Retrospective Review

Effects of Epidural Steroid Injections on Bone Mineral Density and Bone Turnover Markers in Patients Taking Anti-Osteoporotic Medications

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Background: Glucocorticoids adversely affect bone mineral density (BMD) and increase the risk of fracture. Yet, the cause-and-effect relationship between epidural steroid injection (ESI) and BMD has not been thoroughly investigated, and available results are inconsistent. This is probably a consequence of differences in the dose of steroids and follow-up duration.

Objective: This study aimed to evaluate changes in BMD and the risk of fracture according to duration of the follow-up and amount of steroids used for ESI.

Setting: Department of Orthopedic Surgery at Seoul Metropolitan Government Seoul National University (SMG-SNU) Boramae Medical Center, Korea.

Methods: We retrospectively reviewed the medical records of postmenopausal patients who underwent dual-energy x-ray absorptiometry (DEXA) at least 3 times in 5 years. Patients were divided into 2 groups. Group 1 consisted of 73 patients who received ESI, whereas Group 2 consisted of 294 patients who did not receive ESI. All patients took anti-osteoporotic medications. BMD measurements were performed in 4 different regions, and levels of bone turnover markers (BTMs) were measured. In Group 1, BMD and BTMs levels were measured before the last ESI and 1 and 2 years after. A sub-analysis was conducted in Group 1 to compare BMD values in sub-groups with different doses of steroids.

Results: In Group 1, the absolute values of BMD of the spine were decreased at the 1-year follow-up, but by the 2-year follow-up they recovered and approached the values in Group 2. In Group 2, BMD increased both at the 1- and 2-year follow-ups. There was an increase in occurrence of osteoporosis during the first year after ESI, but the prevalence of osteoporosis declined remarkably during the second year. The levels of BTMs increased at the 1-year follow-up and decreased at the 2-year follow-up in Group 1. Higher cumulative doses of steroids induced greater decreases in BMD. However, the changes in spine BMD in the sub-analysis were insignificant.

Limitations: This was a retrospective study. Additionally, administration of anti-osteoporotic medication might have prevented accurate evaluation of the effects of ESI.

Conclusions: ESI adversely affects BMD in postmenopausal women, especially that of the spine, and the adverse effects increase with the dose of steroids. Gradual reduction of the effect of steroids one year after the cessation of ESI resulted in recovery of BMD to a level similar to that in the control group.

Key words: Epidural steroid injection, bone mineral density, osteoporosis, postmenopausal women, glucocorticoids, bone turnover markers, osteoporotic fracture

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Among the various known methods for managing low back pain (1), epidural steroid injection (ESI) is widely used to treat pain originating from the spine, such as pain accompanying spinal stenosis, intervertebral disc herniation, and other degenerative spinal pathologies (2-4).

However, glucocorticoids have multiple adverse effects (5-8). Administration of exogenous glucocorticoids dramatically reduces bone mineral density (BMD) and increases the risk of fracture (9,10). Most complications of oral, intramuscular, and intravenous steroid administration are well defined. Yet, the cause-and-effect relationship between ESI and BMD has not been thoroughly investigated.

The first prospective study of the relationship between ESI and BMD by Manchikanti et al (11) concluded that low doses of steroids injected into the epidural space in patients with chronic symptoms that persist even after conventional treatments are safe and do not affect body weight and BMD. Some other studies also measured BMD after epidural injections of a relatively small number of corticosteroids at low cumulative doses and found no significant relationship between ESI and BMD (12-14). In contrast, some recent reports showed that ESI negatively influences BMD (15-17).

These discordant outcomes are probably due to a failure to consider all relevant variables during the study design. There is an urgent need of studies that efficiently control for confounding, conduct comprehensive and consecutive observation of potential risks of ESI, and investigate its clinical applicability. In the present study, we evaluated serial changes of BMD and the effect of anti-osteoporotic medication after ESI and performed a sub-analysis to clarify the relationship between the amount of steroids used and BMD.

Method

Study Design

The present study retrospectively analyzed the SMG-SNU Boramae Medical Center database of patients who underwent DEXA scans for at least 3 years between January 2012 and December 2016. The study was approved by our Institutional Review Board (approval number: 20170316/16-2017-44/041).

Patient Population

Postmenopausal patients receiving at least one of the following anti-osteoporotic medication: bisphosphonates (risedronate sodium, ibandronate sodium, alendronate sodium), selective estrogen receptor modulators (raloxifene, tamoxifen), parathyroid hormone, or calcium and vitamin D supplementation, were selected. Individuals with a history of use of drugs that can potentially affect bone metabolism, such as long-term oral glucocorticoids and thyroid hormone, were excluded. Patients who had chronic inflammatory diseases, such as rheumatoid arthritis, inflammatory bowel disease, asthma, and thyroid or parathyroid disease or had undergone spinal surgery were also excluded. Outlier BMD values were removed from data analysis.

A total of 602 patients were initially enrolled. After applying the inclusion and exclusion criteria, 73 patients were included in the case group (Group 1), and 4 times as many patients were included in the control group (Group 2) after age and body mass index (BMI) matching (Fig. 1).

Evaluation

BMD measurements from the patients in group 1 were collected and the patients' latest BMD measurement before the last ESI was retrieved to be set as the baseline BMD. BMD was measured using lunar DEXA scanner (Prodigy; Madison, WI) from the whole lumbar spine, 2 regions of the lowest spine (averaged), femoral neck, and total femur as absolute value (g/cm^2). The measurements were taken annually for 2 years since the initial measurement. The changes of absolute value and the mean percent change of BMD from the baseline were recorded for each follow-up.

