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MEDICATION-RELATED OSTEONECROSIS OF THE JAW (MRONJ)

[Diagnosis, Clinical Features, Potential Risk Factors And Clinical Management]

Dissertation

to acquire the degree of Doctor of Philosophy (Ph.D.)

of the Medical faculty of

Ludwig Maximilians University Munich

Submitted by

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from

Jeddah (Saudi Arabia)

Munich

29 June 2018

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Date of oral defense: 26.10.2018

To my husband who has always supported my hustle, drive, and ambition. To my children who taught me the true meaning of unconditional love..

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LIST OF ABBREVIATIONS

ARDs: Antiresorptive drugs

BMD: Bone mineral density

BPs: Bisphosphonates

RANK: Receptor activator of nuclear factor kappa-B

SREs: Skeletal-related effects

FDA: Food and Drug Administration

FREEDOM: Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 Months

DIRECT: Denosumab Fracture Intervention Randomized Placebo Controlled Trial

RANKL: Receptor activator of nuclear factor kappa-B ligand

MRONJ: Medication-related osteonecrosis of the jaw

BRONJ: Bisphosphonate-related osteonecrosis of the jaw

AAOMS: American Association of Oral and Maxillofacial Surgeons

LIST OF PUBLICATIONS

BOOK CHAPTERS

- **Suad Aljohani** and Sven Otto. Medication-related Osteonecrosis of the Jaw. In: Advanced Techniques of Internal Fixation of the Craniomaxillofacial Skeleton: Tumor, Corrective Bone Surgery and Trauma. Joachim Prein, Michael Ehrenfeld, Paul N. Manson, AO Education AO Foundation (in press).
- **Suad Aljohani** and Sven Otto. Complications of the Treatment of Medication-related Osteonecrosis of the Jaw (MRONJ). In: Complications in Cranio-Maxillofacial and Oral Surgery. Robert Gassner (in press).

JOURNAL PUBLICATIONS

- **Suad Aljohani**, Riham Fliefel, Jakob Ihbe, Jan Kühnisch, Michael Ehrenfeld and Sven Otto : What is the Effect of Anti-resorptive Drugs (ARDs) on the Development of Medication-Related Osteonecrosis of the Jaw (MRONJ) in Osteoporosis Patients: A Systematic Review. Journal of Cranio-Maxillo-Facial Surgery 45 9: 1493-1502, 2017.
- **Suad Aljohani**, Robert Gaudin, Julian Weiser, Matthias Tröltzsch, Michael Ehrenfeld, Gabriele Kaeppler, Ralf Smeets, Sven Otto: Osteonecrosis of the Jaw in Patients Treated with Denosumab: a Multicenter Case Series. Journal of Cranio-Maxillo-Facial Surgery, available online 31 May 2018.
- Tamara Kakoschke, **Suad Aljohani**, Gabriele Kaeppler, Michael Ehrenfeld, Sven Otto: Osteomyelitis der Kieferknochen. Osteologie 26 4: 236-243, 2017.

- **Suad Aljohani**, Matthias Tröltzsch, Sigurd Hafner, Gabriele Kaeppler, Gerson Mast, Sven Otto. Surgical Treatment of Medication-Related Osteonecrosis of The Upper Jaw: Case Series. Oral Diseases, available online 16 October 2018.

GENERAL INTRODUCTION

INTRODUCTION

Antiresorptive drugs

Antiresorptive drugs (ARDs) are used to decrease the rate of bone turnover by suppression of osteoclast-mediated bone resorption and thereby improving bone mineral density (BMD) and minimizing the loss of bone mass. Several well-controlled clinical trials have reported that ARDs are effective in the management of osteoporosis, multiple myeloma and metastatic bone disease [1]. These medications include bisphosphonates (BPs) and, more recently, receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor (denosumab).

Indications

Skeletal-related effects (SREs), namely pathological fracture, spinal cord compression, radiation or operative intervention and bone pain, are common among oncology patients. SREs can negatively affect functionality and health-related quality of life [2]. ARDs were shown to decrease SREs and subsequently can improve quality of life and minimize morbidity [3, 4]. Furthermore, recent studies have suggested that ARDs can be useful in suppressing bone involvement with solid tumors [5, 6].

ARDs are considered revolutionary treatment for not only metastatic bone disease and multiple myeloma but also for osteoporosis. It has been shown that ARDs can decrease fracture rates and improve BMD in osteoporosis patients [7]. In 1995, the Food and Drug Administration (FDA) granted approval to alendronate for postmenopausal osteoporosis [8]. Alendronate was reported to minimize the rate of

vertebral fracture by 70% and hip fracture by 50% [9]. In June 2010, the FDA approved denosumab for osteoporosis and it became, therefore, the first biological therapy for this indication [10]. FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 Months) Extension is a Phase III trial conducted to detect the long-term effect of denosumab in the treatment of postmenopausal osteoporosis over 10 years [11, 12]. This study found a persistent increase in BMD, with a 10 year-cumulative gain of 21.7% at lumbar spine and 9.2% at total hip [11]. In addition, a continued decline in vertebral and non-vertebral fracture rates was observed, 0.9 to 1.86% and 0.84 to 2.55% after 10 years of denosumab treatment, respectively. The occurrence of side effects did not increase over the 8 years and a favorable benefit/risk profile was evident. The persistent increase in BMD observed with denosumab is crucial as BMD tend to plateau after 3 years of BPs administration [13]. In Japan, Denosumab Fracture Intervention Randomized Placebo-Controlled Trial (DIRECT), a double-blind placebo-controlled trial, investigated denosumab in osteoporotic patients [14]. In this trial, a consistent increase of BMD and significant reduction of fractures and bone remodeling markers were observed. Furthermore, several clinical trials have shown that denosumab has a greater impact than BPs in increasing BMD, lowering bone turnover markers and minimizing fracture rate [15, 16]. Besides the above-mentioned clinical applications, ARDs are indicated for the treatment of some other rare bone conditions such as giant cell tumor, Paget's disease of bone and osteogenesis imperfecta [17-19].

Mechanism of action

Although both denosumab and BPs are ARDs and result in inhibition of osteoclasts, their mechanisms of action are totally different. BPs are chemically stable derivatives of inorganic pyrophosphates which adsorb onto bone hydroxyapatite crystals and

induce osteoclast apoptosis [20]. In contrast, denosumab is a human monoclonal antibody of RANKL [21]. RANKL is a cytokine synthesized by osteoblasts and binds to the receptor activator of nuclear factor kappa-B (RANK) receptor of preosteoclasts and induces thereby the differentiation of preosteoclasts to osteoclasts [22]. Denosumab binding to RANKL can suppress the development and maturation of these cells and lead to prevention of bone resorption [23]. BPs incorporate into osteoclasts and promote their apoptosis. In contrast, denosumab acts extracellularly and prevents osteoclasts maturation and formation. Moreover, denosumab does not persist in bone tissue and has a short half-life of only 26 days [23]. Denosumab is eliminated via the reticuloendothelial system and not via kidneys [20]. Therefore, unlike BPs, the renal function does not significantly influence denosumab use [24, 25].

Side effects

Despite their wide benefits, BPs can result in potentially serious side effects. Short-term side effects can occur after initiation of therapy and include gastrointestinal complications, fever, myalgias, arthralgias, musculoskeletal pain and hypocalcemia [8]. The long-term complications of BPs include osteonecrosis of the jaw, subtrochanteric femoral fracture and atrial fibrillation [8, 26].

Dyspnea, fatigue and hypophosphatemia are among the most common complications of denosumab [10]. Osteonecrosis of the jaw was also observed during denosumab treatment and is one of the most common causes of treatment discontinuation [27]. Another serious complication that can also lead to denosumab cessation is hypocalcemia [12]. RANKL and RANK are expressed also in activated B lymphocytes. Therefore, long-term administration of denosumab might suppress

immunity and raise the risk of infection. However, this risk has not been proven in humans, although it was observed in preclinical animal studies [10, 12].

Medication-related osteonecrosis of the jaws (MRONJ)

ARDs are effective medications in inhibition of bone turnover and can lessen morbidity and enhance the quality of life of osteoporosis and cancer patients. However, it has been well established that MRONJ is a rare complication of these medications, which can also influence the quality of life and require complex treatments and long follow-ups [28].

Definition

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) was initially described by Marx in 2003 [29]. After that, thousands of cases have been reported. In 2007, the American Association of Oral and Maxillofacial Surgeons (AAOMS) held a special committee to set a definition for this new potentially debilitating complication [30]. A definition of BRONJ was proposed as bone exposure in the maxillofacial region in patients underwent BP treatment, which didn't heal for 8 weeks and with no associated history of radiation to the jaws. In 2009, AAOMS updated her position paper to include the unexposed variant of BRONJ [31]. Several years after the first report of BRONJ, denosumab-related osteonecrosis of the jaw (DRONJ) was also identified in denosumab clinical studies in oncology and osteoporotic patients [14, 25, 32-41]. More cases were reported following denosumab's approval for clinical use in 2010 [42-48]. Aiming to include osteonecrosis lesions diagnosed after denosumab and antiangiogenic agents administration, the AAOMS has changed the nomenclature from BRONJ to MRONJ in its 2014 position paper [49]. In this paper, MRONJ has been defined as exposed bone or bone that can be detected via a fistula in the

maxillofacial region that persisted for 8 weeks in patients with current or previous treatment with ARDs or antiangiogenic medications and who did not have radiotherapy or obvious metastasis to this anatomic site [49].

Incidence

MRONJ is a relatively rare complication of ARDs. Several studies aimed to find the incidence and prevalence of MRONJ. However, most of these studies are based on medical record reviews, mailed surveys or insurance data. Moreover, the incidence of MRONJ is likely to be underestimated as some lesions can be mild and remain undiagnosed. In general, the prevalence of MRONJ in oncology patients treated with intravenous BPs was estimated to be from 1.2% to 9.9% [50]. This incidence in patients with multiple myeloma is 4.5 folds more than that among patients with breast cancer [51]. An Australian national survey estimated MRONJ risk of 0.01% to 0.04% in patients receiving oral BPs for osteoporosis [52]. The risk increased to 0.34% in patients with a history of dental extraction. A large postal survey included 8,572 osteoporotic patients on oral BPs and found a prevalence of 0.10% [53].

Likewise, DRONJ was reported to develop in cancer and osteoporosis patients [43, 49]. As estimated by combined 3 blinded phase 3 trials of 5,723 oncology patients under zoledronate or denosumab, the incidence of MRONJ was 0.5% or 0.8% at 12 months, 1.0% or 1.8% at 24 months, and 1.3% or 1.8% at 36 months of ARD intake, respectively [32]. A plateau was observed after 24 months of denosumab administration. The reported incidence of MRONJ was higher in patients receiving denosumab (1.8%) in comparison to those receiving zoledronate (1.3%). However, the cumulative incidence of MRONJ was almost similar for the two medications [32]. The median duration of ARDs before diagnosis was 14 months. According to the results of FREEDOM trial, only seven DRONJ cases were detected in the long-term

group (1343 patients) who received denosumab for 10 years and six cases in the crossover group (1283 patients) who received denosumab for 7 years [12].

Pathogenesis

Despite the enormous amount of literature generated over more than a decade, the pathogenesis of MRONJ is still not completely elucidated. Many theories have been proposed for the pathogenesis of MRONJ. However, none of them is supported by robust scientific evidence. It is likely that many factors are contributing to MRONJ onset and responsible for its unique localization in the jaws. ARDs act by suppressing bone remodeling, which is indeed essential to neutralize bone microdamage. This process is particularly important in the jawbones, which are more vulnerable to microtraumas caused by masticatory forces and bacterial infection due to the presence of the teeth and the oral flora. Otto et al. suggested that local infection, mainly periodontitis, can increase local acidity and subsequently can induce the release of BPs and maximize their toxic effects [54, 55]. This can explain the high incidence of MRONJ at sites of dental extractions, as most of them are indicated due to local infection, and at sites of periodontitis [56].

Risk factors

The determination of the risk factors related to MRONJ is nearly impossible due to the lack of well-controlled prospective studies. In fact, the conduction of such studies in relation to MRONJ would be unethical. In addition, it is very difficult to investigate risk factors in cancer and osteoporosis patients who have multiple comorbidities and high-risk medications. However, many potential risk factors seem to contribute significantly to MRONJ development. One of the established risk factors is the drug itself, including its duration of intake, dose and potency [57]. Moreover, concomitant

chemotherapy and antiangiogenic agents were shown to aid in MRONJ development [58, 59]. Several studies reported diabetes mellitus and corticosteroids as risk factors [60, 61]. On the other hand, some studies found almost the same number of patients with a history of corticosteroids in the control group [62, 63]. Local factors such as tooth extraction, local surgery, periodontitis and chronic local trauma caused by ill-fitting prosthesis can obviously trigger MRONJ onset and were reported almost in every case series [59, 64]. Therefore, optimizing oral health before and after ARDs administration can minimize these local factors and thus can diminish the risk of MRONJ.

Clinical staging

The AAOMS proposed a staging system for MRONJ (stage 0 to 3) [49]. Stage-specific therapeutic strategies, although are not supported by strong evidence, were also suggested. These stages can be summarized as the following:

Stage 0: nonspecific signs and symptoms, radiographic alterations in absence of exposed bone.

Stage 1: exposed bone or fistula to the underlying hard tissue in absence of pain and infection.

Stage 2: exposed bone or fistula to the underlying hard tissue with infection and/or pain.

Stage 3: exposed bone or fistula to the underlying hard tissue with pain and/or infection, in combination with one of these conditions: involvement of structures other than the alveolar bone leading to pathologic fracture, fistula or maxillary sinus involvement.

This system has several pitfalls, which have been discussed by several authors [65, 66]. Nevertheless, it is the most widely used and accepted staging system of MRONJ so far.

Differential diagnosis

The clinician should be aware of the lesions, which could have a similar clinical presentation to MRONJ in order to avoid errors in diagnosis and management. Among these lesions are osteomyelitis, osteoradionecrosis, alveolar osteitis, sinusitis, fibro-osseous lesions, chronic sclerosing osteomyelitis and oral ulceration and bone sequestration (OUBS) [49, 67, 68].

Treatment

There is an ongoing scientific debate about the optimal treatment of MRONJ. The early recommendations favored the non-surgical treatment [69]. Based on the current experience and knowledge, conservative management of MRONJ can be considered in stage 0 and 1 lesions in patients with limited life expectancy, while surgical treatment is a reasonable option in all stages especially in stage 2 and 3 lesions. Several studies highlighted the efficacy of surgery in achieving complete healing, namely complete mucosal coverage [70-72].

The guidelines of the German Society of Oral and Maxillofacial Surgery allow surgical treatment of MRONJ in all stages (0-3) [73]. The current AAOMS recommendations (2014-update) emphasize the non-surgical treatment for stage 0 and 1 and limit surgery to the more advanced stages [49]. During the last few years, numerous studies have reported good results with surgical treatment of MRONJ [70, 71, 74-76]. Non-surgical management is mostly based on antibacterial mouth rinses and long courses of antibiotics sometimes combined with debridement of superficial

necrotic bone with the objective of minimizing symptoms rather than curing MRONJ. Nicolatou-Galitis et al. reported mucosal healing after a mean of 17.5 months of conservative therapy in only 23% of patients [77]. On the other hand, non-surgical treatment can be reasonable in patients with limited life expectancy and poor general status. Nowadays, the general survival rates of malignancy patients have increased thanks to the remarkable innovations in anticancer therapies. Therefore, a precise evaluation of the patient's overall health and performance status is very essential in regards to the clinical decision-making in MRONJ treatment.

OBJECTIVES OF THE THESIS

The main objectives of this thesis were to:

1) To perform a systematic review to identify the effect of ARDs (Type, time of use prior to the onset of MRONJ, and way of administration) on MRONJ onset in osteoporotic patients. It aims also to determine the associated potential risk factors, demographic and clinical characteristics in this particular group of patients.
2) To understand the clinical course of the newly reported type of MRONJ, DRONJ, and to determine its response to treatment. For that aim, characteristics of ARDs, demographics, systemic factors, local factors, treatment modalities, and their outcomes were analyzed retrospectively. Few case series of DRONJ have been reported so far. Therefore, this case series, which is the largest so far, can aid in understanding the course of DRONJ. Another aim was to detect the effect of BP intake prior to denosumab on the clinical characteristics and treatment outcomes of DRONJ**.**
3) To perform a review of the literature aiming to elucidate the different types of inflammatory diseases of the jawbones, mainly MRONJ, osteomyelitis and osteoradionecrosis and to compare them to osteomyelitis of the other parts of the skeleton. This review aids in improving the understanding of these diseases and can subsequently help to establish the correct diagnosis and management.
4) To retrospectively evaluate the outcomes of surgical treatment of upper jaw MRONJ using single-layer closure (mucoperiosteal flap) and double-layer closure (mucoperiosteal flap followed by buccal fat pad flap). Another aim is to find out the outcomes of using obturator prostheses for the more extensive upper

jaw lesions, which cannot be reconstructed surgically. Few similar studies have been reported, with this study being the largest so far. The management of maxillary MRONJ is particularly challenging due to the limited alveolar bone mass and proximity to the maxillary sinus. Therefore, it is crucial to identify the proper treatment of this entity of MRONJ.

