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Effect of Bisphosphonates on Orthodontic Relapse Prevention: A Systematic Review of Animal Studies

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Abstract

Aim
Orthodontic relapse (OR) frequently compromises post-treatment stability. Bisphosphonates (BPs), as potent inhibitors of bone resorption, have been proposed as potential agents to reduce relapse. This systematic review evaluated the effects of BP administration on OR prevention in animal models.
Methods
Prospective controlled animal studies investigating systemic or local BP administration immediately after orthodontic tooth movement or stabilization were included. Human or in vitro studies or studies not involving OTM were excluded. PubMed, Cochrane, Web of Science, EMBASE, and Scopus were searched to October 13, 2025. Two reviewers independently screened studies, extracted data, and assessed risk of bias using the SYRCLE tool. Evidence certainty was evaluated using GRADE. Owing to marked methodological heterogeneity, data were synthesized qualitatively.
Results
Seven studies (rats n=4, guinea pigs n=2, goats n=1) involving various BPs (risedronate, pamidronate, alendronate, 4-amino-1-hydroxybutylidene-1,1-bisphosphonate) and systemic or localized routes were included. All studies reported reduced OR in BPs-treated groups compared with controls. Quantitative outcomes included decreased relapse distance/percentage and reduced osteoclast counts. However, substantial heterogeneity in animal models, dosing regimens, administration routes, and relapse measurement protocols, combined with consistently high or unclear risk of bias, limited data comparability. The overall certainty of evidence was rated very low (GRADE) due to serious RoB, inconsistency, indirectness, and imprecision.
Conclusion
Preclinical evidence suggests that BPs may reduce orthodontic relapse, particularly with localized delivery; however, confidence in these findings is very low. Current animal data are insufficient to support clinical application. High-quality, standardized, long-term animal studies are needed before translation to human research.

Keywords: Bisphosphonates, Bone remodeling, Orthodontic relapse, Tooth movement, Systematic review

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Background

Orthodontic relapse (OR), with a reported prevalence of 70–90% (1), represents a significant clinical challenge in maintaining the stability of corrected tooth positions. The etiology of relapse is multifactorial and not fully understood. Factors like gingival and periodontal tissue remodeling and growth-related changes can compromise the long-term stability of orthodontic treatment results. The retention phase is necessary after orthodontic treatment to prevent relapse (2). An investigation found that one year was the most commonly used retention period (3). Retaining teeth in the new satisfactory position after orthodontic correction is one of the most challenging tasks in orthodontics (4).

Bisphosphonates (BPs) suppress osteoclast activity while stimulating osteoblast function, thereby reducing bone resorption and enhancing bone formation. These mechanisms may influence orthodontic tooth movement (OTM) and prevent post-treatment relapse. Consequently, BPs have been investigated in animal models for their potential to prevent OR by modulating bone remodeling and osteoclast activity (5–9). However, their application, particularly in orthodontic contexts, requires careful consideration due to potential adverse effects (10,11).

Given these limitations, robust preclinical evidence is required before considering BPs for clinical orthodontic application. Therefore, a systematic review of animal studies is warranted to synthesize the available preclinical evidence, assess the consistency and limitations of current findings, and clarify the potential role of bisphosphonates in preventing orthodontic relapse.

Methods

Protocol and Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure standardized reporting, including the study selection process and flowchart (12). The methodological framework was guided by the Cochrane Handbook for Systematic Reviews of Interventions to define eligibility criteria, data extraction processes, and the risk of bias (RoB) assessment (13,14). The search strategy was informed by the Center for Reviews and Dissemination (CRD) guidelines to ensure a comprehensive and systematic literature search (15).

A prospective protocol was developed and registered with PROSPERO (CRD420250651238)(17) prior to study commencement to enhance transparency and reduce bias. Additionally, this study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (Ethics Code: IR.SBMU.DRC.REC.1403.137).

Eligibility Criteria

Eligible studies were restricted to prospective controlled animal trials to establish essential preclinical evidence, thereby excluding human, in vitro, or ex vivo models. Eligible studies were required to investigate the preventive effects of systemic or local bisphosphonate administration on OR assessed immediately following OTM or a stabilization period. This specific timing was chosen to standardize the assessment window and precisely detect early relapse mechanisms. Interventions focused solely on BPs, excluding the co-administration of other substances to isolate the drug's specific effects. Furthermore, to ensure objective comparability, outcomes were limited to quantitative relapse measures (e.g., distance, rate, or percentage via micro-CT, casts, or histology), explicitly excluding qualitative assessments. Studies lacking a proper control group were also excluded. Table 1 outlines detailed inclusion and exclusion criteria.

