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Review Article

The Effect of Epidural Steroid Injections on Bone Mineral Density and Vertebral Fracture Risk: A Systematic Review and Critical Appraisal of Current Literature

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Abstract

Objective. The aim of this paper is to review the available literature investigating the effect of epidural steroid injections (ESIs) on bone mineral density (BMD) and vertebral fracture risk.

Study design. Systematic review of current literature.

Methods. The sources of the data were PubMed, Embase, Cochrane, and Scopus. Papers included in the review were original research articles in peer-reviewed journals.

Results. A total of 7,233 patients (eight studies) with a mean age ranging between 49 and 74 years and an average follow-up between six and 60 months were studied. Steroids that were used included triamcinolone, dexamethasone, and methylprednisolone (MP), with a mean number of injections ranging from one to 14.7 and an average cumulative dose in MP equivalents between 80 and 8,130 mg. Epidural steroids were associated with significantly decreased BMD in four out of six included studies, and with increased risk of vertebral fracture in one out of two included studies. Significant reductions in BMD were associated with a cumulative MP dose of 200 mg over a one-year period and 400 mg over three years, but not in doses of less than 200 mg of MP equivalents for postmenopausal women and at least 3 g for healthy men. The risk of osteopenia and osteoporosis was lower in patients who were receiving anti-osteoporotic medication during the treatment course.

Conclusions. ESIs should be recommended with caution, especially in patients at risk for osteoporotic fractures, such as women of postmenopausal age. Anti-osteoporotic medication might be considered prior to ESI.

Key Words. Steroid; Epidural Space; Spine; Fractures; Osteoporosis; Osteopenia; Bone Density; Injection; Vertebra; Risk

Introduction

Epidural steroid injections (ESIs) involve the administration of corticosteroid into the spinal epidural space via the insertion of a needle between the ligamentum flavum and the dura. The first documented epidural injection was performed by Sicard, in 1901, who injected cocaine to treat a patient with low back pain and lumbar radiculopathy [1]. Corticosteroids were first injected in the epidural space for the treatment of lumbar

radicular pain in 1952 [2]. ESIs are considered a reasonable approach for patients with lumbosacral radiculopathy refractory to analgesic medications over six weeks who opt for nonsurgical management [3].

It is well established that glucocorticoids (GCs) have multiple systemic effects by maintaining and regulating a multitude of immune and circulatory functions. Chronic exogenous administration of GCs suppresses the hypothalamic-pituitary axis, increases hepatic glucose production, leading to secondary diabetes mellitus, and raises blood pressure, possibly by increasing peripheral vascular sensitivity to adrenergic agonists [4,5]. In addition, GCs affect bone mineral density via multiple mechanisms [6,7] including stimulation of osteoclast-mediated bone resorption while reducing osteoblast-mediated bone formation. Reduced estrogen and testosterone activity increases bone resorption. GCs also suppress the synthesis of collagen, alkaline phosphatase, and osteocalcin and inhibit bone matrix mineralization [8]. Moreover, in patients who are chronically exposed to steroids, calcium absorption in the digestive tract is significantly decreased [9].

Recent studies have yielded conflicting results regarding the effect of ESIs on bone mineral density (BMD) and whether frequent injections and increased exposure over time result in an increased risk of osteoporosis and vertebral fracture [10–17]. Therefore, we carried out a systematic review of the current literature to examine the effect of ESIs on BMD and vertebral fracture with the aim of updating current knowledge and providing directions for future research in this field.

Methods

Data Source and Search Strategy

This systematic review was conducted according to the guidelines in the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) [7]. A Master's-level librarian queried Ovid PubMed/MEDLINE, Ovid Embase, Scopus, and Ovid Cochrane Registry of Clinical Trials for our electronic searches (date of last search: July 7, 2017). Data were collected from published studies from all available years. The key words that were used to identify articles of interest included the Boolean search string: "epidural steroid injections" AND "osteoporosis" or "osteopenia" or "vertebral fracture" or "bone mineral density" (Appendix).

Eligibility Criteria

Studies were eligible for this systematic review if they reported on the effect of ESIs on BMD as well as on the risk of vertebral fracture, osteopenia, or osteoporosis and had a comparison, either a control group or baseline measurement. Articles needed to be original studies available in English and published in peer-reviewed journals.

