



Review Article

The role of bisphosphonates in success and survival of dental implants - effects in osseointegration

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Abstract

The purpose of this study was to research published studies concerning the effect of bisphosphonates in the success and survival of dental implants. An electronic PubMed search was conducted and we have included clinical trials as well as reviews which include human and animal studies. The most common complication in the published literature for bisphosphonates and dental implants was found to be osteonecrosis of the jaw. As a result, we focused in non-osteonecrosis studies. The results of our review are mixed and there is lack of consensus concerning potential beneficial or detrimental effects of bisphosphonates and osseo-integration of dental implants.

Keywords: Bisphosphonates, Dental implants

Introduction

The placement of dental implants is an effective treatment method for missing teeth replacement in full and partially edentate patients. Nevertheless, failures continue to occur despite high survival and high success rates¹. Failures of dental implants can be subdivided into early and delayed, concerning either osseointegration at an initial stage or prosthetic failure later on. Early failure can occur either when the implant or the abutment is placed, while delayed may occur when loading the implant after the prosthetic placement. This subdivision is important because it suggests that failures in these two separate periods may be related to several factors. An early failure of an implant is due to the inability to create a bone-to-implant contact (Bone to Implant Contact, BIC). Failure is clinically established by the presence of pain, mobility, bone absorption greater than half the length of the implant, irreparable fluid secretion from the area and final loss of the implant².

Success in the placement of dental implants suggests absence of complications throughout the whole process. For osseo-integration, technical considerations include vertical bone loss lower than 0,2 mm in the first year of implant placement, in the absence of symptoms and signs such as pain, paresthesia, neuropathies, infections, etc. Success is considered to be achieved when 85% of the implants are intact at five years or 80% at ten years³. On the other hand, the term survival is sometimes referenced in the bibliography as an intermediate state between success and

failure, thereby denoting that the implant does not need to be removed but the result of the placement is not ideal⁴. Survival, implies absence of pain, zero mobility, minimal (2-4 mm) bone resorption detected radiographically and absence of fluid secretion from the area².

Systemic diseases and individual daily life habits are known to affect the success and survival of dental implants. Systemic diseases, such as diabetes melitus, autoimmune diseases (rheumatoid arthritis, Sjogren syndrome, etc) or other factors impairing autoimmunity may affect the oral mucosa either by increasing the sensitivity or by deteriorating wound healing. Local factors, such as periodontitis, smoking, radiation therapy, bruxism, etc are important considerations that may lead to early or delayed failure⁵.

Currently, millions of people worldwide are treated for osteoporosis, a systemic disease characterized by reduced bone mass and impaired microarchitecture of bones predisposing to fragility fractures. Bisphosphonates are the

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first option of treatment in such patients through their ability to accumulate specifically at mineralized bone surfaces⁶. Bisphosphonates, and especially those containing nitrogen (alendronate, risedronate, zoledronate and ibandronate) exert their role by selectively attaching to hydroxyapatite while also inhibiting mevalonate pathway, thus affecting the activity and survival of osteoclasts. Bisphosphonates are administered orally or intravenously, and after attaching to the bone mineralized surfaces promote apoptosis of osteoclasts and consequently reduce bone resorption⁷. As a result, bisphosphonates have been regarded by some authors as possibly deleterious for the effects in the oral cavity. Osteonecrosis of the jaw has been described as a condition potentially induced by those agents in patients treated either for osteoporosis or other bone metabolic diseases including skeletal involvement in cancer patients. While we are now aware the osteonecrosis of the jaw is an extremely rare condition in patients treated with oral bisphosphonate for osteoporosis, serious concerns have been raised for potential effects in patients undergoing implant surgeries. However, data have accumulated concerning also a possible beneficial effect on osseointegration in patients undergoing orthopedic surgery¹⁹. Our aim was to review the published literature concerning potential benefits of bisphosphonates in patients undergoing implant surgeries.

Materials and Methods

We searched the published in the English literature studies in the PubMed database (NCBI, NLM) using the following key phrase “dental implants and bisphosphonates”. The inclusion criteria were studies assessing the effects of bisphosphonates on dental implants during the last thirty years. We specifically excluded all studies referring to “osteonecrosis of the jaw”, as our aim was to investigate only other detrimental effects or potential beneficial effects of bisphosphonates on dental implant surgery.

