BMJ Open

Bisphosphonate in the effectiveness of Glucocorticoid-induced osteoporosis (GIOP) and for the prevention of re-fracture: a protocol for systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-062537
Article Type:	Protocol
Date Submitted by the Author:	04-Mar-2022
Complete List of Authors:	Chu, Hongmin; Ongjin public healthcenter, Daecheong Public Health Subcenter Jang, Bo-Hyoung; Kyung Hee University College of Korean Medicine, Department of Preventive Medicine Kim, GaYoon; Ewha Womans University, Department of Health Convergence Bae, Seowoo; National Cancer Center, National Cancer Control Institute Lee, Hyeju; Ewha Womans University, Nam, Seonghee; Ewha Womans University, Ahn, Jeonghoon; Ewha Womans University, Department of Health Convergence
Keywords:	Bone diseases < ORTHOPAEDIC & TRAUMA SURGERY, CLINICAL PHYSIOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Bisphosphonate in the effectiveness of Glucocorticoid-induced osteoporosis (GIOP) and for the prevention of re-fracture: a protocol for systematic review and meta-analysis

Hongmin Chu, KMD, Ph.D[1,a], Bo-Hyoung Jang KMD, MPH, Ph.D[2,a], GaYoon Kim[3], Seowoo Bae, M.A.[4], Hye Ju Lee, B.A.[3], Seonghee Nam, B.A.[3], Jeonghoon Ahn Ph.D.[3*]

1. Daecheong Public Health Subcenter, Ongjin-gun, Incheon, Korea
2. Department of Preventive Medicine, College of Korean Medicine, Kyung Hee University, Seoul, Republic of Korea
3. Department of Health Convergence, Ewha Womans University, Seoul, Korea
4. National Cancer Control Institute, National Cancer Center, Goyang, Korea

a. Two authors are contributed equally.

*Correspondence: Jeonghoon Ahn, Department of Health Convergence, Ewha Womans University, 52, Ewhayeodae-gil, Seodaemun-gu, Seoul, Republic of Korea (e-mail: ahnjeonghoon@ewha.ac.kr).

Bisphosphonate in the effectiveness of Glucocorticoid-induced osteoporosis (GIOP) and for the prevention of re-fracture: a protocol for systematic review and meta-analysis

Abstract

Introduction: Long-term usage of Glucocorticoid 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, the analysis on the BP`s effect of 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 bisphosphonate in GIOP as the basis for reliable clinical strategies for patients.

Methods and Analysis: Electronic databases searches of the PubMed, Cochrane Library, EMBASE will be performed. Randomized controlled trials (RCTs), quasi-RCTs, controlled trials, and cohort studies evaluating effectiveness of BP to the GIOP patients 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. Assessing risk of bias for included studies is assessed 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 refracture rate on the GIOP patients who experience previous fracture history.

Ethics and dissemination: Formal ethical approval is not required, and findings will be published in a peer-reviewed journal

Protocol registry number of online registry: This study protocol was registered in open Science framework (OSF) (Registration DOI: 10.17605/OSF.IO/GF9WB)

URL of the online registry: https://osf.io/gf9wb

Keywords: FRAX, BMD, GIOP, osteoporosis

1. Introduction

Glucocorticoid-induced osteoporosis (GIOP) is a serious side effect of glucocorticoids (GC), 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 glucocorticoid therapy.[3] The duration and dose of GCs both increase the risk of fracture.[1,4] The incidence of fractures of 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 three 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 to oral drugs, so it is widely used.[8]

In the previous study, there is a study comparing the effects of BP on osteopenic postmenopausal women.[7] However, systematic reviews and meta-analysis according to the type of BP were not performed for GIOP patients. 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 analyzed together. Moreover, in the case of past fractures among GIOP patients, the analysis on the BP`s effect of 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 bisphosphonate in GIOP patients.

2. Methods

2.1 Study registration

The protocol of this study complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA) guidelines.[9] This systematic review protocol was registered in open Science framework (OSF) (Registration DOI: 10.17605/OSF.IO/GF9WB; URL: https://osf.io/gf9wb)

2.2 Eligible criteria for study selection

2.2.1 Types of studies

Peer-reviewed and published experimental randomized controlled trials (RCTs), quasi-randomized controlled trials, controlled trials, observational study indicating will be included in the search. Other reference or studies of related GIOP and Fracture will be checked and hand-searched for prospective inclusion.

2.2.2 Types of participants

Eligible participants will be GIOP patients 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, the severity of symptoms, the length of the condition, or the clinical environment.

2.2.3 Types of interventions and comparators

We will include treatment in which osteoporosis was diagnosed based on using FRAX or

BMD. The comparison will be conducted between the Bisphosphonate treatments and other pharmacological interventions such as denosumab.[10] Placebo or non-treatments group control will also be included.

