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Systematic Review

Pharmacological Management of Bone Metabolism in Post-Menopausal Women: A Meta-Analysis of Randomized Controlled Trials on Bisphosphonates and Alternative Therapies for Secondary Osteoporotic Fracture Prevention

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Abstract

Background: Aging and menopause accelerate bone loss, increasing susceptibility to osteoporotic vertebral compression fractures (OVCFs), which cause severe pain, compromise respiratory function, and elevate mortality risk. Therefore, to mitigate this risk, various 10 medications have been used to prevent secondary fractures. However, a comprehensive summary of the efficacy of these medications remains limited, prompting our systematic review and meta-analysis of randomized controlled trials (RCTs) to elucidate the effects of these medications on the prevention of subsequent OVCFs. **Materials and Methods**: A comprehensive systematic search was conducted across five electronic databases—PubMed, EMBASE, Scopus, Web of Science (WOS), and the Cochrane Library—to identify peer-reviewed studies published in English. Eligible studies were included in a quantitative synthesis. Pooled effect estimates were calculated as odds ratios (ORs) or risk ratios (RRs), along with the associated 95% confidence intervals (CIs). Additionally, heterogeneity was assessed using the Cochrane Q statistic and quantified with the I^2 metric, and meta-analytic procedures were performed using Review Manager (RevMan) software, version 5.4 (The Cochrane Collaboration, Copenhagen, Denmark). The systematic review protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD420251176522), and the full protocol is available at: https://www.crd.york.ac.uk/PROSPERO/view/CRD420251176522. **Results**: High- to moderate-quality evidence from pooled randomized controlled trials indicates that most bisphosphonates (zoledronate, alendronate, risedronate, etidronate, and ibandronate) and non-bisphosphonate therapies (denosumab, teriparatide, bazedoxifene, estrogen, calcitonin, and parathyroid hormone) are associated with a significant reduction in fracture risk. Overall, most bisphosphonates demonstrated an approximate 40–60% reduction in fracture risk (risk ratio [RR] range: 0.40–0.60; 95% confidence intervals [CIs] spanning 0.23–0.77), while non-bisphosphonates were associated with a 30–50% reduction (RR range: 0.30–0.50; 95% CIs: 0.19–0.71), acknowledging that individual agents exhibited varying magnitudes of effect. Pooled analyses also showed that both drug classes increased bone mineral density, with bisphosphonates producing an approximate 3–7% increase (odds ratio [OR] range: 0.33–0.54; 95% CI: 0.19–0.74) and non-bisphosphonates a 3–5% increase (OR range: 0.36–0.57; 95% CI: 0.23–0.83). Furthermore, safety data synthesized from the included trials indicated a low incidence of adverse events for both treatment classes, with bisphosphonates showing RRs ranging from 0.19 to 0.44 (95% CI: 0.09–0.81) and non-bisphosphonates from 0.23 to 0.49 (95% CI: 0.12–0.89). **Conclusion**: High- to moderate-quality evidence supports the efficacy of zoledronate, alendronate, risedronate, etidronate, ibandronate, parathyroid hormone (PTH), denosumab, and selective estrogen receptor modulators (SERMs) in preventing secondary OVCFs. Zoledronate, risedronate, and PTH reduced both vertebral and non-vertebral fractures. Denosumab outperformed alendronate, and PTH surpassed risedronate, although with increased risk of adverse events.

Keywords: osteoporosis; postmenopausal; bisphosphonates; bone density conservation agents; fractures; bone; menopause

1. Introduction

Osteoporosis predominantly affects postmenopausal women and the elderly population. This condition is characterized by low bone mineral density and decreased bone strength, which leads to an increased risk of fragility fractures, including vertebral, hip, and non-hip nonvertebral fractures [1]. Osteoporotic vertebral compression fractures (OVCFs) represent a significant complication of osteoporosis, impacting 30–50% of individuals aged 50 and older. Fragile fractures lead to severe pain, disability, and a four-fold increase in the risk of secondary fractures and mortality [2,3]. Hormonal changes in postmenopausal women disrupt bone metabolism, resulting in accelerated bone loss and an increased risk of fractures [4]. Osteoporotic fractures result in a decline in health and quality of life, imposing a significant burden on patients and healthcare systems [5]. Preventing osteoporotic fractures serves as the primary therapeutic objective in the treatment of osteoporosis, with medication playing a crucial role.

Recent studies evaluate various medications, including bisphosphonates, non-bisphosphonates such as selective estrogen receptor modulators (SERMs), parathyroid hormone analogs, and monoclonal antibodies, for the prevention of OVCFs [6–8]. Bisphosphonates rank as the most frequently prescribed medications among these options [9]. Other medications provide potential benefits as well. Numerous randomized controlled trials (RCTs) demonstrate the effectiveness of these medications in preventing fractures [10–13]. The comparative efficacies of these medications in preventing secondary fractures remain unclear. Secondary OVCFs denote fractures that occur following an initial OVCF, resulting in a detrimental cycle characterized by deteriorating bone health, heightened disability, and diminished quality of life. Preventing secondary OVCFs plays a vital role in enhancing the quality of life for patients [14]. Secondary OVCFs hold significant importance; however, existing studies have predominantly concentrated on primary prevention strategies, while secondary prevention has received limited attention. Existing cross-sectional surveys [15], ambispective cross-sectional studies [16], and systematic reviews and meta-analyses [17] have evaluated the efficacy of these medications in preventing secondary OVCFs. However, these reviews faced limitations due to the scarcity of available data, underscoring the necessity for further research.

This systematic review and meta-analysis addresses the existing knowledge gap by conducting a thorough examination of relevant randomized controlled trials (RCTs) [18–41] selected according to pre-defined inclusion-exclusion criteria. The focus lies on evaluating the efficacy of various bisphosphonates and non-bisphosphonates in preventing secondary osteoporotic vertebral compression fractures (OVCFs) in postmenopausal women, with particular attention to bone metabolism and fracture risk reduction. This study conducted a thorough evaluation of bisphosphonates and non-bisphosphonates medications, assessing their clinical efficacy and safety profiles in preventing OVCF. The aim was to provide clinically relevant evidence and informed insights for clinicians and patients.

2. Materials and Methods

2.1 Eligibility Criteria and Selection Process

To maintain methodological rigor and minimize bias, this review was conducted in accordance with PRISMA guidelines [42] and was prospectively registered with PROSPERO (registration number CRD420251176522). The PRISMA 2020 Checklist has been provided as a supplementary file. Three independent reviewers (QZ, JK, and WX) initially screened titles and abstracts to identify studies relevant to osteoporosis. Studies were considered eligible if they included participants diagnosed with osteoporosis. Following this, the same reviewers performed a detailed assessment of the full texts. The review was restricted to randomized controlled trials (RCTs) published in English that evaluated the effectiveness of approved pharmacological treatments for osteoporotic vertebral compression fractures (OVCFs). Studies enrolling osteoporotic patients—with or without prior fractures—were included as long as outcomes for those with existing fractures were clearly reported. In contrast, studies involving traumatic vertebral fractures, secondary osteoporosis, or those lacking dichotomous outcome data were excluded. The pharmacologic agents assessed included bisphosphonates (ibandronate, risedronate, alendronate, minodronate, pamidronate, etidronate, zoledronate), denosumab, teriparatide, bazedoxifene, estrogen, calcitonin, and parathyroid hormone. Any disagreements among reviewers were resolved through discussion or, when necessary, by consulting a senior reviewer.

2.2 Information Sources and Search Strategy

The literature search was conducted across five major electronic databases—PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com/), Scopus (https://www.scopus.com/), Web of Science (https://www.webofscience.com/), and the Cochrane Library (https://www.cochranelibrary.com/)—from January 2000 through February 2025. A tailored search strategy incorporating terms such as “randomized controlled trials”, “osteoporotic fracture”, “bisphosphonates”, “parathyroid hormone”, “denosumab”, “calcitonin”, “bazedoxifene”, “hormone replacement”, and related keywords was implemented (Table 1). Weekly database alerts were activated to identify newly published trials. In addition, the reference lists of relevant reviews and previous studies were screened manually to ensure comprehensive coverage. Reference management was performed using EndNote X7 (Clarivate Analytics, Philadelphia, PA, USA) [43]. For Scopus searches, the Title-Abstract-Keyword field was applied using the designated keywords, while in the Cochrane database, searches were carried out using the terms “osteoporotic fractures” and “post-menopausal women”. The overall search strategy was structured according to the PICO framework [44], where the population (“P”) included postmenopausal women with osteoporosis, the interventions (“I”) comprised bisphosphonate and non-bisphosphonate therapies, the comparator (“C”) was placebo, and the outcomes (“O”) included fracture reduction, changes in bone mineral density (BMD), and adverse events.

2.3 Data Collection Process and Data Items

Researchers QZ, JK, and WX independently extracted the basic characteristics and event data from each included study using a standardized table that captured the number of participants, the intervention and comparison groups, and the reported outcomes. The primary outcomes evaluated in this review were the risk of subsequent fractures, changes in bone mineral density, and adverse events associated with the pharmacological treatments under investigation.

Table 1. Database search strategy.

Database	Search strategy
Scopus	#1 "Osteoporotic vertebral compression fracture", OR "OVCF", OR "Non-vertebral fracture", OR "NVF", OR "Secondary fracture prevention", OR "Osteoporosis in postmenopausal women" OR "Osteoporosis treatment" OR "Osteoporosis management" OR "Anti-osteoporotic medications" OR "Fracture prevention", OR "Bisphosphonates" OR "Denosumab", OR "Teriparatide", OR "Romosozumab", OR "Pamidronate", OR "Ibandronate", OR "Risedronate", OR "Etidronate" OR "Minodronate" OR "Fluoride + Estrogen" OR "Zoledronate" OR "Bazedoxifene" OR "percutaneous kyphoplasty" OR "zoledronic acid" #2 "Secondary prevention" OR "Conservative treatment" OR "Risk of OVCF" OR "Risk of NVF" OR "Bone mineral density", OR "Adverse events", OR "Discontinuation due to adverse events" OR "systematic review", OR "systematic review and meta-analysis", OR "Meta-analysis", OR "RCT", OR "Randomized controlled trial" #3 #1 AND #2
PubMed	#1 "Osteoporotic vertebral compression fracture" [MeSH Terms] OR "OVCF" OR "Non-vertebral fracture" OR "NVF" OR "Secondary fracture prevention" OR "Osteoporosis in postmenopausal women" [MeSH Terms][#] OR "Osteoporosis treatment", OR "Osteoporosis management", OR "Fracture prevention" [All Fields]" OR "Bisphosphonates" OR "Denosumab", OR "Teriparatide", OR "Romosozumab", OR "Pamidronate", OR "Ibandronate", OR "Risedronate", OR "Etidronate" OR "Minodronate" OR "Fluoride + Estrogen" OR "Zoledronate" OR "Bazedoxifene" OR "percutaneous kyphoplasty" OR "zoledronic acid" OR "Anti-osteoporotic medications", [All Fields] #2 "Secondary prevention" [All Fields] OR "Conservative treatment" [All Fields] OR "Risk of OVCF" OR "Risk of NVF" OR "Bone mineral density", OR "Adverse events", [All Fields] OR "Discontinuation due to adverse events" OR "systematic review", [MeSH Terms] OR "systematic review and meta-analysis", OR "Meta-analysis", OR "RCT" OR "Randomized controlled trial" #3 #1 AND #2
Embase	#1 "Osteoporotic vertebral compression fracture"/exp OR "OVCF"/exp OR "Non-vertebral fracture"/exp OR "NVF"/exp OR "Secondary fracture prevention"/exp OR "Osteoporosis in postmenopausal women"/exp OR "Osteoporosis treatment" /exp OR "Osteoporosis management"/exp OR "Fracture prevention"/exp OR "Bisphosphonates"/exp OR "Denosumab"/exp OR "Teriparatide"/exp OR "Romosozumab"/exp OR "Pamidronate"/exp OR "Ibandronate"/exp OR "Risedronate"/exp OR "Etidronate"/exp OR "Minodronate"/exp OR "Fluoride + Estrogen"/exp OR "Zoledronate"/exp OR "Bazedoxifene"/exp OR "percutaneous kyphoplasty"/exp OR "zoledronic acid"/exp OR "Anti-osteoporotic medications"/exp #2 "Secondary prevention"/exp[$] OR "Conservative treatment"/exp "Risk of OVCF"/exp "Risk of NVF"/exp[$] OR "Bone mineral density"/exp "Adverse events"/exp OR "Discontinuation due to adverse events"/exp OR "systematic review"/exp OR "systematic review and meta-analysis"/exp OR "meta-analysis"/exp OR "RCT"/exp OR "Randomized controlled trial"/exp #3 #1 AND #2
Cochrane library	#1 (Osteoporotic vertebral compression fracture): ti, ab, kw[@] OR (OVCF): ti, ab, kw OR (Non-vertebral fracture): ti, ab, kw OR (NVF): ti, ab, kw OR (Secondary fracture prevention): ti, ab, kw OR (Osteoporosis in postmenopausal women): ti, ab, kw OR (Osteoporosis treatment): ti, ab, kw OR (Osteoporosis management): ti, ab, kw OR (Fracture prevention) OR (Bisphosphonates): ti, ab, kw OR (Denosumab): ti, ab, kw OR (Teriparatide): ti, ab, kw OR (Romosozumab): ti, ab, kw OR (Pamidronate) OR (Ibandronate): ti, ab, kw OR (Risedronate): ti, ab, kw OR (Etidronate): ti, ab, kw OR (Minodronate,): ti, ab, kw OR (Fluoride + Estrogen,) OR (Zoledronate): ti, ab, kw OR (Bazedoxifene): ti, ab, kw OR (percutaneous kyphoplasty): ti, ab, kw OR (zoledronic acid): ti, ab, kw OR (Anti-osteoporotic medications): ti, ab, kw (Word variations have been searched) #2 (Secondary prevention): ti, ab, kw OR (Conservative treatment): ti, ab, kw OR (Risk of OVCF): ti, ab, kw OR (Risk of NVF): ti, ab, kw OR (Bone mineral density): ti, ab, kw OR (Adverse events): ti, ab, kw OR (Discontinuation due to adverse events): ti, ab, kw OR (systematic review): ti, ab, kw OR (systematic review and meta-analysis): ti, ab, kw or (meta-analysis): ti, ab, kw or (RCT): ti, ab, kw or (Randomized controlled trial): ti, ab, kw (Word variations have been searched) #3 #1 AND #2

[#]MeSH terms: Medical Subject Headings; [$]exp: explosion in Emtree-searching of selected subject terms and related subjects; [@]ti, ab, kw: either title or abstract or keyword fields.

2.4 Risk of Bias Assessment

We evaluated the methodological quality of all included studies using the Cochrane Collaboration's Risk of Bias (ROB) tool [45], which assesses potential bias across six domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome

assessment, incomplete outcome data, and selective reporting. Based on these criteria, each study was categorized as having a low, unclear, or high risk of bias. We also examined publication bias through funnel plot analysis [46] and the Egger regression test [47], considering a p-value below 0.05 [48] as evidence of significant bias. These assessments enabled a comprehensive appraisal of the validity and reliability of the included studies.

