

What is the Risk of Developing Medication-Related Osteonecrosis in Patients With Extraction Sockets Left to Heal by Secondary Intention? A Retrospective Case Series Study

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Purpose: Tooth and root extractions represent trigger factors for medication-related osteonecrosis of the jaw (MRONJ). The best healing modality for postextraction sockets is still debated. The aim of the study was to estimate the incidence of MRONJ after extractions whose sockets were left to heal by secondary intention.

Methods: A retrospective case series study was performed at the Department of Odontostomatological and Maxillofacial Sciences, Sapienza University of Rome. Only patients who underwent nonsurgical extractions, healed by secondary intention, were included in the study. The following parameters were considered: age, sex, pathologies for which bisphosphonates or other drugs related to MRONJ were prescribed, any local or systemic risk factors, type of drug used, route of administration, number of extractions performed, and number of sessions required to complete the extraction program. The main outcome variable was the occurrence of MRONJ. Statistical analysis was performed with SPSS statistical software.

Results: Two hundred twenty-one patients were treated from 2007 to 2020 with 639 tooth/root extractions. All patients were treated under antibiotic prophylaxis and with anesthesia without vasoconstrictors. No cases of MRONJ occurred. The mean age of patients was 68.02 ± 11.17 . Most of the study sample was represented by women (201 = 90.95%) undergoing treatment for osteometabolic pathologies, most frequently postmenopausal osteoporosis. Alendronate was the most frequently prescribed drug, taken mainly orally. Most patients had local and/or systemic risk factors. Each patient had from 1 to 17 tooth/root extractions (mean = 2.87 ± 2.59) during 1 to 4 sessions (mean = 1.41 ± 0.64). Extractions mainly involved single-rooted teeth/roots, equally distributed between the maxilla and mandible.

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Conclusions: Secondary intention healing after nonsurgical tooth extraction does not seem to predispose to MRONJ. It can be advisable to perform extractions under antibiotic prophylaxis using anesthetics without vasoconstrictors and chlorhexidine mouth rinses in the 7 following days.

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Introduction

Medication-related necrosis of the jaw (MRONJ) is defined as an adverse reaction characterized by the progressive destruction and necrosis of the bone in subjects exposed to treatment with certain drugs for which an increased risk of such a disease is ascertained, in the absence of previous radiotherapies. Such drugs include bisphosphonates (BPs), monoclonal antibodies with antiresorptive activity (denosumab), antiangiogenic drugs, mTOR inhibitors and tyrosine kinase inhibitors. Since the biological properties of these drugs are numerous, as are the tissues on which they act, the international literature is developing a unique and multifactorial model that involves various factors in the etiopathogenesis of MRONJ: the osteoclastic inhibition induced by both BPs and denosumab, the presence of infectious-inflammatory foci in the bone tissue, the inhibition of angiogenesis induced by BPs and antiangiogenic drugs, the toxicity of BPs on fibroblasts and keratinocytes, hypovitaminosis D, certain systemic pathologies and traumatic factors on bone tissue.¹⁻³

Tooth and root extractions represent trigger factors for MRONJ due to their mechanical-traumatic action on bone tissue altered by drugs and possibly by infectious-inflammatory processes.⁴ In regard to this, the best healing modality of postextraction sockets is still debated. Some authors found that primary wound healing, with the elevation of a mucoperiosteal flap to cover all residual postextraction cavities, reduced the incidence of MRONJ in patients on previous or current therapy with at-risk drugs.⁵⁻⁸ Other authors, alternatively, suggested filling the sockets with platelet concentrate after surgery.⁹⁻¹¹ Since studies in the literature differ from one another in terms of proposed protocols, sample sizes and patient risk categories, it seems difficult to compare them.

The purposes of this study were to estimate the incidence of post-operative MRONJ in a setting of non-surgical extractions healed by secondary intention and to identify factors associated with the risk for developing ONJ.

The specific aim of the study was to evaluate the relationship between MRONJ and each study variable, including those related to patients, medications, local and systemic risk factors, and extracted teeth.

Materials and methods

STUDY DESIGN/SAMPLE

To address the research purpose, a retrospective case series study was specifically designed and implemented.

The study population was extracted from the database of the “Coordination of Research on Osteonecrosis of the Jaws” (CROMa)¹² which started its activity in January 2007 at the Department of Odontostomatological and Maxillofacial Sciences, Sapienza University of Rome, and which, at the time of the survey, had examined and/or treated approximately 1,530 patients who took medications at risk for ONJ. Only patients who underwent non-surgical extractions whose sockets were left to heal by secondary intention and whose wounds were examined in the following weeks until complete healing were included.

