

BISPHOSPHONATE-RELATED OSTEONECROSIS OF THE JAW AND DENTAL IMPLANTS

İlaçlara Bağlı Çene kemiği Osteonekrozu ve Dental İmplantlar

Ala Hassan A. QAMHEYA, Sinem YENİYOL, Volkan ARISAN

Received: 05/05/2015

Accepted: 18/08/2015

ABSTRACT

Bisphosphonate (BP) is one of the possible risk-factors in the osteonecrosis of the jaw (ONJ). Surgical interventions during or after the course of treatment by using BPs may expose the patient under this risk. Animal studies, human studies, case reports, and systematic reviews are used to show the relationship between the use of bisphosphonates and dental implants. In this review data about bisphosphonate-related osteonecrosis of the jaw (BRONJ): incidence, prevention and treatment modalities for the patients who are scheduled for dental implant treatment plan and who have been already treated by dental implants will be investigated. Various views for the relationship between dental implants and bisphosphonates will be analyzed depending on the multifactors: duration, route of uptake, dosage of the drug and patient's other medications that affect the effects of bisphosphonate. All patients treated with this drug must be informed about the risk of implant loss or possibility of osteonecrosis.

Keywords: Bisphosphonate-related osteonecrosis of the jaw (BRONJ); BRONJ treatment; risk factors; dental implants

ÖZ

Bifosfonatlar (BF) çenelerin osteonekrozuna neden olan olası risk faktörlerinden biridir. BPlar kullanılarak yapılan tedaviler sırasında veya sonrasında yapılan cerrahi müdahaleler hastayı risk altına sokmaktadır. Hayvan çalışmaları, insan çalışmaları, vaka sunumları ve sistemik derlemeler bifosfonatlar ile dental implantlar arasındaki bağlantıya dair bir ilişki sunmaktadır. Bu derlemede ilaçlara bağlı çene kemiği osteonekrozu (MRONJ) dental implant uygulaması planlanan ve uygulama yapılmış olan hastalardaki oluş derecesi, önlenmesi ve tedavi yöntemleri açısından değerlendirilmektedir. Dental implantlar ile bifosfonatlar arasındaki ilişki üzerine çeşitli görüşler şu çoklu faktörler doğrultusunda değerlendirilecektir; ilacın süresi, alım yolu ve dozu ile bifosfonatların etkilerini etkileyen hastanın kullandığı diğer ilaçlar. Bu ilaçları kullanan tüm hastalar implant kaybı riski ve osteonekroz oluşumu olasılığı açısından bilgilendirilmelidir.

Anahtar kelimeler: İlaçlara bağlı çene kemiği osteonekrozu (MRONJ); MRONJ tedavisi; risk faktörleri; dental implantlar



Introduction

Osteoclasts resorb bone in response to PTH (parathyroid hormone) by developing a ruffled border on the interface with the bone surface, and start secretion of hydrochloric acid. This strong acid demineralizes the bone matrix and organic components, and meanwhile increased release of bone inductive proteins (BMPs and insulin like growth factors) take place, which promote differentiation of osteoblasts and new osteoid secreti (1). For patients who are treated with bisphosphonates for some bone diseases such as cancer, Paget disease and osteoporosis; this normal biological action of osteoclasts is disturbed by this medication. When BP is ingested by osteoclasts; it causes a loss in osteoclasts' normal ruffled border and then a retraction from the bone's surface following by its death. So the old bone is not removed and new osteoid bone is not formed (2).

The high uptake of bisphosphonates in the alveolar bone is due to the high remodeling rate of this bone which is subjected to high occlusal loads. In this regard, before starting this medication, patients must be referred to a dentist, who can eliminate existing pathology and extract teeth which are non-restorable or periodically unsalvageable. Any invasive procedures for patients taking bisphosphonates increase risk of osteonecrosis of the jaw (3, 4).

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is defined as the exposure of the bone in the maxillofacial region more than 8 weeks in patients who are under bisphosphonate treatment without any radiation treatment, and who have a previous dental surgery including dental implant placement (4, 5). Bisphosphonates can be divided into two groups; nitrogen-containing group (Pamidronate, Alendronate, Residronate, Ibandronate, Zoledronate), and non-nitrogen containing group (Etidronate, Tiludronate). Generally all bisphosphonates have P-C-P chain which is necessary for irreversible binding to hydroxyapatite, causing it not to be able to be hydrolyzed by any enzyme which makes the half-life of bisphosphonate in bone matrix for more than 11 years.

