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Review Paper
Dental Implants

Impact of bisphosphonate therapy on dental implant outcomes: An overview of systematic review evidence

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Abstract. The purpose of this overview was to assess the methods, quality, and outcomes of systematic reviews conducted to evaluate the impact of bisphosphonates on dental implants and the risk of developing bisphosphonate-related osteonecrosis of the jaw after dental implant surgery. An electronic search without date or language restriction was performed in the PubMed/MEDLINE, Cochrane CENTRAL, Web of Science, and LILACS databases (to January 2018). Eligibility criteria included systematic reviews that evaluated the impact of bisphosphonates on implant outcomes. The quality assessment of the included reviews was done using AMSTAR 2 guidelines. The protocol of this overview was registered in PROSPERO (CRD42018089617). The search and selection process yielded seven reviews, published between 2009 and 2017. None of the systematic reviews included in this study obtained the maximum score in the quality assessment. The scientific evidence available demonstrates that patients with a history of bisphosphonate use do not present a higher risk of dental implant failure or marginal bone loss compared to patients who have not used bisphosphonates. The literature also suggests that patients who undergo surgical trauma during the installation of dental implants may be more susceptible to bisphosphonate-related osteonecrosis of the jaw.

Key words: evidence-based dentistry; dental implant; bisphosphonate; bisphosphonate-related osteonecrosis of the jaw; implant survival.

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The bisphosphonates (BPs), such as alendronate, risedronate, ibandronate, and clodronate, are potent osteoclast inhibitor drugs and are considered the first choice therapy in diseases affecting bone metabolism, such as osteoporosis, multiple myeloma, Paget's disease, hypercalcemia of malignancy, and cancer bone metastasis[1]. The two main categories of BPs are the non-nitrogen-containing BPs, which are metabolized rapidly, and the nitrogen-containing BPs, which are more potent and are not metabolized. Once deposited in bone, very small amounts of BPs are released into the circulation during turn-

over. Consequently, the half-life of BPs in bone is estimated to be in the order of years[2].

The therapeutic approach involving the inhibition of osteoclast activity may be positive in orthopaedics and traumatology by diminishing bone resorption and interfering with the formation and growth of bone metastases. On the other hand, osteoclast inhibition and alteration of the bone microenvironment may be very indirectly deleterious in implant dentistry if bone metabolism is blocked, because this can impair dental implant osseointegration[3]. However, there are reports that the local delivery of BPs (via implant surface coating and/or direct application to the surgical site) promotes a positive effect on peri-implant bone formation in animals[4–7] and on improving the fixation of osseointegrated implants in humans[8,9].

A significant adverse effect observed in patients using either oral or intravenous (IV) BPs who have undergone invasive dental procedures, such as implant therapy, is bisphosphonate-related osteonecrosis of the jaw (BRONJ), which is characterized clinically by the painful exposure of bone in the maxillofacial region[10]. Some systematic reviews (SRs) on this subject have reported high survival rates for implants in patients treated with BPs[11–13]. However, others have observed a relationship between BPs, dental implant failure, and BRONJ[14].

The purpose of this overview was to assess the methods, quality, and outcomes of SRs conducted to evaluate the impact of BPs on dental implants and the risk of developing BRONJ after dental implant surgery.

Materials and methods

Protocol registration

The protocol of this overview was registered in the international prospective register of systematic reviews, PROSPERO (number CRD42018089617). There was no deviation from the originally specified protocol as registered. Although not a SR, the basic methodology of the present study followed the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions*[15]. The clinical question established for the search strategy was organized using the PICOS framework[16].

Focused question

In patients on IV, oral, or local application of BPs, what is the impact of BPs on dental implant outcomes and what is the risk of developing BRONJ?

Search strategy

An electronic search without date or language restriction was conducted in the PubMed/MEDLINE, Cochrane Central Register of Controlled Trials, Web of Science, and LILACS databases up until January 2018. Furthermore, a specific electronic search was performed on the websites of the following journals: *Journal of Periodontology*, *Journal of Clinical Periodontology*, *Clinical Oral Implants Research*, *Clinical Implant Dentistry and Related Research*, *International Journal of Oral & Maxillofacial Implants*, *International Journal of Oral & Maxillofacial Surgery*, and *Implant Dentistry*. A search of the Grey Literature Report[17] and OpenGrey[18] databases was used to identify unpublished studies (grey literature). Searches in the reference lists of the included studies (cross-referencing) were also conducted.

Medical subject heading (MeSH) terms, key words, and other free terms related to ''dental implants'', ''osseointegrated implant'', ''implant failure'', ''implant survival'', ''implant success'', ''osteonecrosis'', ''osteonecrosis of the jaw'', ''bisphosphonate(s)'', ''etidronate'', ''clodronate'', ''risedronate'', ''alendronate'', ''ibandronate'', ''pamidronate'', and ''zoledronic acid'' were used with Boolean operators (OR, AND) to combine searches. The search strategy included appropriate changes in the key words and followed the syntactic rules of each database.

