Review Article

Efficacy and Safety of Osteoporosis Medication in Renal Transplantation: A Systematic Review and Meta-Analysis

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Abstract

Background: Osteoporosis is a significant concern, especially for individuals undergoing renal transplantation, as it disrupts bone health and increases the risk of fractures. Interventions for osteoporosis aim to address bone-related challenges in patients with renal transplantation, yet concerns persist regarding both efficacy and potential adverse events.

Materials and Methods: We searched PubMed/MEDLINE, EMBASE, and the Cochrane CENTRAL databases until December 15, 2023, seeking studies that evaluated the efficacy and adverse events of osteoporosis medications in patients with renal transplantation. The Cochrane tool was utilized to assess the quality of the studies. The statistical analysis was performed using Comprehensive Meta-Analysis software, version 3.0.

Results: We enrolled 594 participants from 7 randomized controlled trials. Combining trial results reveals that using anti-osteoporotic agents (Ibandronate, Risedronate, and Pamidronate) reduces the risk of vertebral fractures compared to the placebo. However, the reduction was not statistically significant (OR: 0.49, CI 95%: 0.20-1.22). Additionally, lumbar spine, femoral neck, and total hip BMD showed no significant differences between anti-osteoporotic agents (Denosumab, Zoledronic acid, Ibandronate, Risedronate, and Pamidronate) and placebo. Moreover, there were no significant differences in adverse events between the interventions and placebo.

Conclusion: The study suggests that anti-osteoporotic agents in renal transplantation patients may be associated with a non-significant lower risk of vertebral fractures compared to a placebo. Findings also indicate no significant differences in adverse events between interventions and placebos. Caution is advised in interpreting these results due to the absence of statistically significant differences, emphasizing the need for further research to enhance our understanding of efficacy and safety in renal transplantation.

Keywords: Osteoporosis, Renal transplantation, Adverse events, Efficacy

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Introduction

Osteoporosis, characterized by diminished bone density and heightened fracture susceptibility, poses a significant health burden, particularly for individuals who have undergone renal transplantation[1-6]. The disturbance of mineral and bone metabolism in renal transplantation patients exacerbates fracture risks, creating complexities in osteoporosis management[7-9]. Various pharmacological interventions have been employed to address these challenges and maintain bone health in renal transplantation patients[10,11]. Each of these medications, with distinct mechanisms of action, plays specific roles in osteoporosis management[12-15]. However, concerns have been raised regarding efficacy and adverse events associated with osteoporosis medications in those who have undergone renal transplantation. Despite these concerns, there has been limited comprehensive investigation into these medications' efficacy and adverse effects in renal transplantation patients. Thus, this systematic review was designed to thoroughly evaluate the efficacy and adverse events associated with these osteoporosis treatments within the renal transplantation population.

Methods

Search strategy: We searched PubMed/MEDLINE, EMBASE, and the Cochrane CENTRAL databases until December 15, 2023, seeking studies that evaluated the efficacy and adverse events of osteoporosis medications in patients with renal transplantation. The search terms included "Osteoporosis," "Renal Transplantation," and "randomized controlled trial," and only studies published in English were considered. Our study adhered to the PRISMA statement for its design and reporting (Prospero pending ID: 495499)[16].

Study Selection: The records obtained from the database searches were merged, and duplicate entries were eliminated using EndNote X7 (Thomson Reuters, Toronto, ON, Canada). Two reviewers, TS and MJN, independently scrutinized the records, employing both title/abstract and full-text screening procedures to exclude studies that did not align with the study's objectives.

The studies included in the analysis met the following criteria

Participants:

Individuals diagnosed with renal transplantation.

Intervention:

Anti-osteoporotic agents

Comparison:

placebo

Outcome:

Risk of vertebral fractures, BMD, and adverse effects.

Studies included in the analysis needed to meet the following criteria: The trials involved individuals diagnosed with renal transplantation, and they reported on the efficacy and adverse effects of osteoporosis therapies in these patients.

Data extraction: Two reviewers, TS and MJN, collaborated to create a structured data extraction form and collected information from all eligible studies. Any discrepancies were resolved through mutual agreement. The extracted data encompassed various aspects, including the primary author's name, publication year, study type, mean age, country, renal transplantation patients, interventions, treatment outcomes, and reported adverse events.

Quality assessment: The quality assessment of the included studies was carried out by two reviewers, TS and MJN, utilizing the Cochrane tool. In discrepancies, a third reviewer was engaged to ensure a comprehensive and unbiased evaluation.

