

# Lumbar spondylolisthesis is a risk factor for osteoporotic vertebral fractures: a case–control study

Journal of International Medical Research

2018, Vol. 46(9) 3605–3612

© The Author(s) 2018

Article reuse guidelines:

[sagepub.com/journals-permissions](http://sagepub.com/journals-permissions)

DOI: 10.1177/0300060518776067

[journals.sagepub.com/home/imr](http://journals.sagepub.com/home/imr)



Peng Wang<sup>#</sup>, Feng Wang<sup>#</sup>, Yan-Long Gao,  
Jia-qi Li, Jing-tao Zhang, De-chao Miao and  
Yong Shen

## Abstract

**Objective:** This study aimed to identify the risk factors for vertebral compression fractures in patients with osteoporosis.

**Methods:** A total of 864 patients with osteoporosis were enrolled in a retrospective study from February 2010 to June 2016. Patients with diseases, such as pathological fractures, high-energy direct injury to the thoracic or lumbar vertebrae, and severe spinal deformity, were excluded. The patients were divided into two groups: those with vertebral compression fractures (288) and those with no vertebral compression fractures (576). Information on the patients' age, sex, lumbar bone mineral density (BMD), trauma, body mass index, previous history of vertebral compression fractures, and spondylolisthesis was recorded. Logistic regression analysis and the chi-square test were applied for comparisons.

**Results:** Univariate logistic regression analysis and chi-square test results showed no significant differences in age, sex, body mass index, type 2 diabetes, previous history of vertebral fracture, and trivial trauma between the groups. Multivariate analysis showed significant associations between spondylolisthesis and BMD. Logistic regression analysis showed that spondylolisthesis and BMD were risk factors for vertebral compression fractures.

**Conclusions:** Lumbar spondylolisthesis is an independent risk factor for vertebral compression fractures in patients with osteoporosis. Therefore, patients with osteoporosis and lumbar spondylolisthesis require more attention.

<sup>#</sup>These authors contributed equally to this work.

## Corresponding author:

Yong Shen, Department of Spine Surgery, The Third Hospital of Hebei Medical University, 139 Ziqiang Road, 050051 Shijiazhuang, China.

Email: [shenyong258@126.com](mailto:shenyong258@126.com)

Department of Spine Surgery, The Third Hospital of Hebei Medical University, The Key Laboratory of Orthopedic Biomechanics of Hebei Province, Shijiazhuang, China



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (<http://www.creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

**Keywords**

Osteoporosis, risk factor, spondylolisthesis, vertebral compression fracture, advanced age, bone mineral density

Date received: 5 September 2017; accepted: 17 April 2018

**Introduction**

The incidence of osteoporosis has increased with the advent of an aging society. Osteoporotic vertebral compression fracture (VCF) is one of the major complications of osteoporosis,<sup>1,2</sup> with an estimated prevalence of vertebral fractures of approximately 16% to 21% in different regions of the world.<sup>3-5</sup> Vertebral compression fractures cause severe pain, depression, a long-term stay in bed, functional deterioration, and limited mobility. However, approximately one third of osteoporotic VCFs receive clinical attention.<sup>1</sup> These fractures are frequently undetected, unless kyphosis or height loss is present. In all populations, the prevalence of vertebral fractures increases with age, and can exceed 50% in women aged 85 years and older.<sup>6</sup> Previous studies have shown a different prevalence of vertebral fractures because of differences in their approaches for choosing samples of the population and the methods used for diagnosing vertebral fractures. Although comparing the prevalence of vertebral fractures in various regions of the world is difficult, most studies have shown that the prevalence of vertebral fractures significantly increases with age.<sup>7,8</sup> Postmenopausal women, who have certain medical conditions, such as rheumatoid arthritis and type 2 diabetes (T2DM),<sup>9,10</sup> and medications such as glucocorticoids and immunosuppressive agents, have been suggested as risk factors for osteoporotic fractures. The most widely accepted strongest risk factors for osteoporotic fractures are advanced age