Table 1. Eligibility Criteria

Domain	Inclusion Criteria	Exclusion Criteria
Participants	Animal studies involving orthodontic relapse assessed immediately after orthodontic tooth movement (OTM) or following a stabilization period.	Human studies, in vitro studies, ex vivo studies, or studies not involving OTM.
Interventions	Systemic or local administration of bisphosphonates immediately after OTM or on the last day of the stabilization period, aimed at preventing orthodontic relapse (no classification of relapse severity required, as focus is on prevention).	Co-administration or asynchronous administration of any substance other than bisphosphonates; administration of any pharmacological agents except bisphosphonates.
Comparisons	Placebo intervention or no intervention.	No control group or control groups not subjected to OTM; control groups with a longer stabilization period.
Outcomes	Quantitative numerical measurements of orthodontic relapse after OTM, including relapse rate or percentage, assessed via methods such as micro-CT, dental cast measurements (using landmarks like tooth cusps or alveolar bone edges), or histological analysis (e.g., measuring periodontal ligament width or bone resorption areas).	Qualitative assessments; inadequate or non-numerical results.

Information Sources

A comprehensive literature search was conducted to identify all relevant studies investigating the effects of bisphosphonates (BPs) on orthodontic relapse (OR) prevention. Five electronic databases (PubMed, Scopus, Web of Science, Embase, and Cochrane Library) were systematically searched. In addition, the reference lists of all included studies and relevant review articles were manually screened to identify potentially eligible studies that might not have been captured in the electronic search. Grey literature sources were also explored when available to minimize publication bias.

Search Strategy

The search covered studies published until October 2025. A structured search strategy was developed using Medical Subject Headings (MeSH) and relevant keywords related to orthodontics, orthodontic relapse, bisphosphonates, and their specific drug types. The MeSH term “orthodontics” was combined with terms such as “orthodontic relapse,” “tooth movement,” “bisphosphonate,” and the names of specific bisphosphonate agents (e.g., alendronate, zoledronate, clodronate, pamidronate, and risedronate). Boolean operators (AND, OR) were applied to combine search terms appropriately. The search strategy was adapted for each database according to its indexing system. Additionally, the reference lists of included articles were manually reviewed to ensure that no relevant studies were missed.

Study Selection

Two independent reviewers screened 927 articles based on their titles and abstracts. Eight studies meeting the initial inclusion criteria were assessed in full text to confirm eligibility, and seven were ultimately included.

Data Collection

Two independent reviewers performed data extraction using a form developed for this review. Each study was reviewed in full to ensure accurate and complete extraction of all relevant variables. Reviewers worked independently and were not blinded to study identifiers (e.g., authors, institutions, journals). Any discrepancies or uncertainties encountered during extraction were resolved through discussion and consensus; if agreement could not be reached, a third reviewer was consulted. This process was implemented to minimize errors and reduce reviewer bias.

Data Items

The following key data items were extracted from each included study:

- author name and year of publication,
- study design and experimental methodology,
- animal species, sample size, and subject characteristics,
- method used to induce orthodontic tooth movement (OTM),
- characteristics of orthodontic relapse (OR), including stabilization periods and measurement techniques,
- type, dose, and route of bisphosphonate administration,
- outcome measures related to relapse magnitude and bone remodeling parameters,
- primary results and relevant quantitative findings when available.

Risk of Bias in Individual Studies

RoB in each included study was independently evaluated by two reviewers using the SYRCLE RoB tool for animal studies (16). RoB was categorized as “high,” “low,” or “unclear” for each of the 10 items in the tool.

Effect measures

None of the included studies provided adequate statistical parameters (e.g., standard deviations, standard errors, or confidence intervals) to permit computation of pooled effect estimates. Furthermore, substantial heterogeneity in animal models, bisphosphonate types, dosing protocols, relapse induction methods, and outcome assessment techniques precluded quantitative synthesis. Consequently, findings were summarized using a qualitative approach.

