Actual. Osteol 2023; 19(2): 144-159.
https://ojs.osteologia.org.ar/ojs33010/index.php/osteologia/index

ACTUALIZACIONES / ***Review***

BONE EFFECTS OF EPIDURAL AND INTRA-ARTICULAR GLUCOCORTICOIDS: A SYSTEMATIC LITERATURE REVIEW

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Abstract

Osteoporosis and vertebral and non-vertebral fractures are common in glucocorticoids (GC) treated patients. Oral GC treatment leads to bone loss, particularly of trabecular bone. The benefits of GC used in rheumatological and traumatological disorders are known but they would have possible negative effects on bone. This systematic review aimed to evaluate the effects of epidural steroid injections (ESI), and intra-articular and intramuscular GC administration on bone mineral density (BMD) and fragility fractures. A systematic review of Medline/PubMed, Cochrane, and LILACS up to November 2020 was conducted. Meta-analyses, systematic reviews, randomized and non-randomized controlled trials, and prospective and retrospective studies comparing the effect of ESI, intra-articular or intramuscular GC used compared to a control group or baseline measurements were included. Results: A total of 8272 individuals were included among the 13 selected articles (10 about ESI and 3 about intra-articular GC; no article was found evaluating intramuscular GC). Only a few studies showed a negative effect of ESI on bone in the qualitative analysis considering osteopenia and osteoporosis in lumbar spine, femoral neck and total hip and BMD as surrogate outcomes. On the other hand, the qualitative analysis showed that most studies found an increased risk of

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fragility fracture. However, only two studies could be included in the quantitative analysis, in which there were no differences between patients exposed to ESI versus controls in all evaluated regions. In conclusion, there was insufficient evidence to suggest that ESI and intra-articular GC, unlike oral GC, negatively affect bone mass. Longitudinal studies are needed to obtain more knowledge regarding the effect of ESI or intra-articular GC on BMD and fragility fractures.

Keywords: glucocorticoids, steroids, osteoporosis, fractures, systematic review.

Resumen

La osteoporosis y las fracturas vertebrales y no vertebrales son comunes en pacientes tratados con glucocorticoides (GC). El tratamiento oral con GC conduce a la pérdida ósea, particularmente del hueso trabecular. Los beneficios de los GC utilizados en patologías reumatológicas y traumatológicas son conocidos, pero tendrían posibles efectos negativos sobre el hueso. Esta revisión sistemática tuvo como objetivo evaluar los efectos de las inyecciones epidurales de esteroides (ESI), GC intraarticulares e intramusculares sobre la densidad mineral ósea (DMO) y las fracturas por fragilidad. Se realizó una revisión sistemática de Medline/PubMed, Cochrane y LILACS hasta noviembre de 2020. Se incluyeron metanálisis, revisiones sistemáticas, ensayos controlados aleatorizados y no aleatorizados, estudios prospectivos y retrospectivos que compararon el efecto de ESI, GC intraarticular o intramuscular utilizado en comparación con un grupo de control o mediciones iniciales. Resultados: Se incluyeron un total de 8272 individuos entre los 13 artículos seleccionados (10 sobre ESI y 3 sobre GC intraarticular; no se encontró ningún artículo que evaluara GC intramuscular). Solo unos pocos estudios mostraron un efecto negativo del ESI sobre el hueso en el análisis cualitativo considerando la osteopenia y la osteoporosis en la columna lumbar, el cuello femoral y la cadera total y la DMO como un resultado indirecto. Por otro lado, el análisis cualitativo mostró que la mayoría de los estudios encontraron un mayor riesgo de fractura por fragilidad. Sin embargo, solo dos estudios pudieron incluirse en el análisis cuantitativo, en los que no hubo diferencias entre los pacientes expuestos a ESI versus los controles en todas las regiones evaluadas. En conclusión, no hallamos datos suficientes para sugerir que la ESI y los GC intraarticulares, a diferencia de los GC orales, afectan negativamente a la pérdida ósea. Se necesitan estudios longitudinales para obtener más conocimiento sobre el efecto de ESI o GC intraarticular en la DMO y las fracturas por fragilidad.

Palabras clave: glucocorticoides, esteroides, osteoporosis, fracturas, revisión sistemática.

Introduction

Glucocorticoid (GC) therapy is associated with local and systemic GC adverse effects (AE). Local AE include joint infection, intra-articular and periarticular calcifications, cutaneous depigmentation, cutaneous atrophy, avascular necrosis, tendinopathy, and Charcot's arthropathy, among others.[1]

On bone tissue, low doses of oral GC therapy can impair bone decreasing bone mineral density (BMD) and bone quality and increasing the prevalence of fragility fractures. Further, glucocorticoid-induced osteoporosis (GIO) is considered the most frequent cause of secondary osteoporosis. GC induce a decrease in bone mass due to multiple mechanism: decreased calcium intestinal absorption and increased renal excretion of calcium enhanced PTH secretion, attenuation of sex steroids and growth hormone, decreased muscle strength, and by modifying local bone factors that alter the activity and differentiation of bone cells.[2-4]

The intra-articular GC injections are frequently used to pain and inflammation relief. Intra-articular GC injections are used as a treatment for refractory synovitis in patients with rheumatoid arthritis, psoriatic arthritis, osteoarthritis, and other inflammatory arthropathies when conventional therapy is insufficient. Also, in knee osteoarthritis GC injections may relieve inflammation, and reduce pain and disability. The most common preparations are triamcinolone acetonide, triamcinolone hexacetonide, and methylprednisolone acetate but other preparations are also available (betamethasone acetate, betamethasone sodium phosphate, dexamethasone). However, the clinical benefits of long use of intra-articular GC remain unclear because of the overall quality of the evidence and evidence of small-study effects.[5-7] Moreover, the epidural steroid injections (ESI) are often used to treat patients with lumbar radiculopathy or stenosis when conservative options such as non-steroidal anti-inflammatory drugs, topical modalities, and physical therapy failed, and patients are not candidates for immediate surgical intervention.[8]

Although it has also been demonstrated that intra-articular GC are absorbed more slowly from the joint compared to oral therapy, they can lead to hypothalamic-pituitary-adrenal (HPA) axis suppression for several weeks after administration.[9] The degree of systemic absorption after ESI and intra-articular therapy depends on the preparation used, the dose, and frequency.

Considering the benefits of GC used in rheumatological and traumatological disorders and their adverse effects on the bone tissue previously described, this systematic review aimed to evaluate the effects of ESI, intra-articular and intramuscular GC on BMD and fragility fractures.