PUBLICATION 1

What is the Effect of Antiresorptive Drugs (ARDs) on the Development of Medication-Related Osteonecrosis of the Jaw (MRONJ) in Osteoporosis Patients: A Systematic Review.

Suad Aljohani , Riham Fliefel , Jakob Ihbe , Jan Kühnisch, Michael Ehrenfeld and Sven Otto

Journal of Cranio-Maxillo-Facial Surgery 45 6: 1493-1502, 2017

Journal of Cranio-Maxillo-Facial Surgery 45 (2017) 1493–1502

Contents lists available at ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

What is the effect of anti-resorptive drugs (ARDs) on the development of medication-related osteonecrosis of the jaw (MRONJ) in osteoporosis patients: A systematic review

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ARTICLE INFO

Article history:
Paper received 12 January 2017
Accepted 29 May 2017
Available online 3 June 2017

Keywords:
Systematic review
Osteoporosis
Medication-related osteonecrosis of the jaw (MRONJ)
Anti-resorptive drugs (ARDs)

ABSTRACT

Purpose: To conduct a systematic review of the literature to detect the effect of anti-resorptive drugs (ARDs) and their administration characteristics in the development of medication-related osteonecrosis of the jaw (MRONJ) in osteoporosis patients.
Methods: Systematic search in PubMed, Web of Sciences and Cochrane Library was performed for relevant studies to July 2016. Population variables (age, gender, comorbidities, medications, preceding events, number of patients with MRONJ), ARDs and clinical variables were abstracted independently from these articles.
Results: The 44 eligible studies described 680 MRONJ cases in osteoporotic patients. The mean age of MRONJ patients was 69.7 ± 5.2 years. It was more common in females. Mandible was the most common site. Alendronate was the most frequently administered ARD. Oral route of administration was noted in 86.7% of the patients. The mean duration of BPs intake was 50.4 ± 19 months. Extraction was the most frequently preceding event followed by dentoalveolar surgery. Corticosteroids or immunosuppressants were the most common concomitant medications in MRONJ.
Conclusion: A long duration of ARDs administration seems to be an important risk factor in MRONJ development. Patients under treatment with corticosteroids or immunosuppressants might be at a higher risk even if the BPs duration is less than 4 years.

1. Introduction

Osteoporosis is a major public health concern with over 200 million people suffering from this disease around the globe (Cooper et al., 1992). In Germany alone 6.3 million persons have osteoporosis with more patients are expected to develop osteoporosis each year (Hadji et al., 2013). More than 75 million people in Europe, Japan and the USA have osteoporosis and more than 2.3 million fractures occur as a result of osteoporosis each year in Europe and the USA alone (WHO, 2003). These fractures affect significantly patients' quality of life and cause an enormous economic and social burden in addition to increasing the morbidity and mortality rates. The disease is expected to be more prevalent due to the ageing of the whole population (Lane, 2006; Hadji et al., 2013).

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http://dx.doi.org/10.1016/j.jcms.2017.05.028
1010-5182/

Osteoporosis is defined as a skeletal disorder characterized by low bone density and micro-architectural deterioration of bone tissue predisposing it to an increased risk of fracture (Klibanski et al., 2001). WHO diagnostic criterion for osteoporosis depends on bone mineral density (BMD) (Cooper et al., 1992; Cosman et al., 2014). BMD correlates with fracture rates, so as it increases the fracture risk decreases. Therefore, the treatment or prevention of osteoporosis aims to improve BMD and to increase bone density and strength. FDA-approved medications for the management of osteoporosis are, bisphosphonates (BPs) (alendronate, alendronate plus D, ibandronate, risedronate and zoledronate), estrogens, estrogen agonist/antagonist (raloxifene), tissue-selective estrogen complex (conjugated estrogens/bazedoxifene), parathyroid hormone (teriparatide), and the receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor (denosumab) (Cosman et al., 2014).

Bisphosphonates (BPs) are one of the most prescribed medications worldwide (Paiva-Fonseca et al., 2014). They are also indicated in a variety of less common diseases such as Paget's disease of the bone, osteogenesis imperfecta and cancer (Ruggiero et al., 2014). More than 190 million prescriptions of BPs are written per year (Ruggiero et al., 2014). Oral BPs (alendronate, risedronate and ibandronate) are the most commonly used BPs for osteoporosis. However, an intravenous single yearly dose of zoledronate (Reclast®) and three-monthly intravenous injections of ibandronate (Boniva®) are approved for the prevention and treatment of osteoporosis as a more convenient and less compliance-demanding alternative therapy to oral BPs. In addition, denosumab (Prolia®) as twice-yearly subcutaneous injections is approved for management of osteoporosis and has been shown to be an effective treatment (Bone et al., 2013; Papapoulos et al., 2015).

BPs are generally well tolerated, however, some related side effects such as esophagitis, musculoskeletal pain, hypocalcemia, ocular inflammation, and osteonecrosis of the jaws can occur (Kennel and Drake, 2009). Since the first report of BP-related osteonecrosis of the jaw (BRONJ) in 2003, many similar cases have been reported. Intravenous BPs, which are used mostly for oncological indications, have been linked to jaw osteonecrosis in an incidence of 3–18% (Bamias et al., 2005; Walter et al., 2008). On the other hand, oral BPs have been estimated to cause jaw osteonecrosis at a significantly lower rate, 1.04 to 69 patients in 100,000 patients (Khan et al., 2015). In contrast, the Kaiser Permanente PROBE study reported a higher prevalence in 8572 patients who had received chronic oral BP therapy of 0.10% and 0.21% in those with more than four years of BPs use (Lo et al., 2010). More recently, osteonecrosis of the jaw has been observed in association with other medications such as denosumab and antiangiogenic drugs (Otto et al., 2013a; Papapoulos et al., 2015; Bagan et al., 2016). Therefore, the American Association of Oral and Maxillofacial Surgeons (AAOMS) has suggested a new nomenclature of BPs-related osteonecrosis of the jaws (BRONJ) to be medication-related osteonecrosis of the jaw (MRONJ) in order to include all the medications which have been implicated in the development of osteonecrosis of the jaw (Ruggiero et al., 2014).

Several risk factors appear to be associated with the development of MRONJ. The duration of BPs has been identified as a potential risk factor, which makes BPs long-term use in osteoporosis patients an important issue (Ruggiero et al., 2009). Recognizing other risk factors and comorbidities may also help to minimize the risk and severity of the disease. The increase in MRONJ reported cases had raised the public awareness of the use of ARDs worldwide in osteoporotic patients to help to improve the knowledge about MRONJ in this large group of patients.

Thus, the primary goal of this study is to conduct a systematic review of the literature to elucidate the effect of ARDs (type, duration and route of administration) on MRONJ development in osteoporosis patients. In addition, a secondary goal is to identify the associated risk factors, demographic and clinical characteristics.

2. Materials and methods

This search was registered at PROSPERO International Prospective Register of Systematic Reviews (registration number: CRD42016052011) and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009) to answer the following question: "what is the effect of ARDs on MRONJ development in osteoporosis patients?". Another question to be answered is "what are the risk factors, demographical and clinical characteristics associated with MRONJ in this particular group of patients?"

2.1. Inclusion and exclusion criteria

The selected articles had to meet the following inclusion criteria: (1) Patients received ARDs (BPs or/and denosumab) as a treatment of osteoporosis; (2) Clinically diagnosed MRONJ according to AAOMS (Ruggiero et al., 2014); (3) Studies having four patients or more except for denosumab, for which single case reports have been accepted; (4) Publications in English language.

The exclusion criteria are: (1) Articles presenting less than four cases (except for denosumab); (2) Patients with malignancy; (3) Osteonecrosis other than the maxillofacial region; (4) Patients with other bone diseases such as Paget's disease of bone and renal osteodystrophy; (5) Literature reviews, letters, editorials, doctoral theses, and abstracts; (6) Experimental studies.

2.2. Search strategy

A systematic search of the literature was conducted in the PubMed, Web of Sciences databases, and Cochrane Library without a beginning date specification but the search was ended on the 11th of July 2016. An advanced PubMed search has been done for the following search phrases: (osteonecrosis of jaw AND osteoporosis). A second medical subject headings search (MeSH) in PubMed for (osteonecrosis of jaw AND osteoporosis) was conducted. Web of Sciences database was searched for the following topics (Osteonecrosis of jaw AND osteoporosis). A title, abstract and keywords search in Cochrane Library has been conducted for (osteonecrosis of jaw AND osteoporosis). The results of the database searches were combined and duplicate publications were excluded.

2.3. Study selection

Abstracts of the identified publications using the search strategy were reviewed. The previously determined inclusion and exclusion criteria were considered in articles screening for eligibility, which were performed independently by two investigators (SA and RF). Any inconsistency was resolved by consensus with a third author (SO). Articles that did not meet the eligibility criteria were excluded. Full texts were obtained for those that were found initially compliant with the inclusion criteria. Then a hand search of the reference lists of all articles selected for full-text review was performed to find additional relevant publications.

A critical appraisal of the selected articles was performed independently by two investigators (SA and JI) to assess the validity. Any disagreement was resolved by consultation with a third investigator (SO).

2.4. Data extraction

The two investigators independently abstracted the following data from the included articles and recorded it using a standardized spreadsheet: authors, year of publication, study design, population variables (age, gender, comorbidities, concomitant medications, history of dental surgery, dental disease or trauma, number of patients with MRONJ), ARD variables (type of ARD, dose, route of administration, time to onset of MRONJ) and the clinical variables (location, stage).

2.5. Disease definition

According to the AAOMS last position paper, a case can be considered as MRONJ if all the following three criteria are present: current or previous treatment with anti-resorptive or anti-angiogenic agents, exposed bone or bone that can be probed through an intraoral or extra-oral fistula in the maxillofacial region that has persisted for longer than 8 weeks and no history of radiation therapy to the jaws or obvious metastatic disease to the jaws (Ruggiero et al., 2014). In this study, only MRONJ cases in relation to ARDs as a treatment of osteoporosis were investigated.

2.6. Statistical analysis

The data from the selected publications were analysed using a qualitative data analysis. Demographic and clinical variables as well as risk factors, comorbidities, types of ARDs, route of administration, duration of treatment and MRONJ stages were carefully studied. The mean age of osteoporosis patients with osteonecrosis of the jaw and the ratio of male to female patients were calculated. The proportion of the patients who had a history of comorbid condition (i.e. the proportions of patients having diabetes mellitus or who received immunosuppressive therapy) was detected. Furthermore, the potential local risk factors for this particular group of patients were investigated. The proportions of the different ARDs types and their intake duration were found.

2.7. Assessment of study quality

The quality evaluation of the studies was performed by two investigators (SA and RF) based on ASBMR modifications (Khosla et al., 2007). Nine quality parameters were used (age, sex, primary disease, type of ARD, route of administration, ARD duration, site of MRONJ, risk factors and comorbidities). The quality of each publication was classified as good (7–9 parameters mentioned), moderate (4–6 parameters mentioned), or poor (only 1–3 parameters mentioned).

3. Results

The results of the literature search are presented in the flow chart, showing study selection in accordance with PRISMA statement (Fig. 1). The initial search strategy resulted in 2044 articles from electronic search: 774 results from keywords search in PubMed, 123 publications from the MeSH search in PubMed, 61 publications from Cochrane library and 1086 publications from Web of Sciences. Nine publications were identified using hand search of the relevant reference lists. The total number of abstracts/title screened was 1384 after duplicates removal.

Eighty potentially relevant articles were considered relevant for article retrieval and full-text review. Forty-four publications were included in the qualitative synthesis and 36 papers were excluded after a preliminary review (Supplementary Table 1). The selected 44 articles underwent further quality assessment as described before. 35 articles had a good quality (79.5%); 8 articles had a moderate quality (18.2%); and only one had a poor quality (2.3%) (Table 1).

Of these articles, twenty were case series, three were case reports, twenty were retrospective studies and there was one prospective study (Supplementary Table 1). The data of 680 cases of MRONJ were extracted from the 44 articles and included in our final review.

3.1. Age and gender

The mean age of MRONJ osteoporosis patients in our study was 69.7 ± 5.2 years. Patients' gender was reported in 587 cases: 549 of them were females (93.5%) and only 38 were males (6.5%) (Fig. 2). Six and seven articles did not specify age and gender, respectively. Marked female predilection was found with a male to female ratio of 1:14.4.

3.2. Site

The site of MRONJ was reported for 558 MRONJ cases in 38 articles. The mandible was the most common site (394, 70.6%), followed by maxilla (152 case, 27.2%) and then in both of them (only 12 cases, 2.2%) (Fig. 2). The ratio of mandible to maxilla and both jaws involvement was 2.4:1.

3.3. Characteristics of ARDs treatment

The type of ARD has been described for 643 cases in 41 articles. Only three articles failed to report the ARD type. Alendronate was the most commonly reported ARD in our review with about three quarters of cases (475 cases, 72.6%); this was followed by risedronate and ibandronate with almost equal proportions (5.4% and 5.2%, respectively). Next was zoledronate (28 cases, 4.3%) and then a combination of more than one type of ARDs (26 cases, 4%). Subsequently there were other less common ARDs types (24 cases, 3.7%). Pamidronate was noted in 18 cases (2.8%) and finally denosumab was reported in just 14 cases (2.1%). BPs were administered orally in 86.7% of the patients and intravenously in 7.9% of the patients. Denosumab was injected subcutaneously in 2.4% of our study cases. Combinations of several routes of administration of ARDs were detected in 3% of the cases (Table 2).

3.4. Duration of treatment

There was variability in the duration of BPs therapy, which ranged from 2 weeks to 93 months, with a mean duration of 51.9 ± 18 months. Twelve cases had yearly 5 mg zoledronate infusions (mean number of infusions is 1.6 ± 0.17). Nine of them had a previous history of oral BPs (alendronate or risedronate) for an average of 9 years. The mean number of denosumab doses is 2.1 ± 1.2. Eleven patients out of fourteen had been treated before with oral BPs (78.6%) for an average period of 29 ± 20.4 months. The most common administered oral BP prior to denosumab treatment was Alendronate (62.5%) followed by risedronate (25%) and ibandronate (12.5%) (Table 2).

3.5. Preceding event

Extraction was the most frequently reported preceding event (244 patients, 48.5%). Dentoalveolar surgery was related to MRONJ in 111 cases (21.1%). MRONJ has been related to trauma from prosthesis in 44 cases (8.4%) and to a history of periodontal disease or endodontic treatment in 25 patients only (4.8%). A precipitating event could not be identified in 90 cases (17.2%) (Fig. 1).