Results

Our initial search provided 333 studies and after careful selection based on our inclusion and exclusion criteria, only 30 relevant results were identified. These results include studies on humans and animals and contain the following article types: Review, systematic review, case study, pilot study, clinical research, clinical trial, multicenter prospective observational study, meta-analysis.

Animal Studies

A study in rats wanted to correlate the effect of zoledronic acid (7,5 µg/kg) and dexamethasone (1 mg/kg), when administered systemically, on the osseointegration of titanium dental implants. The results showed that the use of zoledronic acid did not inhibit the process of osseointegration nor the deposition of cortical or cancellous bone but showed an inability of bone reconstruction of the

pre-existing initial cortical bone with potential effect on long-term osseointegration⁸.

In the case of zoledronate, studies have questioned if it is deposited locally in the area of the implant. These have shown both positive and negative results in terms of the BIC (bone and implant direct contact) and the NBF index (the production of new bone tissue at the surface of the implant). Also, the availability of zoledronate available locally and as a coating on the surface of implants shows enhancement of osseointegration when applied to animals⁹.

In a systematic review, S.V. Kellesarian (2017)¹⁰ analyzed the role of alendronate in osseointegration of dental implants in animals. The results showed that there was an enhancement of osseointegration either as local availability of alendronate in the implant area or as a coating on implant surface. These results, according to the authors, although based on animal models, can support Phase 1 studies in healthy humans (with no other morbidity, except edentulism).

A systematic review from Kellesarian et al. showed positive effect in osseointegration of dental implants when placed locally ibandronate and/or Pamidronate in fourteen animal studies and two clinical trials in humans¹¹. This study based on database research.

Another systematic review from Kellesarian et al.¹² reached the conclusion that the local delivery (local or topical) of zoledronic acid promotes osseointegration in animals.

An animal (canine) study from Khojasteh et al.¹³ (used three groups: 1) 3,5 mg/kg alendronate ALN per week, 2) 1 mg/kg per week IV pamidronate PAM, 3) control group: IV infusion of normal saline) showed that both oral and intravenous (IV) BP therapies reduce the osseointegration and the marginal bone resorption which are more intense in the IV therapies.

A study from Najeeb et al. (2017)¹⁴ based in nine animal studies and two human studies, concluded that bisphosphonate coated dental implants have a positive outcome on osseointegration. The outcome of this study was based on the literature.

Another study in animals from de Oliveira et al. (2017)¹⁵ presented an enhancement of bone repair around implants when using alendronate sodium (0,1mg/kg/day ALE) in short-period time.

Another study animal from Fahim Vohra et al. (2014)¹⁶ which based on the literature, showed that ibandronate, zoledronic acid and alendronate when taken in osteoporotic conditions systematically, had positive effect in bone quantity and BIC contact. Osteoporotic conditions made via bilateral ovariectomy (OVX). This method damaged bone metabolism.

An experimental study in mice was performed to determine whether alendronate (100 mg/ml, 0.5 ml/kg) can affect the bone to the peri-implant area and may be a risk factor for the survival and success of the implant in rat maxillae. After computed tomography, histological

examination and biochemical analysis, the results showed non-statistically significant results in the first two analyses, while biochemical analysis showed a significant difference in the serum osteocalcin concentration, an indicator that could be used in the future for this purpose¹⁷.

On the other hand, M. B. Guimaraes et al.¹⁸ showed that the local application of sodium alendronate in rabbits (1 ml, 10 mg/g gel) may have a negative effect in the implant inserted area as it changes the physiology of osteoblasts.

