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Bisphosphonates as Supplement to Dental Treatment: A Network Meta-Analysis

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Abstract

The objective of this study was to assess clinical measurements related to the effectiveness of bisphosphonate (BP) administration as a supplement to conventional dental treatment in patients free of bone-related diseases using a network meta-analysis. Only randomized controlled trials (RCTs) were included that provided dental clinical measurements on human patients treated with BPs with or without similar untreated controls or treated with placebo. Information sources included a systematic search of 17 electronic databases up to August 2020, complemented by manual searches. Risk of bias assessment was performed with the revised Cochrane risk of bias tool for randomized trials (RoB 2.0). Extracted measurements were pooled according to time of evaluation. The random-effects model by DerSimonian and Laird was used to calculate mean differences (MDs) and the respective 95% confidence intervals (CIs). Seven RCTs were included in the network meta-analysis, assessing 391 subjects reporting on periodontal treatment effects after 2 to 12 mo of BP administration. BP treatment was associated with significant improvement of most clinical measurements, compared with BP-naive controls. According to the network ranking, alendronate was more efficient in improvement of probing depth and clinical attachment gain when compared to zoledronate or alendronate/risedronate. Similarly, the local application of alendronate as a gel was more effective than the oral administration. A long-term analysis of the pharmaceutical effects was not possible due to insufficient data. The current review, performed according to existing guidelines, included only RCTs and, through appropriate statistical analyses, provided precise estimates for most assessed outcomes. However, no adverse effects or long-term treatment results were analyzed due to inadequate pertinent data. BP administration seems to be beneficial in the short term for the treatment of periodontal diseases, mainly through controlling periodontal inflammation.

Keywords: drug delivery, periodontal medicine, periodontal diseases, bone remodeling, periodontal tissues, bone biology

Introduction

Rationale

Bisphosphonates (BPs) are a class of drugs that are widely used for the treatment of various diseases related to bone loss such as osteoporosis, primary bone cancer or bone metastasis, and Paget disease (Günaldi et al. 2010; Bauer et al. 2012). Based on their high affinity for bone hydroxyapatite, BPs are incorporated in the bone matrix and enter osteoclasts during bone resorption. Inside the osteoclast, BPs interfere with intracellular enzymatic pathways necessary for the normal function and survival of osteoclasts, thus inhibiting osteoclast-mediated bone resorption (Papapoulos 2008; Bauer et al. 2012; Carini et al. 2012).

Long-term efficacy and safety of BP treatment has been proved in several studies and is currently considered the gold standard for the treatment of several bone loss–related diseases (osteoporosis, bone cancer, Paget disease) (Günaldi et al. 2010; Bauer et al. 2012). In the past few years, a variety of studies have assessed the potential effects of BPs in dental patients, yet the findings remain inconclusive. There are several in vitro studies on the effect of BPs on dental cells, indicating a significant inhibitory effect on differentiation and function of both osteoblasts and osteoclasts (Scheller et al. 2011; Manzano-Moreno et al. 2015; Oliveira et al. 2016).

Data reported from clinical studies on dental patients receiving BPs are ambiguous, with some studies showing favorable effects of BPs, such as proper healing after extractions (Regev et al. 2008; Ferlito et al. 2011) and root canal treatment (Hsiao et al. 2009), but also adverse effects such as bisphosphonate-related osteonecrosis of the jaws (BRONJ) development after dental extractions (Fleisher et al. 2010; Kato et al. 2013). In a large retrospective study (Skrepnek et al.

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2010), no significant association could be found between BPs and any jaw or dental pathologies.

Objective

The aim of the present study was to summarize current evidence deriving exclusively from randomized controlled trials (RCTs) regarding the influence on clinical dental measurements of different types of BPs that were used as a supplement for the treatment of dental diseases in patients without bone-related diseases, compared with patients with similar dental disorders who received other types of BPs, placebo, or no BPs at all, as well as to identify any possible factors that could affect the treatment outcomes.

Materials and Methods

Protocol and Registration

The protocol of the present systematic review was conducted a priori based on the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 (Higgins and Green 2011) and is available upon request. The results of the current investigation are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for network meta-analyses (Hutton et al. 2015) and the respective extension for abstracts (Beller et al. 2013).

Information Sources and Search

The electronic search was performed up to August 2020, including 17 databases (Appendix Table 1). The search strategy was conducted to be broad enough to cover the full spectrum of dental procedures and the various bisphosphonate drugs. For each database, keywords and MeSH words were appropriately selected. No restrictions were placed regarding language, year, or status of publication. Furthermore, the reference lists of the selected trials and pertinent reviews were also checked. Gray literature was examined through appropriate registers and databases. Moreover, authors were contacted when additional information and/or specific clarifications were required. The search strategy was conducted independently by 2 review authors (VFZ, MPY).

Eligibility Criteria and Study Selection

The eligibility criteria for the present review were predetermined (Appendix Table 2). In order to be included, a trial had to include at least one treatment arm involving patients under bisphosphonate administration supplementary for dental treatment, while studies on patients receiving BPs for bone-related diseases were excluded. After the removal of duplicates, all remaining articles were screened on the basis of title, abstract and full text.

