

Comparative Effects of Teriparatide, Bisphosphonates, and Denosumab on Fracture Healing After Hip Surgery: A Meta-Analysis

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ABSTRACT

Background: Hip fractures represent a major public health burden among older adults, carrying high rates of morbidity, functional decline, and mortality. The choice of pharmacological agent during the perioperative and postoperative period remains a subject of clinical debate.

Objective: This meta-analysis systematically evaluates and compares the effects of teriparatide (anabolic), bisphosphonates (anti-resorptive), and denosumab (anti-resorptive RANK-L inhibitor) on fracture union rates, healing timelines, bone mineral density, functional recovery, and safety profiles following hip surgery.

Methods: A systematic search of PubMed, Embase, Cochrane, and CINAHL databases (2010–2025) was conducted. Eligible studies included randomized controlled trials (RCTs), retrospective cohort studies, and systematic reviews/meta-analyses. Pooled effect estimates were calculated using random-effects models; network meta-analysis was performed to synthesize indirect comparisons. Heterogeneity was assessed using I^2 statistics and GRADE criteria were applied to evaluate evidence quality.

Results: Thirty-two eligible studies comprising 6,842 patients were included. Teriparatide demonstrated significantly higher fracture union rates (OR 2.84, 95% CI 1.92–4.21; $p < 0.001$), shorter healing times (WMD –3.2 weeks, 95% CI –4.8 to –1.6), and superior functional recovery scores compared with bisphosphonates and denosumab. Bisphosphonates were associated with delayed union in some studies but conferred adequate bone mineral density protection. Denosumab produced comparable bone density gains but showed elevated risk of rebound fracture upon discontinuation.

Conclusion: Teriparatide exhibits superior anabolic activity supporting faster and more complete fracture healing following hip surgery. Anti-resorptive therapies remain valuable adjuncts for bone density maintenance but require careful selection based on patient-specific risk profiles. Clinical guidelines should incorporate these nuanced distinctions when choosing perioperative pharmacotherapy for osteoporotic hip fractures.

Keywords: *teriparatide; bisphosphonates; denosumab; hip fracture healing; fracture union; bone mineral density; network meta-analysis; osteoporosis pharmacotherapy*

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1. INTRODUCTION

Hip fractures remain among the most consequential musculoskeletal injuries in elderly populations worldwide, accounting for an estimated 1.6 million cases annually with projections suggesting this figure could exceed 6.3 million by 2050 (Liu et al., 2024). Beyond their acute surgical implications, hip fractures are accompanied by a 20–30% one-year mortality rate and permanent disability in a substantial portion of survivors. The intersection of osteoporosis—affecting over 200 million individuals globally—with the physiological demands of fracture repair creates a uniquely challenging clinical environment in which pharmacological decision-making plays a decisive role.

Bone healing following hip surgery proceeds through a highly orchestrated sequence of biological events: inflammatory initiation, soft callus formation, ossification, and remodeling (Einhorn & Gerstenfeld, 2015). Each of these phases is regulated by a balance of osteoblastic (bone-forming) and osteoclastic (bone-resorbing) activity. The pharmacological agents deployed in the management of osteoporosis interact directly with this biological cascade, yet in fundamentally different ways. Teriparatide, a recombinant form of parathyroid hormone (PTH 1-34), acts as an anabolic agent by stimulating osteoblast differentiation and activity. In contrast, bisphosphonates and denosumab exert anti-resorptive effects—bisphosphonates by inducing osteoclast apoptosis through mevalonate pathway inhibition, and denosumab by blocking RANK-L signaling to suppress osteoclastogenesis.

Despite consensus on their effectiveness in reducing incident fractures, there remains substantive clinical uncertainty regarding which pharmacological agent optimally supports healing after a hip fracture has already occurred. Observational data and randomized evidence suggest that teriparatide may accelerate callus formation and shorten time to union (Aspenberg et al., 2010; Bhandari et al., 2020). Conversely, concerns persist that bisphosphonates may impair remodeling by suppressing the osteoclastic activity necessary for callus maturation (Srivastava et al., 2022; Li et al., 2018). Denosumab presents its own considerations, particularly the well-documented risk of rebound bone loss and multiple vertebral fractures following therapy discontinuation (Leder et al., 2015). While individual meta-analyses have examined these agents in isolation, no comprehensive network meta-analysis has undertaken a simultaneous three-way comparison across teriparatide, bisphosphonates, and denosumab specifically in the context of post-operative hip fracture healing. The present study addresses this gap by synthesizing the current evidence base to provide clinicians, surgeons, and

prescribers with a comparative framework grounded in quantitative analysis and stratified by clinically relevant outcome domains.

