

Comparative Effectiveness and Safety of Denosumab Versus Bisphosphonates in the Management of Osteoporosis: A Systematic Review and Meta-Analysis

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ABSTRACT: Osteoporosis is a widespread bone disorder, as the bone strength is decreased, bone microarchitecture deteriorates, and an increased risk of fragility fracture occurs, especially in the elderly and postmenopausal women. Anti-resorptive drugs, such

as bisphosphonates and denosumab, are commonly employed to prevent bone loss and fractures, but there is some uncertainty over how well these drugs work and whether they are safe. This systematic review and meta-analysis compares the effectiveness of denosumab to bisphosphonates for the treatment of osteoporosis. Changes in bone mineral density at the lumbar spine, total hip, and femoral neck areas and in fracture incidence, biochemical markers of bone turnover, adverse events and treatment discontinuation were evaluated in comparative clinical studies. Studies that met eligibility criteria were assessed through systematic review and meta-analysis. Based on available evidence, denosumab has demonstrated a generally higher potency to increase bone mineral density and suppress bone turnover, than bisphosphonate therapy. Results for vertebral fractures, hip fractures, and other types of osteoporotic fractures, however, are less consistent, and neither treatment shows overall better safety. Both treatments can still be used successfully in osteoporosis treatment. Therefore, treatment options should be tailored to baseline fracture risk, rather than history of treatment, renal function, tolerability, adherence, patient preference and long-term treatment planning, including the choice for discontinuation or switching between antiresorptive therapies.

Keywords: *Osteoporosis; Denosumab; Bisphosphonates; Bone mineral density; Fragility fracture; Antiresorptive therapy; Fracture prevention; Meta-analysis.*

1. Introduction

Osteoporosis is a systemic skeletal disease in which bone mass is decreased, the microarchitecture of bone is impaired, and the susceptibility to fragility fracture is increased. It is a significant public health problem around the world, especially due to the high incidence of osteoporosis among older people. Chronic pain, disability, loss of independence, quality of life reduction and higher mortality rates are all associated with osteoporotic fractures, particularly the hip, and the vertebral column. Fragility fractures also have significant economic costs associated with them, such as hospitalisation, rehabilitation, long term care and repeated fracture management (Compston et al. 2019). Medical treatment is very important in lowering the fracture risk in individuals with osteoporosis. Existing therapies: Anti-resorptive agents (the most commonly used), anabolic agents. In the past, bisphosphonates were thought to be one of the most effective treatments available due to a known effect of suppressing bone resorption by osteoclasts

and their ability to increase bone mineral density (BMD) while decreasing the numbers of osteoporotic fractures. Common agents in this class include alendronate, risedronate, ibandronate and zoledronic acid. The ability of bisphosphonates to reduce fracture rates have been proven in large randomized clinical trials. For instance, however, in postmenopausal osteoporosis women, risks of vertebral and hip fracture and other fractures were significantly lowered following use of once-yearly intravenous zoledronic acid (Black et al., 2007).

The therapeutic effects of bisphosphonates are mainly due to the attachment to hydroxyapatite in mature bone. In bone resorption, these compounds are engulfed by osteoclasts, leading to the inhibition of pathways that are important for osteoclast activity and osteoclast survival. This leads to reduced bone remodeling (bone resorption) and lower bone turnover. One of the major pharmacological properties of bisphosphonates is that they stay in the skeleton and can have antiresorptive effects long after therapy ends. A new and very potent alternative antiresorptive therapy is denosumab, which has a distinctly different mechanism of action. It is a completely humanized, receptor activator of nuclear factor-kappaB ligand (RANKL) inhibitor monoclonal antibody. Denosumab blocks the binding of RANKL to RANK, which leads to decreased differentiation of osteoclasts, their activity and survival, and ultimately reduces bone resorption. Denosumab, unlike bisphosphonates, does not itself incorporated into the bone matrix and its anti-resorptive effect is therefore more quickly reversible following the end of treatment (Hanley et al., 2012). However, denosumab is typically given as a 60 mg subcutaneous injection once every 6 months, which is relatively easy to administer as compared to more frequently used oral therapies.

Denosumab' was shown to be effective for the prevention of osteoporotic fractures in the pivotal FREEDOM trial. Denosumab was compared to placebo in this randomized controlled trial of 7,868 postmenopausal women with osteoporosis over 3 years of treatment to assess the efficacy of denosumab in suppressing the occurrence of new radiographic vertebral fractures versus placebo. The cumulative incidence of new vertebral fractures was 2.3% for denosumab and 7.2% for placebo, a 68% relative risk reduction. There were also considerable decreases seen in hip and nonvertebral fractures (Cummings et al., 2009).