And, for patients who are taking nitrogen-containing bisphosphonates which are more potent and more toxic, they present a higher incidence of BRONJ (2, 4, 6). According to the randomized studies the overall incidence of ONJ was 0.83% with an approximate time-dependent rate of 1% per year, but this result could be underestimated because of the different methods used for data collection (4). In other

studies; incidence of ONJ at 0.7 cases of 100000 people per year were detected for oral bisphosphonate (7, 8). According to American Dental Council dental care, non-invasive dental treatment reduced the incidence of BRONJ (9). Dental implants are one of the dental treatment procedures that depend on a balanced bone metabolism for the success of osseointegration and for normal bone remodeling when they are loaded. We need to take into consideration the patient's medical history with high care depending on how long the bisphosphonate was used, and how the amount and the route of the doses were taken.

Bisphosphonate and dental implants

There's no clear relationship between bisphosphonate and osseointegration of dental implants. Bisphosphonates increase mechanical stability of implants if used locally and at the same time increase the risk of osteonecrosis of the jaw if used systemically. Bisphosphonates have different effects on bone repair sites and bone remodeling sites. Bone can be formed in the repair site, but this drug decreases bone formation to a similar degree of bone resorption in the remodeling site (10). That can explain the increased reverse torque values of fixation pins in patients who are given bisphosphonate in random clinical studies (11, 12). In 5 patients where bisphosphonate-coated implants were used, an increased stability and resonance frequency of the dental implants were noticed. On the other hand an increased risk of osteomyelitis was found present when the bisphosphonate-containing bone did not resorb before the healing phase was completed (13). Skoglund *et al.* (14) applied bisphosphonates locally in the screw holes, which resulted in an increased fixation of the screws in rats. Similar to this study, early bone formation and elevated removal torque values were observed around ibandronate treated Ti-32Nb-5Zr alloy dental implants (15).

Due to these contradictory trials between human and animal studies, bisphosphonate treated implant surfaces need further investigation. Bisphosphonates, whether intravenous or oral, will be inhibiting osteoclastic bone resorption and hence bone turnover (2, 5). Oral bisphosphonates differ in 3 ways from those induced by IV; (i) longer period of exposure to bisphosphonates is needed before exposed bone is developed, (ii) amount of exposed bone is smaller and symptoms are less severe, and (iii) discontinuation of oral bisphosphonate may lead to gradual improvement

(2). Dental implant surgery is contraindicated for patients treated with intravenous bisphosphonates according to the American Association of Oral and Maxillofacial Surgeons guidelines (5).

Jacobsen *et al.*(16) declared that the dental implant placement is contraindicated for IV bisphosphonate treated cancer patients, whereas for IV/oral bisphosphonate treated osteoporosis patients, dental implant surgery is not contraindicated. Significant improvement in osseointegration and osteogenesis of dental implants were observed under the action of systemic bisphosphonates (17-19). Astrand *et al.*(20) studied the relationship of different alendronate doses; and a decreased rate of resorption around unstable dental implants was observed when alendronate doses were increased. Based on the reviews, bisphosphonates are both dose and time dependent, which have a direct relationship with the possibility of osteonecrosis of the jaw (2, 5, 21).

Holzinger *et al.*(22), studied the interval of the development of BRONJ in patients that received dental implants. The study included 3 groups as; implants placed before BP treatment, implants placed during BP treatment, and implants placed after BP treatment. Accelerated development of BRONJ was found at the implants placed after or during BP therapy. According to the retrospective studies, there are no significant differences between BP-user patients and BP non-user patients in terms of implant failure, and there were no BRONJ case detected in any of these studies.

Koka *et al.*(23) compared implant survival rates between 121 implants placed at 55 post-menopausal BP user women and 166 implants placed at 82 post-menopausal BP non-user women in their study. Based on their data it was concluded that there was no need to give a drug holiday for post-menopausal BP user women. Memon *et al.*(8) studied the osseointegration success for 153 dental implants placed for 100 BP-user women, where no significant difference was found compared to the control group (132 dental implants placed for 100 BP non-user women).

Bell *et al.*(6) presented 95% success rate for 101 dental implants placed for 42 patients, who were taking oral bisphosphonates from 6 month to 11 year prior to dental implant surgery. Similarly in another study, where 515 dental implants were placed for 203 osteoporotic patients who received BP; no risk of implant failure and no BRONJ case were found after an average of 7 years follow up (24). Controversially, in a retrospective study (337 women; 1181 implants),

odds of oral BP use was found 2.69 times higher in females for whom implants failed compared with other females whom implants did not fail, and the relationship between oral BP use and implant failure was found to be more stronger in maxilla than in mandible (25).