Data Collection Process and Data Items

Two review authors (VFZ, MPY) performed the data extraction in piloted collection forms conducted by the third author (EGK). Ambiguities were resolved after consulting the last author (MAP). Measurements reporting on clinical attachment and probing depth were selected as primary outcomes, since they reflect the progress of the periodontal disease in an accurate manner (Tsoukaki et al. 2013; Tsalikis et al. 2014). When several terms of one variable were used in the original trials, all equivalent names were grouped (Appendix Table 3). The latter were further grouped based on a classification proposed by Morelli et al. (2017) in five subgroups: plaque accumulation, bleeding on probing, probing depth, clinical attachment and gingival recession level, and tooth status.

Geometry of the Network

The various treatments that were to be compared were represented by nodes, the sizes of which were proportional to the sample size of all the patients in the respective network receiving the same form of treatment. Moreover, direct comparisons between the various drugs were represented by edges with size proportional to the number of studies included in the corresponding pairwise meta-analysis. In order to provide a visual estimate of the risk of bias assessment between both the pooled samples per treatment as well as the pooled studies per direct comparison, different colors were used for depicting the risk of bias. The nodes were colored so as to provide a summary of the risk of bias of the assessed studies, while the color of the edges was matched to the highest level of risk of bias of the assessed trials.

Risk of Bias Within Individual Studies

The risk of bias was assessed with the revised Cochrane risk of bias tool for randomized trials (RoB 2.0) (Sterne et al. 2019) by two review authors (VFZ, MPY).

Summary Measures and Planned Method of Analysis

Data were summarized and judged suitable for pooling if the control groups had similar characteristics with the experimental groups except for the BP administration.

Mean differences (MDs) and the respective 95% confidence intervals (CIs) were initially extracted. If the included studies could provide data regarding at least 1 type of BPs used compared to placebo, untreated individuals, or a treatment arm with a different BP, a network meta-analysis was planned to be performed. Random-effects network meta-analysis was performed based on a graph-theoretical approach within a frequentist framework (Rücker 2012). Except for direct comparisons between various types of BPs, the comparative effect of the interventions of interest could be evaluated through performance of

indirect comparisons through a common comparator (Lip et al. 2012). Ranking between the various interventions was determined via *P* scores (Rücker and Schwarzer 2015), which enable the ranking of the examined treatments on a continuous 0 to 1 scale. According to the latter, the relative efficacy of the respective interventions for the specific outcome can be identified, with the treatment collecting the highest score being the most effective one.

In case of measurements reported only for a single type of BPs compared to placebo or untreated control patients, single pairwise meta-analyses were planned to be performed if at least 5 trials could be included. For the latter, the DerSimonian and Laird (1986) random-effects model would be used, because it takes into account existing heterogeneity, and in the present review, the samples were suspected to be heterogenous in matters of patient characteristics and pharmaceutical protocols.

Assessment of Inconsistency

For network meta-analyses, homogeneity and consistency were planned to be assessed by decomposing the *Q*-statistic into variation of the effect estimates within designs (heterogeneity) and between designs (inconsistency) (Krahn et al. 2013). In case of mixed comparisons including both direct and indirect evidence, inconsistency between the latter would be investigated by the "node-splitting" approach (Dias et al. 2010). As far as single pairwise meta-analyses are concerned, the extent and impact of heterogeneity between studies were planned to be assessed by forest plot inspection and calculation of the τ^2 and I^2 statistics, respectively. According to the I^2 scores, heterogeneity was considered probably not important (0% to 40%), moderate (30% to 60%), substantial (50% to 90%), or considerable (70% to 100%).

Risk of Bias across Studies

With regard to the outcomes assessed via network meta-analyses, the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach was used for the rating of the overall quality of clinical recommendations according to the methodology suggested by Salanti et al. (2014).

Furthermore, for the outcomes assessed through single pairwise meta-analyses, if an adequate number of trials could be included ($n > 10$) (Lau et al. 2006), analyses would be performed so as to identify the existence of reporting biases through inspection of contour-enhanced funnel plots (Peters et al. 2008), Begg's test (Begg and Mazumdar 1994), and Egger's test (Egger et al. 1997). If these tests indicated the existence of publication bias, Duval and Tweedie's trim-and-fill procedure (Duval and Tweedie 2000) would be performed. Furthermore, the overall quality of evidence for each primary outcome would be assessed with the GRADE approach (Guyatt et al. 2011), according to the following ratings: high quality, moderate quality, low quality, and very low quality.

In addition, the minimally clinical important effect (MCIE) was evaluated on the basis of cutoff points retrieved from the literature to reflect the respective changes in a more realistic manner. Thus, a change is considered significant for probing depth for the extent of 0.8 ± 0.6 mm (Tsoukaki et al. 2013), while for the clinical attachment level gain, the respective scores are 1.13 ± 1.00 mm (Tsalikis et al. 2014). As a result, the MCIE was determined at 0.8 mm and 1.13 mm for the probing depth reduction and for the clinical attachment level gain measurements, respectively. For these variables, the effect was judged as "large" for scores of MCIE + 1 SD and "very large" for scores of MCIE + 2 SD. Regarding plaque accumulation and bleeding on probing, the clinical effectiveness is considered the total absence of bleeding or plaque. However, this criterion does not account for baseline imbalances regarding the various stages of periodontal inflammation, various patients, teeth, or teeth surfaces. Hence, measurements from the aforementioned categories were omitted from the GRADE analysis.