Exclusion criteria included: 1) fewer than 10 patients in a study arm, 2) animal studies, 3) case reports, case series and letters to the editors, 4) abstracts or poster presentations in conferences, where access to full data report was not available, and 5) editorials, reviews, and commentary articles. Two independent reviewers were responsible for examining the results of the electronic search (PK, two years of experience, and MAA, two years of experience). In cases of discordance, the opinion of the senior author (MB) was counted toward the final decision. In cases of concern for overlapping cohorts, authors of the studies were contacted directly for clarification, and the study with the most complete reporting was selected.

Data Extraction and Processing

The extracted data included the following variables: methodology data, study design, country, number of patients, comorbidities, steroid injection–related data (number of injections, type of steroid, cumulative steroid dose), baseline BMD, and change in BMD, osteopenia, and osteoporosis. We converted dosages to methylprednisolone (MP) equivalents in an attempt to facilitate comparison between studies. We defined low BMD as the presence of either osteopenia or osteoporosis, which was ascertained in the studies based on the Z and T scores. Reference lists were created, compared, and reviewed for relevance and assessed using the prespecified inclusion and exclusion criteria. When mean and standard deviation of values were not available, estimations were made if possible using the reported graphs and published methodologies [18,19]. Data were extracted by the first reviewer (PK), and accuracy of data entry was confirmed by the second reviewer (MAA).

Risk of Bias Assessment

The risk of bias for each study was assessed independently by two reviewers (PK and MAA) using the criteria described by the Newcastle-Ottawa Quality Assessment Scale [20]. Each study was assessed based on study design, limitations, and outcomes.

Results

Literature Search Results

Our search strategy yielded a total of 389 studies. After removal of duplicate publications and applying inclusion/exclusion criteria to titles and abstracts, 11 full-text articles were assessed. Eight articles were eventually included in the current review for qualitative and quantitative analysis. The details of our electronic search and exclusion process are summarized in the PRISMA Flowchart (Figure 1).

All of the included studies were single-institutional, observational cohort studies (two cross-sectional, four retrospective cohorts, and two prospective) (Table 1). Four

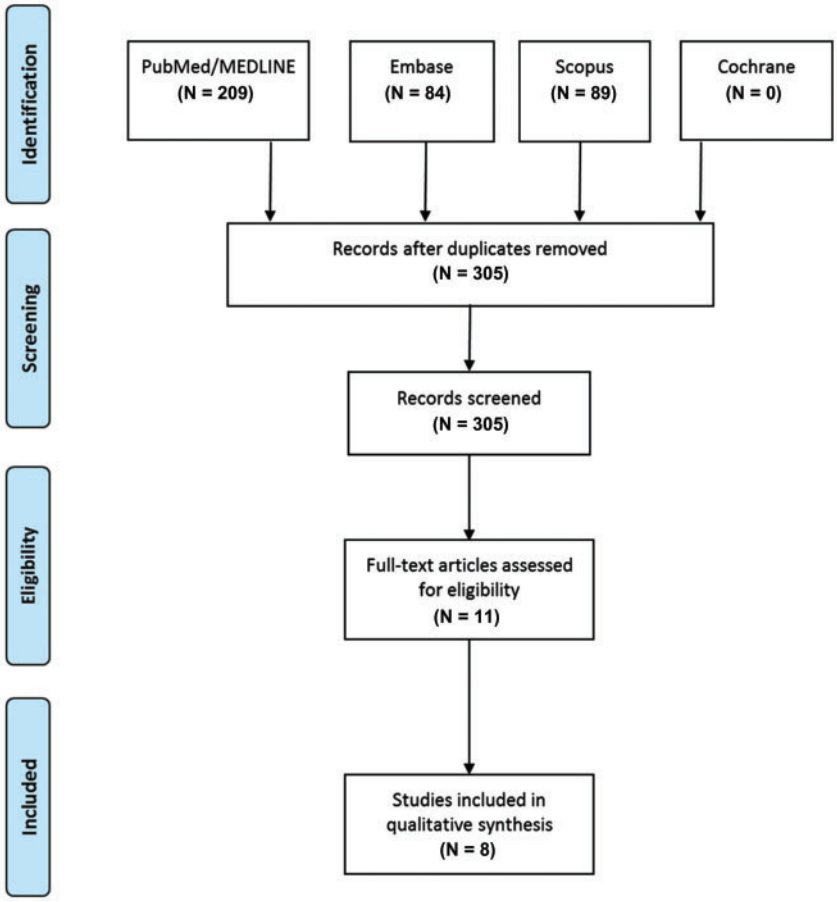

Figure 1 PRISMA flowchart.