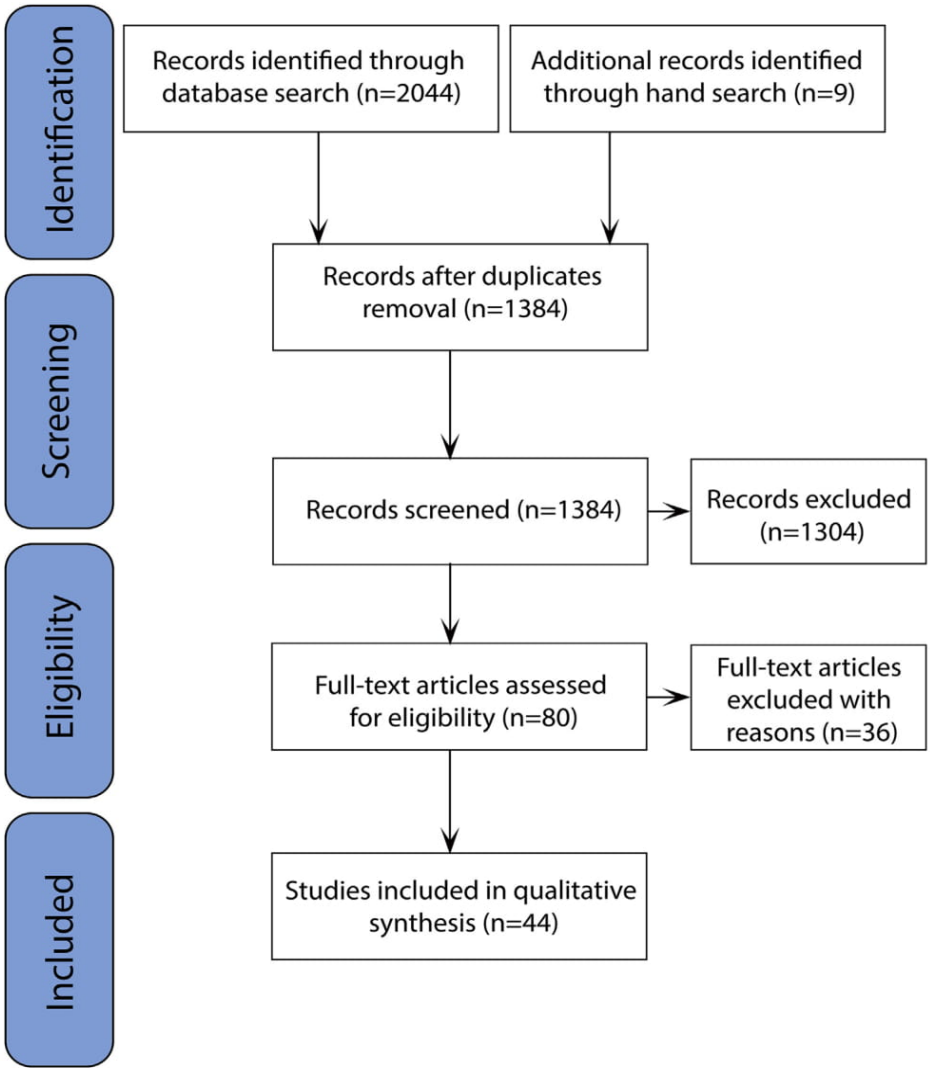

Fig. 1. Flow chart of the search strategy and study selection used in this systematic review.

3.6. Comorbidities

One hundred and fifteen patients underwent corticosteroid treatment (39.1%). Fifty patients had concomitant diabetes mellitus (17%) and seventy-six had hypertension (25.8%). Thirty-seven patients were affected by underlying autoimmune disease (12.6%). A history of smoking in recent years was reported for only 16 patients (5.5%) (Fig. 2).

The most commonly reported stage in the articles, which managed to report MRONJ stage, was stage 2 (203 patients; 50.5%), followed by stage 1 (110 patients; 27.4%). The number of cases with stage 0 is comparable to those with stage 3 (10.2% and 11.9%, respectively) (Table 2).

4. Discussion

The main objective of our systematic review is to detect the effect of ARDs and their administration characteristics in the development of MRONJ in osteoporosis patients. The related demographic and clinical characteristics and the potential local and systemic risk factors were thoroughly investigated. Osteonecrosis of the jaw has been reported in osteoporosis patients treated by ARDs, as a rare but potentially serious side effect of these medications (Farrugia et al., 2006; Diniz-Freitas et al., 2012; Anavi-Lev et al., 2013; Di Fede et al., 2013; Bagan et al., 2016). ARDs, including BPs and denosumab, are effective medications in decreasing osteoporosis-associated mortality and morbidity (Sugimoto et al., 2015; Zhang et al., 2015). Hip or vertebral fractures are the main concern for the prevention of osteoporosis. ARDs can reduce the risk of these fractures (Cosman et al., 2014). MRONJ prevalence in osteoporosis patients treated by ARDs is estimated to be very low (Mavrokokki et al., 2007; Yamazaki et al., 2012; Ulmner et al., 2014). However, it increases significantly with long-term BPs administration, from 0% to 0.21% after at least 4 years (Ruggiero et al., 2014). Furthermore, the number of osteoporosis patients is steadily enlarging and subsequently the associated MRONJ incidence might progressively increase. This highlights the importance of understanding the associated risk factors and comorbidities of MRONJ and to recognize the more susceptible group of patients in order to aid in limiting its incidence in osteoporosis patients.

In accordance with many publications, the mean age of MRONJ osteoporosis patients in our study is 69.7 ± 5.2 (Mavrokokki et al.,

Table 1
The quality of publications in the included studies.

Author, Year	Age	Sex	Primary disease	ARD name	Duration	Mode of administration	Site	Comorbidities	Trigger factors	Total	Quality
Bagan, 2016§ (Bagan et al., 2016)	Y	Y	Y	Y	Y	Y	Y	N	Y	**8**	**Good**
Farrugia, 2006 (Farrugia et al., 2006)	Y	Y	Y	Y	N	Y	Y	N	Y	**7**	**Good**
Jacobsen, 2013 (Jacobsen et al., 2013)	N	N	Y	Y	Y	Y	Y	N	Y	**6**	**Moderate**
Manfredi, 2011 (Manfredi et al., 2011)	Y	Y	Y	Y	Y	Y	Y	Y	Y	**9**	**Good**
Mercer, 2013 (Mercer et al., 2013)	Y	Y	Y	Y	Y	N	Y	N	Y	**7**	**Good**
Ruggiero, 2004 (Ruggiero et al., 2004)	Y	Y	Y	Y	N	Y	Y	N	N	**6**	**Moderate**
Villa, 2011 (Villa et al., 2011)	N	Y	Y	N	N	N	Y	Y	Y	**5**	**Moderate**
Favia, 2016 (Favia et al., 2016)	Y	Y	Y	Y	Y	Y	Y	Y	Y	**9**	**Good**
O'Ryan and Lo, 2012 (O'Ryan and Lo, 2012)	Y	Y	Y	Y	Y	Y	Y	Y	Y	**9**	**Good**
Anavi-Lev, 2013 (Anavi-Lev et al., 2013)	Y	Y	Y	N	Y	Y	Y	Y	Y	**8**	**Good**
Angiero, 2009 (Angiero et al., 2009)	Y	Y	Y	Y	Y	Y	Y	N	N	**7**	**Good**
Saussez, 2009 (Saussez et al., 2009)	N	N	Y	Y	Y	Y	Y	N	Y	**6**	**Moderate**
Yarom , 2007 (Yarom et al., 2007)	Y	Y	Y	Y	Y	Y	Y	Y	Y	**9**	**Good**
Stanton and Balasanian, 2009 (Stanton and Balasanian, 2009)	Y	Y	Y	Y	N	Y	Y	N	N	**6**	**Moderate**
Longobardi, 2007 (Longobardi et al., 2007)	Y	Y	Y	Y	Y	Y	Y	Y	Y	**9**	**Good**
Hong, 2010 (Hong et al., 2010)	Y	Y	Y	Y	Y	Y	Y	N	Y	**8**	**Good**
Chiu, 2010 (Chiu et al., 2010)	Y	N	Y	Y	Y	Y	Y	Y	Y	**8**	**Good**
Park, 2010 (Park et al., 2010)	Y	Y	Y	Y	Y	Y	Y	Y	Y	**9**	**Good**
Lazarovici, 2009 (Lazarovici et al., 2009)	N	N	Y	Y	Y	Y	N	N	N	**4**	**Moderate**
Lazarovici, 2010 (Lazarovici et al., 2010)	N	N	Y	Y	Y	Y	N	N	Y	**5**	**Moderate**
Voss, 2012 (Voss et al., 2012)	Y	Y	Y	Y	Y	Y	Y	Y	Y	**9**	**Good**
Nomura, 2013 (Nomura et al., 2013)	Y	Y	Y	Y	Y	Y	Y	Y	Y	**9**	**Good**
Jabbour, 2012 (Jabbour et al., 2012)	Y	Y	Y	Y	Y	Y	Y	Y	Y	**9**	**Good**
Hutchinson, 2010 (Hutchinson et al., 2010)	Y	Y	Y	Y	Y	Y	Y	Y	Y	**9**	**Good**
Rachner, 2013§ (Rachner et al., 2013)	Y	Y	Y	Y	Y	Y	Y	Y	Y	**9**	**Good**
Otto, 2013§ (Otto et al., 2013b)	Y	Y	Y	Y	N	Y	Y	N	Y	**7**	**Good**
Neuprez, 2014 (Neuprez et al., 2014b)	Y	Y	Y	Y	Y	Y	Y	Y	Y	**9**	**Good**
Otto, 2011 (Otto et al., 2011)	Y	Y	Y	Y	Y	Y	N	Y	N	**7**	**Good**
Marx, 2007 (Marx et al., 2007)	Y	N	Y	Y	Y	Y	Y	Y	Y	**8**	**Good**
Almasan, 2011 (Almasan et al., 2011)	Y	Y	Y	Y	Y	Y	N	N	N	**6**	**Moderate**
Di Fede, 2013 (Di Fede et al., 2013)	Y	Y	Y	Y	Y	Y	Y	Y	Y	**9**	**Good**
Diniz-Freitas, 2012 (Diniz-Freitas et al., 2012)	Y	Y	Y	Y	Y	Y	Y	Y	Y	**9**	**Good**
Giovannacci, 2016 (Giovannacci et al., 2016)	Y	Y	Y	Y	Y	Y	Y	Y	Y	**9**	**Good**
Goss, 2010 (Goss et al., 2010)	Y	Y	Y	Y	Y	Y	Y	Y	Y	**9**	**Good**
Hallmer, 2014 (Hallmer et al., 2014)	Y	Y	Y	Y	N	Y	Y	Y	Y	**8**	**Good**
Jacobsen*, 2012 (Jacobsen et al., 2012)	Y	Y	Y	Y	Y	Y	Y	Y	Y	**9**	**Good**
Lee and Suzuki, 2015 (Lee and Suzuki, 2015)	Y	Y	Y	Y	Y	Y	Y	N	Y	**8**	**Good**
López-Cedrún, 2013 (Lopez-Cedrun et al., 2013)	Y	Y	Y	Y	Y	Y	N	Y	Y	**8**	**Good**
Pelaz, 2014 (Pelaz et al., 2014)	Y	Y	Y	Y	Y	Y	Y	Y	Y	**9**	**Good**
Pichardo, 2013 (Pichardo and van Merkesteyn, 2013)	Y	Y	Y	Y	Y	Y	Y	N	Y	**8**	**Good**
Yamazaki, 2012* (Yamazaki et al., 2012)	Y	Y	Y	Y	Y	Y	N	Y	N	**7**	**Good**
Favia, 2009 (Favia et al., 2009)	Y	Y	Y	Y	Y	Y	Y	Y	Y	**9**	**Good**
Kwon and Kim, 2009 (Kwon and Kim, 2009)	Y	Y	Y	Y	Y	Y	Y	Y	Y	**9**	**Good**
Vescovi, 2014 (Vescovi et al., 2014)	N	N	N	N	Y	N	Y	N	Y	**3**	**Poor**

(Y): Mentioned, (N): Not mentioned, Total: Total score for all the 9 items.

2007; Lo et al., 2010; Diniz-Freitas et al., 2012). In a Swedish cross-sectional survey in patients who had MRONJ and had been treated with oral BPs, the mean age was markedly higher (79.8 ± 7.6 years) (Ulmner et al., 2014). Moreover, our study has shown a high female to male predilection, which was noted also by other authors (Kwon et al., 2014; Ruggiero et al., 2014). The higher prevalence of MRONJ in elderly women is likely a reflection of the nature of osteoporosis, which is more prevalent in postmenopausal women aged 65 or more (Lane, 2006). Interestingly, Park and colleagues addressed the possibility of race contribution in MRONJ development as potential co-risk factor (Park et al., 2010). Asian women were found to have the lowest bone mineral density and body mass and the smallest body size in comparison with other women from other ethnicities (Barrett-Connor et al., 2005). Such a fact may contribute to a higher risk of osteoporosis and accordingly to a higher risk of MRONJ. However, further studies are needed to prove such an assumption.

MRONJ occurs in the mandible twice as often as in the maxilla. This result is consistent with the findings of many previous publications (Abu-Id et al., 2006; Ulmner et al., 2014; Fliefel et al., 2015). MRONJ was reported to occur almost exclusively in the jaws. This selective involvement to jaw bones can be attributed to the unique environment of the oral cavity. Maxilla and mandible are frequently exposed to local infections and to surgical procedures due to presence of teeth and are exposed to oral flora (Sedghizadeh et al., 2009b; Otto et al., 2010a, 2010b; Katsarelis et al., 2015). This challenging nature besides BPs strong anti-resorptive effect can lead to accumulation of bacteria and delay healing of the wounds and subsequently can result in bone necrosis (Ruggiero et al., 2004; Woodis, 2008; Pazianas, 2011; Rasmusson and Abtahi, 2014). Another potentially contributing factor is the higher jawbones remodeling rate, which when suppressed may lead to the accumulation of microdamage (Hoefert et al., 2010; Landesberg et al., 2011; Otto et al., 2012). Moreover, the decreased vascularity of the mandible and its dense compact bone may favor the spread of infection and predispose the mandible to a higher risk of developing necrosis (Fliefel et al., 2015).

Alendronate was the most frequently reported ARD associated with the development of MRONJ (72.6%). Many authors reported a similar high frequency of alendronate (Mavrokokki et al., 2007; Ulmner et al., 2014). In 1995, alendronate (Fosamax®; Merck, Whitehouse Station, NJ) was the first approved drug among oral BPs, followed by risedronate in 2000 (Actonel®; Procter and

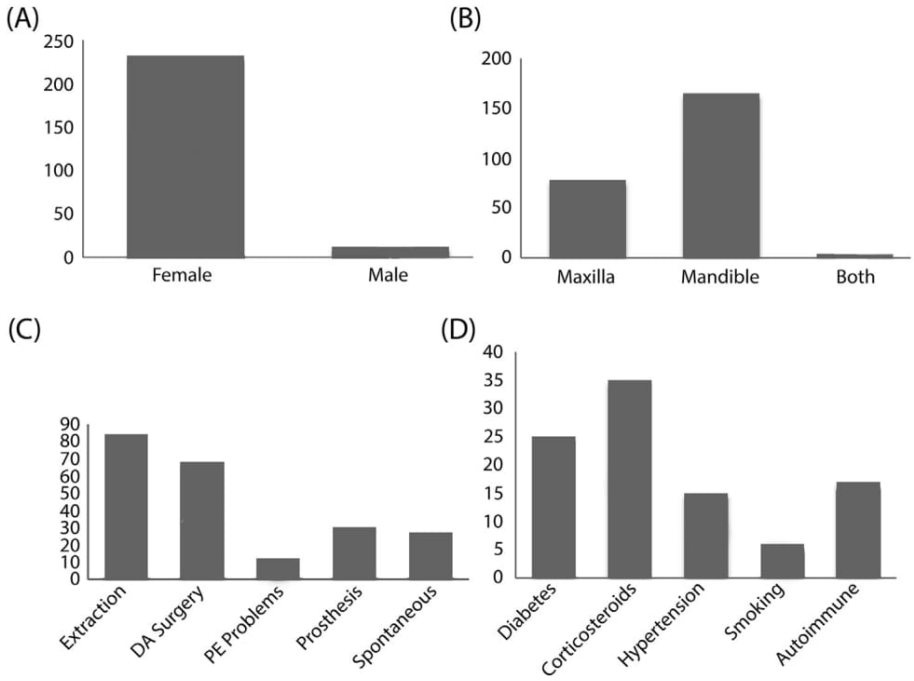

Fig. 2. Demographic data of MRONJ in osteoporotic patients (A) Gender distribution, (B) Site of MRONJ, (C) Proceeding dental event. DA surgery: Dentoalveolar surgery, PE problems: Periodontal and Endodontic problems, (D) associated systemic comorbidities.

Gamble, Cincinnati, OH). In 2005, ibandronate was approved as well for the same indication (Boniva®; Roche, Basel, Switzerland) (Assael, 2009). Among ARDs, alendronate is the most commonly prescribed for treatment and prevention of osteoporosis. Till September 2007, more than 225 million prescriptions for oral BP were written worldwide and alendronate is by far the most frequently prescribed BP (Assael, 2009). Thus, this wide use of alendronate can clarify the fact that most of the patients in our review had received alendronate. 86.7% of the cases in our review had oral BPs (Lo et al., 2010). Although their main indication is mainly to prevent osteoporosis-related fractures, oral BPs are one of the most frequently prescribed medications and their use is expected to increase further. The growing risk of MRONJ in their long-term use obviously exists, however this does not outweigh their wide benefits in decreasing the mortality and morbidity rate in osteoporosis patients (Papapoulos et al., 2012, 2015).