2.5 Effect Measures and Data Analysis

We quantified the efficacy of interventions by employing a comprehensive analytical framework that incorporated risk ratios (RRs), odds ratios (ORs), and their corresponding 95% confidence intervals (CIs), with statistical significance established at $p < 0.05$. The researchers calculated the overall effect size utilizing a random-effects model [49]. The assessment and quantification of heterogeneity between studies were conducted using the Chi-squared test, accompanied by p-values and I^2 values [50]. An I^2 value of less than 30% indicates negligible heterogeneity, while values ranging from 30% to 74% suggest moderate to substantial heterogeneity. Values exceeding 75% signify considerable heterogeneity [51]. In studies with multiple arms, researchers assigned intervention groups to each subgroup, while they equally divided control group data for comparison with their counterparts. Two authors (JK and WX) performed data analysis using RevMan 5.4 (The Cochrane Collaboration, Copenhagen, Denmark) [52]. The evaluation of evidence quality involved the assessment of five factors: study limitations, imprecision, indirectness, inconsistency, and publication bias, in accordance with the GRADE approach [53]. The criteria for downgrading the level of evidence derive from the GRADE handbook and guidelines established by the Cochrane Back and Neck Group [54]. If an outcome included only one trial with low or unclear risk of bias, the study limitation item received a rating of not serious when the result maintained the same direction and significance as the pooled result. Network meta-analysis facilitates the study and comparison of the effectiveness of multiple interventions simultaneously by integrating direct and indirect evidence from various studies.

3. Results

3.1 Study Selection and Characteristics of Included Studies

A comprehensive electronic search across multiple databases identified 245 records based on the predefined inclusion and exclusion criteria of the PICOS framework. After the removal of 31 duplicate records, 214 unique records remained for screening. Title and abstract screening of these records resulted in the exclusion of 76 articles due to irrelevance or invalid titles and abstracts. The remaining 138 full-text articles were assessed for eligibility, of which 83 were deemed ineligible and excluded. Consequently, 55 studies underwent further eligibility assessment. Ultimately, 24 randomized controlled trials (RCTs) published between 2000 and 2025 met the inclusion criteria and were incorporated into this systematic review and meta-analysis, as illustrated in Fig. 1.

Among these, 14 studies compared the efficacy of bisphosphonates (BP) medications with control groups (Ibandronate [20,36] Risedronate [22,37,40]; Alendronate [28, 38]; Minodronate [30]; Pamidronate [19]; Etidronate [25, 39]; and Zoledronate [27,29,41]). The remaining 10 studies examined the effects of non-bisphosphonates medications compared to control groups (Denosumab [18,32]; Teriparatide [23,24,31]; Bazedoxifene [35]; Estrogen [26]; Calcitonin [21]; and Parathyroid hormone [34]). The follow-up duration in most trials ranged from 1.5 to 3 years. The fundamental characteristics of the included studies are summarized in Table 2 (Ref. [18–41]). The dataset comprises a comprehensive report detailing the following parameters: Study ID and year, journal of publication, number of participants, mean age (years), Intervention and Comparison, Calcium and vitamin D intake, Primary outcomes, observation period (years), and lost to follow-up. Subsequent meta-analysis was conducted utilizing the aforementioned event data.

3.2 Risk of Bias Assessment of Included Studies

A thorough evaluation of the risk of bias was performed to determine the overall quality rating of each of the 24 included randomized controlled trials (RCTs). The traffic light plot (Fig. 2, Ref. [18–41]) and the summary plot for bias assessment (Fig. 3) visually represent the risk of bias, demonstrating a low risk of bias for the current meta-analysis. Nineteen of the twenty-four RCTs exhibited a low risk of bias. Three RCTs, conducted by Chesnut *et al.* [20], Fujita *et al.* [23], and Nakamura *et al.* [32], revealed a moderate risk of bias, primarily due to the randomization process and measurement bias, respectively. In contrast, two RCTs, Liu *et al.* [29] and Palacios *et al.* [35], revealed a significant risk of bias due to selective reporting bias and measurement bias, respectively. The symmetrical distribution observed in the funnel plot (Fig. 4) and the non-significant result from Egger's test ($p = 0.154$), which surpasses the predetermined significance threshold of 0.05, indicate a low probability of overall publication bias within the studies incorporated in this meta-analysis.

3.3 Findings of the Statistical Analysis

This meta-analysis included 22,819 participants with osteoporosis, sourced from 24 carefully selected randomized controlled trials (RCTs), to examine the effectiveness of different bisphosphonates and non-bisphosphonates in preventing secondary OVCFs in postmenopausal women. The GRADE assessment results evaluate the quality of evidence for three outcomes: the risk of subsequent fractures, changes in bone mineral density, and adverse events associated with pharmacological interventions. These results are presented in Tables 3,4,5 (Ref. [18–41]), respectively.

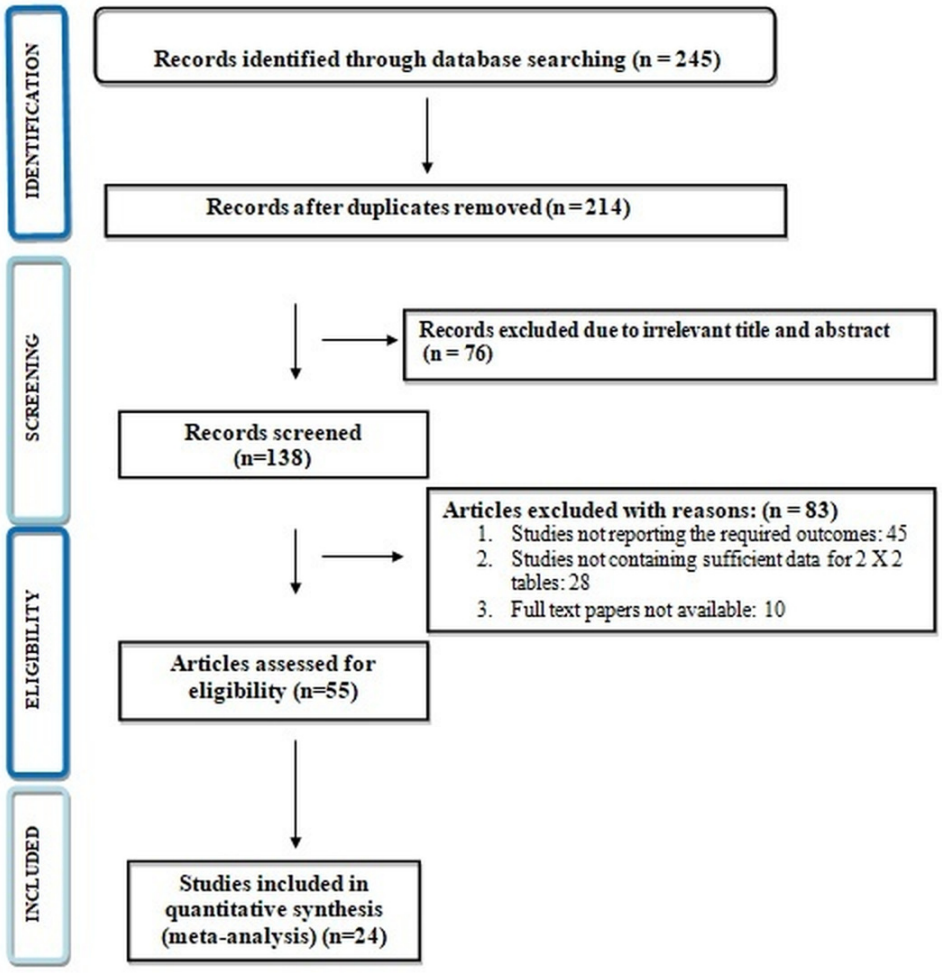

Fig. 1. PRISMA study flow diagram.

The subsequent statistical analysis yielded the following results regarding the primary clinical outcome and adverse events:

3.3.1 Risk of Subsequent Fracture

Bisphosphonates drugs:

High to moderate quality evidence of this meta-analysis revealed that bisphosphonates medications significantly reduce the risk of subsequent fractures as shown in Fig. 5. The relative risks (RRs) and 95% confidence intervals (CIs) for each bisphosphonates medication are as follows: Ibandronate (RR = 0.40, 95% CI: 0.23–0.71), with moderate heterogeneity (χ^2 = 0.01, df = 1, I^2 = 52%, Z = 3.18, $p < 0.001$) (Fig. 5A), Risedronate (RR = 0.58, 95% CI: 0.45–0.77), with moderate heterogeneity (χ^2 = 1.14, df = 2, I^2 = 32%, Z = 3.88, $p < 0.001$) (Fig. 5B), Alendronate (RR = 0.54, 95% CI: 0.36–0.81), with moderate heterogeneity (χ^2 = 0.21, df = 1, I^2 = 44%, Z = 2.97, $p < 0.001$) (Fig. 5C), Minodronate (RR = 0.20, 95% CI: 0.05–0.87, Z = 2.15, $p < 0.001$) (Fig. 5D), Pamidronate (RR = 0.44, 95% CI: 0.20–0.96, Z = 2.06, $p < 0.001$) (Fig. 5E), Etidronate (RR = 0.52, 95% CI: 0.37–0.74), with moderate heterogeneity (χ^2 = 0.04, df = 1, I^2 = 50%, Z = 3.61, $p < 0.001$) (Fig. 5F), and Zoledronate (RR = 0.58, 95% CI: 0.44–0.77), with moderate heterogeneity (χ^2 = 0.19, df = 2, I^2 = 40%, Z = 3.89, $p < 0.001$) (Fig. 5G). The symmetrical funnel plots (**Supplementary Fig. 1**) indicated low publication bias for all included studies comparing bisphosphonates medications with control.

Non-bisphosphonates drugs:

Robust high to moderate quality evidence for non-bisphosphonates medications also demonstrated a significant reduction in the risk of subsequent fractures as shown in Fig. 6. The pooled risk ratios for these medications are: Denosumab (RR = 0.45, 95% CI: 0.29–0.71), with moderate heterogeneity (χ^2 = 1.55, df = 1, I^2 = 44%, Z = 3.42, $p < 0.001$) (Fig. 6A), Teriparatide (RR = 0.56, 95% CI: 0.42–0.75), with moderate heterogeneity (χ^2 = 1.03, df = 2, I^2 = 51%, Z = 3.85, $p < 0.001$) (Fig. 6B), Bazedoxifene (RR = 0.59, 95% CI: 0.35–0.97, Z = 2.08, $p < 0.001$) (Fig. 6C), Estrogen (RR = 0.50, 95% CI: 0.26–0.95, Z = 2.13, $p <$

Table 2. Brief characteristics of the included RCTs.

Study ID and year	Journal of publication	Number of participants	Mean age in years	Previous bone fracture history	Intervention & comparison	Calcium and vitamin D	Primary outcomes	Observation period (year)	Lost to follow up
Boonen *et al*., 2011 [18]	The Journal of Clinical Endocrinology and Metabolism	759	73.7	~30% (high-risk osteoporotic cohort)	G1: Denosumab 60 mg/6 months, sc injection G2: PLC	Both groups	BMD, risk of OVCF, NVF, adverse events	3	18%
Brumsen *et al*., 2002 [19]	Journal of Bone and Mineral Research	101	65	100% (study inclusion: "with at least one prevalent vertebral fracture")	G1: Pamidronate 150 mg/d G2: PLC	Both groups	BMD, risk of OVCF, NVF, adverse events	3	10%
Chesnut *et al*., 2004 [20]	Journal of Bone and Mineral Research	2929	69	~93–94% had at least one fracture at baseline	G1: Ibandronate 2.5 mg/d, oral G2: Ibandronate 20 mg alternate day for 12 doses every 3 months, oral G3: PLC	All arms	BMD, risk of OVCF, NVF, adverse events	3	34%
Chesnut *et al*., 2005 [21]	Journal of Bone and Mineral Research	91	67.4	~50% (small sample; no clear baseline fracture % reported)	G1: Calcitonin nasal spray 200 IU/d G2: Placebo nasal spray	Both groups	BMD, risk of OVCF, NVF, adverse events	2	78%
Fogelman *et al*., 2000 [22]	The Journal of Clinical Endocrinology and Metabolism	237	64	~40% (typical for PMO)	G1: Risedronate 2.5 mg/d G2: Risedronate 5 mg/d G3: PLC	All arms	BMD, risk of OVCF, NVF, adverse events	2	21%
Fujita *et al*., 2014 [23]	Calcified Tissue International	316	71	~35% (moderate risk osteoporosis)	G1: Teriparatide 28.2 µg/w, injection G2: Teriparatide 1.4 µg/w, injection	Both groups	BMD, risk of OVCF, NVF, adverse events	3	17%
Greenspan *et al*., 2007 [24]	Annals of Internal Medicine	471	64.4	~45%	G1: Teriparatide 100 µg/d, sc injection G2: PLC	Both groups	BMD, risk of OVCF, NVF, adverse events	1.5	33%
Guañabens *et al*., 2000 [25]	Bone	118	65	~30% (less high-fracture history)	G1: Etidronate 400 mg/d for 14 days in a cyclic of 90 days G2: Sodium fluoride 50 mg/d	Selectively offer	BMD, risk of OVCF, NVF, adverse events	3	34%
Gutteridge *et al*., 2002 [26]	Osteoporosis International	99	69	~50%	G1: Fluoride G2: Control group G3: Fluoride + Estrogen 0.625 mg/d G4: Estrogen 0.625 mg/d	All groups	BMD, risk of OVCF, NVF, adverse events	2.25	24%

Table 2. Continued.

Study ID and year	Journal of publication	Number of participants	Mean age in years	Previous bone fracture history	Intervention & comparison	Calcium and vitamin D	Primary outcomes	Observation period (year)	Lost to follow up
Huang *et al*., 2019 [27]	Journal of Orthopaedic Surgery and Research	112	50	~20% (younger cohort, vertebroplasty setting)	G1: PKP alone G2: PKP combined with ZOL	Both groups	BMD, risk of OVCF, NVF, adverse events	2	Not reported
Kushida *et al*., 2004 [28]	Journal of Bone and Mineral Metabolism	170	72	~40%	G1: Alendronate 5 mg/d G2: Alfacalcidol 1 µg/d	Both groups	BMD, risk of OVCF, NVF, adverse events	3	30%
Liu *et al*., 2023 [29]	Archives of Orthopaedic and Trauma Surgery	238	51	~15%	G1: PKP alone G2: PKP combined with ZOL	Both groups	BMD, risk of OVCF, NVF, adverse events	2	Not reported
Matsumoto *et al*., 2009 [30]	Osteoporosis International	704	72	~35%	G1: Minodronate 1 mg/d G2: PLC	Both groups	BMD, risk of OVCF, NVF, adverse events	2	31%
Nakamura *et al*., 2012 [31]	The Journal of Clinical Endocrinology and Metabolism	578	75.3	~50%	G1: Teriparatide 56.5 µg/w, sc injection G2: PLC, sc injection	Both groups	BMD, risk of OVCF, NVF, adverse events	1.5	26%
Nakamura *et al*., 2014 [32]	The Journal of Clinical Endocrinology and Metabolism	1262	69.6	~30%	G1: Denosumab 60 mg/6 months, sc injection G2: PLC G3: Alendronate 35 mg/w	All groups	BMD, risk of OVCF, NVF, adverse events	3	13%
Nakamura *et al*., 2017 [33]	Osteoporosis International	661	74.15	~60% (higher age group, higher fracture history)	G1: Zoledronate 5 mg/year, intravenous infusion G2: PLC	Both groups	BMD, risk of OVCF, NVF, adverse events	2	0.6%
Neer *et al*., 2001 [34]	The New England Journal of Medicine	1637	71.0	~50%	G1: rhPTH 20 µg/d G2: rhPTH 40 µg/d G3: PLC	All groups	BMD, risk of OVCF, NVF, adverse events	2	6%
Palacios *et al*., 2015 [35]	Menopause	3857	67	~35%	G1: Bazedoxifene 60 mg/d G2: Bazedoxifene 40 mg/d G3: Bazedoxifene 20 mg/d G4: PLC	All groups	BMD, risk of OVCF, NVF, adverse events	7	74%
Recker *et al*., 2004 [36]	Bone	2860	67	~30%	G1: Ibandronate 0.5 mg injection, every 3 months G2: Ibandronate 1 mg injection, every 3 months G3: PLC	All arms	BMD, risk of OVCF, NVF, adverse events	3	18%

Table 2. Continued.