Methods

As a guideline to prepare this systematic review and meta-analyses PRISMA-P was used.[10]

Search of the literature. We conducted a systematic search for published meta-analyses, systematic reviews, randomized and non-randomized controlled trials, prospective and retrospective studies. The evidence was searched in MEDLINE/PubMed (https://pubmed.ncbi.nlm.nih.gov/), the Cochrane Library (https://www.cochranelibrary.com/), including Cochrane Database of Systematic Reviews and LILACS (https://lilacs.bvsalud.org/es/) from the beginning of each database up to November 30, 2020.Acetonide triamcinolone, disodium phosphate betamethasone, dipropionate betamethasone, osteoporosis, osteopenia, fracture, bone, bone mineral density, bone markers were used as key terms. The search was carried out combining MeSH (Medical Subject Headings) Terms and Entry Terms combined with Boolean operators (OR,

AND, NOT) and some terms were truncated in their root to obtain the greatest number of studies. These terms were searched in Title/Abstract to increase the specificity of the search. The search strategy was carried out according to the clinical questions PICO (Population, Intervention, Comparator and Outcome).

Eligibility Criteria. Studies with inclusion criteria for this systematic review were those in adults (≥18 years) in which reported the effect of ESI, intra-articular or intramuscular GC used compared with a control group or baseline measurements were reported. BMD, changes in BMD, osteopenia, osteoporosis, fragility fractures, and bone marker levels were considered as outcomes. Additionally, observational studies were included due to a low number of articles found. Only articles in English, Portuguese, or Spanish were included. As exclusion criteria were considered: case reports, review, letters to the editor, animal studies, editorials, commentaries, other languages than the described previously, studies with participants <18 years, and if identical data were re-analyzed.

Study Selection. Rayyan software (https://rayyan-prod.qcri.org/welcome) was used to screen the literature search results. We performed duplicate screening of each title and abstract using two independent reviewers and a third reviewer in case of conflicts. Eligible articles underwent full-text screening by two independent reviewers.

Data extraction and processing. The following methodological information was obtained by two authors independently using a standardized data extraction form developed specifically for this review: study design, place/country, participants, groups, age of participants, type of GC, cumulative dose, outcomes, and results. For dichotomous variables, the numbers of events in both groups were registered as the total number of participants. With these data, the absolute risk (AR), the relative risk (RR) and the relative risk reduction (RRR) were calculated. In the case of continuous variables, the mean difference of each group was registered as well as the p-value.[11]

Pooling of the data, when possible, was done using Review Manager (RevMan) software V.5.4.1 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration) for statistical analysis of the data.

In the meta-analysis, RR was calculated using a fixed-effects model to derive pooled estimates of effect size. A p-values <0.05 were considered significant. Statistical heterogeneity was planned to be assessed using the I^2 statistic, with the degree of heterogeneity graded as follows: <25% no heterogeneity, 25-49% low heterogeneity, 50-74% moderate heterogeneity, >75% high heterogeneity.[12]

Assessment of study quality and publication bias. Quality assessment of the included studies was done independently by two reviewers and confirmed by a third reviewer in case of conflicts, by using the Newcastle-Ottawa scale for non-randomized controlled trials.[13] The maximum possible score was 9 stars, and the minimum was zero. A funnel plot was used to assess the risk of publication bias.[14]

Results

Qualitative Synthesis

Description of studies

The total number of studies identified after searching is shown in Figure 1. After screening, 13 articles were selected for their qualitative analysis. Only observational studies were found in this systematic review. Only two studies were included in the quantitative analysis.

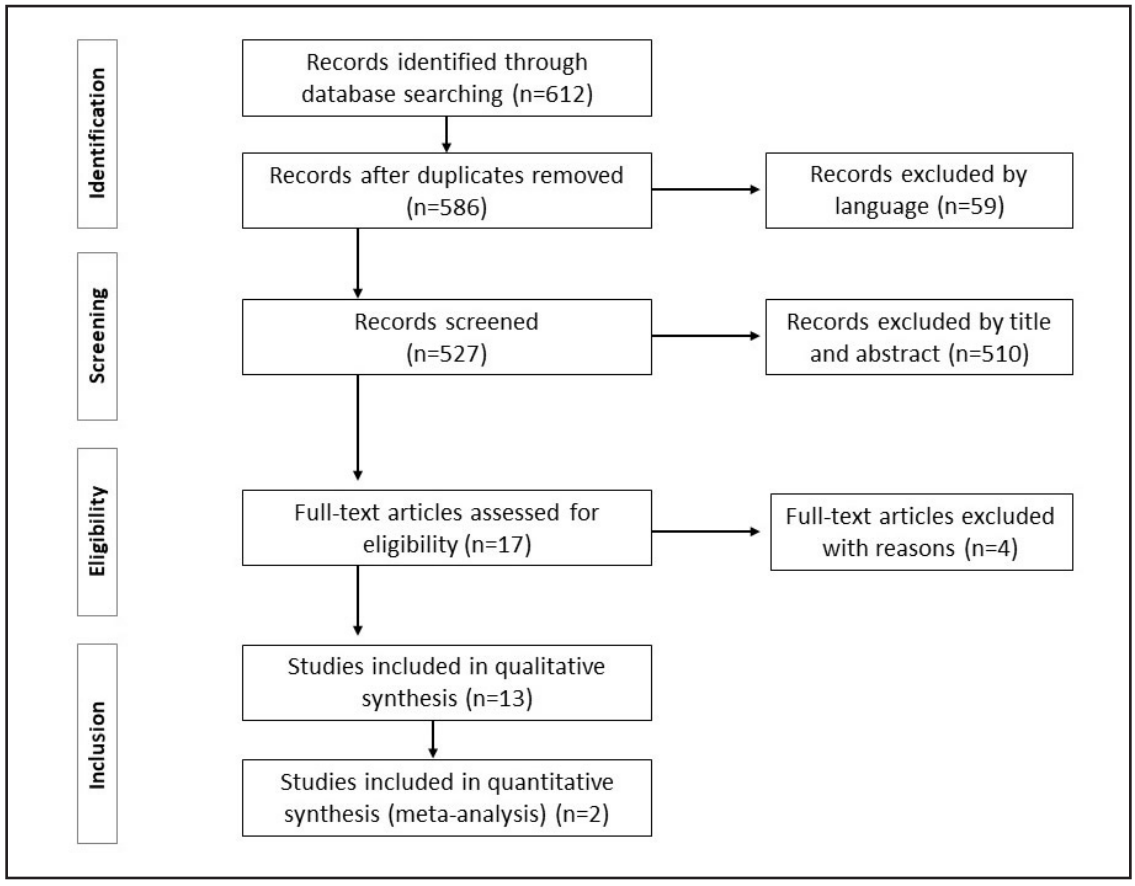

Figure 1. Flow chart of the systematic literature review.

