

# Local bisphosphonates to improve dental implants osteointegration and stability: A systematic review

## Authors

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## ABSTRACT

The use of bisphosphonates to modulate bone remodeling is a widely accepted therapy. Their use is recommended also in dentistry in a wide variety of pathologies and treatments. For that, we performed a systematic review of the literature according to PRISMA statement. Aim of the present work is to evaluate if bisphosphonates locally administrated could improve primary stability of dental implants. As this therapy seems to enhance implant stability and have no drug related complications, there are a limited number of paper in literature to affirm that this could be an established therapy. For that reason, further studies are needed to establish if this could be a real guideline in implant insertion and management.

## INTRODUCTION

The use of bisphosphonates (BP) is widely accepted to manage bone resorption due to metabolic alterations and/or bone manifestations of metastatic neoplastic disease.

In the last years BP were related to a specific Medication Related Osteonecrosis of the Jaws (MRONJ) called Bisphosphonates Related Osteonecrosis of the Jaws (BRONJ), this adverse event seems to be related to a long-term systemic administration, both in oncological and metabolic patients. According to Ruggero et al. [1] BRONJ has a lower rate of incidence in metabolic patients if compared with oncologic one. Moreover, MRONJ seemed to be linked in a strong way to systemic administration of Anti Resorptive Therapy (ART) and to neoplastic pathologies, this last case appeared to be possible in a variable percentage from 1 up to 15% [2].

Hence, the risk of develop MRONJ from a local administration seemed to be not relevant in comparison with possible favorable outcomes in dental pathologies treatment.

Recently, the use of BF by means of topical administration to enhance primary and long-term dental implant stability, was hypothesized in implantology and for other dentistry fields.

Local BF delivery was suggested due to their mechanism of action: these drugs acts in the inhibition of osteoclasts-mediated bone resorption, in order to balance bone remodeling. The use in a local administration form was noticed mainly in periodontal disease management and in orthodontics, while the most

common use in implant surgery was given to an implant coating and not to a true local administration [3].

In light of this, and due to the differences in opinions in literature, a literature review was performed to understand if there is a common vision of the problem and the eventual necessity of more specific studies to clarify the real advantages of this approach.

## MATERIALS AND METHODS

A systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analysis [4] and registered on PROSPERO - International prospective register of systematic reviews [5].

### Literature Search

To identify relevant studies investigating the linking between T1DM and interleukins polymorphisms, a comprehensive search of PubMed, Scopus and Web of Science, using the Patient/Population/Problem, Intervention, Comparison and Outcome (PICO) format, was conducted regarding the last 5 years.

- Population: humans and animals.
- Intervention: locally delivered BP around dental implants.
- Comparator: dental implants insertion without medications.
- Outcomes: correlation between locally BP and dental implant stability or osteointegration.

The following MeSH were "dental implants stability and local bisphosphonates".

### Eligibility Criteria

The inclusion criteria were as follows: all studies analyzing the effects on osteointegration or stability of locally delivered BF during dental implants placement.

The exclusion criteria were as follows: research about dental implants coating with BP,

systemic administration of BP, local administration of BP in conjunction with other elements/drugs, case report, editorials.

### Data Extraction

Studies were screened by two reviewers independently, and a matrix of relevant data was produced. Disagreements were resolved by consensus with a third reviewer. Data extraction included general details relating the characteristics of the studies (e.g., author, year of publication, sources of funding) and specific details about the type of BP administrated, the type of dental implants, the methods used to evaluate bone density and/or stability.

### Assessment of Methodological Quality

A qualitative description of the characteristics of the included studies (Table 1) as well as a narrative data synthesis (Table 2) was performed. The methodological quality of included studies was assessed using the prediction model risk of bias assessment tool Newcastle-Ottawa Quality Assessment Scale [6] (Table 3).

## RESULTS

### Overall scenario

The initial search provided a total of 18 items; in detail 8 from PubMed, 6 from Scopus and 4 from WOS. 8 items were removed for being duplicates. Automation tools were not used so no paper was removed because of this reason, while 1 record was removed for other reasons, in particular because it referred to peri-implant BRONJ treatment. 9 articles accessed the screening phase, and a total of 3 items were removed because of lack of interest in shown data, specifically because they discussed about orthodontic mini-screws integration or BF coated implants. Eligibility was assigned to 6 records from which none was