Study ID and year	Journal of publication	Number of participants	Mean age in years	Previous bone fracture history	Intervention & comparison	Calcium and vitamin D	Primary outcomes	Observation period (year)	Lost to follow up
Reginster *et al*., 2000 [37]	Osteoporosis International	690	71	~47%	G1: Risedronate 5 mg/d G2: Risedronate 2.5 mg/d G3: PLC	All arms	BMD, risk of OVCF, NVF, adverse events	3	42%
Saag *et al*., 2017 [38]	The New England Journal of Medicine	4093	74.3	~55%	G1: Alendronate: 70 mg/w G2: Romosozumab: 210 mg/m sc injection	Both groups	BMD, risk of OVCF, NVF, adverse events	3	11%
Shiota *et al*., 2001 [39]	Journal of Orthopaedic Science	24	61.7	~20%	G1: Etidronate 200 mg/d for 14 days in a cyclic of 84 days G2: 2 g/d calcium and 0.5 µg/d alphacalcidol	Selectively offer	BMD, risk of OVCF, NVF, adverse events	2	Not reported
Sorensen *et al*., 2003 [40]	Bone	212	72	~40%	G1: Risedronate 5 mg/d G2: PLC	Both groups	BMD, risk of OVCF, NVF, adverse events	2	17%
Yi *et al*., 2024 [41]	Journal of Neurological Sciences	600	60	~15%	G1: PKP alone G2: PKP combined with ZOL 1 month later G3: PKP concurrently combined with ZOL	All arms	BMD, risk of OVCF, NVF, adverse events	3	8%

G, Group; RCT, Randomized controlled trial; PLC, placebo; BMD, Bone mineral density; OVCF, osteoporotic vertebral compression fracture; NVF, non-vertebral fracture; PKP, percutaneous kyphoplasty; ZOL, zoledronic acid; PTH, Parathyroid.

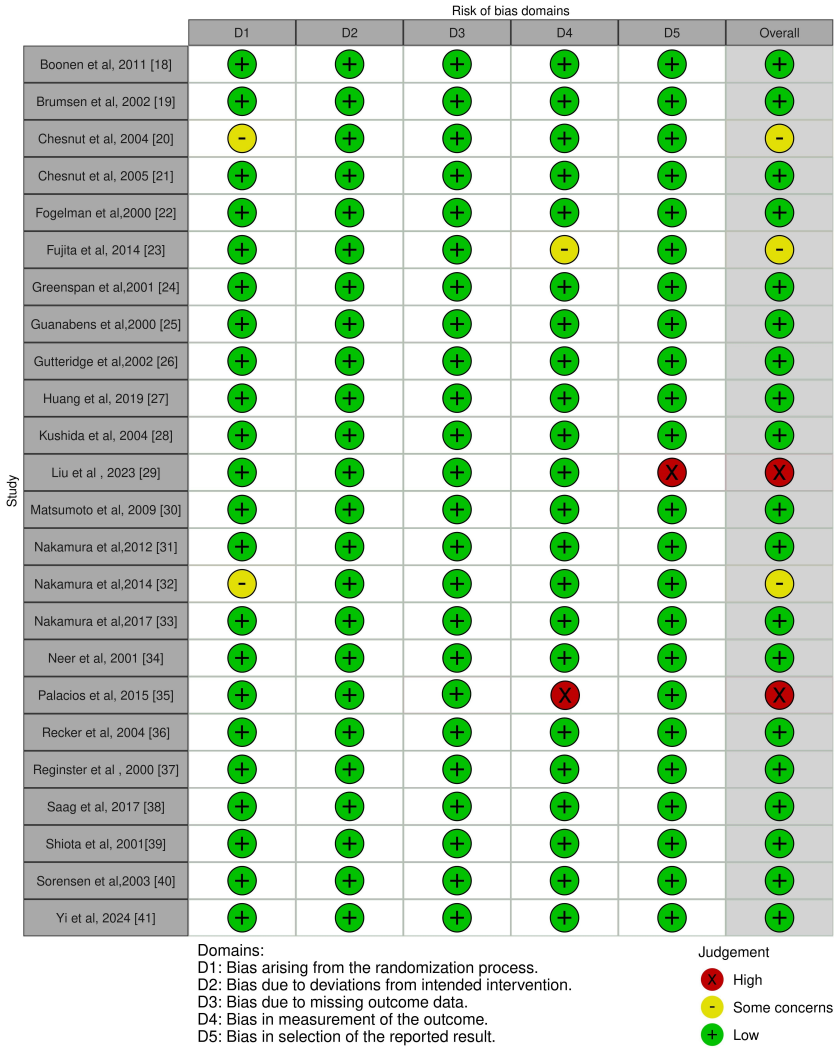

Fig. 2. Traffic light plot to analyze the risk of bias.

0.001) (Fig. 6D), Calcitonin (RR = 0.45, 95% CI: 0.23–0.91, Z = 2.24, $p < 0.001$) (Fig. 6A,E), and Parathyroid hormone (RR = 0.55, 95% CI: 0.33–0.91, Z = 2.33, $p < 0.001$) (Fig. 6F). The funnel plots in **Supplementary Fig. 2** exhibited symmetry, suggesting a minimal risk of publication bias across the studies evaluating non-bisphosphonates medications versus control.

3.3.2 Change in Bone Mineral Density

Bisphosphonates drugs:

The reliable high to moderate grade evidence proved that bisphosphonates medications have a high likelihood of increasing the bone mineral density, as illustrated in Fig. 7. The odds ratios (ORs) and 95% confidence intervals (CIs) for each bisphosphonates medication are as follows: Pamidronate (OR = 0.33, 95% CI: 0.12–0.92; Z = 2.13, $p < 0.001$) (Fig. 7A), Ibandronate (OR = 0.40, 95% CI: 0.23–0.70), with moderate heterogeneity ($\chi^2 = 0.01$, df = 1, $I^2 = 41\%$, Z = 3.18, $p < 0.001$) (Fig. 7B), Etidronate (OR = 0.36, 95% CI: 0.19–0.68), with moderate heterogeneity ($\chi^2 = 1.19$, df = 1, $I^2 = 43\%$, Z = 3.14, $p < 0.001$) (Fig. 7C), Minodronate (OR = 0.16, 95% CI: 0.03–0.79, Z = 2.26, $p < 0.001$) (Fig. 7D), Risedronate (OR = 0.52, 95% CI: 0.38–0.72) with moderate heterogeneity ($\chi^2 = 1.21$, df = 2, $I^2 = 40\%$, Z = 3.92, $p < 0.001$) (Fig. 7E), Alendronate (OR = 0.51, 95% CI: 0.33–0.80), with moderate heterogeneity ($\chi^2 = 0.24$, df = 1, $I^2 = 32\%$, Z = 2.97, $p < 0.001$) (Fig. 7F),and Zoledronate (OR = 0.54, 95% CI: 0.40–0.74), with moderate heterogeneity ($\chi^2 = 0.36$, df = 2, $I^2 = 35\%$, Z = 3.90, $p < 0.001$) (Fig. 7G). The funnel plot analysis (**Supplementary Fig. 3**) revealed a symmetric distribution, indicating a low risk of publication bias across the included studies.

Non-bisphosphonates drugs:

Findings from this meta-analysis, supported by high to moderate grade evidence, clearly establish that bisphosphonates medications are also effective in augmenting the

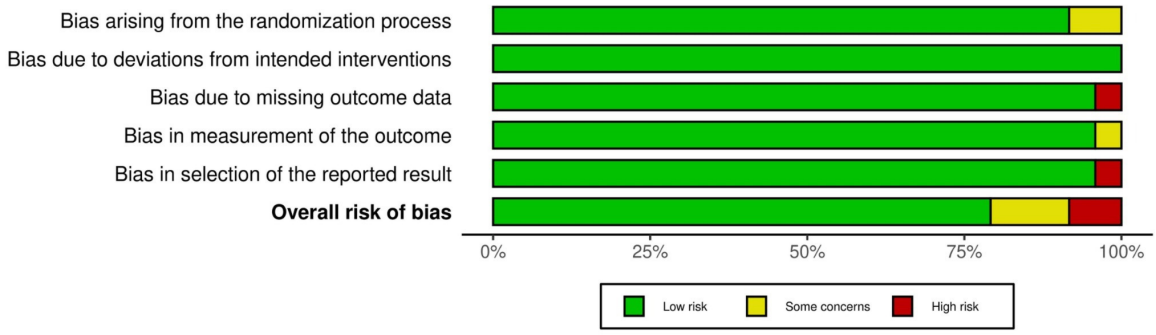

Fig. 3. Summary plot depicting the risk of bias.

Table 3. GRADE assessment for risk of subsequent fractures for each of the included RCTs.

Study ID	a	b	c	d	e	f	g	h	i	j	k	l	m
Boonen *et al*., 2011 [18]	NR	NR	R	R	NR	R	R	R	R	R	R	R	R
Brumsen *et al*., 2002 [19]	NR	NR	R	R	R	R	R	R	R	R	R	R	R
Chesnut *et al*., 2004 [20]	R	NR	R	NR	R	R	R	R	R	R	R	R	R
Chesnut *et al*., 2005 [21]	R	NR	R	R	NR	R	R	R	R	R	R	R	R
Fogelman *et al*., 2000 [22]	NR	NR	R	R	R	R	R	R	R	R	R	R	R
Fujita *et al*., 2014 [23]	R	R	R	NR	NR	R	R	R	R	R	R	R	R
Greenspan *et al*., 2007 [24]	R	R	NR	NR	R	R	R	R	R	R	R	R	R
Guañabens *et al*., 2000 [25]	R	R	R	R	R	R	NR	R	R	R	R	R	R
Gutteridge *et al*., 2002 [26]	NR	R	R	R	R	R	NR	R	R	R	R	R	R
Huang *et al*., 2019 [27]	NR	NR	R	R	R	R	R	R	R	R	R	R	R
Kushida *et al*., 2004 [28]	NR	R	R	R	NR	R	R	R	R	R	R	R	R
Liu *et al*., 2023 [29]	R	NR	R	R	R	R	NR	R	R	R	R	R	R
Matsumoto *et al*., 2009 [30]	R	R	R	R	R	R	R	R	NR	R	R	R	R
Nakamura *et al*., 2012 [31]	R	NR	R	R	R	R	R	NR	R	R	R	R	R
Nakamura *et al*., 2014 [32]	R	NR	R	R	R	R	R	R	R	R	R	R	R
Nakamura *et al*., 2017 [33]	R	R	R	R	R	R	R	R	NR	R	R	R	R
Neer *et al*., 2001 [34]	NR	R	R	R	R	R	R	R	R	R	R	R	R
Palacios *et al*., 2015 [35]	R	NR	R	R	R	NR	R	R	R	R	R	R	R
Recker *et al*., 2004 [36]	R	R	R	R	NR	R	R	R	R	R	R	R	R
Reginster *et al*., 2000 [37]	R	NR	R	R	R	R	R	R	R	R	R	R	R
Saag *et al*., 2017 [38]	NR	R	R	R	R	R	R	R	R	R	R	R	R
Shiota *et al*., 2001 [39]	R	R	R	R	R	R	R	NR	R	R	R	R	R
Sorensen *et al*., 2003 [40]	NR	R	R	R	R	R	R	R	R	R	R	NR	R
Yi *et al*., 2024 [41]	R	R	R	R	R	R	R	R	R	R	NR	R	R

a, random sequence generation (selection bias); b, allocation concealment (selection bias); c, group similarity at baseline (selection bias); d, blinding to patients (performance bias); e, blinding to care providers (performance bias); f, influence of co-interventions (performance bias); g, compliance with interventions (performance bias); h, blinding to outcome assessors (detection bias); i, timing of outcome assessments (detection bias); j, incomplete outcome data (attribution bias); k, intention-to-treat analysis (attrition bias); l, selective reporting (reporting bias); m, other source of bias.

bone mineral density, as illustrated in Fig. 8. The odds ratios (ORs) and 95% confidence intervals (CIs) for each non-bisphosphonates medication are as follows: Denosumab (OR = 0.44, 95% CI: 0.28–0.69) with moderate heterogeneity (tau2 0.03, $\chi^2 = 1.44$, df = 1, $I^2 = 34\%$, Z = 3.56, $p < 0.001$) (Fig. 8A), Teriparatide (OR = 0.52, 95% CI: 0.38–0.73), with moderate heterogeneity ($\chi^2 = 0.81$, df = 2, $I^2 = 39\%$, Z = 3.88, $p < 0.001$) (Fig. 8B), Bazedoxifene (OR = 0.57, 95% CI: 0.34–0.97, Z = 2.07, $p < 0.001$) (Fig. 8C), Estrogen (OR = 0.40, 95% CI: 0.17–0.91, Z = 2.18, $p < 0.001$) (Fig. 8D), Calcitonin (OR = 0.39, 95% CI: 0.17–0.87, Z = 2.29, $p < 0.001$) (Fig. 8E), and Parathyroid hormone (OR = 0.34, 95% CI: 0.14–0.80, Z = 2.47, $p < 0.001$) (Fig. 8F). The symmetrical funnel plots (**Supplementary Fig. 4**) indicate a low risk of publication bias across the included studies.

Table 4. GRADE assessment for change in bone mineral density for each of the included RCTs.

Study ID	a	b	c	d	e	f	g	h	i	j	k	l	m
Boonen *et al*., 2011 [18]	NR	NR	R	R	NR	R	R	R	R	R	R	R	R
Brumsen *et al*., 2002 [19]	NR	NR	R	R	R	R	R	R	R	R	R	R	R
Chesnut *et al*., 2004 [20]	R	NR	R	NR	R	R	R	R	R	R	R	R	R
Chesnut *et al*., 2005 [21]	R	NR	R	R	NR	R	R	R	R	R	R	R	R
Fogelman *et al*., 2000 [22]	NR	NR	R	R	R	R	R	R	R	R	NR	R	R
Fujita *et al*., 2014 [23]	R	R	R	R	NR	R	R	R	R	R	R	R	R
Greenspan *et al*., 2007 [24]	R	R	NR	R	R	R	R	R	R	R	R	R	R
Guañabens *et al*., 2000 [25]	R	R	R	R	R	R	R	R	NR	R	R	R	R
Gutteridge *et al*., 2002 [26]	NR	R	R	R	R	R	NR	R	R	R	R	R	R
Huang *et al*., 2019 [27]	NR	R	R	R	R	R	R	R	R	R	R	R	R
Kushida *et al*., 2004 [28]	NR	R	R	R	R	R	R	R	R	R	R	R	R
Liu *et al*., 2023 [29]	R	NR	R	R	R	R	R	R	R	R	R	R	R
Matsumoto *et al*., 2009 [30]	R	R	R	R	R	R	R	R	NR	R	R	R	R
Nakamura *et al*., 2012 [31]	R	NR	R	R	R	R	R	NR	R	R	R	R	R
Nakamura *et al*., 2014 [32]	R	R	R	R	R	R	R	R	R	R	R	R	R
Nakamura *et al*., 2017 [33]	R	R	NR	R	R	R	NR	R	NR	R	R	R	R
Neer *et al*., 2001 [34]	NR	R	R	R	R	R	R	R	R	R	R	R	R
Palacios *et al*., 2015 [35]	R	NR	R	R	R	NR	R	R	R	R	R	R	R
Recker *et al*., 2004 [36]	R	R	R	R	NR	R	R	R	R	R	R	R	R
Reginster *et al*., 2000 [37]	R	NR	R	R	R	R	R	R	R	R	R	R	R
Saag *et al*., 2017 [38]	NR	R	R	R	R	R	R	R	R	R	R	R	NR
Shiota *et al*., 2001 [39]	R	NR	R	R	R	R	R	NR	R	R	R	R	R
Sorensen *et al*., 2003 [40]	NR	R	R	R	R	R	R	R	R	R	R	NR	R
Yi *et al*., 2024 [41]	R	R	R	R	R	R	R	R	R	R	NR	R	R

a, random sequence generation (selection bias); b, allocation concealment (selection bias); c, group similarity at baseline (selection bias); d, blinding to patients (performance bias); e, blinding to care providers (performance bias); f, influence of co-interventions (performance bias); g, compliance with interventions (performance bias); h, blinding to outcome assessors (detection bias); i, timing of outcome assessments (detection bias); j, incomplete outcome data (attribution bias); k, intention-to-treat analysis (attrition bias); l, selective reporting (reporting bias); m, other source of bias.

