Prospective Study

Observational Study to Evaluate the Effect of Epidural Steroid Injection on Bone Mineral Density and Bone Turnover Markers

Anshul Jain, MD, Paras Gupta, MS, Rachna Chaurasia, MD, Mayank Singh, MD, and Shivali Pandey, MD

From: MLB Medical College Campus Jhansi India

Address Correspondence:
Paras Gupta, MS
Associate Professor
Department of Orthopaedics
MLB Medical College
Campus Jhansi India
E-mail:
parasorth129@gmail.com

Disclaimer: There was no external funding in the preparation of this manuscript.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 01-22-2020
Revised manuscript received: 03-01-2020
Accepted for publication: 03-30-2020

Free full manuscript: www.painphysicianjournal.com

Background: Epidural steroid injection (ESI) is widely used to manage low back pain. ESIs are commonly performed to treat pain accompanying intervertebral disc prolapse, spinal stenosis, facet joint pathologies, and other degenerative spinal pathologies. Corticosteroids for musculoskeletal conditions, regardless of the route of administration, can reduce bone mineral density (BMD) and increase the risk of fracture. With paraspinal administration of steroids, the severity of risk is enhanced as the steroid is being deposited in close proximity to bone. BMD and molecular markers of bone metabolism are the standard methods to assess the effect of any insult on bone strength and bone metabolism. Carboxy terminal crosslinked telopeptides of type 1 collagen (sCTX) and serum Procollagen Type I N-terminal propeptide (P1NP) are the reference markers of bone resorption and formation, respectively.

Objective: We conducted this study to determine the effect of ESI on BMD and bone turnover markers.

Study Design: This was a prospective observational cohort study, involving a cohort of 264 patients between the ages of 40 to 60 years who were advised to undergo ESI at L3-4 or L4-5 by their pain physician.

Setting: Research was conducted at a tertiary care teaching hospital pain clinic in collaboration with the department of orthopaedics and radiodiagnosis.

Methods: Serum CTX-1, P1NP, and pre-ESI BMD of the spine, femur neck, and dual femur were evaluated at baseline; these same parameters were serially evaluated post ESI on follow-ups at 1, 3, and 6 months. Additional follow-up at 10 days post ESI was called for evaluation of bone turnover markers (BTMs). A paired t test was used to analyze changes in BMD and BTMs vs baseline within the group. Cumulative incidence and relative risk of moderate to markedly low BMD were calculated using standard formulas. Any fractures sustained during follow-ups were also evaluated thoroughly and quantified separately. A P value less than .05 was considered statistically significant.

Results: The proportion of pre-ESI moderately to markedly low BMD was 10.22% in the study population. There was a statistically significant increase in serum CTX 10 days post ESI which persisted at the one-month and 3-month follow-ups. There was no significant change in serum P1NP level post ESI after 7 days and at the one-month follow-up. The mean value of serum P1NP was, however, significantly higher at the 3-month follow-up. Statistical comparison of the mean BMD value at the spine and femur neck revealed statistically significant decline 3 months post ESI. There was no significant impact of ESI on the total femur BMD. The cumulative incidence of moderately low to markedly low BMD over a period of 6 months in the study population was 45 out of 223, i.e., 20.17%.

Limitations: The study's primary limitations included its high dropout rate, a larger reference range for BTMs, making them a less specific tool for comparison, and the absence of a control group. ESI has a negative impact on the BMD of the hip and spine. Reduced BMD should be considered as a potential side effect of ESI.

Key words: Bone mineral density, bone turnover markers, epidural steroid injection, low back ache, osteoporosis

Pain Physician 2020: 23:E517-E524

Epidural steroid injection (ESI) is widely being used to manage low back pain. The first documentation of epidural injection dates back to 1901 and was performed by Sicard (1), a radiologist who injected cocaine through the caudal route to treat a patient with low back pain and lumbar radiculopathy. Now in the 21st century, ESIs are commonly being performed for pain accompanying intervertebral disc prolapse, spinal stenosis, facet joint pathologies, and other degenerative spinal pathologies (2-4).

Corticosteroids, regardless of route of administration, are considered to have widespread effects on almost all body systems (5,6). Exogenous glucocorticoids markedly affect the musculoskeletal system, and by reducing bone mineral density (BMD) they increase the risk of fracture (7,8). Regarding paraspinal administration of steroids, the severity of risk is enhanced as the steroid is being deposited in close proximity to bone.