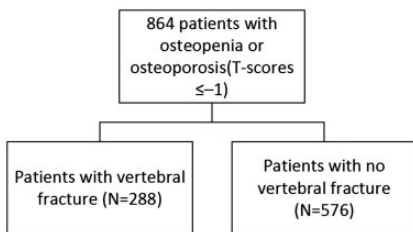
and bone mineral density (BMD).<sup>9,11</sup> For advanced age,<sup>7,8</sup> the 10-year probability of developing a vertebral fracture radiographically increases from 3% at the age of 50 years to 8% at the age of 85 years.<sup>12</sup> With regard to the risk factor of low BMD,<sup>8,13</sup> one third of vertebral fractures are due to the presence of a previous vertebral fracture.<sup>14,15</sup> BMD is also predictive of future VCFs, as well as nonspinal fractures, independently of other risk factors in men.<sup>16</sup> Additionally, physical quality of life, body mass index (BMI), and a history of a fragility fracture are important risk factors that are associated with incident vertebral and nonvertebral fractures.<sup>17</sup>

Lumbar spondylolisthesis is a common indication for spinal surgery worldwide. This condition is most often observed in the lumbar spine at the L4/L5 level. The prevalence of lumbar spondylolisthesis has been estimated to be approximately 4% to 8% in the general population by some authors.<sup>18,19</sup> Lumbar spondylolisthesis is defined as disk and facet degeneration that results in slipping of one vertebral body over the underlying vertebra. Patients with spondylolisthesis may be asymptomatic in the early stage. Furthermore, different treatment plans are selected for different disease periods. Accordingly, early detection of spondylolisthesis has become an important clinical task. Spondylolisthesis often results in low back and leg pain related to spinal stenosis. Clinically, patients with lumbar spondylolisthesis and vertebral fractures are not uncommon.

However, few studies have investigated the use of lumbar spondylolisthesis (L4 or L5) for patients with osteoporosis. The association between spondylolisthesis and other risk factors for osteoporotic vertebral fractures has not been extensively investigated. Therefore, this study retrospectively analysed the relation of spondylolisthesis with vertebral fractures to reduce the risk of vertebral fractures in patients with osteoporosis.

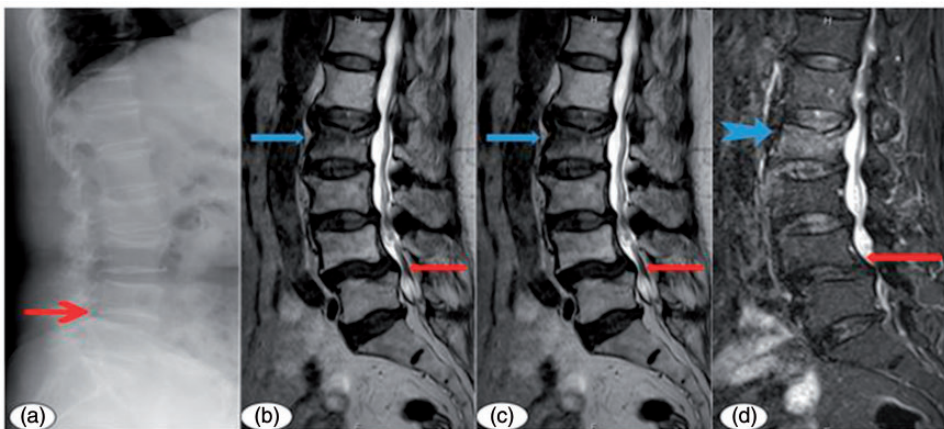
## Materials and methods

A total of 864 patients with osteopenia or osteoporosis were enrolled in a retrospective study from February 2010 to June 2016. The flow chart of the study population is shown in Figure 1. In accordance with the World Health Organization,



