approved by the Chinese University of Hong Kong ethics committee, and written informed consent was obtained from all participants.

Exclusion of participants with surgical or chemical castration (as treatment for prostate cancer), androgen or antiandrogen treatment and missing info on body mass index (BMI), prevalent falls, or incident falls resulted in 1919 men in the US, 2495 in Sweden, and 1469 in Hong Kong (combined 5883 men) who were eligible for analyses.

Assessment of covariates

In the MrOS cohorts, we used a standardized questionnaire to gather information about age, race/ethnicity, self-reported prevalent diseases (Parkinson's disease, angina, cancer, arthritis, diabetes, stroke, myocardial infarction, and hypertension), and use of central nervous system medication (benzodiazepines, nonbenzodiazepine anticonvulsants, narcotic analgesics, selective serotonin reuptake inhibitors, trazodone, and tricyclic antidepressants). Lifestyle factors such as falls (yes/no) during the last 12 months preceding the baseline visit, alcohol consumption, dizziness, use of walking aids (yes/no), and mobility limitation (difficulties walking 2 to 3 blocks or up 10 stairs) were also obtained from self-reports. Types of medication used regularly for the past month were coded during the clinical visit. Alcohol use was expressed as three or more glasses of alcohol-containing drinks per day, calculated from the reported frequency and amount of alcohol use.

Physical performance was estimated by measurements of hand-grip strength, a timed chair stands test, a 6-m walking test, and a 20-cm narrow walking test, as previously described.[30] Briefly, grip strength was measured on a Jamar hand dynamometer (Jackson, MI, USA). The maximum value (kilograms) from two trials from both hands was analyzed. The time to complete five chair stands (seconds) without using arms to rise was recorded. The duration (seconds) of the 6-m walk at usual pace was measured. Two scored trials were performed and the fastest walk was analyzed. The participants also walked the same 6-m course within a 20-cm narrow path as a measure of dynamic balance. Two scored trials with no more than two deviations from the narrow path were performed and the fastest narrow walk was analyzed. All tests were performed and

registered by research nurses or trained research staff according to standardized protocols.

Total body lean mass was assessed in MrOS Sweden at baseline using the Lunar Prodigy DXA (GE Lunar Corp., Madison, WI, USA) in the Uppsala and Malmö cohorts and the Hologic QDR 4500/A-Delphi (Hologic, Inc., Bedford, MA, USA) in the Gothenburg cohort. In MrOS US and Hong Kong, lean mass was measured using the Hologic QDR 4500/A-Delphi (Hologic, Inc.).

Standard equipment was used to measure height and weight. BMI was calculated by dividing the weight in kg by the height in meter squared.

Assessment of incident falls

Information on incident falls was collected by triannual mailed questionnaires (MrOS US and Sweden) or telephone contacts (MrOS Hong Kong). The participants were asked if they had fallen in the previous 4 months. The mean number of incident fall reports was 33.7 (range 1 to 47) for MrOS US, 7.8 (range 1 to 9) for MrOS Sweden, and 9.6 (range 1 to 12) for MrOS Hong Kong. For the combined cohort of 5883 men with available sex steroid measures, a total of 98,170 triannual fall reports were obtained of which 12,998 reported at least one fall. Participants were followed until the end of the study follow-up or death, emigration (for Sweden), or discontinuation from the study.

Serum analyses

A total of 2047 men (1602 randomly sampled and all eligible minorities with sufficient serum stored) from the MrOS US cohort were selected for assessment of sex hormone levels by gas chromatography (GC)-MS (Taylor Technology, Princeton, NJ, USA).[31] For T, the limit of detection was 2.5 ng/dL, the intra-assay coefficient of variation (CV) 2.5%, and the interassay CV 6.0%. For E2, the limit of detection was 0.625 pg/mL, the intra-assay CV 6.4%, and the interassay CV 10.1%. SHBG was assayed using an Immulite Analyzer with chemiluminescent substrate (Diagnostic Products Corp., Los Angeles, CA, USA) on the same samples previously thawed for the sex steroid measurements. The intra-assay CV was 4.6% and the interassay CV 5.8%.