of the studies were conducted in South Korea, three in the United States, and one in the Netherlands. All eight studies had a case group of patients who received ESI per the eligibility criteria. Six out of the eight studies also had a control group, which involved a) patients who did not receive ESI (four studies), b) patients who also received anti-osteoporotic medication during the same study period (one study), or c) patients who received ESI but had no vertebral fractures (one study). In the remaining two studies, the effect of ESI treatment was assessed against baseline measurements. Risk of bias was rated as low in three studies and moderate in five studies (Supplementary Data).

Study Characteristics

Included studies reported data from a total of 7,233 patients with a mean age ranging between 49 and 74 years (Supplementary Data). Five of the studies focused on postmenopausal women only, whereas three studies examined both males and females of all ages. Mean follow-up duration ranged between six and 60 months. Only two studies reported on smoking and alcohol consumption rates, and only four studies reported on body mass index (BMI) distribution within the studied population. Six studies evaluated BMD, and two studies examined vertebral fracture risk as the primary outcome of interest. In terms of the inclusion and exclusion criteria of the studied population, four studies excluded patients who received "medications known to affect bone metabolism" without specifying the medications, and four studies excluded patients with a history of vertebral fracture (two due to osteoporosis, one following kyphoplasty/vertebroplasty, and one due to trauma).

Corticosteroid Injections

Differences were observed among the studies regarding the corticosteroid used in the injection (Table 2). Four of the studies used triamcinolone, one used dexamethasone, one used MP, one used MP or betamethasone, and one study did not specify the corticosteroid used. The dosage in a single injection was reported in only five studies and ranged from 10 to 120 mg. The average number of ESIs across all studies ranged from one to 14.7, with a mean cumulative injection dose in MP equivalents ranging between 80 and 8,130 mg.

Table 1 Summary of design and features of included studies

Author, y	Study Design	Country	Target Population	Comparison Group	Outcome of Interest	Age, Mean (SD), y		Mean F/U Duration, mo	No. of Patients	
						Case Group	Comparison Group		Case Group	Comparison Group
Kim et al. [13], 2016	Retrospective, single-institution	South Korea	Postmenopausal women	ESI patients who also received AOM	BMD	67.38 (6.25)	69.51 (5.98)	19.14–19.75	52	74
Kim [14], 2014	Retrospective, single-institution	South Korea	Postmenopausal women	Patients who did not receive ESI	BMD	69 (8.5)	70 (6.8)	34.4	31	40
Mandel et al. [16], 2013	Retrospective, single-institution	USA	Males and females	Patients who did not receive ESI	Vertebral body fracture	66.41 (10.53)	66.49 (10.61)	60	3,415	3,000
Kang et al. [12], 2012	Retrospective, single-institution	South Korea	Postmenopausal women	Patients who did not receive ESI	BMD	63 (1.2)	61 (1.8)	14–15	42	48
Yi et al. [17], 2012	Retrospective, single-institution	South Korea	Postmenopausal women	Patients without vertebral fracture who received ESI	Vertebral body fracture	74 (5.2)	65 (7.3)	N/A	134	218
Al-shoha et al. [10], 2012	Prospective, single-institution	USA	Postmenopausal women	Baseline measurement	BMD	66.19 (11.07)	N/A	6	28	N/A
Dubois et al. [11], 2003	Retrospective, single-institution	Netherlands	Males and females	Baseline measurement	BMD	61 (9)	N/A	N/A	28	N/A
Manchikanti et al. [15], 2000	Prospective, single-institution	USA	Males and females	Patients who did not receive ESI	BMD	49 (1.47)	51 (3.13)	12	100	23

AOM = anti-osteoporotic medication; BMD = bone mineral density; ESI = epidural steroid injections; F/U = follow-up; N/A = not applicable due to cross-sectional study design.

