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SYSTEMATIC REVIEW

Efficacy of bisphosphonate as an adjunct to nonsurgical periodontal therapy in the management of periodontal disease: a systematic review

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Keywords Bisphosphonates, scaling and root planning, periodontal disease, systematic review

AIMS

The aim of this systematic review was to assess the efficacy of bisphosphonate therapy as an adjunct to scaling and root planing (SRP) in the management of periodontitis.

METHODS

Databases (MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and Cochrane Oral Health Group Trials Register databases) were searched up to and including July 2016. The primary outcome was probing depth (PD), and the secondary outcomes were changes in clinical attachment level (CAL) and bone defect (BD) fill. The mean differences (MD) of outcomes and 95% confidence intervals (CI) for each variable were calculated using random effect model.

RESULTS

Eight clinical studies were included. Seven studies used alendronate as an adjunct to SRP; of these, four studies used topical application and three used oral alendronate. Considering the effects of adjunctive bisphosphonates as compared to SRP alone, a high degree of heterogeneity for PD (Q value = 39.6, $P < 0.0001$, $I^2 = 87.38\%$), CAL (Q value = 13.65, $P = 0.008$, $I^2 = 70.71\%$), and BD fill (Q value = 53.26, $P < 0.0001$, $I^2 = 92.49\%$) was noticed among both the groups. Meta-analysis showed a statistically significant PD reduction (MD = –1.18, 95% CI = –1.91 to –0.44, $P = 0.002$), CAL gain (MD = –0.69, 95% CI = –1.20 to –0.18, $P = 0.008$) and BD fill (MD = –2.36, 95% CI = –3.64 to –1.08, $P < 0.001$) for SRP + bisphosphonate treatment *vs.* SRP alone.

CONCLUSIONS

Adjunctive bisphosphonate therapy appears to be effective in managing periodontitis, however, due to the potential risk of osteonecrosis of the jaws and short-term follow-up of the studies, their clinical application is debatable.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The influence of bisphosphonates on bone turnover and their ability to inhibit periodontal tissue related proinflammatory cytokines have introduced their use as an adjunct to scaling and root planing in the management of periodontal disease.

WHAT THIS STUDY ADDS

- Delivery of bisphosphonates as an adjunct to scaling and root planing in the management of periodontal disease appears to be effective in the short-term; however, due to the potential risk of osteonecrosis of the jaws, their long-term clinical application remains debatable.

Introduction

Reducing bacterial load and inhibiting progression of inflammation are the primary therapeutic goals in the management of periodontal disease [1]. Nonsurgical debridement in the form of scaling and root planing (SRP) has been regarded as the traditional treatment regime in the management of periodontal disease. The purpose of SRP is to remove local irritants such as calculus from the surfaces of the teeth and to minimize tooth surface roughness that may facilitate the accumulation of local irritants around the teeth [2]. However, manual debridement has physical limitations as it does not allow proper access to debride in deep periodontal pockets, furcations and interproximal areas of malposed teeth [3].

Numerous adjunctive treatments have been proposed to complement SRP, including systemic and localized delivery of antibiotics, antiseptics, lasers, and photodynamic therapy to reduce bacterial counts and improve periodontal parameters in periodontal disease [4–8]. Among these compounds, bisphosphonates have recently been introduced for the treatment of periodontal disease. Bisphosphonates are analogues of pyrophosphate, with high affinity for bone tissue. They inhibit osteoclastic bone activity during high bone turnover, resulting in inhibition of bone resorption [9]. Bisphosphonates are leading drugs for the treatment of metabolic bone diseases such as osteoporosis and Paget's disease [10], and they are widely used in the treatment of tumour-associated osteolysis [11]. Research suggests that bisphosphonates not only inhibit osteoclast-mediated bone resorption, but also induce osteoblast cells to promote early bone formation [12]. Furthermore, bisphosphonates may antagonize the action of several matrix metalloproteinase (MMPs) involved in breakdown of structural components of periodontal connective tissue [13, 14]. Thus, their action in bone turnover and their ability to inhibit cytokines of periodontal tissue destruction has introduced bisphosphonates as an adjunct to SRP in the management of periodontitis [15].

Recent evidence has shown the benefits of using bisphosphonates as an adjunct to SRP with regards to clinical periodontal outcomes [16, 17]. For instance, in a randomized clinical trial (RCT) by Pradeep *et al*. [16], periodontitis patients treated with local application of alendronate gel as an adjunct to SRP showed significant improvement in clinical periodontal parameters as compared to those treated with SRP alone. Similar results were reported by Sharma and Pradeep [17]. Results from these studies [16, 17] suggest that local bisphosphonate delivery is a potential treatment strategy for periodontitis. However, Graziani *et al*. [18], in a clinical trial evaluating the adjunctive role of bisphosphonates in the periodontal treatment, concluded that periodontitis patients treated with adjunctive bisphosphonate did not show any improvement in clinical outcomes over the use of SRP at follow-up. Considering the diversity of these results, a systematic review to assess the efficacy of adjunctive bisphosphonate delivery in the management of periodontitis seems desirable. Therefore, the aim of this study was to review systematically the efficacy of bisphosphonate therapy as an adjunct to SRP in the management of periodontitis.

