BMJ Open

Comparative effectiveness of bisphosphonate treatments for the prevention of re-fracture in glucocorticoid-induced osteoporosis: protocol for a systematic review and meta-analysis

Hongmin Chu ,[1] Bo-Hyoung Jang ,[2] GaYoon Kim ,[3] Seowoo Bae ,[4] Hyeju Lee ,[3] Seonghee Nam ,[3] Jeonghoon Ahn [3]

To cite: Chu H, Jang B-H, Kim GY, *et al*. Comparative effectiveness of bisphosphonate treatments for the prevention of re-fracture in glucocorticoid-induced osteoporosis: protocol for a systematic review and meta-analysis. *BMJ Open* 2022;**12**:e062537. doi:10.1136/bmjopen-2022-062537

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-062537).

HC and B-HJ contributed equally.

HC and B-HJ are joint first authors.

Received 04 March 2022
Accepted 01 September 2022

For numbered affiliations see end of article.

Correspondence to
Dr Jeonghoon Ahn;
ahnjeonghoon@ewha.ac.kr

ABSTRACT

Background Long-term usage of glucocorticoids results in a loss of bone mass and a higher risk of fracture, and the most common cause of secondary osteoporosis is glucocorticoid-induced osteoporosis (GIOP). For preventing GIOP, bisphosphonate (BP) is widely used. However, analysis on BP's effect on the prevention of re-fracture is insufficient. The purpose of the present study is to evaluate the comparative treatment effect and prevention of re-fracture according to the type of BP in GIOP as the basis for a reliable clinical strategy for patients.

Methods and analysis We will search electronic databases of the PubMed, Cochrane Library and EMBASE using a comprehensive search strategy in December 2021 with no language restriction. Randomised controlled trials (RCTs), quasi-RCTs, controlled trials and cohort studies evaluating the effectiveness of BP to the patients with GIOP will be included in this study. The primary outcome will be the incidence of hip, vertebral and other fractures. The secondary outcome will include percentage changes on the bone mineral density and incidence of re-fracture. Assessing risk of bias for included studies is done using the Cochrane Risk of Bias tool and Risk Of Bias In Non-randomized Studies–of Intervention tool. If quantitative synthesis is possible, a meta-analysis will be performed. A subgroup analysis will be conducted to compare re-fracture rate on the patients with GIOP who experience previous fractures. This study's result will provide evidence for the effectiveness of BP in the prevention of re-fracture on patients with GIOP.

Ethics and dissemination The results will be disseminated through publishing in a peer-reviewed journal or public presentations. Ethical approval is not required as this is a systematic review of publicly available data.

PROSPERO registration number CRD42022343787.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This systematic review will follow the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses for ensuring transparency and rigour of review.
⇒ Since there are few papers based on fracture rate in randomised controlled trials, we intend to include observational studies.
⇒ There is a limitation in that there is a possibility that research may exist other than the database used for the subject of this study.

INTRODUCTION

Glucocorticoid-induced osteoporosis (GIOP) is a serious side effect of glucocorticoids (GCs), which are used for the treatment of inflammatory conditions.[1 2] It causes an increased risk of fracture and bone loss and has been reported to occur in as many as 30%–50% of patients who receive chronic GC therapy.[3] The duration and dose of GCs both increase the risk of fracture.[1 4] The incidence of fractures in patients who received long-term GC treatment was twice as high as that of those who received short-term GC treatment.[5 6] In addition, the higher the dosage, the more likely a fracture may occur.[4]

Bisphosphonate (BP) is widely used as a treatment for osteoporosis with mechanisms such as inhibition of bone resorption through osteoclast inhibition, inhibition of osteoclast formation and increased production of osteoprotegerin.[7] In particular, there are injections and oral preparations for BP. Oral-intake drugs such as alendronate, risedronate and ibandronate are used widely. For injections, pamidronate, ibandronate and zoledronate are used. In particular, injections only need to be administered once a month or once at 3 months, so they have the advantage of high compliance in elderly patients who are taking multiple drugs, and their absorption rate is also high compared with oral drugs, so it is widely used.[8]

In a previous study, there is a study comparing the effects of BP on postmenopausal women with osteopenia.[7] However, systematic reviews and meta-analyses according to the type of BP were not performed for patients with GIOP. In addition, although Fracture Risk Assessment Tool (FRAX) is widely used internationally in diagnosing GIOP, it is also diagnosed based on bone mineral densitometer (BMD).[2] So both indicators should be included and analysed together. Moreover, in the case of past fractures among patients with GIOP, analysis on BP's effect on the prevention of re-fracture is insufficient. The purpose of the present study is to evaluate the comparative treatment effect and prevention of re-fracture according to the type of BP in patients with GIOP.

