Effect of bisphosphonates on periodontal diseases in menopausal and postmenopausal women: A systematic review and meta-analysis

Linlin Qin, MS, **Xinyue Wu**, MS, **Kunshuang Wu**, MS, **Hanyue Mai**, BS & **Ping Wang**, PhD

Abstract: Purpose: To systematically evaluate the effect of bisphosphonates on periodontal diseases in menopausal and postmenopausal women. **Methods:** Databases (PubMed, Embase, Web of Science, Cochrane Library databases, Chinese Scientific and Technological Journal database, Wan Fang Data, China Biomedical Literature Database, and Chinese National Knowledge Infrastructure) were searched from inception to July 2024, languages are Chinese and English. Randomized controlled trials (RCTs) reporting the effect of bisphosphonates in menopausal and postmenopausal women with periodontitis were included. The risk of bias was performed using the Cochrane collaboration tool. The primary outcome was clinical attachment loss (CAL), and the secondary outcomes were probing depth (PD) and gingival index (GI). The analysis of the data was performed using Rev Man 5.3 and Stata 16.0. **Results:** The meta-analysis incorporated four studies that fulfilled the inclusion criteria. In evaluating the efficacy of bisphosphonates against control treatments, there was high heterogeneity observed in CAL ($P = 0.0002$; $I^2 = 85\%$) and PD ($P < 0.00001$; $I^2 = 93\%$) within the study groups. Meta-analysis showed a significant improvement in CAL gain (MD = - 0.57 mm; 95% CI = -1.04 to -0.11 mm; $P < 0.05$), PD reduction (MD = - 0.50 mm; 95% CI = -0.96 to -0.05 mm; $P < 0.05$), and GI reduction (MD = -1.11; 95% CI = -1.22 to -1.01; $P < 0.00001$) for bisphosphonate treatment vs. bisphosphonate-naïve therapy. (*Am J Dent* 2025;38:33-38).

Clinical significance: Bisphosphonate treatment seems to be beneficial for managing periodontitis in menopausal and postmenopausal women.

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Introduction

Periodontitis is an inflammatory condition marked by the pathological breakdown of the periodontal ligament and alveolar bone. Advanced periodontitis may result in tooth movement, displacement, or even loss of teeth, which can notably impair oral well-being and diminish the overall quality of life.[1,2]

Osteoporosis, characterized by a decrease in bone density and an increased risk of fractures, significantly damages skeletal health.[3] Osteoporosis and associated fractures not only lead to increased morbidity and mortality among older adults but also represent a substantial economic burden on healthcare systems worldwide. The probability of osteoporotic fractures for women over their lifetime is around 40%, while for men, it is notably lower, at approximately 13%.[4]

Most women experience menopause generally between 45 and 55 years worldwide. Menopause brings about significant hormonal changes, particularly a decrease in estrogen levels.[5] Lack of estrogen hinders the typical bone turnover process. Specifically, it elevates the resorption rate by osteoclasts, exceeding the bone formation rate by osteoblasts. This imbalance causes a higher quantity of bone to be resorbed compared to what is deposited, ultimately resulting in a decrease in bone mass.[6,7] Payne et al[8] observed that a deficiency in estrogen correlates with an elevated incidence of alveolar bone density reduction at the crestal level in postmenopausal women suffering from periodontitis. Recent research indicates that osteoporosis and periodontal disease are prevalent conditions among postmenopausal women.[9] A characteristic feature of periodontal disease is the loss of alveolar bone. Furthermore, diminished bone mineral density in women during and after menopause may exacerbate the bone loss associated with periodontal conditions.[10,11]

