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Clinical Issues

Relationship Between Vertebral Fracture Burden, Height Loss, and Pulmonary Function in Postmenopausal Women With Osteoporosis

John H. Krege,[1] David Kendler,[2] Kelly Krohn,[1] Harry Genant,[3] Jahangir Alam,[1] Pierre-Yves Berclaz,[1] Barbara Coffey,[1] and Corina Loghin[1]*

[1]*Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN, USA;* [2]*University of British Columbia, Vancouver, ON, Canada; and* [3]*University of California San Francisco, San Francisco, CA, USA*

Abstract

The purpose of this analysis was to assess the association of osteoporosis-related vertebral fracture burden and pulmonary function. This study also examined the relationship between vertebral fracture burden and height loss, estimated by arm span − height. This was a single-site and single-visit study. Patients had a history of at least 1 moderate or severe vertebral fracture. Vertebral fracture burden was quantified using the spinal deformity index (SDI). Pulmonary function during inspiration was determined by spirometry. Forty-one women aged 70–91 completed the study. Vertebral fracture burden negatively correlated with forced inspiratory vital capacity and inspiratory time. For each unit increase in SDI, forced inspiratory vital capacity decreased by 1.62%, and inspiratory time decreased by 2.39%. There was no correlation between SDI and measures of inspiratory flow. For each unit increase in SDI, height decreased by about 0.5 cm. Vertebral fractures were associated with decreased lung volume and height loss.

Key Words: Height loss; lung volume; osteoporosis; pulmonary function; vertebral fractures.

Introduction

Vertebral fractures are common among people with osteoporosis. In the year 2000, there were an estimated 1.4 million osteoporosis-related vertebral fractures worldwide *(1)*. Individuals with a vertebral fracture have an increased risk of future vertebral fractures and other types of fractures *(2,3)*. Vertebral fracture risk is also increased among patients with chronic obstructive pulmonary disorder (COPD), attributed to their risk for osteoporosis brought on by numerous factors, including glucocorticoid treatment, smoking, and physical inactivity *(4–8)*. Most guidelines, including International Society for Clinical Densitometry positions, emphasize the importance of vertebral fractures in the identification of patients requiring pharmacotherapy. In addition, the combination of vertebral fractures and osteoporosis is associated with increased morbidity and mortality *(7,9–11)*.

This single-visit study was originally conducted to compare 2 inhalation devices for potential use by elderly women with osteoporosis and a history of at least 1 moderate or severe vertebral fracture. Patients also had pulmonary function testing without in line inhalers, and these are the data reported here. Study measures included quantification of vertebral fracture burden using the spinal deformity index (SDI) *(12,13)*, height, arm span, and pulmonary function during inspiration by spirometry. The purpose of this post hoc analysis is to assess the association of osteoporosis-related vertebral fracture burden and pulmonary function and to examine the relationship between vertebral fracture burden and height loss, determined by arm span − height. Arm span is commonly used as a surrogate for maximum adult height for individuals with spinal deformity, and the difference between arm span and height serves as a measure of

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*Address correspondence to: John H. Krege, MD, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN. E-mail: krege_john_henry@lilly.com

height loss *(14–16)*. We hypothesized that increased spine fracture burden would be associated with decreased lung volume and height loss.

Materials and Methods

Study Design

This was a single-visit study at a single site. No investigational product was administered.

Patients

Subjects were required to be women aged 70 yr and older with osteoporosis and a history of at least 1 moderate or severe vertebral fracture as determined by the investigator. Patients could not enter the study if they were active smokers or had a history of moderate to severe asthma, COPD, pulmonary fibrosis, emphysema, or other major lung disease. In addition, study participants could not have taken inhaler-delivered medications within the past 3 mo or have any severe or chronically disabling conditions other than osteoporosis, such as congestive heart failure. Patients were not selected for this study based on their need for an inhaler.