Materials and methods

Based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [19], a specific question was constructed. The addressed focused question was: "Does bisphosphonates as an adjunct to SRP yield better clinical periodontal outcomes than SRP alone in the treatment of periodontal disease?"

Search strategy

Electronic and manual literature searches were conducted by two independent reviewers (Z.A. and T.A.) in the following databases, MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and Cochrane Oral Health Group Trials Register, up to and including July 2016 for articles addressing the focused question. For the PubMed library, combinations of the following MeSH (Medical Subject Headings) and free text words were used: (diphosphonates [MeSH Terms]) OR (alendronate [MeSH Terms]) OR (risedronate sodium [MeSH Terms]) OR (bisphosphonates) OR (neridronic acid) AND (periodontitis [MeSH Terms]) OR (chronic periodontitis [MeSH Terms]) OR (periodontal diseases [MeSH Terms]) OR (periodontal pocket [MeSH Terms]) OR (periodontal attachment loss [MeSH Terms]) OR (tooth mobility [MeSH Terms]) OR (bleeding on probing [MeSH Terms]) AND (dental scaling [MeSH Terms]) OR (root planing [MeSH Terms]) OR (dental prophylaxis [MeSH Terms]).

Selection criteria

Screening and assessment of articles was conducted independently by two reviewers (Z.A. and F.V.). Any disagreement involving the eligibility was resolved through discussion or by consulting a third reviewer (T.A.). Studies, which did not fulfil the inclusion criteria were excluded.

The following eligibility criteria were entailed:

i. Study design: Only RCTs or randomized split-mouth clinical trials (a split-mouth trial is a study design in which anatomical regions of subjects' mouths are divided into homogeneous within-patient experimental units. Subsequently, each of the treatment modalities is randomly assigned to one within-patient experimental unit);
ii. Participants: patients diagnosed with periodontitis having at least 10 subjects per group;
iii. Intervention: subjects allocated to experimental and control/placebo group based on having SRP with adjunctive bisphosphonate therapy or SRP alone;
iv. Outcome: reduction in 'probing depth' (PD; in mm), which is defined as the distance from the gingival margin to the base of the pocket; 'clinical attachment level' (CAL in mm), which is the measurement of the position of the soft tissue in relation to cemento-enamel junction, and 'bone defect' (BD in mm), which is osseous defects in alveolar bone, were included as outcomes;
v. Follow-up: the outcome assessment at minimum of 24 weeks
vi. Articles published only in English language.

In-vitro studies, case series, case reports, animal studies, letters to the editor, opinion articles, abstract, review papers and unpublished articles were excluded.

Screening and selection

Two reviewers (Z.A. and T.A.) independently screened titles and abstracts for eligible papers. If information relevant to the eligibility criteria was not available in the abstract, or if the title was relevant but the abstract was not available, the paper was selected for full reading of the text. Next, full-text papers that fulfilled the eligibility criteria were identified and included in the review. Reference lists of original studies were hand searched to identify articles that could have been missed during the electronic search. Hand searching of the following journals was performed: *Journal of Clinical Periodontology*, *Journal of Periodontology* and *Journal of Periodontal Research*. Studies that fulfilled the selection criteria were processed for data extraction. Figure 1 describes the screening process according to PRISMA guidelines [19].

Data extraction and quality assessment

Two reviewers (Z.A. and F.V.) performed the data extraction independently. The information from the accepted studies