Manchikanti et al (9) conducted the first prospective study to evaluate the relationship between ESI and BMD and they concluded that low-dose administration of neuraxial steroids is safe in patients suffering from chronic pain. Later studies also measured BMD after epidural injection of corticosteroids, and the results were variable, with some recent reports showing that ESI negatively influences BMD (10-12). Molecular markers of bone metabolism are newer tools that detect the dynamics of bone remodelling with respect to bone formation and resorption (13,14). Carboxy terminal crosslinked telopeptides of type 1 collagen (sCTX) and serum Procollagen Type I N-terminal propeptides (P1NP) have been proposed as reference markers of bone resorption and formation, respectively, for the assessment of fracture risk by the International Federation of Clinical Chemistry and Laboratory Medicine (15). By combining BMD and molecular markers, one can study the bone metabolism in a broader way.

In current pain management services, many patients are being prescribed ESI, and if there is risk, that risk should be weighed. Keeping this in view, there is an urgent need for a comprehensive prospective study with efficient control for confounding variables. The current study evaluated baseline serum CTX-1 and P1NP and pre ESI BMD of the spine, femur neck, and dual femur; the same parameters were serially evaluated post-ESI follow-ups so as to determine the effect of ESI on these parameters.

Methods

Study Design and Patients

The current prospective observational cohort study was performed after approval from the institutional ethical committee. The current study included all patients between the ages of 40 to 60 years and weighing between 50 to 80 kg who were advised by the pain physician to undergo ESI at L3-4 or L4-5. Sample size was calculated using Solven's formula keeping the margin of error at 0.02. The exact sample size came out to be 88. Taking into account the exclusions and attrition during follow-up, the sample size was quadrupled to 264. Patients taking antiosteoporotic medication pre-ESI were not included in the current study. Other exclusion criteria included diabetes mellitus, uncontrolled hypertension, hyperthyroidism, and body mass index (BMI) > 40 kg/m^2. Postenrollment exclusion criteria included preexisting osteoporosis, consumption of any medication that accelerates osteoporosis, immobility, patients who missed timely follow-up, and patients who required repeat ESI.

Intervention and Evaluation

All patients were given a number between one and 300 as their study enrollment number and a study enrollment card was handed to them. Post enrollment the patient underwent baseline evaluation of BMD a day before ESI. BMD was measured using a lunar DEXA scanner (Lunar DPX NT, Wipro GE, Bangalore, India) from the lumbar spine (L2-L4), femoral neck, and total femur as absolute value (g/cm^3). LUNAR encore software was used for estimation of T-Scores and categorization. The absolute data was entered into the computer with the patient's study enrollment number; if the BMD came out to be markedly or moderately low, antiosteoporotic medication was advised and the patient was excluded from the study. As per WHO classification, a T-score < -2.5 standard deviations (SD) at one or more sites was used to categorize the patient as having markedly low BMD or osteoporosis; patients with a T-score between -1.0 to -2.5 SD were categorized as having moderately low BMD.

Per institutional protocol all patients underwent overnight fasting prior to ESI. In the morning, samples were drawn according to the standard aseptic venipuncture technique for bone turnover markers P1NP and serum CTX. The samples were processed within 2 hours of collection. The kits used for serum CTX and PINP were the Elabscience® Human β-CTx (Beta Crosslaps) ELISA Kit and the Human P1NP (Procollagen 1 N-Terminal Propeptide) ELISA Kit, respectively.

ESI was performed as per the pain physician under proper aseptic precautions, and the drug used for ESI was methylprednisolone acetate in the dose of 2 mg/kg diluted to 5 mL. The dose was standardized to the nearest multiple of 10 towards the lower side. Following ESI, patients were advised on medications (excluding any antiosteoporotic medication) by the pain physician. All patients were called for follow-ups post ESI after intervals of 10 days, one month, 3 months, and 6 months. During all follow-ups, patients were asked to report with empty stomach in the morning. On the tenth-day follow-up only, samples for bone turnover markers (BTM) were obtained. In all subsequent follow-ups, both BTM and BMD were estimated. Follow-up BMD was performed by the radiographic technician, who had no information about the baseline BMD, and the absolute value was obtained again using the same machine and same site. The values obtained were entered with the enrollment number of the patient by another data operator. Those patients who did not report for follow-up or reported after 7 days of their scheduled follow-up visit were excluded from the study. In the case of any fracture, the patient was advised to report immediately. Patients with markedly low or moderately low BMD were recorded and were advised to take antiosteoporotic medication, as were osteoporotic patients, and were designated as target-achieved.