A validated GC-tandem MS system (Endoceutics, Québec, Canada)[32–34] was used to analyze serum T (limit of detection 0.05 ng/mL, intra-assay CV 2.9%, interassay CV 3.4%) and E2 (limit of detection 2.00 pg/mL, intra-assay CV 1.5%, interassay CV 2.7%) in the samples from MrOS Sweden and Hong Kong. Serum was also assayed for SHBG using an immunoradiometric assay (Spectria, Orion Diagnostica, Espoo, Finland) with an intra-assay CV of less than 5.5% and an interassay CV of less than 6.9%. A random sample of 2645 and 1489 subjects in MrOS Sweden and Hong Kong, respectively, had sufficient serum available for assay of sex steroid hormones.

The majority of the MrOS US serum samples (97%) were morning samples. More than half of the subjects in Sweden (69%) had morning samples (drawn before 10:00 a.m.); the remaining were drawn around noon. All Hong Kong samples were morning samples. Accordingly, the various analyses were adjusted for time of serum sampling (morning sampling yes/no). Because the sex hormones were measured with two different MS methods, a cross-calibration of 50 samples was performed between the Taylor and Endoceutics laboratories. This revealed strong correlations between the E2 ($r = 0.96$) and T ($r = 0.98$) measurements at both sites, with a small bias toward higher E2 values and lower T values in the samples measured at the Taylor laboratory. To compare sex steroid measurements from these two different laboratories, the MrOS US Taylor sex steroid data were thus adjusted as follows: adjusted E2 = Taylor E2 – 1.9 pg/mL, adjusted T = Taylor T + 16.8 ng/dL. BioT and BioE2 levels were calculated using mass action equations described by Södergård and colleagues[35] and a fixed albumin concentration of 4.3 g/dL.

Sex steroid data (using a valid T measurement as reference) were available in 2022 participants in the US, 2639 Swedish men, and 1489 Hong Kong men.

Statistical analyses

The associations between serum levels of sex steroids and SHBG and incident falls were analyzed using generalized estimating equations (GEEs) in which the outcome falls was modeled from the repeated assessment of falls during each participant's follow-up. GEE models are an extension of generalized linear models for analyzing longitudinal data[36,37] and are advantageous in that they accommodate different lengths of follow-up and, within a participant's follow-up period, missing intervals. GEE models were fitted using the geeglm function in the R package geepack and a logit link.[38] The unit of analysis for statistical modeling was the response from the triannual follow-up questionnaires (fallen during the past 4 months yes/no). Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated from the models and expressed as a 1-SD increase (*Z*-score) in serum sex steroid or SHBG levels.

All estimates were adjusted for the following variables: age at baseline, prevalent falls, race, morning sampling (yes/no), site, and for the combined cohort, MrOS study cohort. A variable related to the triannual questionnaire, more specifically the number of the returned questionnaire or telephone contact (report number), was also included in the models as we previously described.[39]

Quadratic models were used to test for possible nonlinearity in the association between serum total T or BioT and likelihood of falls. We also used a restricted cubic spline approach for a flexible nonlinear assessment of the OR in relation to total T or BioT. The models were fitted using the gee function in the R package gee[38] and the rcs function in the rms package.[40] The number of knots was selected based on the smallest quasi-likelihood based information criterion (QIC).[41] We tested fitting 3, 4, and 5 knots and found 3 knots to give the smallest QIC. In these models, age at baseline, prevalent falls, race, morning sampling (yes/no), report number, site, and MrOS study cohort were used as covariates.

To evaluate whether the association between serum total T or BioT and falls was confounded by poor physical performance, further adjustments were made for physical performance variables (grip strength, timed chair stand, walking speed, and narrow walk), total body lean mass, and BMI.