Bisphosphonates (BPs) are currently the most prescribed drugs in the clinical management of osteoporosis.[12,13] They are useful in treating osteopenia and osteoporosis, and in reducing the risk of fractures in postmenopausal women.[14] Additionally, as established antiresorptive agents, BPs have shown potential in inhibiting alveolar bone resorption.[15-17] Rocha et al[18] showed the influence of bisphosphonates (BPs) on the periodontal health of postmenopausal women. The research involved an evaluation of alendronate (ALN) in contrast to a placebo. Their findings revealed that individuals receiving ALN showed superior improvements in both periodontal pocket depth (PD) and gingival bleeding. Bhavsar et al[19] indicated that the integration of bisphosphonate therapy with scaling and root planing procedures may confer considerable clinical benefits to the periodontal health of postmenopausal women diagnosed with moderate to severe chronic periodontitis. However, Grgić et al[20] noted that the gingival index, probing bleeding index, and periodontal pocket depth were significantly higher in the group of osteoporotic women receiving bisphosphonate therapy than in the control group, and that bisphosphonate therapy may harm periodontal health in osteoporotic women. Despite the existing research, a definitive conclusion on the effectiveness of bisphosphonates has not been reached. Additionally, no quantitative studies using meta-analysis have been performed to assess their efficacy.

Therefore, this study performed a thorough review and analysis of the available data regarding the effectiveness of bisphosphonates in treating periodontitis in menopausal and postmenopausal women.

Materials and Methods

Protocol registration - The present meta-analysis was performed based on the Preferred Reporting Items for Systematic

Table 1. Search strategy in PubMed database.

#1	(("Diphosphonates"[Mesh]) OR (Bisphosphonates[Title/Abstract]) OR (Bisphosphonate[Title/Abstract]))
#2	(("Periodontal Diseases"[Mesh]) OR (Disease, Periodontal[Title/Abstract]) OR (Diseases, Periodontal[Title/Abstract]) OR (Periodontal Disease[Title/Abstract]) OR (Parodontosis[Title/Abstract]) OR (Parodontoses[Title/Abstract]) OR (Pyorrhea Alveolaris[Title/Abstract]) OR (Periodontitis[Title/Abstract]) OR (Periodontitides[Title/Abstract]) OR (Pericementitis[Title/Abstract]) OR (Pericementitides[Title/Abstract]))
#1 AND #2	

Review and Meta-Analyses (PRISMA) guidelines.[21] The study was registered in The International Prospective Register of Systematic Reviews database with protocol number CRD42024538520.

Eligibility criteria - Randomized controlled trials (RCTs) assessing the effect of bisphosphonates on periodontal diseases among menopausal and postmenopausal women were included in this systematic review. The study included RCTs that fulfilled the following criteria: (1) Population: Menopausal and postmenopausal women diagnosed with periodontitis; (2) Intervention: Bisphosphonates in combination with scaling and root planing; (3) Comparison: Comparison with placebo or nonadjunct treatment after scaling and root planing; (4) Outcome: Clinical attachment loss, probing depth, gingival index. Therefore, the exclusion of studies was determined by the following criteria: (1) Non-RCT or RCTs with a follow-up < 3 months; (2) Studies including participants with diabetes, cancer, esophagitis, reflux disease, peptic ulcers, or ulcerative colitis; (3) Studies including patients on immunosuppressive treatment, hormone replacement therapy, glucocorticoids, or any other drug known to alter bone calcium metabolism.

Search strategy – The study was conducted thorough searches in electronic databases including PubMed, Embase, Web of Science, Cochrane Library databases, Chinese Scientific and Technological Journal database, Wan Fang Data, Chinese National Knowledge Infrastructure, and China Biomedical Literature Database from inception to July 2024, languages are Chinese and English. The search was conducted using the following keywords: (1) “Diphosphonates” or “Bisphosphonates” or “Bisphosphonate”; (2) “Periodontal Diseases” or “Disease, Periodontal” or “Diseases, Periodontal” or “Periodontal Disease” or “Parodontosis” or “Parodontoses” or “Pyorrhea Alveolaris” or “Periodontitis” or “Periodontitides” or “Pericementitis” or “Pericementitides”. For example, the search strategy employed on PubMed is presented in Table 1.

Study selection - Two researchers (LLQ and XYW) independently evaluated the studies obtained from the above databases. In the preliminary screening phase, duplicate studies were eliminated, and titles and abstracts were examined to select studies fulfilling the inclusion criteria. If the details in the title or abstract were not enough to exclude a study, the study's full text was reviewed to make the ultimate decision on its inclusion. Any discrepancies were addressed through consultation with a third examiner (KSW).

