Observational Report

Low Bone Mineral Density, But Not Epidural Steroid Injection, Is Associated with Fracture in Postmenopausal Women with Low Back Pain

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Free full manuscript: www.painphysicianjournal.com **Background:** Therapy with glucocorticoids often results in bone loss and glucocorticoidinduced osteoporosis. However, the relationship between epidural steroid injection (ESI), bone mineral density (BMD), and vertebral fracture remains to be determined.

Objective: To establish a relationship between ESI, BMD, and vertebral fracture in postmenopausal women with low back pain.

Study Design: This study was a retrospective, nonblinded, cross-sectional clinical study. Setting: University-based pain management center.

Methods: We reviewed the medical records of postmenopausal women with low back pain who were treated with ESI. A total of 352 postmenopausal women were divided into 2 groups. Group 1 consisted of patients without fracture and Group 2 consisted of those with fractures. The results of BMD measurements, as well as any fragility fractures, the anatomical site involved, and the treatment administered, were also recorded. BMD was measured in the lumbar spine, femoral neck, and total femur after the treatment.

Results: Of the 352 patients, 218 (62%) had no fractures while 134 (38%) sustained a fracture. The age was significantly higher among patients who sustained fractures, and BMD at the lumbar spine, total femur, and femoral neck regions was significantly lower among patients who sustained fractures. In each region, the prevalence of osteoporosis was significantly higher in patients with fracture than in patients without fracture (all *P* < 0.05). Age, height, and weight were associated with low BMD. However, our study showed no consistent correlation between BMD and the mean number of ESIs, mean total dose of glucocorticoids, or mean duration of ESIs.

Limitations: First, this study is limited by the fact that it was retrospective. Second, the number of cases receiving very frequent, high-dose glucocorticoid injections was very small.

Conclusions: Older age and lower BMD were associated with osteoporotic fracture in postmenopausal women treated for low back pain with ESI. The ESIs were not associated with low BMD or fracture.

Key words: Bone mineral density, epidural steroid injection, fracture, glucocorticoids, low back pain, postmenopause.

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lucocorticoids are widely used in a variety of inflammatory, autoimmune, pulmonary, and musculoskeletal disorders. While glucocorticoids offer benefits, numerous adverse effects are described, which are directly related to both dose and duration of treatment, such as trunk obesity, moon face appearance, skin atrophy, disturbance in glucose and lipid metabolism, and osteoporosis (1-4). Indeed, glucocorticoids decrease bone mineral density (BMD) and increase bone fragility, resulting in a large increase in fracture risk (1-4). In the setting of epidural steroid injections (ESIs), a minimally invasive procedure used for the effective treatment of low back pain and sciatica (4-21), the development of osteoporosis and fractures is common (2,6), especially in postmenopausal women (1,22).

Osteoporosis is a skeletal disorder characterized by a decrease in BMD and the loss of structural and biomechanical properties of the skeleton, leading to increased risk of fractures as well as increased mortality and morbidity in the elderly (1,23,24). Osteoporosis is classified as primary when occurring spontaneously, or as secondary when caused by another factor or disorder. Glucocorticoid-induced osteoporosis (GIOP) is the most common form of secondary osteoporosis (23,24). GIOP started gaining the attention of physicians in the realization that, as compared to the normal population, patients with chronic low back pain undergoing ESIs have lower bone density at the lumbar spine and an increased incidence of osteopenia and osteoporosis (25). However, some studies have reported no significant change in bone density with epidural steroids (26,27). Further, the relationship between ESI, BMD, and vertebral fracture has not been adequately studied.

To investigate whether the use of epidural glucocorticoids is correlated to vertebral fracture and BMD, we retrospectively analyzed the age; weight; height, BMD at the lumbar spine, femoral neck, and total femur; mean number of ESIs; mean total dose of glucocorticoid administration; and mean duration of ESIs in postmenopausal women undergoing treatment for low back pain.

