

Decision Letter (JCQ-2025-0006)**From:**

To: zhanzirui2009@163.com

CC: zhanzirui2009@163.com

BCC:**Subject:** Journal of Clinical Question - Decision on Manuscript ID JCQ-2025-0006**Body:** 27-February-2025

Dear Dr Zhan:

Manuscript ID JCQ-2025-0006 entitled "Efficacy and Safety of Zoledronate for Osteopenia and Osteoporosis in Postmenopausal Women: A Systematic Review and Meta-Analysis of Randomized Controlled Trials" which you submitted to the Journal of Clinical Question, has been reviewed. The comments of the reviewer(s) are included at the bottom of this letter.

The reviewer(s) have recommended publication, but also suggest some revisions to your manuscript. Therefore, I invite you to respond to the reviewer(s)' comments and revise your manuscript.

To submit your revised manuscript, follow the below steps.

1. Access to <https://mc.manuscriptcentral.com/jcq> and log into the site.

2. Click "Author" at the top left of the screen at "Home" page.

3. Click "Manuscripts with Decisions" on Author Dashboard page.

4. Click "create a revision" on the manuscript you are going to revise.

5. The system creates your revision manuscript form. Provide your comments about the revised points at the response field, fill in on each field step by step as same as you did for the original submission, and submit your revised manuscript.

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Your manuscript number has been appended to denote a revision.

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer. Please also highlight the changes to your manuscript within the document by using the track changes mode in MS Word or by using bold or colored text.

Once the revised manuscript is prepared, you can upload it and submit it through your Author Center.

When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) in the space provided. You can use this space to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Because we are trying to facilitate timely publication of manuscripts submitted to the Journal of Clinical Question, your revised manuscript should be uploaded as soon as possible. If it is not possible for you to submit your revision in a reasonable amount of time, we may have to consider your paper as a new submission.

Once again, thank you for submitting your manuscript to the Journal of Clinical Question and I look forward to receiving your revision.

Sincerely,

Professor Richard Isaacs

Editor in Chief, Journal of Clinical Question

jqc@gleampub.com

[Editor's Comments]

Associate Editor

Comments to the Author:

(There are no comments.)

[Reviewer(s)' Comments]

Reviewer: 1

Comments to the Author

This is a well-conducted and timely systematic review and meta-analysis evaluating the efficacy and safety of zoledronate for osteopenia and osteoporosis in postmenopausal women. The study adheres to PRISMA guidelines and presents high-certainty evidence regarding fracture prevention, bone mineral density (BMD) improvement, and adverse events.

Major Comments:

1. High Heterogeneity in BMD Outcomes ($I^2 = 100\%$)

While the manuscript acknowledges the presence of heterogeneity, it does not sufficiently investigate potential sources. The authors are encouraged to explore subgroup or meta-regression analyses to examine factors such as baseline T-score, follow-up duration, or geographical region. Additionally, the discussion section should better contextualize how this heterogeneity may influence interpretation of the results.

2. Serious Adverse Events – Power Limitation

Although no statistically significant difference in serious adverse events was observed, the total number of events appears small. The authors should comment on whether the included studies were adequately powered to detect rare but clinically significant events, such as osteonecrosis of the jaw (ONJ) or atypical femoral fractures.

3. GRADE Tables and Publication Bias

Figures S5 to S11 visually suggest minimal publication bias; however, a quantitative assessment (e.g., Egger's test) was not reported. Including such an analysis, or explicitly acknowledging its absence and rationale, would strengthen the evaluation of publication bias.

Minor Comments:

Abstract: The word count could be reduced slightly to enhance clarity and conciseness without compromising content.

Page 6, Line 114: The mention of "emerging evidence" regarding zoledronate use in osteopenia would benefit from a specific supporting citation (e.g., Reid et al., 2018).

Study Selection: Consider including a table listing excluded studies with reasons for exclusion to enhance transparency in the selection process.

Reviewer: 2

Comments to the Author

This meta-analysis provides valuable clinical insights into the efficacy of zoledronate in both osteoporotic and osteopenic postmenopausal women. The findings support the potential role of early pharmacologic intervention and may contribute to future updates in clinical practice guidelines and health policy.

However, there are a few areas that warrant improvement:

Comment 1: The statement "without fractures, osteopenia is associated with a reduced quality of life" requires clarification and should be supported by a specific reference to studies on health-related quality of life (HRQoL) in osteopenic populations.

Comment 2: The phrase "improved BMD" in the abstract would be more informative if it explicitly stated the anatomical sites assessed (e.g., lumbar spine, total hip, femoral neck) to enhance clinical relevance and precision.

Date Sent: 27-February-2025

Author's Response to Decision Letter for (JCQ-2025-0006)**Efficacy and Safety of Zoledronate for Osteopenia and Osteoporosis in Postmenopausal Women: A Systematic Review and Meta-Analysis of Randomized Controlled Trials**

Dear Reviewers,

We thank Reviewers for the thorough and insightful evaluation of our manuscript. We appreciate the constructive feedback, which has helped us improve the quality and clarity of our work. Below, we address each comment in detail and describe the corresponding revisions made to the manuscript.