Additional Analyses

Possible sources of heterogeneity were planned to be searched through predetermined mixed-effects subgroup analyses and random-effects meta-regression to identify any possible factors that could influence the treatment results (Ioannidis 2008). These factors were classified as patient related (gender, age, initial dental disorder, smoking) and drug related (dosage, route of administration). In an effort to minimize excessive significance testing, the corresponding analyses were performed exclusively for meta-analyses including at least 5 RCTs. Moreover, in an effort to avoid possible overlap between the various types of bisphosphonates assessed, the aforementioned analyses were performed separately for each type of drug tested.

Similar to the previous case, for meta-analyses including at least 10 trials, robustness of the results was a priori considered to be evaluated via sensitivity analyses based on 1) the use of placebo or not any type of treatment in the control group, 2) the duration of BP treatment, and 3) whether the study was financially supported or not.

The statistical analyses were performed in RStudio Version 3.3.3 (RStudio, Inc.). The packages "netmeta" and "meta" were used. All *P* values were 2-sided with $\alpha = 5\%$, with the exception of the test of between-studies and between-subgroups heterogeneity with $\alpha = 10\%$ (Borenstein et al. 2009). Finally, the GRADE analysis for the network meta-analyses was performed with the CINeMA web application (CINeMA: Confidence in Network Meta-Analysis, University of Bern 2017, available from cinema.ispm.ch).

Results

Study Selection

The initial searches resulted in 14,385 articles (Appendix Fig. 1). Following removal of duplicates and elimination based on title and abstract (Appendix Table 4), 108 full texts remained for further assessment. From those, 97 articles were excluded for various reasons, and thus 11 studies (Rocha et al. 2004;

Lane et al. 2005; Graziani et al. 2009; Sharma and Pradeep 2012a, 2012b; Pradeep et al. 2013, 2017; Sharma et al. 2017; Gupta et al. 2018; Ipshita et al. 2018; Sheokand et al. 2019) were included in the qualitative synthesis. From the latter, the study by Graziani et al. (2009) was omitted from the quantitative synthesis due to missing data that could not be retrieved. Furthermore, the studies by Sharma and Pradeep (2012b), Sharma et al. (2017), and Sheokand et al. (2019) reported data on the basis of the assessed tooth sites rather than the examined patients and were thus included only in the qualitative evaluation to avoid bias due to pooling of different statistical units.

Seven authors were contacted for additional information and/or clarifications; 4 responded, but only 2 provided the requested data. Finally, 2 emails failed to be delivered.

Presentation of Network Structure and Summary of Network Geometry

From the 11 RCTs included in the qualitative synthesis, 7 trials were implemented in at least 1 network meta-analysis. Nearly all of the networks included 2 sets of pairwise comparisons, except for the network meta-analysis for probing depth and clinical attachment levels for the period of 0 to 6 mo that included 3 sets of pairwise meta-analyses. Direct comparisons between the various drugs were not reported in the included trials. So only indirect comparisons were included in the present network meta-analyses for all time intervals. Hence, no closed loops were observed in any of the aforementioned network plots (Appendix Figs. 2–4).

The assumption of transitivity was examined on a theoretical basis, since the characteristics of the patients regarding age, gender, periodontal condition, medical background, history of use of drugs that could affect bone turnover, and type of performed treatment did not seem to differ significantly between the studies.

Study Characteristics and Risk of Bias within Studies

The characteristics of the included RCTs are briefly presented in Table 1. All of them took place in a university setting including 528 subjects and evaluating 23 variables. Despite our attempt to assess all possible dental disorders, the included trials reported exclusively on periodontal diseases. Most patients were treated with alendronate locally administered as a gel application for 2 to 12 mo, while the most common dental disorder was chronic periodontitis. Finally, all controls received placebo, except for the study by Graziani et al. (2009), in which the control group was not pharmaceutically treated.

From the 11 included RCTs, 3 were found to present high risk of bias (Rocha et al. 2004; Graziani et al. 2009; Sheokand et al. 2019), while 7 studies were judged with "some concerns" (Lane et al. 2005; Sharma and Pradeep 2012a, 2012b; Pradeep et al. 2013, 2017; Sharma et al. 2017; Gupta et al. 2018), and 1 study was considered to present low risk of bias (Ipshita et al. 2018) (Appendix Table 5).

Results of Individual Studies

The results of the individual studies included in the network meta-analyses, single pairwise meta-analyses, and exploratory analyses are presented according to the time point of effect evaluation in Appendix Table 6. Each of the aforementioned studies included only 1 treatment arm reporting on patients receiving BPs compared to placebo groups; hence, the respective MDs and 95% CIs are the results of the comparisons between the respective intervention and control groups, without any direct comparisons between BPs.

With regard to the trials that were included only in the qualitative synthesis of the present review, the respective comparisons are briefly presented in Appendix Table 7.

Synthesis of Results

The extracted data were pooled according to the respective treatment periods of evaluation reported in the individual studies. As a result, 5 different time intervals were used.

Time Interval: 0 to 2 mo of Treatment/Observation. Three studies (Sharma and Pradeep 2012a, 2012b; Sharma et al. 2017) reported on data regarding the first 2 mo of treatment. According to qualitative analyses, the average pocket depth and clinical attachment level were significantly improved in BP users compared to drug-naive control individuals, whereas no significant differences were observed regarding most plaque accumulation and bleeding on probing examinations (Appendix Table 7).