METHODS

This study is a retrospective analysis of postmenopausal women with low back pain who were admitted to the pain management practice center of the Kangwon National University Hospital between January 2009 and December 2011. The study was designed according to STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (28) and was approved by the local institutional review board. The study was registered with the Korea Clinical Trial Registry (Code K1202-012) and conducted in accordance with the Declaration of Helsinki. We carried out interviews based on reviews of the patients' medical records.

A total of 352 patients aged 50 years and older who satisfied the inclusion criteria were enrolled in the present study. The patients were divided into 2 groups. Group 1 consisted of patients without fracture and Group 2 consisted of those with fractures.

The inclusion criteria for the study were postmenopausal women with a medical history of ESI for low back pain, and women who had radiographs and BMD assessments performed after treatment for low back pain. The exclusion criteria were a history of comorbidities known to affect bone metabolism, such as cancer, pituitary diseases, thyroid disease, rheumatic disease, renal failure, or adrenal disease; a history of taking medication known to affect bone metabolism; vertebral fractures due to known accidental traumas; and previous lumbar spine surgery.

The ESIs at lumbar spine levels for the 352 participants were performed by one staff member. The results of BMD measurements, as well as any fragility fractures, the anatomical site involved, and the treatment administered, were recorded. BMD at the lumbar spine (L2-L4), femoral neck, and total femur was measured by dual energy x-ray absorptiometry using Lunar Prodigy (GE Healthcare, Waukesha, WI) and expressed as absolute values (g/cm2). Calibration procedures were performed every day by using appropriate phantoms provided by the manufacturer. The long-term precision of the daily scans of the spine phantom was 0.994 g/cm2 in BMD units. The interassay coefficient of variation for BMD was between 0.07% and 0.09%. BMD values were also expressed as T-scores. T-scores for the bone were calculated by taking the difference between the measured BMD and the mean BMD of healthy young adult Korean women (age, 20-40 years) matched for gender and ethnicity divided by the standard deviation of the young adult population. Osteoporosis was defined as a T score < -2.5 and osteopenia as a T score > -2.5 but < -1.0 according to the World Health Organization criteria.

The anteroposterior and lateral radiographs of the thoracic and lumbar spine demonstrating the presence of vertebral fractures were interpreted by radiographic morphometry using Genant's semiquantitative method (29).

Statistical Analysis

The data are presented as the mean ± standard deviation. Unpaired t-test was used to compare differences in age, weight, height, BMD, total number of ESIs, mean duration of glucocorticoid administration, and mean total dose of glucocorticoid between the 2 groups. The prevalence of osteoporosis in the 2 groups was compared using the Mann–Whitney test. Correlation between other variables and BMD was conducted using a Pearson's correlation procedure. Adjustments for age, height, and weight were performed using analysis of covariance. To identify the factors affecting BMD, a multiple linear regression analysis was performed using a stepwise procedure.

In all the comparisons, a *P* value of less than 0.05 was considered statistically significant. The statistical analyses were performed using SPSS 19.0 (IBM Corporation, Armonk, New York).

RESULTS

The baseline characteristics of the patients enrolled in the study are presented in Table 1. Of the 352 patients, 218 (62%) had no fractures and 134 (38%) sustained an osteoporotic fracture. The age was significantly higher among patients who sustained fractures (74 \pm 5.2 years old) than among those without fractures (65 \pm 7.3 years old; *P* < 0.001). BMD at the lumbar spine, total femur, and femoral neck regions was significantly lower among patients who sustained fractures (all P < 0.001). The overall mean number of ESIs was 4.1 ± 3.7 , and the mean total dose of glucocorticoid (triamcinolone) was 164 ± 151 mg. There were no statistically significant differences between the 2 groups with respect to weight, height, mean number of ESIs, mean total dose of glucocorticoid, or mean duration of glucocorticoid administration.