The summary of the study characteristics is shown in Table 1 (see Appendix A). A total of 8272 individuals were included among the 13 selected articles (9 retrospective studies, 3 prospective studies and 1 cross-sectional study). Ten studies[8,15-23] described ESI and three[24-26] intra-articular GC. No article was found evaluating intramuscular GC and the outcomes described previously.

Osteopenia and osteoporosis in lumbar spine (LS), femoral neck (FN), and total hip (TH).

Five retrospective studies and one prospective study evaluated osteopenia and osteoporosis as outcomes. The summaries of findings are shown in Table 2 and Table 3 respectively (see Appendix B). Regarding osteopenia in LS spine, only one study (1/6) showed 39% higer risk than in those with ESI vs control; in FN an increase among 14% to 41% was shown in three studies (3/6) and in TH an increase between12 and17% was observed in three studies (3/6). Regarding osteoporosis in LS spine, three studies (3/5) showed an increase between 77 and 120% in patients with ESI vs control; in FN an increase was shown in two studies (2/5) and in TH an increase was observed in three studies (3/5).

BMD in LS, FN and TH.

Eight studies evaluated the changes in LS BMD (seven by DXA and one by QCT). Seven studies evaluated FN BMD and 6 in TH BMD.

Most studies evaluated ESI except Jensen et al[25] and Florence et al[26] who analyzed intra-articular GC (Table 4, see Appendix B). One study about ESI and another for intra-articular GC found a significant difference between those who received GC versus control. Regarding FN BMD, 3/7 studies found lower BMD in patients under GC treatment versus controls.[15,20,25] In one of them, both groups received ESI as treatment and compared those treated and non-treated with antiosteoporotic medication. Those without antiosteoporotic medication showed significantly lower BMD versus those who received antiosteoporotic medication.[20] For TH 2/6 studies found lower BMD between groups.[15,20] Dubois EF, et al.[15] reported lower BMD in TH in women compared to men, and Kin Y[20] in those with ESI and antiosteoporotic medication versus ESI without anti-osteoporotic medication.

Osteoporotic fractures

Four retrospective studies that evaluated fragility fractures were included (Table 5, see Appendix B). Except for one study, an increased risk of fragility fractures from 9% to 100% was found.[18,22,23]

Bone Markers

Only two studies evaluated changes in bone markers. Al-Shola A (2012) included 28 patients who were evaluated at 3- and 6-months post-ESI.[8] Carboxy-terminal collagen crosslinks (CTX) and bone specific-alkaline phosphatase (BSAP), were assessed across the 6 months. Only BSAP showed a significant increase from 3 to 6 months (p=0.012) and the increase in BSAP and CTX from baseline to 6 months was not significant. On the other hand, Nah SY (2018) included postmenopausal women receiving at least one anti-osteoporotic medication with or without ESI.[22] The levels of CTX and osteocalcin increased at the 1-year follow-up and decreased at the 2-year follow-up in the group with ESI. At baseline, there were no significant differences between the two groups. The corresponding trend was reversed in the group without ESI. There were no significant changes in the bone markers between baseline and follow-up period in both groups.

Quantitative Synthesis (Meta-analysis)

Due to the wide variation in selected outcomes, participants, comparators and interventions, we can meta-analyze only two studies (Kang 2012, Kim 2014)[16,19] which evaluated osteopenia and osteoporosis in patients with or without ESI as treatment without other confounder factors (fracture, anti-osteoporotic medication, sex).

Osteopenia

Both studies showed a wide 95%CI at the LS and no heterogeneity (I^2: 0%). When combined the RR for osteopenia was 1.13 [0.76-1.68] (Figure 2A).

At the FN again both studies showed wide 95%CI, and no heterogeneity (I^2: 0%). When combined the RR for osteopenia was 1.24 [0.93-1.65] (Figure 2B).

At the TH moderate heterogeneity was found (I^2: 66%) with wide 95%CI. For combined results, the RR was 0.87 [0.65-1.17] (Figure 2C).

In all regions, 95%CI crossed the null effect and there were no significant differences among patients exposed to ESI versus control for the outcome osteopenia.

Osteoporosis

At the LS both studies showed wide 95%CI, and there was low heterogeneity (I^2: 29%). The RR was 1.23 [0.75-2.00] when results were combined (Figure 3A).

Al the FN there was no heterogeneity (I^2: 0%) and both studies showed wide 95%CI. The RR for osteoporosis after combined results was 1.58 [0.84-2.95] (Figure 3B).

At the TH the heterogeneity was moderate (I^2: 66%) and wide 95%CI and the combined results showed a RR 0.87 [0.65-1.17] (Figure 3C).

Overall, 95%CI crossed the null effect and there was no difference between patients exposed to ESI versus control in outcome osteoporosis in all regions.