In agreement with other studies, our results confirm that the duration of treatment with ARDs is considered an important factor in development of osteonecrosis (Khosla et al., 2007; Lo et al., 2010; Ruggiero et al., 2014). The mean duration of BPs in our study is 51.9 ± 18 months, which is comparable to the duration mentioned by the last position paper of the AAOMS (Ruggiero et al., 2014). It is well known that BPs can accumulate in bone and knowing their accumulative dose is essential to determine the risk of developing MRONJ. Thus, the risk associated with oral BPs is estimated to increase after 3 years of exposure (Sedghizadeh et al., 2009a; Ruggiero et al., 2014).

In 2010, FDA and the European Medicines Agency approved denosumab as a treatment of osteoporosis (Olate et al., 2014). Denosumab (Prolia®) at a dose of 60 mg subcutaneously is approved in osteoporosis patients, while higher and more frequent doses (XGEVA®, 120 mg) are indicated in oncological patients (Cummings et al., 2009; Smith et al., 2009). Subsequently, the related risk of MRONJ seems to be lower in osteoporosis patients (Ruggiero et al., 2014). Despite the lack of evidence, discontinuation of denosumab six months prior to dentoalveolar surgical procedures seems to be reasonable to decrease MRONJ risk (Ruggiero et al., 2014). Few cases of MRONJ were reported in association with denosumab use. We found 14 cases of MRONJ linked to denosumab in osteoporosis patients (Otto et al., 2013a; Rachner et al., 2013; Neuprez et al., 2014a; Bagan et al., 2016). Eight cases were reported in the FREEDOM extension study, a clinical trial aimed to evaluate denosumab as a treatment of osteoporosis (Cummings et al., 2009). However, the lack of clear reporting in regard to MRONJ led to exclusion of these clinical trials from our systematic review (Papapoulos et al., 2012, 2015; Sugimoto et al., 2015). The mean number of denosumab doses in our review is 2.1 ± 1.2. However, the MRONJ risk seems to be higher directly after denosumab induction regardless of the number of previous denosumab doses (Otto et al., 2013a). Pichardo reported a case after administration of only a single dose of denosumab (Pichardo et al., 2013). Qaisi and colleagues described a life threatening osteonecrosis of the jaw with sepsis in a rheumatoid arthritis patient who had only one dose prior to extraction (Qaisi et al., 2016). This might be attributed to the long period of previous oral and intravenous BPs intake, for 4 years and two years, respectively. Our study confirms the potential contribution of previous BPs history as more than 78.6% of the patients had taken oral BPs for about 29 months on average before they started denosumab. Interestingly, a severe case of MRONJ that started a few months after denosumab treatment without any history of previous BPs intake has been reported (Pichardo et al., 2013). However, this patient had two comorbidities, malignancy and chemotherapy, which can increase the risk to develop MRONJ. Alendronate was the most commonly administered BP prior to denosumab (62.5%). Osteonecrosis in relation to denosumab tends to be self-limiting after cessation of denosumab (Taylor et al., 2010; Malan et al., 2012; You et al., 2015).

Concurring with other authors (Mavrokokki et al., 2007; Assael, 2009; Fliefel et al., 2015), we found extraction to be the most frequent dentoalveolar event prior to MRONJ onset.

Table 2
Summary of included studies with type of study, anti-resorptive drugs used, and route of administration.

Author, Year	study type	Type of ARD								Route of admin				MRONJ develop. (month)	Stage			
		Z	P	A	R	I	O	C	Dmab	IV	OS	SC	C		0	1	2	3
Bagan, 2016§ (Bagan et al., 2016)	CS	0	0	0	0	0	0	0	10	0	0	10	0	3.4#	0	8	2	0
Farrugia, 2006 (Farrugia et al., 2006)	Retro	0	0	4	0	0	0	0	0	0	4	0	0	N/R	N/R			
Jacobsen, 2013 (Jacobsen et al., 2013)	CS	0	1	2	0	1	0	1	0	2	2	0	1	50	N/R			
Manfredi, 2011 (Manfredi et al., 2011)	CS	1	0	11	0	1	3	6	0	4	15	0	6	53.73	15	3	1	0
Mercer, 2013 (Mercer et al., 2013)	CS	3	4	75	4	5	0	0	0	N/R				60	0	7	8	3
Ruggiero, 2004 (Ruggiero et al., 2004)	Retro	0	0	5	1	0	0	1	0	0	6	0	1	N/R	N/R			
Villa, 2011 (Villa et al., 2011)	CS	N/R								N/R				N/R	0	3	4	0
Favia, 2016 (Favia et al., 2016)	CS	8/	0	0	0	0	0	0	0	8	0	0	0	1.5#	0	6	2	0
O'Ryan and Lo, 2012 (O'Ryan and Lo, 2012)	Retro	0	0	26	0	1	0	3	0	0	30	0	3	52.8	0	11	19	0
Anavi-Lev, 2013 (Anavi-Lev et al., 2013)	Retro	N/R							0	0	15	0	0	51.96	0	2¥	9	1
Angiero, 2009 (Angiero et al., 2009)	Retro	3	0	0	0	0	0	1	0	3	0	0	1	15.5	N/R			
Saussez, 2009 (Saussez et al., 2009)	Retro	0	2	2	0	0	0	0	0	2	2	0	0	50.5	0	1	2	1
Yarom, 2007 (Yarom et al., 2007)	Retro	0	0	9	0	0	0	0	0	0	9	0	0	48.66	N/R			
Stanton and Balasanian, 2009 (Stanton and Balasanian, 2009)	Retro	1	0	3	0	0	0	0	0	1	3	0	0	N/R	N/R			
Longobardi, 2007 (Longobardi et al., 2007)	CS	0	0	0	0	0	3	1	0	0	4	0	1	93	N/R			
Hong, 2010 (Hong et al., 2010)	Retro	0	0	16	2	0	0	5	0	0	24	0	0	43.1	0	1	23	0
Chiu, 2010 (Chiu et al., 2010)	CS	0	0	12	0	0	0	0	0	0	12	0	0	37	0	0	3	9
Park, 2010 (Park et al., 2010)	CS	0	0	5	0	0	0	0	0	0	5	0	0	33	N/R			
Lazarovici, 2009 (Lazarovici et al., 2009)	CS	0	0	16	0	0	0	0	0	0	16	0	0	67	N/R			
Lazarovici, 2010 (Lazarovici et al., 2010)	CS	0	0	11	0	0	0	0	0	0	11	0	0	68	N/R			
Voss, 2012 (Voss et al., 2012)	Retro	1	0	3	0	0	0	0	0	1	3	0	0	48.25	0	0	3	1
Nomura, 2013 (Nomura et al., 2013)	CS	0	0	2	3	0	0	0	0	0	5	0	0	31.2	0	3	2	0
Jabbour, 2012 (Jabbour et al., 2012)	Retro	0	0	4	0	0	0	0	0	1	3	0	0	66	0	4	0	0
Hutchinson, 2010 (Hutchinson et al., 2010)	CS	0	0	10	0	0	0	0	0	0	10	0	0	36	10	0	0	0
Rachner, 2013§ (Rachner et al., 2013)	CR	0	0	0	0	0	0	0	1	0	0	1	0	2#	N/R			
Otto, 2013§ (Otto et al., 2013b)	CR	0	0	0	0	0	0	0	2	0	0	2	0	N/R	N/R			
Neuprez, 2014 (Neuprez et al., 2014b)	CR	0	0	0	0	0	0	0	1	0	0	1	0	2#	N/R			
Otto, 2011 (Otto et al., 2011)	Retro	0	0	28	4	3	1	1	0	0	37	0	0	57.8	N/R			
Marx, 2007 (Marx et al., 2007)	Prosp	0	0	27	3	0	0	0	0	0	30	0	0	67.56	0	12	14	4
Almasan, 2011 (Almasan et al., 2011)	Retro	4	0	7	0	1	0	0	0	4	8	0	0	20	N/R			
Di Fede, 2013 (Di Fede et al., 2013)	Retro	0	0	77	2	1	7	0	0	0	87	0	0	44.9	15	12	53	7
Diniz-Freitas, 2012 (Diniz-Freitas et al., 2012)	Retro	0	0	14	0	3	0	0	0	0	17	0	0	62.35	1	0	14	2
Giovannacci, 2016 (Giovannacci et al., 2016)	Retro	0	0	4	0	1	0	1	0	0	6	0	0	74.2	0	1	2	1
Goss, 2010 (Goss et al., 2010)	CS	0	0	3	1	0	0	1	0	0	5	0	0	46.2	N/R			
Hallmer, 2014 (Hallmer et al., 2014)	CS	0	0	22	2	0	0	0	0	0	24	0	0	N/R	0	5	13	6
Jacobsen*, 2012 (Jacobsen et al., 2012)	Retro	3	5	12	1	11	1	0	0	8	25	0	0	42	N/R			
Lee and Suzuki, 2015 (Lee and Suzuki, 2015)	CS	4	0	0	0	0	0	0	0	4	0	0	0	1.75#	0	0	3	1
López-Cedrún, 2013 (Lopez-Cedrun et al., 2013)	CS	0	0	6	0	1	0	0	0	0	7	0	0	69.7	N/R			
Pelaz, 2014 (Pelaz et al., 2014)	CS	0	0	6	0	3	0	0	0	0	9	0	0	54	0	0	0	9
Pichardo, 2013 (Pichardo and van Merkesteyn, 2013)	Retro	0	6	6	1	0	0	5	0	6	8	0	4	67.61	N/R			
Yamazaki, 2012* (Yamazaki et al., 2012)	Retro	0	0	15	7	0	5	0	0	0	21	0	0	42.23	N/R			
Favia, 2009 (Favia et al., 2009)	CS	0	0	15	3	2	4	0	0	2	22	0	0	20	0	5	19	0
Kwon and Kim, 2009 (Kwon and Kim, 2009)	CS	0	0	17	1	0	0	0	0	0	18	0	0	47.28	0	11	7	3
Vescovi, 2014 (Vescovi et al., 2014)	Retro	N/R							N/R	N/R				90.85	0	15	0	0
Total		**28**	**18**	**475**	**35**	**34**	**24**	**26**	**14**	**46**	**503**	**14**	**17**	**51.9 ± 18**	**41**	**110**	**203**	**48**

CS: Case Series, Retro: Retrospective, Prosp: Prospective, CR: Case Report, N/R: Not Reported, §: Cases with denosumab and previous oral BPs, Dmab: Denosumab, IV: Intravenous, SC: Subcutaneous, C: Combination, Z: Zoledronate, P: Pamidronate, A: Alendronate, R: Risedronate, I: Ibandronate, #: Number of denosumab (2.1 ± 1.2) or yearly ZA doses (1.6 ± 0.17), ¥: S0-1 and the stage is not mentioned for 3 patients, *Patients may belong to more than one drug group (no combination has been specified, all denosumab patient had dose of 60 mg/6 months).

Mavrokokki estimated that the frequency of MRONJ would increase from 0.01%–0.04% to 0.09%–0.34% after dental extraction in patients who were administered oral BPs (Mavrokokki et al., 2007). However, it seems to be the underlying chronic local infection, which is usually the main indication of tooth extraction, is the direct trigger of bone necrosis rather than the extraction itself (Otto et al., 2015). Acidity, which can increase in case of infection, can activate and release BPs and can promote their cytotoxicity. Based on these findings, another theory has suggested that pH drop due to local infection can play an important role in MRONJ onset (Otto et al., 2010a, 2010b). A retrospective cohort study was performed on 72 patients with a history of BPs administration and tooth extraction with plastic wound closure (Otto et al., 2015). Only three patients had MRONJ in four of the 216 extraction sites. Dentoalveolar surgery, such as implants insertion or removal or ridge augmentation, was reported in 21.1% of the cases. BPs can interfere with the initial phases of extraction socket remodelling, which may predispose to infection and trigger osteonecrosis (Otto et al., 2015). Kos and colleagues have suggested the direct role of BPs in bacterial adhesion and biofilm formation (Kos et al., 2015). According to this study, bacterial cells adhere to exposed bone surface after extraction or dentoalveolar surgery and the presence of BPs promotes further bacterial colonization and triggers osteomyelitis. Therefore, the primary goal should be to avoid any dentoalveolar infection during treatment with ARDs. This highlights the importance of oral screening before ARDs administration and of planned oral examinations during the treatment. Many authors identified local trauma from prosthesis as a potential trigger of MRONJ (Villa et al., 2011; O'Ryan and Lo, 2012; Chiu et al., 2014; Hallmer et al., 2014). In our review, 8.4% of the patients had it. Prosthesis regular check-ups and maintenance of good oral health are strongly recommended to avoid any trigger that may initiate MRONJ. Periodontal disease or endodontic treatment was described only for 4.8% of the cases. Only in

17.2% of the cases no preceding event prior to MRONJ was identified.

Some concomitant diseases and medications can increase the risk of MRONJ. Corticosteroids and immunosuppressive therapy are considered important risk factors in relation to MRONJ (Ruggiero et al., 2014; Kim et al., 2016). In line with this, 39.1% of the cases in our study had been treated with these medications. Many studies have shown that diabetes could be a risk factor for MRONJ as it can aid in bone atrophy and decrease endothelial growth and reduce metabolism (Khamaisi et al., 2007; Bocanegra-Perez et al., 2012; Ruggiero et al., 2014). In our review, 17% of the patients had a history of diabetes mellitus, which supports this finding. Smoking did not show a significant and consistent relation to MRONJ (Ruggiero et al., 2014). Correspondingly, in our review only 5.5% of the patients were reported to be current or former smokers. Interestingly, Farrugia and colleagues reported the absence of any comorbidities or concomitant medications in relation to MRONJ patients under oral BPs (4 out of 23 patients). On the other hand, comorbidities were reported for those taking the most potent intravenous BPs (Farrugia et al., 2006).

Most of our cases are in stage 2 and stage 1, 50.5% and 27.4% respectively. Stage 0 and stage 3 were detected only in 22% of the patients. Most of the patients seek treatment after the start of signs and symptoms, not during the hardly detectable early stages of the disease and not during the advanced stages in which severe clinical manifestations present. According to AAOMS position paper, the objective of MRONJ staging is mainly to determine treatment methods and this is out of the scope of our systematic review (Ruggiero et al., 2014).

One of the limitations of this study is the possibility of missing some articles despite the broad search as some databases such as EMBASE and SCOPUS were not included in the search. One of the biggest obstacles regarding MRONJ in relation to osteoporosis is the lack of randomized clinical trials that are specified to register MRONJ cases in detail and to report their diagnostic process and disease characteristics. Our review is based on the available literature for this study population, which are mostly retrospective studies, case reports, and case series, which all have their limitations regarding evidence quality.

5. Conclusion

In conclusion, many potential risk factors can play a role in MRONJ development in osteoporosis patients. It is crucial to recognize these factors, to identify the preventable and the unpreventable ones, and to plan strategies to minimize the risk of MRONJ. The duration of BPs intake and local infection seem to be the main risk factors. Patients who are under treatment with corticosteroids and/or immunosuppressants may have a higher risk to develop MRONJ even if the BPs duration is less than 4 years. Before considering long-term treatment with ARDs, the patients should be educated about the prevalence of MRONJ and its associated risk factors. Optimization of oral and dental health before considering treatment with ARDs is mandatory. Teeth with a poor prognosis should be extracted with enough time prior to ARDs induction. Any ill-fitted dentures should be repaired and any local infection should be managed. After starting the therapy, semi-annual thorough oral examinations are recommended. In addition, the patients should be strongly reminded to report any susceptible early signs and symptoms immediately. In case of any detected infection, immediate management with less traumatic procedures should be performed. We strongly stress the importance of comprehensive oral examinations before and during the therapy and to guide the patient to maintain good dental health and optimal oral hygiene in order to limit the potential local risk factors.

Conflicts of interest

Suad Aljohani, Riham Fliefel, Jacob Ihbe, Jan Kühnisch, Michael Ehrenfeld and Sven Otto declare that they have no conflict of interest.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments

SO and RF acknowledge the financial support of AO foundation (AOCMF 14-070) on medication related osteonecrosis of the jaw (MRONJ) research over the years. SO acknowledges the financial support of Friedrich-Bauer and Curt-Bohnewand foundations. SO has received honoraria for scientific talks from Nobel Biocare, CAMLOG and AMGEN.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jcms.2017.05.028.

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PUBLICATION 2

Osteonecrosis of the Jaw in Patients Treated with Denosumab: a Multicenter Case Series.