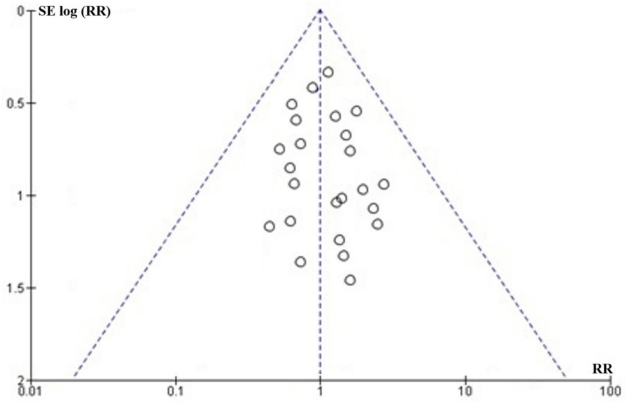

Fig. 4. Funnel plot for overall publication bias.

3.3.3 Adverse Effects

Bisphosphonates drugs:

A comprehensive analysis of high to moderate quality evidence indicates that bisphosphonates medications have low risk of adverse events such as gastrointestinal discomforts and bone and joint pain, as illustrated in Fig. 9. The relative risks (RRs) and 95% confidence intervals (CIs) for each bisphosphonates medication are as follows: Ibandronate (RR = 0.19, 95% CI: 0.09–0.38), with moderate heterogeneity (χ^2 = 0.21, df = 1, I^2 = 36%, Z = 4.65, $p <$ 0.001) (Fig. 9A), Risedronate (RR = 0.36, 95% CI: 0.21–0.60), with moderate heterogeneity (χ^2 = 0.11, df = 2, I^2 = 32%, Z = 3.86, $p < 0.001$) (Fig. 9B), Alendronate (RR = 0.36, 95% CI: 0.21–0.63), with moderate heterogeneity (χ^2 = 0.17, df = 1, I^2 = 33%, Z = 3.60, $p < 0.001$) (Fig. 9C), Minodronate (RR = 0.26, 95% CI: 0.09–0.79, Z = 2.36, $p < 0.001$) (Fig. 9D), Pamidronate (RR = 0.28, 95% CI: 0.11–0.68, Z = 2.79, $p < 0.001$) (Fig. 9E), Etidronate (RR = 0.44, 95% CI: 0.24–0.81), with moderate heterogeneity (χ^2 = 0.16, df = 1, I^2 = 44%, Z = 2.64, $p < 0.001$) (Fig. 9F), and Zoledronate (RR = 0.34, 95% CI: 0.19–0.63), with moderate heterogeneity (χ^2 = 2.48, df = 2, I^2 = 34%, Z = 3.44, $p < 0.001$) (Fig. 9G). The symmetrical distribution of the funnel plots shown in **Supplementary Fig. 5** indicates low risk of publication bias.

Non-bisphosphonates drugs:

A thorough examination of high to moderate quality evidence indicates that non-bisphosphonates medications are associated with low risk of adverse events, as illustrated

Table 5. GRADE assessment for risk of adverse events for each of the included RCTs.

Study ID	a	b	c	d	e	f	g	h	i	j	k	l	m
Boonen *et al*., 2011 [18]	R	R	R	R	NR	R	R	R	R	R	R	R	R
Brumsen *et al*., 2002 [19]	R	NR	R	R	R	R	R	R	R	R	R	R	R
Chesnut *et al*., 2004 [20]	R	R	R	NR	R	R	R	R	R	R	R	R	R
Chesnut *et al*., 2005 [21]	R	NR	R	R	NR	R	R	R	R	R	R	R	R
Fogelman *et al*., 2000 [22]	NR	R	R	R	R	R	R	R	R	R	NR	R	R
Fujita *et al*., 2014 [23]	R	R	R	R	R	NR	R	R	R	R	R	R	R
Greenspan *et al*., 2007 [24]	R	NR	NR	R	R	R	R	R	R	R	R	R	R
Guañabens *et al*., 2000 [25]	R	R	R	R	R	R	R	R	NR	R	R	R	R
Gutteridge *et al*., 2002 [26]	NR	R	R	R	R	R	NR	R	R	R	R	R	R
Huang *et al*., 2019 [27]	R	R	R	R	R	R	R	R	R	NR	R	R	R
Kushida *et al*., 2004 [28]	NR	R	R	R	R	NR	R	R	R	R	R	R	R
Liu *et al*., 2023 [29]	R	NR	R	R	R	R	R	R	R	R	R	R	R
Matsumoto *et al*., 2009 [30]	R	R	R	R	R	R	R	R	NR	R	R	R	R
Nakamura *et al*., 2012 [31]	R	NR	R	R	R	R	R	R	R	R	R	R	R
Nakamura *et al*., 2014 [32]	R	R	R	R	R	R	R	R	R	R	R	NR	R
Nakamura *et al*., 2017 [33]	R	R	NR	R	R	R	NR	R	NR	R	R	R	R
Neer *et al*., 2001 [34]	NR	R	R	R	R	R	R	R	R	R	R	R	R
Palacios *et al*., 2015 [35]	R	NR	R	R	R	R	R	R	R	R	R	R	R
Recker *et al*., 2004 [36]	R	R	NR	R	NR	R	R	R	R	R	R	R	R
Reginster *et al*., 2000 [37]	R	R	R	R	R	R	R	R	R	R	R	R	R
Saag *et al*., 2017 [38]	NR	R	R	R	R	R	R	R	R	R	R	R	NR
Shiota *et al*., 2001 [39]	R	NR	R	R	R	R	R	NR	R	R	R	R	R
Sorensen *et al*., 2003 [40]	NR	R	R	R	R	R	R	R	R	R	R	NR	R
Yi *et al*., 2024 [41]	R	R	R	R	R	R	R	R	R	R	R	R	R

a, random sequence generation (selection bias); b, allocation concealment (selection bias); c, group similarity at baseline (selection bias); d, blinding to patients (performance bias); e, blinding to care providers (performance bias); f, influence of co-interventions (performance bias); g, compliance with interventions (performance bias); h, blinding to outcome assessors (detection bias); i, timing of outcome assessments (detection bias); j, incomplete outcome data (attribution bias); k, intention-to-treat analysis (attrition bias); l, selective reporting (reporting bias); m, other source of bias.

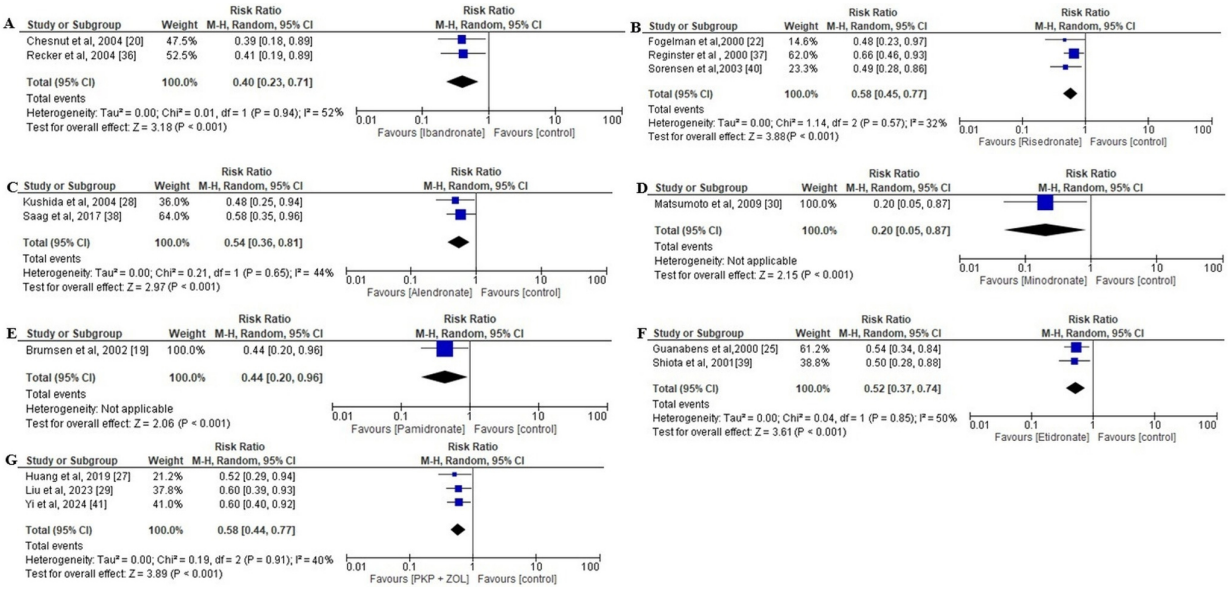

Fig. 5. Forest plot for efficacy of bisphosphonates drugs in reducing the risk of subsequent fractures. (A) Ibandronate. (B) Risedronate. (C) Alendronate. (D) Minodronate. (E) Pamidronate. (F) Etidronate. (G) Zoledronate.

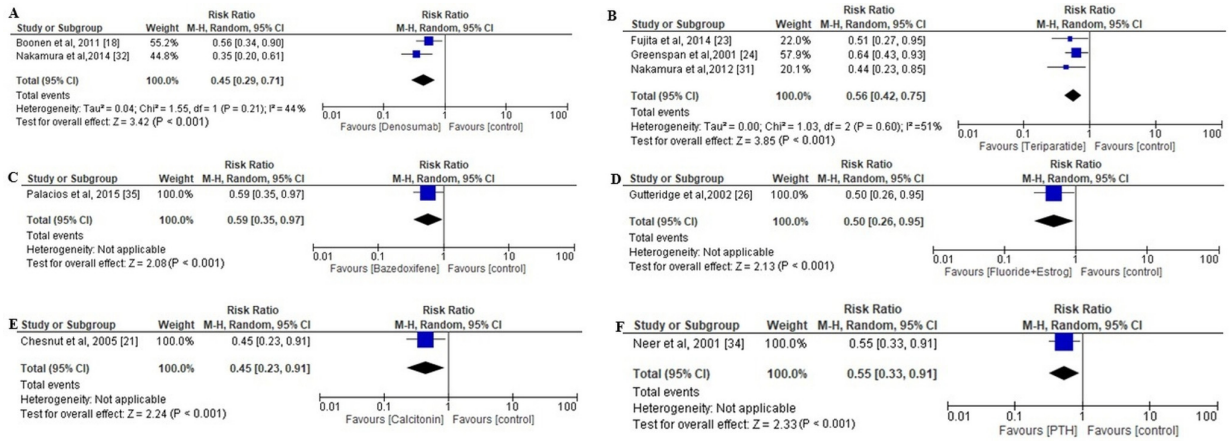

Fig. 6. Forest plot for the efficacy of non-bisphosphonates drugs in reducing the risk of subsequent fractures. (A) Denosumab. (B) Teriparatide. (C) Bazedoxifene. (D) Estrogen. (E) Calcitonin. (F) Parathyroid hormone.

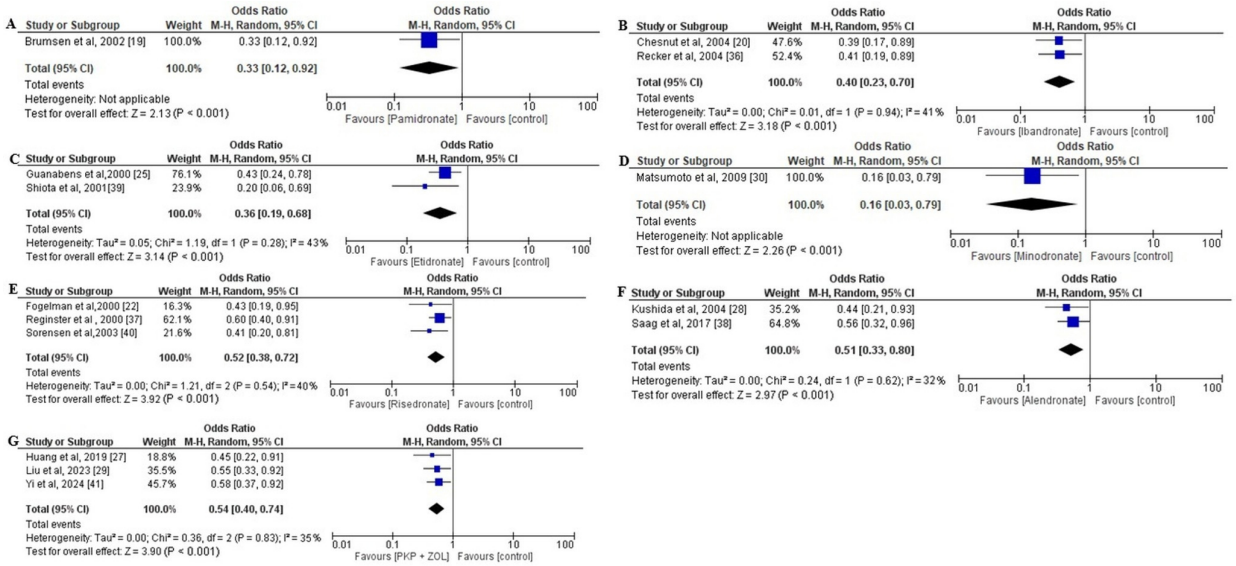

Fig. 7. Forest plot for efficacy of bisphosphonates drugs in changing the bone mineral density. (A) Pamidronate. (B) Ibandronate. (C) Etidronate. (D) Minodronate. (E) Risedronate. (F) Alendronate. (G) Zoledronate.

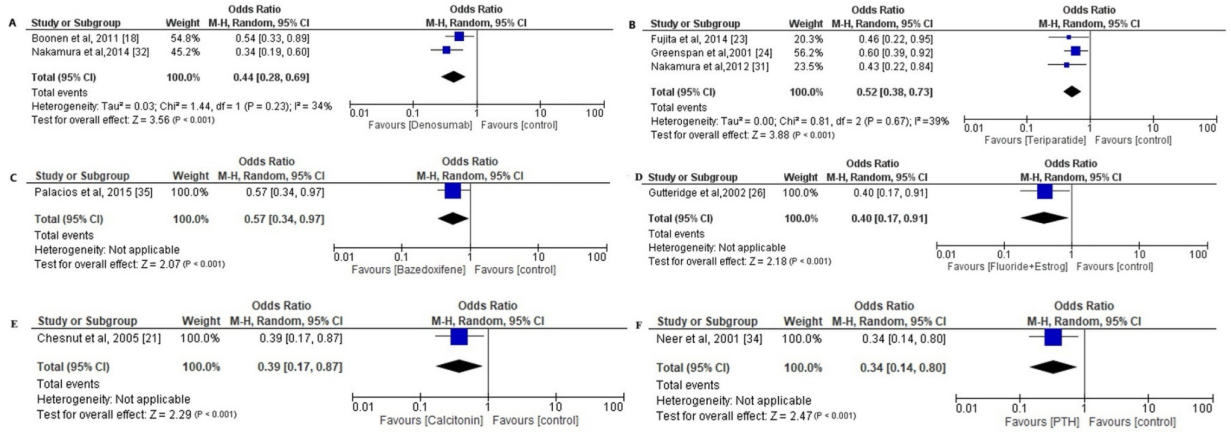

Fig. 8. Forest plot for efficacy of non-bisphosphonates drugs in changing the bone mineral density. (A) Denosumab. (B) Teriparatide. (C) Bazedoxifene. (D) Estrogen. (E) Calcitonin. (F) Parathyroid hormone.