Table 2 Summary of information regarding steroid injections

Author, y	Steroid Used	Approach	No. of ESIs, Mean (SD)		Cumulative Steroid Dose, Mean (SD), mg		MP Equivalents, Mean (SD), mg		On Hormone Therapy, No. (%)	
			Case Group	Comparison Group	Case Group	Comparison Group	Case Group	Comparison Group	Case Group	Comparison Group
Kim et al. [13], 2016	Dexamethasone	–	3.63 (1.91)	3.62 (1.71)	8.94 (4.78)	9.73 (6.35)	44.7 (23.9)	48.7 (31.8)	0 (0)	4 (5.4)
Kim and Hwang [14], 2014	Triamcinolone	–	14.7 (3.1)	0	394 (81)	0	394 (81)	0	Excluded*	Excluded*
Mandel et al. [16], 2013	–	–	–	0	–	–	–	0	–	–
Kang et al. [12], 2012	Triamcinolone	–	5.6 (0.6)	0	212 (32)	0	212 (32)	0	Excluded*	Excluded*
Yi et al. [17], 2012	Triamcinolone	–	4.5 (4.2)	4.0 (3.4)	178 (169)	158 (124)	178 (169)	158 (124)	Excluded*	Excluded*
Al-shoha et al. [10], 2012	Triamcinolone	Interlaminar	1 (0)	N/A	80 (0)	N/A	80 (0)	N/A	9 (32.1)	NA
Dubois et al. [11], 2003	Methylprednisolone	–	–	N/A	8,130 (3,680)	N/A	8,130 (3,680)	N/A	Excluded*	Excluded*
Manchikanti et al. [15], 2000	Methylprednisolone Betamethasone	Transforaminal Medial branchIntra-articular	–	0	146.4 (9.06)	0	–	0	21 (21)	8 (35)

- = not reported; ESI = epidural steroid injections; MP = methylprednisolone; N/A = not applicable due to study design.
*Patients on "medications known to affect bone metabolism" were excluded from the study.

Baseline BMD and Change in BMD

Four studies measured BMD in the lumbar spine, and five studies measured BMD in the femoral neck (Table 3). Bone density ranged between 0.77 and 1.082 g/cm^2 in the lumbar spine and between 0.49 and 0.79 g/cm^2 in the femoral neck. Change in BMD at last follow-up compared with baseline was reported for the lumbar spine in two studies and for the femoral neck in four studies. A mean change between 0.06% and 1.25% was noted in the lumbar spine; in the femoral neck, the mean change was –2.87% to 0.45%, whereas the absolute change was –0.023 to –0.018 g/cm^2.

Osteopenia and Osteoporosis

Sufficient data were available to evaluate the prevalence of osteopenia and osteoporosis in a total of five studies (Table 4). Six studies defined osteopenia and osteoporosis based on the World Health Organization–2 (2004) criteria (use of T-scores) [21], whereas one study defined them based on the International Society of Clinical Densitometry (ISCD) criteria (use of Z-scores instead of T-scores) [22]. Low BMD, as described in the methods, was present in 52.5% to 96.2% (lumbar spine) and 29% to 93.5% (femoral neck) of patients that received ESI.

Summary of Findings

Several studies in this review considered the effects of ESI on BMD in postmenopausal women. Cumulative doses of triamcinolone-ESI exceeding 200 mg over a 12-month period or 400 mg over a three-year period may reduce BMD in postmenopausal women with low back pain [12,14]. In a propensity score–matched case-control study of more than 7,000 patients, Mandel and colleagues demonstrated that each additional injection increases the relative risk of fracture by 1.21 (95% confidence interval = 1.08–1.30) after adjusting for covariates [16]. In addition, a single triamcinolone ESI injection of 80 mg was observed to correlate with a reduction in hip BMD by an average of 1.8% and an elevation in bone turnover markers in postmenopausal women six months following injection [10]. In postmenopausal women who do not take antiosteoporotic medications, ESIs were found to correlate with significant BMD changes in the femoral neck [13].

Other studies have suggested that the impact of ESIs on men and postmenopausal women may not be as detrimental; older age and lower baseline BMD, rather than ESIs per se, are associated with increased risk for osteoporotic fracture in postmenopausal women with LBP treated with ESI [11,15,17].

Discussion

The North American Spine Society and the Agency of Healthcare Research of the Department of Health and Human Services endorse the utilization of ESIs as an integral part of the nonoperative management of lower extremity radicular pain secondary to lumbar disc herniation, yet the efficacy of ESIs remains to be established [23]. In 2014, the US Food and Drug Administration announced a safety communication related to epidural injections of steroids, highlighting the risk for serious albeit rare adverse events including stroke, paralysis, loss of vision, and death [24,25]. The risk of osteopenia-osteoporosis and vertebral fracture have not been thoroughly examined, and available evidence is based only on single-institution observational studies with considerable heterogeneity and limited generalizability. It is worth mentioning that a significant portion of the patients in the current review underwent ESI for a primary diagnosis of low back pain, not specifying whether this included axial pain, radicular pain, or both.