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Journal of Cranio-Maxillo-Facial Surgery, Available online 31 May 2018

Journal of Cranio-Maxillo-Facial Surgery xxx (2018) 1–11

Contents lists available at ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

Osteonecrosis of the jaw in patients treated with denosumab: A multicenter case series

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ARTICLE INFO

Article history:
Paper received 9 October 2017
Accepted 24 May 2018
Available online xxx

Keywords:
Denosumab
Jaw osteonecrosis
MRONJ
ARONJ
DRONJ
ONJ

ABSTRACT

Purpose: Osteonecrosis of the jaw has been recently reported in patients receiving denosumab for the treatment of metastatic bone disease and osteoporosis. It is essential to investigate this disease as a new osteonecrosis entity in order to recognize its optimal management strategies.
Materials and Methods: A total of 63 cases of denosumab-related osteonecrosis of the jaw (DRONJ) diagnosed at two clinical centres were retrospectively reviewed. Demographics, comorbidities, antiresorptive medication use, local preceding event, location, DRONJ stage, treatment and treatment outcomes were analyzed.
Results: In all, 69 MRONJ lesions in 63 patients were diagnosed. The mean patient age was 70 ± 9 years. Denosumab was the only received antiresorptive medication in 50.8% of the patients. Discontinuation of denosumab prior to treatment was recorded for 66.7% of the patients, with a mean period of 6 ± 3.4 months. Stage 2 was the most common stage of the disease (71%). The lesions were predominantly located in the mandible (63.5%). The most common preceding local event was extraction (55.6%). Surgical treatment was performed in 95.7% of the cases, while purely conservative treatment was performed in 4.3%. DRONJ healed after surgical treatment in 71.7% of the treated lesions. Complete mucosal healing was achieved in 77.2% of the lesions treated with fluorescence-guided surgery (17/22). Clinical characteristics and treatment outcomes were not significantly different between patients with and without previous intake of bisphosphonates.
Conclusion: DRONJ is more prevalent at extraction and local infection sites in cancer patients. Within the limitation of this study, surgical treatment, particularly fluorescence-guided surgery, appears to be effective for the management of DRONJ. The prior use of bisphosphonates does not seem to affect severity nor the treatment success rate of DRONJ.

1. Introduction

Bone metastasis is not uncommon in patients with advanced cancer stages. It has been shown in 70–80% of patients with breast or prostate cancer and 30–40% of patients with lung cancer or other solid tumors (Lipton et al., 2012). Skeletal-related events (SREs) that comprise pathologic fracture, spinal cord compression, hypercalcemia, and radiation or surgery to bone are prevalent in patients with bone metastasis (Oster et al., 2013). The cumulative incidence of SREs at 2 years is 54.2% in patients with breast cancer, 41.9% in patients with prostate cancer, and 47.7% in patients with lung cancer (Oster et al., 2013). SREs can negatively affect patients' quality of life and result in bone pain, fractures, bladder and bowel disturbances, anxiety, depression, and increased mortality (Oster et al., 2013). At present, antiresorptive medications, including bisphosphonates and denosumab, are the current treatment

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https://doi.org/10.1016/j.jcms.2018.05.046
1010-5182/

options to prevent SREs. The results of three randomized trials showed that denosumab is superior to bisphosphonates in regard to SREs treatment and prevention (Stopeck et al., 2010; Fizazi et al., 2011; Henry et al., 2014). Furthermore, antiresorptive medications are also used for osteoporosis and are proven to reduce bone turnover markers, improve bone mineral density, decrease fracture risk, and improve the quality of life (McClung et al., 2013).

The first case series of bisphosphonate-related osteonecrosis of the jaw (BRONJ) were published in the early 2000s and followed by hundreds of reports, which raised the awareness of this potential complication (Marx, 2003; Bagan et al., 2016). Denosumab was also shown to be related to jaw osteonecrosis in both cancer and osteoporosis patients (Olate et al., 2014; Ruggiero et al., 2014). Initially, cases of denosumab-related osteonecrosis of the jaw (DRONJ) were reported during randomized clinical trials for the treatment of cancer and osteoporosis (Fizazi et al., 2009, 2011; Aghaloo et al., 2010; Henry et al., 2011; Lipton et al., 2012; Malan et al., 2012; Saad et al., 2012; Bone et al., 2013; Qi et al., 2014; Papapoulos et al., 2015; Sugimoto et al., 2015; Stopeck et al., 2016). As denosumab was approved and came into use, more cases were reported (Diz et al., 2012; Aghaloo et al., 2014; O'Halloran et al., 2014; Olate et al., 2014; You et al., 2015; Owosho et al., 2016; Qaisi et al., 2016). The risk of DRONJ in osteoporosis patients treated with denosumab is estimated to be from 0.01% to 0.03%, and in cancer patients treated with denosumab to be from 1% to 2% (Aljohani et al., 2017). This incidence is comparable to that of BRONJ. In a combined analysis of three phase III trials in patients with metastatic bone disease receiving antiresorptive therapies J, incidence of ONJ was higher in denosumab group in comparison to the bisphosphonates group, 1.8% and 1.3% respectively (Saad et al., 2012). However, the cumulative incidence of ONJ was not significantly different between the treatment groups. In order to accommodate osteonecrosis cases appearing in relation to denosumab and antiangiogenic agents, the American Association of Oral and Maxillofacial Surgeons (AAOMS) changed the name of BRONJ to medication-related osteonecrosis of the jaw (MRONJ) (Ruggiero et al., 2014).

Although the reported cases of DRONJ are limited, DRONJ seems to share several clinical characteristics with BRONJ. Several risk factors appear to be related to their development, such as local infection; mainly periodontitis; dental extraction, dentoalveolar surgery and denture sore spots. Their incidence may increase with chronic corticosteroid therapy, diabetes mellitus, immunosuppressants and chemotherapy (Ruggiero et al., 2014). While favorable treatment outcomes for the surgical treatment in patients suffering from BRONJ have been reported, the information regarding treatment outcomes of DRONJ is still sparse. Indeed, there are limited data regarding the risk factors and natural history of DRONJ as well as management strategies and respective outcomes.

Here we describe the largest clinical series so far of DRONJ patients from two German academic Maxillofacial Surgery departments. The objective of this study is to analyze the antiresorptive medication characteristics, demographics, related comorbidities, local preceding events, treatment strategies, and treatment outcomes of DRONJ. Patients with prior intake of bisphosphonates were included in this series in order to compare bisphosphonate-naive and non–bisphosphonate-naive patients in regards to the clinical characteristics and treatment outcomes.

2. Materials and methods

2.1. Study design

A retrospective medical chart review was carried out at two German institutions: the Department of Oral and Maxillofacial Surgery, Ludwig-Maximilians-University, Munich, and the Department of Oral and Maxillofacial Surgery and University Medical Center Hamburg-Eppendorf, Hamburg. Institutional Review Board approval was obtained at both participating institutions (083-11, Ludwig-Maximilians-University and PV3806, University Medical Center Hamburg-Eppendorf). All patients diagnosed and treated for DRONJ between July 2011 and April 2017 were identified.

This study included all patients diagnosed with DRONJ based on the following criteria: 1) MRONJ diagnosis based on AAOMS criteria (Ruggiero et al., 2014) in patients receiving denosumab with or without history of bisphosphonates intake; and 2) a minimum period of 3 months between the last administration of bisphosphonates and DRONJ onset.

The exclusion criteria were: a history of head and neck radiation, obvious metastasis to jaw bones and a history of bisphosphonates within the 3 months preceding the onset of DRONJ. According to AAOMS, MRONJ can be diagnosed if antiresorptive or antiangiogenic therapy was followed by exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for more than 8 weeks with no history of radiation therapy or obvious metastatic disease to the jaws (Ruggiero et al., 2014).

2.2. Data extraction

A total of 63 patients were identified and fulfilled the entry criteria. The following variables were recorded and reviewed: demographic data, the main indication of denosumab administration, comorbidities (diabetes mellitus, cardiovascular disease, allergy, autoimmune disease, hypothyroidism, corticosteroids and chemotherapy), number of denosumab doses, preceding local event, time between local event and MRONJ onset, clinical stage at initial presentation and location of DRONJ, treatment modalities (if any), follow-up period and outcomes were recorded and reviewed. The lesions were classified into 4 stages (0–3) according to the last position paper of the AAOMS (Ruggiero et al., 2014).

2.3. Data analysis

Descriptive statistics were used to report patient characteristics. Categorical variables such as MRONJ location, treatment modality and treatment outcome were investigated by the Fisher exact test. Continuous variables such as number of denosumab doses were investigated using the Student t test. A p value of less than 0.05 was considered statistically significant. All statistical analyses were performed with SPSS software (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patients

In all, 69 MRONJ lesions in 63 patients were identified. The average age was 70 ± 9 years (Table 1). Demographics including gender, indication of denosumab use and comorbidities are presented in Table 2.

3.2. Antiresorptive medications

The number of denosumab doses was recorded for 47 patients with an average of 16.4 ± 12.6 doses. Table 3 presents denosumab types and doses used and the characteristics of previous bisphosphonate use.

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3.3. Location of DRONJ

The mandible was affected in 40 cases (63.5%), the maxilla in 17 cases (27%) and both jaws in 6 cases (9.5%). MRONJ was located in the molar area in 20 patients (31.7%); in both premolar and molar area in 16 cases (25.4%); in the anterior, premolar and molar areas in 10 cases (15.9%); the anterior area in 6 cases (9.5%); in both anterior and premolar areas in 4 patients (6.3%); premolar area in 3 cases (4.8%) and in anterior and molar area in 3 cases (4.8%); and involving the hard palate in one case (1.6%). In this study, stage 2 was the most common (n = 49, 71%). Stage 3 MRONJ was identified in 10 lesions (14.5%), stage 1 MRONJ in 7 lesions (10.1%) and stage 0 MRONJ in 3 lesions (4.3%).

3.4. Potential local risk factors

Tooth extraction (mainly due to local infection), either as the only preceding event or in combination with other local factors, was recorded for 55.6% of the cases (n = 35) (Table 4). The mean period between the preceding local event and start of signs and symptoms was recorded for 32 cases and was 2.6 ± 1.6 months.

3.5. Treatment strategies

Surgical treatment was performed in 66 lesions in 60 patients (95.7%), of them 27 lesions underwent fluorescence-guided surgery (41%), 38 lesions were treated with conventional surgery (57.5%), and one patient underwent extraction and curettage (1.5%) (Table 5). Surgical treatment included antibiotic treatment, complete surgical removal of necrotic bone, smoothening of sharp bony edges and plastic coverage (Fig. 1 a–l and Fig. 2a–e). For some patients who received operative treatment, prior conservative treatment had been tried without success. Purely conservative treatment was performed for 3 lesions (4.3%). The mean of follow-up period was 10.4 ± 9.5 months (ranging from 3 to 48 months). Of the cohort, 66.7% underwent denosumab holiday prior to the surgical treatment or the conservative therapy. For conservatively treated patients, denosumab were discontinued for a mean period of 10 ± 7 months, while for surgically treated patients, denosumab was discontinued for a mean period of 5.6 ± 3 months.

3.6. Treatment outcomes

Eleven patients (13 lesions) were lost to follow-up. Complete healing was defined as complete mucosal coverage with absence of MRONJ signs and symptoms. Partial healing is defined as improvement of the signs and symptoms without complete resolution of the lesion. A total of 53 lesions treated surgically were followed up. Surgical treatment has led to healing in 38 lesions (71.7%), non-healing in 9 cases (17%), and partial healing in 6 sites (11.3%).

A total of 22 lesions treated with fluorescence-guided bone resection were followed up. Complete mucosal healing was obtained in 77.3% of the patients treated by fluorescence-guided bone surgery (17/22) (Fig. 2f–g). One lesion had partial healing (4.5%), and 4 lesions (18.2%) did not heal.

In all, 31 lesions managed with conventional surgery were followed up. Complete mucosal healing was obtained in 67.7% of the patients treated with this surgical technique (21/31). Five lesions (16.1%) failed to heal, while 5 (16.1%) healed partially. The lesion treated with extraction and curettage of the bony socket healed completely.

Two of the 3 cases treated conservatively healed completely, while 1 case (33.3%) failed to heal. Treatment outcome has no statistically significant relationship with chemotherapy, DRONJ stage and denosumab cessation.

3.7. Impact of previous use of bisphosphonates

A total of 34 lesions in 31 patients with previous bisphosphonates were detected. No significant difference in the demographics, clinical characteristics and DRONJ stage of bisphosphonate-naïve patients (n = 32, 50.8%) and those who had had bisphosphonates before (n = 31, 49.2%) (Table 6). The average number of denosumab doses was slightly less, but still insignificant, in patients who had received bisphosphonates than in patients without a bisphosphonate history (15.3 ± 14.6 and 17.5 ± 10.6 doses, respectively). Moreover, statistical significance between prior bisphosphonate therapy and outcomes of treatment was not observed (p = 0.654).

4. Discussion

Literature searches did not reveal more extensive case series describing the clinical presentation and management of DRONJ. A total of 63 DRONJ patients were identified, 32 of them had denosumab as the only received antiresorptive medication. The available studies are mostly case reports and a few small case series of less than 20 patients. Within the limitations of a retrospective chart review, we aim in the present series to elucidate the clinical characteristics, potential risk factors, treatment modalities and treatment outcomes in DRONJ patients. Another aim is to find the effect of prior administration of bisphosphonates on DRONJ risk, severity and treatment outcomes. Furthermore, the time between the local event, if any, and MRONJ onset were analyzed to further characterize the clinical course of the disease.

In the present study, females (58%) were affected slightly more than males. This is comparable to the findings of de Oliveiro and his colleagues based on a review of 17 reported DRONJ cases (de Oliveira et al., 2016). The same review reported osteoporosis and osteopenia as the most common primary disease (47%) and only 5.9% had breast cancer, while almost half of our cohort was affected by breast cancer (42.9%) and only 14.3% had osteoporosis. In agreement with our findings, a recent case series of 17 DRONJ patients reported that 52.9% of the cases had breast cancer (Hoefert et al., 2017). In general, as estimated by AAOMS, the risk of MRONJ for metastatic cancer patients treated with denosumab is 0.7%–1.9% (Ruggiero et al., 2014). On the other hand, the risk in osteoporosis patients treated with either zoledronate or denosumab is much lower (0.017%–0.04%) (Ruggiero et al., 2014).

Potential systemic risk factors of MRONJ, including comorbidities and concomitant medications, have been evaluated. However, evidence-based findings remain sparse. Saad et al. found that there was no association between anemia, diabetes mellitus, or received chemotherapy and MRONJ. However, the same study reported a slightly greater number of MRONJ among the patients using systemic corticosteroids (Saad et al., 2012). Corticosteroids are known to delay wound healing and, unsurprisingly, could potentially contribute to the development of MRONJ. In our study, 11.1% of the patients received long-term corticosteroid therapy. Antiangiogenic agents can suppress vascular regeneration and subsequently might promote ONJ. In three prospective trials, antiangeogenic medications were associated with MRONJ (15.7%) more than corticosteroids intake (Saad et al., 2012). Several cases of MRONJ in relation to antiangiogenic medications, even with no concomitant intake of antiresorptive medications, were reported (Estilo et al., 2008; Disel et al., 2012; Hopp et al., 2012; Santos-Silva et al., 2013). On the other hand, an analysis of three large prospective trials in advanced breast cancer in 3,560 patients receiving bevacizumab with or without bisphosphonates therapy found that bevacizumab use did

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Table 1
Summary of the clinical characteristics.