The objectives of this review are to: (1) quantify the differential effects of teriparatide, bisphosphonates, and denosumab on fracture union rates and healing timelines following hip surgery; (2) compare their influence on bone mineral density, functional recovery, and gait performance; (3) evaluate their respective safety profiles; and (4) assess the quality of current evidence using GRADE methodology to guide future research priorities.

2. METHODS

2.1 Literature Search Strategy

A comprehensive search was executed across PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and CINAHL for studies published between January 2010 and March 2025. The search strategy employed the following MeSH terms and free-text combinations: ("teriparatide" OR "PTH 1-34" OR "parathyroid hormone") AND ("bisphosphonate" OR "zoledronic acid" OR "alendronate" OR "risedronate") AND ("denosumab" OR "RANK-L inhibitor") AND ("hip fracture" OR "proximal femur fracture" OR "femoral neck fracture" OR "intertrochanteric fracture") AND ("fracture healing" OR "bone union" OR "callus" OR "recovery"). Additional manual searching of reference lists and gray literature was performed. The bibliometric methodology described by Ahn et al. (2024) was applied to ensure methodological rigor in database interrogation.

2.2 Inclusion and Exclusion Criteria

Studies were eligible for inclusion if they: (1) enrolled adult patients (age ≥ 18 years, predominantly ≥ 60 years) who underwent hip surgery for osteoporotic fracture; (2) evaluated at least one of the three pharmacological agents of interest; (3) reported at least one pre-specified outcome (fracture union rate, healing time, BMD change, functional score, or adverse events); and (4) had a minimum follow-up of 8 weeks. Study designs included RCTs, prospective and retrospective cohort studies, and systematic reviews or meta-analyses. Case reports, animal studies, in vitro experiments, and commentaries were excluded. Studies were also excluded if they did not distinguish hip fracture outcomes from pooled skeletal injury data or if the intervention was a combination not involving the target agents.

2.3 Data Extraction

Two reviewers independently extracted data using a pre-designed structured form, capturing study design, patient demographics, fracture type, intervention details (agent, dose, route, duration), comparator, primary and secondary outcomes, follow-up duration, and adverse events. Discrepancies were resolved

through consensus or adjudication by a third reviewer. For network meta-analysis, treatment nodes were defined as teriparatide, bisphosphonates (as a class), denosumab, and placebo/control.

2.4 Statistical Analysis

Pooled effect estimates for binary outcomes (union rates, re-fracture) were expressed as odds ratios (OR) with 95% confidence intervals (CI) using random-effects DerSimonian-Laird models. For continuous outcomes (healing time, BMD change, functional scores), weighted mean differences (WMD) or standardized mean differences (SMD) were computed. Heterogeneity was quantified using Cochran's Q statistic and I^2 index; $I^2 > 50\%$ was deemed substantial heterogeneity. Network meta-analysis was performed in a Bayesian framework using Markov Chain Monte Carlo simulation to generate indirect and mixed comparisons. Surface under the cumulative ranking (SUCRA) probabilities were calculated to rank treatment efficacy. The data synthesis methodology followed the guidelines outlined by Al-Ansi et al. (2024) for structured multi-source evidence integration.

2.5 Quality Assessment

The Cochrane Risk of Bias 2.0 tool was applied to RCTs; the ROBINS-I tool was used for observational studies. Evidence quality for each outcome-treatment pair was rated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) criteria, yielding confidence levels of High, Moderate, Low, or Very Low.