Inclusion criteria were established according to the population, interventions/exposure, comparisons, outcomes, and study design (PICOS strategy)[16]. The 'population' comprised adults ($\geq$18 years) on BP therapy (IV or oral) who had received dental implants. The 'intervention' was the installation of dental implants in patients on BP therapy. With regard to the 'comparisons', there was no comparator group. Regarding outcomes, the primary outcome was the impact of BP therapy on the survival of dental implants. The secondary outcome was the marginal bone loss (MBL) around dental implants and the risk of developing BRONJ after dental implant installation. Articles included had to report systematic reviews, with or without meta-analysis.

Screening process

The search and screening process was performed by two independent review authors (V.M. and V.M.), starting with the analysis of titles and abstracts. Next, full papers were selected for careful reading and analysed according to the eligibility criteria (inclusion/exclusion) for future data extraction. Disagreements between review authors were resolved through careful discussion. When necessary, the authors of the included SRs were contacted by e-mail for clarification of remaining doubts.

Data extraction

When available, the following data were extracted from the included SRs by two independent review authors (V.M. and V.M): authors, focused question, number of studies included, outcome measures, and results of meta-analysis.

Assessment of the quality of the systematic reviews

The quality assessment of the SRs was conducted independently by two review authors (V.M. and V.M). The methodological quality of each SR was evaluated using the AMSTAR 2 tool[19]. The guidelines feature 16 items that are answered with one of four options: 1 indicates 'yes', 2 indicates 'no', 3 indicates 'cannot answer', and 4 indicates 'not applicable'. Only items with option 1 ('yes') were used to generate the score. Therefore, each article could obtain a score of between 0 (no criteria fulfilled) and 16 (all criteria fulfilled).

Statistical analysis

The data collected using the AMSTAR 2 quality assessment tool were analysed using descriptive statistics. The mean and standard deviation values from this analysis were calculated. All statistical analyses were performed using Excel for Mac version 14.0.0 (Microsoft Corp., 2011) and StatPlus:mac LE (AnalystSoft Inc., 2009).

Results

Literature search

The initial search identified 222 titles in MEDLINE/PubMed, one title in the Cochrane Central Register of Controlled Trials, 28 in Web of Science, and none in LILACS. The first evaluation resulted in the selection of 12 complete articles. After critical reading, five reviews were excluded because they did not meet the eligibility criteria of this study (Table 1)[20–24]. Thus,

Table 1. Systematic reviews that were excluded.

Reason for rejection	Authors
Narrative review	Shah et al.[21]; Thirunavukarasu et al.[22]; Javed and Almas[23]
Not focused exclusively on bisphosphonate use and dental implant survival	Boquete-Castro et al.[20]
Included animal studies	Walter et al.[24]

seven SRs, published between 2009 and 2017, were included in the current overview[11–14,25–27]. The search of the grey literature did not result in any additional reviews. The process of searching for and selecting articles can be seen in Fig. 1.

Study characteristics

The characteristics of the included SRs are presented in Table 2. The selected SRs evaluated BPs used via three different routes of administration: oral[11–14,25,27], IV[11,12,14,25], and local[26]. The orally administered drugs were alendronate, risedronate, ibandronate, and etidronate, while those administered intravenously were zoledronic acid, clodronate, and pamidronate. The duration of BP use prior to implant installation varied from 3 months[11,14,25] to 192 months[12–14]. The most commonly reported reasons for BP use were osteoporosis and malignant neoplasm. The number of studies included in the SRs varied from three[26] to 21[12], and the majority used a prospective or retrospective cohort design.

Findings based on previous focused questions

All included SRs reported implant survival rates. Variations in survival rate from 89.2%[12] to 100%[27] (cumulative average 94.8 ± 3.9%) and 96.1%[13] to 99.2%[27] (cumulative average 97.6 ± 1.13%) were observed among the groups that did and did not use BPs by systemic routes, respectively. One SR evaluated only the use of BPs by the local route (surface of the implants), observing a survival rate of 100% for implants with BPs and 91.3% for implants without BPs[26].

Two SRs evaluated the survival of implants through meta-analysis[11,13]. The meta-analysis of Ata-Ali et al. did not demonstrate a significant influence of BPs on implant survival ($P = 0.156$)[11], while in the work of Chrcanovic et al., BPs had a significant influence on implant survival ($P = 0.003$)[13].

Of the seven SRs included, only two (28.6%) observed evidence for an increase in the number of dental implant failures in patients who used BPs (Table 3)[13,14]. In addition, of the SRs that evaluated the oral and IV routes of administration, two reported a greater number of implant failures with IV therapy[14,25].

In the case of BRONJ, three SRs observed a greater number of cases in patients who had been using BPs prior to implant installation compared to patients who had never used the medication (Table 3)[12,14,25].