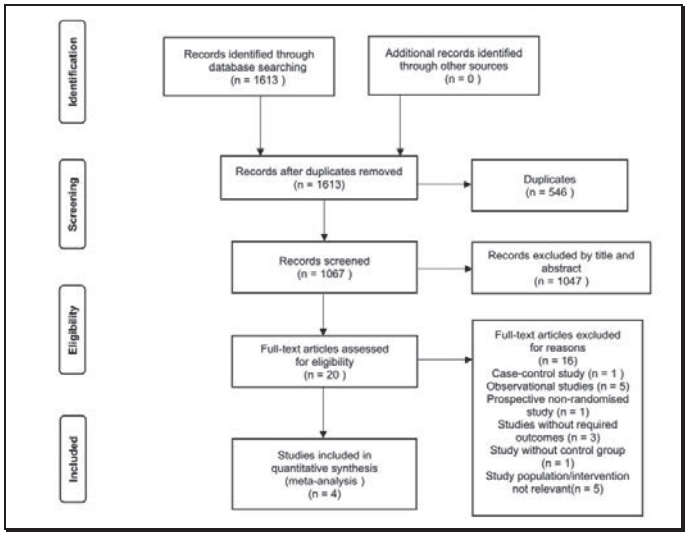

Fig. 1. Prisma flow chart diagram of study selection.

Data collection - Two researchers (LLQ and XYW) carried out the data extraction process, and the results were confirmed for precision by a third reviewer (KSW). The data obtained from the included studies encompassed: first author, publication year, country, type of study, sample and age of participants, drug dose, periodontal parameters, follow-up, and research outcomes.

Risk of bias assessment - The risk of bias in the included studies was estimated by two researchers (LLQ and XYW) independently. Risk of bias in all included studies was assessed using the Revised Cochrane risk-of-bias tool for randomized clinical trials.[22]

Statistical analysis - Review Manager 5.3[a] software and STATA[b] 16.0 software were used for the meta-analysis. The mean differences (MD) with 95% confidence interval (CI) was analyzed for all outcomes. Statistical significance was determined at a threshold of $P< 0.05$, and heterogeneity among the studies was evaluated using the Q-statistic and I^2 statistic.[23] The pooled results were derived using a fixed-effects model when heterogeneity was low. Conversely, the random-effects model was conducted for the analyses with an I^2 value over 50%. When significant heterogeneity was identified within the included studies, sensitivity analysis or subgroup analysis was conducted to investigate the sources of heterogeneity. Assessment of publication bias was performed both visually through funnel plot inspection and statistically using Egger's and Begg's tests.

Results

Study selection - Initially, 1,613 studies were reviewed. After eliminating 546 duplicates, 1,067 studies remained. After reviewing the titles and abstracts, 1,047 records were excluded. Twenty records were selected for full-text review based on the eligibility criteria. This process resulted in the exclusion of 16 articles for a variety of reasons, ultimately leaving four randomized controlled trials (RCTs)[11,18,24,25] in the meta-analysis (Fig. 1).

Characteristics of the included studies - Tables 2 and 3 provide a summary of key study details, including participant characteristics, research design, sample sizes, medication dosages and administration methods, use of adjuvants, duration

Table 2. Characteristics of selected studies.

Author/Year	Country	Study design	BPs sample size (M/F)	BPs age (years)	Controls sample size (M/F)	Controls age (years)	Subjects health status
Gupta 2020	India	RCT	14 (0/14)	51.0-65.0	15 (0/15)	51.0 - 65.0	Chronic periodontitis, menopause
Rocha 2004	Mexico	RCT	20 (0/20)	57.8 ± 2.9	20 (0/20)	58.0 ± 2.8	Chronic periodontitis, at least 1 year postmenopausal
Zhang 2021	China	RCT	30 (0/30)	58. 81 ± 5. 15	30 (0/30)	58. 57 ± 5. 07	Chronic periodontitis, postmenopausal osteoporosis
Zhang 2016	China	RCT	60 (0/30)	50.2 ± 2.6	60 (0/60)	49.2 ± 2.8	Chronic periodontitis, osteoporosis, menopause

RCT: Randomized Control Trial; BPs: bisphosphonates; M: male; F: female.