There is a paucity of available literature on this topic up to this point [26]. The first study describing the effect of ESI on bone density was published in 2000 by Manchikanti and colleagues, who found that the BMD remained unchanged after one year of ESIs of 146 mg of methylprednisolone [15]. Later articles corroborated these findings, reporting that epidural steroids are safe in healthy men of all ages [11,17]. However, more recent studies have increasingly shown that ESIs adversely affect bone health and are not as benign as once thought [10,12–14,17]. The article by Mandel and colleagues [16] is the largest study to date evaluating the impact of ESI on bone fragility and vertebral fracture risk; the authors showed that each additional ESI increases the risk of fracture by 21%. The study design was reinforced by the application of propensity score matching (PSM) in order to account for confounding variables. However, certain caveats exist when PSM is performed in observational studies, such as introducing more bias to the sample and failing to use appropriate statistical methods that account for the matched nature of data [27,28]. In that study, the authors did not provide the propensity score distribution across the two groups before and after PSM, and therefore their balance and potential associated bias are unknown, which may pose limitations to the study results. Moreover, there was no information with regards to the ESI dosage that the patients had received.

In the rest of the included studies, the authors applied the appropriate statistical methods to investigate the effect of ESIs on BMD within or between study groups. The limited sample size, however, precluded performance of multivariable analysis in order to control for key confounding variables, such as BMI, alcohol consumption, and smoking status. Notably, Yi and colleagues mentioned that no correlation was found among BMD, total number of ESIs, mean duration of GC administration, and mean total dose of glucocorticoid after adjusting for age, height, and weight. Residual confounding is mitigated by study selection criteria, as patients with a history of previous osteoporotic fracture, those taking medications known to affect bone metabolism, and those with endocrinopathies were

Table 3 Summary of baseline (before ESI) bone mineral density scan data in included studies

	Bone Mineral Density, Mean (SD), g/cm^2				Change in BMD, %			
	Lumbar Spine		Femoral Neck		Lumbar Spine		Femoral Neck	
Author, y	Case Group	Comparison Group	Case Group	Comparison Group	Case Group	Comparison Group	Case Group	Comparison Group
Kim et al. [13], 2016	0.92 (0.14)	0.88 (0.17)	0.74 (0.10)	0.71 (0.09)	0.69 ± 6.94	1.25 ± 6.01	−1.48 ± 3.84	0.45 ± 4.05
Kang et al. [12], 2012	0.78 (0.26)	0.77 (0.22)	0.75 (0.21)	0.75 (0.18)	0.06 ± 0.12	1.04 ± 0.19	−2.87 ± 0.17	−1.32 ± 0.18
Yi et al. [17], 2012	0.82 (0.32)	0.92 (0.23)	0.64 (0.27)	0.75 (0.26)	–	–	–	–
Al-shoha et al. [10], 2012	1.082 (0.16)	N/A	0.79 (0.09)	N/A	–	N/A	−0.018	N/A
Dubois et al. [11], 2003	–	N/A	–	N/A	–	N/A	–	N/A
Manchikanti et al. [15], 2000	–	–	0.49 (0.11)	0.49 (0.17)	–	–	−0.023	0.0033

- = not reported; N/A = not applicable due to study design.

Table 4 Percentage of patients with postinjection osteoporosis and osteopenia in the included studies

	Osteopenia, No. (%)				Osteoporosis, No. (%)			
	Lumbar Spine		Femoral Neck		Lumbar Spine		Femoral Neck	
Author,	Case Group	Comparison Group	Case Group	Comparison Group	Case Group	Comparison Group	Case Group	Comparison Group
Kim et al. [13], 2016	29 (55.7)	40 (54.0)	21 (40.3)	42 (56.8)	8 (15.4)	25 (33.7)	17 (32.7)	23 (31.1)
Kim and Hwang [14], 2014	14 (45.1)	13 (32.5)	20 (64.5)	19 (47.5)	11 (35.4)	8 (0.2)	9 (29.0)	4 (0.1)
Kang et al. [12], 2012	15 (35.7)	18 (37.5)	23 (54.8)	23 (47.9)	21 (0.5)	23 (47.9)	9 (21.4)	11 (22.9)
Yi et al. [17], 2012	38 (28.3)	92 (42.2)	51 (38.0)	133 (61.0)	91 (67.9)	82 (37.6)	64 (47.8)	17 (7.80)
Al-shoha et al. [10], 2012	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Dubois et al. [11], 2003	12 (43)	N/A	15 (31.3)	N/A	5 (17.8)	N/A	6 (21.4)	N/A
Manchikanti et al. [15], 2000	–	–	19 (19)	7 (30.4)	–	–	11 (11)	2 (8.70)