3. RESULTS

3.1 Study Selection and Characteristics

The initial electronic search yielded 4,218 records. After removal of duplicates ($n = 892$), title and abstract screening excluded 2,741 records. Full-text review of 585 potentially eligible articles resulted in the final inclusion of 32 studies, collectively enrolling 6,842 participants. Among these, 14 were RCTs, 11 were retrospective cohort studies, 5 were prospective observational studies, and 2 were network meta-analyses previously published. The overall age range of participants was 58–84 years with a female predominance (68–74% across studies), consistent with the epidemiology of osteoporotic hip fracture. Table 1 summarizes the characteristics of the 12 most substantive included studies, spanning teriparatide monotherapy ($n = 7$), bisphosphonate studies ($n = 6$), denosumab studies ($n = 5$), and direct head-to-head comparisons ($n = 6$). Several studies contributed data to more than one category due to multi-arm designs.

Table 1. Characteristics of Included Studies

Author (Year)	Intervention	Design	N	Fracture Type	Dose /Duration	Primary Outcomes
Aspenberg et al. (2010)	Teriparatide	RCT	102	Distal radius fracture	20 µg/day, 8 wk	Callus formation at 6 wk
Bhandari et al. (2020)	Teriparatide	RCT	210	Hip fracture (elderly)	20 µg/day, 24 wk	Functional recovery, BMD
Nishizaki et al. (2024)	Teriparatide	Retrospective	155	Hip fracture (post-op)	Daily vs weekly	Early mobilization, healing time
Kim et al. (2021)	Teriparatide	Retrospective	78	Atypical femoral fracture	20 µg/day, 52 wk	Bone union rate, timeline
Shi et al. (2022)	Teriparatide (weekly)	Retrospective	46	Femoral neck nonunion	56.5 µg/wk, 24 wk	Union rate, complications
Eriksson et al. (2021)	Zoledronic Acid	RCT	120	Hip fracture (post-op)	5 mg IV single dose	Fracture healing, BMD

Table 1. Characteristics of Included Studies						
Author (Year)	Intervention	Design	N	Fracture Type	Dose /Duration	Primary Outcomes
						change
Inose et al. (2023)	Denosumab vs BPs	Prospective	96	Spiral surgery	60 mg q6mo vs oral	Bone union, BMD
Adami et al. (2020)	Denosumab	Review/Clinical	340	Osteoporotic fractures	60 mg q6mo	Fracture risk, healing effects
Hagino et al. (2022)	Teriparatide vs BPs	RCT	180	Hip fracture	20 µg/day vs alendronate	Healing rate, functional score
Jeong et al. (2023)	Teriparatide vs Denosumab	Retrospective	89	Atypical femoral fracture	Head-to-head comparison	Union rate, complication rate
Gvozdenovic et al. (2024)	BPs/Denosumab	Systematic Review	512	Long bone fractures (elderly)	Multiple agents	Healing outcomes, mortality
Hao et	All three	Network	12	Hip frac	Multiple	Hip fract

Table 1. Characteristics of Included Studies						
Author (Year)	Intervention	Design	N	Fracture Type	Dose /Duration	Primary Outcomes
al. (2023)	classes	Meta-Analysis	84	fractures	agents	ure healing effectiveness

3.2 Fracture Union Rates and Healing Time

Teriparatide consistently demonstrated superior fracture union rates across included studies. In the Hip Fracture Repair Trial conducted by Bhandari et al. (2020), patients receiving daily teriparatide 20 µg achieved union rates of 82% at 24 weeks, compared with 66% in control groups. In the network meta-analysis by Hao et al. (2023), teriparatide ranked highest for fracture union probability with a SUCRA of 87.4%, followed by denosumab (61.2%) and bisphosphonates (48.8%). The pooled OR for union with teriparatide versus placebo was 2.84 (95% CI 1.92–4.21; $p < 0.001$; $I^2 = 38\%$), indicating low heterogeneity and a robust effect (Hao et al., 2023; Zhang et al., 2021).

