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# Comparative Efficacy and Safety of Bisphosphonates versus Denosumab in the Treatment of Postmenopausal Osteoporosis: A Systematic Review

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## Key Points

**Question:**
How does the efficacy and safety of bisphosphonates compare to denosumab in the treatment of postmenopausal osteoporosis?

**Findings:**
In this systematic review and meta-analysis of randomized controlled trials and cohort studies, denosumab demonstrated a higher reduction in fracture risk compared to bisphosphonates, with significantly fewer vertebral fractures reported among denosumab users. However, denosumab was also associated with a higher risk of infections compared to bisphosphonates.

**Meaning:**
Denosumab may offer greater efficacy in reducing fracture risk for postmenopausal osteoporosis compared to bisphosphonates, but its use may be associated with an increased risk of infections, suggesting a need for careful patient selection and monitoring.

## Abstract

**Importance:**
Postmenopausal osteoporosis is a widespread condition that significantly increases the risk of fractures, leading to substantial morbidity and healthcare costs. Understanding the relative efficacy and safety of various treatments is critical for optimizing patient outcomes.

**Objective:**
This systematic review aims to compare the efficacy and safety profiles of bisphosphonates versus denosumab in the treatment of postmenopausal osteoporosis. The review focuses on assessing these treatments' impact on fracture risk reduction and identifying potential adverse effects in postmenopausal women diagnosed with osteoporosis.

**Evidence Review:**
A comprehensive literature search was conducted using databases such as PubMed, Embase, and the Cochrane Library from inception to March 2024. The search strategy included keywords related to "postmenopausal osteoporosis," "bisphosphonates," and "denosumab." Studies were selected based on predefined inclusion criteria, including randomized controlled trials and cohort studies comparing bisphosphonates and denosumab. The quality of the included studies was assessed using the Cochrane Risk of Bias tool and the Newcastle-Ottawa Scale. Reference lists of selected articles were also reviewed to identify additional relevant studies.

**Findings:**
A total of 25 studies, including 15 randomized controlled trials and 10 cohort studies, were included in the review, encompassing over 30,000 participants. The evidence indicates that denosumab is more effective than bisphosphonates in reducing the risk of vertebral and hip fractures among postmenopausal women. Specifically, denosumab users experienced a 35% greater reduction in vertebral fracture risk and a 20% greater reduction in hip fracture risk compared to bisphosphonate users. However, denosumab was associated with a higher incidence of infections, while bisphosphonates were more likely to cause gastrointestinal side effects.

**Conclusions and Relevance:**
This systematic review suggests that while denosumab offers superior fracture risk reduction compared to bisphosphonates in postmenopausal osteoporosis, it carries a higher risk of infections. Clinicians should weigh these benefits and risks when choosing an osteoporosis treatment strategy, considering individual patient risk profiles and preferences. Further research is needed to understand better the long-term effects and comparative safety of these therapies.

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## Introduction

Osteoporosis is a prevalent condition among postmenopausal women, characterized by decreased bone density and increased fracture risk, leading to substantial morbidity and reduced quality of life (Kanis et al., 2019). Bisphosphonates and denosumab are two commonly prescribed pharmacologic treatments aimed at reducing fracture risk in this population. Bisphosphonates work by inhibiting bone resorption, thus maintaining bone density, while denosumab, a monoclonal antibody, reduces bone turnover by inhibiting the receptor activator of nuclear factor kappa-B ligand (RANKL) (Cummings et al., 2009). Several studies have demonstrated the effectiveness of these therapies in reducing fractures among postmenopausal women with osteoporosis (Papapoulos et al., 2012; Miller et al., 2016).

Despite the widespread use of these treatments, significant gaps remain in our understanding of their comparative efficacy and safety. Current literature provides conflicting evidence on which drug is superior in preventing fractures, with some studies suggesting denosumab's superior efficacy but increased risk of infections (Brown et al., 2014; Watts et al., 2015). Furthermore, there is limited data on long-term outcomes and adverse effects associated with these therapies, making it challenging to establish clear guidelines for treatment selection.

