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Patterns of Menopausal Hormone Therapy Use and Hyperkyphosis in Older Women

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Abstract

Objectives—Hyperkyphosis, an exaggerated anterior curvature of the thoracic spine, is associated with poor physical function, falls, fractures, and earlier mortality. Low bone mineral density (BMD), bone loss and vertebral fractures are strong risk factors for hyperkyphosis. Menopausal hormone therapy (HT) reverses bone loss, prevents vertebral fractures and therefore, we hypothesize, may reduce the risk for developing hyperkyphosis.

Methods—We evaluated the cross-sectional association between Cobb angle of kyphosis from lateral spine radiographs and pattern of self-reported HT use during the prior 15-year period in 1063 women from the Study of Osteoporotic Fractures.

Results—Participants had a mean age of 83.7 ± 3.3 years and a mean Cobb angle of 51.3 ± 14.6 degrees. Forty-six percent of women were characterized as never users of HT, 24% as remote past users, 17% as intermittent users, and 12% as continuous users. In minimally-adjusted models, the mean Cobb angle was 4.0 degrees less in continuous HT users compared to never users ($p=0.01$), however in fully-adjusted models this association was attenuated to 2.8 degrees ($p=0.06$). Remote past HT users had 3.0 degrees less kyphosis compared to never users in minimally-adjusted models ($p=0.01$), attenuated to 2.8 degrees less in fully-adjusted models ($p=0.02$). Intermittent users did not differ from never users in degree of kyphosis.

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Conclusions—Women reporting continuous or remote past HT use had less pronounced kyphosis than never users by their mid-eighties, suggesting a possible role for HT in the prevention of age-related hyperkyphosis.

Keywords

kyphosis; menopause; hormone therapy; vertebral fracture; aging

Introduction

Hyperkyphosis is a clinical geriatric syndrome characterized by an exaggerated anterior curvature of the thoracic spine, creating the appearance of a forward stooped posture. Beyond the adverse aesthetic effects, hyperkyphosis is associated with poor physical function, increased risk for falls and fractures, and earlier mortality.^{1–4} Hyperkyphosis is commonly defined as a modified Cobb angle ≥ 40 degrees, and often progresses to well over 60 degrees in women 75 years of age and older.⁵ Low bone mineral density (BMD), bone loss and vertebral fractures, all of which are common in postmenopausal women, are strong independent risk factors for hyperkyphosis and its progression over time.⁶

The sharp decline in ovarian estrogen production during menopause transition contributes to accelerated bone loss. Menopausal hormone therapy (HT) reverses bone loss and prevents osteoporotic vertebral fractures. Bone density steadily increases during the first 3 years of HT, with maintenance of BMD during continued use thereafter.⁷ In the Women's Health Initiative (WHI) study, HT use was associated with significant approximately 35% reductions in risk of clinical vertebral fracture in both the estrogen-progesterone arm and the estrogen alone arm.^{8,9} Given the strong associations of bone loss and vertebral fractures with hyperkyphosis, HT use may be associated with a reduced risk for developing age-related hyperkyphosis.

Given that hyperkyphosis progresses gradually over time, differences between HT users and non-users may not become evident until many years after menopause. Therefore, in this cross-sectional analysis, we evaluated the modified Cobb angle of kyphosis in women in their mid-80's in association with the pattern and duration of HT use during the prior 15-year period. We hypothesized that greater consistency of HT use would be associated with less kyphosis.

Methods

Participants

The Study of Osteoporotic Fractures is a longitudinal, multicenter, observational study of 9,704 community dwelling women aged 65 and older, able to walk unassisted with no history of bilateral hip replacement, recruited between 1986 and 1988 from four clinics: Baltimore, MD; Minneapolis, MN; Monongahela Valley, PA; and Portland, OR. Nine thousand five hundred seventy-five participants had baseline lateral thoracic spine radiographs technically acceptable for interpretation by vertebral morphometry. From 2,696 women with acceptable baseline spine radiographs who completed follow-up films at year

3.7 and year 15, a random sample of 1000 participants was selected to participate in the current study. An additional 63 women were also included because they were SOF participants who had year 15 Cobb angle readings available for study, but were randomly selected because they either did not have all three films done ($n = 7$) or they happened to also have a sibling who was also a study participant ($n = 56$). Thus, the overall analytic sample included 1063 women, in whom detailed information on HT use over 7 clinic visits (beginning in 1986 and spanning an average of 15 years), and modified Cobb angle of kyphosis at year 15 were available.