2.2.4 Types of outcome measures

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.

2.3 Search strategies for the identification of studies

2.3.1 Electronic searches

The following electronic databases will be searched from inception to 2021: PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL). The specific search strategies (for example, PubMed) are listed in Table 1. For making precise searching strategies, we look up several reviews of osteoporosis.[11–13]

Table 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 ibandronate [TIAB]

#20 zoledronate [TIAB]

#21 #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20

#22 #12 AND #21

#23 limit #22 to human

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.

2.3.2 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 World Health Organization), conference presentations, and expert contacts will also be searched.

2.4 Data collection and analysis

2.4.1 Study selections

Potentially relevant papers will be assessed for eligibility by screening the title and abstract, and then they were finally selected after full-text review on the basis of the predefined selection criteria. The literature searching and selection process was initially performed by 1 review author and subsequently checked by the other author. Disagreements were resolved by discussion between the 2 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 flowchart.

2.4.2 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 that incidence of fractures and influence 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.

2.4.3 Assessment of risk of bias and quality

The Cochrane Collaboration tool for assessing risk of bias 2 will be used to assess risk of bias for RCTs.[14] It contains six domains: selection bias (adequate sequence generation and

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 (ROBINS-I) will be used to assess risk of bias for using quasi-RCT, controlled trials, cohort studies.[15] Two reviewers (CHM and JBH) will assess RoB of included studies independently. Disagreements will be resolved through discussion and, if not resolved, arbitration by other authors (JBH and AJH).

2.4.4 Measurement of treatment effect

For dichotomy data such as the incidence of fractures between the two groups, the pooled results are presented as risk ratio (RR) with 95% CIs. For continuous data, the pooled results are presented as mean differences (MDs) or standardized MDs (SMDs) with 95% confidence intervals (CIs).

2.4.5 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 analyzed.

2.4.6 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, so meta-analysis will not be conducted.[16]

2.4.7 Data synthesis

The Review Manager program (ver. 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 synthesized according to the type of intervention and/or as follows:

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

The heterogeneity levels in the collected literature will be analyzed. If enough studies are available to examine the causes of heterogeneity and its criteria, the categories listed below will be assessed. If the meta-analysis includes more than 10 studies, we will assess publication bias using Egger's test and visualize the results with a funnel plot.[17] If meta-analysis is not possible, it will be synthesized qualitatively, and this will be done according to the study design, the characteristics of the guidelines, and the outcome.

2.4.8 Subgroup analysis and sensitive analysis

We will perform a subgroup analysis to compare refracture rate on the GIOP patients who experience previous fracture history. 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.

2.5. Ethics and dissemination

Because all of the data used in this study cited from published journals, ethical approval is not required.

2.6. Patient and public involvement

This meta-analysis was based on published data, hence no patient or public information will be included.

3. 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 glucocorticoid-induced osteoporosis (GIOP). However, to our knowledge, there has been no systematic review comparing the effectiveness of BP on GIOP. Therefore, we developed a protocol to compare the effectiveness of BP on GIOP systematically. All actions in this review will be carried out following Cochrane Handbook 5.2.0 to provide convincing evidence and better guide clinic practice.

Conflict of interest statement

The authors have no conflict of interest to disclose.

Author contributions

Conceptualization: Jeonghoon Ahn, Bo-Hyoung Jang

Methodology: GaYoon Kim, Seowoo Bae, Hye Ju Lee, Seonghee Nam

Writing – original draft: Hongmin Chu

Writing – review & editing: Bo-hyung Jang, Jeonghoon Ahn

Data sharing

All data generated or analyzed during this study will be published in the peer-review article. Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Funding:

This research was supported by a grant of Patient-Centered Clinical Research Coordinating Center (PACEN) funded by the Ministry of Health & Welfare, Republic of Korea (grant number : HC19C0047). This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Abbreviations:

GIOP = Glucocorticoid-induced osteoporosis, GC = glucocorticoids, BP = Bisphosphonate, FRAX = Fracture Risk Assessment Tool, BMD = Bone Mineral Densitometer, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol, RCTs = randomized controlled trials, RoB = risk of bias

Reference

1. Briot K, Roux C. Glucocorticoid-induced osteoporosis. *RMD Open*. 2015;1(1):e000014-e000014. doi:10.1136/rmdopen-2014-000014

2. Rizzoli R, Adachi JD, Cooper C, et al. Management of Glucocorticoid-Induced Osteoporosis. *Calcif Tissue Int*. 2012;91(4):225-243. doi:10.1007/s00223-012-9630-5

3. Canalis E, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. *Osteoporos Int*. 2007;18(10):1319-1328. doi:10.1007/s00198-007-0394-0

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(3):562-570. doi:10.3803/EnM.2020.659