Data analysis: The statistical analysis was performed using Comprehensive Meta-Analysis software, version 3.0 (Biostat Inc., Englewood, NJ, USA). The pooled odd ratio (OR) was used as the pooled statistic, with a corresponding 95% confidence interval (CI). The degree of heterogeneity among the studies was assessed using the I2 value and p-value. In cases where the statistical heterogeneity between the studies was low ($I2 \leq 50\%$ or $p \geq 0.1$), the fixed-effect model was utilized. Conversely, the random-effects model was employed if inter-study heterogeneity was observed ($I2 > 50\%$ or $p < 0.1$). Cochran's Q test and the I2 statistic were used to assess between-study heterogeneity. Begg's test was applied, where a P value of less than 0.05 was considered indicative of statistically

significant publication bias to evaluate publication bias.

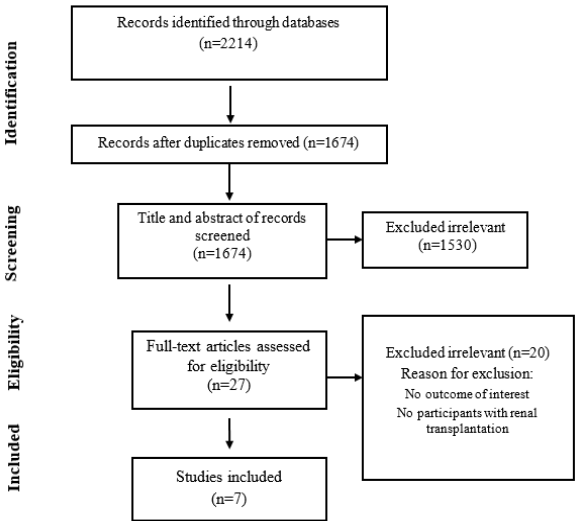
Results

As illustrated in Figure 1, this comprehensive review identified seven records, encompassing 594 patients with renal transplantation, all meeting the specified eligibility criteria.

Table 1 presents findings from multiple studies conducted across various years and regions, assessing the effectiveness of osteoporosis interventions in populations with renal transplantation. The mean ages of the populations ranged from 40 to 50 years. The interventions included Denosumab, Zoledronic acid, Ibandronate, Risedronate, and Pamidronate, each compared against a placebo, with sample sizes ranging from 32 to 129 participants. The follow-up duration for all studies was 12 months except for one study with a 24-month follow-up.

Quality assessment: Table 2 summarizes the risk of bias assessments conducted for the included studies. The studies exhibited low risks across most categories, suggesting robust methodological practices. Nonetheless, specific authors, including Marques, Bonani, and Torregrosa, displayed elevated risks in allocation concealment and blinding.

Vertebral Fracture: Combining trial results indicates that the use of anti-osteoporotic agents (Ibandronate, Risedronate, Pamidronate) reduces the risk of vertebral fractures compared to the placebo, though the reduction was not statistically significant (pooled OR: 0.49, CI95%: 0.20-1.22, I2: 0.00) (Figure 2). There was no evidence of publication bias (p-value < 0.05).



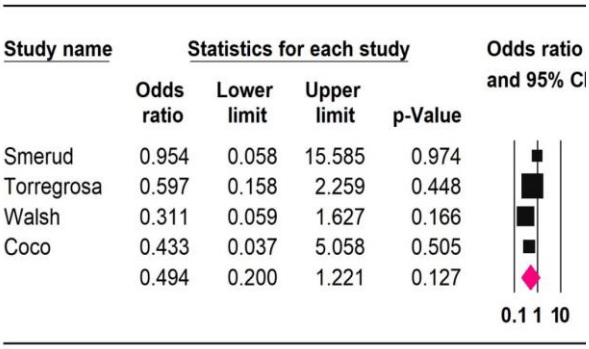


Figure 2. Pooled OR for vertebral fractures in patients with post-renal transplantation treated with bisphosphonates agents

Table 1. Characteristics of included studies**.**

Author	Year	Population	Mean age	Country	Intervention	Control	Sample size	Follow up, month
Sayed [20]	2023	Postmenopausal women with post-renal transplantation	40	Egypt	Denosumab	Placebo	90	12
Marques [21]	2019	Patients with post-renal transplantation	43	Brazil	Zoledronic	Placebo	32	12
Bonani [22]	2016	Patients with post-renal transplantation	50	Switzerland	Denosumab	Placebo	90	12
Smerud [23]	2012	Patients with post-renal transplantation	50	Norway	Ibandronate	Placebo	129	12
Torregrosa [24]	2010	Patients with post-renal transplantation	47	Spain	Risedronate	Placebo	101	12
Walsh [25]	2009	Patients with post-renal transplantation	46	United Kingdom	Pamidronate	Placebo	93	24
Coco [26]	2003	Patients with post-renal transplantation	45	USA	Pamidronate	Placebo	59	12