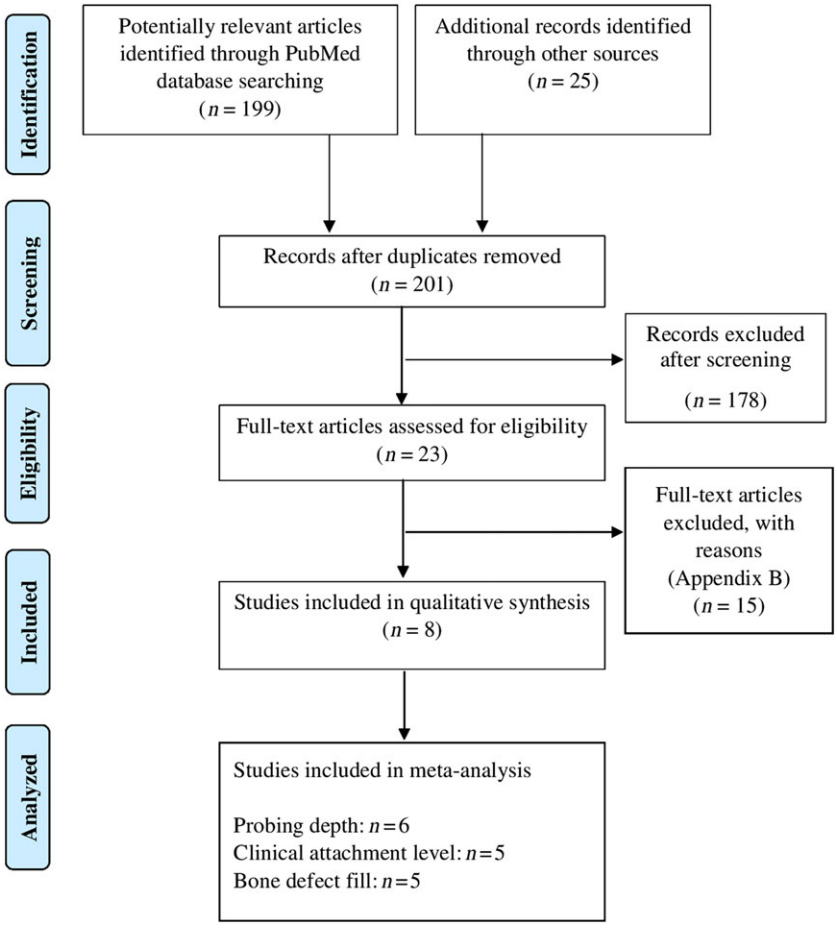

Figure 1

PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) flow diagram for studies retrieved through the searching and selection process

Table 1

General characteristics of included studies

Investigators; Year; Study design	Sample size; Mean age in years (range)	Number of drop outs	Female (%)	Systemic conditions	Study groups (*n*)	Drug used (dosage); Route of administration	Follow-up (weeks)	Study outcome
Pradeep *et al.* [16] 2013; RCT	69; Group 1: NA Group 2: NA (30–50)	Group 1: 6 Group 2: 6	46.3	NA	Group 1: 29 SRP + BP Group 2: 28 placebo + SRP	Group 1: 1% ALN gel (10 mg/mL); topical Group2: placebo gel	Up to 48	Group 1 showed significantly greater improvements in clinical parameters at follow-up
Sharma and Pradeep [17] 2012; RCT	73; Group 1: NA Group 2: NA (30–50)	Group 1: 5 Group 2: 2	46.5	NA	Group 1: 33 SRP + BP Group 2: 33 placebo + SRP	Group 1: 1% ALN gel (10 mg/mL); topical Group2: placebo gel	Up to 24	Group 1 showed significantly greater improvements in clinical parameters at follow-up
Sharma and Pradeep [24] 2012; RCT	20; Group 1: NA Group 2: NA (30–50)	Group 1: 1 Group 2: 2	40	NA	Group 1: 9 SRP + BP Group 2: 8 placebo + SRP	Group 1: 1% ALN gel (10 mg/mL); topical Group2: placebo gel	Up to 24	Group 1 showed significantly greater improvements in clinical parameters at follow-up
Pradeep *et al.* [25] 2012; RCT	43; Group 1: NA Group 2: NA (30–50)	Group 1: 1 Group 2: 1	46.5	Diabetes mellitus	Group 1: 20 SRP + BP Group 2: 21 placebo + SRP	Group 1: 1% ALN gel (10 mg/mL); topical Group2: placebo gel	Up to 24	Group 1 showed significantly greater improvements in clinical parameters at follow-up
Graziani *et al.* [18] 2009; RCT	60; Group 1: 44.7 Group 2: 42.2 (NA)	Group 1: 5 Group 2: 4	65	NA	Group 1: 30 SRP + BP Group 2: 30 SRP	Group 1: Once weekly NE (12.5 mg/intramuscular) / 12 times; systemic	Up to 24	Improvements in clinical parameters for both groups at follow-up were comparable
Lane *et al.* [26] 2005; RCT	70; Group 1: 48.2 Group 2: 46.8 (NA)	Group 1: 2 Group 2: 2	43.9	NA	Group 1: 41 SRP + BP Group 2: 25 placebo + SRP	Group 1: ALN (10 mg/day) or RSD 5 mg/day + calcium citrate 1000 mg/day + Vitamin D3; oral Group 2: placebo + calcium citrate 1000 mg/day + Vitamin D3/oral	Up to 48	Improvements in clinical parameters for both groups at follow-up were comparable
Rocha *et al.* [27] 2004; RCT	40; Group 1: 57.8 Group 2: 58.0 (55–65)	Group 1: 0 Group 2: 0	100	Obese/ overweight; menopause	Group 1: 20 SRP + BP Group 2: 20 placebo + SRP	Group 1: ALN (10 mg/day); oral	Up to 24	Group 1 showed significantly greater improvements in clinical parameters at follow-up
Rocha *et al.* [28] 2001; RCT	40; Group 1: 56.0 Group 2: 55.0 (50–60)	Group 1: 0 Group 2: 0	50	Diabetes mellitus; menopause	Group 1: 20 SRP + BP Group 2: 20 placebo + SRP	Group 1: ALN (10 mg/day); oral Group 2: trivitamin preparation (thiamin 100 mg + pyridoxine 50 mg + cyanocobalamin 250 g)	Up to 24	Group 1 showed significantly greater improvements in clinical parameters at follow-up

RCT, randomized clinical trial; SRP, scaling and root planing; BP, bisphosphonates; ALN, alendronate; RSD, risedronate; NE, neridronic acid; NA, not available.

was tabulated according to the study designs, subject demographics, drop outs, sex distribution, drug administration, follow-up period, main outcomes and clinical periodontal parameters. Data collected were based on the focused question outlined for the present systematic review. The reviewers crosschecked all extracted data. Any disagreement was resolved by discussion until consensus was reached. The present systematic review was conducted using a pre-submission checklist based on the revised recommendations of the Consolidated Standards of Reporting Trials statement [20]. The risk of bias was estimated for each selected RCT based on the Cochrane Handbook for Systematic Reviews of Interventions [21]: (1) low risk of bias (when all criteria were met); (2) high risk of bias (when ≥1 criterion was not met); and (3) unclear (when ≥1 criterion was partially met). The criteria used are listed in Appendix A.