Statistical Analysis

Quantitative data are expressed as mean ± 2 standard deviations (SD). Qualitative variables were expressed as proportions. A paired t test was used to analyze changes in BMD and BTMs vs baseline within the group at the 7- to 10-day, one-month, 3-month, and 6-month follow-ups. Cumulative incidences of osteopenia and osteoporosis were calculated. Cumulative incidence of

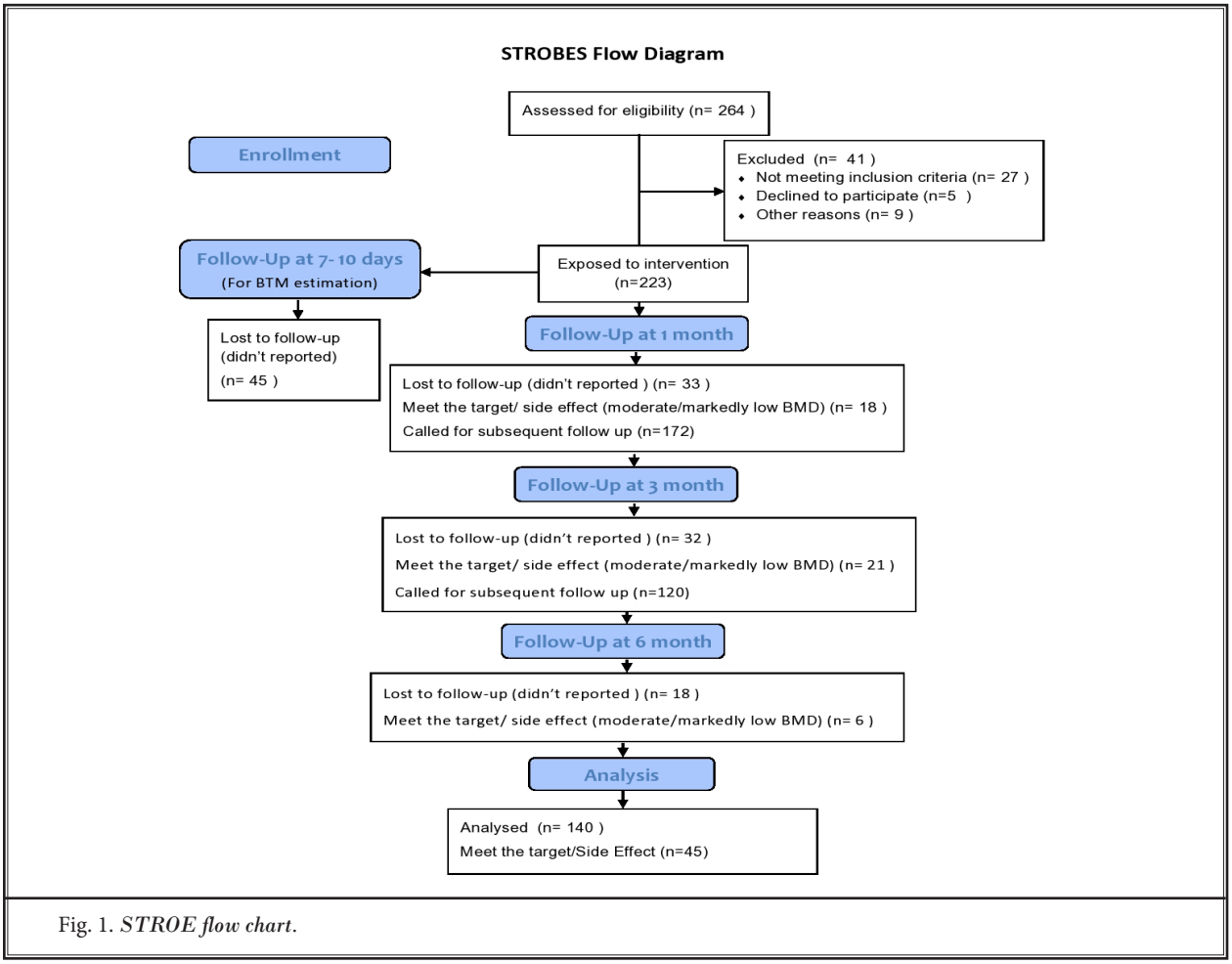

Fig. 1. *STROE flow chart.*

Table 1. *Demographic details.*

Parameter	
Male: Female	151:93
Age (in Years) (Mean ± 2SD)	56.34 ± 6.41
Weight (in Kg) (Mean ± 2SD)	67.18 ± 12.34
Height (in meters) (Mean ± 2SD)	1.12 ± 0.34
Body Mass Index (Kg/m^2) (Mean ± 2SD)	27.23 ± 3.45

moderate to markedly low BMD was calculated using the standard formula. A *P* value less than .05 was considered statistically significant. SPSS Version 22 (IBM Corporation, Armonk, NY) was used for all statistical analyses.