Time Interval: 0 to 3 mo of Treatment/Observation. Data from 3 studies reporting on treatment effects after a 3-mo interval enabled the performance of network meta-analyses (Appendix Fig. 5) and 1 exploratory analysis (Appendix Fig. 6). According to the results of the network meta-analyses (Table 2), significant changes seemed to be caused on probing and clinical attachment measurements in favor the alendronate patients, compared to placebo receivers, whereas nonsignificant clinical changes were observed during plaque and bleeding assessment. Moreover, alendronate seemed to be more efficient than zoledronate for all pertinent measurements. However, based on the qualitative analysis (Appendix Table 7), no significant differences were observed between BP- and placebo-treated individuals.

Time Interval: 0 to 6 mo of Treatment/Observation. The respective network meta-analyses, meta-analyses, and exploratory analyses were performed with data from 7 RCTs, including in total 5 variables (Tables 2, 3). In general, BPs were found to cause favorable effects on most of the statistically analyzed variables.

According to the network meta-analyses (Figs. 1–3), significant improvement of most clinical measurements was observed for the alendronate users compared to control groups. Similar to the previous interval, alendronate was found to be associated with greater changes for all assessed measurements (Table 2).

Table 1. Characteristics of the Studies Included in the Current Systematic Review.

	Study	Design	Setting	Characteristics of Patients
1	Graziani et al. (2009)	RCT	University; Italy	Generalized advanced chronic periodontitis, at least 20 teeth present, good general health, no pregnant or lactating females, no requirement for antibiotic premedication for the performance of periodontal examination and treatment or antibiotic treatment in the previous 3 mo, no bone pathologies or any other systemic diseases, no long-term anti-inflammatory drugs, no course of periodontal treatment within the last 6 mo, not allergic to BPs, no need for required bone metabolism–altering drugs, and able to consent to participate in the study.
2	Gupta et al. (2018)	RCT	University; India	Systemically healthy chronic periodontitis patients (age range, 30 to 50 y) having at least 1 intrabony defect, PDs ≥5 mm or clinical attachment loss ≥4 mm and vertical bone loss ≥3 mm on intraoral periapical radiographs or orthopantomogram, with 3 walled or combined defects without involving the furcation with radiographic defect angle ≤45°, no allergies to BPs or on systemic BP therapy, tobacco and alcohol users, immunocompromised patients or having taken antibiotics within preceding 3 mo, those who have undergone periodontal surgical treatment within the last 6 mo, pregnant or lactating females, and serum creatinine clearance <35 mL/min or in patients with evidence of acute renal impairment.
3	Ipshita et al. (2018)	RCT	University; India	Systemically healthy patients with mandibular class II furcation defects and asymptomatic endodontically vital, mandibular molars with radiolucency in the furcation area with probing depth ≥5 mm; horizontal probing depth ≥3 mm; no history of antibiotic or any periodontal therapy in past 6 mo; not any known systemic disease, bisphosphonate allergies; no systemic alendronate therapy; no alcoholics, tobacco users, or pregnant or lactating women; and no aggressive periodontitis.
4	Lane et al. (2005)	RCT	University; United States	Ambulatory patients with moderate to severe periodontitis without the presence of generalized disease of bone (other than chronic periodontitis); the presence of diseases that may affect bone metabolism or a urinary calcium excretion >400 mg/d; chronic treatment with anabolic steroids, anticonvulsants, or anticoagulants; pharmacologic doses of vitamin A or D supplements within 1 y before start of the study; previous use of bisphosphonates (within 1 y), calcitonin (within 6 mo), or fluoride therapy (>1 mo) prior to start of study; or history of drug abuse, unstable cardiovascular disease or uncontrolled hypertension, or gastrointestinal intolerance to bisphosphonates without physical conditions that would prevent them from receiving the proposed treatment regimens or from completing the study or with senile dementia, paraplegia, or quadriplegia.
5	Pradeep et al. (2013)	RCT	University; India	Patients with presence of buccal class II furcation defects in endodontically vital, asymptomatic mandibular first molars with a radiolucency in the furcation area on an intraoral periapical radiograph with PD ±5 mm and horizontal PD ±3 mm following phase I therapy (SRP); no known systemic disease, known or suspected allergy to the bisphosphonate group, systemic bisphosphonate therapy, aggressive periodontitis, use of tobacco in any form, alcoholism, immunocompromised patients, or pregnant or lactating females.
6	Pradeep et al. (2017)	RCT	University; India	Systemically healthy patients with deepest PDs ≥5 mm or CALs ≥4 to 6 mm and vertical bone loss ≥3 mm on intraoral periapical radiographs with no history of periodontal therapy or use of antibiotics in the preceding 6 mo; no known systemic disease, known or suspected allergy to the bisphosphonate group and ATV/statin group or on systemic bisphosphonate and statin group therapy, no aggressive periodontitis, no use tobacco in any form, no alcoholics or immunocompromised patients, no pregnant or lactating females.
7	Rocha et al. (2004)	RCT	University; Mexico	Nonsmoking women, 55 to 65 y old, at least 1 y postmenopausal, with probing depth ≥3 mm in at least 3 teeth, gingival index of 2 or 3, plaque index of 2 or <3, gingival recession and a minimum of 15 teeth; no history of hysterectomy or ovariectomy; no diabetes, cancer, or recent peptic or esophageal disorders; no treatment with drugs to inhibit gastric acid secretion for more than 2 wk in the past 6 mo; no chronic treatment with NSAIDs, hormone replacement therapy, glucocorticoids, or any other drug known to alter bone calcium metabolism; not currently undergoing radiotherapy.
8	Sharma and Pradeep (2012a)	RCT	University; India	Systemically healthy patients with probing depths ±5 mm or clinical attachment levels ±4 to 6 mm and vertical bone loss ±3 mm on intraoral periapical radiographs with no history of periodontal therapy or use of antibiotics in the preceding 6 mo, without a known systemic disease; known or suspected allergy to the bisphosphonate group; on systemic bisphosphonate therapy; with aggressive periodontitis; no tobacco in any form; no alcoholics, immunocompromised patients, or pregnant or lactating females.
9	Sharma and Pradeep (2012b)	RCT	University; India	Healthy status, except the presence of periodontitis, rapid attachment loss, and bone destruction, proven by radiographs obtained some years apart; familial aggregation and clinical and radiographic diagnosis; generalized interproximal PD and CAL of ±5 mm and radiographic bone loss of ±30% of root length affecting ±3 permanent teeth other than first molars and incisors; no history of periodontal therapy or use of antibiotics in the preceding 6 mo; no known systemic disease; no known or suspected allergy to the BP group; no systemic BP therapy; no use of tobacco in any form; no alcoholics, immunocompromised patients, or pregnant or lactating patients.
10	Sharma et al. (2017)	RCT	University; India	Systemically healthy subjects, smokers, with probing depth ≥5 mm or periodontal attachment level ≥4 to 6 mm and a radiographic bone loss ≥3 mm; no history of periodontal therapy or use of antibiotics in the preceding 6 mo; no known systemic disease; no known or suspected allergy to the bisphosphonate group; no systemic bisphosphonate therapy; no aggressive periodontitis; no use of smokeless tobacco in any form, alcoholism, or immunodeficiency.
11	Sheokand et al. (2019)	RCT	University; India	Selection criteria included pocket depth ≥5 mm, clinical attachment loss ≥3 mm, and radiographic evidence of vertical osseous defects 3 to 6 mm; no known systemic disease, history of use of antibiotics 6 mo prior to the study, suspected allergy to bisphosphonate therapy, alcoholics, immunocompromised patients, or lactating females; both smokers and nonsmokers included.