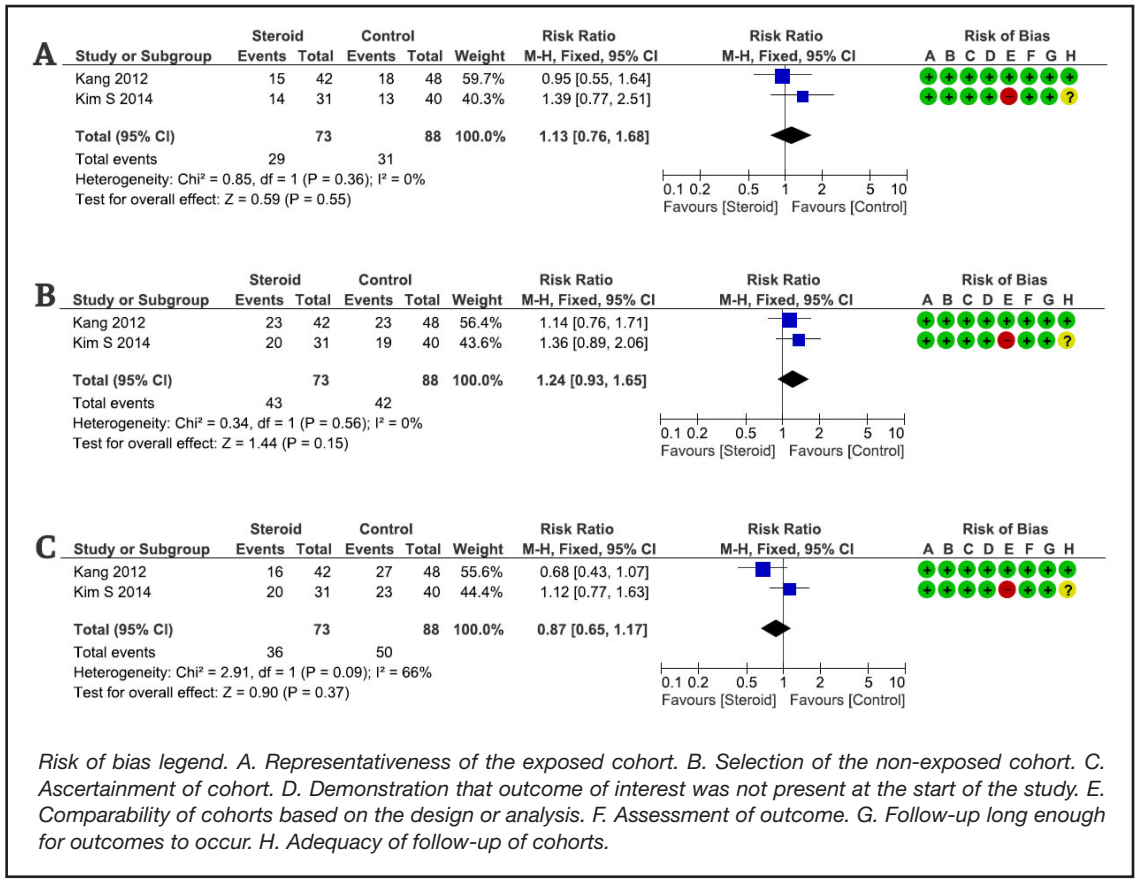

Figure 2. Forest plot of comparison. Osteopenia in lumbar spine (panel 2A), femoral neck (panel 2B) and total hip (panel 2C) in patients with low back pain treated or not with ESI.

Risk of Bias in included studies

Two studies (Al-Shoha 2012 and Dubois 2003) showed inadequate follow-up long enough for outcomes to occur and inadequate follow-up of cohorts.[8,15] Kim S and Kim Y had inadequate comparability of cohorts because of design or analysis,[19,20] and Mandell 2013 because there was no demonstration that outcome of interest was not present at the start of the study.[18] (Figure 4).

Discussion

Considering the common use of GC in rheumatological and traumatological disorders and their potential adverse effects on the bone, we aimed to evaluate the effects of non-oral administration of GC (ESI, intra-articular and intramuscular) on BMD and fragility fractures. In this systematic review showed a low number of studies (n=13) about ESI or intra-articular GC that evaluated BMD or fragility fractures as outcomes; no article was found evaluating intramuscular GC.

Dubois EF (2003)[15] found no significant relationship in patients treated with ESI between the cumulative methylprednisolone dose and the LS, FN and TH BMD. Kang S (2012)[16] described a trend in decreased BMD in the ESI-treated patients but there was no significant difference in mean percentage change from baseline BMD among the groups in all evaluated sites. However, it was reported a significant decrease

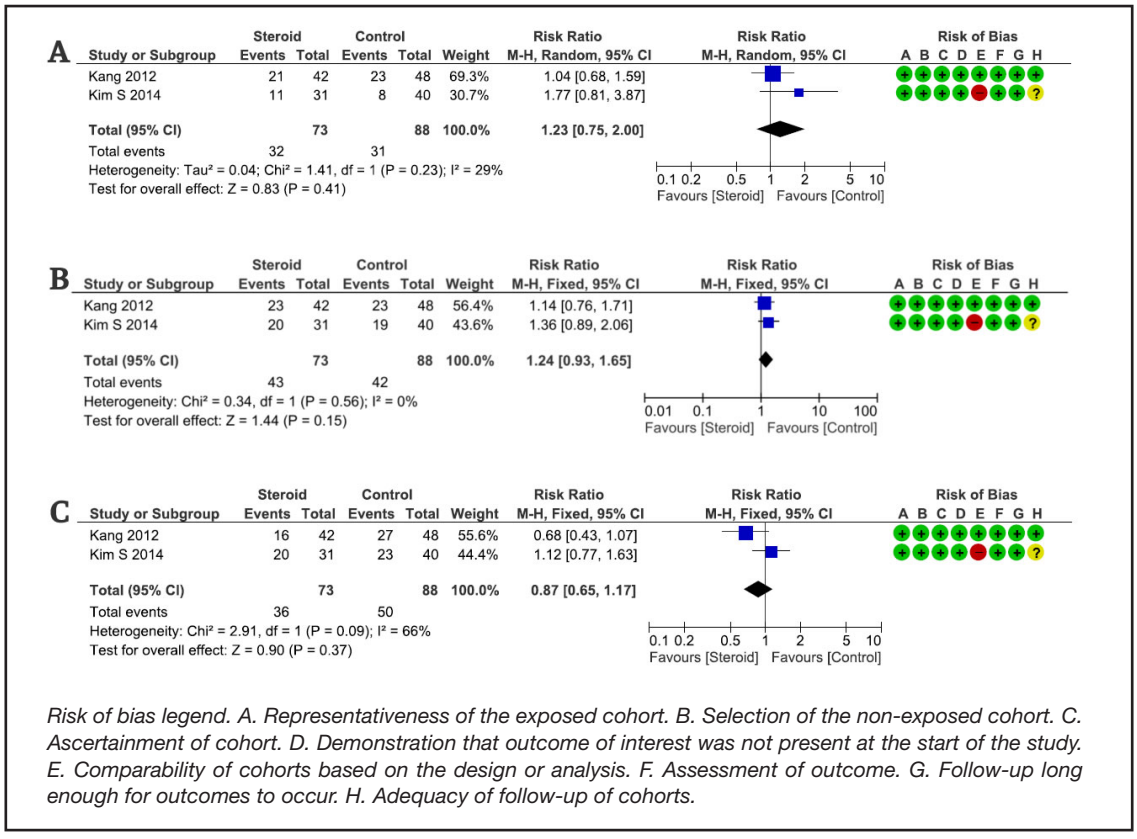

Figure 3. Forest plot of comparison. Osteoporosis in lumbar spine (panel 3A), femoral neck (panel 3B) and total hip (panel 3C) in patients with low back pain treated or not with ESI.

from baseline in TH BMD, without differences in LS and FN BMD, after 6 months of ESI.[8] Further, significantly changes in the BMD from baseline were observed in the FN and TH, but not in the LS after ESI.[20] A significant decrease in LS BMD was described at 2-year follow-up after multiple ESI (~14 injections with a cumulative triamcinolone at dose of 400 mg).[22] In addition, Kim M (2019) found that ESI causes BMD impairment in postmenopausal women without concomitant use of anti-osteoporotic medication.[23] Finally, ESI was associated with an increased likelihood of fracture.[18,22,23]

Regarding intra-articular GC injections Jensen, et al (2014) showed a significant decrease in LS BMD in patients who do not take a bisphosphonate.[25] At lumbar spine, there was no significant difference in trabecular density in BMD by QCT in subjects who had received triamcinolone or methylprednisolone intraarticular injections.[26]

In summary, only a few studies showed a negative effect of ESI on bone in the qualitative analysis considering osteopenia and osteoporosis in LS, FN and TH or BMD as a surrogate outcome. On the other hand, the qualitative analysis showed that most studies found an increased risk of fragility fracture. However, only two studies could be included in the quantitative analysis due to the wide variation in selected outcomes, participants, comparators, and interventions, in which there were no differences between patients exposed to ESI versus controls in all evaluated regions.