Results

The current study enrolled 264 patients as shown in the strobes flow diagram (Fig. 1). The demographic

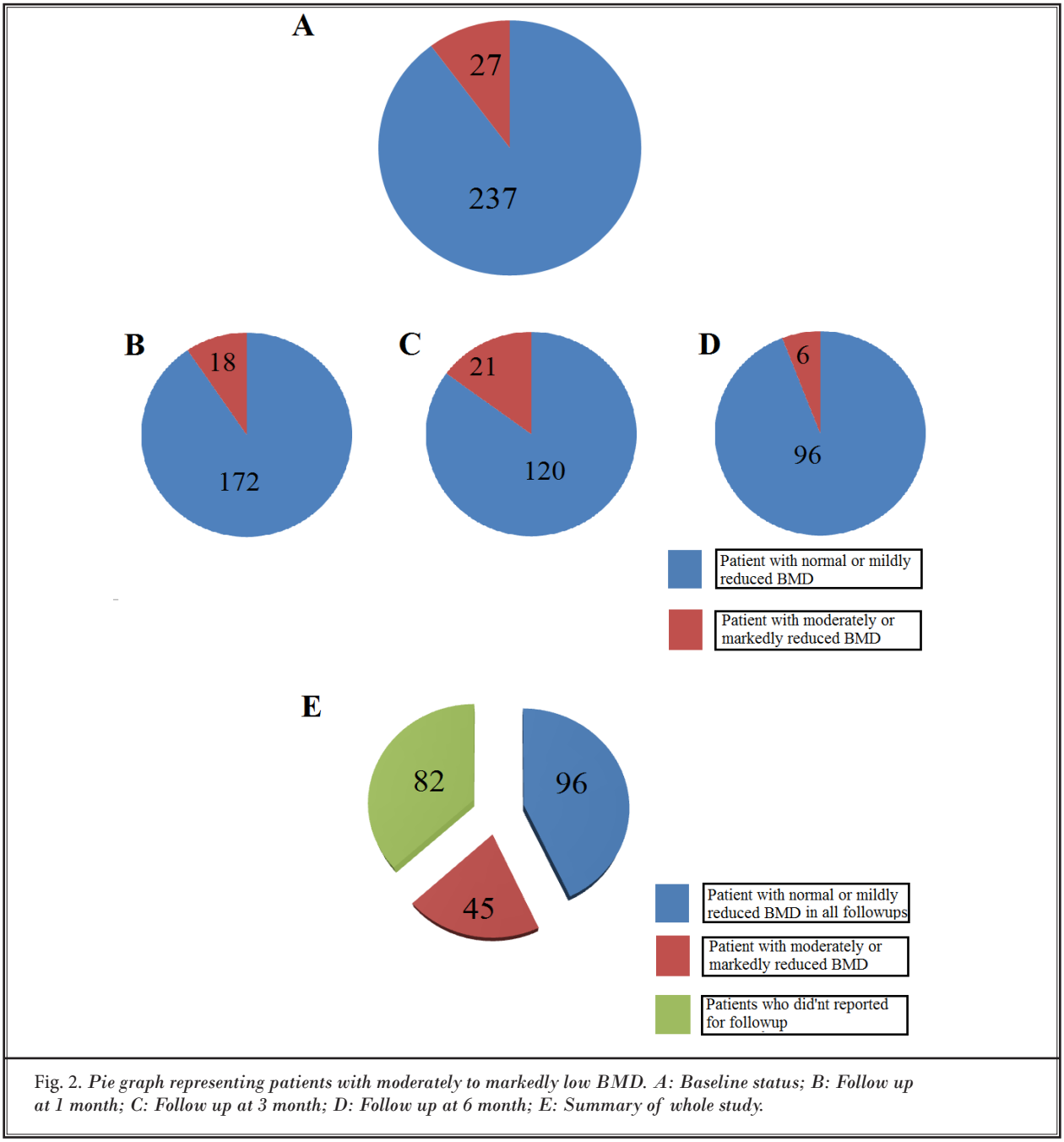

Fig. 2. *Pie graph representing patients with moderately to markedly low BMD. A: Baseline status; B: Follow up at 1 month; C: Follow up at 3 month; D: Follow up at 6 month; E: Summary of whole study.*

variables are shown in Table 1. Out of 264 patients, 27 patients (Fig. 2) were found to have markedly or moderately low BMD at one or more sites of measurement; these patients were advised to take antiosteoporotic medication and were excluded from further study. The proportion of moderately to markedly low BMD was 10.22% in the study population. Five patients declined follow-up and so were excluded. Nine patients were excluded on the basis of preexisting disease and postenrollment exclusion criteria (Fig. 1). Two hundred twenty-three patients (with normal or mildly reduced BMD) were enrolled for further follow-up.