Measurements

Hormone Therapy—HT use was based on self-report and was classified as continuous (current use reported at 6 or more of 7 visits), intermittent (current use reported at between 1 and 5 of 7 visits), remote past (reported past use at study baseline and no current use at any visit) or never.

Modified Cobb Angle of Kyphosis—Recumbent lateral thoracic spine radiographs were obtained at both baseline and year 15, with a tube-to-film distance of 40 inches, centered at T8. Using the year 15 radiographs, a translucent digitizer (GTCO, Rockville, MD) and cursor, a technician marked the four points corresponding to the four corners of the T4 and T12 vertebral bodies. X,Y coordinates for each point were marked on an electronic grid with a resolution of 0.1 mm. From the superior surface of T4 and the inferior surface of T12, a computerized digitization program generated perpendicular lines whose intersection is defined as the modified Cobb angle of kyphosis. The modified Cobb angle uses the anchors of T4 and T12 largely because T1-T3 are typically not well visualized on lateral spine radiographs. The intra-rater reliability intraclass correlation coefficient (ICC) for repeated measurements of digitized modified Cobb angle has been reported as 0.984.¹⁰ Readers were blinded to the HT status of participants.

Spine Radiographs and Vertebral Morphometry—Trained technicians triaged the year 15 lateral thoracic spine radiographs as either normal, probably fractured, or uncertain using semi-quantitative methods.¹¹ Films categorized as uncertain were reviewed by the study radiologist, who determined if the vertebra(e) were normal or probably fractured. Films with probably fractured vertebrae were evaluated with 6-point vertebral morphometry.¹²

Degenerative Disc Disease (DDD)—From the year 15 lateral thoracic spine radiographs, intervertebral disc heights were measured for the 8 discs between T4 and T12. Both anterior disc height (Ha) and posterior disc height (Hp) were measured at each level. Two disc height ratios were calculated at each interspace to define two types of deformity; the disc-wedging ratio (Ha/Hp) and the disc height compression ratio ($(2Ha_i + 2Hp_i)/(Ha_{i-1} + Hp_{i-1} + Ha_{i+1} + Hp_{i+1})$). For the uppermost and lowermost vertebral disc levels, only one adjacent level was used for comparison. Degenerative disc disease was defined as either 1.) a disc-wedging ratio greater than 3SD below the level specific sample mean or 2.) a disc height compression ratio < 0.8 and no vertebral fracture on either side of the disc.¹²

Other—Demographics and lifestyle factors were assessed by questionnaire at year 15, with the exception of family history of hyperkyphosis, which was ascertained at baseline with the question “Did your natural mother (or father) develop a ‘dowager’s hump’ or a spine that was stooped or bent forward”. Health behaviors were assessed, including smoking (current vs. past/never), alcohol use (days of drinking in the last 30 days, 0-6+), physical activity (sweat once per week from activity; yes/no/<1 per week), walking for exercise (yes or no) and self-reported health (excellent/good vs. fair/poor). Study personnel measured the participants’ height and weight, and calculated body mass index (BMI). Total Hip BMD was assessed by DXA (Hologic QDR 1000, Waltham, MA). Details of the DXA measurement and quality controls procedures have been previously described in detail.^{13,14}

Statistical Analysis

Participant characteristics at year 15 based on pattern of HT use were compared using t-tests for continuous and chi-squared tests for categorical variables. Using linear regression analyses, we first examined the cross-sectional association between modified Cobb angle of kyphosis at year 15 and pattern of prior HT use in age and clinic adjusted models. In multivariable linear regression analyses, we considered several potentially confounding and/or explanatory factors, including number of prevalent vertebral fractures, total hip BMD, body mass index, body weight, family history of hyperkyphosis, degenerative disc disease, history of arthritis, self-reported health, self-reported physical activity, alcohol use and smoking. Each potential covariate was chosen either because of a previously shown or postulated association with kyphosis progression. As an intermediate step, each covariate was added individually to the base model that included age and clinic. With age and clinic forced in the model, all other covariates that were individually associated with hyperkyphosis at 15 years in base models ($p < 0.10$) were further evaluated together in a linear regression model using manual backward stepwise selection, with a criterion of remaining in the model of $p < 0.10$. All statistical analyses were completed using SAS version 9.4 (SAS, Inc., Cary, NC).