The commonest site of osteoporotic fracture was the spine (63%), followed by the proximal femur (23%) (Table 2). The majority of spinal fractures occurred at the thoracolumbar junction. More than one vertebra was involved in 43 out of 78 patients.

The outcomes of BMD for the lumbar spine, total femur, and femoral neck regions after treatment are listed in Table 3.

In patients treated with ESIs, in the lumbar spine the prevalence of osteopenia was 37% and for osteoporosis it was 49%; in the total femur osteopenia was 42% and osteoporosis was 22%; and in the femoral neck region osteopenia was 52% and osteoporosis was 23%. The overall prevalence of osteopenia was 37%; for osteoporosis it was 50%.

In patients without fracture, in the lumbar spine the prevalence of osteopenia was 42% and for osteoporosis it was 38%; in the total femur osteopenia was 40% and osteoporosis was 11%; and in the femoral neck region osteopenia was 61% and osteoporosis was 8%.

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	Overall	Without fractures	With fractures	P-value
Number of patients	352	218 (62%)	134 (38%)	
Age (yrs)	68 (7.8)	65 (7.3)	74 (5.2)	< 0.001*
Weight (kg)	57 (4.0)	58 (3.9)	56 (4.1)	0.212
Height (cm)	159 (7.7)	158 (7.4)	159 (8.2)	0.237
BMD (g/cm2)				
Lumbar spine	0.887 (0.272)	0.925 (0.234)	0.824 (0.320)	< 0.001*
Total femur	0.767 (0.233)	0.819 (0.232)	0.682 (0.235)	< 0.001*
Femoral neck	0.711 (0.268)	0.754 (0.264)	0.641 (0.275)	< 0.001*
Mean number of ESIs	4.1 (3.7)	4.0 (3.4)	4.5 (4.2)	0.390
Mean total dose of glucocorticoid (triamcinolone; mg)	164 (151)	158 (124)	178 (169)	0.311
Mean duration of glucocorticoid administration (wks)	8.1 (7.7)	7.8 (5.1)	8.4 (7.2)	0.313

Values are expressed as mean (SD)

Abbreviations: ESI, epidural steroid injection; BMD, bone mineral density

* P < 0.001 compared with the "without fractures" group

In patients with fracture, in the lumbar spine the prevalence of osteopenia was 28% and for osteoporosis it was 68%; in the total femur osteopenia was 45% and osteoporosis was 41%; and in the femoral neck region osteopenia was 38% and osteoporosis was 48%. The overall prevalence of osteoporosis was 38% in patients

Site of fracture	Numbers of patients (%)
Ulnar and radius	12 (10)
Femur	28 (23)
Spine	78 (63)
Pelvis	8 (6)
Humerus	4 (3)
Tibia and fibula	4 (3)
Multiple fractures	10 (8)

Table 2. Sites of fractures (n = 134).

without fracture and 69% in patients with fracture. In each region, the prevalence of osteoporosis was significantly higher in patients with fracture than in patients without fracture (all P < 0.05).

The correlations between BMD and age, weight, height, total number of ESIs, mean duration of glucocorticoid administration, and mean total dose of glucocorticoid are presented in Table 4. In univariate analysis, a positive correlation was observed between BMD and weight at the lumbar spine (P < 0.001), the total femur (P < 0.001), and the femoral neck (P < 0.05); and between BMD and height at the lumbar spine (P < 0.001) and the total femur (P < 0.05). A negative correlation was observed between BMD and age at the lumbar spine (P < 0.001), the total femur (P < 0.001), and the femoral neck (P < 0.001), and the femoral neck the lumbar spine (P < 0.001), and the total femur (P < 0.001). A negative correlation was observed between BMD and age at the lumbar spine (P < 0.001), the total femur (P < 0.001), and the femoral neck (P < 0.001). An analysis following adjustment for age, weight, and height revealed that there was no significantly consistent correlation