Reviewer: 1

Major Comments 1 : While the manuscript acknowledges the presence of heterogeneity, it does not sufficiently investigate potential sources. The authors are encouraged to explore subgroup or meta-regression analyses to examine factors such as baseline T-score, follow-up duration, or geographical region. Additionally, the discussion section should better contextualize how this heterogeneity may influence interpretation of the results.

Response: Thank you for this valuable comment. In response, we conducted subgroup analyses based on treatment duration to explore potential sources of heterogeneity in both fracture prevention and BMD outcomes. The results demonstrated consistent benefits of zoledronate for both 1-year and longer durations, with minimal heterogeneity observed in fracture prevention outcomes ($I^2 = 0\%$). However, high heterogeneity remained in BMD outcomes despite stratification by duration, suggesting that other factors, such as baseline T-score or regional differences, may contribute (Figures S5-S7). Although meta-regression was limited by the number of available studies and incomplete reporting of covariates such as geographic location and baseline T-score, we have added this consideration to the discussion section and emphasized how residual heterogeneity may affect the interpretation and generalizability of our findings.

Major Comment 2 : Although no statistically significant difference in serious adverse events was observed, the total number of events appears small. The authors should comment on whether the included studies were adequately powered to detect rare but clinically significant events, such as osteonecrosis of the jaw (ONJ) or atypical femoral fractures.

Response: Thank you for this important observation. We agree that the small number of SAEs, such as ONJ or atypical femoral fractures, limits the ability to draw firm conclusions regarding their incidence. Most included trials were not specifically powered to detect rare but clinically significant adverse events. We have now addressed this limitation in the discussion section as follows "Additionally, although no significant increase in serious adverse events was observed, the potential for rare but serious complications—such as atypical femoral fractures and osteonecrosis of the jaw—underscores the need for ongoing long-term surveillance."

Major Comment 3 : Figures S5 to S11 visually suggest minimal publication bias; however, a quantitative assessment (e.g., Egger's test) was not reported. Including such an analysis, or explicitly acknowledging its absence and rationale, would strengthen the evaluation of publication bias.

Response: Thank you for this important suggestion. In response, we conducted Egger's test to quantitatively assess publication bias across the primary outcomes. The results indicated no significant publication bias for fracture prevention, lumbar spine BMD, femoral head BMD, and adverse events (all $p > 0.05$). However, statistically significant asymmetry was observed for total hip BMD ($p < 0.01$), suggesting potential publication bias or small-study effects for this outcome. These findings have been incorporated into the revised Results and Discussion sections, and the Egger's test results are now included as annotations in the corresponding funnel plot figures.

Minor Comments 1 : Abstract: The word count could be reduced slightly to enhance clarity and conciseness without compromising content.

Response: Thank you for your helpful comment. In response, we have revised the abstract to enhance clarity and reduce word count without compromising the essential content.

Minor Comments 2 : Page 6, Line 114: The mention of "emerging evidence" regarding zoledronate use in osteopenia would benefit from a specific supporting citation (e.g., Reid et al., 2018).

Response: Thank you for this helpful suggestion. We have now added a citation to Reid et al., 2018 to support the statement regarding emerging evidence on zoledronate use in osteopenia. The revised sentence on Page 6, Line 114 reads: "Emerging evidence suggests that zoledronate may also be effective in reducing fracture risk among women with osteopenia, particularly in older populations."

Minor Comment 3: Study Selection: Consider including a table listing excluded studies with reasons for exclusion to enhance transparency in the selection process.

Response: Thank you for your observation. We have now included the previously excluded study in the PRISMA flow diagram (Figure S1) to ensure transparency in the study selection process.

Reviewer: 2

Comment 1: The statement "without fractures, osteopenia is associated with a reduced quality of life" requires clarification and should be supported by a specific reference to studies on health-related quality of life (HRQoL) in osteopenic populations.

Response: Thank you for pointing this out. We have revised the statement for clarity and added a supporting reference. The sentence now reads: "Even in the absence of fractures, osteopenia has been associated with reduced health-related quality of life (HRQoL), likely due to functional limitations, fear of falling, and decreased physical performance"

Comment 2: The phrase "improved BMD" in the abstract would be more informative if it explicitly stated the anatomical sites assessed (e.g., lumbar spine, total hip, femoral neck) to enhance clinical relevance and precision.

Response: Thank you for this constructive suggestion. Since BMD was assessed separately at the lumbar spine, total hip, and femoral neck, reporting these sites individually provides more clinically relevant information. While the overall effect could be statistically summarized, specifying the anatomical locations enhances interpretability and supports more informed decision-making. We have revised the abstract accordingly to reflect these site-specific results.

We are grateful for your thoughtful comments and suggestions. We believe the revisions made in response to your feedback have strengthened the manuscript and improved its scientific rigor and clarity. We hope that the revised version meets the expectations of the reviewers and editorial team. Thank you again for your time and consideration.

Sincerely,

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References

1. Reid IR, Horne AM, Mihov B, et al. Fracture Prevention with Zoledronate in Older Women with Osteopenia. *N Engl J Med*. Dec 20 2018;379(25):2407-2416. doi:10.1056/NEJMoa1808082