Therefore, in this systematic review, there was insufficient evidence to suggest that ESI

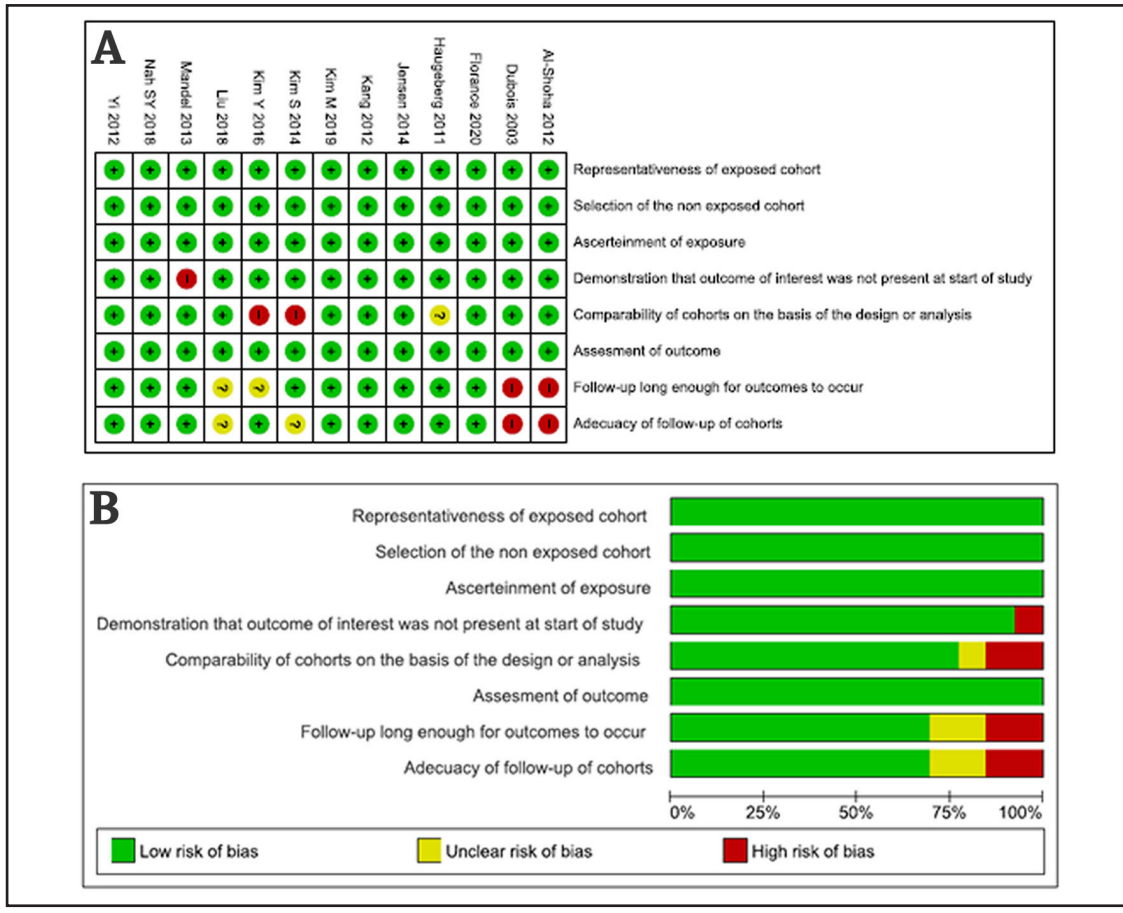

Figure 4. Quality assessment tool for cohort study's (Newcastle-Ottawa scale). **A. Risk of bias summary:** Reviewers' judgements about each risk of bias item for each included study**. B. Risk of bias graph:** Reviewers' judgements about each risk of bias item presented as percentages across all included studies. Green: Low risk of bias >7/9. Yellow: Unclear risk of bias <4/9. Red: High risk of bias <4/9.

and intra-articular GC, unlike oral GC, negatively affect bone loss or bone quality. However, these results should be interpreted with caution because only two studies could be meta-analyzed because of wide variation in selected outcomes, participants, comparators, and interventions among them. Longitudinal studies are needed to obtain more knowledge regarding the effect of ESI or intra-articular GC treatment on BMD and fragility fractures.

Author contributions: All authors have made substantial contributions to this work. MLB, AB, MD, EG, CG, MSL, FB, and AS designed the study; MLB, LARS, IC, MCM, RA, and BP participated in the acquisition and analysis of the data, and all authors interpreted the resultant data. MLB and LRB drafted the manuscript, and all authors participated in the critical revision of the manuscript for important intellectual content.

Declaration of interest: All authors have no conflicts of interest.

Received: May 2023
Accepted: September 2023

Appendix A

Table 1. Summary of findings of qualitative review.