	Normal			Osteopeniab			Osteoporosisc		
	ESI (n = 352)	Without fractures (n = 218)	With fractures (n = 134)	ESI (n = 352)	Without fractures (n = 218)	With fractures (n = 134)	ESI (n = 352)	Without fractures (n = 218)	With fractures (n = 134)
Lumbar spine ^d	49/352	44/218	5/134	130/352	92/218	38/134	173/352	82/218	91/134*
	(14%)	(20%)	(4%)	(37%)	(42%)	(28%)	(49%)	(38%)	(68%)
Total femur ^d	127/352	108/218	19/134	147/352	87/218	60/134	78/352	23/218	55/134*
	(36%)	(49%)	(14%)	(42%)	(40%)	(45%)	(22%)	(11%)	(41%)
Femoral neck ^d	87/352 (25%)	68/218 (31%)	19/134 (14%)	184/352 (52%)	133/218 (61%)	51/134 (38%)	81/352 (23%)	17/218 (8%)	64/134* (48%)
Overall	47/352	44/218	5/134	131/352	92/218	37/134	174/352	82/218	92/134*
prevalence ^d	(13%)	(20%)	(4%)	(37%)	(42%)	(27%)	(50%)	(38%)	(69%)

a BMD data are based on T-scores

b Osteopenia was defined as -2.5 SD < BMD T score < -1.0 SD

c Osteoporosis was defined as BMD T score \leq -2.5 SD

d Values represent the number of patients/total patients (%) Abbreviations: ESI, epidural steroid injection *P < 0.05 compared with the "without fractures" group

Table 4. Pearson's correlation analysis between BMD and multiple variables.

	Lumbar spine	Total femur	Femoral neck
Age	-0.46†	-0.34 [†]	-0.43†
Height	0.19†	0.11*	0.12
Weight	0.31 [†]	0.26†	0.22*
Mean number of ESIs	-0.09	0.02*	0.07
Mean total dose of glucocorticoid	-0.02*	-0.15	0.02*
Mean duration of glucocorticoid administration	0.12	0.11	0.01

Abbreviations: ESI, epidural steroid injection; BMD, bone mineral density

*P < 0.05 and †P < 0.001

between BMD and total number of ESIs, mean duration of glucocorticoid administration, and mean total dose of glucocorticoid (Table 5).

Table 6 shows the effects of factors associated with BMD in postmenopausal women with low back pain. Age was negatively related to BMD at all anatomical sites involved, whereas weight and height were positively related to BMD. However, our study showed no consistent correlation between BMD and the total number of ESIs or mean duration of glucocorticoid administration.

DISCUSSION

Our study showed no consistent correlation between BMD and the mean number of ESIs, mean total dose of glucocorticoids, or mean duration of ESIs in the lumbar spine, femoral neck, and total femur of postmenopausal women with low back pain. However, the age, height, and weight were associated with BMD. The age and prevalence of osteoporosis were significantly higher, and BMD was significantly lower in patients who sustained fractures.

With 25–50% of patients affected (22-24), GIOP remains an important clinical problem. The routes of administration of glucocorticoids and the intervals between doses vary considerably. Glucocorticoids inhibit bone formation besides impairing osteoblast differ-

entiation and function (24), ultimately increasing the risk of fracture (1,2,30). The risk of fracture might be transient, but any damage to the skeleton that is sustained may have a long-term adverse impact (22-24). The consequences of glucocorticoid administration are aggravated by chronic inflammation, malnutrition, and reduced physical activity (24).

The true incidence and prevalence of osteoporosis in patients receiving ESI therapy is not known, and few data are available. Although the effects of glucocorticoid treatment on fractures are complicated by the effects of the underlying bone disorders, fracture risk appears to increase with glucocorticoid therapy (31,32). Moreover, the prevalence of osteoporosis is proportional to corticosteroid dosage (32). In postmenopausal Korean women, the prevalence of osteoporosis has been reported to be 51% in the lumbar spine and 11% in the femoral neck (33), while the overall prevalence of osteoporosis is 56% (34). In agreement, in the present study, the prevalence of osteoporosis was 49% in the lumbar spine and 23% in the femoral neck, and the overall prevalence was 50%; in women with fractures, however, the prevalence was slightly higher, at 68% in the lumbar spine, 48% in the femoral neck, and 69% overall.