Results

Characteristics of the study sample at year 15 are listed in Table 1. Women had a mean age of 83.7 ± 3.3 years, and a mean modified Cobb angle of 51.3 ± 14.6 degrees. Consistent with previous reports, the mean modified Cobb angle was higher in older individuals (mean modified Cobb angle of 49.5 ± 14.6 degrees in those aged 79–83 years versus 53.7 ± 14.3 degrees in those aged 84–97 years). A total of 46% of women were classified as never users of HT, 24% as remote past users, 17% as intermittent users, and 12% as continuous users. Bone mineral density was higher in continuous HT users compared to the other three groups. There were no differences between women categorized by pattern of HT use in body weight, degenerative disc disease, family history of hyperkyphosis, or number of prevalent vertebral fractures.

In age and clinic adjusted models, the mean modified Cobb angle of kyphosis was 4.0 degrees less in continuous HT users compared to never users ($p=0.01$), however in fully adjusted linear regression models (including age, clinic, number of prevalent vertebral

fractures, family history of hyperkyphosis, degenerative disc disease, total hip BMD and BMI) (Table 2), this association was attenuated to 2.8 degrees and of borderline statistical significance ($p=0.06$). Remote past HT users had 3.0 degrees less kyphosis compared to never users in age and clinic adjusted models ($p=0.01$), attenuated to 2.8 degrees in fully adjusted models ($p=0.02$). Intermittent users did not differ from never users in degree of kyphosis.

Discussion

In the first analysis of this kind, we demonstrate that older women reporting consistent or distant past use of HT over the prior 15 years had less pronounced kyphosis than never users by the time they reach their mid-eighties. In fact, those who reported remote use (prior to the mean age of 69.2) seemed to have the strongest protective effect against developing worse kyphosis. Those who were consistent users from the mean age of 69 to 84 also enjoyed a trend towards having less kyphosis, though in these women, the association appears to be mediated by effects on BMD, vertebral fracture, and other factors.

The mechanism by which HT use many years prior may influence hyperkyphosis is worth exploring. Several placebo-controlled studies of HT that followed participants after hormone withdrawal reported accelerated bone loss following HT discontinuation, exceeding rates observed in the placebo groups.^{15,16} Others have shown rates of bone loss after HT withdrawal equivalent to that of age-matched non-hormone users.⁷ One retrospective study which reported similar rates of bone loss in former HT users compared to never users also reported higher Z-scores an average of 3.2 years following HT withdrawal in former users, suggesting a residual benefit on BMD.¹⁷ In a cross-sectional study of 1500 postmenopausal women, categorized either as current, past or never users of HT, past users were found to have higher lumbar spine and total hip BMD than never users.¹⁸ There was also a trend toward higher TBS (trabecular bone scores) among past vs. never users ($p=0.066$).¹⁸

Beyond BMD, there may be other mechanisms by which HT can lead to less pronounced kyphosis in older women. The residual effects of HT may influence not only the vertebral bodies but also and other structures such as paraspinal muscles and intervertebral discs, both important determinants of hyperkyphosis. Lower paraspinal muscle and trunk lean mass are associated with worse kyphosis,^{19–22} and estrogen receptors are present in skeletal muscle.^{23,24} One study demonstrated that postmenopausal women using HT have significantly greater intervertebral disc heights compared to postmenopausal women who do not use HT.²⁵ The intervertebral discs are comprised of 100% collagen, and clinical studies have shown that exogenous estrogen administered to postmenopausal women increases both collagen content and the number of intermediate and mature collagen cross-links based on iliac crest biopsy.^{26–28}