Osteoporosis was defined as a T-score $\leq$ -2.5, and osteopenia as a T-score between -2.5 and -1.0 (18). The prevalence of osteoporosis was determined based on T-scores for 2 years. Occurrence of osteoporotic fracture was monitored during the follow-up period. Where available, serum levels of C-telopeptide of collagen 1 (CTX) and osteocalcin (OC) were used as bone turnover markers (BTMs).

An additional sub-analysis according to total dose of steroids was performed in Group 1. The reference value of the total dose of steroids was determined by considering the number of procedures performed on average at the outpatient department. The steroids administered in this study were triamcinolone acetonide and dexamethasone disodium phosphonate. Each cumulative steroid dose was converted into an equivalent dose in order to compare the effects of different doses of steroids (Table 1) (19).

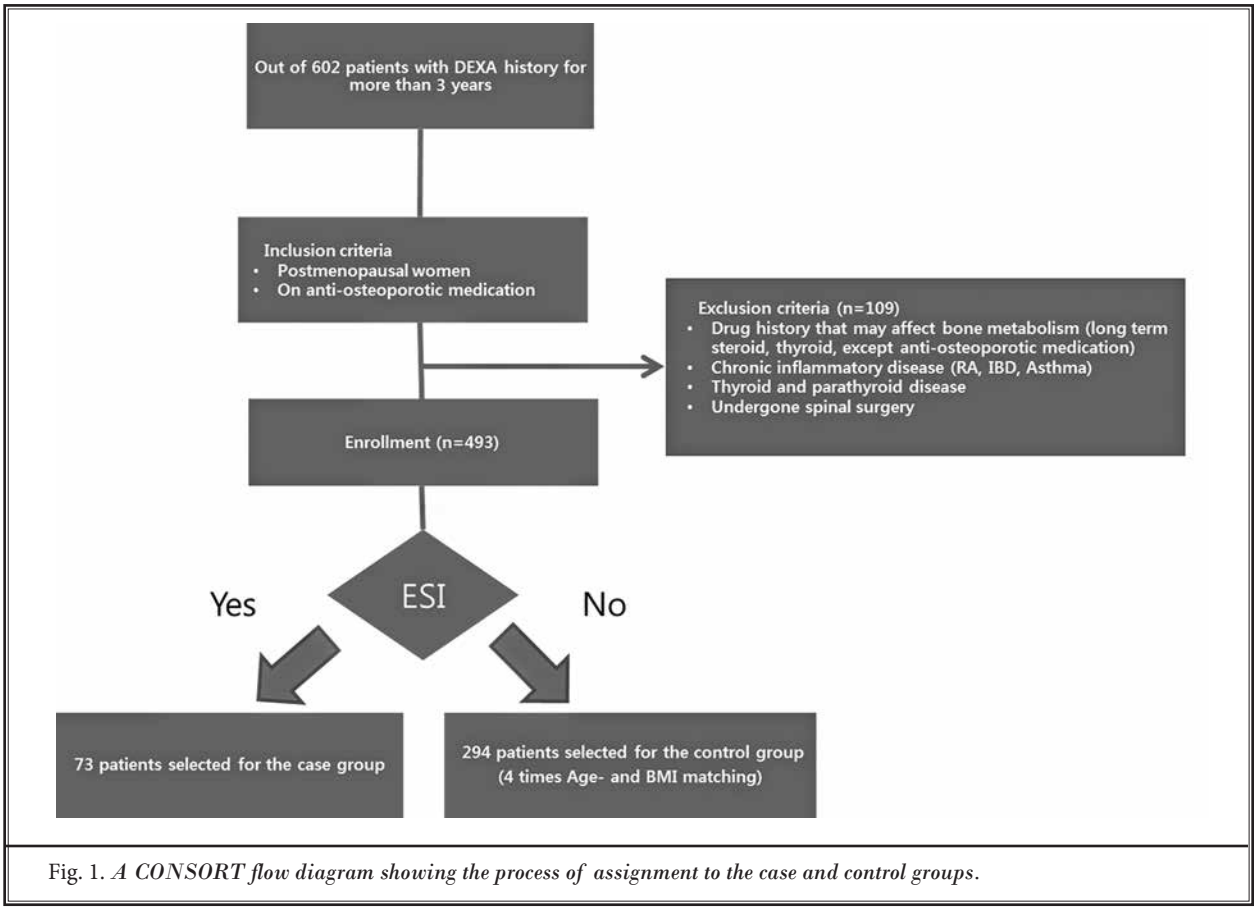

Fig. 1. *A CONSORT flow diagram showing the process of assignment to the case and control groups.*

Statistical Analysis

Data are expressed as mean ± SD. The independent t-test was used to identify differences in age, height, weight, BMI, baseline BMD, baseline BTMs, and duration of the follow-up period. Chi-square statistics were used to confirm absence of significant differences between the groups in prevalence of diabetes mellitus (DM) and numbers of pre-existing fractures and new fractures that occurred during the follow-up. A paired t-test was used to analyze changes in BMD and BTMs versus baseline within each group at the 1-year and 2-year follow-ups. The prevalence of osteoporosis in the 2 groups was compared using the Mann-Whitney test. A *P*-value less than 0.05 was considered to indicate a statistically significant difference. SPSS for Windows (version 22; IBM SPSS Inc., Chicago IL) was used for all statistical analyses.