Outcome measures

In the present review, the primary outcome was the reduction of PD, in mm. Secondary outcomes were changes in CAL in mm and BD fill in mm. All outcome variables to be analysed were measured at 6 months and 12 months of follow-up.

Statistical analysis

Meta-analyses were conducted separately for each of the primary (PD), and secondary outcomes (CAL, BD fill). Heterogeneity among the included studies for each outcome was assessed using the Q-statistic and I^2 statistic [22]. Outcome measures for each periodontal parameter were combined with a random-effects model utilizing the DerSimonian–Laird method due to its robustness in comparison to fixed-effects models in the case of small sample sizes [23]. Forest plots were computed reporting mean difference (MD) of outcomes and 95% confidence intervals (CI). The pooled effect was considered significant if $P < 0.05$. Data unsuitable for quantitative analysis were assessed descriptively. All above statistical analyses were carried out by a specialized statistical software (MedCalc Software v 15.11.04, Ostend, Belgium).

Results

Study selection

A total of 224 study titles and abstracts were initially identified. After removal of the duplicates ($n = 23$), initial screening of titles and abstracts was performed, and 178 articles were excluded as irrelevant to the PICO question. A total of 23 papers were selected for full-text reading. Of these 23 studies, 15 studies were further excluded (Appendix B). After the final stage of selection, 8 studies [16–18, 24–28] were included and processed for data extraction (Table 1). All studies [16–18, 24–28] were performed at either universities or health care centres. Figure 1 shows the study identification flow chart according to PRISMA [16] with the reasons for exclusion of articles.

General characteristics of included studies

All studies [16–18, 24–28] included in the systematic review were RCTs. In all studies [16–18, 24–28], number of subjects ranged between 20 and 73 individuals with mean age ranging between 42.2 and 57.8 years. All studies [16–18, 24–28] reported the percentage of female participants, which ranged between 43.9% and 100%. Smokers were included in two studies [18, 26]. Periodontal diseases were classified according to PD ≥3 mm in two studies [27, 28] and ≥5 mm in five studies [16–18, 24, 25], with CAL ≥3 mm in one study [26], ≥4 mm in two studies [17, 25], and ≥5 mm in one study [24]. In all studies [16–18, 24–28] subjects in the test group received bisphosphonates + SRP. In seven studies [16, 17, 24–28] control group used SRP with placebo gel, while in one study [18], SRP alone was the treatment. Seven studies [16, 17, 24–28] used alendronate (10 mg/day), of which four studies [16, 17, 24, 25] used topical application while three studies [26–28] used oral alendronate. In all the studies [16, 17, 24, 25] that utilized local bisphosphonates, the topical gel was injected into the periodontal pocket using a syringe with a blunt cannula. The topical gel was applied only once in these studies [16, 17, 24, 25]. Only one study [18] used intramuscular neridronic acid (12.5 mg) as an adjunct to SRP for treatment of periodontitis. Two studies recruited patients with diabetes mellitus [25, 28] and menopausal females [27, 28], while one study [27] recruited obese/overweight patients. In all studies [16–18, 24–28] the follow-up period ranged from 24–48 weeks (Table 1). All the enrolled participants had complication-free healing period with no side effects related to bisphosphonates except two studies (with periodontal abscess in three subjects combined) [18, 26].

Quality of the clinical studies

All the included clinical studies [16–18, 24–28] in this systematic review were RCTs. Seven RCTs did not estimate the sample size [16, 17, 24–28]. The masking of assessor(s) and methods of allocation concealment was inadequate in three studies [26–28]. All studies [16–18, 24–28] presented appropriate statistical analysis and description of withdrawals and dropouts. The risk of bias was considered low in one study [18] and high in the other RCTs assessed [16, 17, 24–28] (Table 3).

Periodontal inflammatory parameters of included studies

The results for clinical periodontal (PD and CAL) and BD fill outcomes are summarized in Table 2. All the studies [16–18, 24–28] reported mean PD and CAL, which ranged from 2.8 to 3.96 mm and 2.03 to 5.35 mm, respectively. Six studies [16, 17, 24, 25, 27, 28] reported values of BD fill in mm which ranged from 2.64 to 5.34 mm at follow-up.