All patients who underwent treatments other than nonsurgical extraction of teeth and roots and whose sockets healed by primary intention were excluded from the study.

All study patients were treated at the Operative Units of Oral Surgery and Odontostomatology, from January 2007 to December 2019, according to the CROMa protocols⁹ which included antibiotic prophylaxis, anesthesia without vasoconstrictors and 0.2% chlorhexidine gluconate mouth rinses. No drug holiday was considered for any patients and all patients were followed clinically on a weekly basis until extraction sites healed completely.

The study was approved by the local Ethical Committee with protocol number 5479.

VARIABLES

The primary outcome of the study was the occurrence of osteonecrosis at the level of the extraction sites.

The descriptive analysis of the sample took the distribution of patients into consideration in relation to the following variables age, sex, pathology for which bisphosphonates or other drugs related to MRONJ were prescribed, any local or systemic risk factors, type of drug used, route of administration, number of extractions performed, number of sessions required to complete the extraction program, and type of CROMa protocol used for each risk category (Table 1).

Table 1. MANAGEMENT PROTOCOLS FOR MRONJ RISK PATIENTS

Protocol	Inclusion criteria	Management and Prophylaxis for Surgeries
Protocol n° 1	Patients willing to be treated with BPs and/or other drugs	Preoperative hygiene and calculus removal
Protocol n° 2	Patients treated with BPs and/or other drugs Administration: im/sc < 3 years. Risk factors: no	Preoperative hygiene and calculus removal Amoxicillin: 1gr every 12 hours, from 3 days before to 6 days after surgery Mouth rinsing with 0.2% ChG (7 days following surgery)
Protocol n° 3	Patients treated with BPs and/or other drugs Administration route: os, im/sc > 3 years Risk factors: no Patients treated with BPs and/or other drugs Administration route: os, im/sc < 3 years Risk factors: yes Patients treated with Bps and/or other drugs Administration route: iv	Preoperative hygiene and calculus removal Amoxicillin: 1gr + Metronidazole 500 mg every 12 hours from 3 days before to 6 days after surgery Mouth rinsing with 0.2% ChG (7 days following surgery)
Protocol n° 4	Patients with spontaneous ONJ	Preoperative hygiene and calculus removal Amoxicillin: 1gr every 8 hours + Metronidazole 500 mg every 12 hours from 3 days before to 6 days after surgery Mouth rinsing with 0.2% ChG (7 days following surgery)

Abbreviations: BPs, bisphosphonates; ChG, Chlorhexidine Gluconate; MRONJ, medical-related osteonecrosis of the jaws; ONJ, osteonecrosis of the jaws.

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DATA COLLECTION METHOD

All data, previously recorded on a shared Access file, were transferred to an Excel file, from which a specific worksheet was filtered exclusively for patients included in the sample. Clinical data relating to the extractions, not recorded in the clinical diary section of the Access file, were analyzed individually for each patient on a data transfer paper sheet, to be then transferred directly to the Excel file.

DATA ANALYSIS

Statistical analysis was performed with the Excel program and with the SPSS statistical software (Statistical Package for the Social Sciences, version 20.0, IBM Corporation, Armonk, NY, USA).

Results

All study sample data are reported in Table 2. Two hundred twenty-one patients were treated from 2007 to 2020 with 639 tooth/root extractions. No cases of MRONJ occurred. The mean age of patients was 68.02 ± 11.17 . Most of the study sample was represented by women (201 = 90.95%) undergoing

treatment for osteometabolic pathologies, most frequently postmenopausal osteoporosis. Alendronate was the most prescribed drug, taken mainly orally. Among other drugs, only bevacizumab and denosumab were noted. Most patients had local and/or systemic risk factors and therefore belonged to a medium-high risk category.

Each patient underwent from 1 to 17 tooth/root extractions (mean = 2.87 ± 2.59) during 1 to 4 sessions (mean = 1.41 ± 0.64). Extractions mainly involved single-rooted teeth/roots, equally distributed between the maxilla and the mandible.

As many as 206 patients were treated with CROMa Protocol n. 3 (93.21%), 13 patients with Protocol n. 2, and 2 with Protocol n. 4.

Complete socket closure took place within 2 weeks (1 to 3 weeks) on average, and no patient had problems or late complications.