Synthesis Methods

Due to significant methodological heterogeneity across the included studies regarding animal models, intervention protocols, and measurement techniques, a quantitative meta-analysis was not feasible. Consequently, a qualitative synthesis was conducted. The primary effect measures used to present results were the mean distance of OR, the relapse percentage, and quantitative histological findings (e.g., osteoclast counts), as reported by the primary studies.

Reporting Bias Assessment

Assessment of publication bias was planned; however, due to the small number of included studies and the lack of sufficient quantitative data for meta-analysis, formal evaluation using funnel plots or statistical tests was not feasible. As a result, the presence or extent of publication bias could not be reliably determined.

Certainty Assessment

The certainty of the evidence from the included studies was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework, with ratings of high, moderate, low, or very low assigned based on factors such as risk of bias, inconsistency, indirectness, imprecision, and other relevant considerations. Disagreements between reviewers were resolved through discussion, with consultation of a third reviewer when necessary.

Results

Study Selection

The PRISMA flowchart (Figure 1) illustrates the record screening process. Initially, 927 studies were identified through database searches up to October 13, 2025. After removing duplicates, 469 titles and abstracts were screened. Of these, 461 records were excluded as they clearly did not meet the inclusion criteria based on title and abstract evaluation. Consequently, eight full-text articles were assessed for eligibility, of which one was excluded because it lacked a quantitative relapse rate assessment (17). Ultimately, seven studies were included in the qualitative synthesis.