Measures

Spinal Deformity Index

SDI was assessed as described (Fig. 1) *(12,13,17)*. Briefly, using lateral radiographs of the thoracic and lumbar spines, the investigator visually scored each vertebra as semiquantitative grade 0, 1, 2, or 3. Grade 0 indicates an unfractured vertebra, grade 1 is mild compression (approx 20%–25%), grade 2 is moderate compression (approx 25%–40%), and grade 3 is severe compression (>40%). For each patient, the number of mild, moderate, and severe vertebral fractures was recorded. The SDI is the sum of the semiquantitative scores of T4–L4 vertebrae. All patients had an SDI score of ≥2 because study inclusion criteria required patients to have at least 1 moderate vertebral fracture.

Height Loss

In this study, estimated height loss was calculated as the difference between arm span and height *(14–16)*. Arm span was measured to the nearest centimeter from the tips of the middle fingers of maximally outstretched hands, with the patient standing facing the wall. Height was measured using a Harpenden stadiometer (Holtain Ltd., Crosswell, Crymych, UK). According to a standardized protocol, patients were measured in bare feet or thin socks, with their back against the wall-mounted stadiometer, heels together, and head positioned in the Frankfort horizontal plane. The patient was asked to breathe in, and height was noted and recorded at peak inspiration. Arm span and height measurements were taken one time.

Pulmonary Function

All pulmonary function measures were performed with patients seated upright. Patients were directed by trained staff on proper use of the spirometer. Each measurement was repeated 3–5 times, with at least 1 min between inhalations. The spirometry variables included peak inspiratory flow rate (L/min), forced inspiratory vital capacity (L), average flow rate of inspiration (L/min), forced inspiratory flow 25%–75% (L/s), forced inspiratory flow 50% (L/s), forced inspiratory volume in 1 s (L), and total inspiratory time (s). Expiratory measures were not taken.

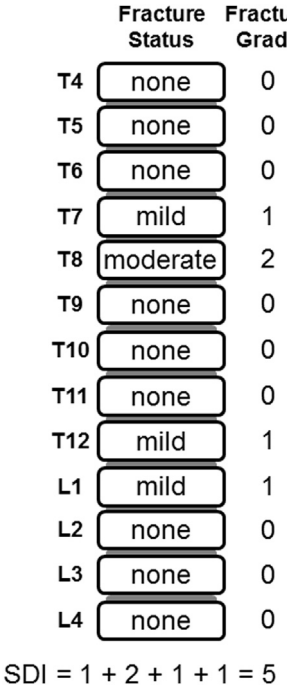

Fig. 1. Spinal deformity index is the sum of fracture grades for T4 to L4 vertebrae. In the example shown, the patient has three mild and one moderate vertebral fracture, for an SDI of 5. SDI, spinal deformity index.

Statistical Analysis

All tests of treatment effects were conducted at a 2-sided alpha level of 0.05 unless otherwise stated. Methods included descriptive statistics, Pearson correlation and regression analysis, and individual patient listings.

Graphs were constructed to illustrate the relationship between SDI and other measured variables, and regression analysis was performed to quantify the relationships. Fitted

Table 1
Patient Characteristics

Patient characteristics (N = 41)	Mean ± SD	Range
Spinal deformity index	7.4 ± 5.6	2.0–22.0
Weight (kg)	59.2 ± 8.7	40.1–77.8
BMI	24.1 ± 3.1	15.1–29.7
Age (yr)	77.8 ± 4.6	70.8–91.3

Abbr: BMI, body mass index; SD, standard deviation.

models with slope and intercept have been displayed along with the scatter plots.

Analyses were performed on the average result of all trials from each patient and also from each patient's best effort. The results were similar (data not shown), and this report includes the findings from the best effort.

Results

Patients

Forty-one women aged 70−91 entered the study. Three patients were East Asian; the rest were Caucasians. Patient characteristics are summarized in Table 1. All patients completed the study.

SDI Assessments

Vertebral Fracture Burden and Pulmonary Function

Vertebral fracture burden, as measured by SDI (Fig. 1), negatively correlated with forced inspiratory vital capacity (Fig. 2A) and inspiratory time (Fig. 2B). For each unit increase in SDI, forced inspiratory vital capacity decreased by 1.62%, and inspiratory time decreased by 2.39%. There was no correlation between SDI and measures of inspiratory flow. A summary of the correlation between SDI and all pulmonary function measures is provided in Table 2.