The following baseline comorbidities were examined: alcohol use, prevalent medical conditions (Parkinson's disease, angina, cancer, arthritis, diabetes, stroke, myocardial infarction, hypertension), dizziness, use of walking aids, mobility limitations, and use of central nervous system medication. All these comorbidities were significantly associated with incident falls (statistical significance was set at $p < 0.05$).

Results

Characteristics of the study subjects

The baseline characteristics of the study subjects in the individual and merged MrOS cohorts are shown in Table 1

Table 1. Baseline Characteristics of the Study Subjects

	All cohorts ($n = 5883$)	MrOS US ($n = 1919$)	MrOS Sweden ($n = 2495$)	MrOS Hong Kong ($n = 1469$)
Age (years)	74.0 (4.8)	73.3 (5.7)	75.5 (3.2)	72.5 (5.0)
Height (cm)	171.4 (8.1)	173.6 (7.1)	174.7 (6.4)	163.0 (5.7)
Weight (kg)	76.6 (14.6)	82.7 (13.5)	80.5 (12.0)	62.1 (9.4)
BMI (kg/m^2)	25.9 (3.9)	27.4 (3.8)	26.3 (3.6)	23.4 (3.1)
Serum sex steroids				
Total T (ng/dL)	470 (184)	426 (157)	457 (176)	548 (204)
BioT (ng/dL)	243 (81)	217 (63)	242 (86)	280 (79)
Total E2 (pg/mL)	22.0 (9.9)	20.9 (7.7)	21.2 (7.5)	24.6 (14.4)
BioE2 (pg/mL)	15.1 (7.0)	14.2 (5.0)	14.7 (5.4)	16.8 (10.4)
SHBG (nmol/L)	49.1 (20.9)	49.1 (19.7)	47.8 (22.1)	51.1 (20.3)
Prevalent falls (*n*, %)	1000 (17.0)	372 (19.4)	407 (16.3)	221 (15.0)
Incident falls				
Follow-up time (years)	5.7 (4.6)	11.2 (4.3)	2.7 (0.6)	3.8 (0.7)
Participants with at least one incident fall (n, %)	2985 (50.7)	1578 (82.2)	963 (38.6)	444 (30.2)
Incident fall rate (number of reports with a fall/participant/year)	0.33 (0.52)	0.50 (0.56)	0.31 (0.56)	0.12 (0.24)

BMI = body mass index; T = testosterone; Bio = bioavailable; E2 = estradiol; SHBG = sex hormone-binding globulin.
Values are given as mean (SD) unless otherwise indicated.

and Supplemental Table S1. The mean age of the men in the combined cohort ($n = 5883$) was 74.0 years. MrOS subjects in Hong Kong had higher total T levels compared with the men in the US and Sweden (Table 1). Incident falls were ascertained triannually during a mean follow-up of 11.2 (US), 2.7 (Sweden), and 3.8 years (Hong Kong). The mean number of missing fall reports per participant and per year is higher in MrOS Sweden (0.13) and MrOS Hong Kong (0.39) compared with MrOS US (0.01). The incident fall rate (number of reports with a fall per participant and per year) was highest in the US and lowest in Hong Kong (Table 1). During an average follow-up time of 5.7 years, 50.7% of the men reported at least one fall. The incident fall rates of the participants in the individual cohorts of the current study (Table 1) are very similar to those in the corresponding total cohorts (MrOS US total cohort 0.52, MrOS Sweden total cohort 0.32, MrOS Hong Kong 0.12 reports with a fall per participant per year). Likewise, the percentage of participants with at least one fall during follow-up was also very similar for the total cohorts (MrOS US total cohort 83.7, MrOS Sweden total cohort 39.2, MrOS Hong Kong 29.4%) compared with the cohorts in the current study. The overall percentage of fallers in the merged total cohorts is higher than in the combined cohorts in the current study (61.8% versus 50.7%) because of a much larger number of participants in the total US cohort compared with the current US cohort and the already higher incident fall rate in MrOS US compared with MrOS Sweden and Hong Kong.

