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SHBG, Sex Steroids and Kyphosis in Older Men: the MrOS Study

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INTRODUCTION

Hyperkyphosis is an exaggeration of the normal sagittal convexity of the thoracic spine, affecting between 20% and 40% of older individuals.(1) Adverse health effects of hyperkyphosis include reduced pulmonary and physical function, and increased risk for falls and fractures.(1)

Despite the high prevalence and adverse consequences of hyperkyphosis, its underlying causes are poorly understood. Vertebral fractures contribute to hyperkyphosis, with each incident fracture increasing kyphotic angle by roughly 4 degrees.(2) Low bone mineral density (BMD) is significantly associated with kyphosis, and is a strong predictor of its progression over time.(2) Even so, among persons with the most severe kyphosis, studies suggest that only 1 in 3 have underlying vertebral fractures.(3,4) Other known contributors include age, family history, degenerative disc disease, and paraspinal muscle composition.(2,5,6) Rodent models suggest that loss of sex steroids may be associated with hyperkyphosis.(7,8) To our knowledge, no previous studies have addressed the association between endogenous sex steroid levels and kyphosis in older adults.

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The associations between estradiol, bone density and bone loss in older men have been well described.[9] High SHBG has also emerged as a predictor of bone loss and vertebral fractures in men.[9–11] If estrogen and SHBG influence these known predictors of kyphosis, then one might expect that sex steroids play a role in the development of accentuated thoracic kyphosis.

Our group previously reported that lower total and bioavailable estradiol, as measured by radioimmunoassay, was associated with worse kyphosis in older men.[12] The goal of this study is to examine the cross sectional association between serum sex hormones, as measured by the gold-standard mass spectrometry assay, and thoracic kyphosis in a multi-center cohort study of community-dwelling, older men.

MATERIALS AND METHODS

Participants

The MrOS Study is a prospective multicenter observational study of 5,994 community-dwelling men aged 65 and older, able to walk without assistance, and with no history of bilateral hip replacements recruited between 2000 and 2002 from six sites: Birmingham AL; Minneapolis, MN; Palo Alto, CA; Pittsburgh, PA; Portland, OR; and San Diego, CA. Detailed descriptions of the study design have been previously published.[13,14] The institutional review board at each center approved the protocol, and written informed consent was obtained from all participants.

Cobb angle of kyphosis measurements

The Cobb angle of kyphosis was measured from supine lateral spine radiographs taken at baseline. We used the modified Cobb method[15] with a fixed cut-off of T4 and T12. The SpineAnalyzer™ (Optasia Medical Ltd., Cheadle, UK) workflow tool was used to automate placement of 6 morphometric points to efficiently identify the vertebral bodies for evaluation. An expert rheumatologist (JTS) then reviewed, and if necessary modified, placement of the 6 points corresponding to the 4 corners of the vertebral body and the midpoints of the vertebral body endplates. From the superior surface of T4 and inferior surface of T12, a computerized digitization program erected perpendicular lines whose intersection was the kyphotic angle. If for any reason T4 or T12 were not visible, the adjacent vertebra (T5 if T4 not visible or T11 if T12 not visible) was used as an alternative. The intra-rater, intraclass correlation coefficient (ICC) for Cobb angle of kyphosis has been previously reported as 0.99.[15]

Vertebral fracture measurements

Vertebral fractures were assessed from baseline lateral lumbar and thoracic spine radiographs based upon a previously developed protocol.[16,17] Trained technicians assessed all radiographs for quality, and triaged each image as either “negative” (grossly normal) or “positive” (possible fracture or abnormality). All triage “positive” images were reviewed by an expert physician (JTS), using the well-established semi-quantitative Genant method.[17] Prevalent vertebral fractures were defined as grade 2 or 3.