- = not reported; N/A = not applicable due to study design.

excluded. Follow-up rates were relatively variable, ranging between six and 34.4 months. As bone loss is greatest during the first six months and the majority of fractures occur during the first two years of oral steroid treatment initiation, respectively, the risk of missing cases is probably small [29,30].

Future Directions

To date, the best evidence for efficacy is based on trials that examined the role of ESIs for patients with radiculopathy secondary to intervertebral disc herniation, which demonstrate short-term, but not long-term benefits [31–33]. However, in the elderly population, who are more likely to suffer from neurogenic claudication due to spinal canal stenosis [34], the appropriateness and effectiveness of ESIs are still debatable. Several parameters with regards to ESI administration, such as number and interval of injections, as well as optimal dosage, remain to be firmly established. Existing evidence shows that for postmenopausal women with chronic low back pain, one injection of 80 mg of MP equivalents can decrease BMD in the femoral neck by 1.8%. In addition, more than 200 mg of MP equivalents within one year and 400 mg within three years seem to negatively affect BMD. Consequently, in patients with poorer bone quality, more than three to four injections per year (assuming an average dose of 40 mg of MP equivalents with each ESI) may pose significant risk [12,14]. On the other hand, in healthy men, the safe cumulative dose limit seems to be increased to 3 g. More selective and appropriate targeting of spinal structures using contemporary imaging methods may help reduce the total amount of steroids injected to the lumbar spine.

The prevalence of vertebral fractures in the elderly population is estimated to be at least 20% [35]. Vertebral fractures are associated with worse quality of life and increased mortality in both men and women [35]. Accordingly, the impact of ESI on BMD and skeletal health must be carefully considered, and patients should be made aware of the potential increase in vertebral fracture risk with each additional injection. Therefore, physicians should disclose all the known effects of steroids to their patients. Moreover, several papers have shown that corticosteroids have systemic effects regardless of administration route [36]; inhaled glucocorticoids have been shown to lead to a dose-related hip bone loss in premenopausal women [37]. We have reviewed how epidural steroids influence bone density in both the axial and appendicular skeleton, most notably the femoral neck, and future research investigating the effect of ESI on hip fractures may be helpful.

The results of the present review suggest that ESIs should be approached with prudence. Many patients receiving ESIs are of older age and seek frequent injections in order to maintain an active lifestyle and/or to avoid undergoing surgery. However, these patients are more likely to have compromised skeletal quality, putting them at greater risk for vertebral fracture and compromised BMD from exogenous glucocorticoid treatment [10,38]. Clinicians who offer ESIs to their patients for symptomatic relief of low back pain or lumbar radiculopathy may also consider prescribing medications that promote bone density, including bisphosphonates, calcium, vitamin D supplementation, teriparatide, or hormone therapy [13]. In the study by Kim and colleagues, bisphosphonates were the most protective of BMD [13]. This observation is further corroborated by multicenter, randomized controlled trials and registry-based cohort studies that showed that bisphosphonates are very effective in treating GC-induced osteoporosis as well as preventing hip and vertebral fractures [30,39–41].

In most of the studies, patients with comorbidities or taking medications known to affect bone metabolism were excluded. As such, clinicians should thoroughly evaluate the patient's medical history during consultation and preprocedural planning and take the additive effect of steroids prescribed for other health conditions (e.g., asthma, rheumatologic conditions, and inflammatory bowel disease) into consideration, as the threshold in these patients for fracture risk may be lower. In addition, elderly patients are more likely to suffer from pain in other large joints as well, including shoulder and knee, which are also treated with corticosteroid injections. Future studies may consider prospectively investigating the effect of ESIs in postmenopausal women. The studies included in the current review suggest that adverse outcomes in terms of vertebral fracture risk or compromised BMD may differ considerably between men and women, although this has never been directly studied. Epidemiologic studies analyzing whether the adverse effects of ESIs vary across gender or genetic background may be very fruitful. The influence of different site injections, that is, transforaminal vs interlaminar epidural injections vs intra-articular injections (zygapophysial, sacroiliac, and peripheral joints), should be evaluated as well.

