Etiologic Role of Bacterial Microorganisms in Medication Related Osteonecrosis of the Jaws: A Systematic Review

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ABSTRACT

Objective: Medication-related osteonecrosis of the jaw (MRONJ) is the condition of bone exposure which lasts more than 8 weeks which can be associated with clinical symptoms like pain, erythema, and infection. In addition to physiologic changes of hard and soft tissue cells, some different etiologic factors have been suggested for MRONJ; although, with no certain etiologic factor yet. Our aim is to determine the microbial etiologic roles in MRONJ through a systematic review of the etiologic roles of bacterial microorganisms in MRONJ conditions. Data Sources: An electronic search was done on January 15, 2018, at the databases of Cochrane Library, Google Scholar, PubMed (NCBI) and Scopus. Study Selection: Only in-vitro studies, clinical trials, and prospective and retrospective case reports were included in this review. Data Extraction: A meta-analysis could not be accomplished due to the lack of quantitative evidence and broad heterogeneity of study types, bacterial strains, treatment options and outcomes of these studies .Data Synthesis: A qualitative report of studies' information has been established in 2 tables. Conclusion: The most frequent bacterial species indexed in our literature were Actinomyces genus, Parvimonas micra, and Streptococcus anginosus. Yet, there is no definite causal relationship between these microorganisms and osteonecrosis of the jaw (ONJ). Also, there are controversies about the treatment options, either to use the antibiotic therapy in association with antimicrobial agents (mouthrinses etc.) besides the standard surgical procedure or not. There needs to be more quantitative results reported in future studies in order to achieve more certain notions about the etiologic role of bacterial microorganisms in MRONJ patients.

Key Words: *Bacterial, Microorganisms, Osteonecrosis.*

eIJPPR 2019; 9(3):64-72

HOW TO CITE THIS ARTICLE: Erfan Shamsoddin, Fatemeh Mahboobi, Kamran Kargar, Fatemeh Latifi (2019). "Etiologic Role of Bacterial Microorganisms in Medication Related Osteonecrosis of the Jaws: A Systematic Review", International Journal of Pharmaceutical and Phytopharmacological Research, 9 (3), pp.64-72.

INTRODUCTION

This systematic review investigated the assumed etiologic role of bacterial species in Medication-related osteonecrosis of the jaw (MRONJ). The term, MRONJ, describes the condition in which an oral or maxillofacial bone region is exposed and lasts for more than 8 weeks without any radiation therapy or malignancy backgrounds [1, 2]. This condition can be resulted from the usage of several drug families; namely bisphosphonates, RANKL inhibitors, antiangiogenic agents, m-TOR inhibitors [3-6]. If the condition is made by using the bisphosphonates, it is called bisphosphonate-related osteonecrosis of the jaw (BRONJ) which was a more frequent term in the 1990s, because of prevalent prescription of bisphosphonates and the term MRONJ, has taken its place for nowadays. Bisphosphonates are the main bone antiresorptive drugs which can induce BRONJ in certain conditions after a period of antiresorptive or antiangiogenic drug use, like Bevacizumab and Sunitinib. Medication-related osteonecrosis of the jaw was primarily discussed with

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest .
Received: 07 January 2019; **Revised:** 02 June 2019; **Accepted:** 09 June 2019