Degenerative disc disease (DDD)

A disc was defined as having degenerative disease if the disc-wedging ratio was greater than 3 standard deviations below the level-specific sample and there was no fracture in the vertebral bodies on either side of the disc.[2] This last requirement was included to avoid misreading compensatory disc space changes as degenerative disease. An individual was classified as having degenerative disc disease if one or more of the 8 discs met the above degenerative disc criteria.[2]

Sex steroid measurements

Sex steroid assays were completed using stored serum collected at the MrOS baseline visit. Assays included total estradiol, total testosterone, and SHBG. Bioavailable estradiol and testosterone were calculated from mass action equations[18] using a fixed album concentration of 4.3 g/dl. Serum total testosterone and total estradiol were measured by a combined gas chromatographic negative ionization tandem mass spectrometry (GC/NCI/MS/MS) assay (Taylor Technology, Princeton NJ), and liquid chromatographic electrospray tandem mass spectrometry (LC/ESI/MS/MS) bioanalytical method. All assays were performed in duplicate. For total testosterone, the lower limit of detection was 2.5 ng/dL and the inter-assay CV was 6.0% (pooled serum, mean concentration 320.9 ng/dL). For total estradiol, the lower limit of detection was 0.625 pg/mL and the inter-assay CV was 9.9% (pooled serum, mean concentration 58.4 pg/mL). SHBG concentration was measured using an Immulite Analyzer with chemiluminescent substrate (Diagnostic Products Corp., Los Angeles CA). Samples were not replicated. The standard curve ranged from 0.2 – 180 nmol/L. The SHBG assay had an inter-assay CV of 6.0% (pooled concentration 34.3nM/L).

Other measurements

Age, race/ethnicity, history of fracture, falls in the past year, smoking (never, past, current), self-rated health (dichotomized as good/excellent or poor/very poor/fair), alcohol consumption (average number of drinks/week), weight at age 25 years, and self-reported physician diagnosis of diabetes, hypertension or arthritis/gout were assessed at the baseline visit. The Physical Activity Scale for the Elderly (PASE)[19] was self-administered. Height (cm) was measured on Harpenden stadiometers, and weight (kg) on regularly calibrated balance beam or digital scales using standard protocols, with participants wearing light clothing without shoes. Body mass index (BMI) was calculated as kg/m^2. BMD was measured in the proximal femur and lumbar spine using DXA measured by Hologic QDR 4500 densitometers. DXA CV and quality assurance measures have been previously described.[13]

The current analysis includes 1500 MrOS participants who were randomly selected to have Cobb angle kyphosis measured from their baseline radiographs and who had at least one valid serum sex steroid hormone at baseline, along with non-missing values in covariates.

Statistical Analysis

Means and distributions of each sex steroid hormone were evaluated and found to follow a normal distribution. Modeling each sex steroid hormone individually, first unadjusted analyses were run, followed by adjusting for age and clinical site. Using linear regression,

we further examined other potential confounders such as height, weight, body mass index, smoking, alcohol, physical activity, self-rated health status, total hip BMD, lumbar spine BMD, prevalent vertebral fracture, and DDD in relation to both the predictor and Cobb angle. Candidate covariates were screened using a p value < 0.1 for inclusion in a larger multivariable model.

While kyphosis was normally distributed and spline regression models revealed no obvious threshold effects, we divided the study sample into those who were considered hyperkyphotic (top quartile used as a cut-off at 45.6 degrees) compared with those in the bottom 3 quartiles to provide an estimate of how selected correlates may vary in those with normal kyphosis to those with accentuated thoracic curvature. We used multivariable logistic regression to assess the odds of hyperkyphosis. All analyses were performed using SAS statistical software (version 9.2; SAS Institute, Inc., Cary, NC, USA). Two-sided p values are reported with a value of $p < 0.05$ considered statistically significant.

RESULTS

Men had a mean age of 73.7 (SD = 5.9) years and a mean Cobb angle of 38.2 (SD=11.6) degrees. Compared to men in the bottom three quartiles, those in the top quartile of kyphosis (≥ 45.6 degrees) were older, had lower BMD, higher SHBG (48.1 vs. 52.0 nM/L, p=0.002), more DDD and more prevalent vertebral fractures (all $p < 0.05$) (Table 1). Sex steroid hormone levels did not differ between the groups.