Mean baseline values of BMD and BTM are shown in Table 2. Out of 223 patients, only 178 reported for the 7- to 10-day follow-up meant for estimation of bone turnover markers; 190 patients reported for the one-month routine follow-up, out of which 18 (9.47%) patients had markedly low or moderately low BMD at at least one site of measurement, so they were advised to take antiosteoporotic medication and excluded from further evaluation in the study group. Out of the remaining 172 participants who were called for their 3-month follow-up, 141 reported for follow-up, among which the BMD of 21 (14.89%) patients were found to be markedly to moderately low. As per the study protocol, they were advised to take bisphosphonates and excluded from further assessment. Out of the remaining 120 (141 minus 21) patients called for their 6-month follow-up, 102 patients reported, among which BMD was moderately or markedly low in 6 (5.88%) patients (Fig. 2).

Serum CTX-1 level was evaluated during each follow-up and additionally 7 to 10 days post ESI. The mean baseline value was 332.83 ± 96.21 ng/L, whereas the mean value at 7 to 10 days' follow-up was 428.12 ± 104.76 ng/L. Statistical comparison using the paired t test showed that this difference was significant (Table 3). At the one-month and 3-month intervals, the mean values were high and the difference was found to be statistically significant. The mean value, however, was

Table 2. *Mean baseline parameters.*

Parameter	Value
BMD (Mean ± 2SD)	
- Spine	1.22 ± 0.21 g/cm^3
- Femur Neck (mean of right and left)	1.20 ± 0.18 g/cm^3
- Dual Femur (mean of right and left)	1.29 ± 0.31 g/cm^3
Bone Turnover Markers	
- Serum CTX (mean ± 2SD)	332.83 ± 96.21 ng/L
- Serum P1NP (mean ± 2SD)	44.14 ± 23.26 µg/L

Table 3. *Estimation and comparison of bone turnover markers on follow-ups.*

Bone Turnover Marker	Serum CTX (in ng/L)		Serum P1NP (in µg/L)	
	Mean ± 2SD	'*P*' Value (Vs Baseline)	Mean ± 2SD	'*P*' Value (Vs Baseline)
Baseline	332.83 ± 96.21	NA	44.14 ± 23.26	NA
10th day Post ESI	428.12 ± 104.76	0.031*	54.38 ± 28.17	0.72
1 month Post ESI	451.57 ± 99.17	0.028*	58.61 ± 29.11	0.091
3 month Post ESI	397.75 ± 121.56	0.042*	65.14 ± 27.25	0.038
6 month follow up	371.45 ± 112.82	0.081	55.12 ± 30.54	0.67

Table 4. *Estimation and Comparison of BMD on follow-ups.*

BMD (in g/cm^3)	Lumbar Spine (L2-L4)	*P* Value (Vs Baseline)	Femur Neck (mean of right and left)	*P* Value (Vs Baseline)	Dual Femur (Mean of right and left)	*P* Value (Vs Baseline)
Baseline (Mean ± 2SD)	1.22 ± 0.21	NA	1.20 ± 0.18	NA	1.29 ± 0.31	NA
1 month follow up (Mean ± 2SD)	1.18 ± 0.19	0.09	1.19 ± 0.21	0.72	1.26 ± 0.29	0.84
3 month follow up (Mean ± 2SD)	1.07 ± 0.21	0.04	1.04 ± 0.24	0.02	1.24 ± 0.32	0.08
6 month follow up (Mean ± 2SD)	1.14 ± 0.21	0.07	1.14 ± 0.31	0.08	1.25 ± 0.26	0.12

reduced at the 6-month follow-up such that the difference from baseline became insignificant. Regarding serum P1NP level, there was no significant difference in the mean baseline serum level and levels at 7 to 10 days and at one month. The mean value of serum P1NP was, however, significantly higher at the 3-month follow-up (Table 3).

The cumulative incidence of moderately low to markedly low BMD in at least one site over a period of 6 months post ESI comes out to be 45 out of 223, i.e., 20.17%; this presumes the patients lost to attrition to have normal BMD, which is very rare. The chances of reduced BMD were highest between one to 3 months post ESI. During the study period, 3 patients sustained fractures, among which 2 fractures were suspected to be osteoporotic in nature, having occurred after a trivial fall.