5. Weinstein RS. Is long-term glucocorticoid therapy associated with a high prevalence of asymptomatic vertebral fractures? *Nat Clin Pract Endocrinol Metab*. 2007;3(2):86-87. doi:10.1038/ncpendmet0372

6. Van Staa TP, Laan RF, Barton IP, Cohen S, Reid DM, Cooper C. Bone density threshold and other predictors of vertebral fracture in patients receiving oral glucocorticoid therapy. *Arthritis Rheum*. 2003;48(11):3224-3229. doi:10.1002/art.11283

7. Dong S li, Jiao Y, Yang H liang. Effectiveness of bisphosphonates on bone mineral density in osteopenic postmenopausal women: A systematic review and network meta-analysis of randomized controlled trials. *Medicine (Baltimore)*. 2021;100(31):e26715. doi:10.1097/MD.0000000000026715

8. Reginster JY, Burlet N, Close P, Bruyere O. Injectable Bisphosphonates for the Treatment of Osteoporosis. *Womens Health*. 2007;3(6):719-723. doi:10.2217/17455057.3.6.719

9. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLOS Med*. 2021;18(3):e1003583. doi:10.1371/journal.pmed.1003583

10. Deeks ED. Denosumab: A Review in Postmenopausal Osteoporosis. *Drugs Aging*. 2018;35(2):163-173. doi:10.1007/s40266-018-0525-7

11. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. *THE LANCET*. 2002;359:8.

12. Lee TH, Song YJ, Kim H, Sung YK, Cho SK. Intervention Thresholds for Treatment in Patients with Glucocorticoid-Induced Osteoporosis: Systematic Review of Guidelines. *J Bone Metab*. 2020;27(4):247-259. doi:10.11005/jbm.2020.27.4.247

13. Marques A, Ferreira RJO, Santos E, Loza E, Carmona L, da Silva JAP. The accuracy of osteoporotic fracture risk prediction tools: a systematic review and meta-analysis. *Ann Rheum Dis*. 2015;74(11):1958-1967. doi:10.1136/annrheumdis-2015-207907

14. Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343(oct18 2):d5928-d5928. doi:10.1136/bmj.d5928

15. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. Published online October 12, 2016:i4919. doi:10.1136/bmj.i4919

16. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I^2 index? *Psychol Methods*. 2006;11(2):193-206. doi:10.1037/1082-989X.11.2.193

17. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634. doi:10.1136/bmj.315.7109.629

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	1
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Title page
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	10
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	10
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	2
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5,6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5,6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Table 1

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5,6,7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7,8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8,9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	8,9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8,9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8,9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	N/A

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Bisphosphonate in the effectiveness of Glucocorticoid-induced osteoporosis (GIOP) and for the prevention of re-fracture: a protocol for systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-062537.R1
Article Type:	Protocol
Date Submitted by the Author:	24-Jul-2022
Complete List of Authors:	Chu, Hongmin; Ongjin public healthcenter, Daecheong Public Health Subcenter Jang, Bo-Hyoung; Kyung Hee University College of Korean Medicine, Department of Preventive Medicine Kim, GaYoon; Ewha Womans University, Department of Health Convergence Bae, Seowoo; National Cancer Center, National Cancer Control Institute Lee, Hyeju; Ewha Womans University, Nam, Seonghee; Ewha Womans University, Ahn, Jeonghoon; Ewha Womans University, Department of Health Convergence
Primary Subject Heading:	Medical management
Secondary Subject Heading:	Evidence based practice
Keywords:	Bone diseases < ORTHOPAEDIC & TRAUMA SURGERY, CLINICAL PHYSIOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Bisphosphonate in the effectiveness of Glucocorticoid-induced osteoporosis (GIOP) and for the prevention of re-fracture: a protocol for systematic review and meta-analysis

Hongmin Chu, KMD, Ph.D[1,a], Bo-Hyoung Jang KMD, MPH, Ph.D[2,a], GaYoon Kim[3], Seowoo Bae, M.A.[4], Hyeju Lee, B.A.[3], Seonghee Nam, B.A.[3], Jeonghoon Ahn Ph.D.[3*]

1. Daecheong Public Health Subcenter, Ongjin-gun, Incheon, Korea
2. Department of Preventive Medicine, College of Korean Medicine, Kyung Hee University, Seoul, Republic of Korea
3. Department of Health Convergence, Ewha Womans University, Seoul, Korea
4. National Cancer Control Institute, National Cancer Center, Goyang, Korea

a. Two authors are contributed equally.

*Correspondence: Jeonghoon Ahn, Department of Health Convergence, Ewha Womans University, 52, Ewhayeodae-gil, Seodaemun-gu, Seoul, Republic of Korea (e-mail: ahnjeonghoon@ewha.ac.kr).