(continued)

Table 1. (continued)

No. of Patients (M/F)	Dental Disorder/ Intervention	Age (SD), y	Drug Used	Dosage	Administration Route	Treatment Duration	Risk of Bias
Gp: 30 (11/19) Ctr: 30 (10/20)	Generalized advanced chronic periodontitis	Gp: 44.7 (NR) Ctr: 42.2 (NR)	Gp: neridronate Ctr: no treatment	12.5 mg/wk	Intramuscular injections	3 and 6 mo	High risk
Gp: 19 (NR) Ctr: 20 (11/9)	Chronic periodontitis	Gp, Ctr: 30 to 50	Gp: zoledronate Ctr: placebo	Gp: 0.05% zoledronate gel (5 mg/100 mL) Ctr: placebo	Local (gel)	3 and 6 mo	Some concerns
Gp: 30 (NR) Ctr: 30 (NR)	Mandibular class II furcation defects	Gp, Ctr: NR	Gp: alendronate Ctr: placebo	Gp: 1% alendronate gel (10 mg/mL) Ctr: placebo	Local (gel)	6 and 12 mo	Low risk
Gp: 41 (20/21) Ctr: 25 (17/8)	Moderate to severe periodontitis	Gp: 48.2 (12.8) Ctr: 46.8 (11.5)	Gp: risedronate or alendronate (plus calcium citrate and vitamin D) Ctr: placebo (plus calcium citrate and vitamin D)	Gp: alendronate at 10 mg/d or risedronate 5 mg/d plus calcium citrate at 1,000 mg/d and vitamin D3 at 400 IU/d Ctr: placebo plus calcium citrate at 1,000 mg/d and vitamin D3 at 400 IU/d	NR	6 and 12 mo	Some concerns
Gp: 29 (NR) Ctr: 28 (NR)	Presence of buccal class II furcation defects in mandibular first molars	Gp, Ctr: 30 to 50	Gp: alendronate Ctr: placebo	Gp: 1% alendronate gel (10 mg/mL) Ctr: placebo	Local (gel)	3, 6, and 12 mo	Some concerns
Gp: 30 (NR) Ctr: 30 (NR)	Chronic periodontitis	Gp, Ctr: 30 to 50	Gp: alendronate Ctr: placebo	Gp: 1% alendronate gel (10 mg/mL) Ctr: placebo	Local (gel)	3, 6, and 9 mo	Some concerns
Gp: 20 (0/20) Ctr: 20 (0/20)	Chronic periodontitis	Gp: 57.8 (2.9) Ctr: 58.0 (2.8)	Gp: alendronate Ctr: placebo	Gp: 10 mg/d Ctr: placebo	Oral	6 mo	High risk
Gp: 33 (NR) Ctr: 33 (NR)	Chronic periodontitis	Gp, Ctr: 30 to 50	Gp: alendronate Ctr: placebo	Gp: 1% alendronate gel (10 mg/mL) Ctr: placebo	Local (gel)	2 and 6 mo	Some concerns
Gp: 9 (NR) Ctr:8 (NR)	Generalized aggressive periodontitis	Both groups: 20 to 35 y	Gp: alendronate Ctr: placebo	Gp: 1% alendronate gel (10 mg/mL) Ctr: placebo	Local (gel)	6 mo	Some concerns
Gp, Ctr: 46 patients (total)	Chronic periodontitis	Gp, Ctr: 30 to 50	Gp: alendronate Ctr: placebo	Gp: 1% alendronate gel (10 mg/mL) Ctr: placebo	Local (gel)	6 mo	Some concerns
Gp, Ctr: 17 patients (total)	Chronic periodontitis	Gp, Ctr: 30 to 50	Gp: alendronate Ctr: placebo	Gp: 1% alendronate gel (10 mg/mL) Ctr: placebo	Local (gel)	3 and 6 mo	High risk