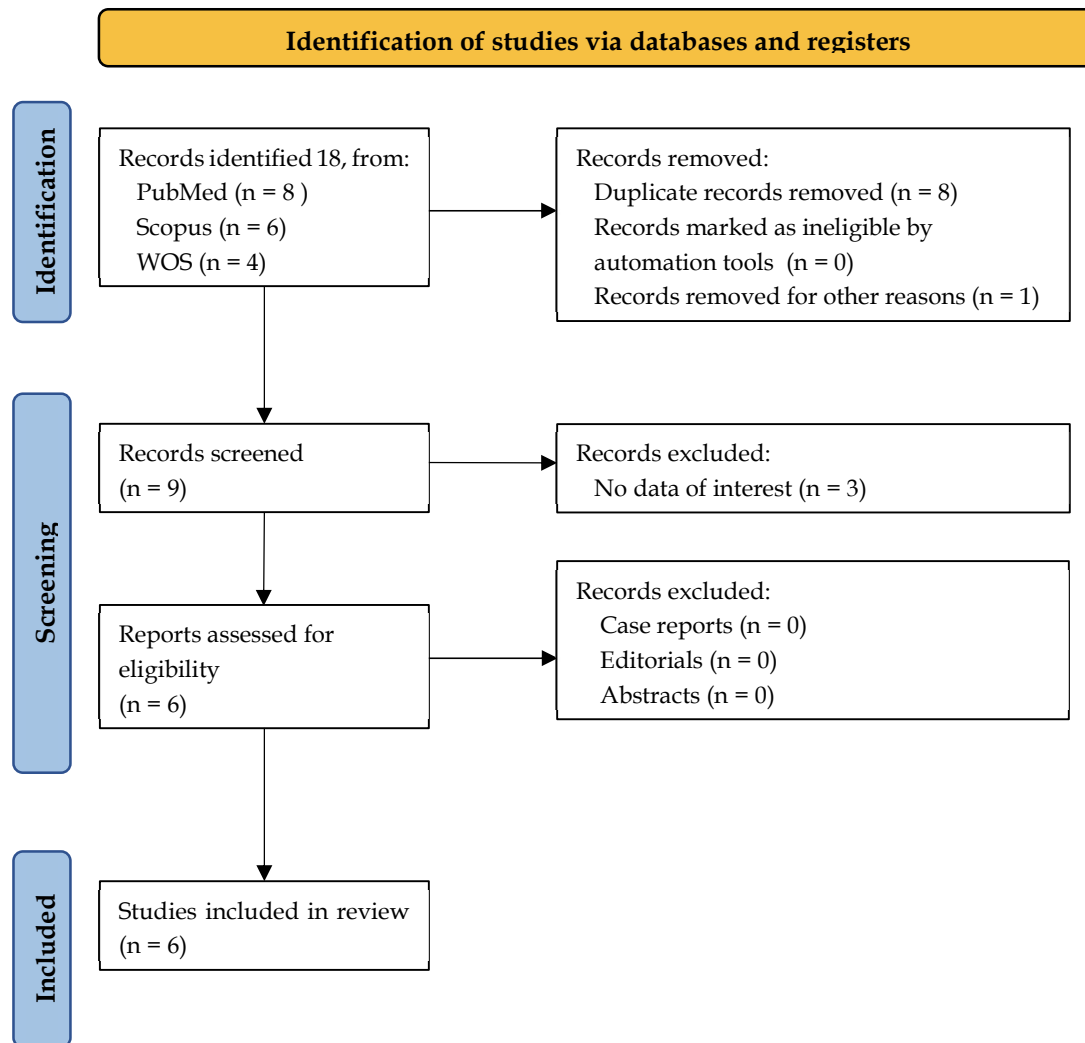


Figure 1. PRISMA flowchart.

removed. Finally, a total of 6 papers were involved for the inclusion phase (Figure 1). A detailed table was drawn up including each eligible article, authors, year, population, type of BF and its formulation, bone density evaluation methods (Table 1). A brief narrative summary is shown in Table 2.

## Detailed Results

33.33% (2/6) of the studies included concerned animals, 33.33% (2/6) was systematic reviews and 33.33% (2/6) was about humans. 50% (3/6) used alendronate gel, 16.7% (1/6) used zoledronate gel and 33.33% (2/6) did not specify the kind of the drug in the abstract. Except for the reviews, 33.33% (2/6) used

histological assessment as a method to evaluate the rate of osteointegration, 16.7% (1/6) used resonance frequency analyzer and 16.7% (1/6) used CBCT. The methodological quality of included studies was assessed using the prediction model risk of bias assessment tool Newcastle-Ottawa Quality Assessment Scale (Table 3).

## DISCUSSION

A systematic review following the PRISMA flowchart was performed in order to assess the state-of-the-art about the relationship between locally administered BF and dental im-

**Table 1.** Key results. n, number of subjects evaluated. CBCT, cone beam computerized tomography. N.S., not specified in the abstract.