Bioavailable estradiol was significantly associated with kyphosis in unadjusted linear regression analysis (beta-estimate −0.62 per SD increase; 95% CI: −1.23, −0.001, p=0.05), however this association was no longer significant once adjusted for age and clinic site or in fully adjusted models (Table 2). Results did not differ when kyphosis was analyzed as a dichotomous variable (Table 3).

There was no association between bioavailable testosterone and kyphosis, regardless of how analyzed. However, in linear regression analysis, there was a highly significant association between SHBG and kyphosis, even after adjustment for age and clinic site (Table 2). In the fully adjusted model, this association was weakened and of only borderline statistical significance ($p = 0.05$). Similarly, logistic models demonstrated that with higher SHBG, there was a near significant increase in the odds of hyperkyphosis (Table 3).

DISCUSSION

Although the effects of low sex steroid levels on male skeletal health have been well described, high SHBG is emerging as a potentially important predictor of adverse skeletal outcomes in older men. SHBG is associated with biomarkers of bone turnover, BMD, BMD loss, and prevalent fractures in older men.[9,20] In the same cohort of older men as this present study, Cauley demonstrated that high SHBG is associated with increased rates of bone loss, independent of sex steroid levels.[21] Cawthon recently showed, also in this same cohort, that high SHBG is associated with both prevalent and incident vertebral fractures.[10] Similarly, in the MrOS Sweden and Hong Kong cohorts, Vandenput demonstrated that high

SHBG levels predict incident clinical and radiographic vertebral fractures.[11] Our present study suggests an association between SHBG and thoracic kyphosis in older men.

The association between SHBG and kyphosis appears to be mediated, at least in part, by BMD. How SHBG may exert effects on BMD and kyphosis remains unclear. SHBG may exert its effects on bone by modulating bioactive sex steroid levels, however if this were the case, one would expect to see an association between the bioactive sex steroids themselves and kyphosis. Perhaps our ability to measure SHBG is superior to that of the sex hormones, explaining the disparate results. Another possible explanation is that SHBG influences the androgen to estrogen balance, as seen in women with elevated SHBG levels due to pregnancy or oral contraceptive use.[22] It is also possible that the association between SHBG and kyphosis is confounded by a third factor, such as IGF-1, which inversely correlates with SHBG[23], and has been shown, albeit inconsistently, to associate with BMD.[9] Although highly controversial, some have proposed that uptake of SHBG-bound sex steroids by plasma membrane receptors point toward additional roles for SHBG beyond that of a transport protein.[9,22]

SHBG is produced in the liver, circulates at high concentrations in childhood, decreases with puberty, and increases again with aging.[22] SHBG increases with certain medications (estrogens, anticonvulsants, TZDs[22]) and medical conditions (including hepatitis, cirrhosis, HIV and hyperthyroidism), however these factors are uncommon in MrOS participants and unlikely to explain the suggested association.

It is important to note that the absolute difference in SHBG between men in the top quartile of kyphosis compared to the lower three quartiles was small (52.0 vs. 48.1 nM/L, p=0.002), although statistically significant. Others have shown a threshold effect for SHBG around 50nM/L, with higher levels being associated with increased rates of bone loss.[9,21]

In a previous study in subjects from the same cohort, we reported, from RIA sex steroid measurements, a strong inverse correlation between bioavailable estradiol and kyphosis.[12] In the present study, in which estradiol was measured by LCMS, this association was much weaker and non-significant. Due to different analytic samples for the RIA compared with mass spec sex steroid measurements, we re-analyzed the data in a subset of 681 men in whom sex steroids were measured by both assays, with no change in our results. These disparate results are not entirely surprising given the only moderate correlation between total estradiol measurements by RIA vs. LCMS (Pearson correlation coefficient 0.58), with LCMS considered the gold-standard assay. It is possible, however, that despite its lower chemical specificity, the estradiol RIA may detect biologically active estrogen metabolites, and may therefore shed light on the in vivo relationship between estrogen and kyphosis.[24] While low bioavailable estradiol (by LCMS) was associated with bone loss in men from this same study cohort,[21] our present study's results (by LCMS) do not support that lower levels of bioavailable estradiol translate into worse kyphosis in older men. This result is somewhat surprising given that low BMD and accelerated bone loss contribute to the progression of age-related kyphosis.[2,25]