Table 2. Quality assessment**.**

Author	Random Sequence generation	Allocation Concealment	Blinding of Participants	Blinding of Outcome Assessors	Incomplete Outcome Data	Selective reporting	Other bias
Sayed	Low	Low	Low	Low	Low	Low	Low
Marques	Low	High	High	High	Low	Low	Low
Bonani	Low	High	High	High	Low	Low	Low
Smerud	Low	Low	Low	Low	Low	Low	Low
Torregrosa	Low	High	High	High	Low	Low	Low
Walsh	Low	Low	Low	Low	Low	Low	Low
Coco	Low	Low	Low	Low	Low	Low	Low

Table 3. Summary of the number of cardiovascular and renal adverse events in included trials**.**

Author	Cardiovascular adverse events	Renal adverse events
Sayed	Not reported	Not reported
Marques	Not reported	There was no notable disparity in eGFR observed between the groups treated with zoledronate and the control groups.
Bonani	Not found	There were no significant differences noted when compared with the control group in the rates of acute rejection, loss of graft function, and the change in eGFR.
Smerud	Not found	In comparison to the placebo group, those treated with Ibandronate exhibited lower rates of biopsy-verified transplant rejections, a reduced incidence of elevated serum creatinine, and a more favorable mean change in serum creatinine.
Torregrosa	Not reported	Not found
Walsh	Not reported	There were no discernible differences between the two groups in terms of acute rejection episodes, non-rejection acute deterioration in kidney function, and serum creatinine levels.
Coco	Not reported	Not reported

BMD: Based on the data obtained from the included studies, there were no significant differences in Lumbar spine, femoral neck, and total hip BMD between anti-osteoporotic agents (Denosumab, Zoledronic acid, Ibandronate, Risedronate, and Pamidronate) and placebo (p-value < 0.05).

Safety: *(Cardiovascular adverse events)* As shown in Table 3, studies indicated no statistically significant differences in stroke, heart failure, and hypertension between the interventions and placebo. Furthermore, the absence of cases involving deep and superficial thrombophlebitis, arteriovenous fistula, graft, dialysis catheter thrombosis, or vasomotor symptoms was noted in one study.

Renal adverse events: The analysis of renal adverse events across interventions revealed no notable differences in the estimated glomerular filtration rate between treatment and control groups (Table 3).

Gastrointestinal adverse events: No statistically significant differences were observed in adverse gastrointestinal events.

Discussion

Principal findings: Our evaluation revealed a statistically non-significant reduction in the risk of vertebral fractures with anti-osteoporotic agents compared to a placebo in patients with renal transplantation.

Furthermore, there were no significant differences in cardiovascular, renal, and gastrointestinal adverse events between the interventions and placebo. However, it is essential to note that further studies should be conducted to substantiate these findings and provide a more comprehensive understanding of the outcomes.

Clinical implications: The findings suggest that, despite lacking statistical significance, the utilization of anti-osteoporotic agents in patients with renal transplantation patients may decrease the risk of vertebral fractures compared to a placebo. This information holds relevance for healthcare providers

involved in managing osteoporosis in renal transplantation patients, offering a degree of reassurance regarding the safety of these medications concerning vertebral fracture risk. However, it is crucial to acknowledge that these implications are drawn from the available evidence, and further research is imperative to validate and build upon these findings.

Additionally, the absence of significant differences in adverse events between interventions and placebos offers reassurance regarding the safety of these interventions concerning heart-related concerns. However, caution should always be exercised, and further studies are needed to deepen our understanding and ensure comprehensive insights into the safety profile of these interventions[17-19].

Strengths and limitations: The strengths and limitations of the evaluation should be considered. On the positive side, the study conducted a robust examination of cardiovascular adverse events, contributing to a comprehensive understanding of intervention safety. Including diverse interventions, ranging from zoledronate to teriparatide, offers a nuanced perspective, aiding healthcare providers in tailored decision-making. Additionally, the longitudinal analysis of renal effects, particularly in patients with renal transplantation, provides valuable insights. However, it is crucial to acknowledge certain limitations, including the necessity for cautious interpretation due to the absence of significant differences in the studied interventions and adverse events. Further studies are needed to comprehend these interventions' efficacy and safety profile thoroughly.

Conclusion

The study suggests that anti-osteoporotic agents in renal transplantation patients may be associated with a non-significant lower risk of vertebral fractures compared to a placebo. Findings also indicate no significant differences in adverse events between interventions and placebos. Caution is advised in interpreting these results due to the absence of statistically significant differences, emphasizing the need for further research to enhance our understanding of efficacy and safety in renal transplantation.

Acknowledgment

None.

Conflict of interest

The authors further declare that they have no conflict of interest.

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