Discussion

The study purpose was to retrospectively estimate the incidence of MRONJ after nonsurgical extractions with sockets left to heal by secondary intention, in relation to all sample variables, including those

Table 2. OVERALL DATA OF THE STUDY SAMPLE

VARIABLES		N (%)
Gender	Male	20 (9.05%)
	Female	201 (90.95%)
Route of administration	Oral	159 (71.94%)
	Intramuscular/ subcutaneous	17 (7.7%)
	Intravenous	28 (12.66%)
	Association	17 (7.7%)
Timing	Current	130 (58.82%)
	Past	91 (41.18%)
	1 month before	26 (11.75%)
	3 months before	20 (9.05%)
	6 months before	13 (5.87%)
	1 year before	8 (3.66%)
	> 1 year before	24 (10.85%)
Underlying diseases	Metabolic diseases	199 (90.04%)
	Post-menopausal osteoporosis	163 (73.75%)
	Secondary/ induced osteoporosis	8 (3.62 %)
	Arthritis/arthritis	8 (3.62 %)
	Other	20 (9.05%)
	Oncologic disease	22 (9.95%)
	Multiple myeloma	2 (0.9%)
	Pulmonary/ prostate/ mammary cancer, bone metastasis	16 (7.24%)
	Other	4 (1.81%)
Local risk factors	Periodontal disease	50 (22.62%)
	Odontogenic infections	52 (23.53%)
	Periodontal disease and odontogenic infections	43 (19.46%)
	Other	71 (32.17%)
Systemic risk factors	Diabetes	11 (4.98%)
	Corticosteroids/ chemotherapy	18 (8.14%)
	Other (anemia, hyperlipidemia, hypothyroidism, smoking, coagulopathy)	182 (82.35%)
Drug	Alendronate	105 (47.51%)
	Risedronate sodium	35 (15.84%)
	Zoledronic Acid	13 (5.88%)

(Continued)

Table 2. Cont'd

VARIABLES		N (%)
Extractions (n =716)	Denosumab	12 (5.43%)
	Other (association, other principles)	54 (24.43%)
	Bevacizumab	2 (0.9%)
	Site	
	Maxilla	318 (47.76%)
	Mandible	321 (52.24%)
	Type	
Treatment protocol use	Single-rooted	258 (40.37%)
	Multi-rooted	381 (59.63 %)
	Protocol n° 2	13 (5.88%)
	Protocol n° 3	206 (93.21%)
	Protocol n° 4	2 (0.90%)

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related to patients, medications, local and systemic risk factors, and extracted teeth.

No cases of MRONJ were found after 639 extractions performed on 221 patients under antibiotic prophylaxis, without the use vasoconstrictors in the anesthetics, with sockets left to heal by secondary intention, and 0.2% chlorhexidine gluconate mouth rinses.

Few studies have been published with a sample size equal to or greater than the present one,^{8,13} whereas many others had smaller samples.^{5-7,9,10,14}

The patient sample corresponds to 14.8% of the total number of at-risk patients in the entire database since 54.1% of them did not undergo surgical procedures and the remaining patients underwent surgical extractions, extractions with primary intention healing and other kinds of surgeries.

The study sample mainly involved (93.21%) patients who took BPs and/or other drugs for over 3 years (orally, subcutaneously, or intramuscularly), without risk factors, or for less than 3 years, with risk factors or who took those drugs intravenously (Table 1).

The present sample consisted mainly of women (90.95%), mostly suffering from postmenopausal osteoporosis (73.75%) and with a mean age of 68.02 ± 11.17 . These factors support those of many previous all-inclusive^{13,15} or semi-inclusive¹⁴ studies, which reflect the normal distribution of diseases for which the treatment with drugs related to ONJ is commonly required. However, in more selective samples, both for the underlying disease or the drug used, the distribution of patient gender is strongly influenced by the diseases^{8,16} and by the drugs.⁷

Current data is not sufficient to correlate patient age and gender with the prevalence of MRONJ since osteoporosis is typically postmenopausal and because some cancers occur only in a specific gender, affecting organs characteristic of each gender. In some studies, age has been correlated with the incidence of MRONJ,¹⁷⁻¹⁹ but it is still necessary to consider, generally in the more advanced age groups, the distribution of certain categories of patients such as women with postmenopausal osteoporosis and metastatic cancer patients.²⁰

Comparative analysis cannot be performed with other published studies since inclusion criteria differ from 1 study to another and from the present study. Actually, to reduce the risk of MRONJ, during the years many protocols have been proposed for tooth/root extractions in which antibiotic prophylaxis, anesthesia with or without vasoconstrictors, and complete coverage of the surgical area with a muco-periosteal flap have been variously combined.