Epidural Steroid Injection							
Reference and Place	Study Design	Groups	Age, years Mean±SD		Type of steroid Cumulative Dose (mg). Mean±SD	Outcomes	Results
			Cases	Control			
Dubois EF, et al. 2003 Netherlands	Cross-sectional study. PM women and men with low back pain treated with ESI (MP minimal cumulative dose of 3 g).	Control:14 men Case: 14 PM women, previously treated with multiple epidural MP depots. The minimal cumulative MP dose received by all 28 subjects was 3 g.	68±9	54±9	MP Men: 7.76±4.23 Women: 8.50±3.13	Changes in BMD measured by DXA after ESI treatment in the LS (L2-L4), FN and TH.	No significant relationship were found in either the men or the women between the cumulative MP dose and the BMD of the LS, FN and TH.
Al-Shoha A, et al. 2012. Detroit	Prospective observational study. PM women treated with ESI.	Control: 28 PM women pre ESI. Case: 28 post ESI PM women. Evaluated at 3 and 6 months post ESI.	>65 years Mean±SD not specified	>65 years Mean±SD not specified	Triamcinolone 80 mg/ml	Changes in BMD measured by DXA after ESI treatment in LS, FN, and TH. Changes in BSAP and serum CTX.	A single ESI adversely affects BMD of the hip. BSAP increased significantly from 3 to 6 months. The rise of CTX was not significant.
Kang SS, et al. 2012 South Korea	Retrospective study. PM women with low back pain treated with or without ESI. From July 2005 to June 2011.	Control: 48 patients who received non steroidal anti-inflammatory drug and muscle relaxant without ESI. Case: 42 patients who received ESI more than 4 times, with a cumulative administered dose of triamcinolone > 120 mg.	63±1.2	62±1.8	Triamcinolone 212±32	Changes in BMD measured by DXA from baseline to one year after ESI treatment in the LS, FN and TH.	No difference in mean percentage change from baseline BMD between or within the groups treated with and without ESI.
Yi Y, et al. 2012 South Korea	Retrospective study. PM women with low back pain treated with ESI From January 2009 to December 2011.	Control: 218 patients without VF. Case: 134 with VF.	74±5.2	65±7.3	Triamcinolone With VF: 178±169 Without VF: 158 ±124	Changes in BMD measured by DXA in the LS, FN, and TH according osteoporotic fractures and ESI.	No correlation between BMD and the mean number of ESIs, mean total dose of glucocorticoids, or mean duration of ESIs.
Mandel S, et al. 2013 Detroit.	Retrospective study. Patients older than 50 years with at least one lumbar ESI.	Control: 3000 matched patients without lumbar ESI with similar metabolic conditions. Case: 3415 patients with at least one lumbar ESI.	66.4±10.5	66.5±10.6		Vertebral fractures	Increased risk of VF after increasing number of injections.
Kim S, et al. 2014. South Korea	Retrospective study. PM women with lower back pain treated with or without ESI. From July 2009 to December 2012.	Control: 40 patients who had received non-ESI medications∞ Case: 31 patients who had received >10 ESIs, with a cumulative triamcinolonedose >200 mg.	69±8.5	70±6.8	Triamcinolone 394±81	Changes in BMD measured by DXA after ESI treatment in the LS (L2-L4), FN, and TH.	Cases showed lower BMD in the FN and TH. The prevalence of osteoporosis and osteopenia were significantly higher in cases.
Kim YU, et al. 2016 Korea	Retrospective study. PM women with lower back pain treated with ESI and with or without AOM. From March 2010 to December 2015.	Control: 52 patients with ESI without any AOM. Case: 74 patients with ESI using while AOM•	69.51 ±5.98	67.38 ±6.25	Dexamethasone 9.73±6.35 (ESI + AOM) 8.94±4.78 (ESI only)	Changes in BMD measured by DXA after ESI treatment in the LS, FN, femoral trochanter, and TH.	There were no significant differences between baseline and post-treatment BMD absolute values in case group. In controls significant changes in the post-treatment BMD were observed in the FN and TH, but not in the LS.
Liu Y, et al. 2018 New York	Retrospective study. Patients with lumbar CT scan in the 5 years prior and ESI (at least three injections). From January 2011 to December 2016.	Control: 121 patients without ESI. Case: 121 patients who received three or more ESIs in the 5 years prior to their CT scans. (49% women)	66±14	65±14	Triamcinolone 340 mg (150-1400 mg) [median and range] Others: Betamethasone Dexamethasone	vBMD measured by QCT from T12 level through L5. Vertebral fracture	Higher cumulative dose was associated with lower vBMD at T12 to L5.

Nah SY, et al. 2018 Korea	Retrospective study. PM patients with at least one of the AOM. From January 2012 to December 2016.	Control: 294 patients. Case: 73 patients	71.84±6.6	70.46±7.7	Triamcinolone 78.3 SD Not specified	Changes of BMD and the effect of AOM after ESI.	ESI adversely affects BMD in PM women, and increase with the dose of steroids.
Kim M, et al. 2019 Korea	Retrospective study. PM women with osteoporosis who had received either ESI or medication for low back pain. From January 2006 to December 2012.	Control: 86 patients with medications for low back pain. Case: 86 patients with ESI. The treatments of osteoporosis in all the participants included bisphosphonates, calcium, and hormone replacement therapy.	67.4±8.0	67.8±8.1	Dexamethasone 31±9.4	Osteoporotic fractures in a 5-year period.	There were no significant differences in the prevalence of osteoporotic fracture between the 2 groups for any follow-up periods.
Intra-articular Steroid Injections							
Haugeberg G, et al. 2011 UK	Prospective study. RA patients with clinically active arthritis with 12 months of evaluation. Compare MTX alone or MTX and intra-articular MP into all joints	40 patients with RA with disease duration <12 months, with symmetrical polyarthritis affecting the metacarpophalangical joints. In the first 3-month period the patients were randomized to receive either MTX alone or MTX and intra-articular MP into all joints with clinically active arthritis (defined as both tender and swollen). From 3 to 12 months, both groups received the same standard treatment with MTX and IAGC.	55.2±15.5 (MTX + IAGC)	53.3±15.7 (MTX)	Intra-articular MP Not described dose.	Changes in BMD measured by DXA in hands in early RA. Changes in LS and FN at 12 months.	IAGC given over 3 months protects against periarticular bone loss in inflamed finger joints in RA. A statistically significant loss in BMD was seen at the hand at 3, 6 and 12 months and at spine L2-4 and FN at 12 months.
Jensen TW. et al. 2014 Copenhagen	Prospective study. 160 patients with early, active RA, received MTX and ciclosporin or MTX alone. Both intra-articular betamethasone. ** In this study the data of the two arms of RA treatment were pooled and analyzed together.	According Z-score the population was divided in two groups: Case: 66 RA patients treatment with calcium, vitamin D and alendronate (when Z-score ≤0 in the FN or LS). Control: 71 RA patients with treatment with calcium and vitamin D but not alendronate.	57 (27-75) Median (range)	52 (20-74) Median (range)	Betamethasone Median (range) Case: 77 (14-357) Control: 70 (7-308)	Investigate the influence of alendronate and intra-articular betamethasone treatment on BMD, measured by DXA, changes in hand, LS and FN during 1 year. (CIMESTRA study).	During 1 year, bone changes in the LS and FN, though a trend in the hand, were negatively correlated to the cumulated intra-articular betamethasone doses only in the alendronate group patients.
Florence J, et al. 2019 Boston	Retrospective study. Patients undergone at least three medium or large joint (shoulder, hip or ankle) corticosteroid injections followed by a non-contrast abdominal CT from 2008 to 2018.	Case: 50 patients with IAGC: (15 patients underwent glenohumeral injections, 24 in hip, 10 in ankle, 1 patient in hip and glenohumeral). All of them had a CT within 5 years of the first injection. Control: 126 without corticosteroid injections and a CT.	69±14	69±13	Triamcinolone acetonide MP acetate	Changes in trabecular density measured by QCT after repeated IAGC injections versus controls: 40–80 mg of triamcinolone or 40–80 mg of MP acetate.	No difference in trabecular density of L1 to L4 between cases and controls was found.