Study Strengths and Limitations

To the best of our knowledge, this is the first study to perform a systematic review of all available studies reporting on the effect of ESIs on BMD and vertebral fracture risk. Based on strict adherence to the PRISMA guidelines, we used an exhaustive literature search strategy to identify all relevant articles to this field. Nevertheless, our study has several limitations. First of all, current evidence is comprised only of observational studies, with the potential of higher risk of bias. Moreover, there was heterogeneity among the studies regarding the patient inclusion criteria and reporting of the outcomes of interest, which may decrease the generalizability of the conclusions. Lastly, in most of the studies, control of confounding factors was limited during the statistical analysis. Ultimately, the results of this study need confirmation by a large, prospective

randomized controlled trial with a significant follow-up period.

Conclusions

According to the current literature, although controversial, ESIs seem to decrease BMD, both locally (lumbar spine) and systemically (femoral neck) in doses as low as 80 mg of MP equivalents and to increase the risk of vertebral fracture. Future studies will hopefully provide further insight into this subject and delineate the safety profile associated with epidural steroids. More importantly, higher-quality evidence will determine whether specific recommendations are needed to be established by medical societies to ensure that benefits outweigh potential risks, particularly in patients at risk for osteoporotic fractures, such as women of postmenopausal age.

Supplementary Data

Supplementary Data may be found online at http://painmedicine.oxfordjournals.org.

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Appendix 1 Search strategy

Table A1 Ovid MEDLINE Epub Ahead of Print, In-Process, & Other Nonindexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE <1946 to Present>

No.	Searches	Results	Type
1	exp glucocorticoids/	182,048	Advanced
2	(steroid* or glucocorticoid* or corticosteroid* or bethamethasone* or dexamethasone*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	485,848	Advanced
3	1 or 2	545,734	Advanced
4	3 and (epidural* or spinal*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	10,458	Advanced
5	injections, epidural/	2,611	Advanced
6	3 and 5	1,061	Advanced
7	(4 and (inject* or administ*).mp.) or 6 [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	4,842	Advanced
8	exp fractures, bone/or fractur*.mp. or osteopor*.mp. or osteopen*.mp. or osteopaen*.mp. or "bone loss".mp.	345,770	Advanced
9	bone mineral density.mp. or bone density/or bmd.mp.	60,631	Advanced
10	7 and (8 or 9)	209	Advanced

Table A2 CENTRAL – 52, same strategy as above; Embase <1988 to 2017 Week 27>

No.	Searches	Results	Type
1	exp triamcinolone/or exp methylprednisolone/or exp steroid/or exp corticosteroid/or exp triamcinolone acetonide/	1,077,919	Advanced
2	exp betamethasone/ei [Epidural Drug Administration]	123	Advanced
3	exp dexamethasone/ei [Epidural Drug Administration]	123	Advanced
4	exp triamcinolone/ei or exp methylprednisolone/ei or exp steroid/ei or exp corticosteroid/ei or exp triamcinolone acetonide/ei	2,102	Advanced
5	(1 or exp betamethasone/or exp dexamethasone/) and epidural drug administration/	1,369	Advanced
6	2 or 3 or 4 or 5	3,383	Advanced
7	exp bone demineralization/or exp osteomalacia/or exp osteopenia/or exp osteoporosis/or exp spine fracture/	130,896	Advanced
8	exp osteolysis/	56,251	Advanced
9	7 or 8	171,943	Advanced
10	6 and 9	109	Advanced
11	10 not case report/	84	Advance

Scopus: (TITLE-ABS-KEY ((steroid* OR glucocorticoid* OR corticosteroid* OR bethamethasone OR betamethasone OR dexamethasone) W/3 (epidural* OR spinal*)) AND TITLE-ABS-KEY ((osteoporo* OR osteopaen* OR osteopen* OR osteoly* OR "bone density" OR "bone loss" OR bmd OR fracture*))) AND (LIMIT-TO (DOCTYPE, "ar") OR LIMIT-TO (DOCTYPE, "re")) 89