BP, bisphosphonate; CAL, clinical attachment level; Ctr, control group; Gp, treatment group; M/F, males/females; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; PD, probing depth; RCT, randomized controlled trial; SRP, scaling and root planing.

Furthermore, pairwise meta-analyses were feasible only for 2 variables (Appendix Fig. 7). Based on the latter, the modified bleeding index and the horizontal clinical attachment were significantly improved. On the contrary, according to the qualitative synthesis, most measurements were associated with nonsignificant changes between the experimental and control groups (Appendix Table 7).

Time Interval: 0 to 9 mo of Treatment/Observation. Only 1 study (Pradeep et al. 2017) provided data regarding this time interval. According to the latter (Appendix Table 7), nearly all of the assessed measurements were found to be altered in favor of the intervention group.

Time Interval: 0 to 12 mo of Treatment/Observation. Since only 3 included RCTs (Lane et al. 2005; Pradeep et al. 2013; Ipshita et al. 2018) reported on the treatment effects of BP administration after 12 mo (Appendix Fig. 8), network meta-analyses and exploratory analyses were feasible only for 2 and 3 variables, respectively (Tables 2, 3). Regarding the network meta-analyses, alendronate alone was found to be more effective than when combined with risedronate in improving probing depth and clinical attachment (Table 2). Based on the exploratory analyses (Appendix Fig. 9), significant improvement was observed for most assessed variables in favor of the BP users.

Exploration of Inconsistency

The present network analyses did not include any direct comparisons between various types of BPs, and the respective evidence derives exclusively from indirect comparisons via a common comparator. As a result, the inconsistency, in matters of variation in effect estimates between designs, could not be assessed. Hence, only heterogeneity (variation within designs) was assessed as planned (Table 2).

Table 2. Details of the Performed Network Meta-Analyses from the Treatment Period of 0 to 3, 0 to 6, and 0 to 12 mo of Treatment, Including the Ranking of the Assessed Drugs According to the *P* Score Results.

	Variable	k	*n*	m	d	Drug[a]	MD	95% CIs	τ^2	I^2 (%)	*P* Value	*P* Score
						Treatment period: 0 to 3 mo						
1	Probing depth reduction	3	3	3	2	Alendronate	1.23	0.16, 2.29	0.0	0.0	0.95	**0.9462**
						Zoledronate	0.14	−1.09, 1.37				0.3418
						Placebo	0	0				0.2120
2	Clinical attachment level gain	3	3	3	2	Alendronate	1.06	0.10, 2.03	0.0	0.0	0.69	**0.9296**
						Zoledronate	0.14	−1.11, 1.39				0.3563
						Placebo	0	0				0.2141
3	Full-mouth plaque index	3	3	3	2	Alendronate	−0.02	−0.08, 0.05	0.0023	91.8	<**0.001**	0.5663
						Zoledronate	−0.02	−0.12, 0.08				**0.5967**
						Placebo	0	0				0.3371
						Treatment period: 0 to 6 mo						
1	Probing depth reduction	7	4	7	3	Alendronate	1.28	0.46, 2.10	0.1854	20.6	0.28	**0.8268**
						Zoledronate	0.80	−0.68, 2.28				0.6038
						Alendronate/risedronate	0.03	−3.16, 3.22				0.3567
						Placebo	0	0				0.2126
2	Clinical attachment level gain	7	4	7	3	Alendronate	1.41	0.80, 2.01	0.0	0.0	0.76	**0.8564**
						Zoledronate	0.87	−0.35, 2.09				0.6068
						Alendronate/risedronate	0.00	−3.38, 3.38				0.3429
						Placebo	0	0				0.1938
3	Full-mouth plaque index reduction	5	3	5	2	Alendronate	0.08	−0.05, 0.20	0.016	99.7	<**0.001**	**0.7322**
						Zoledronate	0.05	−0.20, 0.30				0.5386
						Placebo	0	0				0.2292
						Treatment period: 0 to 12 mo						
1	Probing depth reduction	3	3	3	2	Alendronate	2.29	1.15, 3.43	0	0	0.89	**0.9419**
						Alendronate/risedronate	0.18	−3.09, 3.45				0.3296
						Placebo	0	0				0.2286
2	Clinical attachment level gain	3	3	3	2	Alendronate	2.29	1.40, 3.16	0	0	0.94	**0.9324**
						Alendronate/risedronate	0.21	−3.37, 3.79				0.3405
						Placebo	0	0				0.2271

The most effective treatment is marked with bold letters.
d, number of study designs; k, number of studies included; m, number of pairwise comparisons versus placebo; MD, mean difference; *n*, number of treatments (drugs) including placebo.
[a]Placebo is the common comparator, which is used as reference for all comparisons, and thus the respective relative effect size is noted as zero.