Bisphosphonate in the effectiveness of Glucocorticoid-induced osteoporosis (GIOP) and for the prevention of re-fracture: a protocol for systematic review and meta-analysis

Abstract

Background: Long-term usage of Glucocorticoid 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, the analysis on the BP`s effect of 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 bisphosphonate in GIOP as the basis for reliable clinical strategies for patients.

Methods: Electronic databases searches of the PubMed, Cochrane Library, EMBASE will be performed. Randomized controlled trials (RCTs), quasi-RCTs, controlled trials, and cohort studies evaluating effectiveness of BP to the GIOP patients 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 assessed 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 refracture rate on the GIOP patients who experience previous fracture history.

Results: This study result will provide evidence for the effectiveness of the BP for the prevention of refractrue on the GIOP

Conclusion: This study will provide fundamental data for prospective research on the application of BP in GIOP patients

Protocol registry number of online registry: This study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (Registration ID: CRD42022343787)

URL of the registry: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=343787

Abbreviations: GIOP = Glucocorticoid-induced osteoporosis, GC = glucocorticoids, BP = Bisphosphonate, FRAX = Fracture Risk Assessment Tool, BMD = Bone Mineral Densitometer, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol, RCTs = randomized controlled trials, RoB = risk of bias

Keywords: FRAX, BMD, GIOP, osteoporosis

Strengths and limitations of this study

This systematic review will follow the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) for ensuring transparency and rigor of review.

► This protocol will be the first to assess the treatment effect of BP in GIOP patients.

► In particular, since there are few papers based on fracture rate in RCT, we intend to include observational studies.

► Through this study, it is possible to suggest the direction of future clinical research and help design.

1. Introduction

Glucocorticoid-induced osteoporosis (GIOP) is a serious side effect of glucocorticoids (GC), 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 glucocorticoid therapy.[3] The duration and dose of GCs both increase the risk of fracture.[1,4] The incidence of fractures of 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 three 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 to oral drugs, so it is widely used.[8]

In the previous study, there is a study comparing the effects of BP on osteopenic postmenopausal women.[7] However, systematic reviews and meta-analysis according to the type of BP were not performed for GIOP patients. 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 analyzed together. Moreover, in the case of past fractures among GIOP patients, the analysis on the BP`s effect of 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 bisphosphonate in GIOP patients.

2. Methods

2.1 Study registration

The protocol of this study complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA) guidelines.[9] This systematic review protocol was registered in open 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)

2.2 Eligible criteria for study selection

2.2.1 Types of studies

Peer-reviewed and published experimental randomized controlled trials (RCTs), quasi-randomized controlled trials, controlled trials, observational study indicating will be included in the search. Other reference or studies of related GIOP and Fracture will be checked and hand-searched for prospective inclusion.

2.2.2 Types of participants

Eligible participants will be GIOP patients 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, the severity of symptoms, the length of the condition, or the clinical environment.

2.2.3 Types of interventions and comparators

We will include treatment in which osteoporosis was diagnosed based on using FRAX or BMD. 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 Bisphosphonate treatments and other pharmacological interventions using for treatment GIOP such as selective estrogen receptor modulator (SERM) like denosumab or fluoride (teriparatide) and alendronate, risedronate and placebo controls.[10–12]

2.2.4 Types of outcome measures

The primary outcome will be the incidence of fracture including hip, vertebral, and other kinds of all 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, osteonecrosis of the jaw.[13]

2.3 Search strategies for the identification of studies

2.3.1 Electronic searches

The following electronic databases will be searched from inception to 2021: PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL). The specific search strategies (for example, PubMed) are listed in Table 1. For making precise searching strategies, we look up several reviews of osteoporosis.[14–16]

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.

2.3.2 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 World Health Organization), conference presentations, and expert contacts will also be searched.

2.4 Data collection and analysis

2.4.1 Study selections

Potentially relevant papers will be assessed for eligibility by screening the title and abstract, and then they were finally selected after full-text review on the basis of the predefined selection criteria. The literature searching and selection process was initially performed by 1 review author and subsequently checked by the other author. Disagreements were resolved by discussion between the 2 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 flowchart.

2.4.2 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 that incidence of fractures and influence 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.

2.4.3 Assessment of risk of bias and quality

The Cochrane Collaboration tool for assessing risk of bias 2 will be used to assess risk of bias for RCTs.[17] It contains six domains: selection bias (adequate sequence generation and 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 (ROBINS-I) will be used to assess risk of bias for using quasi-RCT, controlled trials, cohort studies.[18] Two reviewers (CHM and JBH) will assess RoB of included studies independently. Disagreements will be resolved through discussion and, if not resolved, arbitration by other authors (JBH and AJH).

2.4.4 Measurement of treatment effect

For dichotomy data such as the incidence of fractures between the two groups, the pooled results are presented as risk ratio (RR) with 95% CIs. For continuous data, the pooled results are presented as mean differences (MDs) or standardized MDs (SMDs) with 95% confidence intervals (CIs).