reference to BRONJ and nitrogen-containing bisphosphonates [7], and then has become more important as the prevalence of osteoporosis has been increasing in the recent decade [8, 9]. Several pathophysiologic mechanisms have been proposed for MRONJ, including bone turnover reduction, infection consequences, decreased blood flow, wound healing corruption, immune response disruptions and direct drug toxicity to tissues [7, 10-13]. Also, some other etiologic factors have been proposed such as ill-fitting denture use, extraction site, periapical lesion, and traumatic injuries to the bone jaws [14-16]. Yet the certain mechanism of MRONJ is not defined and there is not sufficient evidence to determine the certain etiologic factor of MRONJ in the literature. Several articles indicate a relationship between bacterial infections and BRONJ onset and development. [10, 17-20], whilst, there is no precise piece of evidence defining specific microorganism species as the etiologic factor of the MRONJ. Also, the treatment strategies for MRONJ are not the same protocol between authors, because of different MRONJ stages, different bacterial strains and different immune response conditions as a result of systemic diseases in patients. Tae-Hwan Kim et al. evaluated the predisposing factors in participants with BRONJ and proposed the infection as a risk factor [7]. Likewise, H. Katsarelis et al. suggested the microbial infection as a risk factor and emphasized its importance as an etiologic factor in the development of MRONJ [21] and many studies declared that the filamentous, anaerobe *Actinomyces* is the main bacteria associated with the necrotic lesions in BRONJ lesions [20, 22, 23]. Thus, it is necessary to investigate the variation of microorganisms which are involved in this clinical condition and determine the most frequent species with their reported backgrounds as possible inducing factors of MRONJ. The aim of this study is to systematically review the role of bacterial infections as risk factors or etiologic factors in MRONJ onset and development.

MATERIALS AND METHODS

Electronic databases of Google scholar, Cochrane's library, PubMed (NCBI), and Scopus were searched independently by authors with the keywords of "bisphosphonate-related osteonecrosis of the jaw", "medication-related osteonecrosis of the jaw", "microorganism", and "etiologic factor". The search query was modified with the related keywords to achieve the best results in different occasions. We did not include the studies which reflected information before the year 2000; also, non-English language studies in the databases were not covered. Only clinical trials, prospective and retrospective case reports, and in vitro researches were included in our study and animal studies were excluded from the data. In the next step, 44 studies were selected based on title skimming and abstract screening and any conflicts between authors were resolved by a consensus. From these, we selected 26 studies according to abstract reading and 10 studies were included in our study. Any conflicts about the included studies were discussed and resolved in a consensus between the authors. Then, we manually searched the references of the included studies and retrieved two related studies which were included for data extraction. Finally, based on a consensus among authors, 12 studies were chosen for data extraction. Due to the small sample size of our study, we had no exclusion criteria among the qualified studies in the quality assessment step and we qualitatively evaluated full-texts of these studies in line with the focus question of this systematic review.

Risk of bias and quality of studies

Risk of bias was determined as "considerable" or "non-considerable" by qualitative evaluation of the selected studies. Authors independently evaluated the risk of bias and the quality of these studies using "The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews", "NIH's National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies", and "NTP's Extending a Risk-of-Bias Approach to Address In Vitro Studies" checklists for Case reports, Cohort case series, and in-vitro studies respectively.

Due to the heterogeneity of the data, the studies did not come to a unique conclusion. "Bacterial load" was the effect size in this study which could not be calculated because of inadequate data. We only reported the bacterial species name(s) as a representative for the main bacterial species which were seen in the studies. Also, the prevalence of reported bacterial species in all of the clinical studies of our data was calculated by measuring the patients who had been reported with the certain bacterial species infection.

Software

Flow diagram of retrieving and selecting studies was created by Review Manager application (version 5.3) of Cochrane’s library. all of the tables were created by Microsoft Word 2016 software and the bacterial frequencies was measured by excel 2016 and demonstrated as a pie-chart in Microsoft power point 2016.

RESULTS

Out of 212 articles, 44 studies were chosen for the next steps. finally, 12 articles had the criteria for entering the study and were investigated. Several studies with

qualified validity have been carried out in this field; the information of these studies was summarized in four categories including author's name, sample, sample characteristic and research type (Table 1).

Qualitative evaluation of studies was performed by providing information about microorganisms, intervention or treatment and their outcome (Table 2).

The search results and selection stages of studies are shown in figure 1 and the most prevalent bacterial species in MRONJ patients of 370 included cases in our databases were reported in figure 2. Only definite and precisely reported results were included in this measurement and the repetitive patients who were reported with different bacterial strains were omitted. Also, patients in different groups of each study were only counted once due to the possible disruptions in our results' validity.