These results validated denosumab as a therapeutic agent for those who are at a high risk of osteoporotic fractures. There is since then growing clinical interest in the direct comparative effectiveness of denosumab and bisphosphonates. Both myeloablation and therapeutic continue to markedly inhibit bone resorption rates, but there may be different relative effects on the rates of BMD. Denosumab was directly compared to weekly oral alendronate in a randomized phase III study of women with low bone mass who were postmenopausal. Following 12 months of therapy, the total hip BMD rose about 3.5% with denosumab and 2.6% with alendronate. The increase in BMD at the lumbar spine, femoral neck, trochanter and one-third radius was also significantly larger with denosumab, as compared to control (Brown et al., 2009). The results indicate that denosumab might provide greater densitometric effects than some other frequently used bisphosphonates. However, an incremental increase in BMD is not directly linked to a proportional decrease in clinically relevant fractures. This is significant, since the primary goal of osteoporosis treatment is actually prevention of fragility fractures other than enhancing BMD. Such a head-to-head difference in favor of denosumab has been demonstrated in a meta-analysis of randomized controlled trials, which showed higher increases in BMD of lumbar spine, total hip, and femoral neck compared with bisphosphonates. The available evidence however was not equally convincing of superiority in fracture prevention, suggesting that the two effects of BMD and fracture outcomes should be analyzed separately when assessing between study relative clinical effectiveness (Lyu et al., 2019). Despite in widespread use of both bisphosphonate and denosumab, there have been uncertainties over the comparative effectiveness of the two in clinical use for osteoporosis. The improvements in the previous studies with use of denosumab have been generally larger for BMD, while there was less definitive evidence for improvements in vertebral fracture, hip fracture, nonvertebral fracture, adverse event, and discontinuation. In addition, comparison results may be affected by the type of bisphosphonate used; if patients have been previously treated with antiresorptive drugs; the length of time the patient has received the bisphosphonate; their baseline fracture risk; and their population characteristics.

2. Literature Review

2.1 Pathophysiology of Osteoporosis and Therapeutic Targets

The normal relationship between bone resorption and bone formation is disturbed, leading to a decrease in bone mass and a deterioration in bone microarchitecture over time in cases of osteoporosis. Bone remodeling is ongoing physiological process of bone resorption by the osteoclasts and bone formation by the osteoblasts. In post-menopausal women, estrogen deficiency stimulates more osteoclast activity and faster bone turnover rates which causes gradual mineralization of bone and greater risk of fragility fractures. This is because the suppression of bone resorption is a key component of the pharmacological approach to preventing osteoporotic fractures. Both bisphosphonates and denosumab inhibit bone resorption, but in different ways. Bisphosphonates are incorporated into the mineralized bone matrix, and are then internalized by actively remodeling osteoclasts. By contrast, denosumab is an extracellular mediator, which via inhibition of RANKL, a key control pathway for osteoclast differentiation and survival, achieves these effects. These differences in pharmacology may affect the level and duration of bone-turnover suppression, the bone mineral density response, treatment adherence and the effects of treatment discontinuation.

2.2 Effectiveness of Bisphosphonates in Osteoporosis

Bisphosphonates are widely employed to prevent or treat osteoporosis, and continue to be one of the most established antireceptor drugs. They persist in binding to bone and their effect is still ongoing even when the concentration of the drug drops to low levels in the blood stream. This explains why the unfractured-effects were maintained despite the long periods of therapy and this gives the justification for interrupting treatment in selected patients. Bisphosphonate therapy is still though a long-term process and fracture risk should be carefully evaluated even though treatment is being considered for this purpose. An American Society for Bone and Mineral Research task force recommended that patients be reassessed after about five years of treatment with oral bisphosphonates, or three years with intravenous bisphosphonates. Those at continued high fracture risk could benefit from ongoing treatments; those at low fracture risk could be considered for a short-term (temporary) drug holiday. Importantly, the task force highlighted that the longer duration of treatment, the higher the risk for atypical femoral fracture, as the absolute risk is still low

in light of the number of osteoporotic fractures avoided when using the treatment in the proper high-risk population (Adler et al., 2016). The continued retention of bisphosphonates in the skeleton thus provides a therapeutic advantage and a significant difference from denosumab. Once discontinued, bisphosphonates have residual antiresorptive activity, which varies with the agent, time of therapy and fracture risk of the patient.

2.3 Clinical Effectiveness of Denosumab

Denosumab's anti-osteoclastic effects and its once every six month administration has made this drug an important therapeutic option to bisphosphonates. Extended use of denosumab has shown sustained BMD gain and no early plateau in treatment efficacy. Progressive increases in BMD at the lumbar spine, total hip, femoral neck, and one-third radius and a low rate of vertebral and nonvertebral fractures were seen in women treated with denosumab for up to 10 years in the FREEDOM trial and an open-label extension phase (Bone et al., 2017). A clinical implication of these results is the importance of chronic care of osteoporosis which could require long-term long-term pharmacotherapy. The sustaining BMD response seen with long-term denosumab exposure is slightly different than the response of some other antiresorptive drugs, where an initial response is generally lost with extended use. This does not apply, however, to the long-term treatment regimen, which depends on patients' tolerance to continuous 6-month dosing as denosumab has no long-acting skeletal retention profile like bisphosphonates.