The impact of SDI on forced inspiratory vital capacity and inspiratory time was further investigated by constructing a model with age as an additional covariate; SDI remained a

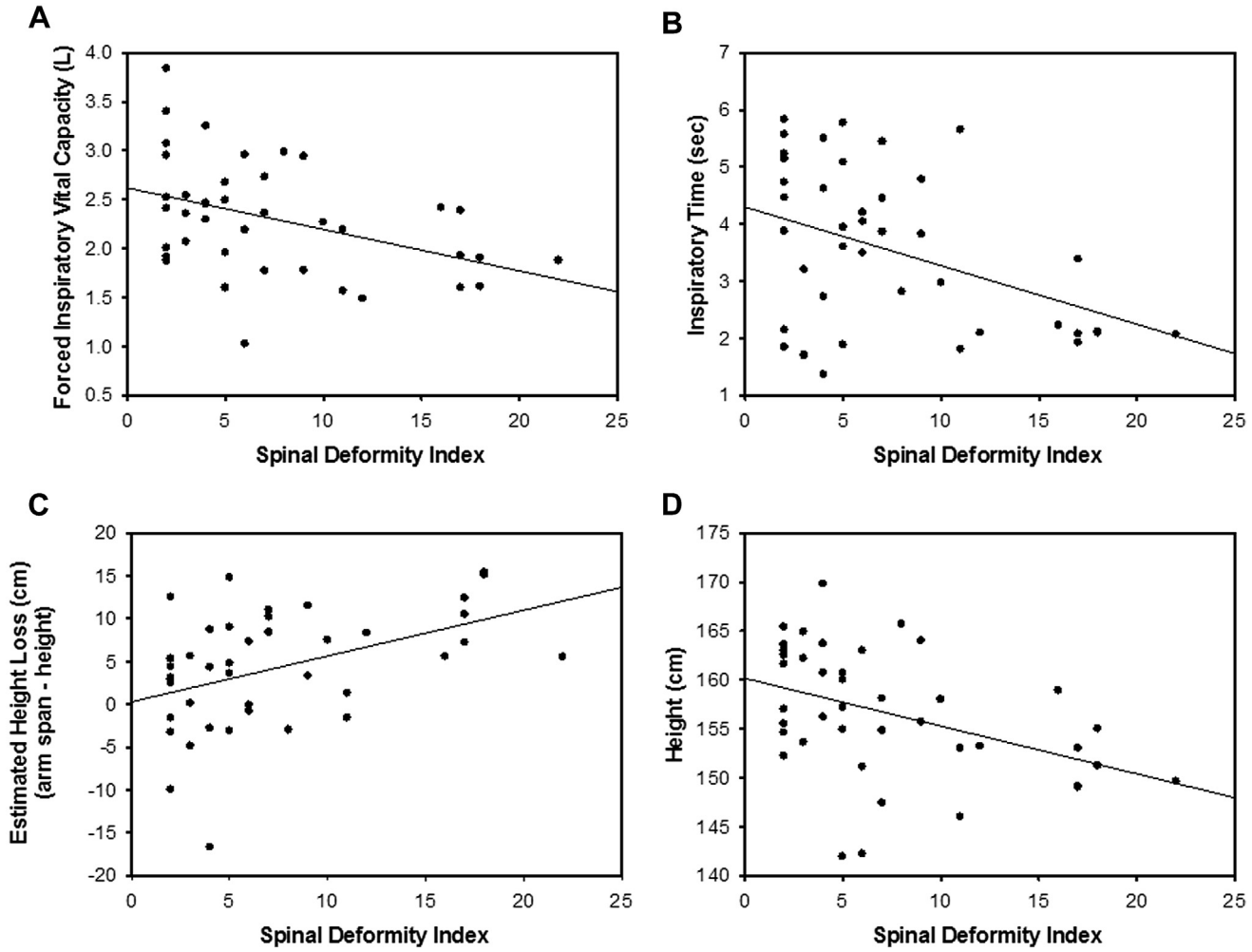

Fig. 2. Correlation between spinal deformity index, inspiratory measures, estimated height loss, and height. Correlation between spinal deformity index (SDI) and **(A)** forced inspiratory vital capacity (R = −0.41, p = 0.008), **(B)** inspiratory time (R = −0.41, p = 0.008), **(C)** estimated height loss (arm span − height) (R = 0.44, p = 0.004), and **(D)** height (R = −0.42, p = 0.007), in 41 postmenopausal women with osteoporosis and vertebral fractures. For each unit increase in SDI, forced inspiratory vital capacity decreased by 1.62%. For each unit increase in SDI, inspiratory time decreased by 2.39%. Respiratory function data represent the maximum value achieved from 3-5 efforts. Regression equations: Forced inspiratory vital capacity = 2.62−.042*SDI. The percentage is calculated as .042*100/2.62 = 1.62%. Inspiratory time = 4.30−.10*SDI. The percentage is calculated as .10*100/4.30 = 2.39%. Estimated height loss (arm span − height) = 0.31 + 0.53*SDI.

Table 2
Summary of Correlations Between SDI and Other Study Measures in 41 Postmenopausal Women With Osteoporosis and Vertebral Fractures

Measurement	Mean ± SD	Range	Correlation with SDI (*R*)	Significance (*p*)
Forced inspiratory vital capacity (L)	2.3 ± 0.6	1.0–3.8	−0.41	0.008
Inspiratory time (s)	3.5 ± 1.4	1.4–5.8	−0.41	0.008
Average flow rate of inspiration (L/min)	70.7 ± 29.8	24.0–163.2	−0.01	0.932
Forced inspiratory flow 25%–75% (L/s)	2.0 ± 0.8	0.8–4.5	0.06	0.691
Forced inspiratory flow 50% (L/s)	2.1 ± 0.9	0.8–4.8	0.07	0.657
Forced inspiratory volume, 1 s (L)	1.8 ± 0.5	0.8–3.2	−0.06	0.722
Peak inspiratory flow rate (L/min)	136.3 ± 50.5	54.0–289.8	0.01	0.954
Height (cm)	156.6 ± 6.5	141.9–169.8	−0.42	0.007
Arm span (cm)	160.8 ± 7.8	145.5–175.5	0.03	0.839
Estimated height loss (arm span − height) (cm)	4.3 ± 6.8	−16.7 to 15.4	0.44	0.004