The following antibiotic therapy regimens were successful in association with surgical removal of necrotic bone:

1. Amoxicillin (2 × 1 g/24 hours) and clavulanic acid (2 × 500 mg/24 hours) for 4 weeks before surgery
2. Clindamycin (3 × 300 mg/24 hours) for 4 weeks before surgery
3. Tetracycline, ciprofloxacin, amoxicillin (discounted 1 week prior to surgery)
4. doxycycline for 2 weeks (before the surgery)
5. Penicillin V potassium (4 × 500 mg/24 hours) for 7 days
6. Clindamycin and metronidazole
7. Oral spiramycin

The antibiotic regimens and treatment options which were applied in the clinical cases can be seen more specifically in table 2. Some qualitative data were extracted from the included studies which are represented in table 1 and table 2. Table 1 is ordered based on the author names alphabetically and table 2 is ordered based on the microorganism names for easier comparisons and data screening.

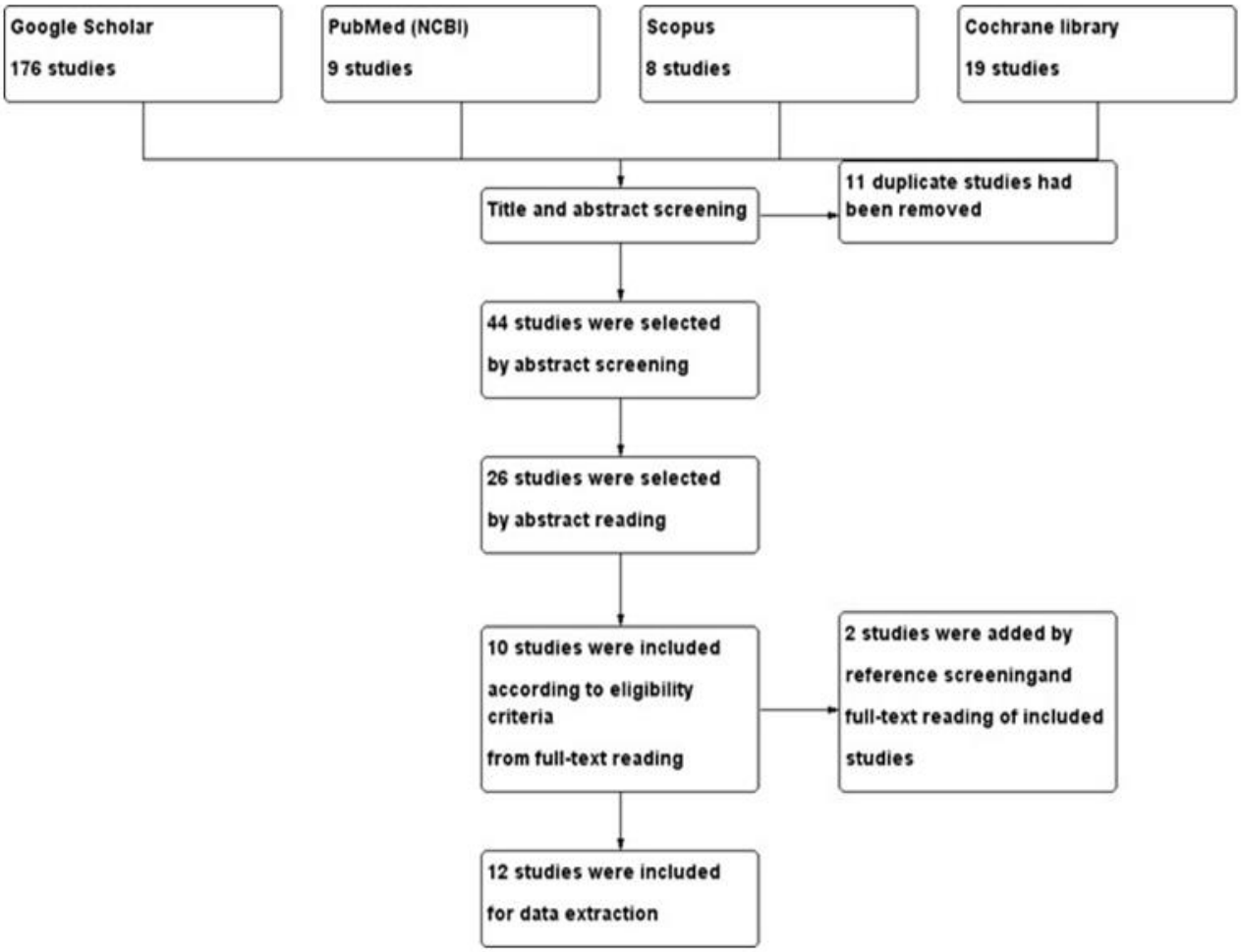

Fig. 1. Study Selection chart.