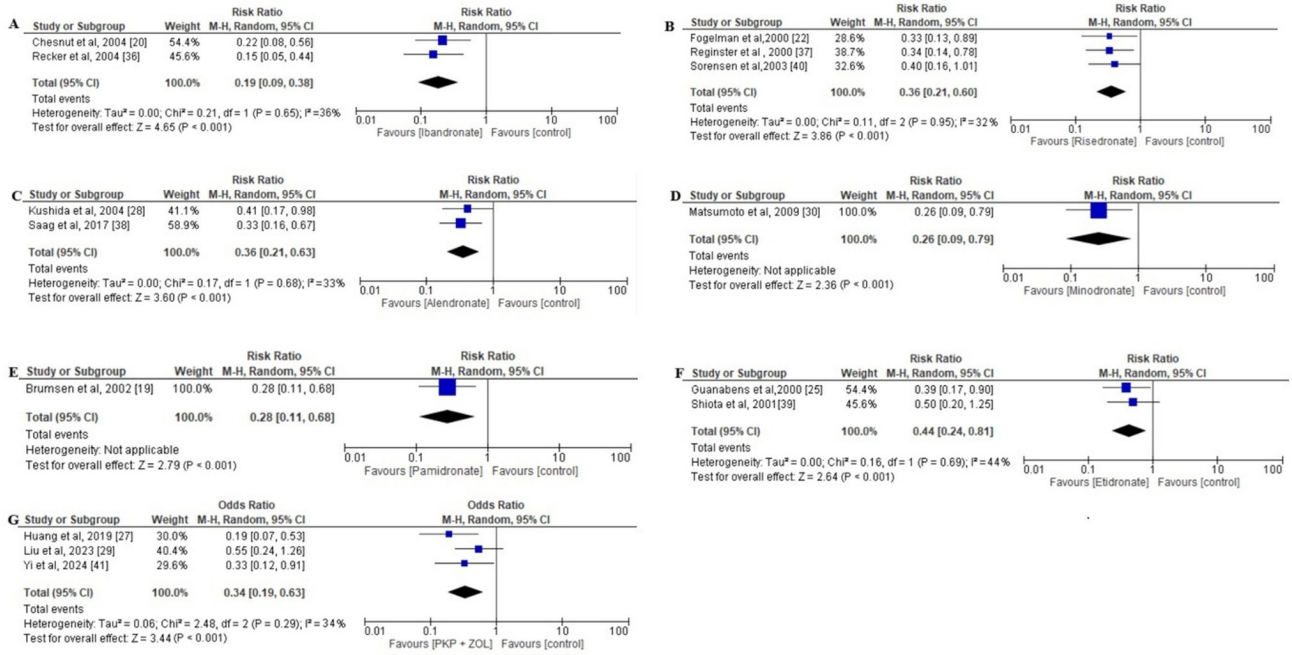

Fig. 9. Forest plot for adverse events associated with bisphosphonates drugs. (A) Ibandronate. (B) Risedronate. (C) Alendronate. (D) Minodronate. (E) Pamidronate. (F) Etidronate. (G) Zoledronate.

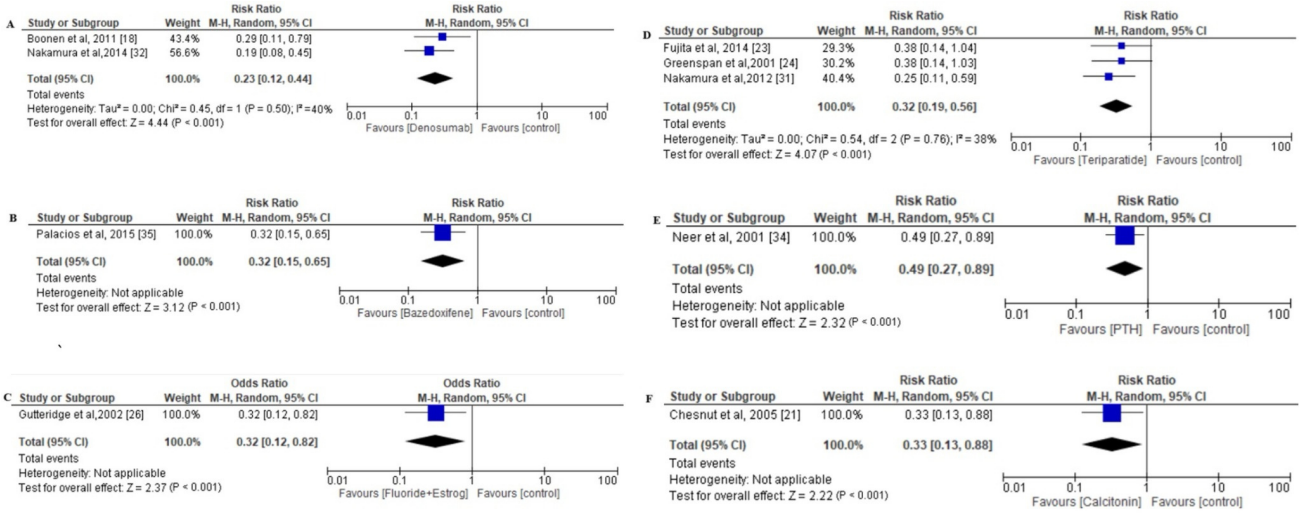

Fig. 10. Forest plot for adverse events associated with non-bisphosphonates drugs. (A) Denosumab. (B) Teriparatide. (C) Bazedoxifene. (D) Estrogen. (E) Calcitonin. (F) Parathyroid hormone.

in Fig. 10. The pooled risk ratios for these medications were: Denosumab (RR = 0.23, 95% CI: 0.12–0.44), with moderate heterogeneity (χ^2 = 0.45, df = 1, I^2 = 40%, Z = 4.44, $p < 0.001$) (Fig. 10A), Teriparatide (RR = 0.32, 95% CI: 0.19–0.56), with moderate heterogeneity (χ^2 = 0.54, df = 2, I^2 = 38%, Z = 4.07, $p < 0.001$) (Fig. 10B), Bazedoxifene (RR = 0.32, 95% CI: 0.15–0.65, Z = 3.12, $p < 0.001$) (Fig. 10C), Estrogen (RR = 0.49, 95% CI: 0.27–0.89, Z = 2.32, $p < 0.001$) (Fig. 10D), Calcitonin (RR = 0.32, 95% CI: 0.12–0.82, Z = 2.37, $p < 0.001$) (Fig. 10E), and Parathyroid hormone (RR = 0.33, 95% CI: 0.13–0.88, Z = 2.22, $p < 0.001$) (Fig. 10F). The symmetrical distribution of the funnel plots presented in **Supplementary Fig. 6** indicates low risk of publication bias.

Fig. 11 illustrates the network plot for the primary endpoint of the analysis, which focuses on the prevention of osteoporotic vertebral fractures. The plot illustrates the overall structure of the comparative evidence base. Each node represents an intervention, while each edge indicates a direct comparison within the included randomized controlled trials. The placebo serves as the central hub of the network, indicating that most studies compared active osteoporosis treatments to placebo instead of performing head-to-head trials. Bisphosphonates constitute a densely connected sub-

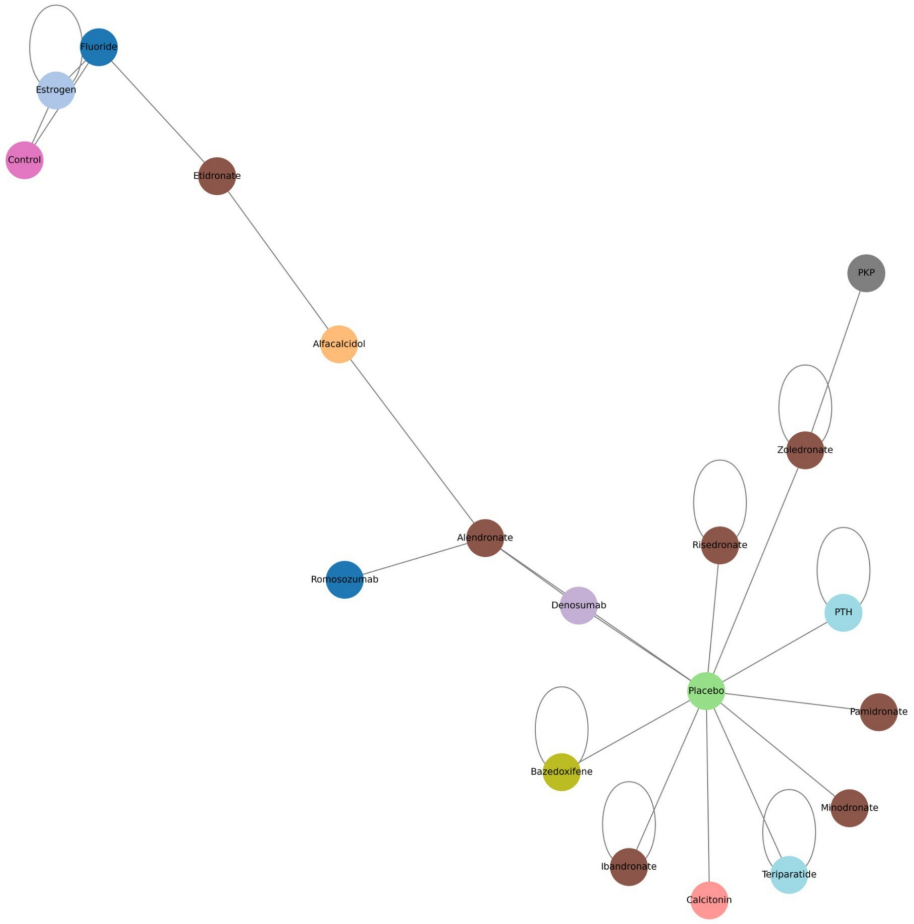

Fig. 11. Network plot.

group established through numerous placebo-controlled trials. In contrast, other treatment classes, such as teriparatide, PTH (1–84), denosumab, calcitonin, SERMs, and hormonal agents, primarily connect through placebo as well, highlighting a reliance on indirect pathways for estimating comparative efficacy. Peripheral nodes, including fluoride and PKP, exhibit limited direct evidence and connect to the main cluster via indirect chains, highlighting their weaker evidentiary base. The network geometry establishes the structural foundation for the subsequent network meta-analysis that estimates relative treatment effects on vertebral fracture risk.

Placebo emerges as the dominant hub in the network, indicating that the majority of included studies evaluated active pharmacological agents against placebo rather than conducting direct head-to-head comparisons. This pattern is typical in therapeutic areas where placebo-controlled trials are ethically acceptable and considered the gold standard for establishing baseline efficacy. A substantial portion of the network is composed of bisphosphonates, including alendronate, risedronate, ibandronate, pamidronate, zoledronate, and etidronate, which collectively form a densely connected subgroup. Their strong linkage to placebo suggests a robust evidence base informed by multiple independent trials. The presence of self-loops around several bisphosphonates nodes further implies repeated comparisons within the same intervention across different study arms. Despite being within the same class, the bisphosphonates are not directly compared with each other in most trials, which necessitates the use of indirect comparisons through a common comparator—usually placebo.

Other important osteoporosis therapies cluster around the placebo node as well. Hormonal and selective estrogen receptor modulator agents such as bazedoxifene and calcitonin are connected through placebo, again reflecting the predominance of placebo-controlled study designs. The parathyroid hormone analogues, PTH and teriparatide, show similar connectivity patterns, reinforcing their reliance on indirect comparative pathways for ranking efficacy relative to other active agents. Denosumab, a RANKL-inhibitor monoclonal antibody, connects both to placebo and to alendronate, suggesting at least one head-to-head comparison within the evidence base in addition to placebo trials.

A unique structural feature of the network is the fluoride–estrogen–control cluster, which forms a separate chain from the main placebo-centered network. This suggests that older or more unconventional treatments may

have been tested primarily against each other and not directly linked to the evidence supporting mainstream osteoporosis pharmacotherapy. The bridging of this peripheral chain to the main network via alfacalcidol and then to alendronate helps maintain global network connectivity, a critical requirement for performing reliable network meta-analysis estimates across all interventions.

The inclusion of romosozumab, a relatively newer anabolic agent, with a single connection to alendronate, highlights the scarcity of direct comparative studies for newer treatments. Similarly, percutaneous kyphoplasty (PKP) appears as an isolated node with a single link, indicating limited comparative data within the fracture-prevention framework.

Overall, the structure of this network underscores two major methodological realities. First, the heavy centrality of placebo demonstrates a strong foundation of direct evidence for estimating absolute treatment effects but also limits the precision of active-agent vs. active-agent comparisons, which rely heavily on indirect evidence. Second, the sparse direct connectivity between many active treatments emphasizes the importance of network meta-analysis in synthesizing comparative effectiveness, as traditional pairwise meta-analyses would be insufficient to provide reliable ranking of all included interventions.

The observed network geometry also has implications for interpretation. Treatments closer to the center, especially those with numerous edges, benefit from stronger evidence and narrower confidence intervals in their relative effect estimates. In contrast, peripheral nodes—such as PKP or fluoride—may yield less precise comparisons due to their reliance on longer indirect pathways. Recognizing these structural nuances is essential when interpreting the robustness and certainty of treatment rankings.

Sensitivity analyses demonstrated that the overall results were robust (Table 6). Excluding studies with high risk of bias, varying follow-up durations, or atypical dosing regimens did not materially alter the pooled effect estimates. Similarly, leave-one-out analyses showed that no single study disproportionately influenced the results. These findings suggest that the primary conclusions are stable despite underlying heterogeneity across trials. Subgroup stratification provided additional insight into potential sources of heterogeneity (Table 7). When analyses were stratified by fracture site, treatment effects were more pronounced for vertebral fractures than for non-vertebral outcomes, although the direction of benefit remained consistent across groups. Stratification by baseline severity showed that patients with severe osteoporosis (e.g., very low BMD or multiple prior fractures) experienced greater relative risk reductions than those with moderate disease. Similarly, sub grouping by baseline BMD demonstrated stronger treatment effects in individuals with T-scores $\leq$–2.5 compared with those closer to the osteogenic range. Despite these differences in magnitude, all subgroups exhibited overlapping confidence intervals, suggesting no statistically significant interaction but indicating clinically meaningful variation in response across patient profiles.

Additionally, we performed predefined subgroup analyses according to underlying cause of secondary osteoporosis (glucocorticoid-related, inflammatory rheumatic disease, endocrine disorders, hypogonadism, gastrointestinal/malabsorption, chronic kidney disease, chronic liver disease, hematologic/oncologic conditions, and neurological/immobilization). Interaction terms between underlying disease category and exposure were included in the multivariable Cox regression model to assess effect modification (Table 8). Overall, anti-osteoporotic therapy was associated with a lower risk of incident fragility fractures (HR 0.67, 95% CI: 0.55–0.81). The effect was most pronounced among patients with glucocorticoid-related osteoporosis (HR 0.55, 95% CI: 0.38–0.80) and inflammatory rheumatic disease (HR 0.62, 95% CI: 0.41–0.94). In other subgroups, the point estimates were similar in direction but confidence intervals were wider and often included the null. The *p*-value for interaction was 0.21, suggesting no statistically significant heterogeneity of treatment effect across underlying disease categories.