Main outcome of the studies

Qualitative analysis. All studies [16–18, 24–28] showed that SRP and adjunctive bisphosphonates was effective in the treatment of periodontitis at follow-up. In six studies [16, 17, 24, 25, 27, 28], periodontal inflammatory parameters (PD, CAL and BD fill) showed significantly higher improvements in test group (bisphosphonate + SRP)

Table 2

Clinical periodontal outcomes of the included studies

Investigators; Year	Probing depth (mm) mean ± SD		Clinical attachment level (mm) mean ± SD		Bone defect fill (mm) mean ± SD	
Pradeep *et al.* [16] 2013	Group 1:[a]	Group 2:	Group 1:[a]	Group 2:	Group 1:[a]	Group 2:
	Baseline: 6.93 ± 0.69	Baseline: 6.77 ± 0.82	Baseline: 8.07 ± 0.64	Baseline: 8.03 ± 0.81	Baseline: 3.94 ± 0.24	Baseline: 3.94 ± 0.25
	Follow-up: 3.14 ± 0.71	Follow-up: 5.39 ± 0.79	Follow-up: 5.00 ± 0.54	Follow-up: 7.03 ± 0.79	Follow-up: 2.64 ± 0.23	Follow-up: 3.84 ± 0.24
Sharma and Pradeep [17] 2012	Group 1:[a]	Group 2:	Group 1:[a]	Group 2:	Group 1:[a]	Group 2:
	Baseline: 7.58 ± 2.13	Baseline: 7.24 ± 2.18	Baseline: 6.06 ± 1.82	Baseline: 5.64 ± 1.72	Baseline: 4.70 ± 1.00	Baseline: 4.71 ± 1.04
	Follow-up: 3.09 ± 1.82	Follow-up: 5.09 ± 1.54	Follow-up: 2.03 ± 1.48	Follow-up: 4.03 ± 2.02	Follow-up: 2.82 ± 0.87	Follow-up: 4.60 ± 1.06
Sharma and Pradeep [24] 2012	Group 1:[a]	Group 2:	Group 1:[a]	Group 2:	Group 1:[a]	Group 2:
	Baseline: 7.85 ± 2.20	Baseline: 7.69 ± 2.22	Baseline: 6.12 ± 1.77	Baseline: 5.96 ± 1.88	Baseline: 5.45 ± 1.18	Baseline: 5.48 ± 0.92
	Follow-up: 3.96 ± 1.28	Follow-up: 6.04 ± 1.68	Follow-up: 2.85 ± 1.82	Follow-up: 4.54 ± 2.12	Follow-up: 2.95 ± 0.86	Follow-up: 5.37 ± 0.90
Pradeep *et al.* [25] 2012	Group 1:[a]	Group 2:	Group 1:[a]	Group 2:	Group 1:[a]	Group 2:
	Baseline: 8.41 ± 2.41	Baseline: 8.31 ± 1.80	Baseline: 6.24 ± 1.65	Baseline: 6.53 ± 1.87	Baseline: 5.40 ± 1.19	Baseline: 5.36 ± 1.34
	Follow-up: 3.85 ± 1.89	Follow-up: 5.94 ± 1.77	Follow-up: 2.65 ± 1.45	Follow-up: 4.92 ± 1.93	Follow-up: 2.97 ± 0.69	Follow-up: 5.22 ± 1.35
Graziani *et al.* [18] 2009	Group 1: (mean with interquartile range)	Group 2: (mean with interquartile range)	Group 1: (mean with interquartile range)	Group 2: (mean with interquartile range)	Not available	Not available
	Baseline: 3.4 (3.2,3.7)	Baseline: 3.5 (3.2,3.7)	Baseline: 4.2 (3.9,4.6)	Baseline: 4.1 (3.6,4.6)		
	Change from baseline: 0.7 (0.8,0.9)	Change from baseline: 0.7 (0.5,0.9)	Change from baseline: 0.5 (0.2,0.8)	Change from baseline: 0.6 (0.3,0.9)		
Lane *et al.* [26] 2005	Group 1:[a]	Group 2:	Group 1:[a]	Group 2:	Not available	Not available
	Baseline: 4.20 ± 1.48	Baseline: 4.13 ± 1.22	Baseline: 3.27 ± 1.63	Baseline: 3.37 ± 1.42		
	Follow-up: 3.40 ± 0.97	Follow-up: 3.68 ± 1.25	Follow-up: 2.24 ± 1.29	Follow-up: 2.76 ± 1.40		
Rocha *et al.* [27] 2004	Group 1:[a]	Group 2:	Group 1:	Group 2:	Group 1:[a]	Group 2:
	Baseline: 3.2 ± 0.6	Baseline: 3.1 ± 0.4	Baseline: 4.3 ± 1.0	Baseline: 4.5 ± 1.0	Baseline: 3.1 ± 1.4	Baseline: 3.5 ± 1.7
	Change from baseline: –0.8 ± 0.3	Change from baseline: –0.4 ± 0.4	Change from baseline: –0.99 ± 0.8	Change from baseline: –0.5 ± 0.8	Change from baseline: –0.4 ± 0.4	Change from baseline: 0.6 ± 0.5
Rocha *et al.* [28] 2001	Group 1:	Group 2:	Group 1:	Group 2:	Group 1:[a]	Group 2:
	Baseline: 4.1 ± 1.0	Baseline: 3.9 ± 0.9	Baseline: 6.66 ± 1.9	Baseline: 6.0 ± 2.1	Baseline: 6.2 ± 2.7	Baseline: 6.4 ± 2.9
	Follow-up: 2.8 ± 0.6	Follow-up: 3.1 ± 0.8	Follow-up: 5.35 ± 1.5	Follow-up: 5.2 ± 1.9	Follow-up: 5.37 ± 2.3	Follow-up: 6.8 ± 2.7