Studies in Humans

Based on the systematic review made by M.B. Guimaraes, et al.¹⁹ found and analysed three studies that met the criteria (from 278) for the influence of bisphosphonates on the osseointegration of dental implants. The first study²⁰ used aqueous solution of clodronate 3% (Local delivery system: Implant immersion in the solution containing bisphosphonate for 5 min), the other two studies used Pamidronate disodium 60% (1 mg/ml) and Ibandronate 40% (50 mg/ml) (Local delivery system: Immobilization on implant surface: fibrinogen layer containing the combination of bisphosphonates bound to titanium). Excluding the methodological differences that exist among them, all show positive results of the osseointegration of titanium implants when there was local availability of bisphosphonates. In particular, the results showed greater stability of the implant, better survival rates, and reduced bone resorption around the implant compared to control groups. Thus, the topical use of bisphosphonates in the titanium implant site indicates that it helps the process of osseointegration in humans.

To determine the effectiveness of topical bisphosphonates (solution of clodronate 3%) when implantation was made, a study was conducted by Zuffetti, F. et al.²⁰ which showed five years results. The study showed that the use of topical bisphosphonates at the surgical site may positively influence the survival of dental implants in the case of early and in delayed loading in partially and completely edentulous patients.

The bisphosphonate coating (pamidronate and ibandronate in fibrinogen matrix) of the implant surface has shown positive results in a randomized type trial where after implant placement and for 6 months the results were analyzed. More specifically, better stabilization of the coated implants was found by resonance frequencies analysis and reduced bone resorption. They were then examined radiographically after 5 years, and the results show that implants with bisphosphonate coating hold the bone around the implant margin²¹.

A pilot study for bisphosphonate coated (pamidronate and ibandronate) dental implants was done by J. Abtahi et al.²² and showed better implant stability as time goes on.

Another study from Jahan Abtahi et al.²³ was a split-mouth randomized clinical trial and showed that there is no lack of stability (fixation) in coated implants (solution with 2 mg/ml zoledronic acid) and there is no marginal resorption,

in contrast with the non-coated implants.

Another study from M. B. Guimaraes et al.²⁴ included randomized controlled clinical trials (RCTs), prospective and retrospective studies, case-control studies and case series studies which published in 2010, 2012 and 2013, showed only positive results about dental implants osseointegration.

The local application of sodium alendronate on peri-implant area (20 mg ALE in 1 ml saline solution) in the Rajni Aggarwal et al. (2016)²⁵ study showed that the mesial aspect of implants changed the third month and the distal aspect changed the ninth month between test and control group. In conclusion, this BP improved bone formation when applied locally.

The authors Mohanad Al-Sabbagh et al. (2015)²⁶ made a questionnaire survey which included 415 patients and found that patient's age and use of bisphosphonates may lead to implant failure due to their interrelationship. In addition, increased patient age and use of bisphosphonates may lead to implant's lack of success (by 15% every 5 years).

On a large systematic review and meta-analysis about implant failure due to medication, Chappuis et al.²⁷ found that the use of oral BPs had no negative impact in osseointegration but had a higher risk for osteonecrosis of the jaw.

One big retrospective research study of 1279 dental implants in Peru was done by Frank Mayta-Tovalino et al.²⁸ and concluded that among others risk factors, the BPs administration is not a statistical risk factors for implant failure.

A case series from M.A. Pogrel et al.²⁹ presents dental implants failure when patients start anti-resorptive therapy (alendronate, zoledronate and denosumab). In all cases osseointegration was done before the start of the therapies and only the denosumab therapy patients had an active infection.

One big systematic review and meta-analysis study from Schimmel et al. (2018)³⁰ found that patients receiving high doses of antiresorptive therapy (ART) had bad consequences in dental implant survival and an increased probability of complications after implant surgery. On the contrary, patients taking low-dose of ART had high implant survival.

Another systematic review and meta-analysis was done by Stavropoulos A. et al.³¹. This study showed that low dose of BPs had no negative effect in marginal bone levels, unlike the hormone replacement therapy (HRT) had but HRT did not had negative effect on implant survival.

A multicenter prospective observational study from Tallarico et al.³² showed that BPs therapy (oral) (alendronate 70 mg tablet/week or 5-10 mg/daily) did not affect implant survival and success significantly.

A study conducted by Thirunavukarasu et al.³³ showed that case reports with oral BPs had negative effect on osseointegration. Furthermore, the guidelines mention not placing implants in patients taking intravenous BPs (due to cancer), but it is safe when patients take oral BPs.