2.4 Direct Comparison of Denosumab With Zoledronic Acid

To some extent, direct comparative studies have provided the evidence of relative antiresorptive potency of denosumab to individual bisphosphonates. Miller et al. performed a double-blind trial, with 643 women with post-menopausal osteoporosis in five intercontinental centers across the world, who were receiving oral bisphosphonates. The study participants were using either denosumab 60 mg every 6 months or intravenous zoledronic acid 5 mg. Taking denosumab for 12 months resulted in a 3.2% rise in BMD at the lumbar spine compared with 1.1% for zoledronic acid. The total hip was the only other site where denosumab showed a corresponding effect, 1.9% increase with denosumab and virtually no increase with zoledronic acid. Denosumab also achieved greater effects on

bone turnover markers. This study suggests that the change to denosumab may lead to a more pronounced short-term BMD increase compared with change to intravenous zoledronic acid (Miller et al., 2016) in women who have previously been on oral bisphosphonates. This study is of great clinical importance as some patients on long-term oral bisphosphonate therapy may need therapy changes due to insufficient BMD response, lack of compliance, intolerance or persistence of high fracture risk. Use of antiresorptive switches appears to have a higher densitometric response compared with switching to a more potent bisphosphonate alone.

2.5 Comparison with Ibandronate

The same results have been shown compared to the oral ibandronate treatment. Denosumab significantly increased BMD more than the once monthly ibandronate in postmenopausal women previously exposed to bisphosphonates in a randomized trial. At 12 months, total hip BMD was +2.3% and lumbar spine BMD was +4.1% with denosumab, but +1.1% and +2.0% with ibandronate. Increased amounts on the femoral neck were also noted (Recknor et al., 2013). The same trial also showed more potent suppression of serum C-terminal telopeptide with denosumab, further evidence for which this effect would enhance the BMD response. Treatment effects were, however, generally comparable, highlighting the importance of assessing effectiveness and safety as distinct parts of comparison of which effects.

2.6 Effect of Switching from Bisphosphonates to Denosumab

Switching to denosumab versus continued FOS according to pooled individual-patient data has also been looked at for patients that are already taking bisphosphonates. Kendler et al. examined four randomized trials of oral bisphosphonates in 2,850 postmenopausal women, who were previously taking bisphosphonates. Patients were switched to the denosumab or to a bisphosphonate, such as alendronate, risedronate, ibandronate or zoledronic acid. These increases in BMD were significantly higher with denosumab at 12 months at the lumbar spine, total hip, femoral neck, and 1/3 radius. Further, denosumab resulted in significantly deeper decreases in both serum CTX and P1NP levels, which could serve as markers of greater inhibition of bone turnover. The rate of adverse events was comparable among treatment groups as per the overall findings (Kendler et al., 2020). The results add

to the proof that denosumab is superior to continued bisphosphonate therapy in terms of achieving higher BMD gain, at least for those that have previously experienced oral bisphosphonate treatment. However, the clinical relevance of moderate differences in BMD will only be determined when they become associated with a decrease in clinical fracture rates (vertebral, hip and others).

2.7 Adherence, Persistence, and Patient Preference

Adherence to therapy is a key determinant of therapeutic effectiveness in osteoporosis. Oral bisphosphonates often must be given on an empty stomach, with water and remain sitting up for a certain amount of time after intake. These needs can play a part in low persistence in routine clinical practice. Denosumab Adherence Preference Satisfaction (DAPS) is a direct comparison of denosumab given every 6 months versus alendronate given orally, weekly, that was performed in a randomized crossover design. Denosumab treatment was more adhered to, complied to, and more persistent with than alendronate treatment, in women. Most participants also said they preferred the six-monthly injection over the other treatments, after both of the other were administered (Freemantle et al., 2012). The results demonstrate the need for guidelines when interpreting the difference between efficacy studies conducted in a controlled clinical trial and effectiveness in the real world. Poor adherence to a pharmacologically effective drug may be associated with decreased clinical effect. A lower frequency of administration may thus help with treatment persistence, albeit treatment with denosumab needs to be taken according to the 6-month regime.

2.8 Treatment Discontinuation and Rebound Fracture Risk

A big drawback of denosumab compared to bisphosphonates is what occurs when you stop using the medication. Denosumab is not incorporated into the skeleton and its antiresorptive activity decreases after cessation of treatment. Bone turnover can subsequently increase rapidly and BMD gained during therapy can be lost. A post hoc evaluation and follow-up analysis of the FREEDOM trial and its extension revealed that the incidence of vertebral fracture rose significantly after stopping denosumab treatment. Multiple fractures were relatively common among those patients who had a vertebral fracture and stopped denosumab, especially among patients with a prior vertebral fracture.

The investigators were thus keen to stress the need to switch patients to a new antiresorptive upon its discontinuation (Cummings et al., 2018). The phenomenon of rebound is important to consider clinically. An unplanned drug holiday should not be considered in patients receiving denosumab, unlike in appropriately selected bisphosphonate treated patients. Pre-procedure planning and availability of subsequent anti-resorptive therapy should therefore be considered prior to initiation of denosumab.

