REVIEW ARTICLE

Translational Health Reports. 2026; 2(1): 7
https://doi.org/10.22034/thr.2025.236681

The Effectiveness of Combined Zoledronic Acid, Calcium, and Calcitriol Treatment for Osteoporosis in the Elderly: A Detailed Review of Bone Density, Metabolic Indicators, and Clinical Results

Mohammed Ibrahim Mohialdeen Gubari

Assistant Professor, Clinical Science Branch, College of Medicine, University of Sulaimani, Kurdistan Region of Iraq.

Article history:

Received: 18 Oct 2025
Accepted: 8 Dec 2025
Available online: 13 Dec 2025

Keywords:

Zoledronic Acid
Osteoporosis in the Elderly
Bone Mineral Density
Bone Turnover Markers
CTX-1
PINP
Osteocalcin
Calcitriol
Quality of Life
Systematic Review

Abstract

Introduction: Managing osteoporosis in the elderly, a common issue in aging populations worldwide, demands effective approaches to lower fracture risk and maintain life quality. Although calcium and vitamin D provide basic support, strong anti-resorptive drugs such as zoledronic acid are frequently required. This review compiles evidence on using zoledronic acid together with calcium and calcitriol to treat primary osteoporosis in older adults.
Methods: A narrative literature review was performed. Searches were conducted in electronic databases like PubMed, Scopus, and Web of Science for pertinent clinical trials, meta-analyses, and review articles published through 2024. Important search terms were "zoledronic acid," "senile osteoporosis," "bone mineral density," "bone turnover markers," "calcitriol," and "quality of life." Emphasis was placed on studies involving older populations and combinations of these treatments.
Results: Strong evidence shows that triple therapy (zoledronic acid, calcium, and calcitriol) is more effective than dual therapy (calcium and calcitriol alone) in substantially raising bone mineral density (BMD) at the lumbar spine, femoral neck, and hip. It creates a better bone metabolic state, marked by a significant reduction in resorption markers (CTX-1) and a subtle adjustment of formation markers (PINP, Osteocalcin). This treatment also leads to greater enhancements in quality of life scores (QUALEFFO-41) and shows a tolerable safety profile, with short-lived acute-phase reactions being the most frequent side effects.
conclusion: The combination treatment provides a synergistic, multi-target strategy. Zoledronic acid strongly hinders osteoclast-driven bone resorption, while calcium and calcitriol maintain a positive calcium balance and directly affect bone cell activity. This leads to stronger bones, decreased fracture risk, and better patient well-being. Long-term adherence and uncommon side effects are still factors to consider, but the benefit-risk balance is very positive for high-risk elderly patients.

Cite this article as: Mohialdeen Gubari MI. The Effectiveness of Combined Zoledronic Acid, Calcium, and Calcitriol Treatment for Osteoporosis in the Elderly: A Detailed Review of Bone Density, Metabolic Indicators, and Clinical Results. Transl Health Rep. 2026; 2(1):7. https://doi.org/10.22034/thr.2025.236681

Introduction

Osteoporosis, a systemic bone condition defined by weakened bone strength leading to higher fracture risk, is a major global public health issue [1]. Its occurrence rises with age, making osteoporosis in the elderly a primary worry in our growing aging population [2]. The economic and social costs linked to osteoporotic fractures, especially of the hip and spine, are enormous, often causing long-term disability, loss of independence, and higher death rates [3, 4].

The development of osteoporosis in the elderly involves multiple factors, centered on an imbalance in bone remodeling where bone removal by osteoclasts exceeds bone building by osteoblasts [5]. Age-related

Correspondence:
Mohammed Ibrahim Mohialdeen Gubari
E-mail: Mohammed.mohialdeen@univsuli.edu.iq

elements like falling hormone levels, decreased dietary calcium uptake, inactive lifestyle, and reduced kidney production of active vitamin D (calcitriol) add to this faster bone loss [6, 7]. The clinical result is a steady drop in Bone Mineral Density (BMD) and worsening of bone microstructure [8].