PM: Postmenopausal; ESI: Epidural Steroid Injection; MP: methylprednisolone; BMD: Bone Mineral Density; DXA: Dual-energy X-ray absorptiometry ;LS: Lumbar Spine; FN: Femoral Neck; TH: Total Hip; BSAP: bone specific-alkaline phosphatase; C-telopeptide of collagen I (CTX); VF: Vertebral Fracture; ESI: Epidural Steroid Injection; AOM: Anti-Osteoporotic Medication; CT: Computed tomography;vBMD: volumetric BMD; QCT: quantitative computed tomography; MTX: methotrexate; RA: rheumatoid arthritis (RA); IAGC: intra-articular glucocorticoid. **Jensen CIMETRA study. ∞: non-ESI medications: (ie, nonsteroidal anti-inflammatory drugs and muscle relaxants). * AOM [bisphosphonates, calcium and vitamin D supplementation, selective estrogen receptor modulators (raloxifene, tamoxifen), hormone therapy].

Appendix B

Summary of findings outcomes osteopenia, osteoporosis, BMD, and fragility fractures.

Table 2. Summary of Findings: Outcome Osteopenia.

Reference	Number of participants. Comparison	Events in Case Group	Events in Control Group	Absolute Risk (%)		Relative Risk	RRR
				Risk in Cases	Risk in Controls		
Outcome: Osteopenia in Lumbar Spine							
Dubois EF, et al.	Case: 14 women Control: 14 men	6 /14	6/14	42.9	42.9	1	0
Kang SS, et al.	Case (ESI): 42 patients Control (No ESI): 48 patients	15/42	18/48	35.7	37.5	0.95	0.05
Yi Y, et al.	Case (with fracture): 134 patients Control (without fracture): 218 patients	38/134	92/218	28.4	42.2	0.67	0.33
Kim S, et al.	Case (ESI): 31 patients Control (No ESI): 40 patients	14/31	13/40	45.5	32.5	1.39	-0.39
Kim Y, et al.	Case (ESI +AOM): 74 patients. Control (ESI only): 52 patients	40/74	29/52	54.1	55.8	0.97	0.03
Nah SY, et al	Case (ESI +AOM): 73 patients Control (No ESI. Only AOM): 294 patients	26/73	105/294	35.6	35.7	1	0
Outcome: Osteopenia in Femoral Neck							
Dubois EF, et al.	Case: 14 women Control: 14 men	4/14	11/14	28.6	78.6	0.36	0.64
Kang SS, et al.	Case (ESI): 42 patients Control (No ESI): 48 patients	23/42	23/42	54.8	47.9	1.14	-0.14
Yi Y, et al.	Case (with fracture): 134 patients Control (without fracture): 218 patients	51/134	133/218	38.1	61	0.62	0.38
Kim S, et al.	Case (ESI): 31 patients Control (No ESI): 40 patients	20/31	19/40	64.5	47.5	1.36	-0.36
Kim Y, et al.	Case (ESI +AOM): 74 patients. Control (ESI only): 52 patients	42/74	21/52	56.8	40.4	1.41	-0.41
Nah SY, et al	Case (ESI +AOM): 73 patients Control (No ESI. Only AOM): 294 patients	44/73	165/294	60.3	56.1	1.07	-0.07
Outcome: Osteopenia in Total Hip							
Dubois EF, et al.	Case: 14 women Control: 14 men	6/14	7/14	42.9	50	0.86	0.14
Kang SS, et al.	Case (ESI): 42 patients Control (No ESI): 48 patients	16/42	27/48	38.1	56.3	0.68	0.32
Yi Y, et al.	Case (with fracture): 134 patients Control (without fracture): 218 patients	60/134	87/218	44.8	39.9	1.12	-0.12
Kim S, et al.	Case (ESI): 31 patients Control (No ESI): 40 patients	20/31	23/40	64.5	57.5	1.12	-0.12
Kim Y, et al.	Case (ESI +AOM): 74 patients. Control (ESI only): 52 patients	39/74	27/52	52.7	51.9	1.02	-0.02
Nah SY, et al	Case (ESI +AOM): 73 patients Control (No ESI. Only AOM): 294 patients	49/73	169/294	67.1	57.5	1.17	-0.17

Table 3. Summary of Findings: Outcome Osteoporosis.

Reference	Number of participants. Type of Study	Events in Case Group	Events in Control Group	Absolute Risk (%)		Relative Risk	RRR
				Risk in Cases	Risk in Controls		
Outcome: Osteoporosis in Lumbar Spine							
Dubois EF, et al	Case: 14 women Control: 14 men	5/14	0/14	35.7	0	-	-
Kang SS, et al.	Case (ESI): 42 patients Control (No ESI): 48 patients	21/42	23/48	50	47.9	1.04	-0.04
Yi Y, et al. *	Case (with fracture): 134 patients Control (without fracture): 218 patients	91/134	82/218	67.9	37.6	1.81	0.81
Kim S, et al. **	Case (ESI): 31 patients Control (No ESI): 40 patients	11/31	8/40	35.5	20	1.77	-0.77
Kim Y, et al.	Case (ESI +AOM): 74 patients. Control (ESI only): 52 patients	25/74	8/52	33.8	15.4	2.2	-1.2
Nah SY, et al	Case (ESI +AOM): 73 patients Control (No ESI. Only AOM): 294 patients	39/73	180/294	53.4	61.2	0.87	0.13
Outcome: Osteoporosis in Femoral Neck							
Dubois EF, et al.	Case: 14 women Control: 14 men	6/14	0/14	42.9	0	-	-
Kang SS, et al.	Case (ESI): 42 patients Control (No ESI): 48 patients	9/42	11/48	**21.4**	**22.9**	0.94	0.06
Yi Y, et al.	Case (with fracture): 134 patients Control (without fracture): 218 patients	64/134	17/134	47.2	7.8	6.12	-5.12
Kim S, et al. ***	Case (ESI): 31 patients Control (No ESI): 40 patients	9/31	4/40	29	10	2.90	-1.90
Kim Y, et al.	Case (ESI +AOM): 74 patients. Control (ESI only): 52 patients	23/74	17/52	31.1	32.7	0.95	0.05
Nah SY, et al	Case (ESI +AOM): 73 patients Control (No ESI. Only AOM): 294 patients	24/73	111/294	32.9	37.8	0.87	0.13
Outcome: Osteoporosis in Total Hip							
Dubois EF, et al.	Case: 14 women Control: 14 men	5/14	0/14	35.7	0	-	-
Kang SS, et al.	Case (ESI): 42 patients Control (No ESI): 48 patients	18/42	11/48	42.9	22.9	1.87	-0.87
Yi Y, et al. ****	Case (with fracture): 134 patients Control (without fracture): 218 patients	55/134	23/218	41	10.6	3.89	-2.89
Kim S, et al.	Case (ESI): 31 patients Control (No ESI): 40 patients	5/31	7/40	16.1	17.5	0.92	0.08
Kim Y, et al.	Case (ESI +AOM): 74 patients. Control (ESI only): 52 patients	19/74	10*52	25.7	19.2	1.34	-0.34
Nah SY, et al	Case (ESI +AOM): 73 patients Control (No ESI. Only AOM): 294 patients	20/73	94/294	27.4	32	0.86	0.14

Table 4. Summary of Findings: Outcome Bone Mineral Density.