Serum total T and BioT as risk factors for incident falls

Prevalent falls at baseline strongly predicted the risk of incident falls in the combined set of cohorts (OR = 2.68, 95% CI 2.57–2.80) and in the three cohorts separately (data not shown). In the combined cohort of 5883 men, both serum total T and BioT were associated with a greater likelihood of incident falls in basic GEE models adjusted for age, prevalent falls, race, morning sample (yes/no), report number, site, and MrOS study cohort (Table 2). In contrast, serum levels of E2, BioE2, and SHBG were not significantly associated with incident falls (Table 2). Quadratic models indicated a nonlinear relationship between serum total T or BioT and fall risk ($p < 0.05$). To further explore this apparent nonlinear association, we performed restricted cubic spline analyses. The resulting plots illustrated that the increased likelihood of falls emerges most prominently for men with total T (Fig. 1*A*) or BioT levels (Fig. 1*B*) in the lowest quartile. In addition, we investigated the likelihood of falling in participants with hypogonadism, defined as serum total T $\leq$300 ng/dL[42] or BioT $<$163 ng/dL.[43,44] Both low total T (OR = 1.21, 95% CI 1.16–1.27) and low BioT (OR = 1.27, 95% CI 1.21–1.33) were associated with increased falls.

Serum total T and BioT as risk factors for incident falls independently of physical performance, lean mass, and comorbidities

To investigate whether the associations between serum total T and BioT and incident falls were mediated by lean mass or physical performance, we added physical performance variables (grip strength, timed chair stand, walking speed, and narrow walk) and total body lean mass to the basic models. The inverse association between both total T and BioT and the likelihood of falls persisted after adjustment for individual physical performance variables (data not shown). In

Table 2. Serum Sex Steroids and the Likelihood of Falls

	All cohorts ($n = 5883$)
Total T (per SD increase)	0.88 (0.86–0.91)
BioT (per SD increase)	0.86 (0.83–0.88)
Total E2 (per SD increase)	1.01 (0.98–1.03)
BioE2 (per SD increase)	1.02 (0.99–1.04)
SHBG (per SD increase)	0.98 (0.96–1.00)

T = testosterone; Bio = bioavailable; E2 = estradiol; SHBG = sex hormone-binding globulin.
Odds ratios are given with 95% CIs within parentheses. All estimates were adjusted for age at baseline, prevalent falls, race, morning sampling (yes/no), report number, site, and MrOS study cohort.