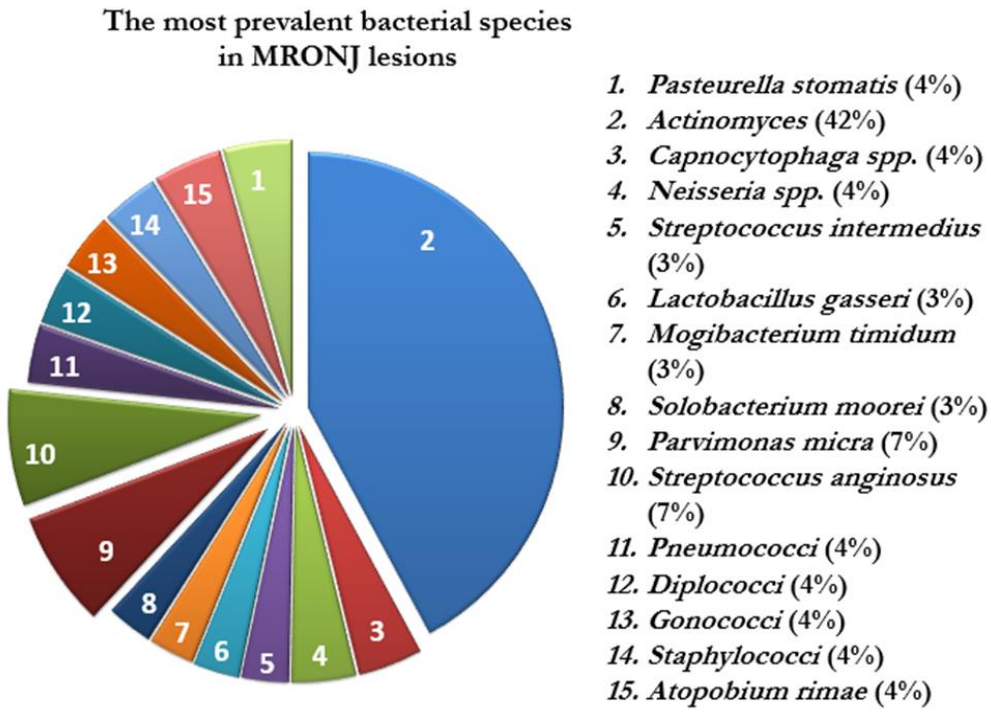

Fig. 2. Bacterial species frequencies.

Table 1. Study characteristics

Authors, date	sample size, gender, age	Sample characteristics	Research design
C. V. Real et al. 2016	28 patients 16 males, 12 females Mean age of 71.96 years	Inclusion criteria: patients with osteonecrosis of the jaws who had undergone oral or intravenous bisphosphonate treatments, as well as those subject to head and neck radiotherapy over the past 8 years.	Retrospective case series
G. Russmueller et al. 2016	111 patients	All patients were histologically identified with MRONJ. Cases with a previous history of radiotherapy were excluded from this study.	Retrospective case series
G.Gaasparini et al. 2010	25 patients 16 females 9 males, mean age of 70.5,	13 patients with osteoporosis, 12 patients with malignancies; Inclusion criteria: pain, sensibility deficits, purulent secretion and bone exposure	Retrospective case series
J. K. Brooks et al. 2015	A 60 years old female patient	Inclusion criteria: patients were with osteopenia, upper respiratory and dermatologic disorders	Case report
M. R. Sacnchez et al. 2015	A 54 years old male patient	The patient had a history of multiple myeloma and treated with zoledronic acid during 3 years.	Case report
Marcin Kos et al. 2013	25 Staphylococcus and 25 *Pseudomonas aeroginosa* strains were cultured	Bacterial culture	Experimental in-vitro study
Marcin Kos et al. 2015	*S. mutans*, *S. aureus* and *P. aeroginosa*	Bacterial culture	Experimental in-vitro study case series

Table 1. Continued.