Other studies have shown that the fracture incidence from oral glucocorticoid-induced bone loss is

	Lumbar spine	Total femur	Femoral neck
Mean numbers of ESIs	-0.02	0.01*	0.03
Mean total dose of glucocorticoid	-0.02*	-0.18	0.02*
Mean duration of glucocorticoid administration	0.11	0.06	0.05

Table 5. Pearson's correlation analysis between BMD and multiple variables adjusted for age, height, and weight

Abbreviations: ESI, epidural steroid injection; BMD, bone mineral density * P < 0.05

Table 6. Multiple regression analysis of BMD measurements as the dependent variable.

		Age	Height	Weight	Mean total dose of glucocorticoid (triamcinolone; mg)	Mean number of ESIs
Lumbar spine	β	-0.300	0.099	0.344	-0.143	-0.096
	P-value	< 0.001	0.008	0.001	0.041	0.344
Total femur	β	-0.281	0.160	0.291	-0.121	0.199
	P-value	0.007	0.006	0.035	0.091	0.013
Femoral neck	β	-0.30	-0.094	0.164	0.191	0.133
	P-value	0.004	0.061	0.016	0.017	0.070

Abbreviations: ESI, epidural steroid injection; BMD, bone mineral density

estimated to be 1.3- to 2.6-fold higher in people receiving glucocorticoids than in those who are not receiving glucocorticoids (31,32). In a large meta-analysis study of glucocorticoid users, van Staa et al (32) found a relative risk increase of 1.91 for any fracture, 2.86 for vertebral fracture, 1.61 for hip fracture, and 1.13 for forearm fracture. In postmenopausal women recruited from the general population, prevalence of asymptomatic vertebral fractures varied from 12% to 20.2% according to different methods to evaluate vertebral morphometrical deformity (35-39). In GIOP, a rate of 13.3%-28.0% has been reported for vertebral fractures (1,30,40,41). This rate seems to increase with age, with 14.8% having been reported for Korean women with a mean age of 59, and 20.9% for Korean women aged 60-69 years (41). In this study, the overall prevalence of fractures in postmenopausal women treated with ESI for low back pain was 38%, and the vertebral column was the most affected, with 63% of the fractures. The true prevalence rate of vertebral fractures was 22%.

Glucocorticoid-induced bone loss is dose and duration related (25,32,42-44). However, bone loss occurs even with low-dose corticosteroid therapy (31,32). Indeed, van Staa et al (45) have found that doses as low as 2.5 mg prednisolone per day are associated with an increased risk of fractures. Luengo et al (37) found no relationship between the dose of steroids and the prevalence of vertebral fractures, whereas others have reported that the glucocorticoid dose is strongly related to the risk of fracture (35,36). Moreover, de Vries et al (39) have found that the risk of GIOP and associated fractures increase substantially with increasing cumulative exposure, and among patients who receive a daily glucocorticoid dose ≥ 30 mg and whose cumulative exposure was more than 5 g. They also found that the relative risk of osteoporotic fracture was 3.63 in patients who received a daily glucocorticoid dose \geq 15 mg, and patients whose cumulative exposure was ≤ 1 g had a slightly increased risk of osteoporotic fractures. It has been well established that the long-term use of glucocorticoids increases the risk of all osteoporotic fractures, and thus, it is recommended that the use of prednisolone \geq 5 mg for 3 months or longer requires proper investigation and treatment so as to prevent osteoporosis (22-25).