Group 1: Bisphosphonates + scaling and root planing
Group 2: Placebo + scaling and root planing
[a]Significantly different from the other group

as compared to control group (SRP + placebo/SRP alone). However, in two studies [18, 26], improvement in the periodontal parameters for bisphosphonate delivery as an adjunct to SRP and SRP alone were comparable among periodontitis patients. Six studies [16, 17, 24, 25, 27, 28] showed improved BD fill in test group (SRP + bisphosphonate) as compared to control group (SRP + placebo/SRP alone) at follow-up.

Quantitative analysis. For quantitative data assessment, a meta-analysis was performed. As significant heterogeneity was observed for PD reduction, CAL gain and BD fill, the random model was employed.

Probing depth. Six studies [16, 17, 24–26, 28] presented data to be included in the meta-analysis considering the effects of adjunctive bisphosphonate delivery on PD. Considering the effects of adjunctive bisphosphonates as compared to SRP alone on PD, a high degree of heterogeneity for PD (Q value = 39.6, $P < 0.0001$, $I^2 = 87.38\%$, Figure 2) was noticed among the groups. Significant statistical differences in PD reduction (MD = –1.18, 95% CI = –1.91 to –0.44,

Table 3

Evaluation of bias risk in the included studies

Investigators	Sample size calculation	Allocation concealment	Randomization	Losses (withdrawals/dropouts)	Masking of assessor(s)	Appropriate statistical analysis	Estimated risk of bias
Pradeep *et al.* [16]	0	2	2	1	2	2	High
Sharma and Pradeep [17]	0	2	2	1	2	2	High
Sharma and Pradeep [24]	0	2	2	1	2	2	High
Pradeep *et al.* [25]	0	2	2	1	2	2	High
Graziani *et al.* [18]	2	2	2	1	2	2	Low
Lane *et al.* [26]	0	0	2	1	1	2	High
Rocha *et al.* [27]	0	0	2	1	1	2	High
Rocha *et al.* [28]	0	0	2	1	1	2	High

Study	Bisphosphonate + scaling and root planing			Scaling and root planing			Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total	
Pradeep *et al.* [16] 2013	3.14	0.71	29	5.39	0.79	28	-2.95 [-3.72, -2.19]
Sharma and Pradeep [17] 2012	3.09	1.82	33	5.09	1.54	33	-1.17 [-1.69, -0.64]
Sharma and Pradeep [24] 2012	3.96	1.28	9	6.04	1.68	8	-1.33 [-2.43, -0.23]
Pradeep *et al.* [25] 2012	3.85	1.89	20	5.94	1.77	21	-1.12 [-1.78, -0.45]
Lane *et al.* [26] 2005	3.4	0.97	41	3.68	1.25	25	-0.25 [-0.75, 0.24]
Rocha *et al.* [28] 2001	2.8	0.6	20	3.1	0.8	20	-0.41 [-1.05, 0.21]
Total			**152**			**135**	**-1.18 [-1.91, -0.44]**

Test for heterogeneity: $Chi^2 = 39.6$; df = 5; ($P < 0.0001$); $I^2 = 87.38\%$
Test for overall effect: Z = -3.17; (P =0.002)

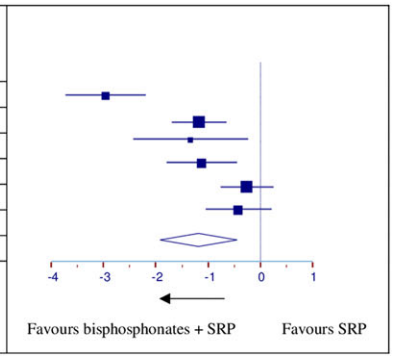

Figure 2

Forest plot presenting post-therapy probing depth reduction by comparing adjunctive bisphosphonate therapy *vs.* scaling and root planing (SRP)

P = 0.002) were observed at follow-up between the test and control groups.

Clinical attachment level. Five studies were included in the meta-analysis for the effect of adjunctive bisphosphonate on CAL [17, 24–26, 28]. Considering the effects of adjunctive bisphosphonates as compared to SRP alone on CAL, a high degree of heterogeneity for CAL (Q value = 13.65, P = 0.008, I^2 = 70.71%, Figure 3) was noticed among both the groups. The overall mean difference for CAL gain between adjunctive bisphosphonate and SRP alone groups were significant (CAL: MD = –0.69, 95% CI = –1.20 to –0.18, p = 0.008) at follow-up.