Case	Age	Sex	Primary disease	Dmab dose	Number of doses	Hx of BPs	Comorbidities	Local factors
1	59	F	OP	60 mg/6 months	1	Yes	Allergy	Extr
2	68	F	OP	60 mg/6 months	2	No	RA, allergy, hypothyrodism	Extr, P, PI
3	67	M	Prostate ca	120 mg/4 weeks	…	Yes	CS, DM II, CVD	Scaling and RP, P
4	63	M	Prostate ca	120 mg/4 weeks	…	Yes	RA, CS	Extr
5	75	F	OP	60 mg/6 months	…	No	HT, COPD, CVD	Extr
6	66	M	Prostate ca	120 mg/4 weeks	18	No	HT, hypothyrodism	Extr
7	66	F	Brest ca	120 mg/4 weeks	22	No	Allergy, DM II	Local trauma
8	76	F	Lung ca	120 mg/4 weeks	3	Yes	HT	Extr
9	56	F	Breast ca	120 mg/4 weeks	7	Yes	Allergy	Extr, local trauma
10	69	M	Prostate ca	120 mg/4 weeks	20	Yes	HT	Extr
11	70	M	Prostate ca	120 mg/4 weeks	…	Yes	CVD	Extr
12	67	F	Breast ca	120 mg/4 weeks	7	No	OP, CS	Extr
13	76	F	OP	60 mg/6 months	6	Yes	RA, CS	P
14	78	M	Prostate ca	120 mg/4 weeks	11	No	DM II, CS	Extr
15	80	F	Breast ca	120 mg/4 weeks	29	No	HT, RA	P
16	65	M	Prostate ca	120 mg/4 weeks	36	Yes	Allergy, CS	Extr
17	58	F	Breast ca	120 mg/4 weeks	35	Yes	Allergy	None
18	63	F	Melanoma	120 mg/4 weeks	…	No	HT, RA, allergy, hypothyrodism	Ext
19	56	F	Breast ca	120 mg/4 weeks	5	Yes	CVD, allergy	Ext
20	74	M	Thyroid ca	120 mg/4 weeks	8	Yes	COPD, allergy, Asthma	P
21	50	F	Breast ca	120 mg/4 weeks	24	No	CVD	Extr
22	74	F	Breast ca	120 mg/4 weeks	45	Yes	HT, allergy	None
23	76	F	Breast ca	120 mg/4 weeks	18	No	None	Extr, local trauma
24	64	F	Breast ca	120 mg/4 weeks	8	Yes	OP, allergy	Extr
25	83	F	Breast ca	120 mg/4 weeks	2	Yes	DM II, allergy	Local trauma
26	72	M	Prostate ca	120 mg/4 weeks	36	No	DM II, HT	None
27	52	F	Breast ca	120 mg/4 weeks	24	No	Allergy	None
28	79	F	Breast ca	120 mg/4 weeks	11	No	DM II	Extr, P
29	67	M	Breast ca	120 mg/4 weeks	10	No	Hypothyrodism, allergy	Extr, local trauma
30	78	M	OP	60 mg/6 months	6	Yes	HT, hyperthyroidism	Local trauma
31	71	M	Breast ca	120 mg/4 weeks	…	No	CVD, hypertension	None
32	74	F	Kidney ca	120 mg/4 weeks	6	Yes	HT, RA, CS, Retuximab	Local trauma
33	72	F	OP	60 mg/6 months	1	Yes	CVD, allergy	P
34	67	F	Breast ca	120 mg/4 weeks	30	No	HT	None
35	78	M	Prostate ca	120 mg/4 weeks	31	Yes	DM II	Extr, P
36	82	F	OP	60 mg/6 months	6	No	CVD, CRD	Extr, P
37	65	M	Prostate ca	120 mg/4 weeks	…	Yes	COPD, DM II	P
38	66	M	MM	120 mg/4 weeks	…	Yes	Hypothyrodism, HT, CVD	Extr
39	80	F	Breast ca	60 mg/3 months	3	Yes	RA, CS	Extr
40	48	F	Breast ca	120 mg/4 weeks	30	No	None	Extr
41	75	F	Breast ca	120 mg/4 weeks	5	Yes	CVD, allergy, hypothyrodism	None
42	71	F	Breast ca	120 mg/4 weeks	22	Yes	OP	None
43	74	F	Breast ca	120 mg/4 weeks	20	Yes	CVD, allergy	P
44	60	F	Breast ca	120 mg/4 weeks	24	No	None	Extr
45	67	M	Prostate ca	120 mg/4 weeks	22	No	None	Extr
46	74	F	Breast ca	120 mg/4 weeks	…	Yes	Renal insufficiency II	None
47	86	F	Breast ca	120 mg/4 weeks	…	Yes	None	Extr
48	84	F	MM	120 mg/2 months	…	No	DM II	Extr
49	73	F	OP	60 mg/6 months	…	Yes	HT	Extr
50	52	M	Kidney ca	120 mg/4 weeks	24	No	Unilateral nephrectomie	Extr
51	74	F	OP	60 mg/6 months	1	No	COPD, HT	Extr
52	55	F	Breast ca	120 mg/4 weeks	48	Yes	None	Extr
53	56	M	Prostate ca	120 mg/4 weeks	…	No	HT	None
54	74	M	Prostate ca	120 mg/4 weeks	6	No	HT	None
55	73	M	Kidney ca	120 mg/4 weeks	12	No	None	Site of implant
56	72	M	Thyroid Ca	120 mg/4 weeks	36	No	HT	PI
57	86	M	Prostate ca	120 mg/2 months	10	Yes	HT, history of kidney cancer	Site of implant
58	77	M	Prostate ca	120 mg/4 weeks	…	No	HT	None
59	73	M	Prostate ca	120 mg/4 weeks	24	Yes	None	Extr
60	83	M	Prostate ca	120 mg/3 months	…	No	DM II	None
61	82	F	Breast ca	60 mg/6 months	5	No	COPD, CVD, HT	Ridge augmentation
62	69	M	Kidney ca	120 mg/4 weeks	12	No	CRD, HT	Extr
63	75	F	Breast ca	120 mg/4 weeks	…	No	HT	Extr

Dmab: denosumab, Hx: history, BPs: bisphosphonates, …: missing data, M: male, F: female, OP: osteoporosis, MM: multiple myeloma, HT: hypertension, RA: rheumatoid arthritis, DM II: type 2 diabetes mellitus, CO: corticosteroids, CVD: coronary vascular disease, COPD: coronary obstructive pulmonary disease, CRD: chronic renal disease, Extr: extraction, P: periodontitis, PI: peri-implantitis, RP: root planing.

not increase BRONJ incidence (0.9–2.4%) (Guarneri et al., 2010). Nevertheless, the same analysis estimated ONJ incidence of 0.3–0.4% in those who received bevacizumab without bisphosphonate therapy. These findings indicate that antiangeogenic agents could potentially contribute to ONJ risk. In our cohort, 7.9% of the cases had received antiangiogenic medications. According to a meta-analysis of events reported in seven denosumab clinical trials, chemotherapy was found to promote DRONJ development (Boquete-Castro et al., 2016). In line with this, 75.9% of our cohort had received chemotherapy. Diabetes mellitus was reported in only

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Table 2
Demographics and comorbidities.

	n (%)
Gender	
Female	37 (59%)
Male	26 (41%)
Indication for denosumab use	
Breast cancer	27 (42.9%)
Prostate cancer	17 (27%)
Osteoporosis	9 (14.3%)
Kidney cancer	4 (6.3%)
Multiple myeloma	2 (3.2%)
Thyroid cancer	2 (3.2%)
Lung cancer	1 (1.6%)
Melanoma	1 (1.6%)
Comorbidities	
Type 2 diabetes mellitus	9 (14.5%)
Rheumatoid arthritis	6 (9.5%)
Corticosteroids	7 (11%)
Allergy	16 (25.4%)
Hypertension	11 (17.5%)
Hypothyrodism	22 (35%)
Asthma	7 (11%)
Osteoporosis	1 (1.6%)
History of kidney cancer	1 (1.6%)
Chronic obstructive pulmonary disease	1 (1.6%)
Chemotherapy	41 (76%)
Long-term steroid use	7 (11%)
Antiangeogenic medications	5 (7.9%)
Rituximab	1 (1.6%)

17.6% of the reported DRONJ cases (de Oliveira et al., 2016), which does not differ greatly from our findings of 14.5%.

Ironically, the pathogenesis of MRONJ has not yet been fully elucidated, despite the large body of literature available. Bone remodeling is very crucial to maintain a healthy osseous tissue. This is particularly essential in jawbones in order to remove the microdamage resulting from masticatory forces and dental infection. However, this important physiological process can be strongly derailed by antiresorptive medications, leading to accumulation of necrotic tissue, and thereby can result in osteonecrosis of jawbones. This might explain the unique localization of MRONJ almost exclusively in the jawbones. The mandible, with its dense bone and single blood supply, is more commonly affected with MRONJ than

Table 3
Antiresorptive medication characteristics.

	n (%)
History of bisphosphonate use	
No	32 (50.8%)
Yes (mean duration was 36.9 ± 23 months)	31 (49.2%)
Type of bisphosphonates	
Zoledronate	21 (67.5%)
Alendronate	2 (6.5%)
Pamidronate	2 (6.5%)
Ibandronate	2 (6.5%)
Zoledronate and pamidronate	4 (12.9%)
Unknown	2 (6.5%)
Type denosumab	
XGEVA®	52 (82.5%)
Prolia®	11 (17.4%)
Denosumab dose	
120 mg every 4 weeks	49 (77.8%)
60 mg every 6 months	10 (15.9%)
120 mg every 2 months	2 (3.2%)
120 mg every 3 months	1 (1.6%)
60 mg every 3 months	1 (1.6%)
Denosumab holiday	
Yes (an average of 6 ± 3.4 months)	42 (66.7%)
No	4 (6.3%)
Unknown	17 (27%)

Table 4
Preceding local event.

Local event	n (%)
Extraction only	28 (44.4%)
Periodontitis	6 (9.5%)
Local trauma from ill-fitted denture	4 (6.3%)
Extraction and trauma from ill-fitted denture	3 (4.8%)
Extraction and periodontitis	3 (4.8%)
Extraction, periodontitis and peri-implantititis	1 (1.6%)
Implant placement	2 (3.2%)
Peri-implantitis	1 (1.6%)
Ridge augmentation	1 (1.6%)
Scaling and root planing due to periodontitis	1 (1.6%)
Unknown	13 (20.6%)

the maxilla, in a 2:1 ratio (Ruggiero et al., 2014; Hoefert et al., 2017). The same ratio was identified for DRONJ localization in this study. The involvement of the two strong bone-targeted osteoclast inhibitors in MRONJ onset strongly suggests the osteoclast suppression, and thereby low bone turnover, as a main causative factor. However this suppression of bone remodeling is not limited to the jaws and could show also in the other skeletal parts, despite the fact that no cases of necrosis there have been reported. It is important to bear in mind that other medications with less potent antiresorptive effects such as oestrogen and calcitonin are not associated with ONJ (Yamashita and McCauley, 2012). Therefore, suppressed bone remodeling does not seem to be satisfactory in verifying the exact pathogenesis of MRONJ. Scintigraphy of the maxilla and mandible did not overly change in comparison with that of other bones in the body, either by bisphosphonates or denosumab in cancer patients (Ristow et al., 2014). All of these findings indicate that there are still missing pieces in the MRONJ pathogenesis puzzle.

Several risk factors can increase the risk of developing MRONJ. Potential local risk factors such as extraction, dento-alveolar surgery, periodontitis and trauma from ill-fitted prostheses were reported. An integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases receiving either zoledronate or denosumab showed that 61.8% of MRONJ patients had tooth extraction prior to its onset (Saad et al., 2012). Tooth extraction was related to 66% and 77% of DRONJ cases in a systematic analysis of events reported in denosumab clinical trials (Boquete-Castro et al., 2016). In agreement with other authors, dental extraction was found to be the most common preceding event to DRONJ onset (55.6%). It is noteworthy that the indication for extraction in most of the cases was local infection. Furthermore, local infection, namely periodontitis as well as peri-implantitis, were detected at sites of necrosis in at least 19% of our cases. The role of infection in BRONJ development was highlighted by the infection-driven MRONJ pathogenesis theory (Otto et al., 2010a, 2010b). Local infection can result in a remarkable increase in local acidity. This can increase the local release of bisphosphonates and lead to suppression of all the cells in the bony tissue, including osteoclasts, osteoblasts, fibroblasts, mesenchymal stem cells and angiogenic cells, and thereby can maximize the antiresorptive effects (Otto et al., 2015). The resulting bone damage can subsequently fail to resolve, and osteonecrosis can develop. Our results suggest that local infection might play a role in DRONJ pathogenesis as in BRONJ pathogenesis and, based on that, preventive dental treatment and meticulous oral hygiene before and during denosumab treatment are highly recommended.

Most of the adverse events of denosumab treatment, including DRONJ, were observed with the dose of 120 mg (Boquete-Castro et al., 2016; de Oliveira et al., 2016; Hoefert et al., 2017). This is similar to the observation of increased risk of BRONJ in relation to

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Table 5
Location, stages, treatment and treatment outcomes.

Case	Site	Stage	Drug holiday	Duration of drug holiday (months)	Treatment	Follow-up (months)	Treatment outcome
1	mandible	2	Yes	6	Surgical	48	Healing
2	mandible	3	Yes	6	Surgical	16	Healing
3	maxilla	2	Yes	6	Surgical	None	
4	mandible	2	Yes	4	Surgical	39	Partial healing
5	mandible	2, 2[a]	Yes	6	Surgical	7	No healing
6	maxilla	2	Unknown		Surgical	None	
7	mandible	0	Yes	18	Non-surgical	29	Healing
8	maxilla	2	Yes	3	Surgical	13	Healing
9	mandible	2	Yes	6	Surgical	4	Healing
10	mandible	2	Yes	6	Non-surgical	12	Healing
11	maxilla	2	Yes	6	Surgical	7	Healing
12	mandible	2	Yes	6	Surgical	2	Healing
13	mandible	0	Yes	6	Surgical	2	Healing
14	mandible	2	Yes	4	Surgical	5	No healing
15	maxilla	2	Yes	3	Surgical	24	Healing
16	mandible	2	Yes	6	Surgical	None	
17	mandible	2	Yes	6	Surgical	None	
18	mandible	1	Yes	6	Surgical	1	Healing
19	both	2, 2[a]	Yes	6	Surgical	12	No healing
20	mandible	1	Yes	13	Surgical	2	Healing
21	mandible	2	Yes	6	Surgical	1	No healing
22	mandible	1	Yes	4	Surgical	6	Healing
23	maxilla	3	Yes	6	Surgical	1	Healing
24	maxilla	3	No		Surgical	12	Healing
25	mandible	2	Yes	8	Surgical	6	Healing
26	maxilla	2	Yes	2	Surgical	6	Healing
27	mandible	2	Yes	6	Surgical	4	Healing
28	mandible	2	Yes	3	Surgical	None	
29	mandible	2	Yes	6	Surgical	2	Healing
30	mandible	2	Yes	6	Surgical	6	Healing
31	mandible	2	Yes	2	Surgical	8	Healing
32	mandible	1	Yes	6	Non-surgical	10	No healing
33	mandible	2	Yes	6	Surgical	6	Healing
34	mandible	1	Yes	3	Surgical	None	
35	both	2, 2[a]	Yes	2	Surgical	None	
36	mandible	2	Yes	7	Surgical	3	Healing
37	both	0, 2[a]	No		Surgical	None	
38	mandible	2	Yes	3	Surgical	20	Partial healing
39	maxilla	1	Yes	6	Surgical	None	
40	mandible	2	Yes	6	Surgical	None	
41	maxilla	2	Yes	18	Surgical	None	
42	maxilla	1, 3[a]	Yes	6	Surgical	3	Healing
43	maxilla	3	Yes	6	Surgical	3	Healing
44	mandible	2	Unknown		Surgical	17	Partial healing
45	mandible	2	Unknown		Surgical	15	Healing
46	mandible	2	Unknown		Surgical	7	Healing
47	mandible	2	Unknown		Surgical	17	Healing
48	maxilla	3	Unknown		Surgical	21	Partial healing
49	mandible	2	Unknown		Surgical	1	Healing
50	mandible	2	Unknown		Surgical	5	Healing
51	mandible	2	Unknown		Surgical	3	Healing
52	mandible	2	Unknown		Surgical	12	No healing
53	maxilla	2	Unknown		Surgical	4	Healing
54	mandible	2	No		Surgical	8	No healing
55	mandible	2	Unknown		Surgical	20	Partial healing
56	mandible	2	Yes	2	Surgical	6	Partial healing
57	maxilla	3	Unknown		Surgical	1	Healing
58	maxilla	3	Unknown		Surgical	2	Healing
59	mandible	2	Yes	4	Surgical	20	Healing
60	maxilla	3	No		Surgical	5	Healing
61	mandible	2, 3[a]	Unknown		Surgical	21	Healing
62	mandible	2	Unknown		Surgical	17	Healing
63	mandible	2	Unknown		Surgical	8	No healing

[a] Two MRONJ lesions in the same patient.

potent intravenous bisphosphonates in oncological dosing (Ruggiero et al., 2014). Denosumab is a very potent antiresorptive medication that can induce dose-dependent osteoclast inhibition just few hours after its subcutaneous injection (Anastasilakis et al., 2012). This high dose of denosumab is used mostly for oncological indications, while the lower dose of 60 mg is indicated for osteopenia and osteoporosis. Increased denosumab concentration combined with the other comorbidities associated with cancer; such as the cancer itself, chemotherapy and antiangeogenic agents; can increase the risk of MRONJ in oncology patients. In agreement with other authors, the majority of DRONJ cases in this study (82.5%) were associated with the dose of 120 mg used for cancer patients (Khan et al., 2015; Boquete-Castro et al., 2016; de Souza Povoa et al., 2016; Favia et al., 2016; Owosho et al., 2016).