Table 3. Details of the Performed Meta-Analyses and Exploratory Analyses for the Time Intervals of 0 to 2, 0 to 3, 0 to 6, and 0 to 12 mo of Treatment.

			Post-Pre in BP Group		Post-Pre in Control Group		Effect Size			Heterogeneity		
	Variable	No. of Studies	MD	SD	MD	SD	MD	95% CIs	*P* Value	*P* Value	τ^2	I^2 (%)
			0 to 3 mo of treatment									
1	Modified sulcus bleeding index reduction	2	1.24	0.02	0.94	0.02	0.29	0.01, 0.58	<**0.05**	<**0.001**	0.042	99.94
			0 to 6 mo of treatment									
1	Modified sulcus bleeding index reduction	4	1.72	0.01	1.03	0.02	0.67	0.15, 1.19	<**0.05**	<**0.001**	0.2815	100.00
2	Horizontal clinical attachment level gain	2	2.69	0.44	1.05	0.41	1.63	1.00, 2.25	<**0.001**	<**0.001**	0.1903	92.90
			0 to 12 mo of treatment									
1	Modified sulcus bleeding index reduction	2	1.64	0.01	1.37	0.02	0.26	−0.14, 0.67	0.20	<**0.001**	0.084	100.00
2	Full-mouth plaque index reduction	2	1.37	0.05	1.36	0.01	0.01	−0.03, 0.05	0.62	<**0.001**	0.001	99.60
3	Horizontal clinical attachment level gain	2	3.38	0.52	1.22	0.44	2.20	2.03, 2.37	<**0.001**	0.37	0.0	0.0

Bold indicates statistical significance ($P < 0.05$).
BP, bisphosphonate; MD, mean difference.

Regarding the network meta-analyses, heterogeneity was judged as moderate in most cases. However, as far as the pairwise meta-analyses are concerned, considerable heterogeneity was observed in most of the statistical comparisons. Thus, the results of the present analyses should be interpreted with caution (Table 3).

Risk of Bias across Studies

Regarding the results from the network meta-analyses, the confidence estimates are very low because of imprecision, inconsistency, and study limitations (Appendix Tables 8, 9; Appendix Fig. 10).

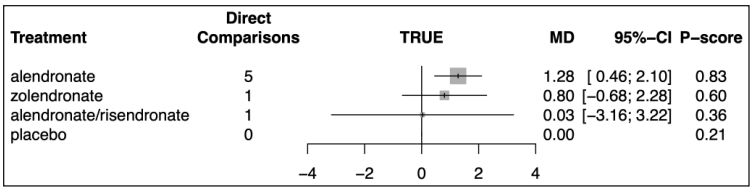

Figure 1. Forest plot of the mean difference of probing depth reduction via network meta-analyses (post-pre increments in millimeters or points) based on the random-effects model together with the 95% confidence intervals (CIs) and the respective ranking for the period of 0 to 6 mo.

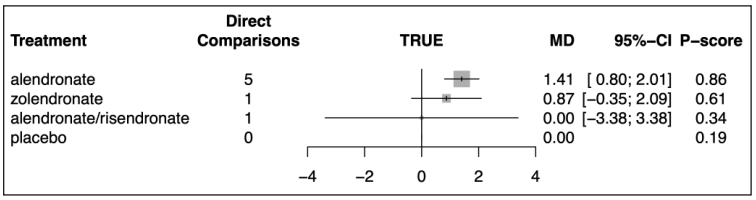

Figure 2. Forest plot of the mean difference of clinical attachment level gain via network meta-analyses (post-pre increments in millimeters or points) based on the random-effects model together with the 95% confidence intervals (CIs) and the respective ranking for the period of 0 to 6 mo.

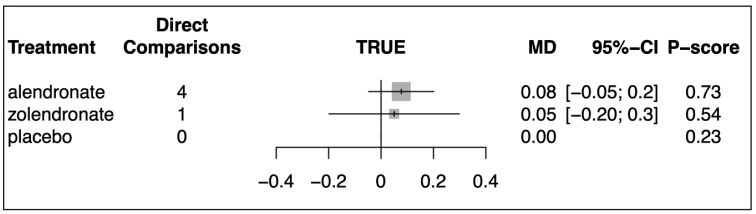

Figure 3. Forest plot of the mean difference of full-mouth plaque index via network meta-analyses (post-pre increments in millimeters or points) based on the random-effects model together with the 95% confidence intervals (CIs) and the respective ranking for the period of 0 to 6 mo.

Additional Analyses

As explained above, subgroup analyses were planned to be performed separately for each drug. As a result, these analyses were feasible only for patients treated with alendronate. Despite the initial plan to assess all possible factors, the respective analyses were feasible only for the dental disorder and the administration route (Appendix Tables 10, 11). According to the latter, only the administration route might influence the treatment results, since the local (gel) administration was found to cause more significant favorable changes for the primary outcomes. Finally, due to an insufficient number of eligible trials, sensitivity analyses could not be performed as well.

Discussion

Summary of Evidence

This systematic review summarized data from 11 RCTs including 528 individuals and assessing the clinical measurements of patients with a periodontal disease after BP treatment compared with respective controls. According to the performed statistical analyses, the use of BPs, especially alendronate, as a supplement to periodontal treatment seems to significantly improve several clinical measurements, primarily probing depth and clinical attachment levels.