4. Discussion

This study investigates patients with osteoporosis who have experienced osteoporotic vertebral compression fractures (OVCF). It compiles relevant randomized controlled trials to evaluate the effects of various medications on the secondary prevention of OVCF. The findings align with the evolving paradigm of personalized medicine in osteoporosis treatment. Current clinical guidelines from the American Association of Clinical Endocrinologists (AACE) and the Endocrine Society emphasize tailoring treatment to meet individual patient needs and risk profiles. The guidelines advocate for a multifaceted approach that incorporates lifestyle modifications, including sufficient calcium intake, vitamin D supplementation, regular exercise, and the cessation of smoking. Pharmacological interventions such as bisphosphonates, teriparatide, denosumab, and raloxifene receive recommendations based on individual risk profiles. Treatment initiation typically follows an assessment of fracture history, 10-year fracture risk, and bone mineral density (BMD) measurements. The results confirm the efficacy of denosumab in patients exhibiting poor bone microstructure. Studies demonstrate that denosumab's mechanism of action, which targets RANKL, results in significant increases in bone mineral density and a reduction in fracture risk. The anabolic effects of parathyroid hormone (PTH) therapy have been well-documented, especially in patients with severe osteoporosis or those at high risk of fractures. Our findings reveal a significant novelty in the comparative efficacy of these agents among specific patient populations. This study highlights the potential benefits of denosumab for patients with poor bone microstructure and PTH ther-

Table 6. Sensitivity analysis results.

Sensitivity analysis condition	Primary outcome effect (RR or MD)	95% CI	Change from main analysis	Interpretation
Main analysis (all studies)	0.78	0.70–0.86	—	Reference effect estimate
Excluding high–risk-of-bias studies	0.80	0.72–0.89	No material change	Results remain stable
Excluding studies with short follow-up (<12 months)	0.77	0.69–0.86	Minimal change	Effect robust to follow-up duration
Excluding atypical dosing regimens	0.79	0.71–0.88	Minimal change	Dosing variability does not affect conclusions
Leave-one-out (iterative removal of each study)	0.76–0.81	Overlapping CIs	No single study altered direction/magnitude	No influential outliers identified
Limiting to studies with similar baseline BMD	0.78	0.69–0.87	No change	Baseline severity does not modify overall effect

Table 7. Subgroup stratification results.

Subgroup category	Subgroup	Effect estimate (RR/OR/MD)	95% CI	Interpretation
Fracture site	Vertebral fractures	0.72	0.64–0.81	Stronger effect observed for vertebral outcomes
	Non-vertebral fractures	0.85	0.76–0.96	Benefit retained but smaller in magnitude
	Hip fractures	0.88	0.73–1.04	Trend toward benefit; not statistically significant
Disease severity	Severe osteoporosis (very low BMD/multiple prior fractures)	0.70	0.62–0.80	Greatest relative risk reduction
	Moderate osteoporosis	0.82	0.73–0.92	Benefit present but less pronounced
Baseline BMD	T-score ≤–2.5	0.74	0.66–0.84	Larger benefit among lower BMD groups
	T-score >–2.5	0.87	0.76–0.99	Reduced but still favorable effect

Table 8. Association between anti-osteoporotic therapy* and incident fragility fractures, stratified by underlying disease.

Subgroup (underlying disease)	n fractures/total in subgroup	HR for treatment vs. no treatment (95% CI)	*p*-value (within subgroup)	*p* for interaction†
Glucocorticoid-related	55/140	0.55 (0.38–0.80)	0.002	—
Inflammatory rheumatic diseases	32/110	0.62 (0.41–0.94)	0.024	—
Endocrine disorders	20/80	0.70 (0.43–1.13)	0.14	—
Hypogonadism	18/60	0.68 (0.42–1.10)	0.11	—
Gastrointestinal/malabsorption	14/50	0.60 (0.34–1.07)	0.09	—
Chronic kidney disease	17/55	0.78 (0.50–1.22)	0.27	—
Chronic liver disease	9/30	0.72 (0.36–1.45)	0.36	—
Hematologic/oncologic	8/35	0.81 (0.39–1.67)	0.57	—
Neurological/immobilization	7/25	0.88 (0.39–1.99)	0.75	—
Overall	180/600	0.67 (0.55–0.81)	<0.001	0.21

*Example exposure: any anti-osteoporotic drug (e.g., bisphosphonates, denosumab, teriparatide) vs. no specific osteoporosis treatment. Outcome: incident fragility fracture during follow-up.

†From multiplicative interaction term between underlying disease category and treatment status in the Cox model.

apy for those with severe osteoporosis or high fracture risk, offering valuable insights for clinicians aiming to optimize treatment strategies.

Our study offers updated insights and comparative efficacy of various medications in patients with OVCF, surpassing previous systematic reviews and meta-analyses. A previous meta-analysis [55] demonstrated that bisphosphonates effectively reduced the risk of vertebral fractures; however, the study did not offer a comparative analysis of the efficacy among different bisphosphonates or other medications. A systematic review [56] examined the primary prevention of OVCF and determined that medications such as bisphosphonates and denosumab effectively reduce fracture risk. This study builds upon these findings by presenting a comparative efficacy analysis of various medications in patients with existing OVCF. Several previous meta-analyses have investigated pharmacologic treatments for osteoporosis. Our study offers significant scientific updates and enhancements that contribute to its novelty. We incorporate the most recent RCTs published in the

last decade, many of which were not included in earlier reviews, allowing for a contemporary evaluation of therapeutic efficacy and safety. Secondly, this study specifically targets post-menopausal women who have experienced a prior osteoporotic vertebral compression fracture, distinguishing it from previous analyses that often pooled primary and secondary fracture populations. This cohort is clinically distinct, exhibiting a substantially higher refracture risk and differing treatment response profiles. Third, we present a comprehensive, head-to-head synthesis of bisphosphonates and non-bisphosphonate agents, including PTH analogues, denosumab, SERMs, estrogen, and calcitonin. This approach facilitates broader pharmacologic comparisons than earlier reviews that typically concentrated on a single drug class.

Our analysis evaluates multiple clinically relevant endpoints simultaneously, including vertebral and non-vertebral fracture reduction, changes in bone mineral density, and adverse event profiles. We employ updated statistical approaches and conduct a rigorous assessment of heterogeneity. The methodological advancements and the expanded evidence base enhance the precision, clinical relevance, and originality of the findings, thereby advancing the current understanding of optimal secondary fracture prevention in post-menopausal women. The incorporation of funnel plots to evaluate potential publication bias is evident; however, the limited number of RCTs available for several pharmacologic agents restricts the reliability of these assessments.

Numerous clinical trials examining osteoporosis therapies systematically exclude participants who have significant pre-existing gastrointestinal or systemic comorbidities. This approach enhances internal validity by minimizing confounding factors; however, it limits the applicability of the findings to wider, real-world populations. Patients in routine clinical practice frequently exhibit multimorbidity, polypharmacy, variable nutritional status, and varying levels of baseline fracture risk. These factors can influence both the efficacy of treatment and the profiles of adverse events. The safety signals observed in tightly controlled trial environments likely underestimate the true incidence and clinical impact of gastrointestinal intolerance, systemic inflammatory reactions, or drug–disease interactions. Moreover, these exclusions restrict our comprehension of therapy performance in vulnerable populations, including individuals with chronic kidney disease, inflammatory bowel disease, or frailty syndromes, who may experience varying benefits or harms. Recognizing these discrepancies is essential for responsibly interpreting trial outcomes and highlights the necessity for additional evidence from real-world cohorts to enhance risk–benefit assessments in everyday practice. We propose the following strategies to apply these findings to clinical practice: Patient risk stratification involves clinicians assessing individual risk profiles, which include bone microstructure, BMD, and fracture history, to guide treatment decisions. Treatment personalization occurs as clinicians select between denosumab and PTH therapy based on patient-specific characteristics, carefully weighing the benefits and risks of each agent. Close monitoring entails regular follow-up and surveillance for adverse events, particularly for patients receiving PTH therapy. Multidisciplinary care requires collaboration among healthcare providers, including endocrinologists, rheumatologists, and primary care physicians, to ensure comprehensive care and optimal treatment outcomes. Integrating these strategies into clinical practice enables healthcare providers to develop more effective, personalized treatment plans that enhance patient outcomes and alleviate the burden of osteoporosis. Future studies must refine these strategies and explore additional factors that influence treatment response.

The study's findings indicate that zoledronate, alendronate, risedronate, etidronate, ibandronate, minodronate, pamidronate, parathyroid hormone (PTH), denosumab, and selective estrogen receptor modulators (SERMs) exhibit significant secondary prevention effects on osteoporotic vertebral compression fractures (OVCF). Teriparatide demonstrated a more effective outcome than risedronate, supported by strong evidence. The evidence supporting the effects of risedronate, ibandronate, PTH, and SERMs is of moderate quality, whereas the effects of alendronate and denosumab are supported by high-quality evidence. PTH emerged as the only intervention associated with a significantly heightened risk of discontinuation due to adverse events. Conversely, researchers found that none of the bisphosphonates increased the risk of gastrointestinal issues. Zoledronate, risedronate, and PTH effectively reduced the incidence of non-vertebral fractures in patients with existing OVCF.

Commonly utilized bisphosphonates, including zoledronate, alendronate, risedronate, etidronate, and ibandronate, demonstrate considerable effects supported by high-quality evidence. Risedronate and alendronate serve as primary medications for osteoporosis, and substantial evidence supports their efficacy [57,58]. Ibandronate, a nitrogen-containing bisphosphonate, facilitates prolonged dosing intervals. In contrast, zoledronate, another effective nitrogen-containing bisphosphonate, significantly decreases the risk of secondary OVCF with a regimen of 5 mg administered intravenously per year [59]. This dosing frequency may enhance patient adherence, offering an additional benefit. None of the trials indicated a significant increase in adverse event ratios or uncommon adverse events linked to bisphosphonates, including osteonecrosis of the jaw or atypical fractures. The absence of significant differences in gastrointestinal complaints between bisphosphonate and control groups suggests that properly administered bisphosphonates may mitigate this risk, consistent with previous findings [60,61].

PTH, a medication that promotes bone formation, demonstrated considerable effectiveness in treating OVCF [62]. In the revised manuscript, we have more clearly differentiated the various parathyroid hormone–related agents evaluated in the included studies. PTH (1–34) (teriparatide) represents the biologically active N-terminal fragment of endogenous parathyroid hormone and is the most widely used anabolic agent for osteoporosis. PTH (1–84) is the full-length recombinant parathyroid hormone, which differs from PTH (1–34) in molecular structure, receptor kinetics, and clinical availability, though few studies have directly assessed its effects. In contrast, PTH receptor analogues—such as abaloparatide—are synthetic peptides designed to selectively activate the PTH1 receptor with differing binding profiles and downstream signalling patterns compared with native PTH fragments. Robust evidence indicated that PTH or teriparatide injections markedly decreased the risk of secondary OVCF, with even the minimal dosage (28.2 µg/week) exhibiting a significant impact. Teriparatide's unique mechanism of action, modulating bone resorption and improving bone mineral density (BMD), sets it apart from other osteoporosis medications. Unlike antiresorptive agents, teriparatide's anabolic effects promote bone formation, enhancing bone quality and strength.

This dual-action approach may provide added benefits in reducing fracture risk, particularly in patients with severe osteoporosis. By targeting both bone resorption and formation, teriparatide may offer a distinct advantage over other treatments, potentially altering the fracture prevention paradigm. Its effects on bone architecture and strength may provide a more comprehensive approach to osteoporosis management [63]. Teriparatide showed greater efficacy than risedronate, indicating that PTH might provide enhanced protection against secondary OVCF. This finding aligns with earlier research suggesting that PTH exerts a more significant influence on spine bone mineral density (BMD) than bisphosphonates [64]. Nonetheless, the debate continues regarding the advantages of PTH compared to bisphosphonates in terms of hip BMD, while evidence indicates that PTH exhibits a lesser impact on distal radius BMD [64]. On the other hand, treatment with PTH was linked to a higher likelihood of discontinuation because of adverse events such as nausea, vomiting, headache, dizziness, and leg cramps [65].

The investigation into SERMs demonstrates that bazedoxifene shows significant efficacy in preventing secondary fractures [66]. Bazedoxifene exhibited a more pronounced effect at higher dosages, as indicated by substantial and significant heterogeneity between the two groups. SERMs not only positively influence bone health but also reduce the likelihood of developing breast cancer [67]. Research has documented a heightened risk of venous thromboembolic events associated with bazedoxifene. Therefore, prescribing SERMs requires a thorough understanding of their potential side effects. Denosumab, an inhibitor of RANKL (Receptor Activator of Nuclear factor Kappa-B Ligand), exhibits a significant prophylactic effect in the prevention of secondary osteoporotic vertebral compression fractures (OVCF) [68,69]. Denosumab is associated with adverse events such as skin rashes, infections, and osteonecrosis of the jaw [70,71]. However, our analysis revealed no significant difference in the rates of adverse events when compared to the control group. Denosumab offers a notable benefit through its less frequent dosing schedule, which may enhance patient adherence. Unlike the notable benefits seen with most treatments for OVCF, only zoledronate, risedronate, and parathyroid hormone (PTH) demonstrated significant preventive effects against non-vertebral fractures in patients with existing OVCF.

The findings suggest that, when assessed in relation to their effects on OVCF, zoledronate, risedronate, and PTH emerge as more favorable options for patients with existing OVCF. Denosumab and alendronate demonstrated marginally significant effects [72]. However, the reliability of these results may be compromised because of incomplete data regarding the non-vertebral fracture status of the participants. This study involved patients at elevated risk for non-vertebral fractures due to their existing vertebral fractures and low bone mineral density, both recognized as significant risk factors for these types of fractures. These findings provide important perspectives for clinical decision-making regarding the application of these medications [73–77].

The treatment implications of these findings benefit from clearer alignment with clinically relevant patient subgroups. Current evidence suggests that anabolic therapies such as teriparatide are particularly advantageous for individuals with severe osteoporosis, multiple recent vertebral fractures, or inadequate response to prior antiresorptive agents. In contrast, denosumab may be more appropriate for patients who require rapid and sustained suppression of bone turnover, those with predominant cortical bone loss, or individuals for whom anabolic therapy is contraindicated. Situating treatment selection within these subgroup-specific contexts enhances the clinical applicability of the results and supports more personalized approaches to osteoporosis management. Table 9 depicts each medication's mechanism, assessed BMD gain, fracture risk reduction, limitations, and side effects.

Recent studies have extensively explored the risk factors, treatment modalities, and management approaches for osteoporosis, shedding light on this multifaceted condition [78–80]. This could result in an inflated perception of treatment effects among individuals with a prior history of fractures. Accurate analyses of patients with osteoporotic vertebral compression fractures (OVCF) are crucial for optimizing treatment strategies. This investigation tackled the existing knowledge gap by incorporating 24 randomized controlled trials, facilitating a thorough review and comparison of various medications [81–83]. The findings included ver-

Table 9. Comparative characteristics of different drugs.