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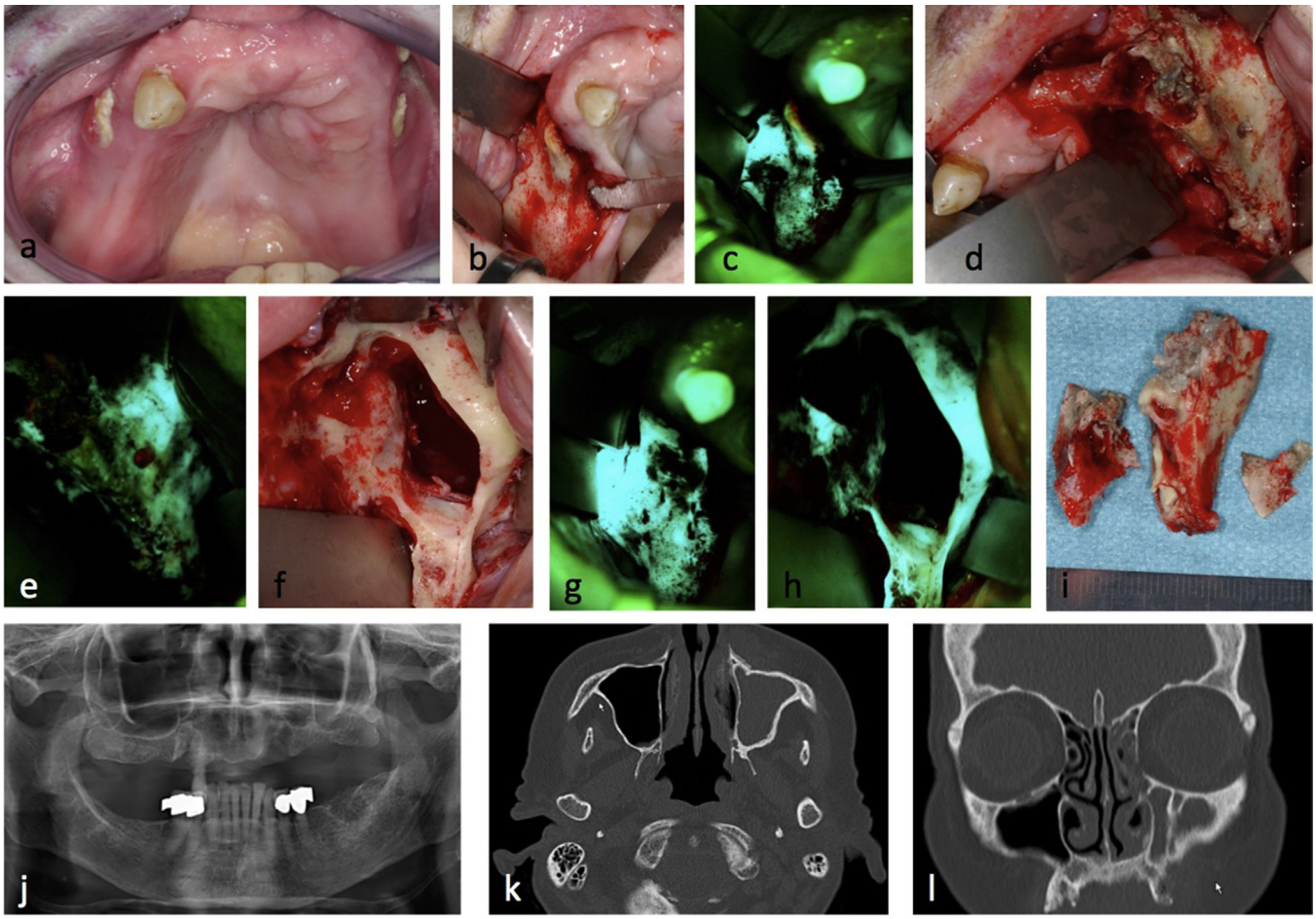

Fig. 1. DRONJ developed spontaneously in a 71-year-old woman (case 42): a) two maxillary lesions, stage 1 on the right side and stage 3 on the left, b) and d) elevation of mucoperiosteal flap reveals a small osteonecrotic lesion on the right side and a large area of necrotic bone on the left side, c and e) the intraoperative fluorescence view prior to removal of the necrotic bone, f) the resulting oro-antral communication after removal of the necrotic bone on the left side, g) and h) After complete removal of the necrotic bone parts and smoothening of sharp bony edges, the fluorescence was homogenously green, i) the size of the necrotic bone on the right side is less than the half of that on the left side, j) preoperative panoramic radiograph showed an alveolar defect and sequestration on the left side and diffuse sclerosis on the right side, k) and l) representative axial and coronal CT scans without contrast showed obliteration of the left maxillary sinus indicating maxillary sinus involvement, while the right maxillary sinus was normal, and the sequestration on the left maxillary alveolar process.

Understanding of the effect of denosumab doses number on DRONJ onset is essential for risk assessment. However, the data in this area remain sparse. It is still unknown whether the cumulative dose of denosumab has an influence on ONJ development comparable to that of bisphosphonates. Owosho et al. reported development of DRONJ after an average of 15 doses of denosumab. A recent case series of 17 patients reported DRONJ onset after 14.1 denosumab doses (Hoefert et al., 2017). An almost-similar finding was noted in our case series (16.4 doses). On the other hand, Rachner et al. reported DRONJ in osteoporosis patients after only a single dose of 60 mg denosumab (Rachner et al., 2013); however, this patient had been previously taking alendronate for 3 years. In this cohort, patients with previous use of bisphosphonates developed DRONJ after a slightly lower number of denosumab doses than those without (15.3 doses versus 17.5 doses).

Denosumab has a shorter half-life of 26 days and, unlike bisphosphonates, does not accumulate in bone. Subsequently, denosumab antiresorptive effects are reversible upon treatment cessation. Based on these pharmacological characteristics, some researchers have suggested favorable effects of stopping denosumab after DRONJ onset or prior to dental extraction on the healing and prevention of DRONJ lesions (O'Halloran et al., 2014). The data regarding this effect of DRONJ holiday are sparse. Spontaneous healing upon denosumab discontinuation was reported (Taylor et al., 2010; Malan et al., 2012; Ohga et al., 2015). Saad et al. indicated that ONJ lesions associated with denosumab had a more rapid healing (40%) than those associated with zoledronate (29%) (Saad et al., 2012). In addition, discontinuation of denosumab but not zoledronate was reported to promote MRONJ healing in a murine model (de Molon et al., 2015). On the other hand, two recent DRONJ case series reported no advantage of denosumab holiday either in promoting spontaneous healing in those cases treated conservatively or in improving surgical treatment outcomes (Owosho et al., 2016; Hoefert et al., 2017). In agreement with these studies, we did not see an association between a denosumab holiday and DRONJ healing. However, a positive effect of denosumab cessation on DRONJ can be assumed, given its short half-life. It is very important to know that pausing denosumab even for short intervals can result in remarkable rebound in bone remodeling and bone mineral density (BMD) and might lead to increased fracture risk (McClung, 2016).

The early management recommendations of BRONJ favored the conservative treatment over surgical intervention. Currently, surgical treatment of MRONJ has gained acceptance, as it was reported to have a success rate of over 85%, while conservative treatment success rate was limited to 15% (Nicolatou-Galitis et al., 2011; Ristow et al., 2015). The initial reports of DRONJ discouraged the

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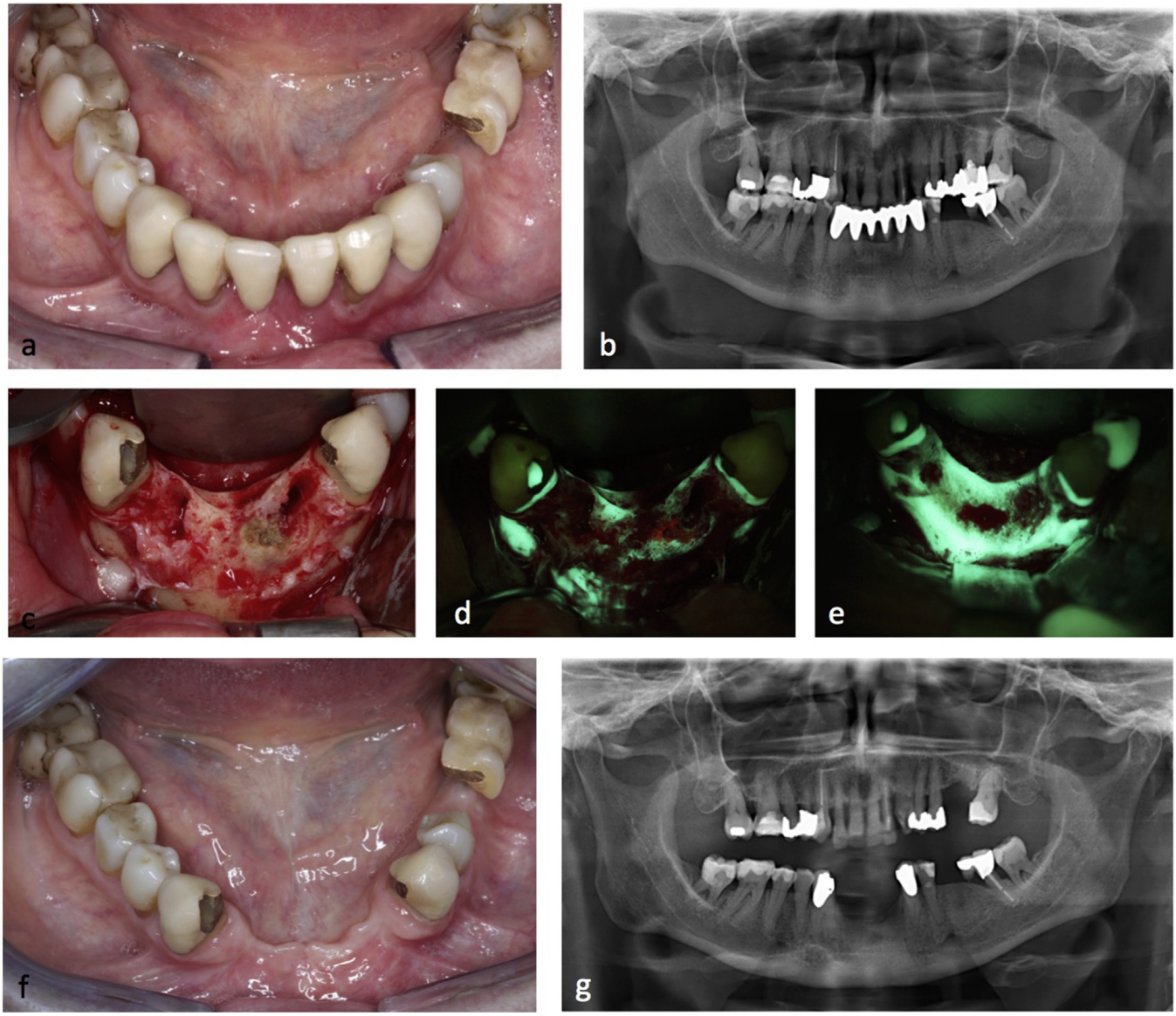

Fig. 2. a) The clinical presentation of DRONJ lesion in a 72-year-old female patient (case 33) who had been treated with denosumab for osteoporosis, b) panoramic radiograph showing 6 unit bridge with periodontitis in relation to abutment teeth, c) intraoperative view after mucoperiosteal flap elevation and extraction of the lateral incisors, d) fluorescence image prior to necrotic bone removal reveals diminished fluorescence at the area of necrosis, e) fluorescence image after removal of the necrotic bone, f) healing was evident 6 months postoperatively, g) panoramic radiograph shows healing of the site 6 months postoperatively.

surgical treatment and reported spontaneous healing of DRONJ (Taylor et al., 2010; Diz et al., 2012). Nevertheless, recent reports have shown that surgical treatment of DRONJ has achieved good treatment outcomes (Otto et al., 2013; You et al., 2015; Favia et al., 2016; Hoefert et al., 2017). Hoefert et al. reported a complete healing in 80% of patients treated with major surgery and only 20% patients treated non-operatively (Hoefert et al., 2017). In the present study, surgical treatment has achieved complete healing in 71.7% of the treated lesions. The success rate of fluorescence-guided osteotomy (77.3%) was higher than that of the conventional surgery (67.7%). A prospective study of 54 MRONJ patients treated with fluorescence-guided surgery reported complete mucosal healing in 86.2% of the lesions (Otto et al., 2016). Indeed, this technique is a reliable treatment option that aids not only in complete removal of necrotic tissue but also in reserving the vital bone underneath.

In this study, about half of the patients had a previous intake of bisphosphonates (49.2 %), while denosumab was the only administered antiresorptive drug in 50.8% of the cohort. Bisphosphonates can affect bone turnover even after years of their discontinuation (Boonen et al., 2012). Bone turnover markers (BTMs) increase slowly after cessation of bisphosphonates with a slow increase to their level before treatment within 3–60 months (Boonen et al., 2012). Based on that, prior intake of bisphosphonates might increase the risk of MRONJ. In addition, one can assume that it might increase the severity of the osteonecrosis or complicate the treatment. These findings, however, have not been seen in a comparison between a bisphosphonate-naïve patient group and that with a history of bisphosphonates. Indeed, there is no statistically significant difference between the two groups in regards to clinical characteristics, MRONJ stage, number of denosumab doses, preceding oral events and treatment outcomes. A slightly lower number of denosumab injections were recorded for patients with bisphosphonate use; however this difference remains statistically insignificant. The present study was the first to

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Table 6
Demographic and clinical characteristics of BP-naïve versus non–BP-naïve patients.

Variable	BP-naïve patients	Non–BP-naïve patients	*P*-value
Number of patients, n (%)	32 (50.8%)	31 (49.2%)	
Age (mean in years)	69.5 ± 10	70.6 ± 8.4	
Gender, n (%)			NS
Female	18 (56.3%)	19 (61.3%)	
Male	14 (43.8%)	12 (38.7%)	
Indications for denosumab use, n (%)			NS
Breast cancer	14 (43.8%)	13 (42%)	
Prostate cancer	8 (25%)	9 (29%)	
Osteoporosis	4 (12.5%)	5 (16%)	
Kidney cancer	3 (9.4%)	1 (3.2%)	
Multiple myeloma	1 (3.1%)	1 (3.2%)	
Thyroid cancer	1 (3.1%)	1 (3.2%)	
Lung cancer	0	1 (3.2%)	
Melanoma	1 (3.1%)	0	
Comorbidities, n (%)			NS
Chemotherapy	18 (72%)	23 (79.3%)	
Diabetes mellitus	5 (7.9%)	4 (6.3%)	
Corticosteroids	1 (1.6%)	6 (9.5%)	
Rheumatoid arthritis	2 (3.2%)	4 (6.3%)	
Local factors, n (%)			NS
Extraction	14 (4.8%)	14 (45.2%)	
Periodontitis	1 (3.1%)	5 (16.1%)	
Local trauma from ill-fitted denture	1 (3.1%)	3 (9.7%)	
Extraction and local trauma	2 (6.3%)	1 (3.2%)	
Extraction and periodontitis	2 (6.3%)	1 (3.2%)	
Implant placement	1 (3.1%)	1 (3.2%)	
Peri-implantitis	1 (3.1%)	0	
Ridge augmentation	1 (3.1%)	0	
Unknown	8 (25%)	5 (16.1%)	
Extraction, periodontitis, peri-implantititis	1 (3.1%)	0	
Scaling and root planing due to periodontitis	0	1 (3.2%)	
Number of doses	17.5 ± 10.6	15.3 ± 14.6	NS
Time between last dose and MRONJ onset (mean in days)	20.8 ± 7.7	28 ± 25	NS
Stage, n (%)			NS
Stage 0	2 (5.7%)	2 (5.9%)	
Stage 1	2 (5.7%)	4 (11.8%)	
Stage 2	25 (71.4%)	24 (70.6%)	
Stage 3	6 (17.1%)	4 (11.8%)	
Site, n (%)			NS
Mandible	25 (71%)	18 (58%)	
Maxilla	8 (23%)	9 (29%)	
Both	2 (6%)	4 (13%)	
Treatment, n (%)			NS
Surgical	31 (97%)	29 (93.5%)	
Non-surgical	1 (3%)	2 (6.5%)	
Treatment outcome, n (%)			NS
Healing	19 (68%)	19 (79.2%)	
Non-healing	5 (18%)	3 (12.5%)	
Partial healing	4 (14%)	2 (8.3%)	

BPs: bisphosphonates, NS: not significant.

establish this comparison, perhaps due to the limited number of patients in the previous case series. Nevertheless, prospective studies with large sample size are necessary to confirm these results.