Only two SRs analysed MBL[13,26]. Chrcanovic et al.[13] did not observe a significant difference ($P = 0.59$) when they performed a meta-analysis of MBL among patients who had used BPs when compared to patients who had never used BPs. Guimarães et al.[26] also did not observe evidence of greater MBL in patients who received local application of BPs during implant installation when compared to patients without BPs.

Quality assessment

None of the SRs included satisfied all AMSTAR 2 criteria (Table 4). The score varied from 5 points[27] to 14 points[13], with an average of 9.5 ± 3.2 out of a possible total of 16 points. Items 1, 7, 9, and 16 were scored as positive for all included reviews. Conversely, no review scored as positive for item 11. Four SRs (57%) reported having followed the PRISMA Statement[28] guidelines for the design of SRs[11,13,14,26].

Discussion

Summary of evidence

The present overview sought scientific evidence for the influence of BPs on the results of dental implant treatment. Although there are SRs on the subject, there is still no consensus in the literature on the actual impact of BPs on the performance of dental implants or on the risk of BRONJ occurrence. By aggregating only SR data, the present study was able to analyse the most convincing scientific evidence[29].

Among the SRs included, the selection of primary studies was pretty distinct. The

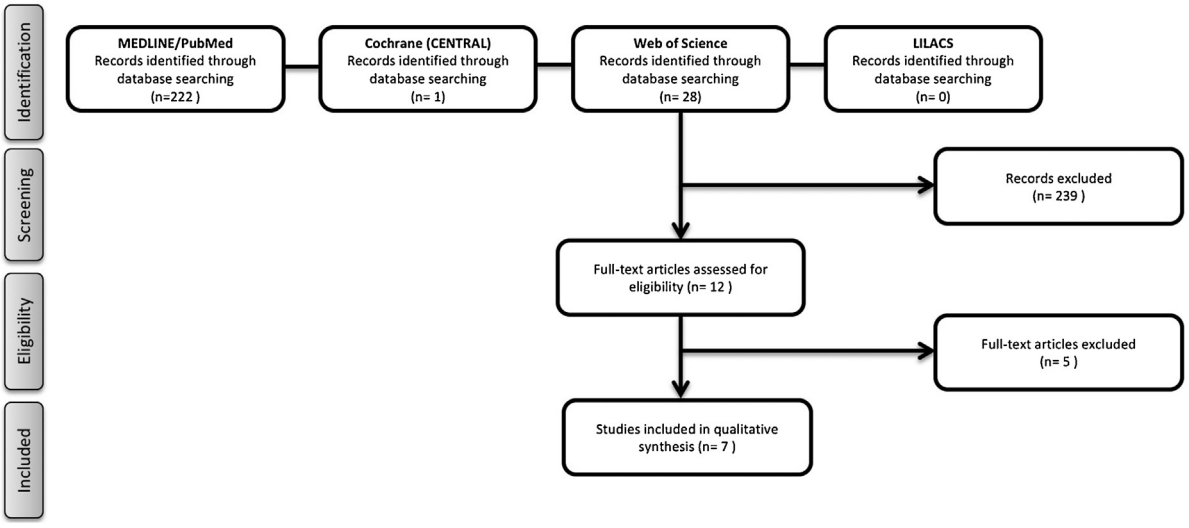

Fig. 1. Flow diagram (PRISMA format) of the screening and selection process.

Table 2. Main characteristics of the systematic reviews included in the overview.

No.	Authors	Focused question	Number of studies included Study types (*n*)	Outcome measures	Meta-analysis results	Number of implants evaluated
1	Madrid and Sanz (2009)[27]	In patients on IV or orally administered BPs, what is the risk of developing BRONJ when dental implants are placed and what is the impact of BP therapy on implant outcome?	4 Prospective (1) Retrospective (3)	Implant survival rate, BRONJ	NP	839
2	Chadha et al. (2013)[12]	(1) Compared to patients with no history of BP use, are patients with a history of oral or IV BP use appropriate candidates for dental implants with respect to successful osseointegration? (2) Compared to patients with no history of BP use, are patients with a history of oral or IV BP use at a higher risk of developing BRONJ following dental implant placement?	21 Prospective (1) Retrospective (5) Case series (5) Case report (10)	Implant survival rate, BRONJ	NP	1090
3	Ata-Ali et al. (2016)[11]	What is the impact of BP therapy upon dental implant survival?	14 Prospective (2) Retrospective (10) Case series (2)	Implant survival rate, BRONJ	Implant survival rate: OR 1.43 (95% CI 0.87–2.34), $P = 0.156$ The use of BP did not significantly affect the survival of the implants	1949
4	Chrcanovic et al. (2016)[13]	In patients treated with dental implants and taking BPs, compared to those not taking BPs, what are the outcomes of dental implant failure rates, MBL, and postoperative infection?	18 CCT (1) Prospective (3) Retrospective (14)	Implant failure rate, MBL	Implant failure rate: RR 1.73 (95% CI 1.21–2.48), $P = 0.003$ The use of BP significantly affects the survival of implants MBL: MD 0.05 (95% CI −0.12–0.22); $P = 0.59$ The use of BP does not significantly affect MBL	1284
5	de Freitas et al. (2016)[14]	In patients under BP therapy, does dental implant placement, compared to healthy patients, increase the failure and loss of implants or the incidence of BRONJ?	15 Prospective (1) Retrospective (8) Case series (6)	Implant failure rate, BRONJ	NP	1330
6	Guimarães et al. (2017)[26]	Does the local delivery of BP influence the osseointegration of titanium implants?	3 RCT (2) Case series (1)	Implant survival rate, MBL	NP	96
7	Guazzo et al. (2017)[25]	Does implant placement in patients on therapy with antiresorptive drugs have any related risk of failure or osteonecrosis development?	10 Prospective (1) Retrospective (7) Cross-sectional (2)	Implant survival rate, BRONJ	NP	NA