In detail, the average depth of periodontal pockets was significantly reduced after combination of bisphosphonate and periodontal treatment, compared with periodontal treatment alone. Furthermore, the reported changes, apart from the statistical significance, were also found to be clinically significant according to the respective cutoff points. However, the latter outcomes are not in accordance with previous studies showing no significant improvement of the respective depths (Brunsvold et al. 1992; O'uchi et al. 1998) in animals that received BPs for experimental periodontitis.

Moreover, most of the included studies reported on a significant improvement of clinical attachment, which was found to be clinically significant after a year of alendronate administration. This finding agrees with split-mouth RCTs (Veena and Prasad 2010; Dutra et al. 2017). Nevertheless, there are animal studies claiming no significant effect (O'uchi et al. 1998) or even a reduction of clinical attachment (Reddy et al. 1995). In addition, both probing depth and clinical attachment (horizontal and vertical) were found to be more pronounced after 1 y of drug administration, possibly implying a time-varying effect of BPs on periodontal disorders.

Furthermore, the use of BPs seems to reduce bleeding on probing, as demonstrated by the reduction of the respective index changes for most intervals. These results seem to be in accordance with studies reporting both on human patients (Dutra et al. 2017) and on monkeys (Brunsvold et al. 1992). However, according to the qualitative synthesis of the current study, most of the respective variables were not significantly changed. The latter might be explained by the fact the BP action is directly targeted on the osteoclastic function and not on the intraoral microbiota. As a result, any pertinent change might be attributed solely to the conventional periodontal treatment (Reddy et al. 1995).

With regards to plaque accumulation, no significant alteration of plaque scores was found between treated and drug-naive patients both for the first 2 mo as well as after a year of drug administration. This is in accordance with a study performed on dogs, in which the bisphosphonate and placebo groups presented similar plaque scores (Reddy et al. 1995). This finding might be explained by the fact that the included subjects were regularly examined during the treatment and observation periods, and their oral hygiene was properly controlled. However, it is reported that the function of salivary glands after BP administration may be impaired (Oliveira et al.

2014), leading to deterioration of the protective action of the saliva. The latter should be taken into account since optimal plaque control is a prerequisite for proper periodontal healing (Rosling et al. 1976).

Furthermore, the only factor that was found to affect the periodontal treatment results regarding the primary outcomes was the administration route, with local application (as gel) being more effective than the oral one (per os) (Appendix Table 10, Appendix Fig. 11). This is in agreement with existing literature as the local administration is thought to be more beneficial compared with the systemic administration since small dosages with high concentrations can be used, while it is more acceptable and causes fewer adverse effects (Needleman et al. 1995; American Academy of Periodontology 2000). Finally, no differences were observed between generalized chronic periodontitis and class II molar defects for any of the primary outcomes assessed between experimental control groups.

Strengths and Limitations

The present study was undertaken according to existing guidelines; assessed exclusively RCTs, which represent the highest level of original studies in evidence-based medicine (Papadopoulos 2003); and enabled the performance of respective network and pairwise meta-analyses, so as to accurately estimate the drug effects. Also, the present results could be generalized to the average patient based on the generic patient characteristics and the various countries where the RCTs were undertaken. In addition, adequate information is provided regarding the number and expertise of involved clinicians and outcome assessors, implying a relative limitation of performance biases (Krishna et al. 2010).

However, despite the broad search strategy, it was possible to assess the influence of BPs only in periodontal patients and not on other dental disorders. In addition, there are still several patient- and drug-related factors that could be used to explore the respective heterogeneity of the performed analyses but could not be investigated for their effect on the treatment results. Also, only 1 study (Graziani et al. 2009) reported adverse effects of BP administration. Furthermore, only 1 trial was judged with low risk of bias, implying a necessity for more careful interpretation of the results. Finally, no information was reported regarding the long-term effects of bisphosphonate treatment for dental issues.

Conclusions

According to existing high-level evidence regarding the administration of BPs as an adjunctive to conservative periodontal treatment of patients free of bone-related systemic disorders, the following conclusions could be drawn:

- The administration of BPs in periodontal patients seems to have in the short term a clinically beneficial effect independent of the specific periodontal treatment.
- BP treatment is associated with significant improvement of most clinical measurements, mainly after the first 6 mo.
- The long-term effectiveness of BPs could not be properly assessed.

Taking into consideration the clinical recommendations from the GRADE framework and the ranking of the assessed BP types, the following can be concluded with limited confidence:

- Alendronate has a superior effect in improving probing depth and clinical attachment measurements when compared to zoledronate or mixed alendronate/risedronate administration for any of the assessed time intervals, when used as a supplement to periodontal treatment.

Despite the abovementioned results, many aspects remain to be investigated through future trials, such as the effectiveness of more than 1 type of BPs both through direct comparison and through a placebo comparator group. These could provide useful conclusions and the possible adverse effects of patients receiving BPs as adjunct for their dental treatment. Finally, additional RCTs are needed to shed more light on the role of BPs in the overall treatment approach of patients with various dental disorders.

Author Contributions

V.F. Zymperdikas, contributed to design, data acquisition, analysis, and interpretation, drafted the manuscript; M.P. Yavropoulou, contributed to conception, design, data acquisition, and interpretation, critically revised the manuscript; E.G. Kaklamanos, contributed to design and data interpretation, critically revised the manuscript; M. A. Papadopoulos, contributed to conception, design, and data interpretation, critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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Declaration of Conflicting Interests

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