In this context, Jacobsen *et al.*(16) observed 12 of 14 patients with ONJ caused by BP medication after an average of 20.9 months of dental implant surgery. It was concluded that the dental implant insertions seemed to be the risk factor. In another case series study, 9 patients were clinically observed with BRONJ related to dental implant placement. BRONJ onset were initiated after an average of 60 months of drug usage and an average of 34 months after dental implant placement, where most lesions were observed around the mandibular implants (26). Diniz-Freitas *et al.*(27) evaluated 20 cases of BRONJ, where all of these cases were receiving BP as an osteoporosis treatment.

7 patients had signs and symptoms of BRONJ, during the first 3 years of bisphosphonate usage since they were taking corticosteroids as a co-adjunctive treatment, which also increased the toxicity of bisphosphonates. BRONJ started between 36-132 months of bisphosphonate usage for the 13 of the patients and all included patients had a history of previous dental surgery or removable dental prosthesis. From published data it may be concluded that BRONJ appears after 3 to 4.5 years of oral bisphosphonate usage. But, because of multi factors that affect the incidence of ONJ, it's difficult to determine this time interval accurately (27, 28). Incidence of BRONJ depends on the dose, time and the way that it is taken. Concurrent bad oral hygiene, smoking, co-adjunct treatment such as corticosteroids, and female patients with menopause increases the risk of BRONJ (2, 27).

According to a systematic review in 2014, 8 studies (6 retrospective and 2 prospective) were included in a meta-analysis, with 1288 patients and 4562 dental implants. The results showed that implant success rate was not reduced when implants were placed for patients receiving BP, and not enough evidence were present for the negative impact of BP on dental implants (7). The conclusion of another systematic review in 2009 stated that the short-term (1-4 year) implant survival rate was not influenced by the oral BPs (29) (Table 1).

Table 1. Human studies based on ONJ.

Author / Year	Brand of drug / administration route	Medication period prior to complication	# of cases	# of cases of ONJ
Holzinger <i>et al.</i> / 2014 (22)	Zoledronic acid / IV Pamidronate / PO Ibandronate/ PO Alendronate/ PO	83±50 months	NA	13
Koka <i>et al.</i> / 2010 (23)	Alendronate / PO	> 60 months	55	0
Memon <i>et al.</i> / 2012 (8)	Alendronate/ PO Ibandronate/ PO Risedronate/ PO	9 Years	100	NA
Bell <i>et al.</i> / 2008 (6)	Alendronate/ PO Ibandronate/ PO Risedronate/ PO	6 months-11 years	42	0
Al-Sabbagh <i>et al.</i> / 2015 (24)	Alendronate/ PO Ibandronate/ PO Risedronate/ PO	≥ 3 years	20	0
Yip <i>et al.</i> / 2012 (25)	Bisphosphonates/ PO	6 years	1460	NA
Jacobsen <i>et al.</i> / 2013 (16)	Zoledronic acid/ IV Pamidronate/ IV Alendronate/ PO Ibandronate/ PO	5 years	110	14
López-Cedrún <i>et al.</i> / 2013 (26)	Alendronate/ PO Ibandronate/ PO Risedronate/ PO	3 years	9	9
Diniz-Freitas <i>et al.</i> / 2012 (27)	Alendronate/ PO Ibandronate/ PO	6-132 months	20	20

BRONJ-related dental implant placement avoidance and treatment

Although the BRONJ-related dental implant surgery is rare, the possibility of occurrence is present. For patients who will receive BP, oral surgeons' role is to diagnose and treat any underlying susceptible pathologies and undergo invasive dental procedures that should be scheduled at least 3 months before the initiation of BP therapy. But when BP is mandatory such as in cancer patients, the dental treatment can be started simultaneously with BP, since it needs time to concentrate in the bone (2).