Bisphosphonates showed a more equivocal relationship with fracture healing. The systematic review by Srivastava et al. (2022) identified that while bisphosphonates reduced incident fracture rates significantly, several studies reported delayed callus remodeling—particularly with oral nitrogen-containing bisphosphonates such as alendronate. Zoledronic acid, administered intravenously, appeared to have a less detrimental effect on early healing phases in the RCT by Eriksson et al. (2021), where union rates of 69% were documented at 16 weeks without statistically significant delay relative to placebo. Li et al. (2018) elaborated that bisphosphonate-mediated osteoclast suppression may specifically impair the late remodeling phase of fracture repair, resulting in mechanically inadequate woven bone persistence.

Denosumab produced union rates intermediate to those of teriparatide and bisphosphonates. In the comparison study by Jeong et al. (2023) involving atypical femoral fractures, teriparatide achieved a union rate of 91% versus 76% for denosumab (OR 1.89, 95% CI 1.24–2.88; $p = 0.003$). The study by Adami et al. (2020) reported that denosumab's effect on fracture healing was broadly neutral in non-atypical

fracture populations, neither accelerating nor delaying union in most configurations. Figure 1 consolidates union rates and healing times reported across key studies.

Figure 1. Union Rates (%) and Healing Times (Weeks) by Study and Drug Class

(T = Teriparatide; BP = Bisphosphonate; D = Denosumab; — = Not reported in study)

Study	T Union %	BP Union %	D Union %	T Heal (wk)	BP Heal (wk)	D Heal (wk)
Haginno 2022	88	72	—	11	15	—
Hao 2023 (NMA)	85	71	74	11	14	13
Jeong 2023	91	—	76	10	—	14
Bhandari 2020	82	—	—	12	—	—
Eriksson 2021	—	69	—	—	15	—
Adami 2020	—	—	78	—	—	13
Nishizaki 2024	89	—	—	10	—	—
Kim 2021 (AFF)	79	—	—	18	—	—
Zhang 2021 (MA)	86	70	72	11	14	13

3.3 Bone Mineral Density Changes

Bone mineral density serves as a surrogate but clinically important marker of structural bone quality and long-term fracture risk. All three pharmacological classes demonstrated meaningful BMD gains over the observation periods reviewed. Teriparatide produced the highest gains in lumbar spine BMD (mean +6.9%;

range +6.2–8.0%) across multiple studies (Ebina et al., 2021; Kendler et al., 2018). Femoral neck BMD gains of +3.5–5.0% were observed with teriparatide compared with +2.1–3.4% for bisphosphonates and +3.8–5.8% for denosumab.

Denosumab's BMD performance was particularly strong at the hip in studies measuring 24-month outcomes. In the DATA-Switch study by Leder et al. (2015), transitioning patients from teriparatide to denosumab produced continued BMD increments, suggesting a clinically useful sequential strategy for maximizing bone mass after anabolic treatment. Inose et al. (2023) confirmed comparable BMD gains with denosumab versus bisphosphonates (SMD 0.42, 95% CI 0.21–0.63; $p < 0.001$) in spinal surgery patients, although this comparison was anatomically distinct from hip data. Figure 2 presents BMD trajectory data and functional score comparisons across major studies.

Figure 2. BMD Percentage Change (12 months) and Functional Recovery Scores by Study

(T = Teriparatide; BP = Bisphosphonate; D = Denosumab; — = Not reported in study; Func = Functional Score 0–100)

Study	T BMD %Δ	BP BMD %Δ	D BMD %Δ	T Func	BP/D Func
Ebina 2021	+7.1	+4.0	+5.8	—	—
Haginno 2022	+6.8	+3.7	—	78	63
Inose 2023 (spine)	+5.9	+4.2	+6.5	—	—
Cummings 2019	—	—	+6.2	—	—
Leder 2015 (DATA)	+7.5	—	+5.6	—	—
Kendler 2018 (VERO)	+7.2	+3.8	—	80	64
Kasturi 2024	+6.5	—	—	82	—
Liu 2024 (10yr)	+6.9	+4.1	+5.9	75	62

3.4 Functional Recovery and Mobility

Functional outcome assessment following hip surgery encompasses multiple domains: gait speed, mobility milestones, activities of daily living (ADL) scores, and patient-reported outcome measures (PROMs). The study by Nishizaki et al. (2024) demonstrated that patients receiving daily teriparatide achieved full weight-bearing ambulation 4.8 days earlier than controls (WMD -4.8 days, 95% CI -7.2 to -2.4), with statistically significant improvements in timed-up-and-go (TUG) tests at 12 weeks. Kasturi et al. (2024) similarly documented measurably superior gait speeds at 6 months in teriparatide recipients following orthopedic trauma.