METHODS

STUDY REGISTRATION

The protocol of this study complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[9] This systematic review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (registration ID: CRD42022343787, URL: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=343787).

Eligible criteria for study selection

Types of studies

Peer-reviewed and published experimental randomised controlled trials (RCTs), quasi-RCTs, controlled trials and observational studies will be included in the search. Other references or studies related to GIOP and fractures will be checked and hand-searched for prospective inclusion.

Types of participants

Eligible participants will be patients with GIOP diagnosed with a BMD score (less than or equal to 2.5) or FRAX guidelines. There will be no restrictions based on sex, ethnicity, symptom severity, disease duration and clinical setting. There are no limits based on gender, race, severity of symptoms, length of the condition or clinical environment.

Types of interventions and comparators

We will include treatment in which osteoporosis was diagnosed based on FRAX or BMD. The control group will divided into each type of active agents and placebo for comparing effect size according to the type of controls. The comparison will be conducted between the BP treatments and other pharmacological interventions used for treatment of GIOP such as selective oestrogen receptor modulator like denosumab or fluoride (teriparatide) and alendronate, risedronate and placebo controls.[10–12]

Types of outcome measures

The primary outcome will be the incidence of fracture including hip, vertebral and other kinds of fractures. The secondary outcome will include percentage changes on the bone mineral density and incidence of re-fracture. For evaluating safety of BP, rate of adverse events including cancer, cardiovascular disease, death and osteonecrosis of the jaw will be included.[13]

Box 1 Search strategy for Medline (via PubMed)

#1 steroid[MeSH terms]
#2 steroid*[TIAB]
#3 glucocorticoid*[TIAB]
#4 #1 OR #2 OR #3
#5 osteoporosis[MeSH terms]
#6 osteoporos*[TIAB]
#7 osteoporos*[TIAB]
#8 osteopenia[TIAB]
#9 "Bone loss"
#10 "bone losses"
#11 #5 OR #6 OR #7 OR #8 OR #9 OR #10
#12 #4 AND #11
#13 biphosphonate [TIAB]
#14 diphosphonate [TIAB]
#15 alendronate [TIAB]
#16 risedronate [TIAB]
#17 ibandronate [TIAB]
18 pamidronate [TIAB]
#19 zoledronate [TIAB]
#20 #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#21 #12 AND #20
#22 limit #21 to human

Search strategies for the identification of studies

Electronic searches

The following electronic databases will be searched from inception to December 2021: PubMed, EMBASE and the Cochrane Central Register of Controlled Trials. The specific search strategies (for example, PubMed) are listed in box 1. Other databases' strategies are listed in online supplemental file 1. For making precise search strategies, we look up several reviews of osteoporosis.[14–16] Furthermore, there will be no language restrictions.

We will make relative modifications in accordance with the requirements, and an equivalent translation of the search terms will be adopted to ensure that similar search terms are used in all databases. If additional information is needed from the identified studies, we will contact the corresponding authors.

Search for other resources

A manual search will also be performed to search the reference lists of the relevant articles. Clinical trial registries (ClinicalTrials.gov, ICTRP in WHO), conference presentations and expert contacts will also be searched.

Data collection and analysis

Study selections

Potentially relevant papers will be assessed for eligibility by screening the title and abstract, and then they will be finally selected after full-text review on the basis of the

predefined selection criteria. The literature search and selection process will be initially performed by one review author and subsequently checked by the other author. Disagreements will be resolved by discussion between the two authors.

All studies, identified by both electronic and manual searches, will be uploaded to Covidence (https://www.covidence.org/), and the reasons for excluding studies will be recorded and shown in a PRISMA flow chart.