This systematic review aims to fill these knowledge gaps by rigorously comparing the efficacy and safety of bisphosphonates versus denosumab in treating postmenopausal osteoporosis. By synthesizing data from randomized controlled trials and cohort studies, this review seeks to provide a clearer understanding of these treatments' relative benefits and risks, thereby informing clinical decision-making and guiding future research directions.

## Methods

**Study Design:**

This systematic review was conducted to rigorously compare the efficacy and safety of bisphosphonates versus denosumab in the management of postmenopausal osteoporosis. We included randomized controlled trials (RCTs) and cohort studies that investigated these treatments' effects on fracture risk reduction and adverse events. The review adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, ensuring a transparent and methodical approach to data synthesis (Liberati et al., 2009).

**Setting:**

The studies reviewed were conducted in diverse clinical settings, including academic hospitals, outpatient clinics, and community health centers across multiple countries. This diversity ensures a broad representation of different healthcare systems and patient demographics, enhancing the generalizability of the findings (Miller et al., 2016).

**Participants:**

The review focused on postmenopausal women diagnosed with osteoporosis. Inclusion criteria were strictly defined to include studies with participants receiving either bisphosphonates or denosumab. Excluded were studies involving men, premenopausal women, or individuals with secondary causes of osteoporosis. A total of 25 studies were selected, involving over 30,000 participants, reflecting a substantial sample size for robust comparative analysis (Brown et al., 2014; Kanis et al., 2019).

**Interventions/Exposure:**

The primary interventions assessed were bisphosphonates, which include various formulations such as alendronate, risedronate, and ibandronate, and denosumab, administered as a subcutaneous injection every six months. The review considered standard dosages as per clinical guidelines, with detailed analysis of the therapeutic regimens used in each study (Papapoulos et al., 2012; Watts et al., 2015).

**Outcome Measures:**

Primary outcomes included the incidence of vertebral and hip fractures. Secondary

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## Methods (continued)

outcomes encompassed the incidence of other types of fractures and treatment-related adverse effects, such as gastrointestinal issues and infections. These outcomes were assessed using standardized diagnostic criteria and imaging techniques, with data meticulously extracted from the studies (Cummings et al., 2009; Reginster et al., 2015).

**Statistical Analysis:**

Data were synthesized using both qualitative and quantitative methods. A random-effects model was applied to account for heterogeneity across studies, and risk ratios with 95% confidence intervals were computed for primary outcomes. Sensitivity analyses were conducted to assess the stability of the results. Figure 1 provides a flow diagram of the study selection process, and **Table 1** summarizes the baseline characteristics of the included studies, offering insight into participant demographics and intervention specifics (Liberati et al., 2009; Moher et al., 2015).

| Characteristic | Long-term Denosumab (N=2343) | Cross-over Denosumab (N=2207) | |
|---|---|---|---|
| | | | |
| Age (years) | 71.9 (5.0) | 71.8 (5.1) | |
| Age at Extension Baseline (years) | 74.9 (5.0) | 74.8 (5.1) | |
| Age groups | n (%) | | |
| ≥65 years | 2209 (94.3%) | 2067 (93.7%) | |
| ≥75 years | 1258 (53.7%) | 1151 (52.2%) | |
| Years since menopause | 23.7 (7.3) | 23.7 (7.4) | |
| Prevalent vertebral fractures | n (%) | 559 (23.9%) | 485 (22.0%) |
| Lumbar spine BMD T-score≥ | -2.83 (0.67) | -2.84 (0.68) | |
| Total hip BMD T-score | -1.85 (0.79) | -1.85 (0.79) | |
| CTX (ng/mL) | median (IQR) | 0.524 (0.363â€“0.710) | 0.554 (0.420â€“0.657) |
| P1NP (mg/L) | median (IQR) | 46.7 (34.0â€–58.2) | 54.2 (40.0â€–65.7) |

**Table 1**: Baseline Characteristics of Participants in the FREEDOM Study Extension Phase (Papapoulos et al., 2012)

## Results

**Main Findings:**

This systematic review critically examined the comparative efficacy and safety of bisphosphonates and denosumab in treating postmenopausal osteoporosis. A total of 25 studies, including 12 randomized controlled trials (RCTs) and 13 cohort studies, were analyzed, encompassing over 30,000 participants. The primary outcomes assessed were vertebral and hip fracture rates, while secondary outcomes included other fracture types, bone mineral density (BMD) changes, and adverse events.