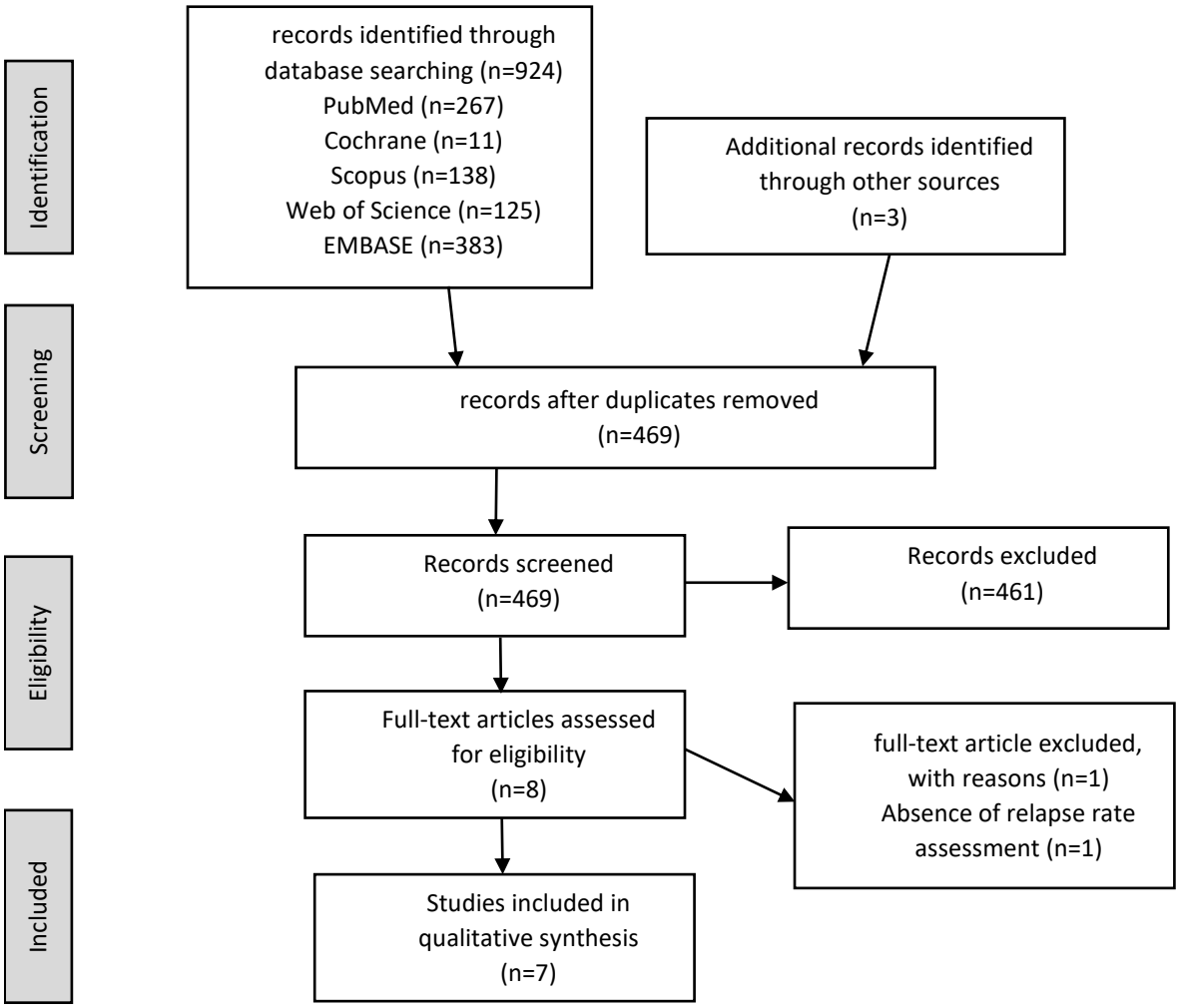

Figure 1. PRISMA flowchart depicting the systematic search, screening process, and phase-specific exclusions leading to the final study selection.

Study Characteristics

The included studies primarily used small animal models, with rats in four studies (18–21), guinea pigs in two (22,23), and goats in one (24). The BPs evaluated included risedronate (21–23), pamidronate disodium (18,19), alendronate sodium (24), and 4-amino-1-hydroxybutylidene-1,1-bisphosphonate (AHBuBP) (20). Administration methods varied, with systemic routes (e.g., intraperitoneal (18), intravenous (19), and subcutaneous (20)) used in four studies and local routes (e.g., topical (21,22), intra-periodontal (24), and intrasulcular (23)). OTM was induced using mechanical devices such as nickel-titanium coil springs (20–22), elastic bands (17,18), or elastomeric chains (24), applying forces ranging from 15 to 130 centiNewtons (cN) for up to 21 days. Relapse was measured as the numerical distance of tooth movement after force cessation, with observation periods extending up to 42 days. For detailed study-specific information, refer to Table 2.

Risk of Bias in Studies

Table 3 summarizes the RoB assessment using a modified SYRCLE tool. All studies had an unclear RoB for allocation concealment, blinding of caregivers/investigators, random selection for outcome assessment, and allocation sequence generation, except one (21). High RoB was noted across all studies for randomization and blinding at any level. Baseline similarity and random housing were generally low or unclear risk, with two exceptions for random housing (22,23). Incomplete outcome data were adequately addressed in all studies. These pervasive methodological shortcomings confirm a substantial risk of performance and detection bias across the included studies.

Results of Individual Studies

As detailed in Table 2, all studies demonstrated decreased OR in the bisphosphonate groups compared to controls, with effects observed across various administration routes and dosages.

Reporting Biases

Across the included studies, several methodological shortcomings—such as unclear randomization, lack of blinding, and incomplete reporting of experimental details—posed a substantial risk of bias. Selective reporting could not be excluded, as no study provided a prior protocol and inconsistencies were noted in outcome reporting. Publication bias could not be assessed due to the small number of studies and absence of quantitative data for meta-analysis.

Certainty of Evidence

The overall quality of evidence was rated as very low using the GRADE approach (Table 4), due to serious risks of bias (as indicated by the SYRCLE assessment), inconsistency (highly variable relapse measurement protocols and follow-up periods), indirectness (animal models limiting human applicability), and imprecision (small sample sizes).