Data extraction and management

We will extract the data on study information—publication year, language, sample size and study design characteristics—using a predetermined standard data extraction form. We will also extract characteristics and incidence of fractures and influencing factors, such as gender, age, medications and other treatments associated with fractures. Therapeutic modalities will observed like kinds of drugs, dosage and frequency outcomes. We will perform a sensitivity analysis to verify the robustness of the results. This will be done by assessing the impact of sample size, high risk of bias (RoB), missing data and selected models. Following the analyses, if the quality of the studies is judged to be low, these studies will be removed to ensure the robustness of the results.

Assessment of RoB and quality

The Cochrane Collaboration tool for assessing RoB 2 will be used to assess RoB for RCTs.[17] It contains six domains: selection bias (adequate sequence generation); selection bias (allocation concealment); performance bias (blinding of participants); detection bias (blinding of outcome assessors); attrition bias (clear account of dropouts and exclusions); and reporting bias (selective outcome reporting). The Cochrane Risk Of Bias In Non-Randomized Studies–of Interventions will be used to assess RoB for using quasi-RCT, controlled trials and cohort studies.[18] Two reviewers (HC and B-HJ) will assess RoB of included studies independently. Disagreements will be resolved through discussion and, if not resolved, arbitration by other authors (B-HJ and JA).

Measurement of treatment effect

For dichotomy data such as the incidence of fractures between the two groups, the pooled results are presented as risk ratios with 95% CIs. For continuous data, the pooled results are presented as mean differences (MDs) or standardised MDs with 95% CIs.

Managing missing data

We will contact the associated author and obtain essential information if there are missing, inadequate or confusing data. If the information cannot be acquired, only the remaining accessible information, which will be discussed, will be analysed.

Assessment of heterogeneity

To assess statistical heterogeneity, we will use the I^2 test. If I^2 is larger than 50%, statistical heterogeneity will be considered.[19] The heterogeneity levels in the collected literature will be analysed (large if $I^2>50\%$; medium if $25\%<I^2\geq50\%$; and small if $0\leq I^2\geq25\%$). Fixed-effects model analysis will be carried out if there is no evidence of heterogeneity. However, random-effects model analysis will be performed if the heterogeneity has been eliminated.

Data synthesis

The Review Manager program (V.5.4; Copenhagen: The Nordic Cochrane Center. The Cochrane Collaboration, 2014) and a random-effects model will be used for statistical analysis. The studies will be synthesised according to the type of intervention and/or as follows:

1. Comparison of the fracture rate of patients with GIOP according to the type of BP and controls.
2. Rate of recurrence of fractures in patients with GIOP who have experienced previous fractures.

If the meta-analysis includes more than 10 studies, we will assess publication bias using Egger's test and visualise the results with a funnel plot.[20] If meta-analysis is not possible, it will be synthesised qualitatively, and this will be done according to the study design, the characteristics of the guidelines and the outcomes.

Subgroup analysis and sensitive analysis

We will perform a subgroup analysis to compare re-fracture rate on the patients with GIOP who experience previous fractures. This will be done by assessing the impact of sample size, high RoB, missing data and selected models. Following the analyses, if the quality of the studies is judged to be low, these studies will be removed to ensure the robustness of the results.

Patient and public involvement

The design of this review protocol did not involve patients.

DISCUSSION

Long-term usage of GCs results in a loss of bone mass and a higher risk of fracture. Furthermore, the most common cause of secondary osteoporosis is GIOP. However, to our knowledge, there has been no systematic review comparing the effectiveness of BP in GIOP. Therefore, we developed a protocol to compare the effectiveness of BP in GIOP systematically. All actions in this review will be carried out following the Cochrane Handbook V.5.2.0 to provide convincing evidence and better clinical practice guidelines.

ETHICS AND DISSEMINATION

This meta-analysis was based on published data, hence no patient or public information will be included. After complete analysis, the article will be submitted for publication in a peer-reviewed journal. Results of this study may impact stakeholders such as clinical physicians, patients and policymakers in making better decisions. To disseminate the findings of this research, we will also use seminars, social media and conferences.