No.	Authors	Type of BP (route of administration)	Duration of BP intake at implant placement (months)	Follow-up (months)	Implant survival rate in the BP group (%)	Implant survival rate in the non-BP group (%)	Number of cases of BRONJ	AMSTAR 2 score (16 items)
1	Madrid and Sanz (2009)[27]	Alendronate (oral) Risedronate (oral) Ibandronate (oral)	12–60	4–89	100	99.2	0	4
2	Chadha et al. (2013)[12]	Alendronate (oral) Risedronate (oral) Ibandronate (oral) Clodronate (IV) Pamidronate (IV) Zoledronic acid (IV)	6–192	4–89	89.2	97.6	54	8
3	Ata-Ali et al. (2016)[11]	Alendronate (oral) Risedronate (oral) Ibandronate (oral) Etidronate (oral) Zoledronic acid (IV)	3–120	4–146	94.8	97.6	6	7
4	Chrcanovic et al. (2016)[13]	Alendronate (oral) Risedronate (oral) Ibandronate (oral)	6–192	2–264	96.3	96.1	NA	9
5	de Freitas et al. (2016)[14]	Alendronate (oral) Risedronate (oral) Ibandronate (oral) Pamidronate (IV) Zoledronic acid (IV)	3–192	1–132	91.5	98.3	78	6
6	Guimarães et al. (2017)[26]	Clodronate (local) Pamidronate (local) Ibandronate (local)	0	60	100	91.3	NA	10
7	Guazzo et al. (2017)[25]	Alendronate (oral) Risedronate (oral) Ibandronate (oral) Pamidronate (IV) Zoledronic acid (IV)	3–132	NA	97	NA	NA	7

BP, bisphosphonate; BRONJ, bisphosphonate-related osteonecrosis of the jaw; CCT, controlled clinical trial; CI, confidence interval; IV, intravenous; MBL, marginal bone loss; MD, mean difference; NA, not available; NP, not performed; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk.

Table 3. Effect of bisphosphonates in relation to the outcomes.

Authors	Outcome[a]		
	Implant failure	BRONJ	MBL
Madrid and Sanz (2009)[27]	–	–	NA
Chadha et al. (2013)[12]	–	+	NA
Ata-Ali et al. (2016)[11]	–	–	NA
Chrcanovic et al. (2016)[13]	+	NA	–
de Freitas et al. (2016)[14]	+	+	NA
Guimarães et al. (2017)[26]	–	NA	–
Guazzo et al. (2017)[25]	–	+	NA

BRONJ, bisphosphonate-related osteonecrosis of the jaw; MBL, marginal bone loss.
[a] '–', not associated; '+', associated; NA, not evaluated.

number of studies included in the SRs varied from three[26] to 21[12]. A comprehensive search strategy is critical to increasing the reliability of results and decreasing the risk of bias. A summary of the search strategy used in each eligible systematic review is summarized in the **Supplementary Material** (Table S1).

BPs are potent inhibitors of osteoclast activity normally employed in the treatment of skeletal diseases such as primary and secondary osteoporosis and bone metastases[30,31]. As BPs interfere with the bone turnover process, this characteristic led to the hypothesis that such drugs could have a negative impact on the osseointegration process of dental implants. Furthermore, the surgical trauma of implant installation combined with a possible inhibition of the bone turnover process could be related to a greater probability of the occurrence of BRONJ[32].

Numerous case reports are detailed in the literature describing the use of BPs and complications in the installation of dental implants[33–37]. However, a blinded clinical trial evaluating complications in 50 participants (25 with a history of BP use and 25 with no history of use) did not observe a greater number of implant failures or BRONJ cases in the group of participants who had used BPs[38]. Other cohort studies also did not observe any statistically significant differences regarding implant failures and BRONJ for participants who had used BPs[39,40].

Contrary to the hypothesis of BPs having a negative influence on dental implants, there are contemporary studies suggesting that BPs could have a supportive role in osseointegration by biomodulating the process of bone remodelling[26]. The positive effect of local use of BPs on osseointegration has been demonstrated in preclinical studies on different animal models[41–44] and in a SR of studies on humans included in the present overview[26].