Statistical comparison of mean BMD values at the spine revealed statistically significant decline 3 months post ESI. At the one-month and 6-month follow-ups, the BMD of the spine was low; this difference, however, was not significant. BMD measurements of the femur neck revealed no significant change at the one-month interval; however, the BMD values declined at the 3-month follow-up and this difference was highly statistically significant. The difference at the 6-month follow-up, though reduced, was still found to be significant (Table 4). There was no significant impact of ESI on the BMD of the total femur, and values remained comparable to that of baseline.

Discussion

An inflammatory process was found to be the main cause behind the pain secondary to disc herniation, radiculitis, and lumbar canal stenosis (16). According to published literature, high levels of phospholipase A2 and other precursors of prostaglandins E2 have been found in herniated discs (17,18). Thus, it has been postulated that local injections of steroids (potent anti-inflammatory drugs) reduce inflammation by inhibiting the inflammatory cytokines and thereby reducing pain. This is the pathophysiologic basis behind the clinical use of ESIs in the treatment of lumbar radiculopathies.

Glucocorticoids affect bone metabolism in several ways. Irrespective of the site of administration, glucocorticoids profoundly affect osteoblastic cell differentiation, number, and functions simultaneously; by stimulating osteoclastogenesis, they enhance bone destruction. Further, by increasing the expression of the receptor activator of nuclear factor-kappa B ligand and colony-stimulating factor-1, glucocorticoids reduce the number of osteoblasts (7,19). Increases in the death of mature osteoblasts also contributes to reduced bone formation. Various studies have postulated that the enhanced bone resorption is the prime factor responsible for the initial bone loss after glucocorticoid exposure. Eventually, the inhibition of bone formation leading to decreased bone remodelling takes the upper edge and contributes to osteoporosis, thereby increasing the risk of fractures (19-21).

Currently, ESIs are an integral part of the nonoperative management of pain related to radiculopathy secondary to lumbar disc herniation. ESIs are often prescribed as a first-line treatment option when other remedies fail (2,22-24). The US Food and Drug Administration in 2014 issued caution regarding ESI, highlighting the risk for serious albeit rare adverse events including stroke, paralysis, loss of vision, and death (25). The publication, however, did not comment about the risk of osteoporosis because the studies relating the effects of ESI on BMD have produced inconsistent results. Taking into account the frequency of the procedure, around 500 ESIs per year are performed in our institution alone, so it is essential to estimate the risk of this potential problem.

The current study is the first and most comprehensive study to include a normal population in terms of BMD, and observes the effects of epidural steroids on BMD in the same patient population so as to calculate the cumulative incidence. Further, none of the studies conducted in the past have estimated bone turnover markers one week post ESI; this provided key results in the current study. The experts in various studies have endorsed the serum CTX and serum P1NP as short-term monitoring tools for the assessment of osteoporosis earlier than BMD (14,15). P1NP is derived from post-translational cleavage of type I procollagen molecules by proteases at the N terminal. PINP is preferred over PICP (procollagen type I C-terminal propeptide) as a marker of bone formation in view of its predictable response and the reliability of P1NP assays as evidenced by low intraindividual variability and smaller circadian variation. Unlike PINP, PICP is cleared by the mannose receptor, which in turn can be regulated by growth hormone and thyroid hormones, thus complicating the interpretation in patients with pituitary or thyroid dysfunction (26). Under usual physiological conditions, bone resorption takes place in around 10 days and bone formation takes about 3 months. Changes in bone resorption marker levels can be detected as early as 10

days after the insult and response can be seen within one month of initiation of therapy (27). Various societies recommend measurements of BTM at baseline, 3 months, 6 months, and 12 months in patients who are receiving antiresorptive therapies; this recommendation formed the basis of the protocol for serial measurement of BTM under current study (15).

In the current study, the steroid dose to be administered was standardized to the nearest multiple of 10 towards the lower side. The purpose of this was to reduce the bias secondary to variability in dosing, as there is wide variability in the weight of patients (50 kg to 80 kg) in the study population.

The current study demonstrated that after ESI, there was significant reduction in the BMD of the femur neck and spine along with a rise in the markers of bone remodelling. Further, the decline in BMD was high at the femur neck; this finding suggests systematically circulating absorbed from the injection site also play a role along with locally deposited corticosteroids. This can also be explained by the fact that, due to its cortical nature, bone turnover rate is high at the proximal femur (28). In a previous similar study, Ahmad Al-Shoha et al (30) reported similar findings; the patients in that study were postmenopausal women, which is itself a risk factor for osteoporosis, and the sample size was too low.