**Figure 1.** Flow chart of the study population

BMD was evaluated as osteopenia depending on T-scores (T-scores  $\leq -1$ ). Patients with diseases, such as a pathological fracture, high-energy direct injury to the thoracic or lumbar vertebrae, and severe spinal deformity, were excluded. Inclusion criteria were as follows: (1) back pain related to the location of osteoporotic VCFs on radiography; (2) bone marrow oedema on magnetic resonance imaging T2-weighted short-tau inversion recovery sequences in the corresponding collapsed vertebral body (Figure 2); (3) simple osteoporotic VCF detected using X-ray film, BMD, and magnetic resonance imaging; and (4) only thoracolumbar (T10–L2) compression fractures. Spondylolisthesis was diagnosed by lateral lumbar X-ray, and it was limited to spondylolisthesis (L4 or L5) of degrees I to II (Figure 2). The BMI was calculated as the weight in kilograms divided by the square of the height in meters ( $\text{kg}/\text{m}^2$ ). BMD was measured at the lumbar spine or femoral neck of patients. Additionally, the percentage of slipping of one vertebral body over the underlying vertebra was calculated and scored as follows: Grade 1, 0% to 25%; Grade 2, 26% to 50%; Grade 3, 51% to 75%; Grade 4, 76% to 99%; and spondylolisthesis, more than 99%.



**Figure 2.** A 59-year-old woman with lumbar spondylolisthesis with vertebral compression fractures

BMD measurement was usually manually performed by radiologists. The participants completed questionnaires via interview regarding demographics (age, sex, and BMI), BMD and fracture segment, diabetes, history of trauma, previous history of vertebral fracture, and spondylolisthesis (Grade 1 or spondyloptosis). The 864 patients were divided into the following two groups to identify risk factors: those with vertebral fracture (288 patients) and those with no vertebral fracture (576 patients).

The study was approved by the Ethics Committee of the Third Hospital of Hebei Medical University in China. All participants gave their informed consent to assess and use their data. The methods were conducted in accordance with the approved guidelines.

### Statistical analysis

Patients aged between 55 and 85 years were eligible for this study. BMD at the lumbar spine and femoral neck was evaluated and categorized as osteopenia or osteoporosis depending on T-scores. The BMI was divided into three groups: underweight ( $<18.5$  kg/m<sup>2</sup>), normal (18.5–24.9 kg/m<sup>2</sup>), and overweight ( $\geq 25$  kg/m<sup>2</sup>). The trauma status was divided into the presence or absence of low-energy forces. The comorbidity status was divided into the presence or absence of diabetes. The chi-square test and logistic regression analysis were used to evaluate the association between risk factors and prevalent vertebral fractures, and factors with  $P < 0.05$  were used in multiple logistic regression analysis. IBM SPSS Statistics, Version 21.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis and a  $P$  value  $< 0.05$  was considered significant.

### Results

The data of 864 subjects were analysed. We found that 6.9% of the patients had spondylolisthesis. Spondylolisthesis accounted for 4.2% of patients without vertebral fractures, and spondylolisthesis with vertebral fractures accounted for 9.7% of patients. The chi-square test showed no significant differences in age, sex, BMI, T2DM, previous history of VCFs, and trivial trauma between the two groups with and without vertebral fractures (Table 1). Significant differences were observed in spondylolisthesis and BMD between the two groups (both  $P < 0.05$ ) (Table 1). Univariate analysis showed significant differences in spondylolisthesis (OR = 1.831,  $P = 0.025$ ) and BMD (OR = 1.663,  $P = 0.001$ ) between the two groups with and without VCFs (Table 2). In multivariate analysis, spondylolisthesis (OR = 1.819,  $P = 0.027$ ) and BMD (OR = 1.658,  $P = 0.001$ ) were significantly associated (Table 3). Logistic regression analysis showed that spondylolisthesis and BMD were risk factors for VCFs.

### Discussion

The most important finding of this study was the significant association between VCFs and spondylolisthesis in older patients. Patients whose vertebral body slipped over the underlying vertebra were at increased risk of vertebral fractures compared with patients without spondylolisthesis after osteoporosis.