Result

Patient Demographics and Baseline Status

Patient baseline characteristics are presented in Table 2. There were no statistically significant differences between the case and control groups in age, weight, height, BMI, and baseline BMD. There were no differences in prevalence of DM, history of pre-existing fractures, and occurrence of new fractures during the follow-up period. The mean measurement interval from baseline to the 1-year follow-up was 14.5 months in Group 1 and 13.6 months in Group 2. The mean interval from baseline to the 2-year follow-up was 28.4

Table 1. *Comparison of the different steroids in terms of glucocorticoid potencies (19).*

Steroid	Relative glucocorticoid potency*
Hydrocortisone	1
Methylprednisolone	5
Triamcinolone	5
Betamethasone	33
Dexamethasone	27

*Relative potency to hydrocortisone

Table 2. *Characteristics of the patients and mean value of baseline BMD and BTMs.*

	Group 1 (n = 73)	Group 2 (n = 294)	*P* value
Age (years)	71.84 ± 6.60	70.46 ± 7.70	NS
Height (cm)	150.54 ± 5.44	150.58 ± 5.75	NS
Weight (kg)	53.39 ± 7.61	53.73 ± 7.74	NS
BMI (kg/m^2)	23.52 ± 2.84	23.68 ± 3.08	NS
DM history	13 (17.8%)	42 (14.3%)	NS
Pre-existing fracture history	27 (37.0%)	122 (41.5%)	NS
Newly occurred fracture during F/U	16 (21.9%)	65 (22.1%)	NS
Baseline BMD (g/cm^2)			
Whole lumbar spine	0.818 ± 0.106	0.804 ± 0.106	NS
Two regions of the lowest spine (averaged)	0.755 ± 0.104	0.754 ± 0.105	NS
Femoral neck	0.685 ± 0.081	0.688 ± 0.095	NS
Total femur	0.745 ± 0.096	0.739 ± 0.104	NS
Bone turnover markers			
CTX	0.239 ± 0.115	0.271 ± 0.181	NS
OC	6.041 ± 1.950	6.191 ± 3.809	NS
F/U duration of 1 year Follow-up (months)	14.5 ± 2.87	13.6 ± 2.02	0.015
F/U duration of 2 year Follow-up (months)	28.4 ± 5.10	26.4 ± 3.16	0.007
Mean total numbers of ESIs	2.2		
Mean total dose of corticosteroid (triamcinolone, mg)	78.3		

Data presented as mean ± SD.
Group 1: patients who received ESI, Group 2: patients who received no ESI.
BMI = body mass Index; DM = diabetic mellitus; BMD = bone mineral density;
ESI = epidural steroid injection; CTX = Serum C-telopeptide of collagen 1; OC = osteocalcin.
$P < 0.05$ considered as statistically significant.
NS: not significant

months in Group 1 and 26.4 months in Group 2. The mean total number of ESIs was 2.2, and the mean cumulative administered dose of steroids in Group 1 was equipotent to 78.3 mg of triamcinolone.

Serial Changes of BMD

The serial changes of absolute values of BMD are presented in Fig. 2. In Group 1, the absolute values of BMD of the spine decreased at the 1-year follow-up, but approached the values in Group 2 at the 2-year follow-up. In Group 2, the BMD values continuously increased both at the 1- and 2-year follow-ups. The absolute values of hip joint BMD in Group 1 decreased at the 1-year follow-up and increased at the 2-year follow-up. In contrast, in Group 2, the absolute values of BMD consistently decreased. All the absolute values of BMD are listed in Supplemental Table 1.

The mean changes in the absolute value of BMD between baseline and the 1-year follow-up and between baseline and the 2-year follow-up in both groups are shown in Table 3. In Group 1, the absolute value of BMD decreased in all 4 evaluated regions. However, the differences were not significant, except for the total femur values. In Group 2, the values for the spine increased significantly at the 1-year follow-up. At the 2-year follow-up, an increase in the BMD of the spine of approximately 0.025 g/cm^2 from baseline was observed both groups.

The mean percentage changes of BMD are illustrated in Fig. 3 and listed in Supplemental Table 2. The mean changes of BMD were decreased by 0.58 ± 0.70% in the whole lumbar spine and 0.59 ± 0.79% in the 2 regions of the lower spine (averaged) in Group 1; whereas in Group 2 they were increased by 1.97 ± 0.41% in the whole lumbar spine and 1.38 ± 0.43% in the 2 regions of the lower spine (averaged). At the 2-year follow-up, the mean percent changes were positive and reached approximately 3% compared to baseline values in both groups.