Table 2. General characteristics of studies included in the systematic review

First Author, Reference Year	BP	Animal (Species, Age, Gender)	OTM Model (Mechanism, Type of OTM, Amount of Force, Duration)	Group Characteristics (Groups, Sample Size, Dose, Route, Administration)		Timeline of tooth relapse measurements; Results
				Experimental Group	Control Group	
Igarashi et al. (1994)20	4-amino-1-hydroxybutylidene-1,1-bisphosphonate (AHBuBP)	Rats, 9-10 weeks, male	Expansion spring: Right and left maxillary first molars; Not specified; 21 days	AHBuBP: 3 subgroups (n=4-5); 0.02-0.5 mg P/kg; Subcutaneous; Daily for 21 days	n=6; 0.9% NaCl; Subcutaneous; Daily for 21 days	Days 0, 3, 7, 14, 21; Decreased relapse (dose-dependent)
Adachi et al. (1994)21	Risedronate	Rats, 9-10 weeks, male	Nickel-titanium expansion spring: Right and left maxillary first molars; 16.5 cN; 21 days	Risedronate (split-mouth): n=40; 125-500 μmol/L; Topical (left side); Every 3 days after OTM	n=40; 0.9% NaCl (right side); Topical; Every 3 days after OTM	Days 0, 3, 7, 14, 21; Decreased relapse (dose-dependent)
Kim et al. (1999)19	Pamidronate disodium	Rats, 7 weeks, male	Elastic band: Right and left maxillary first and second molars; Not specified; 21 days	Pamidronate disodium: n=7; 1.5 mg/mL/kg; Intravenous; Once on last day of OTM (subgroups at 0, 5, 10 days)	n=7; Phosphate-buffered saline (1.0 mL/kg); Intravenous; Once	Days 0, 5, 10; Decreased relapse
Osman and Afify, (2006)18	Pamidronate disodium	Rats, 7 weeks, male	Elastic band: Right and left maxillary first and second molars; Not specified; 21 days	Pamidronate disodium: n=4; 0.01 mg/kg; Intraperitoneal; Once on last day of OTM (subgroups at 0, 5, 10 days)	n=4; No intervention (subgroups at 0, 5, 10 days)	Days 0, 5, 10; Decreased relapse
Utari et al. (2021)23	Risedronate	Guinea pigs, Not specified, male	Nickel-titanium open coil spring: Right and left mandibular incisors; 25-130 cN; Until 3 mm distance	Risedronate: n=25; 250-500 mmol/L in 5 mL PBS; Intrasulcular; Every 3 days after OTM	n=25; Phosphate-buffered saline (5 mL); Intrasulcular; Every 3 days	Days 0, 3, 7, 14, 21; Decreased relapse
Tokhtah and Alhadlaq, (2022)24	Alendronate sodium	Goats, 2 years, Not specified	Elastomeric chain: Right and left mandibular first and third incisors; 15 cN; Until contact	Alendronate sodium (split-mouth): n=4; Not specified; Intra-periodontal; Once after stabilization	n=4; Normal saline; Intra-periodontal; Once after stabilization	Days 0, 42; Decreased relapse
Utari et al. (2023)22	Risedronate	Guinea pigs, Not specified, Not specified	Open coil spring: Right and left mandibular incisors; Not specified; 7 days	Risedronate emulgel: n=3; 1.5 mg; Topical (labial/lingual mucosa); Once on last day of stabilization (subgroups at 0, 3, 7 days)	n=3; No intervention (subgroups at 0, 3, 7 days)	Days 0, 3, 7; Decreased relapse

Abbreviations: cN = centiNewton; OTM = orthodontic tooth movement; P = phosphorus; PBS = phosphate-buffered saline; Not specified = information not provided in the original study.

Table 3. Summary of Risk of Bias assessment according to a modified SYRCLE RoB tool

	Signaling questions									
Study	1	2	3	4	5	6	7	8	9	10
Igarashi et al. (1994)20	Y	Y	U	Y	U	U	U	Y	N	N
Adachi et al. (1994)21	U	Y	U	Y	U	U	U	Y	N	N
Kim et al. (1999)19	U	Y	U	Y	U	U	U	Y	N	N
Osman and Afify, (2006)18	U	Y	U	Y	U	U	U	Y	N	N
Utari et al. (2021)23	U	U	U	U	U	U	U	Y	N	N
Tokhtah and Alhadlaq, (2022)24	U	Y	U	Y	U	U	U	Y	N	N
Utari et al. (2023)22	U	U	U	U	U	U	U	Y	N	N

Signaling questions: (1) Was the allocation sequence adequately generated and applied? (2) Were the groups similar at baseline or adjusted for confounders? (3) Was the allocation adequately concealed? (4) Were the animals randomly housed during the experiment? (5) Were the caregivers and/or investigators blinded? (6) Were animals selected at random for outcome assessment? (7) Was the outcome assessor blinded? (8) Were the incomplete outcome data adequately addressed? (9) Was it stated that the experiment was randomized at any level? (10) Was it stated that the experiment was blinded at any level?; N, no; Y, yes; U, unclear.

Table 4. GRADE Summary of Findings: Quality of Available Evidence. The overall certainty of evidence regarding the effect of bisphosphonates on orthodontic relapse was assessed across five domains. The evidence was downgraded uniformly to 'Very Low' due to cumulative methodological limitations.