Authors, date	sample size, gender, age	Sample characteristics	Research design
R. C. S. Póvoa et al. 2016	A 58 years old male patient	Inclusion criteria: without signs and symptoms of inflammation, infection, pain, purulent discharge, erythema and spontaneous bleeding	Case report
S. Panya et al. 2017	95 patients man age of 69.85 ± 8.71	Patients missing clinical, radiographic or follow-up data were excluded or if they had a history of head and neck radiotherapy. only strongly positive culture results in patients (+2) was considered as positive culture	Retrospective case series
S. Pushalkar et al. 2014	30 patients 73% female, 27% male mean age of 62.2 ± 15.4 (years)	10 patients with periodontal disease and without a history of blood pressure therapy; 5 patients with periodontal disease having history of blood pressure therapy but without osteonecrosis of the jaw; 15 patients with BRONJ.	Retrospective case series
T. H. Kim et al. 2016	54 BRONJ patients 50 females 4 males mean age of 73.9 ± 5.27 (years)	50 patients with osteoporosis 4 patients with cancer inclusion criteria: surgical therapy with diabetes mellitus, medication of steroids, malignancies, chemotherapy; exclusion criteria: head and neck radiation therapy or osteopetrosis or florid osseous dysplasia after biopsy	Retrospective case series

Table 1. Continued.

Authors, date	sample size, gender, age	Sample characteristics	Research design
X Ji et al. 2011	20 patients 16 females and 4 males, the age range was 49–84 years mean of 67.05 years	Number of patients with breast cancer, renal/rectal cancer or multiple myeloma on intravenous BPs equals to 14 number of patients with osteoporosis on oral BPs equals to 6	Retrospective case series

Table 2. Qualitative evaluation of the studies.

Authors, date	Microorganisms	treatment summary	treatment failure or success
T. H. Kim et al. 2016	*Actinomyces*	surgical therapy	patients with diabetes or who were prescribed to use steroids and Parenteral medication of BP showed poorer results after surgery
S. Panya et al. 2017	*Actinomyces*	not mentioned	successful
C. V. Real et al. 2016	*Actinomyces* spp., *Capnocytophaga* sp., *Neisseria* sp., and other aerobes and anaerobes.	Variable antibiotics were used , although the combination of amoxicillin with clavulanic acid gave the best results	not always successful
G. Russmueller et al. 2016	*Actinomyces* spp.	conservative pre-treatment followed by surgical removal of necrotic bone and soft tissue closure. all patients received systemic antibiotic treatment with amoxicillin (2 × 1 g/24 hours) /clavulanic acid (2 × 500 mg/24 hours)	successful

		or clindamycin (3 × 300 mg/24 hours) for approximately 4 weeks between admittance and surgery.	

Table 2. Continued.