Two works included in the present study analysed the survival of implants using meta-analysis, observing divergent results[11,13]. Ata-Ali et al.[11] expressed their results in terms of the odds ratio (OR), and Chrcanovic et al.[13] in terms of the relative risk (RR). The SRs also differed in relation to the inclusion criteria and the numbers of studies included in the meta-analyses. These characteristics may explain the difference in results between the two SRs. Only prospective and retrospective cohort studies were included in the meta-analyses, which may have increased the risk of biased outcomes[45,46]. Therefore, the results should be analysed and interpreted with caution.

The cumulative average survival rate of implants observed in the groups of patients who had used BPs was 94.8%, while in the groups with no BP use history it was 97.6%. Although the patients with no BP use history presented a lower number of implant failures, this difference was only considered significant in two of the included SRs[13,14]. A recently published SR evaluating the survival rate of dental implants in healthy patients observed a rate of 94.6% over an average of 13.4 years of follow-up[41]. This previously reported rate is similar to that observed in patients who had used BPs in the present overview, thus not showing a greater number of failures in patients with a history of BP use.

Three SRs observed a significant risk of BRONJ occurrence after implant installation in patients undergoing BP therapy[12,14,25]. In two of these SRs, it was observed that the majority of BRONJ cases were related to more invasive procedures, such as bone regeneration procedures and the installation of multiple implants[12,25]. Chadha et al.[12] also observed a higher occurrence of BRONJ in studies that evaluated patients who had used BPs orally for a period of more than 5 years. There were very few cases of BRONJ following oral use for less than 5 years.

With regard to BRONJ, none of the SRs reported a more prevalent BP administration route or a specific anatomical area (maxilla or mandible). Publications on BRONJ have normally been in the form of case studies or case series. A lack of evidence of significant scientific impact was observed by all SRs investigating the relationship between BRONJ and dental implants. Thus, robust data related to the occurrence of BRONJ after surgical trauma in patients who have used BPs are still lacking.

Currently, the pathogenesis of BRONJ is debated, but there is strong evidence that it is multifactorial[42]. Factors such as a reduction in bone turnover (inhibition of osteoclasts) with subsequent bone necrosis[43], reduction in extracellular matrix production by fibroblasts[44], decreased angiogenesis[45], and the toxic effect of BPs on mucosal tissue[46] are strongly associated with inflammatory and infectious processes (osteomyelitis) in the surgical area. In addition, genetic factors such as polymorphisms may also be associated with a greater susceptibility to developing BRONJ[47].

Use of the marker test of carboxy-terminal telopeptide of type I collagen (CTX) has been proposed as a means to determine the risk and prognosis for patients who have used BPs and are scheduled to undergo jaw surgery[48–50]. Type I collagen is the main constituent of the extracellular organic matrix, and during bone resorption, CTX is released. However, a recent SR, after reviewing the results from eight prospective studies, showed that the use of CTX is not valid in determining the risk of BRONJ[51].

Only two SRs evaluated MBL and neither of these observed a significant difference between patients with a history of BP use and those with no history of use. Although the SR of Chrcanovic et al. evaluated MBL through meta-analysis, only two studies (the minimum possible) were included in the analysis[13]. The two studies included in the meta-analysis reported a total of 1461 implants (180 in the BP group and 1281 in the non-BP group), showing no statistically significant difference for MBL ($P = 0.59$). However, due to the limited number of studies included in the meta-analysis and the design of the studies (retrospective), this analysis should be interpreted with caution because of the possibility of a high risk of bias.

An average quality in SR methodology was observed during the analysis conducted (average of 9.5 points out of a

Table 4. Quality assessment checklist for systematic reviews (AMSTAR 2).

AMSTAR questions	Madrid and Sanz (2009)[27]	Chadha et al. (2013)[12]	Ata-Ali et al. (2016)[11]	Chrcanovic et al. (2016)[13]	de Freitas et al. (2016)[14]	Guimarães et al. (2017)[26]	Guazzo et al. (2017)[25]
(1) Was an 'a priori' design provided?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(2) Was there duplicate study selection and data extraction?	NA	Yes	Yes	Yes	NA	Yes	Yes
(3) Was a comprehensive literature search performed?	Yes	Yes	No	Yes	No	Yes	Yes
(4) Was the status of publication (i.e., grey literature) used as an inclusion criterion?	NA	No	NA	NA	NA	Yes	NA
(5) Was a list of studies (included and excluded) provided?	No	Yes	Yes	Yes	Yes	Yes	Yes
(6) Were the characteristics of the included studies provided?	No	No	Yes	Yes	Yes	Yes	Yes
(7) Was the scientific quality of the included studies assessed and documented?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(8) Was the scientific quality of the included studies used appropriately in formulating conclusions?	No	Yes	No	Yes	Yes	Yes	No
(9) Were the methods used to combine the findings of studies appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(10) Was the likelihood of publication bias assessed?	No	Yes	Yes	Yes	No	Yes	No
(11) Was the conflict of interest stated?	NA	NA	No	NA	NA	No	NA
(12) Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	No	Yes	Yes	No	No	No
(13) Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No	No	Yes	Yes	No	Yes	No
(14) If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	NA	NA	Yes	Yes	NA	NA	NA
(15) If meta-analysis was justified, did the review authors use appropriate methods for statistical combination of results?	NA	NA	Yes	Yes	NA	NA	NA
(16) Did the review authors use a satisfactory technique for assessing the RoB in individual studies that were included in the review?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Total (Yes)	5	9	12	14	7	12	8