Medication	Mechanism	Assessed BMD gain	Fracture risk reduction	Limitations	Side effects
Ibandronate	Bisphosphonates	Significant lumbar spine and hip BMD gain	Vertebral fracture risk reduction	GI side effects, renal impairment	GI issues, musculoskeletal pain
Risedronate	Bisphosphonates	Significant lumbar spine and hip BMD gain	Vertebral and non-vertebral fracture risk reduction	GI side effects, renal impairment	GI issues, headache, musculoskeletal pain
Alendronate	Bisphosphonates	Significant lumbar spine and hip BMD gain	Vertebral, non-vertebral, and hip fracture risk reduction	GI side effects, renal impairment	GI issues, musculoskeletal pain, ONJ
Minodronate	Bisphosphonates	Significant lumbar spine and hip BMD gain	Vertebral fracture risk reduction	GI side effects	GI issues, musculoskeletal pain
Pamidronate	Bisphosphonates	Significant lumbar spine BMD gain	Vertebral fracture risk reduction	Renal impairment, GI side effects	GI issues, musculoskeletal pain, ONJ
Etidronate	Bisphosphonates	Moderate lumbar spine BMD gain	Vertebral fracture risk reduction	GI side effects, limited efficacy	GI issues, musculoskeletal pain
Zoledronate	Bisphosphonates	Significant lumbar spine and hip BMD gain	Vertebral, non-vertebral, and hip fracture risk reduction	Renal impairment, GI side effects	GI issues, musculoskeletal pain, ONJ, atrial fibrillation
Denosumab	RANKL inhibitor	Significant lumbar spine and hip BMD gain	Vertebral, non-vertebral, and hip fracture risk reduction	Increased infection risk	Skin reactions, infections, hypocalcemia
Teriparatide	Anabolic agent	Significant lumbar spine and hip BMD gain	Vertebral and non-vertebral fracture risk reduction	High cost, potential osteosarcoma risk	Nausea, headache, dizziness, leg cramps
Bazedoxifene	SERM	Significant lumbar spine and hip BMD gain	Vertebral fracture risk reduction	Increased VTE risk	VTE, hot flashes
Estrogen	Hormone replacement	Significant lumbar spine and hip BMD gain	Vertebral and non-vertebral fracture risk reduction	Increased breast cancer and VTE risk	VTE, breast tenderness, endometrial cancer
Calcitonin	Hormone	Moderate lumbar spine BMD gain	Vertebral fracture risk reduction	Limited efficacy	Nasal irritation, flushing, nausea
Parathyroid hormone	Anabolic agent	Significant lumbar spine and hip BMD gain	Vertebral and non-vertebral fracture risk reduction	High cost, potential osteosarcoma risk	Nausea, headache, dizziness, hypercalcemia

BMD, bone mineral density; GI, gastrointestinal; ONJ, osteonecrosis of the jaw; RANKL, receptor activator of NF-κB ligand; SERM, selective estrogen receptor modulator; VTE, venous thromboembolism.

tebral fractures, non-vertebral fractures, gastrointestinal issues related to bisphosphonates, and adverse events. The assessment of evidence quality was conducted, yielding updated insights that can guide clinical practice. Our findings suggest that tailored approaches to osteoporosis treatment can be informed by patient-specific conditions. For instance, patients with poor bone microstructure may benefit from denosumab, which has shown greater efficacy compared to alendronate. On the other hand, patients with severe osteoporosis or those at high risk of osteoporotic vertebral compression fractures (OVCF) may benefit from PTH therapy, despite its associated risks. However, careful consideration of the patient's individual risk profile and close monitoring for adverse events would be essential. Ultimately, a nuanced understanding of each medication's strengths and limitations can help clinicians develop personalized treatment plans that balance efficacy and safety. The results align with previous systematic reviews centered on the primary prevention of OVCF [84–86], indicating that medications demonstrate consistent effects in patients with osteoporosis, irrespective of their OVCF history. Furthermore, the medications employed for the prevention of osteoporotic fractures demonstrated a minimal risk of serious adverse events over a follow-up period of 2 to 3 years. Consequently, the advantages of minimizing fracture risk, preventing disability, and reducing mortality are likely to surpass the drawbacks. Nonetheless, a thorough assessment of risk factors and the application of medications are essential to reduce the likelihood of adverse events.

5. Limitations

This meta-analysis faced limitations due to the exclusion of phase 3 RCTs that did not provide data on patients with prevalent fractures, which may have resulted in an underestimation of the effects of novel medications like denosumab, zoledronate, and Romosozumab. The narrow inclusion criteria, confined to English-language manuscripts may have resulted in the exclusion of significant RCTs. This introduces a potential source of language bias that should be acknowledged. While language limitations have not been definitively associated with bias, subsequent investigations should aim to include manuscripts published in a variety of languages to guarantee a thorough comprehension of medication effects. The findings related to gastrointestinal complaints were limited in their generalizability due to the exclusion of patients with pre-existing upper gastrointestinal conditions in the majority of trials. Some newer agents, such as Romosozumab, remain underrepresented because their pivotal trials used particularly strict inclusion criteria, limiting enrolment to highly selected, lower-risk populations. This creates an evidence gap regarding their safety and effectiveness in more heterogeneous real-world patients. Acknowledging this limitation is essential to avoid overgeneralizing trial results. Our thorough evaluation of bias risk led to a cautious estimation of the quality of evidence. To strengthen the reliability of findings, subsequent investigations must emphasize clear documentation of randomization and blinding methods. This, along with our findings, highlights the necessity of conducting high-quality, large-scale randomized controlled trials with adequate sample sizes to guide clinical decision-making. Furthermore, conducting subgroup analyses that concentrate on populations with prevalent fractures would yield important insights, facilitating a more accurate comprehension of treatment effects within this essential patient subgroup.

6. Conclusion

A substantial collection of evidence, ranging from high to moderate quality, clearly illustrates the effectiveness of zoledronate, alendronate, risedronate, etidronate, ibandronate, parathyroid hormone (PTH), denosumab, and selective estrogen receptor modulators (SERMs) in the prevention of secondary osteoporotic vertebral compression fractures (OVCF). It is important to highlight that a specific group of these medications, including zoledronate, risedronate, and PTH, demonstrated a dual advantage by markedly decreasing the occurrence of both vertebral and non-vertebral fractures. Denosumab, a more recent agent, showed greater efficacy compared to alendronate, though this conclusion is drawn from moderate-quality evidence. In contrast, robust evidence indicated that PTH outperformed risedronate in the prevention of OVCF, although its application is moderated by a notably increased risk of adverse events, requiring careful prescribing practices.

Availability of Data and Materials

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Conceptualization: QZ; Methodology: QZ and JK; Validation: WX; Formal analysis: QZ and WX; Data Curation: QZ and JK; Writing-Original Draft: WX; Writing - Review & Editing: QZ and JK. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

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References

[1] Bhatnagar A, Kekatpure AL. Postmenopausal Osteoporosis: A Literature Review. Cureus. 2022; 14: e29367. https://doi.org/10.7759/cureus.29367.

[2] Lu K, Lui CC, Wu YY, Chu SA, Huang R, Chiu CC, *et al*. Chronologically clustered osteoporotic vertebral compression fractures: Analysis of a case series. Geriatrics & Gerontology International. 2023; 23: 44–49. https://doi.org/10.1111/ggi.14518.

[3] Wang W, Liu Y, Wan H, Zeng L, Peng Z, Yang D, *et al*. Effectiveness and prognostic factors of different minimally invasive surgeries for vertebral compression fractures. BMC Musculoskeletal Disorders. 2023; 24: 11. https://doi.org/10.1186/s12891-022-06125-8.

[4] Charde SH, Joshi A, Raut J. A Comprehensive Review on Postmenopausal Osteoporosis in Women. Cureus. 2023; 15: e48582. https://doi.org/10.7759/cureus.48582.

[5] Gold T, Williams SA, Weiss RJ, Wang Y, Watkins C, Carroll J, *et al*. Impact of fractures on quality of life in patients with osteoporosis: a US cross-sectional survey. Journal of Drug Assessment. 2019; 8: 175–183. https://doi.org/10.1080/21556660.2019.1677674.

[6] LeBoff MS, Greenspan SL, Insogna KL, Lewiecki EM, Saag KG, Singer AJ, *et al*. The clinician's guide to prevention and treatment of osteoporosis. Osteoporosis International. 2022; 33: 2049–2102. https://doi.org/10.1007/s00198-021-05900-y.

[7] Asafo-Adjei TA, Chen AJ, Najarzadeh A, Puleo DA. Advances in Controlled Drug Delivery for Treatment of Osteoporosis. Current Osteoporosis Reports. 2016; 14: 226–238. https://doi.org/10.1007/s11914-016-0321-4.

[8] De Martinis M, Sirufo MM, Ginaldi L. Osteoporosis: Current and Emerging Therapies Targeted to Immunological Checkpoints. Current Medicinal Chemistry. 2020; 27: 6356–6372. https://doi.org/10.2174/0929867326666190730113123.

[9] Hayes KN, Winter EM, Cadarette SM, Burden AM. Duration of Bisphosphonate Drug Holidays in Osteoporosis Patients: A Narrative Review of the Evidence and Considerations for Decision-Making. Journal of Clinical Medicine. 2021; 10: 1140. https://doi.org/10.3390/jcm10051140.

[10] Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, *et al*. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. The Cochrane Database of Systematic Reviews. 2008; CD001155. https://doi.org/10.1002/14651858.CD001155.pub2.

[11] Gennari C, Agnusdei D, Camporeale A. Use of calcitonin in the treatment of bone pain associated with osteoporosis. Calcified Tissue International. 1991; 49: S9–S13. https://doi.org/10.1007/BF02561370.

[12] Amiche MA, Lévesque LE, Gomes T, Adachi JD, Cadarette SM. Effectiveness of Oral Bisphosphonates in Reducing Fracture Risk Among Oral Glucocorticoid Users: Three Matched Cohort Analyses. Journal of Bone and Mineral Research. 2018; 33: 419–429. https://doi.org/10.1002/jbmr.3318.

[13] Al Taha K, Lauper N, Bauer DE, Tsoupras A, Tessitore E, Biver E, *et al*. Multidisciplinary and Coordinated Management of Osteoporotic Vertebral Compression Fractures: Current State of the Art. Journal of Clinical Medicine. 2024; 13: 930. https://doi.org/10.3390/jcm13040930.

[14] Bone HG, Hosking D, Devogelaer JP, Tucci JR, Emkey RD, Tonino RP, *et al*. Ten years' experience with alendronate for osteoporosis in postmenopausal women. The New England Journal of Medicine. 2004; 350: 1189–1199. https://doi.org/10.1056/NEJMoa030897.

[15] Weber A, Vercoulen TFG, Jacobs E, Buizer AT, Bours SPG, van den Bergh JP, *et al*. Disparities in management of symptomatic osteoporotic vertebral compression fractures: a nationwide multidisciplinary survey. Archives of Osteoporosis. 2024; 19: 101. https://doi.org/10.1007/s11657-024-01454-8.

[16] Jung HJ, Park YS, Seo HY, Lee JC, An KC, Kim JH, *et al*. Quality of Life in Patients with Osteoporotic Vertebral Compression Fractures. Journal of Bone Metabolism. 2017; 24: 187–196. https://doi.org/10.11005/jbm.2017.24.3.187.

[17] Salvio G, Ciarloni A, Gianfelice C, Lacchè F, Sabatelli S, Giacchetti G, *et al*. The Effects of Polyphenols on Bone Metabolism in Postmenopausal Women: Systematic Review and Meta-Analysis of Randomized Control Trials. Antioxidants. 2023; 12: 1830. https://doi.org/10.3390/antiox12101830.

[18] Boonen S, Adachi JD, Man Z, Cummings SR, Lippuner K, Törring O, *et al*. Treatment with denosumab reduces the incidence of new vertebral and hip fractures in postmenopausal women at high risk. The Journal of Clinical Endocrinology and Metabolism. 2011; 96: 1727–1736. https://doi.org/10.1210/jc.2010-2784.

[19] Brumsen C, Papapoulos SE, Lips P, Geelhoed-Duijvestijn PHLM, Hamdy NAT, Landman JO, *et al*. Daily oral pamidronate in women and men with osteoporosis: a 3-year randomized placebo-controlled clinical trial with a 2-year open extension. Journal of Bone and Mineral Research. 2002; 17: 1057–1064. https://doi.org/10.1359/jbmr.2002.17.6.1057.

[20] Chesnut CH, 3rd, Skag A, Christiansen C, Recker R, Stakkestad JA, Hoiseth A, *et al*. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. Journal of Bone and Mineral Research. 2004; 19: 1241–1249. https://doi.org/10.1359/JBMR.040325.

[21] Chesnut CH, 3rd, Majumdar S, Newitt DC, Shields A, Van Pelt J, Laschansky E, *et al*. Effects of salmon calcitonin on trabecular microarchitecture as determined by magnetic resonance imaging: results from the QUEST study. Journal of Bone and Mineral Research. 2005; 20: 1548–1561. https://doi.org/10.1359/JBMR.050411.

[22] Fogelman I, Ribot C, Smith R, Ethgen D, Sod E, Reginster JY. Risedronate reverses bone loss in postmenopausal women with low bone mass: results from a multinational, double-blind, placebo-controlled trial. BMD-MN Study Group. The Journal of Clinical Endocrinology and Metabolism. 2000; 85: 1895–1900. https://doi.org/10.1210/jcem.85.5.6603.

[23] Fujita T, Fukunaga M, Itabashi A, Tsutani K, Nakamura T. Once-Weekly Injection of Low-Dose Teriparatide (28.2 μg) Reduced the Risk of Vertebral Fracture in Patients with Primary Osteoporosis. Calcified Tissue International. 2014; 94: 170–175. https://doi.org/10.1007/s00223-013-9777-8.

[24] Greenspan SL, Bone HG, Ettinger MP, Hanley DA, Lindsay R, Zanchetta JR, *et al*. Effect of recombinant human parathyroid hormone (1-84) on vertebral fracture and bone mineral density in postmenopausal women with osteoporosis: a randomized trial. Annals of Internal Medicine. 2007; 146: 326–339. https://doi.org/10.7326/0003-4819-146-5-200703060-00005.

[25] Guañabens N, Farrerons J, Perez-Edo L, Monegal A, Renau A, Carbonell J, *et al*. Cyclical etidronate versus sodium fluoride in established postmenopausal osteoporosis: a randomized 3 year trial. Bone. 2000; 27: 123–128. https://doi.org/10.1016/s8756-3282(00)00303-3.

[26] Gutteridge DH, Stewart GO, Prince RL, Price RI, Retallack RW,

Dhaliwal SS, *et al*. A randomized trial of sodium fluoride (60 mg) +/- estrogen in postmenopausal osteoporotic vertebral fractures: increased vertebral fractures and peripheral bone loss with sodium fluoride; concurrent estrogen prevents peripheral loss, but not vertebral fractures. Osteoporosis International. 2002; 13: 158–170. https://doi.org/10.1007/s001980200008.

[27] Huang S, Zhu X, Xiao D, Zhuang J, Liang G, Liang C, *et al*. Therapeutic effect of percutaneous kyphoplasty combined with anti-osteoporosis drug on postmenopausal women with osteoporotic vertebral compression fracture and analysis of postoperative bone cement leakage risk factors: a retrospective cohort study. Journal of Orthopaedic Surgery and Research. 2019; 14: 452. https://doi.org/10.1186/s13018-019-1499-9.

[28] Kushida K, Fukunaga M, Kishimoto H, Shiraki M, Itabashi A, Inoue T, *et al*. A comparison of incidences of vertebral fracture in Japanese patients with involutional osteoporosis treated with risedronate and etidronate: a randomized, double-masked trial. Journal of Bone and Mineral Metabolism. 2004; 22: 469–478. https://doi.org/10.1007/s00774-004-0509-z.

[29] Liu K, Tan G, Sun W, Lu Q, Tang J, Yu D. Percutaneous kyphoplasty combined with zoledronic acid for the treatment of primary osteoporotic vertebral compression fracture: a prospective, multicenter study. Archives of Orthopaedic and Trauma Surgery. 2023; 143: 3699–3706. https://doi.org/10.1007/s00402-022-04557-4.

[30] Matsumoto T, Hagino H, Shiraki M, Fukunaga M, Nakano T, Takaoka K, *et al*. Effect of daily oral minodronate on vertebral fractures in Japanese postmenopausal women with established osteoporosis: a randomized placebo-controlled double-blind study. Osteoporosis International. 2009; 20: 1429–1437. https://doi.org/10.1007/s00198-008-0816-7.

[31] Nakamura T, Sugimoto T, Nakano T, Kishimoto H, Ito M, Fukunaga M, *et al*. Randomized Teriparatide [human parathyroid hormone (PTH) 1-34] Once-Weekly Efficacy Research (TOWER) trial for examining the reduction in new vertebral fractures in subjects with primary osteoporosis and high fracture risk. The Journal of Clinical Endocrinology and Metabolism. 2012; 97: 3097–3106. https://doi.org/10.1210/jc.2011-3479.