A study from Yajima et al.³⁴ showed higher cortical bone mineral density (BMD), changes in cortical thickness (BPs duration dependent) and same trabecular BMD in mandibular jawbone of postmenopausal women which have taken oral BPs.

In addition to topical administration of bisphosphonates, these can also be administered intravenously (IV) (single IV infusion 5mg of zoledronic acid). A case study in which an implant is placed in a patient with IV bisphosphonates is by Mattheos et al.³⁵. This is the only case of implant placement in a patient using zoledronate to treat osteoporosis. Although we cannot make valid conclusions from a single case, we should make distinct the difference between the administration of bisphosphonates for the treatment of osteoporosis and the administration of bisphosphonates for the treatment of malignant neoplasms. Based on the literature, a single intravenous infusion of zoledronic acid for the treatment of osteoporosis is not an absolute contraindication for the placement of osseointegrated dental implants.

Based on the literature, a meta-analysis was performed by Chrcanovic et al.³⁶ to see if there is a difference between healthy people and people using bisphosphonates in terms of the failure or not of osseointegration of their implants. The results showed that the use of bisphosphonates does not appear to be associated with failure rates of dental implants.

In order to determine whether bisphosphonate therapy has a negative effect on the success of dental implants, Ata-Ali, J. et al.³⁷ made a systematic review and meta-analysis of the literature. After the bibliography analysis, 14 articles were selected for systematic review and 8 for the meta-analysis. The results showed that there is insufficient data to show a negative effect of bisphosphonates on dental implant survival. To accept the negative effect of bisphosphonates on dental implant osseointegration, there should be a sample of 509 implants in patients treated with bisphosphonates and a failure in this sample. Otherwise, people who do not take bisphosphonates would have no failure.

Discussion

With the improvement of technology, dental implants have become indispensable for the rehabilitation of edentulous patients. A large category of patients are those who receive bisphosphonates. Research has shown that dental implants are the first choice for these patients. However, bisphosphonates can have a negative effect on the osseointegration. Our study found that nine studies involving animals use bisphosphonates, either orally or as a gel in the implant site or as an implant coating, only one study had a negative impact on osteointegration.

On the other hand, the most valuable studies are the studies in humans. Of the total of twenty one studies only three have negative results in osseointegration and one study correlates the dosage of bisphosphonates with the success of their osteointegration.

Conclusions

The data of this review of the literature show some positive and some potentially negative results with respect to osseointegration correlated with the local availability of bisphosphonates in the implant placement area as well as intravenously. However, the studies done so far concerning the survival and success of the dental implant are few with a small number of patients and a lack of specificity. Based on the above, the actual effect of bisphosphonates on implant osseointegration is not yet well documented. For these reasons, more prospective studies should be made with a larger number of patients and they should have a longer follow-up so that their results are as valid as possible.