Table 3. Clinical characteristics of selected studies.

Author/Year	Intervention		Drug dose	Administration route	Adjuvant	Follow-up (months)	Clinical outcomes
	Test	Control					
Gupta 2020	SRP + ALN	SRP+ Placebo	ALN 70 mg once weekly	Oral	None	6	CAL, PD
Rocha 2004	SRP + ALN	SRP + Placebo	ALN 10 mg daily	Oral	None	6	CAL, PD
Zhang 2021	SRP + ZA	SRP	ZA 5 mg	intravenous infusion	Calcium/Vit D	3	CAL, PD, GI
Zhang 2016	SRP + ZA	SRP	ZA 5 mg	intravenous infusion	Calcium/Vit D	3	CAL, PD, GI

SRP: Scaling and root planing; ALN: Alendronate; ZA: Zoledronic acid; CAL: Clinical attachment loss; PD: Probing depth; GI: Gingival index.

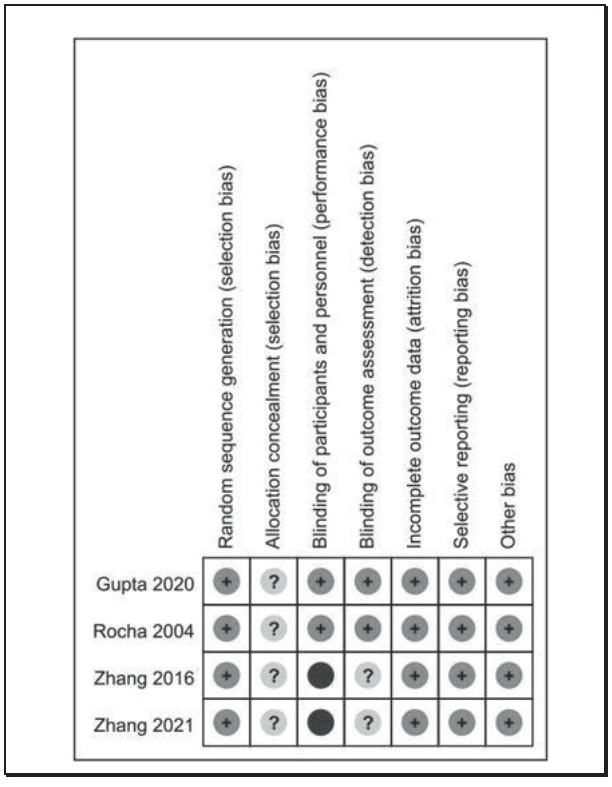

Fig. 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study. +, no bias; –, bias; ?, bias unknown.

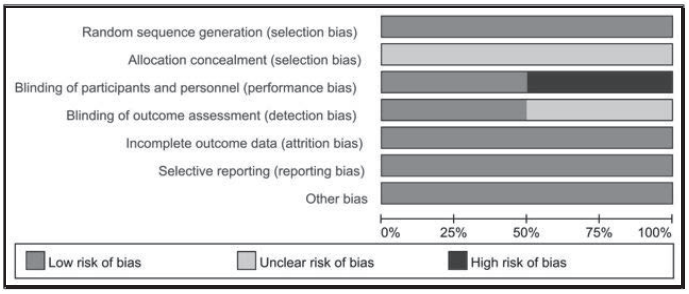

Fig. 3. Risk of bias graph: Review authors' judgements about each risk of bias item presented as percentages across all included studies.

of follow-up, and clinical outcomes. The trials, published between 2004 and 2021, involved a cumulative total of 249 female patients. The duration of patient follow-up in these studies extended from 3 to 6 months. All studies[11,18,24,25] reported data of probing depth (PD) and clinical attachment loss (CAL); only two studies[24,25] provided available results for gingival index (GI).