Evaluation of Osteoporosis

The initial prevalence of osteoporosis of the whole

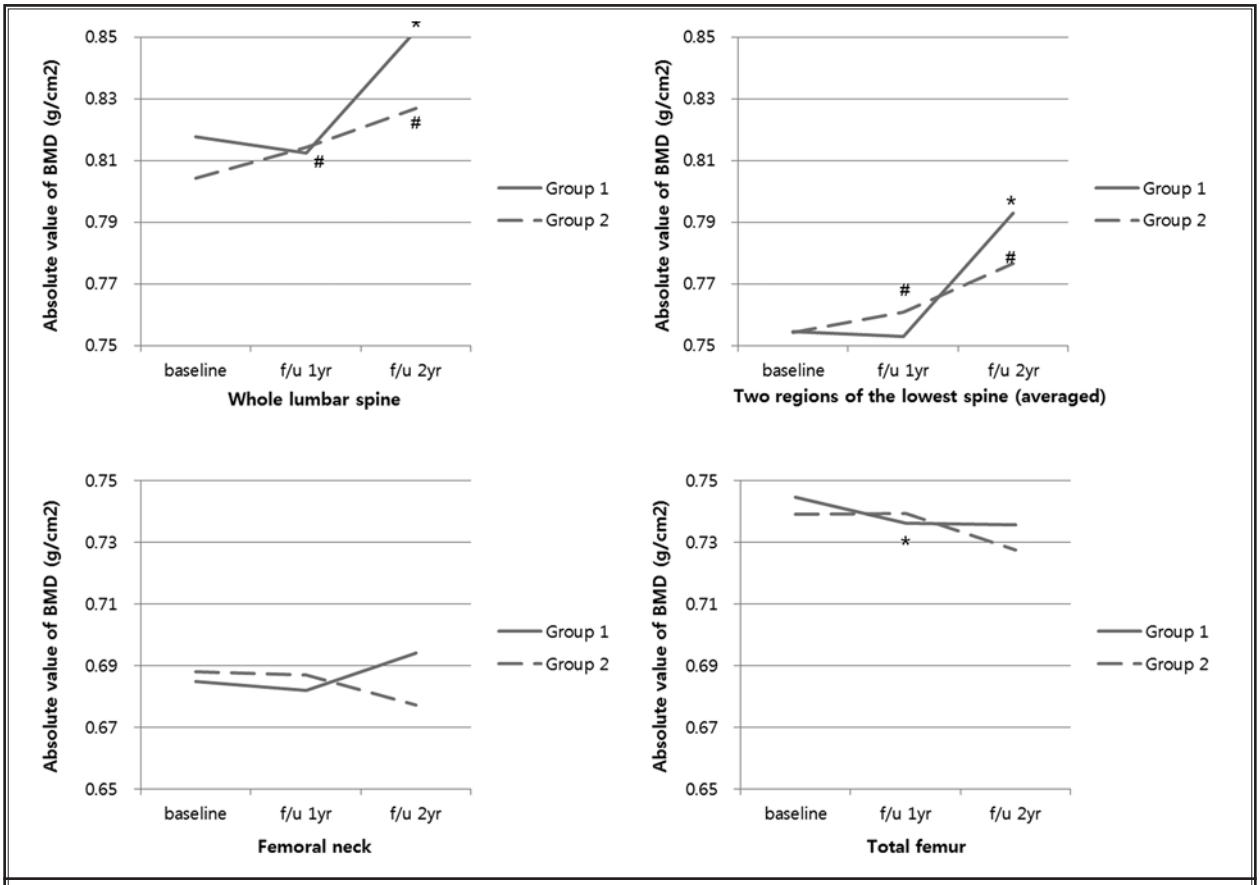

Fig. 2. *The serial changes in the absolute values of BMD.*
Group 1: patients who received ESI, Group 2: patients who received no ESI.
95% trimmed mean absolute value of BMD (g/cm^2).
**Significant interval change ($P < 0.05$) between baseline and each follow-up period in Group 1*
#Significant interval change ($P < 0.05$) between baseline and each follow-up period in Group 2

lumbar spine in the group of patients who were treated with ESI was 68.1%, and the corresponding baseline value for the 2 regions of the lower spine (averaged) was 73.6%. The prevalence increased to 73.6% and 79.2% at the 1-year follow-up, respectively. At the 2-year follow-up, the prevalence showed a sharp decrease to 54.2% and 65.3%, respectively (Table 4). In contrast, in the patients who were not treated with ESI, the prevalence of osteoporosis of the whole lumbar spine at baseline was 67.0%, and the corresponding value for the 2 regions of the lower spine (averaged) was 75.2%. The prevalence decreased to 65.0% and 72.8%, respectively, at the 1-year follow-up and to 61.2% and 65.6%, respectively, at the 2-year follow-up. There were no significant differences in the prevalence of osteoporosis between the groups for any follow-up period.

Evaluation of BTMs

The mean changes in the levels of the BTMs are illustrated in Fig. 4 and listed in Supplemental Table 3. At baseline, there were no significant differences between the 2 groups. In Group 1, the level of CTX increased by 0.044 (18.41%) at the 1-year follow-up and then decreased at the 2-year follow-up. The corresponding trend was reversed in Group 2. Similar trends were observed for OC.

Sub-analysis According to the Total Dose of Steroids

The results of the additional sub-analysis according to the total dose of steroids are listed in Table 5. Higher doses of steroids clearly resulted in greater decreases of BMD of the spine compared to the reference. Although

Table 3. *The Changes of the absolute value of BMD between baseline and follow-up period.*

	Interval change	*P* value	Interval change	*P* value
1 year follow-up	**Group 1**		**Group 2**	
Whole lumbar spine	-0.0053 ± 0.0460	NS	0.0147 ± 0.0522	0.000
Two regions of the lowest spine (averaged)	-0.0034 ± 0.0467	NS	0.0100 ± 0.0487	0.001
Femoral neck	-0.0057 ± 0.0302	NS	-0.0010 ± 0.0391	NS
Total femur	-0.0147 ± 0.0327	0.001	-0.0013 ± 0.0335	NS
2 year follow-up	**Group 1**		**Group 2**	
Whole lumbar spine	0.0255 ± 0.0572	0.002	0.0266 ± 0.0568	0.002
Two regions of the lowest spine (averaged)	0.0247 ± 0.0575	0.002	0.0260 ± 0.0035	0.003
Femoral neck	0.0036 ± 0.0883	NS	-0.0064 ± 0.0351	NS
Total femur	-0.0096 ± 0.0511	NS	-0.0078 ± 0.0364	NS