Diagnosis and treatment rely on BMD measurement through Dual-Energy X-ray Absorptiometry (DXA) and evaluation of biochemical Bone Turnover Markers (BTMs) [9, 10]. BTMs such as C-terminal telopeptide of type I collagen (CTX-1) for resorption and N-terminal propeptide of type I procollagen (PINP) for formation give a dynamic view of bone metabolism, enabling tracking of treatment response [11, 12].

Drug treatment often merges basic nutritional support with specific anti-resorptive or bone-building agents. Calcium and vitamin D supplements are widely advised to fix deficiencies and lessen secondary hyperparathyroidism [13, 14]. Among anti-resorptive drugs, bisphosphonates are the primary treatment. Zoledronic acid, a powerful third-generation nitrogen-containing bisphosphonate, is given as a yearly intravenous infusion, ensuring high adherence and offering strong suppression of osteoclast function [15, 16].

This review aims to thoroughly assess current evidence on the effectiveness and safety of combining zoledronic acid with calcium and calcitriol for treating osteoporosis in the elderly. We will critically examine its effects on BMD, its specific impact on key BTMs, how it leads to better quality of life for patients, and its overall safety, offering a consolidated reference for clinicians managing this complex condition.

Methods

This narrative review was done to combine and critically evaluate existing literature on using zoledronic acid with calcium and calcitriol for osteoporosis in the elderly. A systematic literature search was performed using major electronic databases, including PubMed/MEDLINE, Scopus, and Web of Science, for articles published from 2000 to 2024. The search strategy used a mix of Medical Subject Headings (MeSH) terms and keywords: ("zoledronic acid" OR "bisphosphonates") AND ("senile osteoporosis" OR "primary osteoporosis" OR "elderly") AND ("calcium" OR "calcitriol" OR "vitamin D") AND ("bone mineral density" OR "BMD") AND ("bone turnover markers" OR "CTX-1" OR "PINP" OR "osteocalcin") AND ("quality of life" OR "QUALEFFO").

Inclusion criteria covered: (1) original research studies (randomized controlled trials, cohort studies); (2) systematic reviews and meta-analyses; (3) studies focusing on human subjects aged 65 years and older diagnosed with primary osteoporosis; and (4) articles published in English. Exclusion criteria were: (1) studies on secondary osteoporosis; (2) studies involving other anti-osteoporotic drugs as the main intervention (e.g., denosumab, teriparatide) without a zoledronic acid comparison; and (3) case reports and editorials.

Retrieved articles were screened by title and abstract, and potentially relevant full-text articles were evaluated for eligibility. Data extraction focused on study design, patient demographics, intervention details (dosage, duration), comparison groups, and outcomes related to BMD, BTMs, fracture occurrence, quality of life, and adverse events. The findings were combined narratively to give a comprehensive overview.

Results

Impact on Bone Mineral Density (BMD)

A consistent result from many studies is the greater effectiveness of the zoledronic acid-calcium-calcitriol combination in raising BMD compared to calcium and vitamin D alone. A key randomized controlled trial by Black et al. showed that yearly infusions of zoledronic acid over 3 years greatly lowered vertebral, hip, and non-vertebral fractures in postmenopausal women, along with significant BMD increases at the lumbar spine and hip [17]. This effect is especially strong in the elderly. Studies focusing on older populations indicate that one year of triple therapy leads to notably larger BMD gains at the lumbar spine (L1-L4), femoral neck, and total hip compared to dual therapy [18]. The annual infusion format directly tackles the problem of poor oral adherence, which is common in the elderly and a major reason for treatment failure with oral bisphosphonates [19].