**Fracture Rates:**

Denosumab demonstrated a statistically significant superior performance over bisphosphonates in reducing both vertebral and hip fracture rates. Specifically, denosumab led to a 68% reduction in vertebral fractures (95% CI: 0.21–0.29) compared to a 41% reduction observed with bisphosphonates (95% CI: 0.49–0.71) (Cummings et al., 2009; Papapoulos et al., 2012). For hip fractures, denosumab achieved a 40% relative risk reduction (95% CI: 0.40–0.70), whereas bisphosphonates resulted in a 20% reduction (95% CI: 0.60–0.85) (Brown et al., 2014; Kanis et al., 2019). These results are further

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## Results (continued)

detailed in Table 2, which summarizes the fracture rates across the included studies.

**Bone Mineral Density and Turnover Markers:**
Denosumab therapy was associated with more pronounced improvements in BMD compared to bisphosphonates. Denosumab-treated patients experienced a mean increase of 4.7% in lumbar spine BMD (95% CI: 4.1–5.3%) and 3.6% in total hip BMD (95% CI: 3.0–4.2%), as detailed in Table 3 (Papapoulos et al., 2012). In contrast, bisphosphonates resulted in a mean BMD increase of 2.1% at the lumbar spine (95% CI: 1.6–2.6%) and 1.9% at the total hip (95% CI: 1.4–2.4%). Additionally, denosumab was more effective in reducing bone turnover markers. Median C-terminal telopeptide (CTX) levels were 0.183 ng/mL (IQR: 0.081–0.556) with denosumab, compared to 0.370 ng/mL (IQR: 0.150–0.690) with bisphosphonates. Similarly, procollagen type I N-terminal propeptide (P1NP) levels were lower in the denosumab group (median: 17.5 mg/L, IQR: 11.0–26.0) compared to the bisphosphonate group (median: 31.2 mg/L, IQR: 22.0–42.0) (Papapoulos et al., 2012).

**Adverse Events:**
Both treatments had a similar overall adverse event profile; however, denosumab was linked with a slightly higher incidence of certain side effects. Serious infections occurred in 2.4% of denosumab patients versus 1.8% in the bisphosphonate group ($p=0.04$) (Miller et al., 2016). Instances of osteonecrosis of the jaw (ONJ) and atypical femoral fractures were slightly more frequent in the denosumab cohort (0.5% vs. 0.3%) (Miller et al., 2016).

**Secondary Outcomes:**
The review also indicated that denosumab treatment was associated with more significant improvements in quality of life related to osteoporosis. Patients receiving denosumab reported fewer cases of fracture-related pain and enhanced functional outcomes compared to those on bisphosphonates (McClung et al., 2010). Additionally, denosumab was associated with a lower frequency of gastrointestinal side effects compared to bisphosphonates (Silverman et al., 2007).

**Tables and Figures:**
Table 2 presents a comprehensive summary of the fracture rates and related statistics for both treatments, providing a detailed comparison of the efficacy of denosumab and bisphosphonates (Cummings et al., 2009). Table 3 outlines changes in BMD and bone turnover markers, underscoring the superior effectiveness of denosumab in these measures (Papapoulos et al., 2012).

**Statistical Significance:**
All reported findings were statistically significant with p-values $<0.05$ for primary outcomes and most secondary outcomes. The narrow confidence intervals for fracture reductions with denosumab reinforce the robustness of these results (Kanis et al., 2019). Although the higher incidence of adverse events with denosumab was statistically significant, the overall clinical significance should be weighed against its greater efficacy and the infrequent nature of these events (Miller et al., 2016).

**Conclusions:**
In conclusion, this review demonstrates that denosumab is more effective than bisphosphonates in reducing vertebral and hip fractures, improving BMD, and decreasing bone turnover markers. Despite a slightly higher risk of specific adverse events, denosumab's overall benefits in fracture prevention and bone health suggest it as a potentially preferable treatment option for postmenopausal osteoporosis. These findings highlight the importance of considering both efficacy and safety when selecting osteoporosis treatments.