2.4.5 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 analyzed.

2.4.6 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 analyzed (large if $I^2 > 50\%$; medium if $25\% < I^2 \geq 50\%$; and small if $0 \leq I^2 \geq 25\%$). Fixed-

effect model analysis will be carried out if there is no evidence of heterogeneity. However, random-effects model analysis will be performed if the heterogeneity have been eliminated.

2.4.7 Data synthesis

The Review Manager program (ver. 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 synthesized according to the type of intervention and/or as follows:

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

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

2.4.8 Subgroup analysis and sensitive analysis

We will perform a subgroup analysis to compare re- fracture rate on the GIOP patients who experience previous fracture history. This will be done by assessing the impact of sample size, high Risk of Bias, 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.

2.5. Ethics and dissemination

Because all of the data used in this study cited from published journals, ethical approval is

not required.

2.6. Patient and public involvement

This meta-analysis was based on published data, hence no patient or public information will be included.

3. 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 glucocorticoid-induced osteoporosis (GIOP). However, to our knowledge, there has been no systematic review comparing the effectiveness of BP on GIOP. Therefore, we developed a protocol to compare the effectiveness of BP on GIOP systematically. All actions in this review will be carried out following Cochrane Handbook 5.2.0 to provide convincing evidence and better guide clinic practice.

Ethics and dissemination

This is protocol for systematic review and institutional review board approval and consent of the subject are not required.

Conflict of interest statement

No, there are no competing interests for any author

Author contributions

Conceptualization: Jeonghoon Ahn, Bo-Hyoung Jang

Methodology: GaYoon Kim, Seowoo Bae, Hyeju Lee, Seonghee Nam

Writing – original draft: Hongmin Chu

Writing – review & editing: Bo-hyung Jang, Jeonghoon Ahn

Data sharing

Not applicable

Funding:

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

Reference

1. Briot K, Roux C. Glucocorticoid-induced osteoporosis. *RMD Open*. 2015;1(1):e000014-e000014. doi:10.1136/rmdopen-2014-000014

2. Rizzoli R, Adachi JD, Cooper C, et al. Management of Glucocorticoid-Induced Osteoporosis. *Calcif Tissue Int*. 2012;91(4):225-243. doi:10.1007/s00223-012-9630-5

3. Canalis E, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. *Osteoporos Int*. 2007;18(10):1319-1328. doi:10.1007/s00198-007-0394-0

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(3):562-570. doi:10.3803/EnM.2020.659

5. Weinstein RS. Is long-term glucocorticoid therapy associated with a high prevalence of asymptomatic vertebral fractures? *Nat Clin Pract Endocrinol Metab*. 2007;3(2):86-87. doi:10.1038/ncpendmet0372

6. Van Staa TP, Laan RF, Barton IP, Cohen S, Reid DM, Cooper C. Bone density threshold and other predictors of vertebral fracture in patients receiving oral glucocorticoid therapy. *Arthritis Rheum*. 2003;48(11):3224-3229. doi:10.1002/art.11283

7. Dong S li, Jiao Y, Yang H liang. Effectiveness of bisphosphonates on bone mineral density in osteopenic postmenopausal women: A systematic review and network meta-analysis of randomized controlled trials. *Medicine (Baltimore)*. 2021;100(31):e26715. doi:10.1097/MD.0000000000026715

8. Reginster JY, Burlet N, Close P, Bruyere O. Injectable Bisphosphonates for the Treatment of Osteoporosis. *Womens Health*. 2007;3(6):719-723. doi:10.2217/17455057.3.6.719

9. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLOS Med*. 2021;18(3):e1003583. doi:10.1371/journal.pmed.1003583

10. Deeks ED. Denosumab: A Review in Postmenopausal Osteoporosis. *Drugs Aging*. 2018;35(2):163-173. doi:10.1007/s40266-018-0525-7

11. Riggs. Teriparatide in the management of osteoporosis. *Clin Interv Aging*. 2008;Volume 2:499-507. doi:10.2147/CIA.S241

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(3):600-613. doi:10.1210/clinem/dgz023

13. Lin SY, Hung MC, Chang SF, Tsuang FY, Chang JZC, Sun JS. Efficacy and Safety of Postmenopausal Osteoporosis Treatments: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials. *J Clin Med*. 2021;10(14):3043. doi:10.3390/jcm10143043

14. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. *THE LANCET*. 2002;359:8.