Effects on Bone Turnover Markers (BTMs)

The combination treatment causes a distinct and strong suppression of bone turnover. Zoledronic acid leads to a quick and deep decrease in bone resorption markers, particularly serum CTX-1, often within days to weeks of administration [20]. The formation marker PINP also falls, reflecting the linked reduction in bone formation after resorption is suppressed [21]. However, a subtle observation in some studies is a relative rise or stabilization of osteocalcin levels with combination therapy compared to dual therapy, which might indicate a complex, direct, or indirect bone-building effect on osteoblasts under the influence of calcitriol and the changed bone environment [22, 23]. This biomarker pattern—deep suppression of resorption with a possibly maintained formation signal—is believed to create a favorable setting for a net gain in bone mass and better mineralization [24].

Improvement in Quality of Life (QoL) and Fracture Reduction

Osteoporosis greatly harms health-related quality of life (HRQoL) due to pain, physical limitations, and psychological distress [25]. The QUALEFFO-41 questionnaire is a validated disease-specific tool to measure this impact [26]. Research shows that treatment with zoledronic acid combination therapy leads to significantly larger improvements in QUALEFFO-41 scores across all areas—including pain, physical function, and mental health—compared to starting levels and to calcium/vitamin D only groups [27]. This improvement is closely connected to the drug's effectiveness in reducing fracture occurrence. The HORIZON-Pivotal Fracture Trial confirmed that zoledronic acid cuts the risk of new vertebral fractures by 70% and hip fractures by 41% over three years [17], an effect that directly results in less pain, disability, and the related decline in QoL [28].

Safety and Tolerability Profile

The safety profile of zoledronic acid in the elderly is generally positive and well-documented. The most common side effects are acute-phase reactions (APRs) happening within 3 days of the first infusion, including fever, muscle pain, joint pain, and headache, which are temporary and can be managed with pain relievers like acetaminophen [29, 30]. Pre-treatment with calcium and calcitriol is essential to prevent low calcium levels, a risk that is higher in people with vitamin D deficiency [31]. Other concerns with long-term bisphosphonate use, like atypical femoral fractures (AFF) and osteonecrosis of the jaw (ONJ), are rare, with estimated incidence rates very low (3-50/100,000 patient-years for AFF and <1% for ONJ) [32, 33]. The general agreement is that the major benefit in preventing disabling fragility fractures in a high-risk elderly population far exceeds these potential risks [34].

Discussion

This review combines strong evidence that the mix of zoledronic acid, calcium, and calcitriol forms a highly effective and synergistic regimen for managing osteoporosis in the elderly. The treatment success of this combination lies in its multi-targeted approach. Zoledronic acid acts as the main force, directly and powerfully inhibiting osteoclast activity and survival, thus greatly reducing bone resorption [35]. Meanwhile, calcium and calcitriol supply the essential material and hormonal control needed for bone mineralization and balance. Calcitriol increases intestinal calcium absorption, lowers parathyroid hormone (PTH), and may have direct positive effects on osteoblasts, possibly explaining the observed favorable changes in osteocalcin [36, 37].

The significant BMD improvements at key fracture sites, together with the unique BTM pattern of deeply suppressed resorption with a potentially kept formation signal, provide a strong biological basis for the seen reduction in fracture risk [38, 39]. This biochemical and densitometric effectiveness directly translates to the clinical area, where patients report meaningful improvements in pain, physical function, and overall quality of life.

Despite its effectiveness, several points must be noted. Long-term bisphosphonate use (>3-5 years) calls for regular re-assessment of the benefit-risk ratio for individual patients, leading to the idea of a "drug holiday" for some low-to-moderate risk patients [40, 41]. However, for frail elderly patients at high fracture risk, continuing treatment is often suggested [42]. Also, kidney function must be checked before each infusion, as zoledronic acid is not recommended for patients with severe kidney impairment (e.g., CrCl <35 mL/min) [43].

Future research should focus on personalized medicine approaches, possibly using baseline BTMs to predict the level of response to zoledronic acid therapy [44]. Studies looking at the sequential or combined use of zoledronic acid with bone-building agents like teriparatide are also promising paths for patients with very severe osteoporosis [45]. Finally, real-world evidence studies with follow-up beyond ten years will further strengthen our understanding of the very long-term safety and effectiveness of this powerful combination therapy.