Bone defect fill. Five studies were included in the meta-analysis for the effect of adjunctive bisphosphonate on BD fill [16, 17, 24, 25, 28]. Similar to PD and CAL, a high degree of heterogeneity for BD fill (Q value = 53.26, $P < 0.0001$, I^2 = 92.49%, Figure 4) was also noticed among both the groups. The overall mean difference for BD fill between adjunctive bisphosphonate and SRP alone groups were significant (BD: MD = –2.36, 95% CI = –3.64 to –1.08, $p < 0.001$) at follow-up.

Grazianin *et al.* [18] reported mean with interquartile range; Rocha *et al.* [27] reported change from baseline; while Pradeep *et al.* [16] did not report mean CAL. Hence these studies were excluded from quantitative synthesis. Two studies [18, 26] did not report BD fill in their findings. The latter authors were contacted in order to collect missing data, but no response was received.

Discussion

The present systematic review was based on the hypothesis that bisphosphonate delivery as an adjunct to SRP improves clinical periodontal parameters and enhances bone formation in periodontal disease conditions. Seventy-five percent

Study	Bisphosphonate + Scaling and root planing			Scaling and root planing			Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total	
Sharma and Pradeep [17] 2012	2.03	1.48	33	4.03	2.02	33	-1.11 [-1.64, -0.59]
Sharma and Pradeep [24] 2012	2.85	1.82	9	4.54	2.12	8	-0.81 [-1.84, 0.21]
Pradeep *et al.* [25] 2012	2.65	1.45	20	4.92	1.93	21	-1.29 [-1.98, -0.61]
Lane *et al.* [26] 2005	2.24	1.29	41	2.76	1.40	25	-0.38 [-0.89, 0.12]
Rocha *et al.* [28] 2001	5.35	1.5	20	5.2	1.9	20	0.08 [-0.54, 0.71]
Total			**123**			**107**	**-0.69 [-1.20, -0.18]**

Test for heterogeneity: $Chi^2 = 13.65$; df = 4; (P =0.008); $I^2 = 70.71\%$
Test for overall effect: Z = -2.66; (P =0.008)

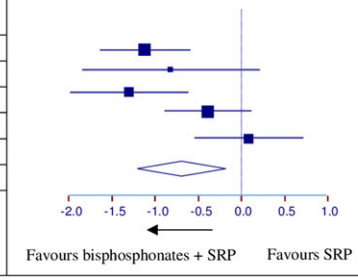

Figure 3

Forest plots presenting post-therapy clinical attachment level gain by comparing adjunctive bisphosphonate therapy *vs.* scaling and root planing (SRP)

Study	Bisphosphonate + Scaling and root planing			Scaling and root planing			Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total	
Pradeep *et al.* [16] 2013	2.64	0.23	29	3.84	0.24	28	-5.03 [-6.11, -3.95]
Sharma and Pradeep [17] 2012	2.82	0.87	33	4.60	1.06	33	-1.81 [-2.39, -1.23]
Sharma and Pradeep [24] 2012	2.95	0.86	9	5.37	0.90	8	-2.61 [-3.98, -1.24]
Pradeep *et al.* [25] 2012	2.97	0.69	20	5.22	1.35	21	-2.04 [-2.81, -1.27]
Rocha *et al.* [28] 2001	5.37	2.3	20	6.8	2.7	20	-0.55 [-1.19, 0.08]
Total			**111**			**110**	**-2.36 [-3.64, -1.08]**

Test for heterogeneity: $Chi^2 = 53.26$; df = 4; (P < 0.0001); $I^2 = 92.49\%$
Test for overall effect: Z = -3.63; (P <0.001)

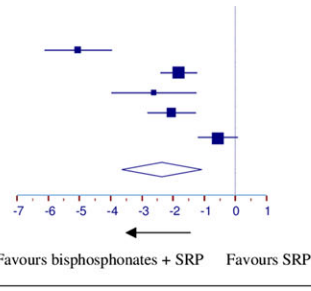

Figure 4

Forest plots presenting post-therapy bone defect fill by comparing adjunctive bisphosphonate therapy *vs.* scaling and root planing (SRP)

of the studies [16, 17, 24, 25, 27, 28] in the present systematic review supported the aforementioned hypothesis. The efficacy of adjunctive bisphosphonates in improving periodontal parameters may be explained by their role in modulating alveolar bone. Delivery of bisphosphonates in periodontal disease inhibits bone resorption through decrease in osteoclast recruitment and increase in osteoblast differentiation with concomitant reduction in PD and CAL gain [29, 30].