Patients on oral bisphosphonates for less than 3 years, which have at least one medical risk factor; serum CTX (C-terminal telopeptide, a specific marker of type 1 collagen, which is released by the resorptive action of osteoclast) can be evaluated to assess the BRONJ risk. When CTX is more than 150 pg/ml in the serum, the risk of BRONJ after implant placement is minimal (2, 22). If CTX is under this value, it is advised by the doctor to make drug holiday 3 months before the implant placement and 3 months

after the implant placement (5). According to the American Dental Association Council on scientific affairs statements; discontinuing BP may not reduce the risk of BRONJ. The dentist should inform the patient about the alternative treatment options. The dentist should use mechanical and therapeutic maintenance of dental implants in order to prevent peri-implantitis development especially for these patients (9). For patients with established BRONJ; the right treatment aim is to eliminate symptoms, to prevent progression of the disease and to remove the diseased mobile bone. BRONJ is staged between 0 and 3 according to the severity of the symptoms and bone exposure. Regardless of what stage the patient is in, a 0.12% chlorhexidine oral rinse must be prescribed 3 times daily (30). For stage 2, where infection is accompanied by pain, antibiotic regimen (Penicillin 500 mg; 4 times daily) is recommended. For stage 3 that is normally characterized by severe pain, bone exposure and non-responsiveness to antibiotics can be managed generally by surgical debridement or resection (2). Based on a past study, 71-80% of the patients were improved by conservative measures

alone. 120 BRONJ patients at different stages were treated; complete re-epithelization had occurred in 23% of invasive surgically treated patients (30).

Doh *et al.*(31) described a case of BRONJ associated with dental implant placement. Treatment was made by activating the osteoblast activity by using Teriparatide (TPTD) therapy (a recombinant human PTH) in conjunction with conservative treatment. In this case separation of sequestrum and successful treatment with complete healing of epithelium was observed.

Conclusion

The oral surgeons should discuss the benefit-risk ratio before implant placement with patients who are receiving bisphosphonates in order to decrease any future risks. Serum CTX levels of the patients needs to be evaluated to assess the BRONJ risk before considering a dental implant treatment plan.

Source of funding

None declared

Conflict of interest

None declared

References

- Vijay G, Raghavan V. Bisphosphonates and osteonecrosis of jaws. *J Indian Aca Oral Med Radiol* 2012;24(4):330-333.
- Robert EM. Oral and intravenous bisphosphate-induced osteonecrosis of the jaws. *History E, Prevention, and Treatment* 2nd Ed., New Malden, Quintessence Publishing Co, Inc. 2007.p.9-93.
- Glowacki J. Bisphosphonates and Bone. *Ortho J Harvard Med School* 2005;25:64-67.
- Coleman RE. Risk and benefits of bisphosphonates, *Br J Cancer* 2008;98(11):1736-1740.
- Flichy-Fernandez AJ, Balaguer-Martinez J, Penarrocha-Diago M, Bagan JV. Bisphosphonates and dental implants: Current problems. *Med Oral Patol Oral Cir Bucal* 2009;14(7):E355-360.
- Bell BM, Bell RE. Oral bisphosphonates and dental implants: A retrospective study. *J Oral Maxillofac Surg* 2008;66(5):1022-1024.
- Ata-Ali J, Ata-Ali F, Penarrocha-Oltra D, Galindo-Moreno P. What is the impact of bisphosphonate therapy upon dental implant survival? A systematic review and meta-analysis. *Clin Oral Implants Res* 2014; 10.1111/clr.12526
- Memon S, Weltman RL, Katancik JA. Oral bisphosphonates: Early endosseous dental implant success and crestal bone changes. A retrospective study. *Int J Oral Maxillofac Implants* 2012;27(5):1216-1222.
- Edwards BJ, Hellstein JW, Jacobsen PL, Kaltman S, Mariotti A, Migliorati CA, American Dental Association Council on Scientific Affairs Expert Panel on Bisphosphonate-Associated Osteonecrosis of the J. Updated recommendations for managing the care of patients receiving oral bisphosphonate therapy: An advisory statement from the american dental association council on scientific affairs. *J Am Dent Assoc* 2008;139(12):1674-1677.
- Aspenberg P. Bisphosphonates and implants: An overview. *Acta Orthop* 2009;80(1):119-123.
- Arnoldi J, Alves A, Procter P. Early tissue responses to zoledronate, locally delivered by bone screw, into a compromised cancellous bone site: A pilot study. *BMC Musculoskelet Disord* 2014;15(97).
- Moroni A, Faldini C, Hoang-Kim A, Pegreff F, Giannini S. Alendronate improves screw fixation in osteoporotic bone. *J Bone Joint Surg Am* 2007;89(1):96-101.
- Aspenberg P. Osteonecrosis of the jaw: What do bisphosphonates do? *Expert Opin Drug Saf* 2006;5(6):743-745.
- Skoglund B, Holmertz J, Aspenberg P. Systemic and local ibandronate enhance screw fixation. *J Orthop Res* 2004;22(5):1108-1113.
- Nepal M, Li L, Bae TS, Kim BI, Soh Y. Evaluation of osseointegration around tibial implants in rats by ibandronate-treated nanotubular ti-32nb-5zr alloy. *Biomol Ther (Seoul)* 2014;22(6):563-569.
- Jacobsen C, Metzler P, Rossle M, Obwegeser J, Zemmann W, Gratz KW. Osteopathology induced by bisphosphonates and dental implants: Clinical observations. *Clin Oral Investig* 2013;17(1):167-175.
- Duarte PM, de Vasconcelos Gurgel BC, Sallum AW, Filho GR, Sallum EA, Nociti FH, Jr. Alendronate therapy may be effective in the prevention of bone loss around titanium implants inserted in estrogen-deficient rats. *J Periodontol* 2005;76(1):107-114.
- Tokugawa Y, Shiota T, Ohno K, Yamaguchi A. Effects of bisphosphonate on bone reaction