15. Lee TH, Song YJ, Kim H, Sung YK, Cho SK. Intervention Thresholds for Treatment in Patients with Glucocorticoid-Induced Osteoporosis: Systematic Review of Guidelines. *J Bone Metab*. 2020;27(4):247-259. doi:10.11005/jbm.2020.27.4.247

16. Marques A, Ferreira RJO, Santos E, Loza E, Carmona L, da Silva JAP. The accuracy of osteoporotic fracture risk prediction tools: a systematic review and meta-analysis. *Ann Rheum Dis*. 2015;74(11):1958-1967. doi:10.1136/annrheumdis-2015-207907

17. Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343(oct18 2):d5928-d5928. doi:10.1136/bmj.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*. Published online October 12, 2016:i4919. doi:10.1136/bmj.i4919

19. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I^2 index? *Psychol Methods*. 2006;11(2):193-206. doi:10.1037/1082-989X.11.2.193

20. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634. doi:10.1136/bmj.315.7109.629

Table 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 ibandronate [TIAB]
#20 zoledronate [TIAB]
#21 #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20
#22 #12 AND #21
#23 limit #22 to human

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	1
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Title page
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	10
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	10
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	2
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5,6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5,6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Table 1

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5,6,7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7,8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8,9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	8,9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8,9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8,9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	N/A

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-062537.R2
Article Type:	Protocol
Date Submitted by the Author:	24-Aug-2022
Complete List of Authors:	Chu, Hongmin; Ongjin public healthcenter, Daecheong Public Health Subcenter Jang, Bo-Hyoung; Kyung Hee University College of Korean Medicine, Department of Preventive Medicine Kim, GaYoon; Ewha Womans University, Department of Health Convergence Bae, Seowoo; National Cancer Center, National Cancer Control Institute Lee, Hyeju; Ewha Womans University, Nam, Seonghee; Ewha Womans University, Ahn, Jeonghoon; Ewha Womans University, Department of Health Convergence
Primary Subject Heading:	Medical management
Secondary Subject Heading:	Evidence based practice
Keywords:	Bone diseases < ORTHOPAEDIC & TRAUMA SURGERY, CLINICAL PHYSIOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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, KMD, Ph.D[1,a], Bo-Hyoung Jang KMD, MPH, Ph.D[2,a], GaYoon Kim[3], Seowoo Bae, M.A.[4], Hyeju Lee, B.A.[3], Seonghee Nam, B.A.[3], Jeonghoon Ahn Ph.D.[3*]

1. Daecheong Public Health Subcenter, Ongjin-gun, Incheon, Korea
2. Department of Preventive Medicine, College of Korean Medicine, Kyung Hee University, Seoul, Republic of Korea
3. Department of Health Convergence, Ewha Womans University, Seoul, Korea
4. National Cancer Control Institute, National Cancer Center, Goyang, Korea

a. Two authors are contributed equally.

*Correspondence: Jeonghoon Ahn, Department of Health Convergence, Ewha Womans University, 52, Ewhayeodae-gil, Seodaemun-gu, Seoul, Republic of Korea (e-mail: ahnjeonghoon@ewha.ac.kr).

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

Abstract

Background: Long-term usage of Glucocorticoid 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, the analysis on the BP`s effect of 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 bisphosphonate in GIOP as the basis for reliable clinical strategies for patients.

Methods and analysis: We will search electronic databases searches of the PubMed, Cochrane Library, EMBASE using a comprehensive search strategy in Dec 2021 with no language restriction. Randomized controlled trials (RCTs), quasi-RCTs, controlled trials, and cohort studies evaluating effectiveness of BP to the GIOP patients 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 assessed 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 refracture rate on the GIOP patients who experience previous fracture history. This study result will provide evidence for the effectiveness of the BP for the prevention of refractrue on the 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 ID: CRD42022343787

Abbreviations: GIOP = Glucocorticoid-induced osteoporosis, GC = glucocorticoids, BP = Bisphosphonate, FRAX = Fracture Risk Assessment Tool, BMD = Bone Mineral Densitometer, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol, RCTs = randomized

controlled trials, RoB = risk of bias

Keywords: FRAX, BMD, GIOP, osteoporosis

Strengths and limitations of this study

►This systematic review will follow the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) for ensuring transparency and rigor of review.

► In particular, since there are few papers based on fracture rate in RCT, we intend to include observational studies.

► There is a limitation in that there is a possibility that research may exist other than the database that was the subject of this study.

1. Introduction

Glucocorticoid-induced osteoporosis (GIOP) is a serious side effect of glucocorticoids (GC), 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 glucocorticoid therapy.[3] The duration and dose of GCs both increase the risk of fracture.[1,4] The incidence of fractures of 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 three 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 to oral drugs, so it is widely used.[8]

In the previous study, there is a study comparing the effects of BP on osteopenic postmenopausal women.[7] However, systematic reviews and meta-analysis according to the type of BP were not performed for GIOP patients. 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 analyzed together. Moreover, in the case of past fractures among GIOP patients, the analysis on the BP`s effect of 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 bisphosphonate in GIOP patients.