2.9 Drug Holidays and Long-Term Treatment Strategy

A drug holiday has been known for a long time in a selected group of bisphosphonate treated patients due to the fact that bisphosphonates store in mineralized bone and continue to have their antiresorptive action after they leave the body forever. But no other drug in the class of antiresorptives can be treated exactly like this one. After some years of bisphosphonate use, in some patients with lower risk, bisphosphonate interruption may be considered, based on a European Menopause and Andropause Society position statement, which required a period of interruption to depend on the type of bisphosphonate and the fracture risk of the patient. On the other hand, when denosumab is discontinued, there is a need for significantly more care, due to rapid denosumab reversal of a state of bone turnover inhibition and the possibility of fracture rebound (Anagnostis et al 2017).

2.10 Overall Evidence and Remaining Research Gap

Previous comparative evidence has shown similar and moderate improvements in BMD with denosumab versus individual bisphosphonates. It has been shown against the oral drugs ibandronate, alendronate and intravenous zoledronic acid. Often, too, there is a more pronounced suppression of biochemical markers of bone turnover. However, the quality of the BMD improvements does not necessarily equate to quality of clinical effect. Fragility fracture is the main outcome of all osteoporosis management, and many direct comparative trials are based on outcomes related to changes in BMD, not are fracture endpoints. Sample sizes and follow-up durations might then be too small and too short to reliably look for differences in relatively rare outcomes like hip fractures. Additionally, patients may vary in terms of their risk for fracture prior to treatment, as well as previous exposure to bisphosphonates, comparator drug, method of administration, treatment duration, and variance across studies may influence results. Safety is also multi-dimensional to consider

as there are different long-term concerns of therapeutic classes. Denosumab has rebound when discontinued and Bisphosphonates can have long-term negative effects after extended use. Extended use of denosumab has the potential for rebound effects whereas Bisphosphonates are negatively affected after prolonged use with skeletal retention. Systematic review and meta-analysis examining BMD outcome, fracture outcomes, markers of bone metabolism, adverse event, and discontinuation rates of the therapies are needed to offer a balanced comparison between denosumab and bisphosphonates.

3. Methodology

3.1 Study Design

This study will be a systematic review and meta-analysis of the comparative effectiveness and safety of denosumab vs bisphosphonates in the treatment of osteoporosis. The review will be done in harmony with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 which ensure transparent reporting of study identification, screening, eligibility assessment, data extraction and evidence synthesis (Page et al., 2021). The research question will follow the Population, Intervention, Comparator and Outcomes format. Study population will consist of adults with osteoporosis, especially post menopausal women. The intervention will be denosumab, and commonly used bisphosphonates (alendronate, risedronate, ibandronate and zoledronic acid) will be used as comparators. Primary outcomes will consist of changes in bone mineral density, fractures, bone turnover markers, adverse events and discontinuation of treatment.

3.2 Search Strategy and Information Sources

PubMed/MEDLINE, Embase, Scopus, Web of Science and Cochrane Central Register of Controlled Trials will be searched using a comprehensive literature search. Databases will be searched from the beginning to the last date automatically set for the search. A hand search of reference lists of relevant and suitable studies and systematic reviews will also be conducted for further studies. A search strategy of combining Medical Subject Headings and free keywords to demonstrate osteoporosis, denosumab and bisphosphonates will be used. Boolean operators will be used to combine terms like "osteoporosis" and "bone mineral density" (BMD) and "denosumab" (RANKL inhibitor) and "bisphosphonate" and

"alendronate" and "risedronate" and "ibandronate" and "zoledronic acid". Search strategies will be tailored to the indexing of the various databases they will be searching for and will be detailed to facilitate Reproducibility in accordance with PRISMA recommendations (Page et al., 2021).

3.3 Eligibility Criteria

Studies will be incorporated if they examine adults suffering from osteoporosis and compare denosumab with at least one bisphosphonate. Effectiveness and/or safety outcomes relevant to the topic of the research will be included in the data sets. Effectiveness will be reported by randomized controlled trials and comparative clinical studies. Studies will need to give adequate quantitative information necessary for extracting or calculating treating effects. Only studies involving pediatric populations, malignancy-related bone disease for which there is no separate data on osteoporosis, animal or laboratory experiments, case report, narrative review, editorials and studies that report the results without comparison will be excluded. Multiple publications from the same study population will be reviewed carefully and only the longest (most detailed) report should be used in the comparison of the study population to the same outcome.

3.4 Outcomes of Interest

The major endpoints will be percentage change from baseline in bone mineral density of the lumbar spine, total hip, and femoral neck and incidence of clinical fracture, vertebral fracture, hip fracture, and nonvertebral fracture. Secondary outcomes will include changes in plasma biochemical markers of bone turnover, including the C-terminal telopeptide and procollagen type I N-terminal propeptide. Safety endpoints will be overall adverse events, serious adverse events, treatment discontinuation, hypocalcemia, osteonecrosis of the jaw, and atypical femoral fractures. If possible, adherence and persistence to treatment will also be addressed.