The effectiveness of antibiotic prophylaxis in reducing the risk of MRONJ has been shown.²¹ Despite protocols proposed in clinical studies having been quite different from each other,^{8,10,21,22} amoxicillin (with or without clavulanic acid), associated or not with other drugs such as metronidazole and sulbactam, has been the first-choice drug in most studies, including the present one, and was more frequently administered orally.

In the present sample, infection control also involved careful preoperative professional oral hygiene and postextraction wound disinfection by topical application of chlorhexidine gluconate in the form of mouthwash or spray for 7 days after each procedure. Chlorhexidine gluconate was used postoperatively in almost all published studies for its antibacterial properties. However, since it was found to inhibit fibroblast, myoblast, and osteoblast proliferation through a block of collagen and noncollagen intracellular proteins, it should be used carefully.^{23,24}

The use of anesthetics with vasoconstrictors during surgery in patients at risk for MRONJ has not specifically been dealt with in the past. In some studies, vasoconstrictors were not mentioned at all^{5,7,14,22,25} thus suggesting their circumstantial use. In others they were used for all patients,⁸⁻¹⁰ whereas a more recent review recommended avoiding vasoconstrictors during extractions.¹ Adrenaline is commonly used to reduce intraoperative bleeding and to prolong the anesthetic effect, but it was found to have side effects on bone and soft tissues which may predispose to MRONJ. Actually, adrenaline was found to cause a strong vessel constriction of periodontal ligament and mucosa,²⁶ and bone resorption, indirectly through the production of prostaglandin E, and directly through the overexpression of mRNA encoding the

ODF/RANKL factor in osteoblastic cells, with consequent osteoclast activation,²⁷ and also by stimulating osteoclast maturation.²⁸ Since bone metabolism is already compromised in patients on bisphosphonate and antiresorptive treatments, in the light of all these published data, from its beginning the CROMa project has allowed extractions without the use of vasoconstrictors.

The complete coverage of residual extraction sockets with a soft tissue flap has been proposed in MRONJ prevention by several authors during the years in order to protect exposed bone from superinfection during healing and to maintain the clot.^{9,10} However, flap creation involves a reduction of the blood supply to the underlying bone tissue due to the incision of soft tissue vessels and detachment of the periosteal blood supply from the underlying bone.²⁹ Since all processes involved in postextraction socket healing do not depend only on the functional activity of the osteoblasts, but also on the blood perfusion, the maintenance of the overlying soft tissue vascularization appears essential.³⁰ Moreover, an additional risk factor may also be the surgical trauma resulting from the routine regularization of the alveolar bone edges by means of rotary or manual instruments, which is proposed as a prophylactic method aimed at eliminating the high-turnover bone component in which the osteonecrosis process possibly begins after extraction trauma.⁵ For all these reasons, from its beginning the CROMa project¹² has provided for secondary intention healing of all nonsurgical extractions to be performed. Only when particularly sharp bone edges could represent a risk factor for difficult healing, their regularization with a rasp, without flap incision, but only with a gentle soft tissue detachment and subsequent suture to stabilize the detached soft tissue to the underlying bone plane, were carried out. To support these reasons, no difference in the incidence of MRONJ between first and second intention postextraction healing was found in several studies.^{8,13,25}

The co-presence of local and/or systemic risk factors represents an important trigger for MRONJ, and most patients included in literature studies have at least 1 local or systemic risk factor. In the 2019 study by Hasegawa et al,²⁵ 11% of patients had diabetes, 61% had undergone or were undergoing chemotherapy and 41% had a dental or periodontal inflammatory condition. In the same study,²⁵ 9.3% of patients had rheumatoid arthritis, 9.4% had diabetes, and 27.3% had other unspecified systemic problems. In the 2013 study by Mozzati et al,⁸ 15% of patients had diabetes and 34.5% were smokers, but there is no available data on local risk conditions.

In the present sample all local and systemic factors were carefully investigated and recorded. Only 14%

of patients did not have risk factors and most patients had local risk factors including periodontal disease, odontogenic infections, and others such as poor oral hygiene, tori and exostoses, incongruous prostheses, and pronounced mylohyoid lines (Table 2). This difference can be explained by the fact that studies did not likely include the full range of predisposing conditions for MRONJ.