Age (yr)	77.8 ± 4.6	70.8–91.3	0.18	0.262

Note: Inspiratory variables are the maximum value of multiple tests.
Abbr: SD, standard deviation; SDI, spinal deformity index.

statistically significant determinant of these parameters, and the effect of each unit increase in SDI was quite similar to the model that did not consider age (data not shown). Additionally, the impact of SDI on forced inspiratory vital capacity and inspiratory time was investigated by excluding mild vertebral fractures from the computation of SDI. This revised SDI remained a statistically significant determinant of these parameters, and the effect of each unit increase in SDI was quite similar to the model that included the mild fractures (data not shown).

Vertebral Fracture Burden and Height Loss

SDI positively correlated with estimated height loss (arm span − height) and negatively correlated with height (Fig. 2C and D; Table 2). For each unit increase in SDI, estimated height loss (arm span − height) increased by 0.5 cm and height decreased by 0.5 cm.

Safety

There were no adverse events, and clinical laboratory tests were not performed.

Discussion

The purpose of this analysis was to assess the impact of osteoporosis-related vertebral fracture burden on pulmonary function. This study demonstrated that increased spine fracture burden was associated with significant decreases in forced inspiratory vital capacity (lung volume) and inspiratory time. Each unit increase in SDI was associated with a 1.62% reduction in forced inspiratory vital capacity and a 2.39% reduction in inspiratory time. The impact of spine fracture burden to reduce inspiratory time likely is consistent with a reduced lung volume. However, there was no significant relationship between spine fracture burden and the measures of flow rates. Thus, increased spine fracture burden significantly reduced lung volume but not flow, indicating that spine fracture burden is linked with restrictive, but not obstructive, lung disease.