NA, not available; RoB, risk of bias.

possible total of 16). Low sensitivity and limited scope (e.g., grey literature) and deficiency in the discussion and incorporation of heterogeneity/risk of bias in the studies were commonly observed deficiencies.

Strengths and limitations

This overview presents several strengths, such as a record of the protocol, an unrestricted search of the literature (including the grey literature), and a duplicate review process for the search, data extraction, and quality analysis of the included SRs. However, it is also subject to some limitations. Firstly, the vast majority of SRs included were conducted by analysing cohort studies (prospective and retrospective), case reports, and case series. These studies, when compared to controlled clinical trials, may present a greater potential risk of bias. Secondly, some of the SRs did not present individualized data by drug type, route of administration, and specific locations of implant failures, BRONJ, and MLB. This can make it difficult to analyse and interpret the data. In addition, the quality analysis conducted demonstrated numerous methodological shortcomings in the performance of the SRs.

Implications for clinical practice

The evidence does not demonstrate a considerable difference with respect to the survival of implants and MBL between patients who undergo BP therapy and those who do not. Thus, there appears to be no specific procedure regarding the successful osseointegration of dental implants. In contrast, current evidence shows a greater manifestation of BRONJ in patients with a history of BP use. To date, there is no valid method for the analysis of the risk of BRONJ prior to surgical procedures. Therefore, clinical analysis should be individualized and based on the route of administration of the drug, the duration of treatment and the time since cessation of treatment, and the expectation of surgical trauma.

Recommendations for further research

Based on the data analysed in this overview, a greater number of prospective studies individualizing the effect of different types of BP and routes of administration (oral and IV) are encouraged in the future.

In conclusion, the available scientific evidence demonstrates that patients with a history of BP use do not present a higher risk of dental implant failure or MBL compared to patients who have not used BPs. The literature also suggests that patients with a history of BP use who experience surgical trauma during the installation of dental implants may be more susceptible to BRONJ when compared to patients without a history of BP use. However, additional clinical studies are necessary for a better understanding of the risk factors.

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Competing interests

The authors declare that there was no conflict of interest during the elaboration of this study.

Ethical approval

Not required–the study did not involve human subjects.

Patient consent

Not required–the study did not involve human subjects.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijom.2018.09.006.