2. Methods

2.1 Study registration

The protocol of this study complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA) guidelines.[9] This systematic review protocol was registered in open 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)

2.2 Eligible criteria for study selection

2.2.1 Types of studies

Peer-reviewed and published experimental randomized controlled trials (RCTs), quasi-randomized controlled trials, controlled trials, observational study indicating will be included in the search. Other reference or studies of related GIOP and Fracture will be checked and hand-searched for prospective inclusion.

2.2.2 Types of participants

Eligible participants will be GIOP patients 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, the severity of symptoms, the length of the condition, or the clinical environment.

2.2.3 Types of interventions and comparators

We will include treatment in which osteoporosis was diagnosed based on using FRAX or BMD. 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 Bisphosphonate treatments and other pharmacological interventions using for treatment GIOP such as selective estrogen receptor modulator (SERM) like denosumab or fluoride (teriparatide) and alendronate, risedronate and placebo controls.[10–12]

2.2.4 Types of outcome measures

The primary outcome will be the incidence of fracture including hip, vertebral, and other kinds of all 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, osteonecrosis of the jaw.[13]

2.3 Search strategies for the identification of studies

2.3.1 Electronic searches

The following electronic databases will be searched from inception to December 2021: PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL). The specific search strategies (for example, PubMed) are listed in Table 1. Other database`s strategies are listed in Supplement 1. For making precise searching 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.

2.3.2 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 World Health Organization), conference presentations, and expert contacts will also be searched.

2.4 Data collection and analysis

2.4.1 Study selections

Potentially relevant papers will be assessed for eligibility by screening the title and abstract, and then they were finally selected after full-text review on the basis of the predefined selection criteria. The literature searching and selection process was initially performed by 1 review author and subsequently checked by the other author. Disagreements were resolved by discussion between the 2 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 flowchart.

2.4.2 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 that incidence of fractures and influence 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.

2.4.3 Assessment of risk of bias and quality

The Cochrane Collaboration tool for assessing risk of bias 2 will be used to assess risk of bias for RCTs.[17] It contains six domains: selection bias (adequate sequence generation and 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 (ROBINS-I) will be used to assess risk of bias for using quasi-RCT, controlled trials, cohort studies.[18] Two reviewers (CHM and JBH) will assess RoB of included studies independently. Disagreements will be resolved through discussion and, if not resolved, arbitration by other authors (JBH and AJH).

2.4.4 Measurement of treatment effect

For dichotomy data such as the incidence of fractures between the two groups, the pooled results are presented as risk ratio (RR) with 95% CIs. For continuous data, the pooled results are presented as mean differences (MDs) or standardized MDs (SMDs) with 95% confidence intervals (CIs).

2.4.5 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 analyzed.

2.4.6 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 analyzed (large if $I^2 > 50\%$; medium if $25\% < I^2 \geq 50\%$; and small if $0 \leq I^2 \geq 25\%$). Fixed-

effect model analysis will be carried out if there I as no evidence of heterogeneity. However, random-effects model analysis will be performed if the heterogeneity have been eliminated.

2.4.7 Data synthesis

The Review Manager program (ver. 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 synthesized according to the type of intervention and/or as follows:

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

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

2.4.8 Subgroup analysis and sensitive analysis

We will perform a subgroup analysis to compare re- fracture rate on the GIOP patients who experience previous fracture history. This will be done by assessing the impact of sample size, high Risk of Bias, 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.

2.4.9 Patient and Public Involvement

The design of this review protocol did not involve patients.

3. 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 glucocorticoid-induced osteoporosis (GIOP). However, to our knowledge, there has been no systematic review comparing the effectiveness of BP on GIOP. Therefore, we developed a protocol to compare the effectiveness of BP on GIOP systematically. All actions in this review will be carried out following Cochrane Handbook 5.2.0 to provide convincing evidence and better guide clinic practice.

4. 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 policy-makers in making better decisions. To disseminate the findings of this research, we also use seminars, social media, and conference.

Competing interests

No, there are no competing interests for any author

Contributors

Conceptualization: Jeonghoon Ahn, Bo-Hyoung Jang

Methodology: GaYoon Kim, Seowoo Bae, Hyeju Lee, Seonghee Nam

Writing – original draft: Hongmin Chu

Writing – review & editing: Bo-hyung Jang, Jeonghoon Ahn

Funding:

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

References

1. Briot K, Roux C. Glucocorticoid-induced osteoporosis. *RMD Open*. 2015;1(1):e000014-e000014. doi:10.1136/rmdopen-2014-000014

2. Rizzoli R, Adachi JD, Cooper C, et al. Management of Glucocorticoid-Induced Osteoporosis. *Calcif Tissue Int*. 2012;91(4):225-243. doi:10.1007/s00223-012-9630-5