3.5 Study Selection and Data Extraction

Anything found on the electronic databases will be imported into reference-management software and duplicated information will be deleted prior to screening. Articles will first be assessed for relevance by their titles and abstracts followed by assessment of full texts for

possible eligibility. Ideally, two reviewers will independently conduct the screening and study-selection process. Any disagreement will be made by discussing and agreeing issues with a third reviewer, if needed. This will be abbreviated in the last study-selection process utilizing a PRISMA flow graph (Page et al., 2021). A standard data-extraction form will be used to extract data. Data gathered will contain the following elements from the studies: study author(s), publication year, country, study design, sample size, age of patients, prior osteoporosis treatment, characteristics of the intervention and comparator, study duration, baseline BMD status, changes in BMD, incidence of fractures, biochemical markers, adverse events, and the number of subjects who discontinued treatment. The kind and method of bisphosphonate administration will also be documented as this can affect effectiveness comparison.

3.6 Risk of Bias Assessment

Existing criteria from the Cochrane Handbook of Systematic Reviews to be used to assess risk of bias in the included randomized controlled trials (RCTs) will be applied. These important domains will encompass events such as the generation of random sequences, allocation concealment, blinding, missing outcome data, outcome measurement, and selective reporting (Higgins et al., 2011). If nonrandomized comparative studies are reported, they will be assessed independently by a validated risk-of-bias tool. Two reviewers will make independently conducted risk-of-bias assessments and disagreements will be resolved by consensus. These evaluations will be taken into account in interpreting pooled treatment effect.

3.7 Statistical Analysis

When two or more studies are sufficiently similar and make the same finding, quantitative synthesis will be done. Pooled mean differences with 95% confidence intervals will be derived for continuous outcomes that are measured on a common scale, e.g., mean difference in % change in BMD. If more than one scale is used standardized mean differences will be used. Pooled risk ratios with 95% confidence intervals will be computed for dichotomous conversion events such as vertebral fractures, hip fractures, non-vertebral fractures and adverse events. A random-effects model is preferred as clinical heterogeneity is likely to exist between studies in terms of patient demography, previous

osteoporosis therapy, type of bisphosphonate used, and length of time followed. The results of the Cochran's Q test and I^2 will be used to assess statistical heterogeneity. The I^2 statistic is an index that quantifies the amount of variability in pooled estimates which could be explained by a real difference in study effects, as opposed to a sampling error (Higgins et al., 2003). Similar to differences in study populations, interventions, and methodological characteristics, heterogeneity will also be discussed in terms of differences.

3.8 Publication Bias and Certainty of Evidence

According to Michelangelo, when enough studies are present on a specific outcome the issue of publication bias will be evaluated. Funnel plots can be looked at visually for small study effects, and Egger's regression test can be performed to determine if a small study effect is present (Egger et al., 1997). When there are few studies included, the term such analyses will be used with a modicum of caution. The overall certainty of evidence to major outcomes can be assessed by applying the GRADE approach. The Confidence in the findings of the pooled estimates approach used in this system takes into account risk of bias, inconsistency, indirectness, imprecision and publication bias. This approach to determining confidence in the pooled estimate of the effect of the system includes risk of bias, inconsistency, indirectness, imprecision, and publication bias. BMD data and fracture incidence, as well as serious adverse events will be considered as major outcomes for certainty assessment.

4. Results

4.1 Study Selection and Characteristics

The body of literature studying the relative efficacy of denosumab and bisphosphonates included mostly postmenopausal women with osteoporosis or BMD loss. Bisphosphonate comparators outlined in each study ranged from alendronate to risedronate, ibandronate and zoledronic acid. There were several direct comparative trial follow-up periods, typically from 6 to 24 months, and extension and long-term observational data were available for selected outcomes. The final PRISMA flow chart should include the actual counts of identified records, excluded duplicate records, records screened, articles for which full text was obtained, excluded articles as to why, and why articles were included in the quantitative synthesis. These numbers must be determined after completion of the last

stages of database search and screening process, not estimated beforehand. A larger BMD response has been confirmed by recent comparative evidence with denosumab. The systematic review and meta-analysis (Zhu et al., 2026) of 13 RCTs and 3364 participants was performed in 2026, revealing statistically significant increases in BMD in the lumbar spine, femoral neck, distal radius and total hip for denosumab compared to alendronate.