Risk of bias assessment - The summary of the risk of bias assessment is presented in Figs. 2 and 3. Two trials[24,25] had high risk of bias, while the risk was deemed unclear in two others.[11,18] All studies[11,18,24,25] reported on the randomization process, and a proper sequence for randomization was generated in each trial. However, allocation concealment was not discussed in any of the four articles. Furthermore, the clarity of blinding procedures for outcome assessments was not specified in two trials.[24,25]

Meta-analysis of CAL (mm) - This analysis was conducted on data from four trials,[11,18,24,25] which included a total of 249 participants. As significant heterogeneity was noticed for CAL (P= 0.0002; I^2 = 85%), the random effect model was adopted. The meta-analysis of the CAL in studies favored the bisphosphonate group over the control group (Overall MD = -0.57 mm; 95% CI = -1.04 to -0.11 mm; P< 0.05; Fig. 4). Due to the high heterogeneity (P= 0.0002; I^2 = 85%), subgroup analy-

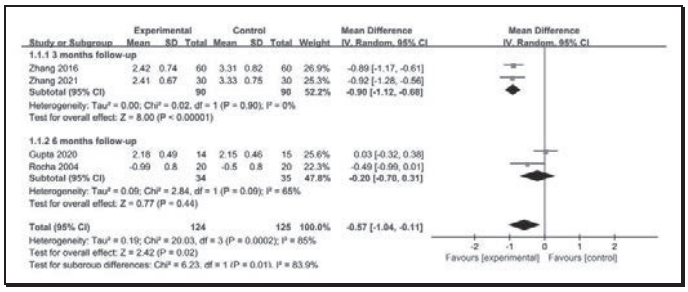

Fig. 4. Forest plot of CAL.

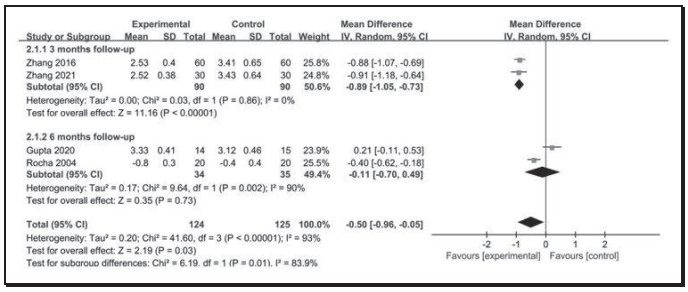

Fig. 5. Forest plot of PD.

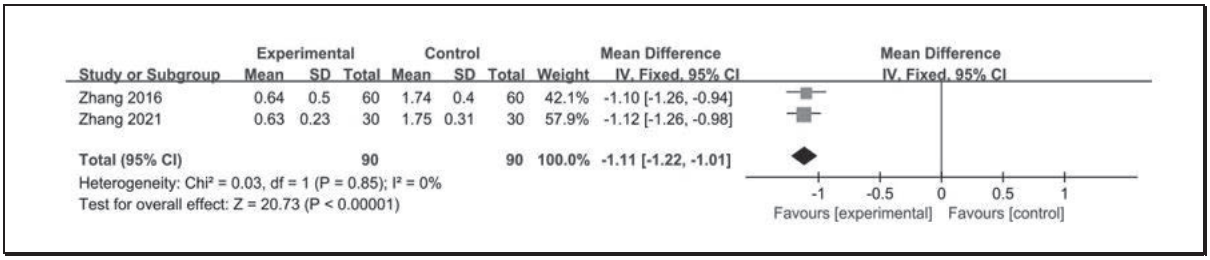

Fig. 6. Forest plot of GI.

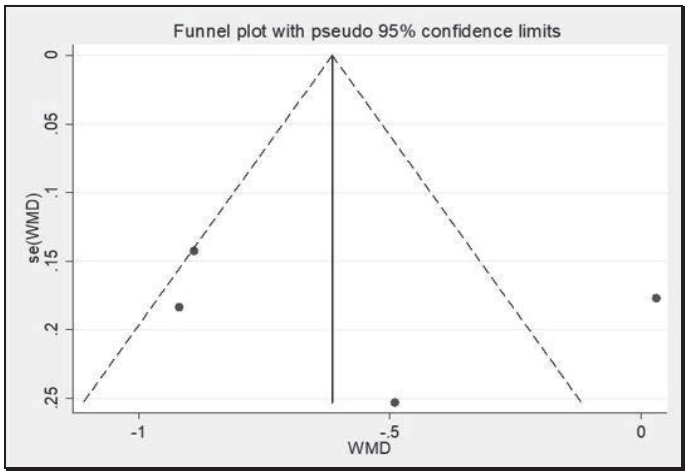

Fig. 7. Funnel plot of CAL.