A retrospective study by Kang et al (29) found a decreasing trend in BMD of the total hip and femoral neck, but there was no detectable decline in BMD of the lumbar spine after ESI; however, in the current study, there was decline in BMD of the spine. This contrary finding can be explained by differences between patients in the 2 studies with respect to preexisting osteoporosis and osteopenia in the patients enrolled by Kang et al, whereas the current study enrolled patients with normal or only mildly reduced BMD. Systematic effects of steroid injection were previously reported by Even et al (30), who reported significant elevation of blood glucose of persons with diabetes after the injection.

In the current study, there was a significant rise in serum CTX after ESI, which persisted until 3 months. Ahmad Al-Shoha et al (31) also reported an increase in serum CTX; this increase was not statistically significant, however; this can be attributed to the small sample size of their study. As far as serum P1NP is considered, the current study is the first study in which this reference marker has been evaluated. The significant increase in serum P1NP at 3 months' follow-up suggested high bone turnover and bone formation, which was further supported by the data at 6 months, when all BTM returned to near baseline values and BMD also improved.

The results of the current study should be interpreted with a few limitations in mind. First, the current study enrolled a broad age group; age itself is an important variable, as in normal physiological bone metabolism, bone resorption increases as age advances. Second, BTM, particularly the CTX level, is affected by many additional factors like age and gender. Moreover, the reference interval is very large for both CTX (~100 to ~700 ng/L) and P1NP (~15 to ~70 µg/L). Third, there was a high dropout rate in our study; at each follow-up around 10% of patients did not report. Fourth, the current study does not provide any information about the effect of different steroids used for ESI on BMD; this should be the subject of future randomized controlled trials.

Conclusion

ESI has a negative impact on the BMD of the hip and spine. ESI increases bone breakdown, which peaks at one to 3 months, and after 6 months, the bone metabolism returns to normal. Reduced BMD should be considered as a potential side effect of ESI.

References

1. Sicard MA. Les injections medicamenteuse extraduraqles per voie saracoccygiene. C R Seances Soc Biol Fil 1901; 53:396-398.
2. Byun JM, Park HS, Woo JH, Kim J. The effects of a forceful transforaminal epidural steroid injection on radicular pain: A preliminary study. *Korean J Pain* 2014; 27:334-338.
3. Manchikanti L, Cash KA, McManus CD, Pampati V, Benyamin RM. A randomized, double-blind, active-controlled trial of fluoroscopic lumbar interlaminar epidural injections in chronic axial or discogenic low back pain: Results of 2-year follow-up. *Pain Physician* 2013; 16:E491-E504.
4. Murakibhavi VG, Khemka AG. Caudal epidural steroid injection: A randomized controlled trial. *Evid Based Spine Care J* 2011; 2:19-26. doi:10.1055/s-0031-1274753
5. Patt H, Bandgar T, Lila A, Shah N. Management issues with exogenous steroid therapy. *Indian J Endocrinol Metab* 2013; 17:S612-S617. doi:10.4103/2230-8210.123548
6. Ferrara G, Petrillo MG, Giani T, et al. Clinical use and molecular action of corticosteroids in the pediatric age. *Int J Mol Sci* 2019; 20:444. doi:10.3390/ijms20020444
7. van Staa TP. The pathogenesis, epidemiology and management of

glucocorticoid-induced osteoporosis. *Calcif Tissue Int* 2006; 79:129-137.

