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Thoracic Kyphosis and Rate of Incident Vertebral Fractures:

The Fracture Intervention Trial

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Wendy B. Katzman, Eric Vittinghoff, Deborah M. Kado, Nancy E. Lane, Kristine E. Ensrud, and Kathy Shipp declare that they have no conflict of interest.

Mini-abstract: Biomechanical models support the theory that thoracic spine hyperkyphosis increases risk of new vertebral fractures. While greater kyphosis increased the rate of incident vertebral fractures, our analysis does not show causal effects of kyphosis on incident fracture. Excessive kyphosis may still be a clinical marker for prevalent vertebral fracture.

Purpose. Biomechanical models suggest hyperkyphosis increases risk of incident vertebral fracture by increasing load on vertebral bodies during daily activities. We propose to assess the association of kyphosis with incident radiographic vertebral fracture. **Methods.** We used data from the Fracture Intervention Trial among 3,038 women 55-81 years of age with low baseline bone mineral density (BMD). Baseline kyphosis angle was measured using a Debrunner kyphometer. Vertebral fractures were assessed at baseline and follow-up from lateral radiographs of the thoracic and lumbar spine. We used Poisson models to estimate the independent association of kyphosis with incident fracture, controlling for age and femoral neck BMD. **Results.** Mean baseline kyphosis was 48 (SD=12) (range 7-83) degrees. At baseline, 962 (32%) of participants had a prevalent fracture. There were 221 incident fractures over a median of 4 years. At baseline, prevalent fracture was associated with 3.7 degree greater average kyphosis (95% CI 2.8-4.6, $p<0.0005$), adjusting for age and femoral neck BMD. Before adjusting for prevalent fracture, each 10-degree greater kyphosis was associated with 22% increase (95% CI: 8% to 38%, $p=0.001$) in annualized rate of new radiographic vertebral fracture, adjusting for age and femoral neck BMD. After additional adjustment for prevalent fracture, estimated increased annualized rate was 8% per 10 degrees kyphosis (95% CI -4% to 22%, $p=0.18$). **Conclusions.** While greater kyphosis increased rate of incident vertebral fractures, our analysis does not show causal effects of kyphosis on incident fracture. Excessive kyphosis may still be a clinical marker for prevalent vertebral fracture.

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Introduction

Age-related hyperkyphosis, an excessive anterior curvature in the thoracic spine, is common among older women and men, and is associated with substantial increase in morbidity and mortality. Longitudinal cohort studies have reported an increase in total number of fractures over 4 years,¹ as well as an increase in non-spine fracture risk over 15 years among older women with hyperkyphosis.² Biomechanical evidence suggests that hyperkyphosis increases the load on vertebral bodies,^{3,4} and may increase the risk of incident vertebral fractures in individuals with low bone mineral density (BMD), in particular when the spine is flexed during activities of daily living (ADL).^{4,5} In addition, vertebral fracture contributes to hyperkyphosis.⁶⁻⁸ Based on these observations, we speculate that hyperkyphosis may be a marker for a past vertebral fracture and a modifiable risk factor for incident vertebral fracture.

To our knowledge there are no published studies that have examined whether hyperkyphosis is an independent risk factor for incident vertebral fracture. We used data from the Fracture Intervention Trial to assess the association of kyphosis with incident morphometric vertebral fracture over a median of 4 years among 3,038 women 55-81 years of age with low baseline BMD.

Methods

Overview

The Fracture Intervention Trial (FIT) was a randomized, controlled multicenter trial among 6,459 women with osteopenia or osteoporosis who were randomized to alendronate or placebo to test the efficacy of alendronate for reduction of risk of osteoporotic fractures.¹⁰ Women randomized to the placebo arm of FIT, including women with and without radiographic vertebral fracture, were included in these analyses.

Subjects. Women included in FIT were required to be 55-80 years of age, post-menopausal for at least 2 years, live independently in the community, and have a bone mineral density (BMD) of the femoral neck 1.6 or more standard deviations (SD) below peak premenopausal femoral neck BMD (less than 0.68 g/cm²). Of the 3,223 women in the placebo arm of FIT 3,038 women with complete data were included in our analyses. One third of the women randomized to the

placebo arm of the study had prevalent radiographic fractures at baseline.

Co-variates. Baseline kyphosis angle was measured using a Debrunner kyphometer (Proteck AG, Bern, Switzerland), a protractor-like instrument. The ends of the device are placed over the spinous process of C7 superiorly and T12 inferiorly, and the protractor reads the kyphosis angle formed at the crotch of the 2 arms (Figure 1).⁶ This measurement of kyphosis angle has excellent reliability and repeatability (intra-rater and interrater correlation coefficients both 0.91).⁹ Baseline height was measured using a standard stadiometer protocol and height loss (mm) was calculated compared to self-reported height at age 25. Bone mineral density at the hip and spine was measured using the QDR 2000 (Hologic, Inc., Waltham, MA, USA). Quality control measures have been detailed in other publications.¹⁰ Vertebral fractures were assessed at baseline and follow-up using a standardized digitization and semi-quantitative classification method from lateral radiographs of the thoracic and lumbar spine that has been described previously.¹⁰

Statistical analysis. We used Poisson models with robust standard errors¹¹ to estimate the independent association of kyphosis with incident VF, using an offset to account for variations in trial follow-up, and controlling for age and femoral neck BMD. Based on preliminary analysis using the Lowess smoother, we modeled the effect of kyphosis angle using a linear spline with a single knot at 36 degrees. In addition to models with and without adjustment for baseline VF, we estimated the association of kyphosis with incident VF stratified by this factor, and tested for interaction.