Data presented as mean ± SD.
95% trimmed mean value of the change of the absolute BMD (g/cm^2).
Group 1: patients who received ESI, Group 2: patients who received no ESI.
$P < 0.05$ considered as statistically significant.
NS: not significant

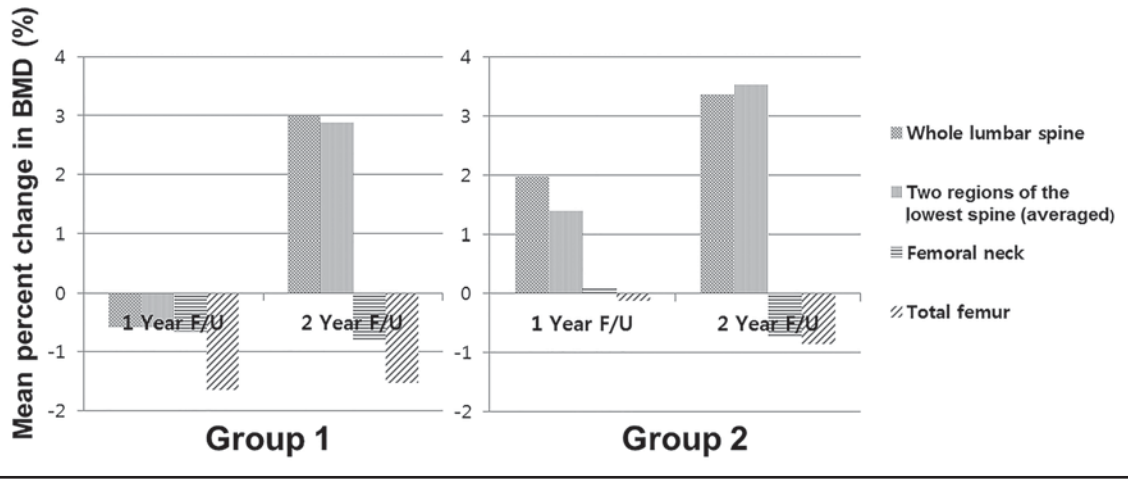

Fig. 3. The mean percentage changes of BMD.
Group 1: patients who received ESI, Group 2: patients who received no ESI.
95% trimmed mean value of the percentage changes of BMD (%).

the reference values were selected arbitrarily, the correlation between the extent of decrease of the BMD of the spine and the dose of steroids appears convincing. However, the changes in BMD of the spine were not significant ($P > 0.05$).

Discussion

Studies of the effects of glucocorticoids administered to the epidural space have produced inconsistent results. An increasing demand for efficient control of pain originating from the spine has necessitated a comprehensive study of the effects of ESI on BMD. The present study is the first to analyze sequential changes in BMD for 2 years in patients who had undergone ESI.

BMD appears to decrease most rapidly during the first 6 months after an exogenous treatment, followed by a reduction in the rate of decrease (20,21). The steroid therapy would be expected to further reduce BMD and increase bone turnover until the second year after ESI. In the present study, BMD decreased significantly

Table 4. *The prevalence of osteoporosis and osteopenia in both groups.*

		Group 1 (n = 73)			Group 2 (n = 294)		
		baseline	1 year F/U	2 year F/U	baseline	1 year F/U	2 year F/U
Whole lumbar spine	normal	3 (4.2%)	3 (4.2%)	8 (11.1%)	6 (2.0%)	8 (2.7%)	9 (3.1%)
	osteopenia	21 (29.2%)	17 (23.6%)	26 (36.1%)	91 (31.0%)	95 (32.3%)	105 (35.7%)
	osteoporosis	49 (68.1%)	53 (73.6%)	39 (54.2%)	197 (67.0%)	191 (65.0%)	180 (61.2%)
Two regions of the lowest spine (averaged)	normal	2 (2.8%)	2 (2.8%)	1 (1.4%)	5 (1.7%)	4 (1.4%)	8 (2.7%)
	osteopenia	18 (25.0%)	14 (19.4%)	25 (34.7%)	68 (23.1%)	76 (25.9%)	93 (31.6%)
	osteoporosis	53 (73.6%)	57 (79.2%)	47 (65.3%)	221 (75.2%)	214 (72.8%)	193 (65.6%)
Femoral neck	normal	4 (5.6%)	2 (2.8%)	5 (6.9%)	28 (9.5%)	26 (8.8%)	18 (6.1%)
	osteopenia	46 (63.9%)	43 (59.7%)	44 (61.1%)	164 (55.8%)	169 (57.5%)	165 (56.1%)
	osteoporosis	23 (31.9%)	28 (38.9%)	24 (33.3%)	102 (34.7%)	99 (33.7%)	111 (37.8%)
Total femur	normal	7 (9.7%)	7 (9.7%)	4 (5.6%)	46 (15.6%)	41 (13.9%)	31 (10.5%)
	osteopenia	49 (68.1%)	46 (63.9%)	49 (68.1%)	158 (53.7%)	167 (56.8%)	169 (57.5%)
	osteoporosis	17 (23.6%)	20 (27.8%)	20 (27.8%)	90 (30.6%)	86 (29.3%)	94 (32.0%)

Group 1: patients who received ESI, Group 2: patients who received no ESI.
Values represent the number of patients who have osteoporosis and osteopenia.
% represents the number of patients out of the total patients in each group.
No significant difference between groups by using Mann-Whitney test.