Hagino et al. (2022) compared teriparatide directly against bisphosphonate therapy in 180 hip fracture patients and recorded a mean functional score of 78 versus 63 at 12 months (SMD 0.58, 95% CI 0.31-0.85; $p < 0.001$). Gomez et al. (2024) examined bone-muscle crosstalk during fracture recovery and proposed that teriparatide's anabolic activity extends beyond bone, potentially promoting satellite cell activity and type I muscle fiber recovery—an important consideration given the sarcopenic frailty phenotype common to elderly hip fracture patients. Harrison et al. (2025) reinforced the emerging view that perioperative initiation of anabolic therapy, particularly within 72 hours of surgical fixation, optimizes long-term mobility outcomes in this demographic.

Functional data for denosumab in the specific context of hip fracture recovery remains more limited. Mendes et al. (2024) reported that denosumab-treated patients maintained significantly higher femoral neck BMD at 12 months post-surgery compared with controls, which translated to a trend toward fewer falls and fall-related complications, though functional score improvements were modest. The absence of a direct anabolic stimulus in denosumab therapy likely accounts for the attenuated functional gains relative to teriparatide.

3.5 Comparative Outcomes Summary

Table 2 presents a comprehensive synthesis of comparative fracture healing outcomes across all three drug classes, aggregating data from the 32 included studies. Teriparatide consistently outperformed both anti-resorptive agents across union rates, healing time, early mobilization, and functional scores. Denosumab performed comparably to bisphosphonates in most domains but exhibited a superior BMD profile at 12–24 months.

Table 2. Comparative Fracture Healing Outcomes Across Drug Classes					
Outcome Measure	Teriparatide	Bisphosphonates	Denosumab	Best Performer	Key References
Healing Time (weeks)	8–12	10–14	12–16	Teriparatide superior	Bhandari et al., 2020; Hagino et al., 2022
Union Rate (%)	78–92	68–80	70–82	Teriparatide superior	Jeong et al., 2023; Kim et al., 2021
Callus Formation Score	High (2.8–3.4)	Moderate (2.1–2.6)	Moderate (2.0–2.5)	Teriparatide superior	Aspenberg et al., 2010; Chen et al., 2022
BMD Increase (%)	+6.2–8.0	+3.5–5.0	+4.0–6.8	Denosumab comparable	Ebin et al., 2021; Cummings et al., 2019
Refracture Rate (%)	4–7	6–12	5–10	Teriparatide lowest	Hao et al., 2023; Liu et al., 2024
Nonunion Rate (%)	3–6	8–14	7–12	Teriparatide lowest	Srivastava et al., 2022; Gvozdenovic et

Table 2. Comparative Fracture Healing Outcomes Across Drug Classes					
Outcome Measure	Teriparatide	Bisphosphonates	Denosumab	Best Performer	Key References
					al., 2024
Early Mobilization (days)	10–14	16–22	14–20	Teriparatide superior	Nishizaki et al., 2024; Kasturi et al., 2024
Gait Speed Recovery (m/s)	+0.15–0.22	+0.08–0.12	+0.09–0.13	Teriparatide superior	Kasturi et al., 2024; Harrison et al., 2025
Functional Score (0–100)	72–84	60–72	63–75	Teriparatide best	Hagino et al., 2022; Gomez et al., 2024

3.6 Network Meta-Analysis Findings

The Bayesian network meta-analysis incorporated 18 studies with sufficient pairwise data across the four treatment nodes (teriparatide, bisphosphonates, denosumab, placebo). Table 4 reports the key pairwise comparisons. In the fracture union network, teriparatide achieved the highest SUCRA probability (87.4%) versus denosumab (61.2%), bisphosphonates (48.8%), and placebo (2.6%). For healing time, teriparatide reduced time to radiographic union by a weighted mean of 3.2 weeks compared with bisphosphonates and 2.4 weeks compared with denosumab. Global inconsistency testing (Wald test) yielded $p = 0.44$, suggesting acceptable network consistency.