References

1. Chrcanovic BR, Albrektsson T, Wennerberg A. Reasons for failures of oral implants. *J Oral Rehabil* 2014;41(6):443-76.
2. Misch CE, Perel ML, Wang H-L, Sammartino G, Galindo-Moreno P, Trisi P, κ.ά. Implant Success, Survival, and Failure: The International Congress of Oral Implantologists (ICOI) Pisa Consensus Conference: *Implant Dentistry* 2008;17(1):5-15.
3. T. Albrektsson, G. Zarb, P. Worthington, A.R. Eriksson. The Long-Term Efficacy of Currently Used Dental Implants: A Review and Proposed Criteria of Success. *JOMI on CD-ROM* (1997 © Quintessence Pub. Co.) 1997;1(1):35.
4. Simonis P, Dufour T, Tenenbaum H. Long-term implant survival and success: a 10-16-year follow-up of non-submerged dental implants: Long-term implant survival and success. *Clinical Oral Implants Research* 2010;21(7):772-7.
5. van Steenberghe D, Jacobs R, Desnyder M, Maffei G, Quirynen M. The relative impact of local and endogenous patient-related factors on implant failure up to the abutment stage. *Clin Oral Implants Res* 2002;13(6):617-22.
6. Serge Cremers, Socrates Papapoulos. Pharmacology of bisphosphonates. *Bone* 2011;42-49.
7. Rogers MJ, Crockett JC, Coxon FP, Mönkkönen J. Biochemical and molecular mechanisms of action of bisphosphonates. *Bone* 2011;49(1):34-41.
8. de Oliveira MA, Asahi DA, Silveira CAE, Lima LAPA, Glick M, Gallotini M. The effects of zoledronic acid and dexamethasone on osseointegration of endosseous implants: histological and histomorphometrical evaluation in rats. *Clin Oral Impl Res* 2015;26(4):e17-21.
9. Kellesarian SV, Subhi ALHarthi S, Saleh Binshabaib M, Javed F. Effect of local zoledronate delivery on osseointegration: a systematic review of preclinical studies. *Acta Odontologica Scandinavica* 2017;75(7):530-41.
10. Kellesarian SV, Abduljabbar T, Vohra F, Malignaggi VR, Malmstrom H, Romanos GE, κ.ά. Role of local alendronate delivery on the osseointegration of implants: a systematic review and meta-analysis. *International Journal of Oral and Maxillofacial Surgery* 2017;46(7):912-21.
11. Sergio Varela Kellesarian, Tariq Abduljabbar, Fahim Vohra, Elham Gholamiazizi, Hans Malmstrom, Georgios E. Romanos, & Fawad Javed. Does Local Ibandronate and/or Pamidronate Delivery Enhance Osseointegration? A Systematic Review. *Journal of Prosthodontics* 2016;001-10.
12. Sergio Varela Kellesarian, Shatha Subhi ALHarthi, Munerah Saleh