Finally, it should be mentioned that although healing always occurred, there was a slight delay in the re-epithelialization process which sometimes took as long as 3 weeks. Actually, the toxicity on soft tissues and the interference on wound healing of zoledronic acid, pamidronate, and alendronate have already been demonstrated in vitro studies³¹⁻³³ and have also been found to be statistically significant and not related to the route of drug administration in the 2013 human prospective study by Migliorati et al.³⁴ However, a complete re-epithelialization of the alveolus does not indicate complete healing of the postextraction site and it has not been related to the likelihood of osteonecrosis, but it can only suggest that bone healing is occurring regularly and is protected from the risk of superinfection. This is the main reason for which some authors¹ have suggested a period of drug therapy discontinuation, the so-called drug holiday, before oral surgical procedures.

The main strength of the present study is that wounds of all the 639 extracted teeth normally healed by second intention healing and no cases of MRONJ occurred.

Nevertheless, some limitations are also present. The first is that the study is retrospective in nature. Secondly, the sample size was not so wide as a so rare complication would have needed. Lastly, the percentage of oncologic patients, which are worldwide considered at highest risk for MRONJ, was relatively low (9.95%).

In conclusion, nonsurgical tooth extraction with socket left to heal by secondary intention under antibiotic prophylaxis, without the addition of vasoconstrictors in local anesthetics, and 0.2% chlorhexidine gluconate mouth rinses is a low-risk procedure for MRONJ.

References

- Di Fede O, Panzarella V, Mauceri R: The dental management of patients at risk of medication-related osteonecrosis of the jaw: new paradigm of primary prevention. *BioMed Res Int* 16:2684924, 2018
- Campisi G, Mauceri R, Bertoldo F: Medication-Related Osteonecrosis of Jaws (MRONJ) prevention and diagnosis: Italian consensus update 2020. *Int J Environ Res Public Health* 17(16):5998, 2020
- Terenzi V, Della Monaca M, Raponi I: When a single letter leads to substantial differences. *Oral Oncol* 110:104817, 2020
- Lombard T, Neirinckx V, Rogister B: Medication-related osteonecrosis of the jaw: new insights into molecular mechanisms and cellular therapeutic approaches. *Stem Cells Int* 16:8768162, 2016
- Ferlito S, Puzzo S, Liardo C: Preventive protocol for tooth extractions in patients treated with zoledronate: a case series. *J Oral Maxillofac Surg* 69(6):e1-e4, 2010
- Lodi G, Sardella A, Salis A: Tooth extraction in patients taking intravenous bisphosphonates: a preventive protocol and case series. *J Oral Maxillofac Surg* 68(1):107-110, 2010
- Matsumoto A, Sasaki M, Schmelzeisen S: Primary wound closure after tooth extraction for prevention of medication-related osteonecrosis of the jaw in patients under denosumab. *Clin Oral Invest* 21(1):127-134, 2017
- Mozzati M, Arata V, Gallesio G: Tooth extraction in osteoporotic patients taking oral bisphosphonates. *Osteopor Int* 24(5):1707-1712, 2013
- Scoletta M, Arduino P, Pol R: Initial experience on the outcome of teeth extractions in intravenous bisphosphonate-treated patients: a cautionary report. *J Oral Maxillofac Surg* 69(2):456-462, 2011
- Scoletta M, Arata V, Arduino P: Tooth extractions in intravenous bisphosphonate-treated patients: a refined protocol. *J Oral Maxillofac Surg* 71(6):994-999, 2013
- Tenore G, Zimbalatti A, Rocchetti F: Management of Medication-Related Osteonecrosis of the Jaw (MRONJ) using Leukocyte- and Platelet-Rich Fibrin (L-PRF) and photobiomodulation: a retrospective study. *J Clin Med* 9(11):3505, 2020
- Capocci M, Romeo U, Cocco F: The "CROMa" Project: a care pathway for clinical management of patients with bisphosphonate exposure. *Int J Dent*, 2014. 719478
- Gaudin E, Seidel L, Bacevic M: Occurrence and risk indicators of medication-related osteonecrosis of the jaw after dental extraction: a systematic review and meta-analysis. *J Clin Periodontol* 42(10):922-932, 2015
- Bodem J, Kargus S, Eckstein S: Incidence of bisphosphonate-related osteonecrosis of the jaw in high-risk patients undergoing surgical tooth extraction. *J Craniomaxillofac Surg* 43(4):510-514, 2015
- Kato GF, Lopes RN, Jaguar GC: Evaluation of socket healing in patients undergoing bisphosphonate therapy: experience of a single Institution. *Med Oral Patol Oral Cir Bucal* 1(4):e650-e656, 2013
- Fusco V, Porta C, Saia G: Osteonecrosis of the jaw in patients with metastatic renal cell cancer treated with bisphosphonates and targeted agents: results of an Italian multicenter study and review of the literature. *Clin Genitourinary Cancer* 13(4):287-294, 2013
- Şahin O, Odabaşı O, Aliyev T: Risk factors of medication-related osteonecrosis of the jaw: a retrospective study in a Turkish subpopulation. *J Korean Assoc Oral Maxillofac Surg* 45(2):108-115, 2019
- Hoff AO, Toth BB, Altundag K: Frequency and risk factors associated with osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates. *J Bone Miner Res* 23(6):826-836, 2008
- Auzina D, Slaidina A, Sevastjanova M: A population-based study of multiple myeloma patients with medication-related osteonecrosis of the jaw. *Stomatologija* 21(1):13-17, 2019
- Kuroshima S, Sasaki M, Sawase T: Medication-related osteonecrosis of the jaw: a literature review. *J Oral Biosci* 61(2):99-104, 2019
- Montefusco V, Gay F, Spina F: Antibiotic prophylaxis before dental procedures may reduce the incidence of osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates. *Leuk Lymphoma* 49(11):2156-2162, 2008
- Saia G, Blandamura S, Bettini G: Occurrence of bisphosphonate-related osteonecrosis of the jaw after surgical tooth extraction. *J Oral Maxillofac Surg* 68(4):797-804, 2010
- Liu JX, Werner J, Kirsch T: Cytotoxicity evaluation of chlorhexidine gluconate on human fibroblasts, myoblasts, and osteoblasts. *J Bone Jt Infect* 10(4):165-172, 2018