Apart from self-reported HT use, we have previously examined the association between endogenous sex steroid hormone levels and kyphosis in older men from the MrOS study.²⁹ While high SHBG was more strongly associated with worse kyphosis in men, there was a trend toward an association between low bioavailable estradiol and greater degree of kyphosis in minimally adjusted models that appeared to be mediated by low BMD.²⁹

Clinical practice in terms of prescribing HT was dramatically altered by the publication of the WHI results in 2002. However, many skeptics still believe that there can be an important role of HT with health benefits outweighing the risks in the early postmenopausal woman. Our study results add evidence to that belief as those women who reported early use of HT enjoyed the strongest benefit against age-related kyphosis. Thus, there may be a window of time in which HT has a particular beneficial role. As an example of potential lingering benefit, more recent publications suggest that there may be a continued protective effect that extends for over a five year post-discontinuation.³⁰ Although the National Osteoporosis Risk Assessment longitudinal, observational study reported a rebound increase in hip fracture risk during the first five years after HT discontinuation,³¹ this rebound increase in fracture risk was not observed in post-intervention follow up studies from the WHI.^{31–33} In fact, extended post-intervention follow up, in which the intervention and post-intervention periods were evaluated together (mean 13.2 years cumulative follow up), there was demonstrated a 19% reduction in hip fracture risk in the estrogen-progesterone arm, but no risk reduction in the estrogen alone arm.³⁴ Watts reported the results of a per protocol analysis of the WHI, in which 10,134 participants from the estrogen-progesterone arm and 5053 participants from the estrogen alone arm were followed for 5 years after study termination. In the five-year post-intervention period, a 15% reduced risk for total fractures was observed in former estrogen alone users compared to the former placebo group.³⁰ This residual benefit was not observed in the estrogen-progesterone arm. Thus some but not all studies suggest that perhaps, contrary to earlier reports, HT may have residual benefits on BMD and fracture risk following cessation of therapy, re-opening the debate as to whether HT should be used in clinical practice, despite recent ACP guidelines that no longer support an indication for fracture prevention.³⁵

In addition to the protective effect against worse kyphosis observed in women who reported past or continuous HT use, we noted that women who reported intermittent use seemed to enjoy no benefit against worse kyphosis assessed 15 years later. These results are not necessarily unexpected. First, the window of most beneficial effect may actually be in the early post-menopausal period, not the time during which the intermittent use was assessed. Second, there may be unmeasured characteristics of those who report intermittent adherence versus those who are fully adherent that could influence health outcomes such as degree of kyphosis.

Strengths of this study include its relatively large sample size, long duration of follow up, and repeat assessments of HT use at 7 visits spanning an average of 15 years. Our study had several important limitations. We were unable to address total duration of HT use since menopause, or timing in relation to menopause, both of which may have influenced our results. HT use was self-reported, and restricted to systemic, oral formulations. As this is an observational study, a healthy user effect cannot be excluded. Finally, based on the study design, survivor bias is a potential concern. In the WHI, HT use was not associated with mortality risk³⁶ however more severe kyphosis is associated with greater mortality risk^{4,37}, thus those who might have become the most kyphotic may not have been included in this study.

Although 15 years have passed since the initial publication of the WHI results, the debate over HT use continues. While prescription rates for HT have declined dramatically since 2002,³⁸ survey data suggest that 2.5 million US women use compounded or bioidentical hormone therapy annually.³⁹ In 2015, the Endocrine Society published guidelines endorsing the use of HT for women < 60 years or < 10 years post-menopause, with bothersome vasomotor symptoms and no contraindications to treatment.⁴⁰ In 2017, the American College of Physicians Clinical Practice Guideline Update on Osteoporosis recommended against using menopausal estrogen or estrogen plus progesterone therapy for the treatment of osteoporosis in women.³⁵ However, these latest recommendations differ from their previous guideline in 2008 that reported high quality evidence of fracture prevention benefit in postmenopausal women or those with low bone density because more recent publications suggest more limited benefit in women with established osteoporosis. When evaluating the risks and benefits of HT for individual patients, in those who are <10 years post-menopause, fracture prevention and additional benefits such as prevention of age-related hyperkyphosis progression may outweigh the risks. However, as the results from the current study are based only upon observational data and not the findings from a randomized controlled trial, HT use should not be used solely for the prevention of hyperkyphosis, unless prescribed for other better-proven indications.