From the studies reviewed, adjunctive bisphosphonates in periodontal disease appear to be effective in improving periodontal inflammatory parameters but several factors such as dosage of drug, frequency of application and route of administration need to be taken into consideration. It is noteworthy that bisphosphonate dosage, frequency of delivery, route of administration and patient follow-up varied among the included studies [16–18, 24–28]. For example, in the studies by Sharma and Pradeep [17] and Pradeep *et al.* [16], local alendronate at a dosage of 10 mg/mL was delivered once throughout the study period, whereas Rocha *et al.* [27] and Grazaini *et al.* [18] administered 10 mg of oral alendronate daily for 6 months and 12.5 mg of intramuscular neridronic acid once a week for 12 weeks respectively throughout the study period. Although these clinical studies reported oral and systemic bisphosphonate delivery to enhance bone formation, a precise dosage and frequency of the drug that would yield the most favourable clinical outcome remains unclear. It can be inferred from the results of the metaanalysis that maybe by increasing the dosage and frequency of bisphosphonates administration, the changes in clinical periodontal parameters may have showed good response.

It is well-recognized that patients who receive bisphosphonate may develop osteonecrosis of the jaw bone (ONJ) as one of the long-term side effects of bisphosphonate therapy [31, 32] and duration of bisphosphonate therapy is a significant factor associated with an increased likelihood of ONJ [33]. In the studies included [16–18, 24–28], which evaluated changes in clinical and radiographic parameters of periodontal disease, the follow-up period ranged from 24–48 weeks. Outcomes based on such short-term observations are debatable and therefore further long-term clinical trials should be performed to assess the possible occurrence of ONJ from adjunctive bisphosphonate therapy in periodontal disease. In addition, there are other periodontal therapeutic strategies used as adjunct to SRP such as local antibiotics [34], laser therapy [7, 35], enamel matrix derivative and bone grafts [36], which have fewer side effects. Therefore, such interventions should be compared with local bisphosphonate therapy as an adjunct to SRP to prove their efficacy in improving clinical periodontal outcomes.

Another fact that is worthy of note is that in four studies [18, 26–28], included in the present review, systemic bisphosphonates as an adjunct to SRP in the management of chronic periodontitis was compared to SRP alone. In

twostudies [18, 26], delivery of systemic bisphosphonates showed comparable clinical periodontal parameters between test and control groups. This in contrast to the studies [16, 17, 24, 25] that used local bisphosphonates showing significant improvement in the clinical periodontal outcomes as compared to SRP. A possible explanation in this regard may lie in the ability of local drug delivery system to allow high drug concentrations and have controlled long-term release of the therapeutic agents at target sites [37]. Moreover, the results of a study on adult cynomolgus monkeys have indicated that effects of bisphosphonates without SRP on periodontitis showed no change in PD [38]. In the present systematic review, the significant change in PD reduction (MD = –1.18, 95% CI = –1.91 to –0.44, $p = 0.002$) may be explained by the mechanical debridement (SRP) performed in study groups to arrest inflammatory disease process, highlighting the critical role of SRP in the management of periodontal disease.

It is well-known that osteoporosis, besides having a direct association with oestrogen deficiency [39], is also related to chronic hyperglycaemia. Research reports, that persistent hyperglycaemia leads to increased formation of advanced glycation end products in periodontal tissues [40]. In addition, advanced glycation end products tend to jeopardize the normal function of osteoblasts and augment inflammatory response in periodontal tissue [41]. It is pertinent to mention that subjects with menopause/osteoporosis, diabetes mellitus and obesity were included in the studies reviewed [25, 27, 28]. Therefore, the inflammatory burden and compromised immune response due to the systemic diseases [42–44], could possibly have altered the outcomes in the studies included [16–18, 24–28]. Therefore, further RCTs with strict inclusion and exclusion criteria should be undertaken to assess the efficacy of adjunctive bisphosphonates in the management of periodontitis.

Findings from the study show that clinical and radiographic parameters of periodontal disease appear to improve by bisphosphonate therapy both qualitatively and quantitatively in the short term but certain heterogeneities (such as dosage, frequency, and route of administration along with patient follow-up) among the included studies cannot be overruled. This indicates that although bisphosphonates are effective, but clinically it should be used with caution since there is risk of development of ONJ due to systemic and long-term use of bisphosphonates [33]. Therefore, in light of current evidence, to benefit from the antiresorptive effects of bisphosphonates, the authors suggest their localized use as adjunct to SRP rather than systemic administration. Moreover, to assess the risk of ONJ and the role of bisphosphonate therapy as an adjunct to SRP in the management of periodontal disease, further RCTs with standardized dosage and frequency of local drug application, strict inclusion and exclusion criteria and long-term follow-up are warranted.

Conclusion

The available evidence suggests that adjunctive bisphosphonate therapy appears to be effective in improving clinical outcomes of periodontitis in the short term. However, due to the potential risk of ONJ and short-term follow-up period of the studies, the clinical application of adjunctive bisphosphonate delivery in the management of periodontitis patients is debatable.

Competing Interest

The authors declare that they have no conflict of interest and all authors have read and approved the final draft.

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Contributors

Z.A. initiated the idea, researched and authored the topic background, compiled the initial draft, revised late drafts, data analysis and edited the final draft. F.V. provided guidance throughout, reviewed the manuscript, extracted the data, edited the text and helped with data analysis. T. A. and M.I.A.H contributed to the initial conception, were involved in the initial draft, revised late drafts and edited the article. F.J. and S.V.K. provided guidance, contributed to the text, extracted the data, and revised and edited the article.

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