Advancing age has been found to be a risk factor of vertebral fractures.<sup>7,8</sup> Although a previous study<sup>20</sup> showed that a history of fractures, T2DM, and age were associated with a higher risk of vertebral fracture, our study showed that some risk factors, such as T2DM, a history of fractures, and trivial trauma, had little or no influence on vertebral fractures. As expected, compared with the osteopenia

**Table 1.** Comparisons of age, sex, BMI, BMD, DM, trauma, spondylolisthesis, and a previous history of vertebral fracture between those with VCFs and those without VCFs

Variable	Total	VCF	No VCF	$\chi^2$ value	P value
Age (years)				0.871	0.647
55–65	137 (15.8%)	41	96		
66–75	277 (32.1%)	95	182		
76–85	450 (52.1%)	152	298		
Sex				2.623	0.105
Male	174 (20.1%)	67	107		
Female	690 (79.9%)	221	469		
BMI (kg/m <sup>2</sup> )				1.135	0.567
<18.5	110 (12.7%)	38	72		
18.5–24.9	400 (46.3%)	126	274		
≥25	354 (41.0%)	124	230		
BMD*				10.466	0.001*
–2.5–1.0	351 (40.6%)	99	138		
<–2.5	485 (56.1%)	189	438		
DM					
Yes	99 (11.5%)	27	72		
No	755 (88.5%)	261	494	2.085	0.149
Previous history of vertebral fracture				0.245	0.621
Yes	34 (3.9%)	10	24		
No	830 (96.1)	278	552		
Spondylolisthesis*				5.158	0.023*
Yes	60 (6.9%)	28	32		
No	804 (93.1%)	260	544		
Trauma				1.227	0.268
Yes (trivial)	676 (78.2%)	219	457		
No	188 (21.8%)	69	119		

Group comparisons were performed with the chi-square test. \*P < 0.05.

BMI, body mass index; DM, diabetes mellitus; BMD, bone mineral density; VCF, vertebral compression fracture.

**Table 2.** Risk factors for vertebral compression fractures in univariate analysis

Variable	P	Odds ratio	95% confidence interval for EXP(B)
BMD	0.001	1.663	1.220–2.265
Spondylolisthesis	0.025	1.831	1.079–3.105

EXP(B), exponentiation of the B coefficient; BMD, bone mineral density.

**Table 3.** Risk factors for vertebral compression fractures in multiple logistic regression analysis

Variable	P	Odds ratio	95% confidence interval for EXP(B)
BMD	0.001	1.658	1.216–2.262
Spondylolisthesis	0.027	1.819	1.069–3.096

EXP(B), exponentiation of the B coefficient; BMD, bone mineral density.

(BMD) status, the presence of osteoporosis remarkably increased the probability of vertebral fractures in subjects whose BMD data were available. Low BMD is a primary

risk factor of vertebral fractures.<sup>8,13</sup> Generally, the risk of fracture approximately doubles for each standard deviation below the mean young adult BMD (or for



each -1 decrease in the T-score), regardless of fracture type and BMD measurement site.<sup>21</sup> BMD and prevalent vertebral fractures are strong, complementary predictors of the vertebral fracture risk. Other studies have suggested that BMD is implicated in VCFs. However, Gourlay et al.<sup>22</sup> found that the risk of major osteoporotic fractures was relatively low, unless patients had osteoporosis on their first BMD test, and they were unlikely to benefit from BMD rescreening before the age of 65 years.

Vertebral fractures comprise the majority of osteoporotic fractures. In our study, a low BMD alone was an unreliable predictor of VCFs in patients,<sup>23</sup> although BMD levels were similar to or even higher than those in subjects with no fractures. This suggested that other factors moderated the risk of fracture. Further, spondylolisthesis was a significant risk factor for vertebral fractures (Figure 2). Two main reasons might explain this relationship between spondylolisthesis and vertebral fractures. First, spondylolisthesis might be associated with curvature of the spine, such as increased lumbar lordosis or thoracic kyphosis. Kyphosis of the thoracic spine is an independent risk factor for vertebral osteoporotic fractures.<sup>24</sup> Kyphosis posture and age could lead to a sagittal balance of the spine,<sup>25</sup> leading to falls and VCFs. Previous studies have shown that kyphosis could adversely affect physical function,<sup>26</sup> and poor physical function is also a well-known risk factor for falls. Additionally, these studies included neurophysiological properties, such as trunk muscle activation (which might increase spinal load) and compromised balance (which might increase the falls risk).<sup>27</sup> However, Grade 1 or spondylolisthesis is less associated with balance deficits. Second, recent evidence suggests that an increase in sagittal curvature is a significant and independent predictor of fractures.<sup>24</sup> Previous studies showed that pelvic parameters were involved in compensatory