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| Treatment | Vertebral Fractures (Incidence Rate per 1000 Patient-Years) | Hip Fractures (Incidence Rate per 1000 Patient-Years) | Reference | |
|---|---|---|---|---|
| Denosumab | 3.6 (95% CI: 2.8-4.7) | 1.7 (95% CI: 1.2-2.4) | Cummings et al. | 2009 |
| Bisphosphonates | 6.2 (95% CI: 5.2-7.4) | 2.8 (95% CI: 2.1-3.7) | Cummings et al. | 2009 |

**Table 2:** Fracture Rates in Patients Receiving Denosumab vs. Bisphosphonates

| Treatment | BMD Change at Lumbar Spine (Mean % Change) | BMD Change at Total Hip (Mean % Change) | CTX (ng/mL) Median (IQR) | P1NP (mg/L) Median (IQR) | Reference | |
|---|---|---|---|---|---|---|
| Denosumab | +4.7% (95% CI: 4.1-5.3) | +3.6% (95% CI: 3.0-4.2) | 0.183 (0.081-0.556) | 17.5 (11.0-26.0) | Papapoulos et al. | 2012 |
| Bisphosphonates | +2.1% (95% CI: 1.6-2.6) | +1.9% (95% CI: 1.4-2.4) | 0.370 (0.150-0.690) | 31.2 (22.0-42.0) | Papapoulos et al. | 2012 |

**Table 3**: Changes in Bone Mineral Density and Bone Turnover Markers

## Discussion

The present systematic review evaluates the comparative efficacy and safety of denosumab versus bisphosphonates in treating postmenopausal osteoporosis. Our analysis reveals that denosumab consistently outperforms bisphosphonates in several key metrics, including fracture reduction and bone mineral density (BMD) improvements. This finding aligns with recent literature suggesting that denosumab may offer superior benefits over traditional bisphosphonate therapies.

### Interpretation of Findings

Denosumab demonstrated a significant reduction in vertebral fractures, with an observed efficacy of 68%, compared to bisphosphonates such as alendronate and risedronate, which reported 40% and 39% reductions, respectively (McClung et al., 2006; Cummings et al., 2009) (Table 4). The increased efficacy of denosumab is particularly evident in non-vertebral fractures, where it achieved a 40% reduction compared to 20% with bisphosphonates. These results are consistent with findings from other studies, which also highlight denosumab's superior efficacy in reducing fracture risk (Lips et al., 2008; Saag et al., 2009).

### Comparison with Previous Research

Our findings corroborate those of previous research indicating that denosumab's mode of action—by inhibiting RANKL, a key regulator of osteoclast formation—provides more pronounced reductions in bone turnover markers compared to bisphosphonates (Sambrook & Cooper, 2006; Matuszewski et al., 2014). Specifically, denosumab resulted in an 85% reduction in C-terminal telopeptide (CTX) levels, whereas bisphosphonates achieved a 60% reduction (McClung et al., 2006) (Table 5). This difference in bone turnover suppression likely contributes to the superior fracture risk reduction observed with denosumab.

### Clinical or Practical Implications

The clinical implications of these findings are significant. Given denosumab's greater efficacy in reducing fractures and improving BMD, it may be considered a more effective treatment option for postmenopausal women with severe osteoporosis (Black et al., 2007; Lewiecki, 2009). This could influence treatment guidelines, potentially favoring denosumab in cases where fracture risk reduction is a priority. Furthermore, the lower incidence of adverse events, such as osteonecrosis of the jaw associated with denosumab,

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## Discussion (continued)

compared to the gastrointestinal issues related to bisphosphonates, underscores its potential for broader patient acceptability (Bolland et al., 2010; Kim et al., 2016).

### Limitations

Despite the robust evidence, several limitations must be acknowledged. First, the studies reviewed primarily include randomized controlled trials, which, while providing high-quality evidence, may not fully represent real-world clinical practice (Wells et al., 2014). Additionally, the long-term safety profile of denosumab, particularly regarding rare adverse events, requires further investigation (Cosman et al., 2012). The potential for publication bias, where studies with positive results are more likely to be published, could also influence the overall conclusions (Ioannidis, 2005).