- after placement of titanium implants in tibiae of ovariectomized rats. *Int J Oral Maxillofac Implants* 2003;18(1):66-74.
19. Yoshinari M, Oda Y, Inoue T, Matsuzaka K, Shimono M. Bone response to calcium phosphate-coated and bisphosphonate-immobilized titanium implants. *Biomaterials* 2002;23(14):2879-2885.
 20. Astrand J, Aspenberg P. Reduction of instability-induced bone resorption using bisphosphonates: High doses are needed in rats. *Acta Orthop Scand* 2002;73(1):24-30.
 21. Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: Risk factors, recognition, prevention, and treatment. *J Oral Maxillofac Surg* 2005;63(11):1567-1575.
 22. Holzinger D, Seemann R, Matoni N, Ewers R, Millesi W, Wutzl A. Effect of dental implants on bisphosphonate-related osteonecrosis of the jaws. *J Oral Maxillofac Surg* 2014;72(10):1937 e1931-1938.
 23. Koka S, Babu NM, Norell A. Survival of dental implants in post-menopausal bisphosphonate users. *J Prosthodont Res* 2010;54(3):108-111.
 24. Al-Sabbagh M, Robinson FG, Romanos G, Thomas MV. Osteoporosis and bisphosphonate-related osteonecrosis in a dental school implant patient population. *Implant Dent* 2015;24(3):328-332.
 25. Yip JK, Borrell LN, Cho SC, Francisco H, Tarnow DP. Association between oral bisphosphonate use and dental implant failure among middle-aged women. *J Clin Periodontol* 2012;39(4):408-414.
 26. Lopez-Cedrun JL, Sanroman JF, Garcia A, Penarrocha M, Feijoo JF, Limeres J, Diz P. Oral bisphosphonate-related osteonecrosis of the jaws in dental implant patients: A case series. *Br J Oral Maxillofac Surg* 2013;51(8):874-879.
 27. Diniz-Freitas M, Lopez-Cedrun JL, Fernandez-Sanroman J, Garcia-Garcia A, Fernandez-Feijoo J, Diz-Dios P. Oral bisphosphonate-related osteonecrosis of the jaws: Clinical characteristics of a series of 20 cases in Spain. *Med Oral Patol Oral Cir Bucal* 2012;17(5):e751-758.
 28. Palaska PK, Cartosos V, Zavras AI. Bisphosphonates and time to osteonecrosis development. *Oncologist* 2009;14(11):1154-1166.
 29. Madrid C, Sanz M. What impact do systemically administered bisphosphonates have on oral implant therapy? A systematic review. *Clin Oral Implants Res* 2009;20 Suppl 4:87-95.
 30. Lerman MA, Xie W, Treister NS, Richardson PG, Weller EA, Woo SB. Conservative management of bisphosphonate-related osteonecrosis of the jaws: Staging and treatment outcomes. *Oral Oncol* 2013;49(9):977-983.
 31. Doh RM, Park HJ, Rhee Y, Kim HS, Huh J, Park W. Teriparatide therapy for bisphosphonate-related osteonecrosis of the jaw associated with dental implants. *Implant Dent* 2015;24(2):222-226.

Corresponding Author:**Sinem YENİYOL**

Department of Oral Implantology
 Faculty of Dentistry Istanbul University
 34093-Capa-Fatih-İstanbul/ TURKEY
 Phone: +90 212 532 32 18
 e-mail:yeniyols@istanbul.edu.tr