Results

The mean age of our cohort was 68 (SD=6.1) years, with a mean total hip BMD of 0.58 (SD=.06) g/cm² (Table 1). Mean baseline kyphosis was 48 (SD=12) (range 7-83) degrees. At baseline, 962 (32%) of participants had a prevalent radiographic vertebral fracture. There were 221 incident fractures over a median follow-up of 4.0 years (range 1.0-4.8). The vertebral fracture incidence proportions increased linearly across quartiles of kyphosis (Table 2).

In the stratified analysis, the estimated effect for each 10-degree greater baseline kyphosis was 1.06 (0.93-1.22 p = 0.39) among women with a prevalent vertebral fracture at

baseline. This increased to 1.17 (95% CI 0.93-1.47, $p = 0.18$) among those without vertebral fracture at baseline (p -value for interaction 0.48). Given no evidence for interaction, the groups with and without prevalent vertebral fracture were combined for all subsequent analyses.

At baseline, prevalent radiographic vertebral fracture was associated with a 3.7-degree greater average kyphosis angle (95% CI 2.8-4.6, $p < 0.0005$), after adjustment for age and femoral neck BMD. Before adjustment for prevalent vertebral fracture, each 10-degree greater kyphosis above 36 degrees was associated with a 22% increase (95% CI: 8% to 38%, $p = 0.001$) in the annualized rate of new morphometric vertebral fracture, controlling for age and femoral neck BMD (Table 3). After additional adjustment for prevalent vertebral fracture, the estimated increase in the new vertebral fracture rate was 8% per 10 degrees in kyphosis (95% CI -4% to 22%, $p = 0.18$). In this final model, prevalent vertebral fracture was independently associated with a 4.2-fold increase in the new vertebral fracture rate (95% CI 3.1-5.5, $p < 0.0005$). Results were similar in a sensitivity analysis adjusting for lumbar spine rather than femoral neck BMD. Specifically, the estimated effect of each 10-degrees in baseline kyphosis declined from 1.16 (95% CI 1.02 -1.31, $p = 0.19$) before adjustment for prevalent vertebral fracture to 1.05 (95% CI 0.93-1.18, $p = 0.43$) after adjustment.

Discussion

In this analysis of 3,038 women in the Fracture Intervention Trial, we found a statistically significant 22% increase in the annualized rate of incident morphometric vertebral fracture for each 10-degree increase in kyphosis angle, after adjustment for age and BMD. However, after additional adjustment for baseline prevalent vertebral fracture, the estimated increase was only 8% and no longer statistically significant.

Prevalent vertebral fracture is a well-established risk factor for incident vertebral fracture. In prior analysis in the FIT cohort, incidence of new vertebral fracture was 50% among women with prevalent vertebral fractures and osteoporosis defined by BMD, compared to 9% among women with no vertebral fracture and normal BMD.¹² Although unnecessary adjustment for history of the outcome can induce bias and/or reduce efficiency,¹³ we concluded that prevalent vertebral fracture should be regarded as a confounder in this analysis, and included it as a

covariate in the fully adjusted model. Specifically, we hypothesized that past vertebral fracture is a likely cause of increased kyphosis,⁶⁻⁸ and independently linked to incident vertebral fracture through shared risk factors including a low body mass index, current smoking, low levels of daily physical activity, and having a fall, as well as via direct causal effects.¹⁴ Prevalent vertebral fracture likely is a surrogate for unmeasured confounders as well, such as parameters of bone strength that are not captured by DXA assessment. In the FIT cohort, prevalent vertebral fracture was strongly and independently associated with kyphosis angle and incident vertebral fracture. Accordingly, adjustment for prevalent vertebral fracture explained 60% of the age-and-BMD adjusted association of kyphosis with incident vertebral fracture. While the 95% upper confidence bound from the fully adjusted analysis remained consistent with a 22% increase in the incident vertebral fracture rate for each 10-degree increase in kyphosis, we were no longer able to demonstrate a statistically significant independent effect.

Computer models suggest that greater degree of kyphosis confers significantly more compressive load and shear force to the vertebral bodies compared to lesser degree of kyphosis.³ Theoretically this could increase the risk of vertebral fracture during activities of daily living (ADLs) in individuals with hyperkyphosis. We did not find that greater kyphosis predicted incident fractures, and it is possible that the spinal muscles adapt to hyperkyphosis to reduce the load. However certain abrupt movements from coughing and flexion of the spine may confer risk of an incident vertebral fracture, in particular when there has been a past vertebral fracture and/or low bone mass, irrespective of the degree of kyphosis.

This study has several limitations. The participants were healthy post-menopausal women 55-80 years old with low bone mineral density, and the results cannot be generalized to other populations, including older men and women with normal bone density. In addition, reliability of the Debrunner kyphometer was assessed among 31 healthy volunteers, including 21 women and 10 men, with a mean age of 32 years (SD=11) (range, 16-61), and may overestimate the reliability of the measurements obtained among the older women with greater kyphosis in FIT.

Conclusion

While greater kyphosis increased the rate of incident vertebral fractures, our analysis does not show a causal effect of kyphosis on incident vertebral fracture. However, excessive kyphosis may still be a clinically useful marker for history of vertebral fracture, an easily identifiable signal that further investigation for possible vertebral fracture is indicated. Identifying underlying vertebral fractures, that frequently go undiagnosed, may be important for reducing incident vertebral fractures. Most vertebral fractures occur among those with low bone mineral density,¹⁵ thus recognizing that treatment may be indicated.

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