The results suggest that a low burden of spine fractures may have a small effect on lung volume and inspiratory time. However, the patient's respiratory status and the location of the fracture are 2 important considerations. Even a small reduction in lung volume in a patient with marginally compensated respiratory status might be clinically relevant, especially under conditions of respiratory stress *(18)*. This has been noted in a study of COPD patients *(5)* and a study of women older than 65 yr, which found that patients with vertebral fractures were 2–3 times more likely to die of respiratory-related causes than those without vertebral fractures *(11)*. A larger burden of spine fractures may be associated with substantial reductions in volume.

Other studies have used expiratory measures to explore the relationship between spinal deformity or vertebral fractures and pulmonary function. Leech et al *(15)* estimated that for every thoracic vertebral fracture, the forced vital capacity declined approx 9%. The magnitude of difference between these results and ours could be partially attributed to the differences in expiratory vs inspiratory measurements. Two other studies also showed that patients with osteoporosis and vertebral fractures have reductions in expiratory vital capacity *(18,19)*. In a 2007 review of 4 studies on the relationship between osteoporotic kyphosis and pulmonary function, including the aforementioned 2 studies, the authors concluded that there was an association between osteoporosis-related kyphosis, the number of vertebral fractures, and decreased vital capacity *(20)*. More recently, an analysis of 282 men and women with vertebral fractures led the authors to conclude the relationship between vertebral fractures and pulmonary function was not clinically relevant *(21)*. Despite the overall conclusion, however, the study revealed a significant difference in the ratio of forced expiratory volume in 1 s to forced

vital capacity percent predicted between men with and without vertebral fracture. Thus, some studies have suggested a large impact of vertebral fractures on lung volume *(15,18)*, whereas 1 study has suggested little or no impact *(21)*, and the findings from our study suggest a moderate effect. Our analysis is unique in its quantitative approach to the relationship between vertebral fracture burden and pulmonary function.

This analysis also quantified the relationship between vertebral fracture burden and height loss defined as arm span − height. This relationship was statistically significant, with each unit increase in SDI conferring about 0.5 cm of height loss. This finding suggests that the typical 2-cm measured height loss threshold for defining height loss is unlikely to detect a small change in spine fracture status *(22)*. The results of this study confirm and extend the findings of several other studies *(15,18,23)*.

As a post hoc analysis of a small number of patients, this study has some limitations. Respiratory function analyses typically assess expiration, whereas this study collected inspiratory-based measurements. The study measured forced inspiratory vital capacity as a measure of lung volume, but total lung capacity was not formally measured. Thus, although unlikely, the measured reduction in forced inspiratory vital capacity could be related to an increase in residual volume rather than a decrease in total lung volume. The study included only 41 patients at a single center and lacks longitudinal data to confirm height loss prospectively. Women with no or only mild fractures were not included in the study, which may have limited our ability to fully assess the impact of fractures. Single height and arm span measurements, as well as single-read radiographs, are also study limitations. The location of each vertebral fracture was not recorded, so the study did not assess the impact of lumbar vs thoracic vertebral fractures, although the location of the fracture likely affects pulmonary function. Finally, no data were analyzed with respect to patients' history of glucocorticoid use, although patients were excluded from the study if they had used inhaler-delivered medications within the past 3 mo or had significant pulmonary disorders. History of glucocorticoid use is an important issue, and inclusion of these patients might have yielded different results.

In conclusion, this study quantified the relationship between vertebral fracture burden and pulmonary function and estimated height loss. Vertebral fractures had statistically significant effects on lung volume, and these effects may be clinically relevant in some patients. For example, a patient with marginally compensated pulmonary function taking glucocorticoids for lung disease who develops vertebral fractures might further compromise their pulmonary function. Our study reinforces the adverse health consequences of vertebral fractures. Technologies such as vertebral fracture assessment provide opportunities to identify vertebral fractures at point of care. The data presented will help radiologists and dual-energy X-ray absorptiometry clinicians to better understand the clinical relevance of vertebral fractures in their patients.

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All patients in this study were competent and freely provided their own written informed consent approved by Eli Lilly and the ethical review board governing the site. Procedures performed in this study were in accordance with applicable laws and regulations, good clinical practices, and the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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