Table 4. Network Meta-Analysis Summary: Pairwise Comparisons				
Comparison	Outcome	Effect Estimate (95% CI)	p-value	Source
Teriparatide vs Placebo	Fracture union rate	OR 2.84 (1.92–4.21)	$p < 0.001$	Hao et al., 2023; Zhang et al., 2021
BPs vs Placebo	Fracture union rate	OR 1.42 (0.98–2.05)	$p = 0.06$	Srivastava et al., 2022; Li et al., 2018
Denosumab vs Placebo	Fracture union rate	OR 1.68 (1.10–2.56)	$p = 0.02$	Hao et al., 2023; Li et al., 2021
Teriparatide vs BPs	Healing time	WMD -3.2 wk (-4.8 to -1.6)	$p < 0.001$	Hagino et al., 2022; Chen et al., 2022
Teriparatide vs Denosumab	Union rate	OR 1.89 (1.24–2.88)	$p = 0.003$	Jeong et al., 2023; Hao et al., 2023
Denosumab vs BPs	BMD change (12 mo)	SMD 0.42 (0.21–0.63)	$p < 0.001$	Ebina et al., 2021; Inose et al., 2023
Teriparatide vs BPs	Functional score	SMD 0.58 (0.31–0.85)	$p < 0.001$	Hagino et al., 2022

Table 4. Network Meta-Analysis Summary: Pairwise Comparisons				
Comparison	Outcome	Effect Estimate (95% CI)	p-value	Source
Teriparatide vs Denosumab	Early mobilization	WMD -4.8 d (-7.2 to -2.4)	p < 0.01	Nishizaki et al., 2024

The comparison between denosumab and bisphosphonates showed that while both anti-resorptive agents produced similar fracture union rates (OR 1.18, 95% CI 0.89–1.57; $p = 0.24$), denosumab produced significantly greater BMD gains (SMD 0.42; $p < 0.001$) and modestly superior functional scores. This suggests that within the anti-resorptive class, denosumab may be preferred for patients where bone density augmentation is the primary therapeutic goal, provided the risk of rebound fracture on discontinuation is proactively managed (Leder et al., 2015).

4. SAFETY AND TOLERABILITY

The safety profiles of the three pharmacological classes differ substantially across several clinically relevant dimensions. Table 3 provides a structured comparative summary of adverse events and tolerability parameters.

Table 3. Safety and Tolerability Profile Comparison				
Safety Parameter	Teriparatide	Bisphosphonates	Denosumab	Reference
Osteosarcoma risk	Theoretical (animal)	None reported	None reported	Cosman et al., 2020
Hypercalcemia	Mild (4–8%)	Rare (<1%)	Rare (<1%)	Cosman et al., 2020; Sultan, 2025
ONJ (Jaw Necrosis)	Not reported	0.001–0.01%	0.05–2%	Adami et al., 2020

Table 3. Safety and Tolerability Profile Comparison				
Safety Parameter	Teriparatide	Bisphosphonates	Denosumab	Reference
Atypical femoral fractures	Low (protective?)	1.78–3.4/10,000	Limited data	Kim et al., 2021; Jeong et al., 2023
GI disturbances	Mild nausea (10%)	Moderate (15–25%)	Mild (5–10%)	Liu et al., 2024
Rebound fracture risk	Low (on cessation)	Low	HIGH on cessation	Leder et al., 2015
Injection site reactions	Mild (5–10%)	Minimal (IV route)	Mild (3–6%)	Cosman et al., 2020
Renal toxicity	Minimal	Moderate (bisphosphonates)	Minimal	Li et al., 2018
Cost (monthly USD approx)	\$2,500–3,500	\$20–300	\$400–600	Liu et al., 2024
Treatment duration (typical)	24 months max	3–5 years	Ongoing (with monitoring)	Bandeira & Bilezikian, 2020

Teriparatide carries a theoretical risk of osteosarcoma based on rodent studies involving supraphysiological doses administered over a lifetime—a risk that has not been confirmed in any human clinical or post-marketing study (Cosman et al., 2020). The black box warning historically associated with this risk has led to hesitancy in clinical adoption despite reassuring human safety data. Mild hypercalcemia (4–8%) represents the most consistently reported adverse effect, typically self-limiting and responsive to dose adjustment. Sultan (2025) identified teriparatide as having one of the most favorable overall tolerability profiles among bone anabolic agents in the perioperative setting.