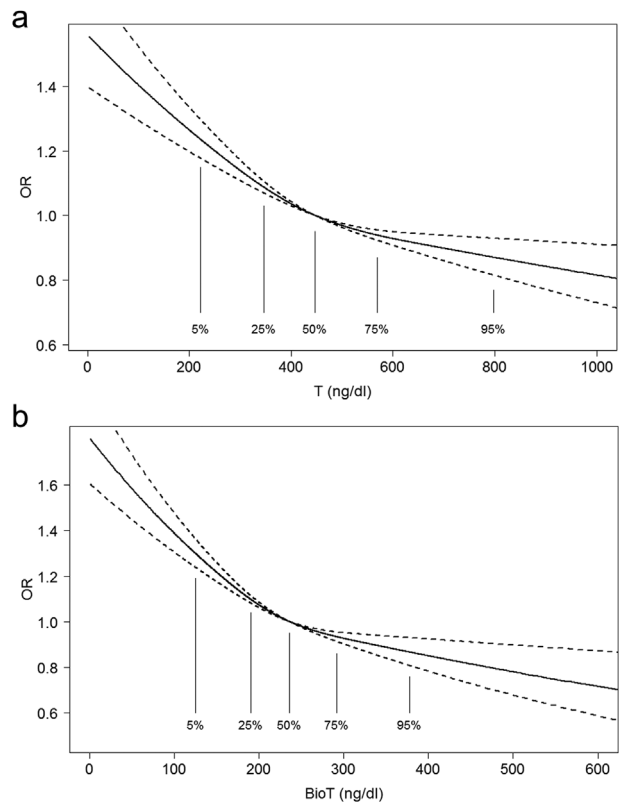

Fig. 1. Smoothed plots of the likelihood of incident falls according to serum total T and BioT concentrations. Odds ratios (ORs, solid line) and 95% confidence intervals (CIs, dashed lines) were estimated by restricted cubic spline analyses using the median total testosterone (T, 447 ng/dL) (Fig. 1*A*) or bioavailable testosterone (BioT, 236 ng/dL) (Fig. 1*B*) concentration as reference values. Three knots positioned at the 25th, 50th, and 75th percentiles of the serum total T or BioT concentration were used. The models were adjusted for age at baseline, prevalent falls, race, morning sampling (yes/no), report number, site, and MrOS study cohort. The cut-offs for the 25th and 75th percentiles are 346 and 569 ng/dL, respectively, for total T, and 190 and 292 ng/dL, respectively, for BioT.

addition, the associations were only slightly attenuated after simultaneous adjustment for all physical performance variables and lean mass (Table 3).

Similarly, the addition of multiple fall-related comorbidities (dizziness, walking aids, mobility limitations, alcohol use, use of central nervous system medication, and prevalent diseases [Parkinson's disease, angina, cancer, arthritis, diabetes, stroke, myocardial infarction, and hypertension]) to the basic models did not substantially change the associations between serum total T or BioT and falls (Table 3). Also, the addition of narcotic analgesics use alone to the model instead of combined central nervous system medication use did not affect the associations between total T (combined cohort: OR per SD increase = 0.94, 95% CI 0.91–0.96) or BioT (combined cohort: OR per SD increase = 0.91, 95% CI 0.88–0.94) and incident falls. Comparable results were obtained for total T and BioT when the basic models were adjusted for physical performance variables, lean mass, and comorbidities simultaneously (Table 3). Serum levels of E2, BioE2, and SHBG were not significantly associated with falls in any of the above multivariate models, confirming the data from the basic models (data not shown).

Table 3. The Effect of Physical Performance, Lean Mass and Comorbidities on the Association Between Serum Total T or BioT and Falls

	All cohorts
Base model	
Total T (per SD increase)	0.88 (0.86–0.91)
BioT (per SD increase)	0.86 (0.83–0.88)
Base model + physical performance	
Total T (per SD increase)	0.94 (0.91–0.96)
BioT (per SD increase)	0.91 (0.89–0.94)
Base model + comorbidities	
Total T (per SD increase)	0.94 (0.92–0.96)
BioT (per SD increase)	0.92 (0.89–0.94)
Base model + physical performance + comorbidities	
Total T (per SD increase)	0.97 (0.94–1.00)*
BioT (per SD increase)	0.94 (0.91–0.97)

T = testosterone; Bio = bioavailable.

Odds ratios are given with 95% CIs within parentheses. All estimates were adjusted for age at baseline, prevalent falls, race, morning sampling (yes/no), report number, site, and MrOS study cohort. Physical performance includes further adjustment for grip strength, timed chair stand, walking speed, narrow walk, lean mass, and BMI ($n = 5262$ after adjustment for physical performance and lean mass variables). Comorbidities include prevalent diseases (Parkinson's disease, angina, cancer, arthritis, diabetes, stroke, myocardial infarction, and hypertension), dizziness, walking aids, mobility limitations, alcohol use, and use of central nervous system medication ($n = 5701$ after adjustment for comorbidities). The models with combined adjustment for physical performance variables and comorbidities included 5105 participants.

*$p = 0.033$.

The association between serum total T or BioT and falls in relation to the duration of follow-up

We next evaluated the effect of the follow-up time on the associations between baseline serum total T or BioT and the likelihood of falls. The inverse associations between serum total T or BioT and incident falls were already significant after 1 year of follow-up (Table 4). Moreover, the results were essentially unchanged after 2, 3, and even 16 years of follow-up. To reduce the potential effect of subclinical or unrecognized disease, we performed the analyses excluding the first year of follow-up. This restriction did not affect the association between serum total T (combined cohort: OR per SD increase = 0.88, 95% CI 0.86–0.90) or BioT (combined cohort: OR per SD increase = 0.85, 95% CI 0.83–0.88) and incident falls.