Reference	Groups and number of participants	Control Group Mean ±SD	Cases Group Mean ±SD	Mean Difference IV, Fixed, 95% CI	
Outcome: BMD in Lumbar Spine					
Dubois EF, et al.	Case: 14 women Control: 14 men	1.23±0.20 (g/cm^2)	1.00±0.19 (g/cm^2)	-0.23 [-0.37, -0.09]	0.002
Kang SS, et al.	Case (ESI): 42 patients Control (No ESI): 48 patients	0.772±0.221 (g/cm^2)	0.781± 0.260 (g/cm^2)	0.01 [-0.09, 0.11]	ns
Al-Shoha A, et al.	Control: 28 PM women pre ESI Case: 28 women post ESI Evaluation at pre ESI and at 6 months post ESI	1.082,0±0,155 (g/cm^2)	1.071,0±0,163 (g/cm^2)	-0.01 [-0.09, 0.07]	ns
Kim Y, et al.	Control: 52 patients with ESI but without AOM. Case: 74 patients with ESI and AOM.	0.69±6.94 % change	1.25±6.01 % change	0.56 [-1.77, 2.89]	ns
Nah SY, et al	Case (ESI +AOM): 73 patients Control (No ESI. Only AOM): 294 patients Both with anti-osteoporotic drugs At 2 years follow-up.	0.827 ± 0.101 (g/cm^2)	0.852 ± 0.118 (g/cm^2)	0.03 [-0.00, 0.05]	ns
Kim M, et al	Control (No ESI): 86 patients Case (ESI): 86 patients	0.806±0.12 (g/cm^2)	0.799±0.12 (g/cm^2)	-0.01 [-0.04, 0.03]	ns
Jensen TW, et al	Control: 71 patients without alendronate Case: 66 patients with alendronate	-1.8 % change	1.8 % change	Not estimated	p<0.01
Outcome: BMD in Femoral Neck					
Dubois EF, et al.	Case: 14 women Control (male): 14 men	0.92±0.12 (g/cm^2)	0.74±0.14 (g/cm^2)	-0.18 [-0.28, -0.08]	p<0.01
Kang SS, et al.	Case (ESI): 42 patients Control (No ESI): 48 patients	0.752±0.184 (g/cm^2)	0.749±0.205 (g/cm^2)	-0.00 [-0.08, 0.08]	ns
Al-shoha	Control: 28 PM women pre ESI Case: 28 women post ESI Evaluation at pre ESI and at 6 months post ESI	0,785±0,091 (g/cm^2)	0,774±0,094 (g/cm^2)	-0.01 [-0.06, 0.04]	ns
Kim Y, et al.	Control: 52 patients with ESI but without AOM. Case: 74 patients with ESI and AOM.	-1.48±3.84 % change	0.45±4.05 % change	1.93 [0.54, 3.32]	0.007
Nah SY, et al	Case (ESI +AOM): 73 patients Control (No ESI. Only AOM): 294 patients Both with anti-osteoporotic drugs At 2 years follow-up.	0.677 ± 0.093 (g/cm^2)	0.694 ± 0.105 (g/cm^2)	0.02 [-0.01, 0.04]	ns
Kim M, et al	Control (No ESI): 86 patients Case (ESI): 86 patients	0.615±0.10 (g/cm^2)	0.606±0.09 (g/cm^2)	-0.01 [-0.04, 0.02]	ns
Jensen TW, et al	Control: 71 patients without alendronate Case: 66 patients with alendronate	-2.2 % change	0.8 % change	Not estimated	p=0.02
Outcome: BMD in Total Hip					
Dubois EF, et al.	Case: 14 women Control: 14 men	0.98±0.12 (g/cm^2)	0.79±0.14 (g/cm^2)	-0.19 [-0.29, -0.09]	p<0.001
Kang SS, et al.	Case (ESI): 42 patients Control (No ESI): 48 patients	0.692±0.215 (g/cm^2)	0.686±0.235 (g/cm^2)	-0.01 [-0.10, 0.09]	ns
Al-shoha	Control: 28 PM women pre ESI Case: 28 women post ESI Evaluation at pre ESI and at 6 months post ESI	0,979±0,116 (g/cm^2)	0,961±0,112 (g/cm^2)	-0.02 [-0.08, 0.04]	ns
Kim Y, et al.	Control: 52 patients with ESI but without AOM. Case: 74 patients with ESI and AOM.	-2.23±4.52 % change	0.21±3.64 % change	2.44 [0.96, 3.92]	0.001
Nah SY, et al	Case (ESI +AOM): 73 patients Control (No ESI. Only AOM): 294 patients Both with anti-osteoporotic drugs At 2 years follow-up.	0.727 ± 0.103 (g/cm^2)	0.736 ± 0.093 (g/cm^2)	0.01 [-0.02, 0.03]	ns
Kim M, et al	Control: 71 patients without alendronate Case: 66 patients with alendronate	0.691±0.12 (g/cm^2)	0.673±0.14 (g/cm^2)	-0.02 [-0.06, 0.02]	ns

Table 5. Summary of Findings: Outcome Fragility Fractures.

Outcome: Osteoporotic Fractures							
Reference	Number of participants. Type of Study	Events in Case Group	Events in Control Group	Absolute Risk (%)		Relative Risk	RRR
				Risk in Cases	Risk in Controls		
Mandel S, et al.	Control: 3000 patients Cases: 3415 patients	Not described	Not described	-	-	1.21 (95% CI 1.08-1.30)	
Liu Y, et al.	Case (ESI): 121 patients Controls (No ESI): 121 patients	10/121	11/121	8.3	9.1	0.91	0.09
Nah SY, et al	Case (ESI +AOM): 73 patients Control (No ESI. Only AOM): 294 patients	20/72	74/294	27.4	25.2	1.09	-0.09
Kim M, et al	Control (No ESI): 86 patients Case (ESI): 86 patients	19 (vertebral) 2 (hip)	21 (vertebral) 4 (hip)	24.4 4.7	22.1 2.3	1.11 2	-0.11 -1

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