Quality Assessment Criteria							
Studies	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Consideration**	**Effect on Orthodontic Relapse**	**Quality**
Risedronate							
3	Serious	Serious[a]	Serious[c]	Serious[d]	None	Decrease	⊕OOO VERY LOW
Pamidronate disodium							
2	Serious	Some inconsistency[b]	Serious[c]	Serious[d]	None	Decrease	⊕OOO VERY LOW
Alendronate sodium							
1	Serious	Not serious	Serious[c]	Serious[d]	None	Decrease	⊕OOO VERY LOW
AHBuBP							
1	Serious	Not serious	Serious[c]	Serious[d]	None	Decrease	⊕OOO VERY LOW

a Downgraded for serious inconsistency: Significant heterogeneity was observed in both the intervention protocols (e.g., varying dosages and delivery methods) and the animal populations across the studies evaluating Risedronate.
b Downgraded for inconsistency: Noticeable variation in intervention methods was noted among the studies evaluating Pamidronate disodium.
c Downgraded for serious indirectness: All data originate exclusively from animal models (e.g., rats, guinea pigs). Therefore, the results cannot be directly extrapolated to human clinical settings without significant caveats.
d Downgraded for serious imprecision: The overall number of animals analyzed within each intervention group was inherently limited, reducing the statistical robustness of the observed effects.

Discussion

This systematic review, conducted under a rigorous protocol, identified seven animal studies of generally low methodological quality, all reporting reduced relapse after bisphosphonate administration. However, given the pervasive RoB across the included literature, these positive outcomes must be interpreted with caution. The reported effect sizes for relapse prevention may be

overestimated, casting doubt on the assumption of clinical efficacy.

BPs mitigate OR primarily by selectively inhibiting osteoclast activity and modulating alveolar bone remodeling (25,26), a mechanism consistent with their established use in treating bone diseases characterized by increased bone resorption (27). Although most included studies used commonly prescribed formulations (except AHBuBP) to stabilize the bone microenvironment, applying these animal model findings to human clinical practice requires caution. Histological and micro-CT analyses directly correlate this inhibitory mechanism, consistently revealing a notable reduction in active osteoclasts and smaller bone-resorptive lacunae at the compression side (18,20,21,23). Interestingly, while BPs theoretically prevent resorption by inducing apoptosis at the ruffled borders (26), histological evidence presented a more complex picture: treated osteoclasts exhibited irregular configurations, yet some still displayed well-developed ruffled borders and clear zones (18,19). Furthermore, BP treatment altered their spatial distribution; osteoclasts clustered predominantly around blood vessels within the alveolar bone's vascular canals, while remaining sparse in the PDL proper at the compressed area (19). These specific cellular disruptions correlated with broader structural changes, including significantly narrower PDL widths (24) and the observation of newly formed cementum on orthodontically induced root resorption lacunae, though the latter finding remains subject to caution due to methodological heterogeneity across studies.

Across the included studies, BPs demonstrated a dose-dependent capacity to mitigate OR via both systemic and local routes (18–23). While systemic administration effectively reduces relapse, single-dose regimens may lose efficacy over time, and broader systemic use risks disrupting bone metabolism (19) or becoming ineffective due to gastrointestinal metabolism, pH changes, and enzyme interactions (28). Consequently, to avoid pain and systemic side effects, localized topical delivery has become a priority (29). To optimize this, studies used advanced controlled-release carriers: gelatin hydrogels, which manage water content and tailored degradability through cross-linking mechanisms (30–32), emulgel formulations, which prolong mucosal retention and improve handling (29), and intra-periodontal gel formats enable the slow, non-invasive release of agents like alendronate (24). Collectively, these localized systems present a distinct theoretical advantage for relapse prevention by sustaining drug release directly at the site of tooth movement while mitigating local toxicity (28). Beyond preventing relapse, broader evidence indicates that localized BP administration also effectively restricts active OTM. Local application of various BPs—such as Clodronate (8,33), Zoledronate (34,35), AHBuBP (20), Risedronate (21), and Ibandronate (36) —has been shown to impede OTM predominantly at the application site, with limited impact on adjacent areas. However, methodological inconsistencies currently make direct comparisons challenging. Optimizing both relapse and OTM regimens—such as using more potent BPs at lower doses or less potent BPs more frequently (37)—requires further validation through standardized protocols.