Table 5. *Change of the absolute BMD according to the total amount of steroid used in Group 1.*

	Interval change (g/cm2)	*P* value	Interval change (g/cm^2)	*P* value
	< 90 mg (n = 55)		≥ 90 mg (n = 18)	
Whole lumbar spine	-0.0032 ± 0.0470	NS	-0.0101 ± 0.0444	NS
Two regions of the lowest spine (averaged)	-0.0014 ± 0.0473	NS	-0.0056 ± 0.0455	NS
Femur neck	-0.0116 ± 0.0277	0.004	0.0131 ± 0.0320	NS
Total femur	-0.0197 ± 0.0340	0.000	-0.0013 ± 0.0251	NS
	< 120 mg (n = 59)		≥ 120 mg (n = 14)	
Whole lumbar spine	-0.0017 ± 0.0464	NS	-0.0178 ± 0.0444	NS
Two regions of the lowest spine (averaged)	-0.0006 ± 0.0479	NS	-0.0098 ± 0.0415	NS
Femoral neck	-0.0096 ± 0.0284	0.015	0.0104 ± 0.0344	NS
Total femur	-0.0181 ± 0.0338	0.000	-0.0035 ± 0.0267	NS

Data presented as mean ± SD.
Total amount of steroid used was calculated as equivalent dose of triamcinolone.
Interval change means the difference in the absolute value of BMD between baseline and 1 year follow-up regarding the reference value in Group 1.
NS: not significant

during the first year, whereas at the 2-year follow-up this drop was compensated, leading to a recovery.

In general, BMD of the lumbar spine decreases by approximately 1% per year in postmenopausal Korean women (20). In the present study, it increased by 0.015 g/cm^2 (1.97%) in the patients who did not undergo ESI and decreased by 0.005 g/cm^2 (0.58%) in those who received this therapy at the 1-year follow-up. The BMD in Group 1 decreased despite the administration of anti-osteoporotic medication, indicating that ESI does have some negative influence on BMD.

Manchikanti et al (11) first reported that low-dose ESI does not affect BMD of the spine. However, this study enrolled both premenopausal and postmenopausal women as well as men and did not exclude patients with underlying thyroid disease. Kang et al (12) concluded that ESI with a maximum cumulative triamcinolone dose of 200 mg per year is safe. The lat-

ter study, however, did not consider the recent history of administration of anti-osteoporotic medications, which could influence the changes in BMD significantly. Yi et al (13) found no correlation between ESIs, BMD, and vertebral fracture. Unfortunately, a cross-sectional observation design of their study prevented serial and continuous examination of the patients. In another study (14), there was no significant relationship between a cumulative dose of methylprednisolone of less than 3 g and BMD. However, the patients of that study were healthy people without any bone-related diseases.

In contrast, some studies have reported adverse effects of ESI on BMD. Kim et al (15) suggested that multiple ESIs (more than 10 times, a cumulative dose of triamcinolone of 200 mg) caused a BMD drop in postmenopausal women. There was a sharp reduction in BMD in the ESI recipients who did not take anti-osteoporotic medication, while no significant changes were observed in the patients who took the medication (16). According to Al-Shoha et al (17), a single ESI induced an average BMD decrease of 1.8% in postmenopausal women and increased the rate of bone turnover.

In addition to demonstrating that ESI adversely affects BMD, the present study revealed that the initial decrease in BMD in Group 1 was compensated, and the BMD values approached those in Group 2 at the 2-year follow-up. Both groups showed a dramatic increase in spine BMD of approximately 0.025 g/cm^2 at the 2-year follow-up compared to the baseline values (Table 3). This outcome suggests that although BMD was reduced in patients who underwent ESI, a combination of anti-osteoporotic medication and gradual reduction of the effect of steroids led to a recovery.

Although a history of anti-osteoporotic medication might influence changes in BMD, we included patients who had received anti-osteoporotic drugs since the majority of individuals in need of ESI had likely undergone some kind of an anti-osteoporotic treatment.

In this study, bisphosphonate, SERM, parathyroid hormone, and calcium with vitamin D4 were prescribed. All the patients took more than one of these drugs during the follow-up period (Supplemental Table 4). In several studies, bisphosphonate was the most effective anti-osteoporotic medication for the treatment of glucocorticoid-induced osteoporosis and prevention of osteoporotic fracture (23-25). In the present study, 61 (83.6%) of the 73 patients in Group 1 and 231 (78.6%) of the 294 patients in Group 2 took bisphosphonate to treat osteoporosis. As a result, BMD of the spine increased at the 2-year follow-up in both groups. These local increases of the BMD of the spine are likely caused by the anti-osteoporotic medication, in particular, bisphosphonate. Since bisphosphonate, which affects cancellous bone far more strongly than cortical bone, was the most popular anti-osteoporotic medication in this study, the changes between the baseline and follow-up values were more dramatic for the spine than for the femur (26).

Patients with a history of fracture were excluded from the previous studies (15-17). Given that age is a major risk factor in osteoporotic fracture, patients with osteoporotic fracture are very common in clinical practice. Even though a history of fracture might enhance the risk of a new fracture, this study was designed to recapitulate clinical settings rather than the research environment. Therefore, we included patients with previous osteoporotic fracture.

Exogenous steroid recipients among postmenopausal women have a higher risk of fracture (27-29), which appears to increase with the number of steroid treatments (10). During the follow-up period, 20 new osteoporotic fractures (16 patients) occurred in the 73 (27.40%) patients in Group 1 and 74 new fractures (65 patients) occurred in the 294 (25.17%) patients in Group 2 (Table 6). The prevalence of new fractures was slightly higher than that in the general population of postmenopausal Korean women (30). Two factors explain this outcome: 1) the risk of fracture rises sharply with age, and 2) patients with a fracture history are more prone to experience subsequent fractures (31,32). The patients of our study were on average over 70 years old, and 37.0% of patients in Group 1 and 41.5% in Group 2 had a history of fracture.