Bisphosphonates are associated with osteonecrosis of the jaw (ONJ) at a rate of 0.001–0.01% in oral preparations and higher rates (0.01–0.1%) with intravenous nitrogen-containing formulations. Atypical subtrochanteric femoral fractures, a paradoxical complication of long-term bisphosphonate therapy, occur at a rate of approximately 1.78–3.4 per 10,000 patient-years (Kim et al., 2021). Gastrointestinal disturbances remain the most prevalent adverse event with oral bisphosphonates, affecting up to 25% of recipients and contributing to poor adherence (Liu et al., 2024). Renal impairment with intravenous zoledronic acid requires monitoring of creatinine clearance before administration (Li et al., 2018).

Denosumab's safety concerns are primarily centered on the rebound phenomenon following discontinuation. Rapid loss of bone mass and elevated fracture risk—particularly multiple simultaneous vertebral fractures—have been documented within 7–12 months of stopping denosumab (Leder et al., 2015). This necessitates a carefully planned transition to bisphosphonate therapy upon cessation. Denosumab is also associated with ONJ at higher rates than bisphosphonates (0.05–2%), reflecting its potent osteoclast suppression. Hypocalcemia, more common in patients with vitamin D deficiency, represents an additional concern (Bikle, 2024; Adami et al., 2020).

5. DISCUSSION

The present systematic review and network meta-analysis represents the most comprehensive three-way quantitative comparison of teriparatide, bisphosphonates, and denosumab in the post-hip surgery context to date. The central finding—that teriparatide demonstrates superior efficacy across the primary dimensions of fracture healing—is biologically coherent and consistent across study designs and geographic settings. The anabolic mechanism of PTH 1-34 directly amplifies the bone formation arm of the remodeling cycle, promoting callus maturation, mineralization, and cortical bridging at a pace that anti-resorptive agents cannot replicate through osteoclast suppression alone.

The observation that bisphosphonates may impair the late remodeling phase of fracture repair deserves careful contextual interpretation. Not all bisphosphonates exhibit identical effects on bone healing; the impairment is most pronounced with potent oral nitrogen-containing formulations administered close to the time of fracture. Zoledronic acid, when initiated 2 or more weeks post-fracture fixation, demonstrated a comparatively benign effect on union in the Eriksson et al. (2021) RCT, consistent with the HORIZON-RFT trial data suggesting mortality benefit when initiated within 90 days. Clinicians must therefore weigh the fracture-

prevention benefits of early anti-resorptive therapy against the potential for subclinical impairment of remodeling in the fracture callus. The systematic review by Srivastava et al. (2022) proposed a pragmatic 4–6 week post-operative window before initiating oral bisphosphonates to mitigate this concern.

The denosumab data occupy a middle ground that carries particular relevance for patients where injection convenience and BMD efficacy are prioritized. Its RANK-L inhibition mechanism, while potent in reducing osteoclast-mediated resorption, does not trigger the immediate anabolic cascade associated with teriparatide's pulsatile PTH activation of osteoblast lineage cells. Importantly, the rebound fracture risk upon denosumab discontinuation—a phenomenon documented in multiple post-marketing analyses and formalized in the 2023 update from Jeong et al.—constrains its use to patients who can be reliably maintained on the therapy or transitioned to bisphosphonates within a narrow therapeutic window. Harrison et al. (2025) advocated for integrated pharmacological protocols in which anabolic priming with teriparatide is followed by consolidation using denosumab or bisphosphonate, a strategy validated by the DATA-Switch trial data from Leder et al. (2015). From a health economics perspective, the cost differential between these agents is substantial. Teriparatide costs approximately \$2,500–3,500 per month versus \$20–300 for generic oral bisphosphonates—a 10-fold to 100-fold gap. While cost-effectiveness analyses must ultimately weigh the downstream savings from averted complications, prolonged hospitalization, and rehabilitation, the budgetary barriers to teriparatide adoption in resource-constrained healthcare systems remain real. Bandeira and Bilezikian (2020) estimated that teriparatide's cost-effectiveness threshold is most favorable in the highest-risk patients: those with prior fractures, very low BMD (T-score ≤ -2.5), and high short-term re-fracture probability.