Authors, date	Microorganisms	treatment summary	treatment failure or success
X Ji et al. 2011	Bacterial species, *Streptococcus intermedius*, *Lactobacillus gasseri*, *Mogibacterium timidum*, and *Solobacterium moorei*, were higher in antibiotic group; patients without antibiotics had greater amounts of *P. micra* and *Streptococcus anginosus*	Antibiotic therapy with tetracycline, ciprofloxacin, amoxicillin (discounted 1 week prior to treatment) and doxycycline for 2 weeks (based on the BRONJ stages of patients)	Not always successful (based on the BRONJ stage)
J. K. Brooks et al. 2015	Not mentioned	The patient was given discharge prescriptions of 500 mg penicillin V potassium, four times daily, for 7 days	Successful
M. R. Sacnchez et al. 2015	Not mentioned	Antibiotic therapy with clindamycin and metronidazole	Successful
M. Kos et al. 2013	*P. aeroginosa* and *S. aureus*	Not applicable	Not applicable
S. Pushalkar et al. 2014	*P. micra*, *S. anginosus*, *A. rimae*, *P. stomatis* and *Eubacterium* dominated the BRONJ lesions; *P. denticola* and *S. sputigena* were exclusively found in BRONJ cohort.	Not mentioned	Not mentioned
M. Kos et al. 2015	*S. mutans*, *S. aureus* and *P. aeroginosa*	Not applicable	Not applicable
G. Gaspariniet al. 2010	Streptococci, Pneumococci, Diplococci, Gonococci and Staphylococci	Antibiotic therapy with oral spiramycin	Successful
R. C. S. Póvoa et al. 2016	Some foci of bacterial colonies were revealed in the histologic slides.	Conservative surgical therapy, antibiotic therapy (500 mg amoxicillin every 8 hours for 7 days), discontinuation of denosumab use	Successful

The risk of bias and study quality were determined before the final step of study selection using three different checklists according to study designs. Our quality assessment results are shown in supplementary data. Measurement of effect size and heterogeneity assessment was not accomplished because of insufficient evidence, so no meta-analysis could be done in this systematic review.

DISCUSSION

Bacterial species have been considered to have a possible etiologic role in MRONJ lesions through the last decade. Nowadays, BRONJ and MRONJ are among the growing medical issues, specifically in patients with cancer or osteoporosis diagnosis. To define the exact bacterial species responsible in the induction of ONJ, we need to determine the most prevalent bacterial species seen in previous clinical cases in order to narrow the spectrum for further research. We evaluated two in-vitro studies by M. Kos et al. about bacterial adhesion and biofilm formation

on the bone hydroxyapatite. The species *S. aureus*, *S. mutans*, and *P. aeruginosa* showed significantly higher colonization on hydroxyapatite in the presence of bisphosphonates versus control and adherence was higher with pamidronate in comparison to other bisphosphonates. Increased bacterial adhesion and biofilm formation can develop osteomyelitis and local infection to exacerbate the ONJ [24, 25]. This mechanism can be considered as a critical etiologic role for these bacterial species.

Three different stages of BRONJ have been previously recommended:

1. Stage 1 represents Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection;
2. Stage 2 represents Exposed/necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage;
3. Stage 3 represents Exposed/necrotic bone in patients with pain, infection, and one or more of the following: pathologic fracture, extra-oral fistula, or osteolysis extending to the inferior border [26].

There were 7 retrospective case series which have focused on antibiotic therapy, oral microbiota, etiologic factors of BRONJ and MRONJ, *Actinomyces* and inflammation. G. Gasparini et al. in 2010, suggested anti-angiogenic properties of BPs and *Streptococcus mutans* adhesion as the etiologic factors of the BRONJ of the jaw. They had a problem with resistant lines of bacteria due to the wide use of Amoxicillin and clavulanic acid in dentistry, so they prescribed patients with spiramycin. All patients were completely treated with no purulent secretions, anesthesia, and paresthesia after 2nd cycle of spiramycin use [1]. The team of S. Pushalkar et al. have done two retrospective case series with different participants. Their first study was done on 20 BRONJ subjects, divided into two groups, antibiotic cohort, and non-antibiotic cohort. They suggested cytotoxicity and antiangiogenic effect of BPs and also the oral bacteria as the possible etiologic factors for BRONJ. This study denounced systemic antibiotic therapy for BRONJ subjects and also did not observe a high abundance of *Actinomyces* in BRONJ samples [18]. The second study of this team with the sample size of 30 subjects, expressed the immune response impairment as a major factor in the onset of BRONJ disease. In this study *P. micra*, *S. anginosus*, *A. rimae*, *P. stomatis* and *Eubacterium nodatum* dominated the BRONJ lesions. These species and phyla have different roles such as polymicrobial infection, abscess formation, and the root canal or periodontal pocket infection. [27]. Multiple factors can aid to suppress immune responses in BRONJ patients, like bone sclerosis, patient age, cancer and chemotherapy. These 2 studies used molecular tests like 16S sequencing, and both of them showed that there were no significant differences in bacterial diversity of BRONJ lesions between antibiotic treated or non-antibiotic treated patients. Another retrospective study on 28 ONJ patients suggested the use of amoxicillin and clavulanic acid combination in association with antimicrobial treatment like 0.12% chlorhexidine. The histologic results showed that *Capnocytophaga* sp., *Neisseria* sp. and *Actinomyces* sp. exhibited significant differences related to the ONJ involvement stage. Also, the degree of inflammation was not correlated to the density of the *Actinomyces* which was present at 87.5% of patients with a bone sequestrum biopsy [10].