Table 1. Summary of Recent Comparative Evidence

Study	Design/Population	Comparison	Follow-up	Main Finding
Thal et al. (2023)	Meta-analysis of 7 RCTs in postmenopausal osteoporosis	Denosumab vs bisphosphonates	Varied	No significant reduction in clinical or osteoporotic fractures with denosumab
Kobayashi et al. (2024)	Meta-analysis of 11 RCTs; 5,545 patients	Denosumab vs bisphosphonates	12–24 months	Overall safety broadly comparable, but differences were observed for selected adverse outcomes
Zhu et al. (2026)	Meta-analysis of 13 RCTs; 3,364 patients	Denosumab vs alendronate	6–24 months	BMD improvement generally favored denosumab
Tang et al. (2026)	Randomized comparative study; 80 postmenopausal women	Denosumab vs zoledronic acid	12 months	Greater BMD improvement and stronger suppression of bone-turnover markers with denosumab
Xu et al. (2026)	Prospective randomized study after osteoporotic vertebral fracture	Denosumab vs zoledronate	24 months	Lower early secondary vertebral fracture incidence with denosumab, but difference was not sustained at 24 months

4.2 Bone Mineral Density Outcomes

The largest difference evident between denosumab and bisphosphonate therapy was for BMD. In comparative studies, denosumab has tended to do the best job of improving mineral bone density at the lumbar spine, total hip, and femoral neck. Zhu et al recently performed a meta-analysis of 13 RCTs and found denosumab to be superior to alendronate across multiple important skeletal sites in increasing BMD. The authors also found significant treatment difference in the lumbar spine (LS), femoral neck (FN), total hip (TH), and distal radius (DR) with varying degrees depending on skeletal site, duration of follow-up, and patient subgroups (Zhu et al., 2026). This can be seen by recent HTO comparisons between denosumab and intravenous zoledronic acid. A total of 80 women aged 45 to 80 years with postmenopausal osteoporosis entered a randomized, comparative trial of 1 year of either denosumab or zoledronic acid. After treatment, BMD at the hip, femoral neck, and lumbar spine was significantly higher in the denosumab than in the zoledronic-acid group. Denosumab also led to higher levels of suppression of P1NP and β -CTX, indicating more effect on bone turnover inhibition (Tang et al., 2026).

4.3 Fracture Outcomes

Results for fracture prevention are more ambiguous than results for BMD. Seven randomized controlled trials specifically assessing fracture outcomes were analyzed in a meta-analysis that showed no statistically significant difference between denosumab and bisphosphonates with respect to clinical fracture or osteoporotic fracture. In addition, the researchers found there to be no distinct correlation between the difference in BMD with the relative effects of fracture (Thal et al., 2023). Later, individual's studies are less consistent but confirm this. Xu et al investigated postmenopausal women with primary osteoporosis who had undergone vertebroplasty for osteoporotic vertebral compression fractures (OVCF). At 12 months, 7.6% of women with vertebral compression fracture had occurred for the first time after receiving zoledronate, while 2.0% of those receiving denosumab had experienced a new vertebral compression fracture. After 24 months, however, those differences became not statistically different, the incidence for the control group was 5.8% and for the intervention group was 8.2%. (Xu et al., 2026) The results suggest a benefit of denosumab on fracture prevention in certain high-risk subjects or in the very early phase of follow-up, while the available evidence suggests a lack of

consistent overarching benefit with respect to fracture prevention as a class compared with bisphosphonates.

4.4 Bone Turnover Markers

The results of the biochemical markers correlated with changes in the BMD. Comparative studies often revealed greater bone resorption and formation markers reductions with denosumab treatment. In the randomized comparison reported by Tang et al., for instance, P1NP and β -CTX levels were significantly lower after denosumab treatment than after zoledronic acid at follow-up. This greater decrease of the markers is in line with denosumab's (Tang et al., 2026) potent inhibition of RANKL-mediated osteoclast activity. While these results show greater inhibition of bone remodeling, intermediate biological endpoints such as the biochemical marker changes should not be used to replace fracture endpoints.

4.5 Safety Outcomes

Overall, the profile of denosumab and bisphosphonates were generally also well tolerated in the randomized comparative trials. But a recent comparison based on meta-analysis pointed out distinct variations in some particular harmful effects. Kobayashi et al. reviewed 11 randomized studies with 5,545 patients with primary osteoporosis. The incidence of discontinuations for adverse events (AEs) was also lower with denosumab than bisphosphonates (RR 0.49; 95% CI 0.34-0.71). There were, however, some outcomes in a selected list that had a risk that was above the pooled risk for the combined studies, such as infections and cardiovascular adverse events. The authors pointed out that due to the limitations of the trials included, all of them had potential risks for bias, and that these signs should not be taken as conclusive evidence of a true difference in harm (Kobayashi et al., 2024). However, adverse effects were reported by 2.5% of patients given denosumab to 27.5% of those given zoledronic acid in the smaller, randomized trial by Tang et al. This disparity may be due to the specific population studied and comparator and should not be extended beyond these individual bisphosphonates until pooled data exists (Tang et al., 2026).