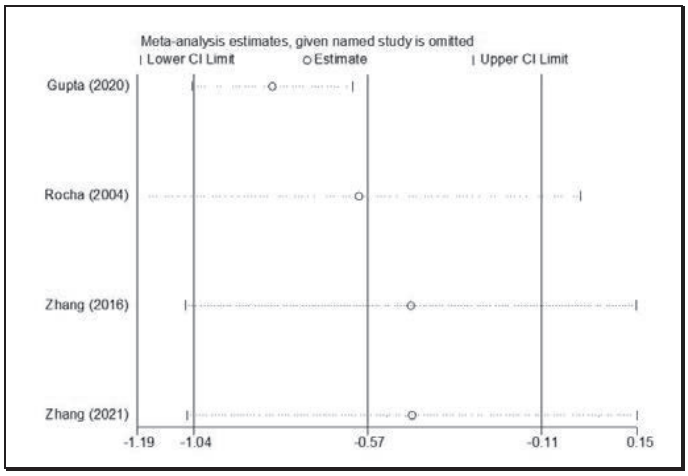

Fig. 8. Sensitivity analysis of CAL.

ses were conducted to evaluate the influence of varying follow-up durations on periodontal health, as presented in Fig. 4. In subgroup analyses, heterogeneity continued to be observed, especially among studies with 6-month follow-up (P= 0.09; I ² = 65%).

Meta-analysis of PD (mm) - Data on PD was obtained from four trials[11,18,24,25] involving 249 patients, which were included in the analysis. As significant heterogeneity was noticed for PD (P< 0.00001; I^2 = 93%), the random effect model was utilized for analysis. PD was notably higher in the control group compared to those who received bisphosphonate treatment (Overall MD = - 0.50 mm; 95% CI = -0.96 to -0.05 mm; P< 0.05; Fig. 5). Due to the high heterogeneity (P< 0.00001; I^2 = 93%), a subgroup analysis of the PD was conducted according to the different follow-up periods. In subgroup analyses, the heterogeneity was still high among studies with 6-month follow-up (P = 0.002; I^2= 90%) (Fig. 5).

Meta-analysis of GI - This analysis involved two trials[24,25] with a total of 180 patients. Due to low heterogeneity (P= 0.85, I^2= 0%), the fixed effect model was employed. GI was significantly reduced in the group treated with bisphosphonates than in the control group (MD= -1.11; 95% CI= -1.22 to -1.01; P< 0.00001; Fig. 6).

Publication bias - In the meta-analysis assessing the impact of bisphosphonates on clinical attachment loss, the absence of publication bias was confirmed through the examination of the funnel plot (Fig. 7) and by conducting statistical tests (Egger's test, P= 0.682; Begg's test, P= 0.734). A sensitivity analysis was conducted to evaluate the stability of the outcomes across the studies. Among most studies, the overall effect size of the results did not significantly change following the sequential exclusion of individual studies. This suggests that the results were statistically stable and reliable (Fig. 8).

Discussion

This meta-analysis included studies assessing the effect of bisphosphonates on periodontal diseases in menopausal and postmenopausal women. Results showed that systemically administered bisphosphonates, compared with control groups, significantly increased CAL by 0.57 mm (95% CI = -1.04 to -0.11 mm), reduced PD by 0.50 mm (95% CI = -0.96 to -0.05 mm) and reduced GI by 1.11 (95% CI = -1.22 to -1.01). These

findings show that bisphosphonates appear to be effective in managing menopausal and postmenopausal women with periodontitis.