8. Hardy RS, Zhou H, Seibel MJ, Cooper MS. Glucocorticoids and bone: Consequences of endogenous and exogenous excess and replacement therapy. *Endocr Rev* 2018; 39:519-548.
9. Manchikanti L, Pampati V, Beyer C, Damron K, Cash K, Moss T. The effect of neuraxial steroids on weight and bone mass density: A prospective evaluation. *Pain Physician* 2000; 3:357-366.
10. Kim YU, Karm MH, Cheong Y, et al. Effect of epidural steroid injection on bone mineral density in postmenopausal women according to antiosteoporotic medication use. *Pain Physician* 2016; 19:389-396.
11. Kerezoudis P, Rinaldo L, Alvi MA, et al. The effect of epidural steroid injections on bone mineral density and vertebral fracture risk: A systematic review and critical appraisal of current literature. *Pain Med* 2018; 19:569-579.
12. Kim M, Yang YH, Son HJ, et al. Effect of medications and epidural steroid injections on fractures in postmenopausal women with osteoporosis. *Medicine (Baltimore)* 2019; 98:e16080.
13. N Brandt J, Krogh TN, Jensen CH, Frederiksen JK, Teisner B. Thermal instability of the trimeric structure of the N-terminal propeptide of human procollagen type I in relation to assay technology. *Clin Chem* 1999; 45:47-53.
14. Garnero P, Fledelius C, Gineyts E, Serre CM, Vignot E, Delmas PD. Decreased beta-isomerization of the C-terminal telopeptide of type I collagen alpha 1 chain in Paget's disease of bone. *J Bone Miner Res* 1997; 12:1407-1415.
15. Vasikaran S, Eastell R, Bruyère O, et al. Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: A need for international reference standards. *Osteoporos Int* 2011; 22:391-420.
16. Benoist M, Boulu P, Hayem G. Epidural steroid injections in the management of low-back pain with radiculopathy: An update of their efficacy and safety. *Eur Spine J* 2012; 21:204-213.
17. De Geer CM. Cytokine involvement in biological inflammation related to degenerative disorders of the intervertebral disk: A narrative review. *J Chiropr Med* 2018; 17:54-62.
18. Saal JS , Franson RC, Dobrow R, Saal JA, White AH, Goldthwaite N. High levels of inflammatory phospholipase A2 activity in lumbar disc herniations. *Spine (Phila Pa 1976)* 1990; 15:674-678.
19. Canalis E, Delany AM. Mechanisms of glucocorticoid action in bone. *Ann N Y Acad Sci* 2002; 966:73-81.
20. Ilias I, Zoumakis E, Ghayee H. An overview of glucocorticoid induced osteoporosis. In: Feingold KR, Anawalt B, Boyce A, et al (eds). *Endotext (Internet)*. South Dartmouth, MA: MDText.com, Inc.; 2018. www.ncbi.nlm.nih.gov/books/NBK278968/. Date Accessed 08/01/2019.
21. Canalis E. Mechanisms of glucocorticoid-induced osteoporosis. *Curr Opin Rheumatol* 2003; 15:454-457.
22. Hassan KZ, Sherman AI. Epidural steroids. In: *StatPearls (Internet)*. Treasure Island, FL: StatPearls Publishing; 2020. www.ncbi.nlm.nih.gov/books/NBK537320/. Date Updated 12/16/2019. Date Accessed 08/06/2019.
23. Hashemi M, Dadkhah P, Taheri M, Ghasemi M, Hosseinpour A. Lumbar transforaminal epidural steroid injection in patients with lumbar radicular pain: Outcome results of 2-year follow-up. *Bull Emerg Trauma* 2019; 7:144-149.
24. Kennedy DJ, Zheng PZ, Smuck M, McCormick ZL, Huynh L, Schneider BJ. A minimum of 5-year follow-up after lumbar transforaminal epidural steroid injections in patients with lumbar radicular pain due to intervertebral disc herniation. *Spine J* 2018; 18:29-35.
25. US Food and Drug Administration. FDA Drug Safety Communication: FDA requires label changes to warn of rare but serious neurologic problems after epidural corticosteroid injections for pain. www.fda.gov/downloads/Drugs/DrugSafety/UCM394286.pdf. Date Published 04/23/2014. Date Accessed 10/13/2019.
26. Shetty S, Kapoor N, Bondu JD, Thomas N, Paul TV. Bone turnover markers: Emerging tool in the management of osteoporosis. *Indian J Endocrinol Metab* 2016; 20:846-852.
27. Chih-Hsing W, Yin-Fan C, Chung C, et al. Consensus statement on the use of bone turnover markers for short-term monitoring of osteoporosis treatment in the Asia-Pacific region [published online ahead of print March 20, 2019]. *J Clin Densitom* 2019. doi.org/10.1016/j.jocd.2019.03.004. Date Accessed 09/19/2019.
28. Kučukalić-Selimović E, Valjevac A, Hadžović-Džuvo A, Skopljak-Beganović A, Alimanovic-Alagić R, Brković A. Evaluation of bone remodelling parameters after one year treatment with alendronate in postmenopausal women with osteoporosis. *Bosn J Basic Med Sci* 2011; 11:41-45.
29. Kang SS, Hwang B, Son H, Cheong IY, Lee SJ, Chung TY. Changes in bone mineral density in postmenopausal women treated with epidural steroid injections for lower back pain. *Pain Physician* 2012; 15:229-236.
30. Even JL , Crosby CG , Song Y, et al. Effects of epidural steroid injections on blood glucose levels in patients with diabetes mellitus . *Spine (Phila Pa 1976)* 2012; 37:E46-E50.
31. Al-Shoha A, Rao DS, Schilling J, et al. Effect of epidural steroid injection on bone mineral density and markers of bone turnover in postmenopausal women. *Spine (Phila Pa 1976)* 2012; 37:E1567-E1571.