Table 2. Overall Pattern of Comparative Outcomes

Outcome	Comparative Evidence	Overall Pattern
Lumbar spine BMD	Consistent improvement in comparative trials/meta-analyses	Favors denosumab
Total hip BMD	Greater increase reported in many direct comparisons	Favors denosumab
Femoral neck BMD	Generally greater increase with denosumab	Favors denosumab
Bone turnover markers	Greater suppression frequently observed with denosumab	Favors denosumab biologically
Clinical/osteoporotic fractures	No consistent significant overall difference in meta-analysis	No established superiority
Vertebral fractures	Possible benefit in selected populations and analyses	Evidence remains heterogeneous
Overall adverse events	Generally similar overall	No consistent major difference
Withdrawal due to adverse events	Lower with denosumab in a recent safety meta-analysis	May favor denosumab
Specific safety outcomes	Signals vary according to event and study	Requires cautious interpretation

5. Discussion

5.1 Principal Findings

While both denosumab and bisphosphonates are effective antiresorptive osteoporosis treatments, there are important differences in their effects on bone mineral density, fracture outcomes, treatment persistence and management after drug discontinuation. The largest increases in BMD that have been reported with denosumab occur at major skeletal sites such as the femoral neck, total hip, and lumbar spine. But the evidence for matching improvement in the prevention of fractures is less consistent, especially in head-to-head randomized studies. This separation is clinically relevant because although a BMD increase may be an important treatment outcome it is not the real treatment target. However, the key objective of osteoporosis management is to prevent such fractures as

vertebral, hip, and other fragility fractures. Several oral drugs for osteoporosis were associated with a decrease in fracture risk and showed varying effects related to fracture type and therapeutic class in a large network meta-analysis of randomized clinical trials (RCs) (Händel et al., 2023).

5.2 Interpretation of the BMD Advantage With Denosumab

The increased BMD seen with denosumab is biologically plausible due to the high inhibitors of the RANKL pathway. The inhibition of RANKL-induced osteoclastogenesis and activation by denosumab leads to substantial inhibition of bone resorption. Bisphosphonates have in addition inhibitory effects on the bone resorption by osteoclasts but work by being taken up into mineralized bone after incorporation and by active osteoclasts. Because of the difference in their mechanisms, part of the reason why denosumab tends to induce larger increases in BMD in many head-to-head trials. However, more recent clinical reviews have persistently described denosumab as a powerful antiresorptive drug that can produce significant and prolonged (on going treatment) BMD loss improvements while denosumab is being administered (Diab and Watts, 2024). However, the numerical value of the increase in BMD cannot be taken as a direct measure of proportional fracture protection. BMD is just one measure of bone strength, and other factors, such as age, fracture history, falls, bone quality, cortical and trabecular architecture, comorbidities, and treatment adherence, all factor into fracture risk.

5.3 Fracture Prevention and Real-World Effectiveness

The increased BMD gain with denosumab compared to other drugs in prior randomized trials was one of the study's biggest unknowns whether the relationships result in clinically meaningful differences in fracture rates. The many head-to-head randomized trials often had primary endpoints focused on changes in BMD and were not necessarily powered to measure fracture outcomes and thus likely were not sufficiently powered to demonstrate differences in relatively rare events like hip fracture. These are interesting observations that add value to the story from more recently sourced parts of the story. The use of denosumab in nearly half a million treatment-naïve postmenopausal women was linked to a reduction in the risk of major osteoporotic fracture, hip fracture, nonvertebral fracture, and hospitalized vertebral fracture relative to alendronate, in a large, retrospective cohort study.

However, the extent of the observed decrease increased with treatment time as discussed by Curtis et al. (2024). The evidence, however, should be taken with a grain of salt, due to the limitation of observational research. The allocation of treatment in real-world studies is not random; however, treatment effects are likely to be influenced by residual confounding even after applying sophisticated statistical adjustment. Furthermore, the rich industry participation in the Curtis et al. study needs to be taken into account when considering the results.

5.4 Safety and Long-Term Treatment Considerations

The safety profile of denosumab and bisphosphate drugs are generally acceptable when patients are carefully selected and monitored. The two therapeutic classes have different types of risks that are specific to long term management, however. They have broad long-term clinical experience with few reported side effects, including atypical femoral fracture and osteonecrosis of the jaw (especially with long-term use). Concurrently, their long skeletal retention causes them to have long-lasting antiresorptive effects following withdrawal of therapy. Among the different safety profiles is that of denosumab. Infections, hypocalcemia, dermatological events, osteonecrosis of jaw and Atypical Femoral Fracture have been a concern with it in the past. However, as the drug was used more recently, many of these potential risks have been alleviated (Diab and Watts, 2024); management question remains on treatment duration and its discontinuation.

5.5 Importance of Denosumab Discontinuation

One of the biggest and most important differences between the two treatments is that one is given the chance to discontinue. Bisphosphonates are still present in mineralized bone after cessation of therapy and may even continue to have an anti-resorptive effect. This persistent skeletal reservoir is not seen with Denosumab. After denosumab withdrawal, bone turnover secondary to the drug may accelerate and result in higher than pretreatment levels, which may be offset by loss of BMD during therapy. Recent studies have helped to confirm worries that this rebound effect may lead to subsequent rebound vertebral fractures when treatment is discontinued without proper follow-up antiresorptive therapy. Based on the current review, bisphosphonates may be used to maintain BMD following the discontinuation of denosumab and are likely to be more effective after short, timed

exposures; the pattern after longer duration of denosumab use is not well known (Kumar et al., 2025). This is corroborated by real world evidence from drug safety pharmacoepidemiology. Martín-Pérez et al. were able to conclude that the discontinuation of denosumab resulted in higher risk of multiple vertebral fractures, not only when compared with continued denosumab use, but also when compared with discontinuation of bisphosphonates. The highest relative risk occurred shortly after the patient left the platform and after increased, cumulative exposure (Martín-Pérez et al., 2025).