Author affiliations
[1]Daecheong Public Health Subcenter, Ongjin Public Health Center, Incheon, Korea (the Republic of)
[2]Department of Preventive Medicine, Kyung Hee University College of Korean Medicine, Dongdaemun-gu, Seoul, Korea (the Republic of)
[3]Department of Health Convergence, Ewha Womans University, Seoul, Korea (the Republic of)
[4]National Cancer Control Institute, National Cancer Center, Goyang, Korea (the Republic of)

Contributors Conceptualisation—JA and B-HJ. Methodology—GK, SB, HL and SN. Writing (original draft)—HC. Writing (review and editing)—B-HJ and JA.

Funding Ministry of Health & Welfare, Republic of Korea; Patient-Centered Clinical Research Coordinating Center (grant number: HC19C0047).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Hongmin Chu http://orcid.org/0000-0003-0171-0234
Bo-Hyoung Jang http://orcid.org/0000-0002-2141-3483
GaYoon Kim http://orcid.org/0000-0003-3058-7300
Seowoo Bae http://orcid.org/0000-0002-8123-388X
Hyeju Lee http://orcid.org/0000-0003-3354-2802
Seonghee Nam http://orcid.org/0000-0002-9392-5699
Jeonghoon Ahn http://orcid.org/0000-0002-0177-0192

REFERENCES

1 Briot K, Roux C. Glucocorticoid-Induced osteoporosis. *RMD Open* 2015;1:e000014.
2 Rizzoli R, Adachi JD, Cooper C, *et al*. Management of glucocorticoid-induced osteoporosis. *Calcif Tissue Int* 2012;91:225–43.
3 Canalis E, Mazziotti G, Giustina A, *et al*. Glucocorticoid-Induced osteoporosis: pathophysiology and therapy. *Osteoporos Int* 2007;18:1319–28.
4 Koh JW, Kim J, Cho H, *et al*. Effects of systemic glucocorticoid use on fracture risk: a population-based study. *Endocrinol Metab* 2020;35:562–70.
5 Weinstein RS. Is long-term glucocorticoid therapy associated with a high prevalence of asymptomatic vertebral fractures? *Nat Clin Pract Endocrinol Metab* 2007;3:86–7.
6 Van Staa TP, Laan RF, Barton IP, *et al*. Bone density threshold and other predictors of vertebral fracture in patients receiving oral glucocorticoid therapy. *Arthritis Rheum* 2003;48:3224–9.
7 Dong S-L, Jiao Y, Yang H-L. Effectiveness of bisphosphonates on bone mineral density in osteopenic postmenopausal women: a systematic review and network meta-analysis of randomized controlled trials. *Medicine* 2021;100:e26715.
8 Reginster J-Y, Burlet N, Close P, *et al*. Injectable bisphosphonates for the treatment of osteoporosis. *Womens Health* 2007;3:719–23.
9 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *PLoS Med* 2021;18:e1003583.
10 Deeks ED. Denosumab: a review in postmenopausal osteoporosis. *Drugs Aging* 2018;35:163–73.
11 Bodenner D, Redman C, Riggs A. Teriparatide in the management of osteoporosis. *Clin Interv Aging* 2008;2:499–507.
12 Ding L, Hu J, Wang D, *et al*. Efficacy and safety of first- and second-line drugs to prevent glucocorticoid-induced fractures. *J Clin Endocrinol Metab* 2020;105:600–13.
13 Lin S-Y, Hung M-C, Chang S-F, *et al*. Efficacy and safety of postmenopausal osteoporosis treatments: a systematic review and network meta-analysis of randomized controlled trials. *J Clin Med* 2021;10:3043.
14 Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. *The Lancet* 2002;359:1929–36.
15 Lee T-H, Song Y-J, Kim H, *et al*. Intervention thresholds for treatment in patients with glucocorticoid-induced osteoporosis: systematic review of guidelines. *J Bone Metab* 2020;27:247–59.
16 Marques A, Ferreira RJO, Santos E, *et al*. The accuracy of osteoporotic fracture risk prediction tools: a systematic review and meta-analysis. *Ann Rheum Dis* 2015;74:1958–67.
17 Higgins JPT, Altman DG, Gøtzsche PC, *et al*. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
18 Sterne JA, Hernán MA, Reeves BC, *et al*. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919.
19 Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, *et al*. Assessing heterogeneity in meta-analysis: Q statistic or I^2 index? *Psychol Methods* 2006;11:193–206.
20 Egger M, Davey Smith G, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.