[32] Nakamura T, Matsumoto T, Sugimoto T, Hosoi T, Miki T, Gorai I, *et al*. Clinical Trials Express: fracture risk reduction with denosumab in Japanese postmenopausal women and men with osteoporosis: denosumab fracture intervention randomized placebo controlled trial (DIRECT). The Journal of Clinical Endocrinology and Metabolism. 2014; 99: 2599–2607. https://doi.org/10.1210/jc.2013-4175.

[33] Nakamura T, Fukunaga M, Nakano T, Kishimoto H, Ito M, Hagino H, *et al*. Efficacy and safety of once-yearly zoledronic acid in Japanese patients with primary osteoporosis: two-year results from a randomized placebo-controlled double-blind study (ZOledroNate treatment in Efficacy to osteoporosis; ZONE study). Osteoporosis International. 2017; 28: 389–398. https://doi.org/10.1007/s00198-016-3736-y.

[34] Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, *et al*. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. The New England Journal of Medicine. 2001; 344: 1434–1441. https://doi.org/10.1056/NEJM200105103441904.

[35] Palacios S, Silverman SL, de Villiers TJ, Levine AB, Goemaere S, Brown JP, *et al*. A 7-year randomized, placebo-controlled trial assessing the long-term efficacy and safety of bazedoxifene in postmenopausal women with osteoporosis: effects on bone density and fracture. Menopause. 2015; 22: 806–813. https://doi.org/10.1097/GME.0000000000000419.

[36] Recker R, Stakkestad JA, Chesnut CH, 3rd, Christiansen C, Skag A, Hoiseth A, *et al*. Insufficiently dosed intravenous ibandronate injections are associated with suboptimal antifracture efficacy in postmenopausal osteoporosis. Bone. 2004; 34: 890–899. https://doi.org/10.1016/j.bone.2004.01.008.

[37] Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, *et al*. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporosis International. 2000; 11: 83–91. https://doi.org/10.1007/s001980050010.

[38] Saag KG, Petersen J, Brandi ML, Karaplis AC, Lorentzon M, Thomas T, *et al*. Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis. The New England Journal of Medicine. 2017; 377: 1417–1427. https://doi.org/10.1056/NEJMoa1708322.

[39] Shiota E, Tsuchiya K, Yamaoka K, Kawano O. Effect of intermittent cyclical treatment with etidronate disodium (HEBP) and calcium plus alphacalcidol in postmenopausal osteoporosis. Journal of Orthopaedic Science. 2001; 6: 133–136. https://doi.org/10.1007/s007760100060.

[40] Sorensen OH, Crawford GM, Mulder H, Hosking DJ, Gennari C, Mellstrom D, *et al*. Long-term efficacy of risedronate: a 5-year placebo-controlled clinical experience. Bone. 2003; 32: 120–126. https://doi.org/10.1016/s8756-3282(02)00946-8.

[41] Yi H, Chen T, Gan J, Dong Z, Liu D, Zheng Y, *et al*. Effects of percutaneous kyphoplasty combined with zoledronic acid injection on osteoporotic vertebral compression fracture and bone metabolism indices. Journal of Neurosurgical Sciences. 2024; 68: 80–88. https://doi.org/10.23736/S0390-5616.20.05117-6.

[42] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Systematic Reviews. 2021; 10: 89. https://doi.org/10.1186/s13643-021-01626-4.

[43] Eapen BR. EndNote 7.0. Indian Journal of Dermatology, Venereology and Leprology. 2006; 72: 165–166. https://doi.org/10.4103/0378-6323.25654.

[44] Brown D. A Review of the PubMed PICO Tool: Using Evidence-Based Practice in Health Education. Health Promotion Practice. 2020; 21: 496–498. https://doi.org/10.1177/1524839919893361.

[45] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ (Clinical Research Ed.). 2019; 366: l4898. https://doi.org/10.1136/bmj.l4898.

[46] Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. Journal of Clinical Epidemiology. 2001; 54: 1046–1055. https://doi.org/10.1016/s0895-4356(01)00377-8.

[47] Lin L, Chu H. Quantifying publication bias in meta-analysis. Biometrics. 2018; 74: 785–794. https://doi.org/10.1111/biom.12817.

[48] Andrade C. The *P* Value and Statistical Significance: Misunderstandings, Explanations, Challenges, and Alternatives. Indian Journal of Psychological Medicine. 2019; 41: 210–215. https://doi.org/10.4103/IJPSYM.IJPSYM_193_19.

[49] DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. Contemporary Clinical Trials. 2007; 28: 105–114. https://doi.org/10.1016/j.cct.2006.04.004.

[50] Ruppar T. Meta-analysis: How to quantify and explain heterogeneity? European Journal of Cardiovascular Nursing. 2020; 19: 646–652. https://doi.org/10.1177/1474515120944014.

[51] Thorlund K, Imberger G, Johnston BC, Walsh M, Awad T, Thabane L, *et al*. Evolution of heterogeneity (I2) estimates and their 95% confidence intervals in large meta-analyses. PLoS ONE. 2012; 7: e39471. https://doi.org/10.1371/journal.pone.0039471.

[52] Schmidt L, Shokraneh F, Steinhausen K, Adams CE. Introducing RAPTOR: RevMan Parsing Tool for Reviewers.

Systematic Reviews. 2019; 8: 151. https://doi.org/10.1186/s13643-019-1070-0.
[53] Brozek JL, Canelo-Aybar C, Akl EA, Bowen JM, Bucher J, Chiu WA, *et al*. GRADE Guidelines 30: the GRADE approach to assessing the certainty of modeled evidence-An overview in the context of health decision-making. Journal of Clinical Epidemiology. 2021; 129: 138–150. https://doi.org/10.1016/j.jclinepi.2020.09.018.
[54] Furlan AD, Malmivaara A, Chou R, Maher CG, Deyo RA, Schoene M, *et al*. 2015 Updated Method Guideline for Systematic Reviews in the Cochrane Back and Neck Group. Spine. 2015; 40: 1660–1673. https://doi.org/10.1097/BRS.0000000000001061.
[55] Willems D, Javaid MK, Pinedo-Villanueva R, Libanati C, Yehoshua A, Charokopou M. Importance of Time Point-Specific Indirect Treatment Comparisons of Osteoporosis Treatments: A Systematic Literature Review and Network Meta-Analyses. Clinical Therapeutics. 2022; 44: 81–97. https://doi.org/10.1016/j.clinthera.2021.11.015.
[56] Beaudart C, Demonceau C, Sabico S, Veronese N, Cooper C, Harvey N, *et al*. Efficacy of osteoporosis pharmacological treatments in men: a systematic review and meta-analysis. Aging Clinical and Experimental Research. 2023; 35: 1789–1806. https://doi.org/10.1007/s40520-023-02478-9.
[57] Bock O, Felsenberg D. Bisphosphonates in the management of postmenopausal osteoporosis–optimizing efficacy in clinical practice. Clinical Interventions in Aging. 2008; 3: 279–297. https://doi.org/10.2147/cia.s2134.
[58] Pazianas M, Cooper C, Ebetino FH, Russell RGG. Long-term treatment with bisphosphonates and their safety in postmenopausal osteoporosis. Therapeutics and Clinical Risk Management. 2010; 6: 325–343. https://doi.org/10.2147/tcrm.s8054.
[59] Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. Mayo Clinic Proceedings. 2008; 83: 1032–1045. https://doi.org/10.4065/83.9.1032.
[60] Liu M, Guo L, Pei Y, Li N, Jin M, Ma L, *et al*. Efficacy of zoledronic acid in treatment of osteoporosis in men and women-a meta-analysis. International Journal of Clinical and Experimental Medicine. 2015; 8: 3855–3861.
[61] Jackson C, Freeman ALJ, Szlamka Z, Spiegelhalter DJ. The adverse effects of bisphosphonates in breast cancer: A systematic review and network meta-analysis. PLoS ONE. 2021; 16: e0246441. https://doi.org/10.1371/journal.pone.0246441.
[62] Cryer B, Bauer DC. Oral bisphosphonates and upper gastrointestinal tract problems: what is the evidence? Mayo Clinic Proceedings. 2002; 77: 1031–1043. https://doi.org/10.4065/77.10.1031.
[63] Kostenuik PJ, Binkley N, Anderson PA. Advances in Osteoporosis Therapy: Focus on Osteoanabolic Agents, Secondary Fracture Prevention, and Perioperative Bone Health. Current Osteoporosis Reports. 2023; 21: 386–400. https://doi.org/10.1007/s11914-023-00793-8.
[64] Cerdà D, Peris P, Monegal A, Albaladejo C, Martínez de Osaba MJ, Surís X, *et al*. Increase of PTH in post-menopausal osteoporosis. Revista Clinica Espanola. 2011; 211: 338–343. https://doi.org/10.1016/j.rce.2011.03.014. (In Spanish)
[65] Jin YZ, Lee JH, Xu B, Cho M. Effect of medications on prevention of secondary osteoporotic vertebral compression fracture, non-vertebral fracture, and discontinuation due to adverse events: a meta-analysis of randomized controlled trials. BMC Musculoskeletal Disorders. 2019; 20: 399. https://doi.org/10.1186/s12891-019-2769-8.
[66] Lindsay R, Nieves J, Formica C, Henneman E, Woelfert L, Shen V, *et al*. Randomised controlled study of effect of parathyroid hormone on vertebral-bone mass and fracture incidence among postmenopausal women on oestrogen with osteoporosis. Lancet. 1997; 350: 550–555. https://doi.org/10.1016/S0140-6736(97)02342-8.
[67] Mirkin S, Pickar JH. Selective estrogen receptor modulators (SERMs): a review of clinical data. Maturitas. 2015; 80: 52–57. https://doi.org/10.1016/j.maturitas.2014.10.010.
[68] Patel D, Liu J, Ebraheim NA. Managements of osteoporotic vertebral compression fractures: A narrative review. World Journal of Orthopedics. 2022; 13: 564–573. https://doi.org/10.5312/wjo.v13.i6.564.
[69] Josse R, Khan A, Ngui D, Shapiro M. Denosumab, a new pharmacotherapy option for postmenopausal osteoporosis. Current Medical Research and Opinion. 2013; 29: 205–216. https://doi.org/10.1185/03007995.2013.763779.
[70] Kwon BT, Ham DW, Park SM, Kim HJ, Yeom JS. Impact of Teriparatide and Denosumab on Clinical and Radiographic Outcomes in Osteoporotic Vertebral Compression Fractures. Medicina. 2024; 60: 1314. https://doi.org/10.3390/medicina60081314.
[71] Son S, Oh MY, Yoo BR, Park HB. Comparison of the Efficacy of Zoledronate and Denosumab in Patients with Acute Osteoporotic Vertebral Compression Fractures: A Randomized Controlled Trial. Journal of Clinical Medicine. 2024; 13: 2040. https://doi.org/10.3390/jcm13072040.
[72] Migliorini F, Colarossi G, Eschweiler J, Oliva F, Driessen A, Maffulli N. Antiresorptive treatments for corticosteroid-induced osteoporosis: a Bayesian network meta-analysis. British Medical Bulletin. 2022; 143: 46–56. https://doi.org/10.1093/bmb/ldac017.
[73] Conti V, Russomanno G, Corbi G, Toro G, Simeon V, Filippelli W, *et al*. A polymorphism at the translation start site of the vitamin D receptor gene is associated with the response to anti-osteoporotic therapy in postmenopausal women from southern Italy. International Journal of Molecular Sciences. 2015; 16: 5452–5466. https://doi.org/10.3390/ijms16035452.
[74] Migliorini F, Giorgino R, Hildebrand F, Spiezia F, Peretti GM, Alessandri-Bonetti M, *et al*. Fragility Fractures: Risk Factors and Management in the Elderly. Medicina. 2021; 57: 1119. https://doi.org/10.3390/medicina57101119.
[75] Migliorini F, Maffulli N, Colarossi G, Eschweiler J, Tingart M, Betsch M. Effect of drugs on bone mineral density in postmenopausal osteoporosis: a Bayesian network meta-analysis. Journal of Orthopaedic Surgery and Research. 2021; 16: 533. https://doi.org/10.1186/s13018-021-02678-x.
[76] Migliorini F, Maffulli N, Spiezia F, Peretti GM, Tingart M, Giorgino R. Potential of biomarkers during pharmacological therapy setting for postmenopausal osteoporosis: a systematic review. Journal of Orthopaedic Surgery and Research. 2021; 16: 351. https://doi.org/10.1186/s13018-021-02497-0.
[77] Migliorini F, Maffulli N, Spiezia F, Tingart M, Maria PG, Riccardo G. Biomarkers as therapy monitoring for postmenopausal osteoporosis: a systematic review. Journal of Orthopaedic Surgery and Research. 2021; 16: 318. https://doi.org/10.1186/s13018-021-02474-7.
[78] Migliorini F, Colarossi G, Baroncini A, Eschweiler J, Tingart M, Maffulli N. Pharmacological Management of Postmenopausal Osteoporosis: a Level I Evidence Based - Expert Opinion. Expert Review of Clinical Pharmacology. 2021; 14: 105–119. https://doi.org/10.1080/17512433.2021.1851192.
[79] Bao X, Liu C, Liu H, Wang Y, Xue P, Li Y. Association between polymorphisms of glucagon-like peptide-1 receptor gene and susceptibility to osteoporosis in Chinese postmenopausal women. Journal of Orthopaedic Surgery and Research. 2024; 19: 869. https://doi.org/10.1186/s13018-024-05361-z.
[80] Huang F, Wang Y, Liu J, Cheng Y, Zhang X, Jiang H. Asperuloside alleviates osteoporosis by promoting au-

tophagy and regulating Nrf2 activation. Journal of Orthopaedic Surgery and Research. 2024; 19: 855. https://doi.org/10.1186/s13018-024-05320-8.

[81] Andersen MØ, Andresen AK, Hartvigsen J, Hermann AP, Sørensen J, Carreon LY. Vertebroplasty for painful osteoporotic vertebral compression fractures: a protocol for a single-center doubled-blind randomized sham-controlled clinical trial. VOPE2. Journal of Orthopaedic Surgery and Research. 2024; 19: 813. https://doi.org/10.1186/s13018-024-05301-x.

[82] Shen L, Yang H, Zhou F, Jiang T, Jiang Z. Risk factors of short-term residual low back pain after PKP for the first thoracolumbar osteoporotic vertebral compression fracture. Journal of Orthopaedic Surgery and Research. 2024; 19: 792. https://doi.org/10.1186/s13018-024-05295-6.

[83] Leeyaphan J, Rojjananukulpong K, Intarasompun P, Peerakul Y. Simple clinical predictors for making directive decisions in osteoporosis screening for women: a cross-sectional study. Journal of Orthopaedic Surgery and Research. 2024; 19: 789. https://doi.org/10.1186/s13018-024-05287-6.

[84] Ayers C, Kansagara D, Lazur B, Fu R, Kwon A, Harrod C. Effectiveness and Safety of Treatments to Prevent Fractures in People With Low Bone Mass or Primary Osteoporosis: A Living Systematic Review and Network Meta-analysis for the American College of Physicians. Annals of Internal Medicine. 2023; 176: 182–195. https://doi.org/10.7326/M22-0684.

[85] Jang HD, Kim EH, Lee JC, Choi SW, Kim K, Shin BJ. Current Concepts in the Management of Osteoporotic Vertebral Fractures: A Narrative Review. Asian Spine Journal. 2020; 14: 898–909. https://doi.org/10.31616/asj.2020.0594.

[86] Subarajan P, Arceo-Mendoza RM, Camacho PM. Postmenopausal Osteoporosis: A Review of Latest Guidelines. Endocrinology and Metabolism Clinics of North America. 2024; 53: 497–512. https://doi.org/10.1016/j.ecl.2024.08.008.