The association between serum total T or BioT and falls in the individual cohorts

Analyses in the individual cohorts showed that in MrOS US and Sweden, serum total T and BioT associated inversely with incident falls in basic models adjusted for age, prevalent falls, race, morning sample (yes/no), report number, and site (Supplemental Table S2). In contrast, the associations were not significant in the MrOS Hong Kong cohort. Further exploratory analyses were performed in the Asian men participating in the MrOS US cohort (ie, not only Hong Kong Chinese but also men from other parts of Asia) with an incident fall rate of 0.33 reports with falls/participant/year. For these

Table 4. The Association Between Serum Total T or BioT and Falls in Relation to the Duration of Follow-up

	Total T (per SD increase)	BioT (per SD increase)
Follow-up time		
0–1 year	0.90 (0.85–0.96)	0.87 (0.82–0.93)
0–2 years	0.93 (0.89–0.97)	0.90 (0.86–0.94)
0–3 years	0.92 (0.88–0.95)	0.89 (0.85–0.92)
0–16 years (all data)	0.88 (0.86–0.91)	0.86 (0.83–0.88)

T = testosterone; Bio = bioavailable.

Odds ratios are given with 95% CIs within parentheses ($n = 5883$ for the combined cohort). All estimates were adjusted for age at baseline, prevalent falls, race, morning sampling (yes/no), report number, site, and MrOS study cohort.

participants ($n = 169$), baseline serum total T (OR per SD increase = 0.75, 95% CI 0.65–0.86) and BioT (OR per SD increase = 0.66, 95% CI 0.58–0.75) were significant predictors of incident falls in the basic models. Similar results were obtained when the follow-up time of the Asian men in MrOS US was limited to that of the MrOS Hong Kong cohort (total T: OR per SD increase = 0.67, 95% CI 0.55–0.83; BioT: OR per SD increase = 0.63, 95% CI 0.50–0.79).

Discussion

In this large, prospective study of older men, subjects with low total T or BioT had an increased fall risk. The association between both total T and BioT and falls was at least partly independent of physical performance and lean mass and remained relatively unchanged over time.

With aging, the serum levels of androgens in men decline, and these changes are related to the age-related occurrence of sarcopenia, frailty, and physical disabilities.[4] Because the reductions in muscle strength and physical performance in turn increase the likelihood of falling, it is postulated that the lower T levels in older men may contribute to the risk of falling. The associations between serum T and falls have earlier been prospectively investigated with contradictory results.[7,21] In the US MrOS cohort, serum T levels were associated with falls, whereas the association was not found to be present in LASA. However, in both studies, serum sex steroid concentrations were assessed by radioimmunoassay, a technique known to have a reduced specificity and accuracy, especially at lower concentrations.[22–25] In the present study, we evaluated the associations between serum sex steroids levels and SHBG and fall risk in a larger number of men participating in the three international MrOS cohorts, with serum E2 and T levels measured by the gold standard MS. We show that both low total T and BioT levels, but not E2, BioE2, or SHBG levels, were associated with an increased likelihood of falls in the combined cohort of older men during an average follow-up of 5.7 years. Further analyses showed that the relation between total T or BioT and fall risk was most prominent for those men with total T or BioT levels in the lowest quartile (total T <346 ng/dL, BioT <190 ng/dL). Similarly, the likelihood of falling was higher in hypogonadal men based on either low total T or low BioT levels. These data, using state-of-the-art MS for the assessment of serum sex steroids, confirm and extend a previous report in the US MrOS cohort using immunoassay for sex steroid measurement and with a shorter follow-up time.[21]

Adjustment for multiple fall-related comorbidities did not materially change the association between total T or BioT and fall risk. Also, in our study, the association between both baseline serum total T and BioT and the likelihood of falls did not diminish over time. The relation was already apparent after 1 year of follow-up and persisted up to 16 years of follow-up (the maximal follow-up time in MrOS US). In addition, the observed associations are most likely not confounded by prevalent diseases because results of models adjusting for comorbidity were similar and exclusion of the first year of follow-up did not alter the association between total T and BioT and falls.