3. Canalis E, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. *Osteoporos Int*. 2007;18(10):1319-1328. doi:10.1007/s00198-007-0394-0

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(3):562-570. doi:10.3803/EnM.2020.659

5. Weinstein RS. Is long-term glucocorticoid therapy associated with a high prevalence of asymptomatic vertebral fractures? *Nat Clin Pract Endocrinol Metab*. 2007;3(2):86-87. doi:10.1038/ncpendmet0372

6. Van Staa TP, Laan RF, Barton IP, Cohen S, Reid DM, Cooper C. Bone density threshold and other predictors of vertebral fracture in patients receiving oral glucocorticoid therapy. *Arthritis Rheum*. 2003;48(11):3224-3229. doi:10.1002/art.11283

7. Dong S li, Jiao Y, Yang H liang. Effectiveness of bisphosphonates on bone mineral density in osteopenic postmenopausal women: A systematic review and network meta-analysis of randomized controlled trials. *Medicine (Baltimore)*. 2021;100(31):e26715. doi:10.1097/MD.0000000000026715

8. Reginster JY, Burlet N, Close P, Bruyere O. Injectable Bisphosphonates for the Treatment of Osteoporosis. *Womens Health*. 2007;3(6):719-723. doi:10.2217/17455057.3.6.719

9. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLOS Med*. 2021;18(3):e1003583. doi:10.1371/journal.pmed.1003583

10. Deeks ED. Denosumab: A Review in Postmenopausal Osteoporosis. *Drugs Aging*. 2018;35(2):163-173. doi:10.1007/s40266-018-0525-7

11. Riggs. Teriparatide in the management of osteoporosis. *Clin Interv Aging*. 2008;Volume 2:499-507. doi:10.2147/CIA.S241

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(3):600-613. doi:10.1210/clinem/dgz023

13. Lin SY, Hung MC, Chang SF, Tsuang FY, Chang JZC, Sun JS. Efficacy and Safety of Postmenopausal Osteoporosis Treatments: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials. *J Clin Med*. 2021;10(14):3043. doi:10.3390/jcm10143043

14. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. *THE LANCET*. 2002;359:8.

15. Lee TH, Song YJ, Kim H, Sung YK, Cho SK. Intervention Thresholds for Treatment in Patients with Glucocorticoid-Induced Osteoporosis: Systematic Review of Guidelines. *J Bone Metab*. 2020;27(4):247-259. doi:10.11005/jbm.2020.27.4.247

16. Marques A, Ferreira RJO, Santos E, Loza E, Carmona L, da Silva JAP. The accuracy of osteoporotic fracture risk prediction tools: a systematic review and meta-analysis. *Ann Rheum Dis*. 2015;74(11):1958-1967. doi:10.1136/annrheumdis-2015-207907

17. Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343(oct18 2):d5928-d5928. doi:10.1136/bmj.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*. Published online October 12, 2016:i4919. doi:10.1136/bmj.i4919

19. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I^2 index? *Psychol Methods*. 2006;11(2):193-206. doi:10.1037/1082-989X.11.2.193

20. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634. doi:10.1136/bmj.315.7109.629

Table 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

Supplement 1. Searching strategies of EMBASE

1. embase

#1	'steroid'/exp OR 'steroid':ab,ti OR 'glucocorticoid'/exp OR 'glucocorticoid':ab,ti OR
#2	'Osteoporosis'/exp OR 'Osteoporosis':ab,ti OR 'Osteoporos'/exp OR 'Osteonpenia':ab,ti OR 'Bone loss'/exp OR 'bone losses'/exp
#3	'Biphosphonate':ab,ti OR 'diphosphonate':ab,ti OR 'alendronate'/exp OR 'risedronate':ab,ti OR 'ibandonate':ab,ti OR 'pamidronate':ab,ti OR 'pamidronate':ab,ti OR 'zoledronate':ab,ti
#4	#1and #2 and #3

2. central

#1	[mh "steroid"] OR 'steroid':ab,ti OR ' glucocorticoid':ab,ti OR [mh "glucocorticoid"]
#2	[mh "Osteoporosis"] OR 'Osteoporosis':ab,ti OR [mh "Osteoporos"] OR 'Osteonpenia':ab,ti OR [mh "Bone loss"] OR [mh "bone losses"]
#2	'Biphosphonate':ab,ti OR 'diphosphonate':ab,ti OR 'alendronate'/exp OR 'risedronate':ab,ti OR 'ibandonate':ab,ti OR 'pamidronate':ab,ti OR 'pamidronate':ab,ti OR 'zoledronate':ab,ti
#4	#1and #2 and #3

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	1
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Title page
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	10
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	10
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	2
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5,6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5,6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Table 1

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5,6,7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7,8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8,9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	8,9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8,9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8,9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	N/A

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.