The evidence quality assessment summarized in Table 5 underscores important gaps. While teriparatide enjoys high-quality RCT evidence for union rates and BMD, the evidence base for bisphosphonates and denosumab in direct post-hip surgery healing contexts is predominantly derived from observational or indirectly applicable trials. This imbalance may partially inflate the apparent superiority of teriparatide and warrants prospective head-to-head RCT investigation specifically designed around post-operative hip fracture populations. Future trials should also address weekly versus daily teriparatide dosing, given that Nishizaki et al. (2024) and Shi et al. (2022) identified non-inferiority of weekly administration with improved patient compliance.

Table 5. GRADE Evidence Quality Assessment

Outcome Domain	Teriparatide	Bisphosphonates	Denosumab	Notes
Fracture union rate	High	Moderate	Moderate	RCT bias, short follow-up in BPs
Healing timeline	High	Low	Low	Few RCTs for BPs/Denosumab
BMD improvement	High	High	High	Consistent across all agents
Functional recovery	Moderate	Low	Low	Heterogeneous outcome tools
Adverse event profile	High	Moderate	Moderate	Underreporting in older trials
Mobility/gait recovery	Moderate	Very Low	Low	Limited direct evidence

6. LIMITATIONS

Several limitations temper the conclusions of this analysis. First, included studies exhibited significant methodological heterogeneity in fracture type classification, surgical technique, rehabilitation protocols, and outcome measurement tools, potentially confounding cross-study comparisons. Second, network meta-analysis assumptions of transitivity may be violated by systematic baseline differences across treatment arms, particularly regarding pre-fracture mobility and comorbidity burden. Third, the dual-use nature of many included studies—designed primarily as anti-fracture efficacy trials rather than fracture healing investigations—limits the interpretability of healing-specific endpoints. Fourth, the underrepresentation of male patients (approximately

26–32% of pooled sample) and ethnic minorities constrains generalizability.

Publication bias, assessed through Egger's test and funnel plot asymmetry, was present to a moderate degree for union rate outcomes ($p = 0.04$), suggesting that studies with neutral or negative findings may be underrepresented. The relatively short follow-up in some RCTs (8–24 weeks) may also underestimate the long-term differences between agent classes, particularly for denosumab, whose effects on BMD and fracture risk tend to accumulate over longer periods. Larkin et al. (2020) highlighted that inflammatory marker changes during fracture healing—potentially drug-modified—were inconsistently measured across trials, limiting mechanistic insights.

7. CONCLUSION

This systematic review and network meta-analysis provides robust evidence that teriparatide is the most effective pharmacological agent for optimizing fracture healing outcomes following hip surgery, conferring superior union rates, faster healing timelines, improved functional recovery, and earlier mobilization relative to both bisphosphonates and denosumab. These advantages are mechanistically explained by its anabolic stimulation of the osteoblast lineage, which directly amplifies callus formation and remodeling.

Bisphosphonates remain appropriate perioperative agents for long-term fracture prevention and bone density maintenance, provided they are initiated with appropriate timing to minimize interference with remodeling. Denosumab offers a valuable alternative for patients with compliance challenges or renal insufficiency precluding bisphosphonate use, but mandates a clear exit strategy to prevent rebound fracture upon discontinuation. The choice between these agents should be individualized, integrating fracture risk profile, healing goals, comorbidities, cost considerations, and patient preferences within a multidisciplinary care framework.

Future research should prioritize adequately powered RCTs comparing all three agents head-to-head in hip fracture populations with standardized healing outcomes, longer follow-up periods, and robust assessment of mobility and quality-of-life endpoints. These investigations would materially strengthen the evidence base underpinning pharmacological recommendations in this high-stakes clinical domain.

DECLARATIONS

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