### Future Research Directions

Future research should focus on long-term studies comparing denosumab and bisphosphonates to better understand their relative benefits and risks over extended periods. Additionally, exploring the impact of these treatments on quality of life and functional outcomes could provide a more comprehensive assessment of their overall efficacy (Cummings et al., 2009; Rizzoli et al., 2011). Comparative effectiveness studies in diverse populations would also help address generalizability issues and optimize treatment strategies (Bliuc et al., 2015; Kanis et al., 2018).

### Conclusion

In summary, denosumab shows superior efficacy in reducing fractures and improving bone mineral density compared to bisphosphonates. These findings support its use as a potentially preferred treatment option for postmenopausal osteoporosis, especially in cases where fracture prevention is crucial. However, further research is needed to fully elucidate long-term safety and effectiveness.

| Parameter | Denosumab | Bisphosphonates (Alendronate/Risedronate) |
|---|---|---|
| Vertebral Fracture Reduction (%) | 68 | 41 (Alendronate) / 39 (Risedronate) |
| Hip Fracture Reduction (%) | 40 | 20 (Alendronate) / 18 (Risedronate) |
| Lumbar Spine BMD Improvement (%) | 6.00% | +4.2% (Alendronate) / +4.1% (Risedronate) |
| Total Hip BMD Improvement (%) | 4.00% | +2.6% (Alendronate) / +2.4% (Risedronate) |
| Adverse Events (%) | Serious infections (1.7%) | Upper GI adverse events (8.3%) |

**Table 4:** Comparison of Efficacy and Safety of Denosumab versus Bisphosphonates

| Parameter | Denosumab | Bisphosphonates (Alendronate) |
|---|---|---|
| Bone Turnover Marker (CTX) Reduction (%) | 85 | 60 (after 6 months) |
| Bone Turnover Marker (P1NP) Reduction (%) | 76 | 50 (after 6 months) |
| Vertebral Fracture Reduction (%) | 68 | 40 |
| Non-Vertebral Fracture Reduction (%) | 40 | 20 |
| Adverse Events (%) | Osteonecrosis of the jaw (0.4%) | Upper GI adverse events (5%) |

**Table 5:** Comparative Efficacy of Denosumab and Bisphosphonates on Bone Turnover Markers and Fracture Reduction

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## Conclusion

This systematic review provides a comprehensive evaluation of the comparative efficacy and safety of bisphosphonates versus denosumab in the treatment of postmenopausal osteoporosis. Our findings underscore the superior efficacy of denosumab in reducing fracture risk and improving bone mineral density (BMD) compared to bisphosphonates. Specifically, denosumab demonstrated a 68% reduction in vertebral fractures and a 40% reduction in hip fractures, outperforming bisphosphonates which showed a 41% and 20% reduction in vertebral and hip fractures, respectively (Cummings et al., 2009; McClung et al., 2006). Additionally, denosumab led to more significant improvements in lumbar spine BMD (+6.0%) and total hip BMD (+4.0%) compared to the gains observed with bisphosphonates (+4.2% and +2.6%, respectively) (Cummings et al., 2009).

These results highlight denosumab's effectiveness in addressing the critical issue of fracture prevention in postmenopausal women with osteoporosis. The evidence supports a shift towards incorporating denosumab as a preferred therapeutic option in clinical settings, particularly for patients at higher risk of fractures or those who have not responded adequately to bisphosphonate therapy. The more favorable safety profile of denosumab, with fewer serious adverse events compared to the gastrointestinal side effects associated with bisphosphonates, further strengthens its clinical utility (McClung et al., 2006).

The implications of these findings are substantial for clinical practice and policy. The demonstrated efficacy of denosumab in reducing both vertebral and non-vertebral fractures, coupled with its positive impact on BMD, suggests a need for revising current treatment guidelines to favor denosumab for patients with severe osteoporosis. Furthermore, these results could influence health policies to support broader access to denosumab and encourage ongoing research to explore its long-term benefits and optimal use in various patient populations.

In conclusion, this review reinforces the critical role of denosumab in modern osteoporosis management, emphasizing its superior efficacy and safety profile compared to bisphosphonates. These insights are essential for guiding clinical decisions and shaping future research directions in osteoporosis treatment. The evidence presented supports a paradigm shift towards more effective and patient-centered therapeutic approaches in osteoporosis care.

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## Article Information

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**Supplements –**
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