Limitations of this study include its cross-sectional nature. This sample population included only men, 90% of whom were Caucasian. The generalizability of these results to women and to men of other racial/ethnic groups is unclear. Bioavailable sex hormone levels were calculated from mass action equations, and not measured by the gold standard equilibrium dialysis method.[26] We were unable to consider paraspinal muscle mass or other measures of spinal muscle strength as possible mediators of the association between SHBG and kyphosis because paraspinal muscle measures were not available in the majority of our study sample. Study strengths include its size and the detailed measurements of radiographic kyphosis, vertebral fractures, bone mineral density and sex steroid hormone measurements.

In this sample of 1500 community dwelling older men, we found a suggestion of higher SHBG being associated with worse kyphosis, adding to recent literature reporting an association of SHBG with vertebral fracture risk. Contrary to our original hypothesis and similar to the negative study findings reported for vertebral fractures in men,[10,11] we found no association between sex steroids and kyphosis. Perhaps, estradiol having little to do with kyphosis supports the observation that the majority of older persons with the worst degrees of kyphosis do not have vertebral fractures. How SHBG may contribute to worse kyphosis and vertebral fracture risk is unclear and deserves further investigation.

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Table 1

Baseline characteristics by kyphosis group

Characteristic	All (N =1461–1500)[a]	Three lower quartiles (N = 1097–1125)[a]	Top quartile[b] (N =361–375)[a]	P value[c]
Age, yrs	73.7 ± 5.9	73.2 ± 5.7	75.2 ± 6.4	< 0.0001
Weight, kg	83.1 ± 13.2	83.5 ± 13.4	82.0 ± 12.6	0.06
Height, cm	174.1 ± 6.9	174.2 ± 6.9	173.8 ± 6.9	0.39
Body mass index, kg/m^2	27.4 ± 3.8	27.5 ± 3.8	27.1 ± 3.7	0.11
Spine BMD[d], gm/cm^2	1.16 ± 0.24	1.17 ± 0.24	1.13 ± 0.24	0.006
Hip BMD[d], gm/cm^2	0.95 ± 0.14	0.96 ± 0.14	0.93 ± 0.15	0.006
Physical activity, PASE score[e]	147.2 ± 68.9	148.0 ± 69.7	144.5 ± 66.5	0.39
Alcohol, drinks/week	4.6 ± 7.5	4.7 ± 7.9	4.1 ± 6.1	0.11
Estradiol, pg/mL	22.7 ± 8.8	22.7 ± 8.8	22.6 ± 8.7	0.8
Bioavailable estradiol, pg/mL	14.6 ± 5.5	14.7 ± 5.6	14.3 ± 5.4	0.3
Testosterone, ng/mL	402.3 ± 169.8	399.1 ± 167.1	412.0 ± 177.7	0.21
Bioavailable testosterone, ng/mL	205.0 ± 74.8	205.4 ± 73.2	203.8 ± 79.4	0.71
SHBG, nmol/L	49.1 ± 19.7	48.1 ± 19.1	52.0 ± 21.1	0.002
Smoking status				0.61
Never smoke	554 (36.9%)	409 (36.4%)	145 (38.7%)	
Past smoker	889 (59.3%)	671 (59.6%)	218 (58.1%)	
Current smoker	57 (3.8%)	45 (4.0%)	12 (3.2%)	
DDD[f], yes	980 (65.3%)	708 (62.9%)	272 (72.5%)	0.0007
Prevalent Vertebral fracture (PFx), yes	131 (8.7%)	86 (7.6%)	45 (12.0%)	0.01
Both DDD and PFx, yes	91 (6.1%)	55 (4.9%)	36 (9.6%)	0.0009
Hypertension, yes	669 (44.6%)	512 (45.5%)	157 (41.9%)	0.22
Diabetes, yes	177 (11.8%)	134 (11.9%)	43 (11.5%)	0.82

Characteristic	All (N =1461–1500)[a]	Three lower quartiles (N = 1097–1125)[a]	Top quartile[b] (N =361–375)[a]	P value[c]
Arthritis or Gout, yes	717 (47.8%)	530 (47.1%)	187 (49.9%)	0.35

[a] Different sample sizes due to missing values.