Authors/Year	Population/n	#Dental Implants	Type of BF/formulation	Bone Density Evaluation
Al-Assaf DA. et al. 2022 [7]	Humans/27	71	Alendronate/gel	Resonance frequency analyzer
Al-Assaf DA. et al. 2022 [8]	Humans/27	71	Alendronate/gel	Hounsfield units (HUs) using CBCT
Sokmen N. et al. 2022 [9]	Animals/24	N.S.	Zolendronate/N.S.	Histological analysis
Khamis AK et al. 2018 [10]	Humans/5-39 Review	N.S.	N.S./N.S.	Radiographic analysis, implant stability quotient (ISQ) and histological analysis
Guimaraes MB et al. 2017 [11]	Humans/Review	N.S.	N.S.	N.S.
Guimaraes MB et al. 2015 [12]	Animals/10	50	Alendronate/gel	Histological analysis

**Table 2.** Articles matching inclusion criteria. Za, zoledronic Acid.

Authors/Year	Selection	Comparability	Exposure	Total Score
Al-Assaf DA. et al. 2022 [7]	3	1	2	6
Al-Assaf DA. et al. 2022 [8]	3	1	2	6
Sokmen N. et al. 2022 [9]	2	1	2	5
Khamis AK et al. 2018 [10]	2	1	2	5
Guimaraes MB et al. 2017 [11]	3	2	1	6
Guimaraes MB et al. 2015 [12]	2	2	2	6

plants osteointegration and stability. Due to a considerable heterogeneity in drug molecules, formulation and methods of osteointegration evaluation, a formal meta-analysis was not carried out.

Due to the increase demand of dental implants, a great effort was done by oral surgeons to increase the possibility to achieve a primary stability of the inserted implants, and subsequently a higher survival of implant supported prostheses.

At a first sight, results didn't seem encouraging. Guimaraes et al. [12] tested a Sodium

Alendronate gel in an animal experimental model performing a comparison between a test group, in which BP was delivered by means of a gel formulation directly inside the implant socket preparation, and a control one, in which there was used only saline. Animals were sacrificed at 28 days from implant insertion and a torque evaluation and an histomorphometric analysis were performed. In this study the use of gel didn't reached the desired result, test sites being harmed from the drug solution instead of being helped.

However, a systematic review on humans

**Table 3.** Newcastle-Ottawa Quality Assessment Scale. Possible total points were 4 points for selection, 2 points for comparability and 3 points for exposure.

Authors/Year	Conclusions
Al-Assaf DA. et al. 2022 [7]	There was no significant treatment effect regarding marginal bone level differences of study groups against control, although there were significant differences on palatal and mesiodistal surfaces among the study (test) groups.
Al-Assaf DA. et al. 2022 [8]	There was a significant increase in bone density in alendronate groups comparing with control groups in preloading period.
Sokmen N. et al. 2022 [9]	Systemic and local administration of ZA may increase implant osseointegration.
Khamis AK et al. 2018 [10]	The local use of a bisphosphonate appears to favour the osseointegration of titanium implants in humans.
Guimaraes MB et al. 2017 [11]	The local use of a bisphosphonate appears to favour the osseointegration of titanium implants in humans.
Guimaraes MB et al. 2015 [12]	The osseointegration of titanium implants is not favoured by the local application of sodium alendronate gel in rabbits.

from the same group, demonstrated that the use of BP to enhance the implant osseointegration seemed to give adequate results to confirm its usefulness. In that systematic review, only three papers were considered adherent to the inclusion criteria, and they were unsuitable to assess both the type of drug that could be better in the treatment and a metanalysis due to the lower amount of cases and differences in drug type and administration. Therefore a positive relation between the use of BP and implants osteointegration was found [11]. These results seem to be coherent with another paper published in 2018, in which a systematic review of the literature was performed with no selection of publication date, language and type of study. Only three studies between 2010 and 2013 met the inclusion criteria, and the outcome on dental implants stability after local BP administration was achieved in comparison with controls. Authors concluded that BP are effective in promoting osseointegration [10].

Recently, a paper by Sokmen et al., highlighted that there is a close relationship between primary stabilization (PS) and Zoledronic

Acid (ZA) administration both local and systemic. Primary stabilization and Zoledronic Acid administration had a positive influence on Bone Implant Connection, significantly from the statistical point of view. Authors concluded that there was a positive relationship between ZA and osteointegration [9].

Finally, Al-Assaf and Bede [7;8], in two different papers highlighted two fundamental outcome of the local BP administration. In the first one three different groups were established: 1) gel of Alendronate, 2) Bone Morphogenetic Protein 2 and 3) a combination of both and compared with a control group. Gels were administered locally immediately before implant insertion. Controls were made at time 0, 8 weeks, 12 weeks and 14 weeks post functional loading. No statistical differences were found regarding marginal bone level, while there was in mesio distal dimension. In the second one, they demonstrated that there was a significant increase in Bone Density both with Alendronate or BMP2 administration in the preloading period.



## CONCLUSIONS

As a conclusion, our review seems to highlight that local administration of BP could have positive effects both in primary stability and in bone density, independently from the BP type. The low amount of the studies and the esiguity of patients treated require more clinical trials to asses the real applicability of this procedure.

## Conflict of interest

Authors declare no conflict of interest

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## Contribution

Authors equally contributed to ideation, writing, revision and conceptualization of this study

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