Extensive research has focused on understanding the relationship between the body's immune system and oral bacteria in the development of periodontal disease.[26] Although bacteria are the main cause of periodontal disease, the extent and severity of tissue damage caused by periodontitis depends on the host's immune and inflammatory responses to these bacteria.[27] Upon exposure to endotoxins originating from periodontal pathogens, various osteoclast-associated mediators are activated, which can lead to the breakdown of alveolar bone. Matrix metalloproteinases (MMPs), cathepsins, and other osteoclast-derived enzymes are primarily responsible for this aggressive tissue destruction.[28-30] In the field of treatment, employing host-modulating agents has emerged as a crucial approach. Williams et al[31] reported that adjusting the host response could potentially halt the progression of periodontal disease. Recently, bisphosphonates have shown significant clinical efficacy in inhibiting the expression of MMPs.[32-34] MMPs can induce osteoclast migration and adhesion, while directly contributing to the breakdown of bone matrix and promoting bone remodeling imbalance.[35] The use of bisphosphonates to modulate the host's response and inhibit the destruction of periodontal tissues has demonstrated potential in the treatment of periodontitis in osteoporotic patients.[36,37]

Review of existing studies indicated that bisphosphonates may effectively reduce periodontal inflammation in menopausal and postmenopausal women. However, several critical factors need to be considered. Notably, the included studies showed variations in bisphosphonate dosage, administration methods, and duration of follow-up.[11,18,24,25] For example, in some studies,[24,25] participants received a single intravenous dose of 5 mg zoledronic acid for the entire duration of the study. In contrast, Gupta et al[11] and Rocha et al[18] provided 70 mg of oral alendronate weekly and 10 mg of oral alendronate daily respectively. Although these clinical trials showed that bisphosphonates improved periodontal parameters in postmenopausal and postmenopausal women, the most effective dosage and treatment frequency for optimal results remain undetermined. Since the duration of the follow-up in all the studies reviewed for this meta-analysis ranged from 3 to 6 months, the brevity of this period could potentially influence the outcomes of the analysis. Studies with longer duration are necessary to confirm the durability of the clinical effects. Patients treated with bisphosphonates for prolonged periods may develop a serious adverse effect known as osteonecrosis of the jaw (ONJ).[38,39] A meta-analysis by Chen et al[40] indicated that systemic administration of alendronate could increase CAL by 0.39 mm (95% CI = 0.11-0.68 mm). Nonetheless, bisphosphonate-related osteonecrosis of the jaw continues to be a potential adverse event.[40,41] Thus, the potential risks must be considered alongside the benefits when administering systemic bisphosphonate therapy to menopausal and postmenopausal women.

As far as the authors know, this systematic review and meta-analysis is the initial study to assess the impact of bisphosphonates for periodontal health in women during and after menopause. This study solely assessed RCTs, which represent the highest level of original research in evidence-based medicine.[42] However, there were several limitations. First, significant heterogeneity was noticed for CAL and PD. Within the subgroup analyses conducted, heterogeneity was not substantially altered by the follow-up period. The heterogeneity may be attributed to the differences in bisphosphonate dose, sample size, and adjuvant therapy (calcium and vitamin D supplement) in the studies included. Nevertheless, the sensitivity analysis did not reveal any substantial alterations in the overall effect size, indicating that the results were stable and reliable. Second, the included trials were deemed to have a high risk and uncertain risk of bias. Essential elements of clinical trial design, such as randomization, allocation concealment, and blinding of participants and evaluators, are crucial for preventing biases related to selection, performance, and detection.[43] However, certain included studies did not report the procedures performed in these aspects, which may have affected the results. Third, in the meta-analysis, only four studies[11,18,24,25] met the criteria for inclusion. These eligible studies involved only two types of bisphosphonates (alendronate and zoledronic acid). Additionally, two studies[24,25] out of four were executed within the same geographical region (China). Consequently, the examination of a wider variety of bisphosphonates and the inclusion of a more diverse population sample are crucial for substantiating the study's results.

In summary, current evidence implies that bisphosphonate treatment may effectively enhance the short-term clinical results for periodontitis in menopausal and postmenopausal women. Nevertheless, the long-term use of bisphosphonates for treating periodontitis in menopausal and postmenopausal women is under scrutiny due to the associated risk of osteonecrosis of the jaw. To mitigate the potential for periodontal deterioration, menopausal and postmenopausal women are advised to undergo routine dental examinations and obtain essential periodontal care. It is evident that further studies with a more rigorous design, including double-blind, placebo-controlled trials, are necessary to validate or refine the preliminary findings from this research.

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b. Stata Corp. LP, College Station, TX, USA.

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