Conclusion

This cross-sectional analysis of patterns of HT use in association with kyphosis in older women found that continuous and remote past HT users had less hyperkyphosis than never users, assessed after an average of 15 years of study. The degree of difference between those who reported HT use ranged between three and four degrees, equivalent to the expected change in kyphosis caused by one vertebral fracture.⁴¹ As older women worry about their posture with age and wish to avoid development of the dowager's hump, our study results lend credence to the importance of reconsidering whether there might be a role for early postmenopausal treatment with HT to preserve bone mineral density, decrease fracture risk and perhaps even the likelihood of developing hyperkyphosis.

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Characteristics of the Study Sample, Year 15

Table 1

Characteristic, n(%) or mean (SD)	Pattern of HT use			
	Continuous	Intermittent	Remote Past	Never
n (%)	132 (12)	185 (17)	252 (24)	494 (46)
Age (yrs)	83.3 ± 3.0	83.4 ± 2.8	83.7 ± 3.0	83.9 ± 3.6
Cobb angle (degrees)	48.9 ± 15.4	51.5 ± 14.6	49.9 ± 14.0	52.6 ± 14.7
Total hip BMD (g/cm ²)	0.805 ± 0.136	0.733 ± 0.128	0.715 ± 0.116	0.704 ± 0.133
Weight (kg)	64.7 ± 11.4	64.0 ± 10.5	65.9 ± 12.1	65.6 ± 12.8
Family history of hyperkypnosis (%)	26.7	23.7	29.9	24.5
# Prevalent vertebral fractures *	0 (1, 6)	0 (1, 10)	0 (1, 7)	0 (1, 10)
DDD (%)	17.4	23.2	22.6	20.2

*Numbers are median (interquartile range, range).

Table 2

Linear Regression Analyses of the Association between Pattern of HT Use over 15 Years and Degree of Kyphosis at Year 15

Covariate	Age/Clinic adjusted model		Fully adjusted model*	
	β -estimate	p-value	β -estimate	p-value
Pattern of HT Use **				
Continuous	-4.0 (-7.0, -1.0)	0.01	-2.8 (-5.6, 0.1)	0.06
Intermittent	-1.5 (-4.1, 1.0)	0.24	-1.5 (-3.9, 0.9)	0.22
Remote Past	-3.0 (-5.3, -0.7)	0.01	-2.8 (-4.9, -0.6)	0.02
Never	Referent			
Age	0.5 (0.2, 0.8)	0.0002	0.2 (-0.02, 0.5)	0.07
Clinic ***				
Baltimore	-0.6 (-3.2, 2.0)	0.65	0.4 (-1.9, 2.8)	0.72
Pittsburgh	-1.9 (-4.2, 0.4)	0.10	-1.0 (-3.1, 1.1)	0.36
Portland	0.4 (-2.3, 3.0)	0.78	0.1 (-2.4, 2.6)	0.93
# Prevalent Vertebral Fractures ****				
1			5.8 (3.3, 8.2)	<0.0001
2+			13.3 (10.5, 16.0)	<0.0001
0	Referent			
Family History of Hyperkyphosis			3.7 (1.8, 5.6)	0.0001
Degenerative Disc Disease			1.3 (-0.9, 3.5)	0.24
Total Hip BMD (g/cm ²)			-11.0 (-18.5, -3.5)	0.004
Weight (kg)			-0.09 (-0.2, -0.01)	0.03

* Adjusted for age, clinic, #prevalent vertebral fractures, family history hyperkyphosis, degenerative disc disease, total hip BMD, and body weight

** Reference is Never use

*** Reference is CLINIC = 2 (Minneapolis) [1=Baltimore, 2=Minneapolis, 3=Pittsburgh, 4=Portland]

**** Reference is # Prevalent Vertebral Fractures = 0