References

1. Guay DR. Ibandronate, an experimental intravenous bisphosphonate for osteoporosis, bone metastases, and hypercalcemia of malignancy. *Pharmacotherapy* 2006;**26**:655–73.
2. Lin JH. Bisphosphonates: a review of their pharmacokinetic properties. *Bone* 1996;**18**:75–85.
3. Zeng Y, Lai O, Shen B, Yang J, Zhou Z, Kang P, Pei F. A systematic review assessing the effectiveness of alendronate in reducing periprosthetic bone loss after cementless primary THA. *Orthopedics* 2011:34. http://dx.doi.org/10.3928/01477447-20110228-09.
4. Ramalho-Ferreira G, Faverani LP, Prado FB, Garcia Jr IR, Okamoto R. Raloxifene enhances peri-implant bone healing in osteoporotic rats. *Int J Oral Maxillofac Surg* 2015;**44**:798–805.
5. Meraw SJ, Reeve CM. Qualitative analysis of peripheral peri-implant bone and influence of alendronate sodium on early bone regeneration. *J Periodontol* 1999;**70**:1228–33.
6. Back DA, Pauly S, Rommel L, Haas NP, Schmidmaier G, Wildemann B, Greiner SH. Effect of local zoledronate on implant osseointegration in a rat model. *BMC Musculoskelet Disord* 2012;**22**:42.
7. Guimarães MB, Bueno RS, Blaya MB, Shinkai RS, Marques LM. Influence of the local application of sodium alendronate gel on osseointegration of titanium implants. *Int J Oral Maxillofac Surg* 2015;**44**:1423–9.
8. Abtahi J, Tengvall P, Aspenberg P. A bisphosphonate-coating improves the fixation of metal implants in human bone. A randomized trial of dental implants. *Bone* 2012;**50**:1148–51.
9. Abtahi J, Agholme F, Sandberg O, Aspenberg P. Effect of local vs. systemic bisphosphonate delivery on dental implant fixation in a model of osteonecrosis of the jaw. *J Dent Res* 2013;**92**:279–83.
10. Khan AA, Morrison A, Hanley DA, Felsenberg D, McCauley LK, O'Ryan F, Reid IR, Ruggiero SL, Taguchi A, Tetradis S, Watts NB, Brandi ML, Peters E, Guise T, Eastell R, Cheung AM, Morin SN, Masri B, Cooper C, Morgan SL, Obermayer-Pietsch B, Langdahl BL, Al Dabagh R, Davison KS, Kendler DL, Sándor GK, Josse RG, Bhandari M, El Rabbany M, Pierroz DD, Sulimani R, Saunders DP, Brown JP, Compston J, International task force on osteonecrosis of the jaw. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. *J Bone Miner Res* 2015;**30**:3–23.
11. Ata-Ali J, Ata-Ali F, Peñarrocha-Oltra D, Galindo-Moreno P. What is the impact of bisphosphonate therapy upon dental implant survival? A systematic review and meta-analysis. *Clin Oral Implant Res* 2016;**27**:e38–e46.
12. Chadha GK, Ahmadieh A, Kumar S, Sedghizadeh PP. Osseointegration of dental implants and osteonecrosis of the jaw in patients treated with bisphosphonate therapy: a systematic review. *J Oral Implantol* 2013;**39**:510–20.
13. Chrcanovic BR, Albrektsson T, Wennerberg A. Bisphosphonates and dental implants: a meta-analysis. *Quintessence Int* 2016;**47**:329–42.
14. de Freitas NR, Lima LB, de Moura MB, Veloso Guedes CC, Simamoto Júnior PC, de Magalhães D. Bisphosphonate treatment and dental implants: a systematic review. *Med Oral Patol Oral Cir Bucal* 2016;**21**:e644–51.
15. Higgins JP, Green S. *Cochrane handbook for systematic reviews of interventions version 4.2.6 [updated September 2006]*. The Cochrane Library; 2006.
16. Schardt C, Adams MB, Owens T, Keitz S, Fontelo P. Utilization of the PICO framework to improve searching PubMed for clinical questions. *BMC Med Inform Decis Mak* 2007;**15**:7–16.