Another hypothesis regarding the role of *Actinomyces* in ONJ was represented by Tae-Hwan Kim et al.: physical pressure during mastication and iatrogenic stimulations such as injuries from denture use may facilitate *Actinomyces* to penetrate through the jaw, possibly leading to actinomycosis [7]. This hypothesis is supported by the results of antibiotic therapy regimens and also detection of *A. israelli* in the BRONJ lesion sites. It is shown that using the polymerase chain reaction (PCR) technique is the most reliable method for the detection of microorganisms in BRONJ lesions of patients with systemic disorders like cancer, diabetes mellitus or cardiovascular disease. The highly frequent presence of *Actinomyces* in BRONJ lesions was approved by this method earlier [28]. This finding was also favored by histological reports like the retrospective study of G. Russmueller et al. which showed *Actinomyces* sp. in a high abundance in BRONJ lesions. A possible causal link was suggested by this study which detected *Actinomyces* sp. together with pathognomonic sulfur granules and signs of subacute or chronic inflammation, granulation tissue, and osteonecrosis. This study proposed the beta-lactam antimicrobial agents as a good complement to the standard surgical treatment. John K. Brooks et al. also suggested a beta-lactam antimicrobial agent (penicillin V potassium) after the grafting surgery for 7 days [29, 30].

Denosumab-related osteonecrosis of the jaw (DRONJ) is a disease that is caused by an IgG2 human monoclonal antibody named denosumab. A DRONJ case was reported by R. C. S. Povoa et al. which was successfully treated by discontinuation of denosumab for 5 months before surgery, surgical debridement and antibiotic therapy in association with antimicrobial agent usage (chlorhexidine gel) [31]. Treatment of BRONJ is a challenge as we see in the case of M. R. Sanchez et al. that they faced the recurrence of the lesion 6 months postoperatively. At the recurrence time, they prescribed antibiotic therapy (clindamycin and metronidazole) in association with an

antimicrobial agent (mouthrinse) for 2 years to achieve complete gingival coverage. They proposed local microbial infection as the most challenging factor for complete treatment [17]. Through all these studies we can see a wide range of suggested bacteria in MRONJ and BRONJ lesions; however, as we reported three of the most prevalent bacterial species in our database were *Actinomyces*, *Parvimonas micra*, and *Streptococcus anginosus*. Knowing these species can lead to conduct more specific future researches in the laboratory-level or clinical-level and this can pave the way to reach a new era in MRONJ and BRONJ management through more bacterial-oriented therapies. The main limitation of our systematic review was the small sample size and the broad heterogeneity between studies. Though we assessed the quality of studies, we could not set any exclusion criteria at the final step due to the limited studies in this field. Due to the lack of evidence, for more precise commentaries about microorganisms' etiologic role in BRONJ development, there needs to be a quantitative analysis of the bacterial load and BRONJ stages in the future researches.

CONCLUSION

According to all these literature, bacterial infection is among the major etiologic factors in the development or exacerbation of BRONJ. Among successful therapies, antibiotic therapy in association with antimicrobial agents like mouthrinses is suggested in several studies; though, there are different assessments about using systemic antibiotics and their efficacy besides the standard surgical debridement in BRONJ management. The most prevalent bacterial species reported in our databases were *Actinomyces* genus, *Parvimonas micra*, and *Streptococcus anginosus*; however, the causal link between these species and the secondary infection is not certain and no molecular tests supported this idea yet.

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