The onset of fracture risk appears to be very rapid, with the maximum risk of fracture occurring within 3 months of starting therapy (31,32). Furthermore, GIOP is reversible after glucocorticoid treatment is interrupted (46,47). A reduction of fracture risk has been seen

after one year of discontinuing therapy with glucocorticoids. There is a rapid decline in bone density during the first few months of glucocorticoid treatment, which continues subsequently at a slower rate. This gradual deterioration in bone density does not appear to influence the risk of fracture further. Furthermore, it would be unlikely that an improvement in bone density could explain the relatively rapid offset of fracture risk after glucocorticoids were stopped. For patients taking intermittent glucocorticoids, the risk of fracture does not appear to increase significantly after 1-2 short courses of glucocorticoid treatment. However, patients with cumulative exposure to greater that one g prednisolone or an equivalent are at greater risk, which increases further with increasing cumulative glucocorticoid exposure (39). Other typical risk factors for osteoporosis, such as low body weight, advanced age, female gender, and underlying disease, may have an independent and additive effect on bone loss in glucocorticoid-treated patients (22-25).

The risk of fracture rises rapidly with age. Therefore, the absolute increase in fracture risk is much higher in the elderly (45-48). The greatest increase in fracture incidence is seen in postmenopausal women and elderly men. In the present study, the patients with fracture had a mean age of 74. Previous studies have reported the effects of oral administration of relatively high doses of glucocorticoids on BMD (30-32). However, in the present study, glucocorticoids were administered at comparatively lower doses (mean, 164 mg). Also, mean duration of glucocorticoid administration was relatively short (mean, 8.1 weeks). Nevertheless, the prevalence of vertebral fractures was similar to that reported in other studies. This result may be caused by older age and underlying diseases causing low back pain.

In this study, age was negatively related to BMD at all sites, whereas weight and height were positively related to BMD. We found age, weight, and height to be correlated with BMD, which was consistent with other studies (34,36,44,49). Moreover, our study showed no consistent correlation between the mean number of ESIs, mean total dose of glucocorticoids, or mean duration of ESIs and BMD. Some previous studies reported no significant relationship between epidural glucocorticoid therapy and BMD in postmenopausal women with low back pain (50,51). In contrast, other studies have noted that those with high-dose glucocorticoid therapy are at risk for lower BMD (2,24,32). This interesting observation may be caused by the difference of doses and duration of glucocorticoid administration, and implies that the intermittent use of glucocorticoids with ESIs in postmenopausal women with low back pain is not associated with relevant loss of bone mass. However, cumulative glucocorticoid administration might be associated with decreased BMD.

BMD is a major determinant of the risk of fracture in patients with GIOP (24). Adequate monitoring of bone health and therapeutic intervention are recommended when drugs with an adverse bone safety profile are used, particularly in patients with additional risk factors for osteoporosis (1,24). All patients initiating long-term treatment with glucocorticoids should obtain a baseline BMD of the spine and hip (1,45). There should be a low threshold for offering treatment to patients older than 65 years if the cumulative glucocorticoid exposure exceeds the equivalent of one g prednisolone (39). In previous studies, BMDs were measured at the lumbar spine (0.99 - 0.92), femoral neck (0.84-0.68), and trochanter (0.70 – 0.64) in Korean postmenopausal women (43,52). In this study, BMD measurements at the lumbar spine (0.887), femoral neck (0.767), and trochanter (0.711) were similar to those previously reported.

There were some limitations to this study. First, this study is limited by the fact that it was retrospective. Second, the number of cases with very frequent, highdose glucocorticoid injections was small. High-dose corticosteroids are infrequently used in the clinic because of adverse effects. In spite of the above limitations, to our knowledge, this was the first study carried out to evaluate the relationship between BMD, ESIs, and vertebral fractures in postmenopausal women with low back pain.

CONCLUSION

In conclusion, older age and lower BMD were associated with osteoporotic fracture in postmenopausal women treated with ESIs for low back pain. The ESIs were not associated with BMD.

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