17. Grey Literature Report. The New York Academy of Medicine. http://www.greylit.org [Accessibility verified December 15, 2017].
18. OpenGrey. System for Information on Grey Literature in Europe. http://www.opengrey.eu [Accessibility verified December 15, 2017].
19. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 2017;**21**. j4008.
20. Boquete-Castro A, Gómez-Moreno G, Calvo-Guirado JL, Aguilar-Salvatierra A, Delgado-Ruiz RA. Denosumab and osteonecrosis of the jaw. A systematic analysis of events reported in clinical trials. *Clin Oral Implants Res* 2016;**27**:367–75.
21. Shah NP, Katsarelis H, Pazianas M, Dhariwal DK. Periodontal disease, dental implants, extractions and medications related to osteonecrosis of the jaws. *Dent Update* 2015;**42**:878–80.
22. Thirunavukarasu A, Pinto HG, Seymour KG. Bisphosphonate and implant dentistry—is it safe? *Prim Dent J* 2015;**4**:30–3.
23. Javed F, Almas K. Osseointegration of dental implants in patients undergoing bisphosphonate treatment: a literature review. *J Periodontol* 2010;**81**:479–84.
24. Walter C, Al-Nawas B, Wolff T, Schiegnitz E, Grötz KA. Dental implants in patients treated with antiresorptive medicationöa systematic literature review. *Int J Implant Dent* 2016;**2**:9.
25. Guazzo R, Sbricoli L, Ricci S, Bressan E, Piattelli A, Iaculli F. Medication-related osteonecrosis of the jaw and dental implants failures: a systematic review. *J Oral Implantol* 2017;**43**:51–7.
26. Guimarães MB, Antes TH, Dolacio MB, Pereira DD, Marquezan M. Does local delivery of bisphosphonates influence the osseointegration of titanium implants? A systematic review. *Int J Oral Maxillofac Surg* 2017;**46**:1429–36.
27. Madrid C, Sanz M. What impact do systemically administrated bisphosphonates have on oral implant therapy? A systematic review. *Clin Oral Implants Res* 2009;**20**(Suppl 4):87–95.
28. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;**151**:264–9.
29. Murad MH, Asi N, Alsawas M, Alahdab F. New evidence pyramid. *Evid Based Med* 2016;**21**:125–7.
30. Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. *Mayo Clin Proc* 2008;**83**:1032–45.
31. Rodan GA, Reszka AA. Bisphosphonate mechanism action. *Curr Mol Med* 2002;**2**:571–7.
32. Yarom N, Yahalom R, Shoshani Y, Hamed W, Regev E, Elad S. Osteonecrosis of the jaw induced by orally administered bisphosphonates: incidence, clinical features, predisposing factors and treatment outcome. *Osteoporos Int* 2007;**18**:1363–70.
33. Brooks JK, Gilson AJ, Sindler AJ, Ashman SG, Schwartz KG, Nikitakis NG. Osteonecrosis of the jaws associated with use of risedronate: report of 2 new cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007;**103**:780–6.
34. Wang HL, Weber D, McCauley LK. Effect of long-term oral bisphosphonates on implant wound healing: literature review and a case report. *J Periodontol* 2007;**78**:584–94.
35. Bedogni A, Bettini G, Totola A, Saia G, Nocini PF. Oral bisphosphonate-associated osteonecrosis of the jaw after implant surgery: a case report and literature review. *J Oral Maxillofac Surg* 2010;**68**:1662–6.
36. Park W, Kim NK, Kim MY, Rhee YM, Kim HJ. Osteonecrosis of the jaw induced by oral administration of bisphosphonates in Asian population: five cases. *Osteoporos Int* 2010;**21**:527–33.
37. Narongroeknawin P, Danila MI, Humphreys Jr LG, Barasch A, Curtis JR. Bisphosphonate-associated osteonecrosis of the jaw, with healing after teriparatide: a review of the literature and a case report. *Spec Care Dentist* 2010;**30**:77–82.
38. Jeffcoat MK. Safety of oral bisphosphonates: controlled studies on alveolar bone. *Int J Oral Maxillofac Implants* 2006;**21**:349–53.
39. Bell BM, Bell RE. Oral bisphosphonates and dental implants: a retrospective study. *J Oral Maxillofac Surg* 2008;**66**:1022–4.
40. Grant BT, Amenedo C, Freeman K, Kraut RA. Outcomes of placing dental implants in patients taking oral bisphosphonates: a review of 115 cases. *J Oral Maxillofac Surg* 2008;**66**:223–30.
41. Moraschini V, Poubel LA, Ferreira VF, Barboza Edos S. Evaluation of survival and success rates of dental implants reported in longitudinal studies with a follow-up period of at least 10 years: a systematic review. *Int J Oral Maxillofac Surg* 2015;**44**:377–88.
42. Otto S, Schreyer C, Hafner S, Mast G, Ehrenfeld M, Stürzenbaum S, Pautke C. Bisphosphonate-related osteonecrosis of the jawsücharacteristics, risk factors, clinical features, localization and impact on oncological treatment. *J Craniomaxillofac Surg* 2012;**40**:303–9.
43. Wehrhan F, Hyckel P, Amann K, Ries J, Stockmann P, Schlegel K, Neukam F, Nkenke E. Msx-1 is suppressed in bisphosphonate-exposed jaw bone analysis of bone turnover-related cell signalling after bisphosphonate treatment. *Oral Dis* 2011;**17**:433–42.
44. Simon MJ, Niehoff P, Kimmig B, Wiltfang J, Acil Y. Expression profile and synthesis of different collagen types I, II, III, and V of human gingival fibroblasts, osteoblasts, and SaOS-2 cells after bisphosphonate treatment. *Clin Oral Investig* 2010;**14**:51–8.
45. Reid IR. Osteonecrosis of the jaw: who gets it, and why? *Bone* 2009;**44**:4–10.
46. Açil Y, Möller B, Niehoff P, Rachko K, Gassling V, Wiltfang J, Simon MJ. The cytotoxic effects of three different bisphosphonates in-vitro on human gingival fibroblasts, osteoblasts and osteogenic sarcoma cells. *J Craniomaxillofac Surg* 2011;**40**:e229–e235.
47. Stockmann P, Nkenke E, Englbrecht M, Schlittenbauer T, Wehrhan F, Rauh C, Beckmann MW, Fasching PA, Kreusch T, Mackensen A, Wullich B, Schett G, Spriewald BM. Major histocompatibility complex class II polymorphisms are associated with the development of anti-resorptive agent-induced osteonecrosis of the jaw. *J Craniomaxillofac Surg* 2013;**41**:71–5.
48. Marx RE, Cillo Jr JE, Ulloa JJ. Oral bisphosphonate-induced osteonecrosis: risk factors, prediction of risk using serum CTX testing, prevention, and treatment. *J Oral Maxillofac Surg* 2007;**65**:2397–410.
49. Dodson TB. CTX and its role in managing patients exposed to oral bisphosphonates. *J Oral Maxillofac Surg* 2010;**68**:487–8.
50. Kwon YD, Kim DY, Ohe JY, Yoo JY, Walter C. Correlation between serum C-terminal cross-linking telopeptide of type I collagen and staging of oral bisphosphonate-related osteonecrosis of the jaws. *J Oral Maxillofac Surg* 2009;**67**:2644–8.
51. Dal Prá KJ, Lemos CA, Okamoto R, Soubhia AM, Pellizzer EP. Efficacy of the C-terminal telopeptide test in predicting the development of bisphosphonate-related osteonecrosis of the jaw: a systematic review. *Int J Oral Maxillofac Surg* 2017;**46**:151–6.

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