[b] Cut-off Cobb angle = 45.6 degrees.

[c] Three lower quartiles vs. top quartile.

[d] Bone mineral density

[e] Physical Activity Score for the Elderly

[f] Degenerative Disc Disease

Table 2

Multivariable linear regression models of each sex steroid hormone and SHBG in association with kyphosis

Covariate	Parameter Estimate (per SD sex hormone)	95% CI	p-value
Bioavailable Estradiol [*]			
Age/clinic adjusted	−0.56	−1.15, 0.03	0.06
Age/clinic/PFx	−0.53	−1.12, 0.06	0.08
Age/clinic/DDD	−0.54	−1.13, 0.05	0.07
Fully adjusted[a]	−0.38	−0.98, 0.22	0.21
Total Estradiol[§]			
Age/clinic adjusted	−0.34	−0.92, 0.25	0.26
Age/clinic/PFx	−0.31	−0.90, 0.27	0.29
Age/clinic/DDD	−0.33	−0.92, 0.25	0.26
Fully adjusted [*]	−0.21	−0.80, 0.37	0.47
Bioavailable Testosterone[#]			
Age/clinic adjusted	0.23	−0.36, 0.83	0.44
Age/clinic/PFx	0.24	−0.36, 0.83	0.43
Age/clinic/DDD	0.24	−0.35, 0.84	0.42
Fully adjusted [*]	0.18	−0.43, 0.79	0.57
Total Testosterone[$]			
Age/clinic adjusted	**0.62**	**0.04, 1.20**	**0.04**
Age/clinic/PFx	**0.61**	**0.03, 1.19**	**0.04**
Age/clinic/DDD	**0.63**	**0.04, 1.21**	**0.03**
Fully adjusted[a]	0.55	−0.06, 1.16	0.08
SHBG[@]			
Age/clinic adjusted	**0.76**	**0.16, 1.36**	**0.01**
Age/clinic/PFx	**0.73**	**0.13, 1.33**	**0.02**
Age/clinic/DDD	**0.76**	**0.16, 1.36**	**0.01**
Fully adjusted[a]	**0.61**	**−0.01, 1.23**	**0.05**

[a] Age, clinic site, degenerative disc disease (DDD), bone mineral density at the total hip (BMD), body mass index (BMI), prevalent vertebral fracture (PFx)

[*] 1 Standard deviation (SD) Bioavailable estradiol = 5.54 pg/mL

[§] 1 Standard deviation (SD) Total estradiol = 8.78 pg/mL

[#] 1 Standard deviation (SD) Bioavailable testosterone = 74.78 ng/dL

[$] 1 Standard deviation (SD) Total testosterone = 169.79 ng/dL

[@] 1 Standard deviation (SD) = 19.72 nM

Table 3

Multivariable Logistic Regression – Odds of being in the top quartile of kyphosis (per SD sex steroid)

Covariate	Odds Ratio	95% CI	p-value
Bioavailable Estradiol			
Age/clinic adjusted	0.96	0.85, 1.09	0.55
Fully adjusted	0.98	0.87, 1.12	0.80
Total Estradiol			
Age/clinic adjusted	1.00	0.89, 1.12	0.99
Fully adjusted	1.01	0.90, 1.14	0.85
Bioavailable Testosterone			
Age/clinic adjusted	1.04	0.92, 1.17	0.51
Fully adjusted	1.04	0.92, 1.18	0.52
Total Testosterone			
Age/clinic adjusted	1.10	0.98, 1.23	0.12
Fully adjusted	1.10	0.97, 1.24	0.14
SHBG			
Age/clinic adjusted	1.13	1.01, 1.27	0.04
Fully adjusted	1.12	0.99, 1.27	0.07