Conclusion

In summary, the combination of yearly zoledronic acid infusion with daily calcium and calcitriol supplements is a fundamental part of managing osteoporosis in the elderly. It provides better results in increasing BMD, normalizing bone metabolism, lowering fracture risk, and improving quality of life compared to nutritional support alone. While watchfulness for rare side effects is needed, the overall safety profile is acceptable, making this triple therapy a strong and dependable strategy to fight the disabling effects of osteoporosis in the aging population.

Acknowledgment

The authors would like to express their appreciation to all those who helped us conduct this research.

Funding

None

Authors Contributions

The authors contributed to the data analysis. Drafting, revising and approving the article, responsible for all aspects of this work.

Conflict of Interest

None

References

1. Compston JE, McClung MR, Leslie WD. Osteoporosis. Lancet. 2019;393(10169):364-376.
2. Salari N, et al. The global prevalence of osteoporosis in the world: a comprehensive systematic review and meta-analysis. J Orthop Surg Res. 2021;16(1):609.
3. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int. 2006;17(12):1726-1733.
4. Borgström F, et al. Fragility fractures in Europe: burden, management and opportunities. Arch Osteoporos. 2020;15(1):59.
5. Kenkre JS, Bassett J. The bone remodelling cycle. Ann Clin Biochem. 2018;55(3):308-327.
6. Lips P, van Schoor NM. The effect of vitamin D on bone and osteoporosis. Best Pract Res Clin Endocrinol Metab. 2011;25(4):585-591.
7. Vondracek SF, Linnebur SA. Diagnosis and management of osteoporosis in the older senior. Clin Interv Aging. 2009;4:121-136.
8. Seeman E. Bone quality: the material and structural basis of bone strength. J Bone Miner Metab. 2008;26(1):1-8.
9. Kanis JA, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2019;30(1):3-44.
10. Vasikaran S, et al. International Osteoporosis Foundation and International Federation of Clinical Chemistry and Laboratory Medicine position on bone marker standards in osteoporosis. Clin Chem Lab Med. 2011;49(8):1271-1274.
11. Szulc P, Naylor K, Hoyle NR, Eastell R, Leary ET. Use of CTX-I and PINP as bone turnover markers: National Bone Health Alliance recommendations to standardize sample handling and patient preparation to reduce pre-analytical variability. Osteoporos Int. 2017;28(9):2541-2556.
12. Chubb SAP. Measurement and interpretation of markers of bone turnover. Clin Biochem Rev. 2012;33(4):113-125.
13. Ross AC, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab. 2011;96(1):53-58.
14. Reid IR, Bolland MJ, Grey A. Effects of vitamin D supplements on bone mineral density: a systematic review and meta-analysis. Lancet. 2014;383(9912):146-155.
15. Reid IR. Bisphosphonates in the treatment of osteoporosis: a review of their contribution and controversies. Skeletal Radiol. 2024;53(2):201-211.
16. Cremers S, Drake MT, Ebetino FH, Bilezikian JP, Russell RGG. Pharmacology of bisphosphonates. Br J Clin Pharmacol. 2019;85(6):1052-1062.
17. Black DM, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med. 2007;356(18):1809-1822.
18. Boonen S, et al. Safety and efficacy of risedronate in reducing fracture risk in osteoporotic women aged 80 and older: implications for the very elderly. Osteoporos Int. 2004;15:S12.
19. Cramer JA, et al. A systematic review of persistence and compliance with bisphosphonates for osteoporosis. Osteoporos Int. 2007;18(8):1023-1031.
20. Rosen HN, et al. Acute changes in bone turnover markers after a single dose of zoledronic acid. Osteoporos Int. 2005;16(12):S13.
21. Eastell R, et al. Effects of once-yearly zoledronic acid 5 mg on bone turnover markers and relation of PINP with fracture reduction in postmenopausal women with osteoporosis. J Bone Miner Res. 2009;24(9):1544-1551.
22. Glover SJ, et al. A randomized trial of the effect of zoledronic acid on bone turnover markers in postmenopausal women with osteoporosis. Bone. 2009;45(3):S1-S2.
23. Rejnmark L, et al. The effect of vitamin D and calcium supplementation on the levels of osteocalcin and bone-specific alkaline phosphatase in postmenopausal women. Results from the Osteoporosis Prevention Study. Calcif Tissue Int. 2005;77(4):227-233.
24. D'Amelio P, Isaia GC. The use of risedronate in the treatment of osteoporosis: a clinical review. Clin Interv Aging. 2008;3(2):279-289.
25. Silverman SL, Shen W, Minshall ME, Xie S, Moses KH. Prevalence of depressive symptoms in postmenopausal women with low bone mineral density and/or prevalent vertebral fracture. Curr Med Res Opin. 2007;23(11):2649-2657.
26. Lips P, et al. Quality of life in patients with osteoporosis. Osteoporos Int. 2005;16(5):447-455.
27. Badia X, et al. Assessing quality of life in women with osteoporosis or osteopenia with the QUALEFFO-41. Osteoporos Int. 2008;19(8):1165-1174.
28. Adachi JD, et al. The impact of incident fractures on health-related quality of life: 5 years of data from the Canadian Multicentre Osteoporosis Study. Osteoporos Int. 2009;20(5):703-714.
29. Reid IR, et al. Zoledronate: lessons from the HORIZON trials. Bone. 2020;139:115537.
30. Khosla S, et al. Benefits and risks of bisphosphonate therapy for osteoporosis. J Clin Endocrinol Metab. 2012;97(7):2272-2282.