mechanisms.<sup>28</sup> Spondylolisthesis may affect sagittal curvature or spinal sagittal balance, but this possibility needs to be confirmed in future studies. A previous study showed a decrease in lumbar lordosis in older osteoporotic women compared with controls, although this difference was not significant.<sup>29</sup> Further studies analysing the increase in lumbar lordosis are warranted. The primary outcome in this study was that spondylolisthesis was a significant risk factor for VCFs. This observation has the clinical implication that special attention should be paid to older patients with lumbar spondylolisthesis.

Despite the advantages of a large, prospective observational cohort study in a single institution, the present study has some limitations. First, previous studies showed that the shape of prevalent fractures was important in predicting incident vertebral fractures.<sup>30</sup> However, in our study, some of the data gathered from the interviews were dependent on patients recalling their disease history because most of the data were retrospectively recorded in a database. Second, some factors might have contributed to outcomes not accounted for in this analysis, such as smoking.

In conclusion, most vertebral fractures are not recognized clinically. Low bone density increases the risk of future vertebral fractures. Older patients with spondylolisthesis are at a higher risk compared with those without spondylolisthesis. Special attention should be paid to older patients with lumbar spondylolisthesis to prevent the growing problem of osteoporosis in Asia.

#### **Declaration of conflicting interest**

The authors declare that there is no potential conflict of interest.

## Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

## References

- Cooper C, O'Neill T and Silman A. The epidemiology of vertebral fractures. *Bone* 1993; 14: 89–97.
- Melton LJ 3rd. Epidemiology of spinal osteoporosis. *Spine (Phila Pa 1976)* 1997; 22(24 Suppl): 2S–11S.
- Ling X, Cummings SR, Mingwei Q, et al. Vertebral fractures in Beijing, China: the Beijing Osteoporosis Project. *J Bone Miner Res* 2000; 15: 2019–2025.
- Eastell R, Cedel SL, Wahner HW, et al. Classification of vertebral fractures. *J Bone Miner Res* 1991; 6: 207–215.
- Black DM, Palermo L, Nevitt MC, et al. Comparison of methods for defining prevalent vertebral deformities: the Study of Osteoporotic Fractures. *J Bone Miner Res* 1995; 10: 890–902.
- Cummings SR and Melton LJI. Epidemiology and outcomes of osteoporotic fractures. *Lancet* 2002; 359: 1761–1767.
- O'Neill TW, Felsenberg D, Varlow J, et al. The prevalence of vertebral deformity in European men and women: the European Vertebral Osteoporosis Study. *J Bone Miner Res* 1996; 11: 1010–1018.
- Cauley JA, Zmuda JM, Wisniewski SR, et al. Bone mineral density and prevalent vertebral fractures in men and women. *Osteoporos Int* 2004; 15: 32–37.
- Ishida O, Furuya T, Inoue E, et al. Risk factors for established vertebral fractures in Japanese patients with rheumatoid arthritis: Results from a large prospective observational cohort study. *Mod Rheumatol* 2015; 25: 373–378.
- Chung DJ, Choi HJ, Chung YS, et al. The prevalence and risk factors of vertebral fractures in Korean patients with type 2 diabetes. *J Bone Miner Metab* 2013; 31: 161–168.
- Harvey N, Dennison E and Cooper C. Osteoporosis: impact on health and economics. *Nat Rev Rheumatol* 2010; 6: 99–105.
- Kanis JA, Johnell O, Oden A, et al. The risk and burden of vertebral fractures in Sweden. *Osteoporos Int* 2004; 15: 20–26.
- Shin CS, Kim MJ, Shim SM, et al. The prevalence and risk factors of vertebral fractures in Korea. *J Bone Miner Metab* 2012; 30: 183–192.
- Melton LJ III, Atkinson EJ, Cooper C, et al. Vertebral fractures predict subsequent fractures. *Osteoporos Int* 1999; 10: 214–221.
- Hasserius R, Karlsson MK, Jónsson B, et al. Longterm morbidity and mortality after a clinically diagnosed vertebral fracture in the elderly—a 12- and 22-year follow-up of 257 patients. *Calcif Tissue Int* 2005; 76: 235–242.
- Freitas SS, Barrett-Connor E, Ensrud KE et al. Rate and circumstances of clinical vertebral fractures in older men. *Osteoporos Int* 2008; 19: 615–623.
- Papaioannou A, Joseph L, Ioannidis G, et al. Risk factors associated with incident clinical vertebral and nonvertebral fractures in postmenopausal women: the Canadian Multicentre Osteoporosis Study (CaMos). *Osteoporos Int* 2005; 16: 568–578.
- Fredrickson BE, Baker D, McHolick WJ, et al. The natural history of spondylolysis and spondylolisthesis. *J Bone Joint Surg Am* 1984; 66: 699–707.
- Brooks BK, Southam SL, Mlady GW, et al. Lumbar spine spondylolysis in the adult population: using computed tomography to evaluate the possibility of adult onset lumbar spondylolysis as a cause of back pain. *Skeletal Radiol* 2010; 39: 669–673.
- Tracy JK, Meyer WA, Grigoryan M, et al. Racial differences in the prevalence of vertebral fractures in older men: the Baltimore Men's Osteoporosis Study. *Osteoporos Int* 2006; 17: 99–104.
- Leib ES, Lewiecki EM, Binkley N, et al. Official positions of the International Society for Clinical Densitometry. *J Clin Densitom* 2004; 7: 1–6.
- Gourlay ML, Overman RA, Fine JP, et al. Baseline age and time to major fracture in younger postmenopausal women. *Menopause* 2015; 22: 589–597.
- Marshall D, Johnell O and Wedel H. Meta-analysis of how well measures of bone

- mineral density predict occurrence of osteoporotic fractures. *BMJ* 1996; 312: 1254–1259.
24. Huang MH, Barrett-Connor E, Greendale GA, et al. Hyperkyphotic posture and risk of future osteoporotic fractures: the Rancho Bernardo study. *J Bone Miner Res* 2006; 21: 419–423.
  25. Kado DM, Huang MH, Barrett-Connor E, et al. Kyphotic posture and poor physical functional ability in older community dwelling men and women: The Rancho Bernardo Study. *J Gerontol Med Sci A* 2006; 60: 633–637.
  26. Sinaki M, Brey RH, Hughes CA, et al. Balance disorder and increased risk of falls in osteoporosis and kyphosis: significance of kyphotic posture and muscle strength. *Osteoporos Int* 2005; 16: 1004–1010.
  27. Briggs AM, Greig AM and Wark JD. The vertebral fracture cascade in osteoporosis: a review of aetiopathogenesis. *Osteoporos Int* 2007; 18: 575–584.
  28. Fechtenbaum J, Etcheto A, Kolta S, et al. Sagittal balance of the spine in patients with osteoporotic vertebral fractures. *Osteoporos Int* 2016; 27: 559–567.
  29. Cortet B, Houvenagel E, Puisieux F, et al. Spinal curvatures and quality of life in women with vertebral fractures secondary to osteoporosis. *Spine* 1999; 24: 1921–1925.
  30. Karlsson MK, Kherad M, Hasserijs R, et al. Characteristics of prevalent vertebral fractures predict new fractures in elderly men. *J Bone Joint Surg Am* 2016, 98: 379–85.