24. Mariotti AJ, Rumpf DA: Chlorhexidine-induced changes to human gingival fibroblast collagen and non-collagen protein production. *J Periodontol* 70(12):1443-1448, 1999
25. Hasegawa T, Hayashida S, Kond E: Medication-related osteonecrosis of the jaw after tooth extraction in cancer patients: a multicenter retrospective study. *Osteoporos Int* 30(1):231-239, 2019
26. Tanaka K, Kudo K, Ambe K: A histological study of vasoconstriction by local anesthetics in mandible. *Anesth Prog Winter* 65(4):244-248, 2018
27. Takeuchi T, Tsuboi T, Arai M: Adrenergic stimulation of osteoclastogenesis mediated by expression of osteoclast differentiation factor in MC3T3-E1 osteoblast-like cells. *Biochem Pharmacol* 61(5):579-586, 2001
28. Arai M, Nagasawa T, Koshiharab Y: Effects of h-adrenergic agonists on bone-resorbing activity in human osteoclast-like cells. *Biochim Biophys Acta* 1640(2-3):137-142, 2003
29. Nobuto T, Suwa F, Kono T: Microvascular response in the periosteum following mucoperiosteal flap surgery in dogs: angiogenesis and bone resorption and formation. *J Periodontol* 76(8):1346-1353, 2015
30. Nobuto T, Suwa F, Kono T: Microvascular response in the periosteum following mucoperiosteal after flap surgery in dogs: 3-dimensional observation of an angiogenic process. *J Periodontol* 76(8):1339-1345, 2005
31. Rawosa MJ, Ning J, Liu Y: Biphosphonate effects on the behaviour of oral epithelial cells and oral fibroblasts. *Arch Oral Biol* 56(5):491-498, 2011
32. Saito T, Izumi K, Shiomi A: Zoledronic acid impairs re-epithelization through down-regulation of integrin avb6 and transforming growth factor beta signalling in a 3-dimensional in vitro wound healing model. *Int J Oral Maxillofac Surg* 43(3):373-380, 2014
33. Landesberg R, Cozin M, Cremeres S: Inhibition of oral mucosal cell wound healing by biphosphonates. *J Oral Maxillofac Surg* 66(5):839-847, 2008
34. Migliorati CA, Saunders D, Conlon MS: Assessing the association between biphosphonate exposure and delayed mucosal healing after tooth extraction. *J Am Dent Assoc* 144(4):406-414, 2013