5.6 Adherence and Practical Treatment Selection

Factors other than the pharmacological potencies are also important for the effectiveness of osteoporosis therapy in clinical practice, including the capability and willingness of patients to take the therapy. Although treatment for osteoporosis is highly effective, it still is significantly under-utilized, and barriers such as concerns for adverse effects, lack of patient education, non-adherence and health-system barriers are obstacles to the use of these effective treatments have hindered their uptake (Ayub et al., 2021). There are a number of practical benefits to bisphosphonates. There are plentiful evidence-based fracture-prevention data and relatively low cost and many generic oral formulations readily available. Administration by mouth, however, may be impractical since the patient has to follow certain special rules for fasting and posture. In others, adherence is even more reduced, due to gastrointestinal intolerance. The advantage of giving denosumab six times per year by injection into a muscle is that it will not have many of the practical difficulties that might otherwise prevent patients from swallowing bisphosphonates. This convenience requires more rescue, however, because of the greater need for prompt administration. If a dose is not taken or is taken significantly late, the antiresorptive effect may be lost, so this is particularly important when follow-up is needed.

5.7 Clinical Implications

Results of this review indicate that a one-size-fits-all osteoporosis anti-resorptive therapy does not exist. Bisphosphonates have proven to be effective drugs and are still considered a good choice of treatment in patients where oral or intravenous administration is appropriate and there is a benefit of the long-term continuing residual skeletal activity. Patients who are intolerant of oral bisphosphonates, who have poor capacity to take oral

bisphosphonates or who need a potent antiresorptive agent that will cause a significant increase in BMD benefit could particularly benefit from denosumab. However, current reviews acknowledge denosumab as an effective treatment alternative in patients at high fracture risk, especially those who have an inadequate response to other treatments (Diab and Watts, 2024).

5.8 Strengths and Limitations

The focus of this review on two widespread strategies for the treatment of antiresorptives is an important strength. When assessing the effectiveness of an intervention, using multiple surrogate measures in addition to evaluating BMD and fracture outcomes gives a more comprehensive assessment of effectiveness than a single surrogate measure. The other aspect of strength is the inclusion of evidence with random controlled designs as well as clinically relevant, relevant contemporary comparative evidence. Fracture outcomes may be obtained from large real-world studies, which may be underpowered to explore the results of single randomized head-to-head trials. There are, however, some caveats to remember. Second, there is clinical heterogeneity since the different bisphosphonates are classified in a single comparator category and can have different potencies, routes of administration, dosing frequency, and evidence of fractures. Second, is the variation of study populations based on age and baseline BMD, fracture history and prior therapy for osteoporosis. Third, many direct randomized comparisons has relatively short follow-up periods and were primarily directed toward the BMD endpoints. Lastly, there is a large treatment gap in the osteoporosis field. Rare adverse effects and fear thereof can lead to non-initiation or inappropriate cessation of therapy in the context of significantly higher burden to be borne by the untreated fragility fracture risk (Ayub et al., 2021).

5.9 Future Research

Future studies must focus on sufficiently powered head-to-head studies focusing on fracture results and not only BMD. Follow-up will be especially useful for patients with hip fractures, long-term adverse events, and treatment persistence, in particular, for lengths of follow-up. Further studies are also needed to identify a best-prescribed management approach after discontinuing denosumab treatment. Evidence suggests sequential bisphosphonate-based therapy may be effective to decrease rebound bone loss, depending

on the duration of denosumab use and time of bisphosphonate administration (Kumar et al., 2025). Longer comparative studies should consequently consider not just the first therapy (denosumab or bisphosphonate) but the whole therapeutic course. This type of strategy is more consistent with the chronicity of osteoporosis and could help to gain a clinically relevant understanding of long-term fracture prevention.

Conclusion

This systematic review and meta-analysis should prove useful in identifying that the use of denosumab is as effective as bisphosphonates for osteoporosis management. Comparative evidence suggests that denosumab typically achieves higher increases at the lumbar spine, total hip and femoral neck in terms of bone mineral density and delivers a more potent effect on biochemical markers of bone turnover. However, the higher densitometric effects seen with denosumab have not necessarily been reflected in a convincing advantage over bisphosphonates in reducing vertebral, hip and overall osteoporotic fractures. Both treatments are safe, well studied and can be used when appropriately prescribed, however, they can have very different long-term management. Although the effects of bisphosphonates on the skeleton persist after discontinuation, with denosumab care must be taken when discontinuation due to rapid reversing of bony effect is required. Treatment chosen should be tailored to the fracture risk, prior treatment, renal function, ability to adhere to treatment and patient preference, tolerability and ability to implement an appropriate long-term therapy.

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