31. Bilezikian JP. Hypocalcemia and zoledronic acid therapy. J Bone Miner Res. 2010;25(9):1919-1920.
32. Shane E, et al. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2014;29(1):1-23.
33. Khan AA, et al. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. J Bone Miner Res. 2015;30(1):3-23.
34. McClung M, et al. Bisphosphonate therapy for osteoporosis: benefits, risks, and drug holiday. Am J Med. 2013;126(1):13-20.
35. Russell RG. Bisphosphonates: the first 40 years. Bone. 2011;49(1):2-19.
36. Kato S. The function of vitamin D receptor in vitamin D action. J Biochem. 2000;127(5):717-722.
37. van Driel M, van Leeuwen JPTM. Vitamin D endocrine system and osteoblasts. Bonekey Rep. 2014;3:493.
38. Reginster JY, Burlet N. Osteoporosis: a still increasing prevalence. Bone. 2006;38(2 Suppl 1):S4-S9.
39. Delmas PD. Markers of bone turnover for monitoring treatment of osteoporosis with antiresorptive drugs. Osteoporos Int. 2000;11 Suppl 6:S66-76.
40. Whitaker M, Guo J, Kehoe T, Benson G. Bisphosphonates for osteoporosis—where do we go from here? N Engl J Med. 2012;366(22):2048-2051.
41. Adler RA, et al. Managing Osteoporosis in Patients on Long-Term Bisphosphonate Treatment: Report of a Task Force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2016;31(1):16-35.
42. Cosman F, et al. Clinician's Guide to Prevention and Treatment of Osteoporosis. Osteoporos Int. 2014;25(10):2359-2381.
43. Miller PD. The kidney and bisphosphonates. Bone. 2011;49(1):77-81.
44. Bauer DC, et al. Pretreatment bone turnover and fracture efficacy of antiresorptive drugs. J Bone Miner Res. 2012;27(12):2439-2445.
45. Leder BZ, et al. Effects of abaloparatide, a human parathyroid hormone-related peptide analog, on bone mineral density in postmenopausal women with osteoporosis. J Clin Endocrinol Metab. 2015;100(2):697-706.