The association of both total T and BioT with incident falls persisted and was only slightly attenuated after adjustment for physical performance and lean mass, similarly as previously reported in the US MrOS cohort.[21] This suggests that T affects the likelihood of falls at least partly independently of muscle mass and physical performance. Other factors contributing to fall risk are neuromuscular coordination and vision. Serum androgen levels were found to be associated with balance parameters. In the MINOS study, hypogonadism (total T <257 ng/dL) was associated with impaired static and dynamic balance.[20] Also, BioT was positively associated with balance in healthy men.[45] In the present study, we adjusted for balance by using our narrow walk performance test and results were only partially attenuated. In addition, we adjusted for medications affecting the central nervous system, dizziness, and alcohol use.

Analyses of the association between sex steroids and falls in the individual MrOS cohorts revealed distinct results. In both MrOS US and Sweden, serum total T and BioT were inversely associated with incident falls, whereas the associations were not significant in MrOS Hong Kong. The finding that total T and BioT significantly predicted fall risk in the MrOS US Asian participants (who not only originate from China but also from other Asian countries) suggests that the absence of a significant association between total T or BioT and falls in MrOS Hong Kong is not owing to ethnic differences but rather to environmental factors. Alternatively, this discrepancy can be explained by the difference in fall rate or reporting frequency in the three cohorts. The fall rate (number of fall reports per participant and per year) in Hong Kong is much lower than in the US and Sweden. The latter may, at least partly, be linked to the higher serum T levels in the Hong Kong men compared with men in the US and Sweden.[34] Also, the low fall rate and the lack of a significant association between total T and incident falls in MrOS Hong Kong may be linked to the fact that in this cohort fall data were collected by telephone contact, whereas incident falls were collected via questionnaires in the two other MrOS cohorts. Finally, the reduced prevalence of fall-related comorbidities in the MrOS Hong Kong cohort might also contribute to the lack of a significant association between serum T and falls in MrOS Hong Kong.

Our study has a number of strengths. It consists of the largest fall data set in men to date with a substantial follow-up period. Moreover, sex steroid levels are determined by the gold standard MS method. The ability to statistically adjust for a large number of fall-related covariates to limit cofounding is also a strength. This study has, however, limitations. The fall events are based on self-report, which may have resulted in recall bias. The fact that the number of missing fall reports is higher in the MrOS Hong Kong and MrOS Sweden cohorts compared with MrOS US is also a limitation. Moreover, the results are based on

single serum sex steroid measurements and may thus underestimate true associations. Other limitations include the inclusion of some non-morning samples, which might have contributed to increased variability, but this was adjusted for in all the analyses by time of sampling. In addition, a main limitation of the present study is that bioavailable sex steroid levels were calculated and not, as preferable, directly measured.[46] Yet, results for total hormone levels as well as less validated calculated bioavailable levels are shown because the latter have been and are still used in epidemiological studies. Finally, we have tried to adequately adjust for confounders in all our analyses but cannot rule out residual confounding.

In summary, we show that low total T and BioT, but not low E2 or SHBG, are associated with increased falls in older men. These data, using state-of-the-art MS for assessment of serum sex steroids, confirm and extend previous findings in the US MrOS cohort. Also, the effect of T on the likelihood of falling is mediated, at least partly, by muscle mass and physical performance. Both falls and bone strength parameters are independent predictors of fracture risk in older men. With the present data, we propose that low serum T influences fracture risk via an increased risk of falls, whereas low E2 might increase fracture risk mainly through reduced bone strength.

Disclosures

All authors state that they have no conflicts of interest.

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