Appropriate preventive management can reduce the risk of osteoporotic fracture in patients receiving a steroid treatment (33,34). Moreover, cessation of oral corticosteroid treatment drove the risk of fracture towards the baseline levels regardless of the cumulative dose of steroids (35,36). In the present study, there was an increase in osteoporosis occurrence during the first year after ESI, but this trend reversed during the second year, with the prevalence of osteoporosis declining remarkably (Table 4).

In addition to BMD, BTMs could be utilized in the management of patients with osteoporosis since high bone remodeling rates have been associated with more severe forms of osteoporosis (37,38). Levels of BTMs rapidly decrease during bisphosphonate therapy in postmenopausal women, and the decline is associ-

Table 6. *The prevalence of the pre-existing osteoporotic fracture and subsequent osteoporotic fracture.*

		Group 1 (n = 73)	Group 2 (n = 294)
Pre-existing fracture	Spine	23 (31.51%)	109 (37.07%)
	Hip	2 (2.74%)	13 (4.42%)
	Distal radius	4 (5.48%)	13 (4.42%)
	Total	29 (39.73%)	135 (45.92%)
Newly occurred fracture	Spine	11 (15.07%)	51 (17.35%)
	Hip	1 (1.37%)	4 (1.36%)
	Distal radius	8 (10.96%)	19 (6.46%)
	Total	20 (27.40%)	74 (25.17%)

Group 1: patients who received ESI, Group 2: patients who received no ESI.
Values represent the number of patients in each group.
% represents the number of fractures out of the total patients in each group.
Only osteoporotic fractures occurred in spine, hip and distal radius were considered as fractures.

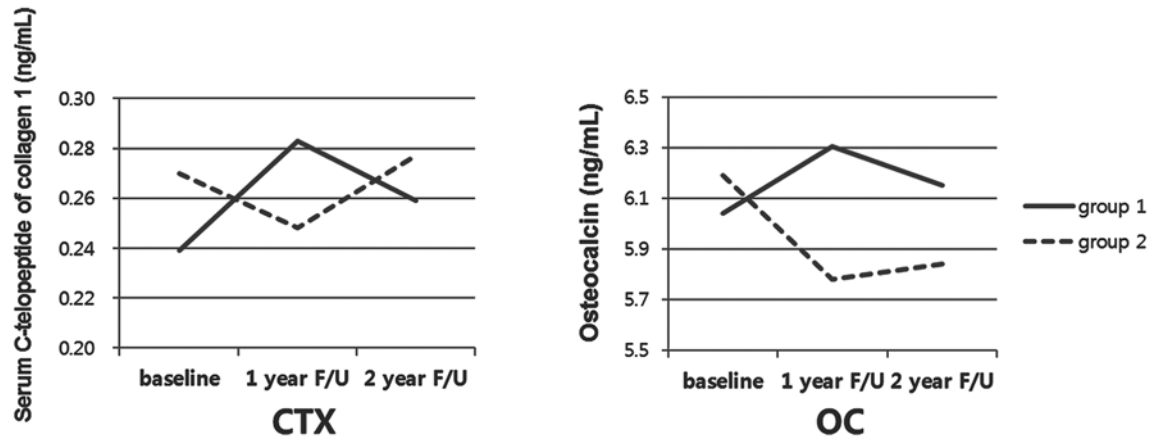

Fig. 4. The serial changes of the levels of BTMs.
Group 1: patients who received ESI, Group 2: patients who received no ESI.
95% trimmed mean value of the levels of BTMs (ng/mL).
No significant difference in both groups as determined using the paired t-test.

ated with increased BMD and a reduced rate of fracture (39-41). In the present study, the levels of CTX and OC were increased at the 1-year follow-up in Group 1 and decreased in Group 2 (Fig. 4 and Supplement Table 3). Although the differences were not significant, a decreasing trend similar to that observed for serial BMD changes in Group 1 could be interpreted as evidence indicating that ESI does not negatively influence BMD. However, BTMs levels were not measured in all the patients at each follow-up. The results are thus not reliable enough to make a solid conclusion, but the overall trends are comparable to those in previous studies that analyzed an inverse correlation between BMD and BTMs (42,43).

A dose of steroids that could be considered safe has not been reliably determined for ESI or other delivery methods, and the issue is generally poorly addressed, although the total annual dose of steroids was limited to 3 mg/kg of triamcinolone (44). Establishing a safe steroid dose is an important issue for clinical practitioners. In this study, the dose for ESI was selected based on the dosage used in our clinical practice for the treatment with 2 or 3 injections (40 mg of triamcinolone per injection).

We performed a sub-analysis of the correlation between the decrease in BMD and total dose of glucocorticoids (Table 5). The interval change of the absolute

value of BMD in Group 1 increased as the reference dose of triamcinolone increased. Of note, the doses utilized in this study for a single ESI may deviate from values used at other institutions. Nevertheless, this sub-analysis could provide some insight into the above relationship. Since higher steroid doses increase the risk of adverse effects, patients receiving large amounts of steroids require additional attention. Further studies are needed to demonstrate a relationship between the total dose of steroids and adverse effects at relatively low total doses and to establish a reference steroid dose for ESI.