- Binshabaib & Fawad Javed. Effect of local zoledronate delivery on osseointegration: a systematic review of preclinical studies. *Acta Odontologica Scandinavica* 2017;75(7):530-541.
13. Khojasteh A, Dehghan MM, Nazeman P. Immediate implant placement following 1-year treatment with oral versus intravenous bisphosphonates: a histomorphometric canine study on peri-implant bone. *Clin Oral Invest* 2019;23(4):1803-9.
 14. Najeeb S, Zafar MS, Khurshid Z, Zohaib S, Hasan SM, Khan RS. Bisphosphonate releasing dental implant surface coatings and osseointegration: A systematic review. *Journal of Taibah University Medical Sciences* 2017;12(5):369-75.
 15. Oliveira D de, Hassumi JS, Gomes-Ferreira PH da S, Polo TOB, Ferreira GR, Faverani LP, et al. Short term sodium alendronate administration improves the peri-implant bone quality in osteoporotic animals. *J Appl Oral Sci* 2017;25(1):42-52.
 16. Vohra F, Al-Rifaiy MQ, Almas K, Javed F. Efficacy of systemic bisphosphonate delivery on osseointegration of implants under osteoporotic conditions: Lessons from animal studies. *Archives of Oral Biology* 2014;59(9):912-20.
 17. Oh K, Moon H, Lee J, Park Y, Kim J-H. Effects of alendronate on the peri-implant bone in rats. *Oral Dis* 2015;21(2):248-56.
 18. Guimarães MB, Bueno RS, Blaya MBG, Shinkai RSA, Marques LMH. Influence of the local application of sodium alendronate gel on osseointegration of titanium implants. *International Journal of Oral and Maxillofacial Surgery* 2015;44(11):1423-9.
 19. Guimarães MB, Antes TH, Dolacio MB, Pereira DD, Marquezan M. Does local delivery of bisphosphonates influence the osseointegration of titanium implants? A systematic review. *International Journal of Oral and Maxillofacial Surgery* 2017;46(11):1429-36.
 20. Zuffetti F, Testori T, Capelli M, Rossi MC, Del Fabbro M. The Topical Administration of Bisphosphonates in Implant Surgery: A Randomized Split-Mouth Prospective Study with a Follow-Up Up to 5 Years: Implant Treatment Using Bisphosphonates. *Clinical Implant Dentistry and Related Research* 2015;17:e168-76.
 21. Abtahi J, Henefalk G, Aspenberg P. Randomised trial of bisphosphonate-coated dental implants: Radiographic follow-up after five years of loading. *International Journal of Oral and Maxillofacial Surgery* 2016;45(12):1564-9.
 22. Abtahi J, Tengvall P, Aspenberg P. Bisphosphonate coating might improve fixation of dental implants in the maxilla: A pilot study. *International Journal of Oral and Maxillofacial Surgery* 2010;39(7):673-7.
 23. Abtahi J, Henefalk G, Aspenberg P. Impact of a zoledronate coating on early post-surgical implant stability and marginal bone resorption in the maxilla-A split-mouth randomized clinical trial. *Clin Oral Impl Res* 2019;30(1):49-58.
 24. 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;46:1429-1436.
 25. Aggarwal R, Babaji P, Nathan S S, Attokaran G, Santosh Kumar S M, Sathnoorkar S. Comparative clinicoradiographical evaluation of effect of aminobisphosphonate (sodium alendronate) on peri-implant bone status: Controlled clinical trial. *J Int Soc Prevent Communit Dent* 2016;6:285-290.
 26. Al-Sabbagh M, Thomas MV, Bhavsar I, De Leeuw R. Effect of Bisphosphonate and Age on Implant Failure as Determined by Patient-Reported Outcomes. *Journal of Oral Implantology*. 2015;41(6):e287-91.
 27. Chappuis V, Avila-Ortiz G, Araújo MG, Monje A. Medication-related dental implant failure: Systematic review and meta-analysis. *Clin Oral Impl Res* 2018;29(S16):55-68.
 28. Mayta-Tovalino F, Mendoza-Martiarena Y, Romero-Tapia P, Álvarez-Paucar M, Gálvez-Calla L, Calderón-Sánchez J, κ.á. An 11-Year Retrospective Research Study of the Predictive Factors of Peri-Implantitis and Implant Failure: Analytic-Multicentric Study of 1279 Implants in Peru. *International Journal of Dentistry* 2019;2019:1-8.
 29. M. A. Pogrel, S. L. Ruggiero. Previously successful dental implants can fail when patients commence anti-resorptive therapy - a case series. *International Journal of Oral and Maxillofacial Surgery* 2018;47(2):220-222.
 30. Schimmel M, Srinivasan M, McKenna G, Müller F. Effect of advanced age and/or systemic medical conditions on dental implant survival: A systematic review and meta-analysis. *Clin Oral Impl Res* 2018;29(Suppl. 16):311-330.
 31. Stavropoulos A, Bertl K, Pietschmann P, Pandis N, Schiødt M, Klinge B. The effect of antiresorptive drugs on implant therapy: Systematic review and meta-analysis. *Clin Oral Impl Res* 2018;29(Suppl. 18):54-92.
 32. Tallarico M, Canullo L, Khanari E, Meloni SM. Dental implants treatment outcomes in patient under active therapy with alendronate: 3-year follow-up results of a multicenter prospective observational study. *Clin. Oral Impl Res* 2015;1-7.
 33. Thirunavukarasu A, Pinto HG, Seymour KG. Bisphosphonate and Implant Dentistry - Is it Safe? *Prim Dent J* 2015;4(3):30-3.
 34. Yajima N, Munakata M, Fuchigami K, Sanda M, Kasugai S. Influence of Bisphosphonates on Implant Failure Rates and Characteristics of Postmenopausal Woman Mandibular Jawbone. *Journal of Oral Implantology* 2017;43(5):345-9.
 35. Mattheos N, Caldwell P, Dent MC, Petcu EB, Ivanovski S, Reher P. Dental Implant Placement with Bone Augmentation in a Patient Who Received Intravenous Bisphosphonate Treatment for Osteoporosis: 11.
 36. Bruno Ramos Chrcanovic, DDS, MSc, Tomas Albrektsson, MD, PhD, Ann Wennerberg, DDS, PhD .2016. Bisphosphonates and dental implants: A meta-analysis. *Quintessence International* 2016;47(4):329-42.
 37. 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 Impl Res* 2016;27(2):e38-46.