Despite widespread BP prescriptions, adverse effects like gastroesophageal irritation and medication-related osteonecrosis of the jaw may limit BP use in some patients (10,38). Therefore, potential effects on other tissues must be carefully considered. However, local administration of BPs is hypothesized to enhance local bone regeneration similarly to systemic use, while theoretically aiming to reduce systemic exposure (39). BPs can inhibit tooth movement when applied topically (20,22) and locally (23). In one of the included studies, topical administration of BP showed a greater inhibitory effect than systemic administration at a higher dose (20). However, we cannot state that it has no systemic effects (21). Consequently, despite the potential of localized delivery to minimize risks, the ethical justification for substituting safe, proven mechanical retainers with pharmacological agents remains questionable. Given that orthodontic retention is primarily an aesthetic and functional objective, until future studies can guarantee the absolute elimination of severe adverse effects like medication-related osteonecrosis of the jaw, the clinical translation of BPs for this purpose cannot be recommended.

Strengths and Limitations

This review was the first to evaluate the evidence on the effects of BPs on OR. We performed an extensive search up to October 13, 2025, and used dual review for screening, data extraction, risk-of-bias assessment, and evidence appraisal. Quality assessment was conducted according to study-specific protocols and included studies that consistently reported reduced relapse.

A primary limitation of this review is the systematically high RoB identified by the SYRCLE tool. The critical lack of rigorous experimental protocols—most notably the absence of blinding and proper random sequence generation — undermines the internal validity of the primary

studies and prevents drawing any definitive clinical conclusions. Consequently, the overall GRADE certainty of evidence was rated as very low, driven by this high RoB, small sample sizes, and the indirectness of animal data to humans. Beyond these fundamental methodological flaws, the evidence is further limited by the small number of available studies, notable heterogeneity across animal models and OTM methods, and short follow-up periods (≤42 days). Additional limitations include restrictions to English-language publications, incomplete reporting of treatment details (e.g., biomechanics, tooth movement rates), and misalignment of BP dosing and timing with clinical practice. Furthermore, none of the studies (40–42) investigated potential adverse effects of BPs, such as osteonecrosis of the jaw, which significantly restricts the clinical relevance and ethical translation of these findings.

Recommendations for Future Research

Given the high RoB across all studies, more high-quality animal studies are required to make definitive recommendations based on these findings for human studies. Therefore, further research should follow standardized protocols regarding the duration of drug administration, dose equivalence, and route to simulate a human clinical scenario. Additionally, the mechanisms used to induce tooth movement should be clearly described. Given the small sample sizes in the included studies, future research should prioritize sample size calculation to enhance study power and the significance of its results (43). The possible adverse effects of BPs should be investigated in preclinical studies. Given the lower incidence of medication-related osteonecrosis of the jaw associated with oral BPs compared with intravenous formulations, future studies may favor agents such as risedronate and alendronate to optimize safety outcomes (44,45). Moreover, it is suggested that local administration be emphasized in future research, given its lower systemic consequences and greater effectiveness compared to systemic administration at higher doses (20). Further research is needed to determine the lowest topical dose that inhibits OR without causing systemic effects. For future studies, if histological analysis is not essential, researchers may consider keeping the animals alive to better adhere to the ethical principles of animal research. This approach would align with the 3Rs framework (Replacement, Reduction, and Refinement), emphasizing the reduction of animal use and the refinement of experimental procedures to minimize harm and distress (46,47). Future studies should prioritize standardized animal models closer to human physiology, such as pigs, longer follow-up periods exceeding 42 days, and rigorous randomization and blinding to reduce bias and improve evidence quality, paving the way for more reliable preclinical data that could justify human trials.

Conclusion

Based on current preclinical evidence, bisphosphonates (BPs) may contribute to enhancing post-orthodontic stability. Nonetheless, the overall certainty of the evidence remains very low, with substantial risk of bias observed across the included animal studies. Consequently, these findings should be interpreted with caution. At this stage, the available data are insufficient to warrant clinical application or to justify progression to human trials. Future rigorously designed animal studies—particularly those examining localized delivery approaches, employing standardized experimental protocols, and assessing long-term safety—are required to establish a more reliable foundation for potential clinical translation.

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Conflicts of Interest

The authors declare no conflicts of interest

Data availability statements

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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