Limitations

Our observations must be interpreted within a framework of limitations. First, this study had a retrospective design. However, all the possible confounding variables, except the ones described above, were excluded. Furthermore, age matching and BMI matching were performed to increase the accuracy of analysis. Second, all the patients took anti-osteoporotic medication, which could obscure the adverse effects of ESI. About half of the patients experienced osteoporotic fracture. Moreover, anti-osteoporotic medication was prescribed even to those without such events to prevent osteopenia- or osteoporosis-related fracture. Third, there were differences in anti-osteoporotic drugs that the patients received. The present study did not focus on the effects of a particular anti-osteoporotic medication. Rather, it was conducted to provide some recommendations to practitioners on how to manage patients receiving ESI in general clinical practice. Moreover, according to a previous meta-analysis, all anti-osteoporotic medications have similar effects on BMD, with an exception of calcium with vitamin D (45,46).

Notwithstanding the aforementioned limitations, this is the first study to analyze intermediate-term (2 years) sequential changes in BMD in patients receiving ESIs. Based on the results, we suggest that practitioners need to be aware that such patients require continuous care rather than simple, temporary, one-off management. The present study allows predicting changes in BMD after the adverse effects of steroids vanish. This may help practitioners manage patients after ESI, the demand for which is currently growing.

Conclusion

ESI adversely affects BMD, especially that of the spine, in postmenopausal women, and the adverse effects increase with the dose of steroids. The gradual decrease of the effects of the steroid therapy one year after the cessation of ESI resulted in recovery of BMD to the values similar to those in the control group. Both patients and practitioners should be aware of the increased risk of fracture, especially after approximately 1 year post-treatment, as well as of the fact that this risk decreases owing to increasing BMD after cessation of ESI.

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Supplemental Table 1. The absolute value of BMD between 2 groups at baseline and follow-up.

	Group 1 (n = 73)			Group 2 (n = 294)		
	baseline	1 year F/U	2 year F/U	baseline	1 year F/U	2 year F/U
Whole lumbar spine	0.8176 ± 0.1059	0.8125 ± 0.1012	0.8523 ± 0.1177	0.8043 ± 0.1061	0.8143 ± 0.0975	0.8268 ± 0.1015
Two regions of the lowest spine (averaged)	0.7546 ± 0.1042	0.7530 ± 0.1061	0.7930 ± 0.1181	0.7542 ± 0.1051	0.7609 ± 0.0958	0.7767 ± 0.1017
Femoral neck	0.6848 ± 0.0805	0.6818 ± 0.0772	0.6940 ± 0.1045	0.6880 ± 0.0953	0.6869 ± 0.0959	0.6771 ± 0.0932
Total femur	0.7445 ± 0.0956	0.7360 ± 0.0949	0.7356 ± 0.0929	0.7390 ± 0.1037	0.7394 ± 0.1013	0.7274 ± 0.1030

Group 1: patients who received ESI, Group 2: patients who received no ESI.
Data presented as mean ± SD (g/cm^2).

Supplemental Table 2. The mean percentage changes of BMD (%).

	Group 1 (n = 73)		Group 2 (n = 294)	
	1 year F/U	2 year F/U	1 year F/U	2 year F/U
Whole lumbar spine	-0.5825 ± 0.6988	3.0019 ± 0.9698	1.9662 ± 0.4138	3.3562 ± 0.4701
Two regions of the lowest spine (averaged)	-0.5871 ± 0.7868	2.8754 ± 1.0727	1.3830 ± 0.4305	3.5177 ± 0.4949
Femoral neck	-0.6556 ± 0.5318	-0.7888 ± 1.8994	0.1195 ± 0.3367	-0.7235 ± 0.3294
Total femur	-1.6471 ± 0.5645	-1.5286 ± 0.9663	-0.1286 ± 0.2881	-0.8600 ± 0.3163

Group 1: patients who received ESI, Group 2: patients who received no ESI.
Data presented as mean ± SD (%).

Supplemental Table 3. Changes of the BTMs between baseline and follow-up period.

	Group 1				Group 2			
	CTX		OC		CTX		OC	
	Mean ± SD	Interval change	Mean ± SD	Interval change	Mean ± SD	Interval change	Mean ± SD	Interval change
Baseline	0.239 ± 0.115	-	6.041 ± 1.950	-	0.271 ± 0.181	-	6.191 ± 3.809	-
1 year follow-up	0.283 ± 0.125	0.044	6.304 ± 2.408	0.263	0.248 ± 0.151	-0.023	5.781 ± 2.618	-0.410
2 year follow-up	0.259 ± 0.105	0.020	6.150 ± 1.976	0.109	0.277 ± 0.157	0.006	5.841 ± 3.430	-0.350

Group 1: patients who received ESI, Group 2: patients who received no ESI.
CTX: C-telopeptide of collagen 1; OC: osteocalcin.
95% trimmed mean value of BTMs (ng/mL).
Interval change was compared to the baseline.
There were no significant interval changes in both groups.

Supplemental Table 4. The percentages of the different types of anti-osteoporotic medications.

	Group 1 (n = 73)	Group 2 (n = 294)
bisphosphonate	61 (83.6%)	231 (78.6%)
SERM	31 (42.5%)	112 (38.1%)
PTH	1 (1.4%)	9 (3.1%)
Calcium + vit D	62 (84.9%)	254 (86.4%)

Group 1: patients who received ESI, Group 2: patients who received no ESI.
Values represent the number of patients who took respective type of anti-osteoporotic medication during follow-up period.
% represents the number of patients out of the total patients in each group.
SERM: Selective Estrogen Receptor Modulators
PTH: parathyroid hormone

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