The present retrospective study has some limitations. First, the retrospective nature of this study did not allow us to draw final conclusions regarding the treatment modalities and the effect of denosumab discontinuation. Second, our results are based on analysis of a small sample size due to the rarity of DRONJ. Third, information on some clinical variables was missing. However, important preliminary considerations can be withdrawn from the present study as it included the largest cohort studied to date. Retrospective studies in medicine, especially for rare diseases, are of great importance to understand disease course and pathophysiology and to identify its optimal management. Well-controlled prospective studies are required to further investigate our preliminary findings, particularly in relation to systemic and local risk factors, denosumab holiday, treatment modalities and treatment outcomes, as well as the effect of previous bisphosphonate intake on DRONJ severity and treatment outcomes.

5. Conclusion

In conclusion, osteonecrosis of the jaw in patients treated with denosumab seems to be a relevant concern in antiresorptive drug therapy. The applications of this innovative medication are expected to expand, and subsequently the prevalence of DRONJ is expected to increase. Within the limitations of this retrospective study, characteristics of DRONJ were investigated. DRONJ tends to develop after administration of 16.4 doses. The previous use of bisphosphonates does not appear to affect DRONJ severity or treatment response. Based on our findings, we recommend surgical treatment, particularly fluorescence-guided surgery, to allow complete removal of necrotic bone and to prevent ONJ progression.

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Conflicts of interest

Suad Aljohani, Robert Gaudin, Julian Weiser, Matthias Tröltzsch, Ralf Smeets, Gabriele Kaeppler, Michael Ehrenfeld and Sven Otto declare that they have no conflict of interest.

Acknowledgements

Sven Otto acknowledges the financial support of AO foundation (AOCMF 14-070 and AOCMF 64-210) for the research of medication related osteonecrosis of the jaw (MRONJ). He also acknowledges the financial support of Friedrich-Baur (65/09 and 71/11) and Curt-Bohnewand foundations. Sven Otto has received honoraria for scientific talks from Nobel Biocare, CAMLOG and AMGEN.

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PUBLICATION 3

Osteomyelitis der Kieferknochen

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Osteologie 26 4: 236-243, 2017

Osteomyelitis der Kieferknochen

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Schlüsselwörter

Osteomyelitis, Knochenmarkentzündung, Osteonekrose, medikamentenassoziierte Osteonekrose des Kiefers (MRONJ), Bisphosphonate, Denosumab, Osteoradionekrose

Zusammenfassung

Entzündliche Erkrankungen des Kieferknochens stellen eine relevante klinische Herausforderung dar. Die Therapieoptionen und vor allem die Erfolgschancen unterscheiden sich hierbei je nach zugrunde liegender Entität. Die prophylaktischen Maßnahmen ähneln sich hingegen und umfassen vor allem eine optimale Mundhygiene sowie die adäquate Therapie von dentogenen Infektionen. Dieser Artikel gibt eine Übersicht über den aktuellen Kenntnisstand zu den verschiedenen Formen der entzündlichen Erkrankungen des Kiefers und ihre Unterschiede zu Osteomyelitiden anderer Körperregionen. Ein fächerübergreifendes Wissen sowie eine interdisziplinäre Zusammenarbeit ist Voraussetzung für eine ideale Prophylaxe, das frühzeitige Erkennen, eine adäquate Versorgung und das Vermeiden von Komplikationen der Osteomyelitiden und Nekrosen der Kieferknochen.

Keywords

Osteomyelitis, infection and inflammation of the bone, osteonecrosis, medication-related osteonecrosis of the jaw (MRONJ), bisphosphonates, Denosumab, osteoradionecrosis

Summary

Inflammatory diseases of the jaws are a clinical challenge. Therapeutic options and especially chances of success in treatment vary depending on the underlying entity. Prophylactics on the other hand are very similar. They include a good oral hygiene and care as well as an adequate therapy of dental infections. This article gives an overview of the state of knowledge concerning the various types of inflammatory diseases of the jaws and their differences to osteomyelitis of other body regions. An interdisciplinary knowledge and collaborations are essential for preventing, detecting and treating osteomyelitis or osteonecrosis of the jaw and to avoid major complications.

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Osteomyelitis of the jaws

Osteologie 2017; 26: 236–243
eingereicht: 11. Oktober 2017
angenommen: 13. Oktober 2017

Der Begriff „Osteomyelitis" wird allgemein für eine Knochenentzündung verwendet. Streng genommen bezieht sich der Name nur auf Entzündungen des Knochenmarks (griech. myelos = Mark). Meist sind allerdings die anderen Teile des Knochens – wie die Spongiosa mit ihren Trabekeln, die Kortikalis und häufig auch das umliegende Periost – ebenfalls betroffen. Deswegen wird heutzutage im deutschsprachigen Raum auch öfter der umfassendere Begriff Osteitis verwendet. Dieser Begriff findet im angloamerikanischen Sprachraum dagegen kaum Anwendung. Im Folgenden soll der Begriff „Osteomyelitis" allgemein eine Entzündung von Knochengewebe bezeichnen.

Eine Knochenentzündung ist in den meisten Fällen infektiös bedingt. Keime gelangen entweder durch hämatogene Aussaat, posttraumatisch bei (offenen) Knochenbrüchen, iatrogen im Rahmen von osteosynthetischen Versorgungen bzw. orthopädischer Chirurgie (z. B. künstlicher Gelenkersatz) oder auch durch Ausbreitung per continuitatem in den Knochen. In der Regel sind Bakterien die verursachenden Krankheitserreger. Aber auch Pilzinfektionen des Knochens besonders bei immungeschwächten Patienten sind auf dem Vormarsch. Durch ihre ubiquitäre Präsenz sind Infektionen mit Aspergillus- und Candida-Spezies gefürchtet (1, 2), aber auch Osteomyelitiden insbesondere der Wirbelkörper oder langer Röhrenknochen verursacht durch dimorphe Pilze wie *Coccidioides immitis* und *Blastomyces dermatitidis* werden beobachtet (3, 4). Selbst viral bedingte Osteomyelitiden sind in der Literatur vereinzelt beschrieben (5).

Es gibt aber auch Knochenentzündungen, bei denen kein Erreger nachgewiesen werden kann. Diese werden oft als sterile oder abakterielle Osteitiden bzw. Osteomyelitiden bezeichnet. Hierzu gehört zum Beispiel die zu dem rheumatischen Formenkreis zählende chronisch rezidivierende multifokale Osteomyelitis (CRMO). Diese wird häufig als Manifestationsform des SAPHO-Syndroms (Synovitis, Akne, Pustulosis, Hyperostosis, Osteitis) bei Kindern und Jugendlichen diagnostiziert (6, 7).

Die am häufigsten von Osteomyelitiden betroffenen Knochen des menschlichen Skelettsystems sind die langen Röhrenknochen Tibia, Femur und Humerus. Aber auch die Wirbelkörper und die Kieferknochen Mandibula und Maxilla gehören dazu (8).

Eine infektiöse Ursache haben die meisten Osteomyelitiden gemein. Dennoch unterscheiden sich die Entzündungen der Kiefer in wesentlichen Punkten von denen der übrigen Knochen, hinsichtlich des Keimspektrums, der Ätiologie und der Therapieoptionen.

Dank enormer Fortschritte in der Therapie der Osteoporose und von Knochenmetastasen kamen zudem immer mehr potente antiresorptive Medikamente auf den Markt, wie Bisphosphonate oder der RANKL-Inhibitor Denosumab. Allerdings

traten im Zusammenhang mit deren Einnahme gehäuft Krankheitsbilder der Kieferknochen auf, die denen der bisher bekannten Osteomyelitiden stark ähnelten: die medikamentenassoziierten Kiefernekrosen.

In dieser Arbeit wird der aktuelle Kenntnisstand über die Osteomyelitiden der Kiefer und ihre Sonderformen wiedergegeben. Auch Ärzte außerhalb des Fachgebietes der Mund-, Kiefer- und Gesichtschirurgie sollen für diese Krankheitsbilder sensibilisiert und darin fortgebildet werden. Interdisziplinäre Zusammenhänge sollen deutlicher und fächerübergreifendes Erkennen sowie Vorbeugen der Erkrankungen erleichtert werden.

Tab. 1 Einteilung von Entzündungen des Kieferknochens nach ICD-10-GM (9)

Table 1 ICD-10-GM classification of Inflammatory diseases of the jawbones

K10.2	**Entzündliche Zustände der Kiefer**	
	• Osteomyelitis (neonatal) • Osteonekrose (bestrahlungsinduziert) (medikamenteninduziert) • Osteoradionekrose • Ostitis • Periostitis • Sequester des Kieferknochens	(akut) (chronisch) (eitrig)
K10.28	**Sonstige näher bezeichnete entzündliche Zustände der Kiefer**	
K10.3	**Alveolitis der Kiefer**	
	• Alveoläre Ostitis • trockene Alveole (dry socket)	

Einteilungen

Entzündliche Zustände des Kiefers werden nach ICD-10 wie in ▶Tabelle 1 eingeteilt und verschlüsselt, wobei runde Klammern optionale Ergänzungen beinhalten (9).

Mehrere Vorschläge zur Einteilung der Osteomyelitis des Kiefers sowie das Benutzen unterschiedlicher Terminologien erschweren den Überblick und den direkten Vergleich gleicher Entitäten (10–15).

Eine klinisch übersichtliche Klassifikation gelang Baltensperger et al. 2004 (16) und wird in ▶Abbildung 1 grafisch wiedergegeben. Hier werden drei Formen der Osteomyelitis des Kiefers beschrieben: Die akute Osteomyelitis, welche nach vier Wochen in die sekundär chronische Osteomyelitis übergehen kann und als dritte Form die primär chronische Osteomyelitis, welche nochmals in die juvenile Form, die adulte Form und syndromassoziierte Form (SAPHO oder CRMO) unterteilt wird. Die primär chronische Form wird hierbei als nicht eitrige Variante klassifiziert.

Eine chronisch eitrige Osteomyelitis wird der sekundär chronischen Osteomyelitis gleichgesetzt und stellt die häufigste Osteomyelitisform des Kiefers dar.

Infektiöse Osteomyelitiden des Kiefers

Während bei den Osteomyelitisformen der langen Röhrenknochen die hämatogene bakterielle Streuung die häufigste Ursache darstellt, sind es im Kieferbereich am häufigsten lokale odontogene Infektionsherde, die sich in den Kieferknochen ausbreiten. Anatomisch prädestiniert durch die Verankerung des Zahnes durch den Zahnhalteapparat direkt in der Knochenalveole sind apikale und pulpale Eintrittspforten (▶Abb. 2).

Auch das Erregerspektrum unterscheidet sich deutlich. Ist bei Osteomyelitisformen durch hämatogene Aussaat häufig eine Monokultur mikrobiologisch isolierbar (vorwiegend *Staphylococcus aureus*) (18), ist es bei der odontogenen Osteomyelitis in der Regel eine Mischkultur mit typischen Pathogenen der Mundflora (wie *Streptococcus spp.*, *Staphylococcus spp.*, *Peptostreptococcus spp.*, *Fusobacterium spp.*, *Prevotella spp.*, *Actinomyces spp.*) (19, 20). Die Invasion der Bakterien führt zu lokaler Entzündungsreaktion im Knochen mit anschließender Pusbildung. Dies führt letztendlich zu einem erhöhten intramedullären Druck, der zusätzlich die örtliche Mikrozirkulation beeinträchtigt. Bei Druck auf den Nervus alveolaris inferior kann es auch zu Hyp- und Parästhesien in dessen Versorgungsgebiet (auffallend besonders im Bereich der ipsilateralen Unterlippenseite) kommen (sogenanntes Vincent-Zeichen). Größere Eiterherde können zur Abhebung des Periosts führen oder dieses sogar durchbrechen. Dadurch kann es zu Abszessbildung im umliegenden Gewebe oder zu Fistelbildungen zur Mundhöhle oder äußeren Haut kommen. Lokal entwickelt sich zusätzlich häufig eine Nekrose des Kieferknochens (21). Je nach Abwehrlage des Patienten können kleinere Nekrosen abgebaut, größere durch Sequesterbildung vom restlichen Körper abgeschottet werden. Die Ausbreitung einer Osteomyelitis ist ebenfalls von der aktuellen Immunabwehr abhängig (▶Abb. 3).

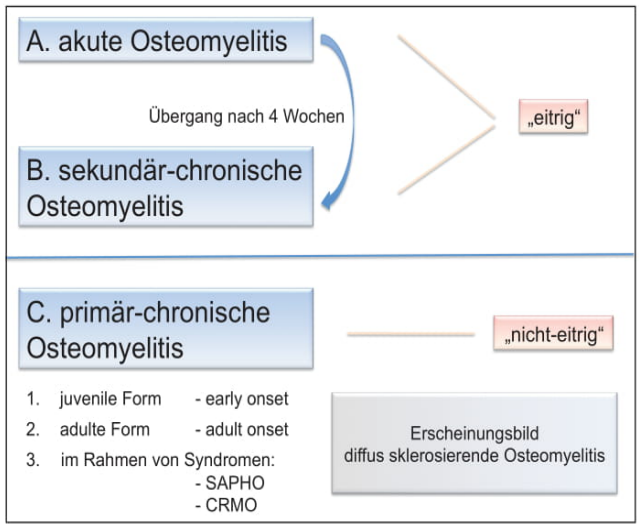

Abb. 1 Klassifikation nach Baltensperger (16); mod. nach (17)

Fig. 1 Classification by Baltensperger (16), modified according to (17)

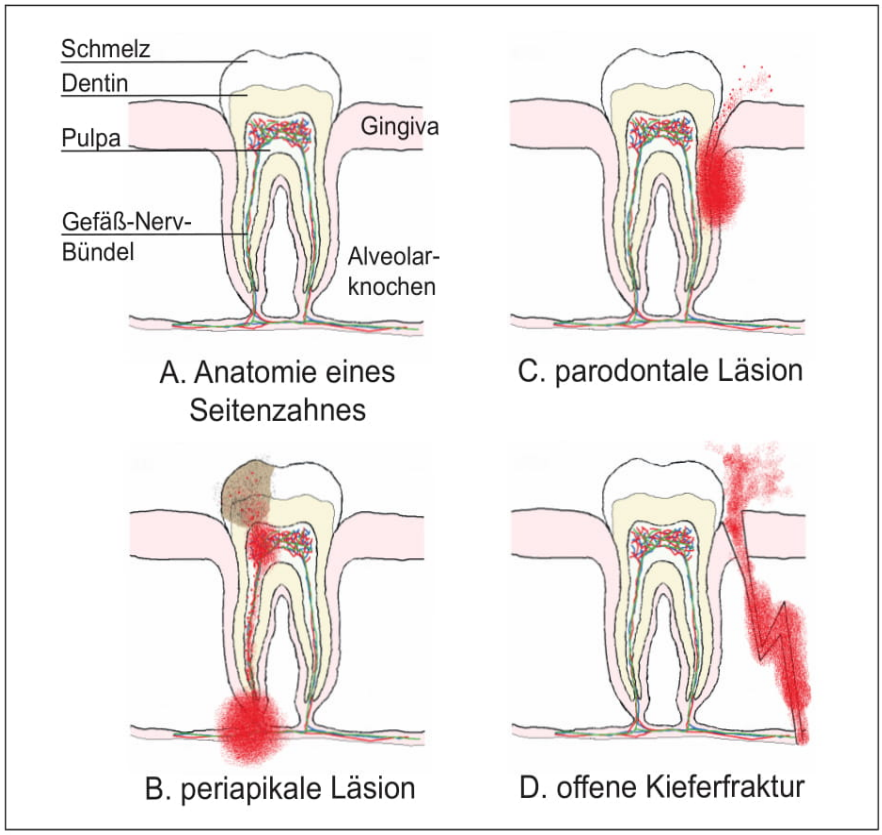

Abb. 2 Typische Formen der Pathogenese „eitriger" Osteomyelitiden des Kiefers: (A) anatomisches Schema Seitenzahn, (B) durch eine kariöse Läsion dringen Bakterien in die Pulpa des Zahnes und gelangen über den Wurzelkanal nach apikal, (C) Eintrittspforte ist hier eine Läsion im Bereich des parodontalen Spalts. (D) Hier wird eine zur Mundhöhle offene Kieferfraktur symbolisiert.

Fig. 2 Examplary routes for the development of "suppurating" osteomyelitis: (A) anatomical structures of a molar, (B) due to a decayed lesion bacteria can penetrate the pulp and take their way through the root canal to the apical region, (C) bacterial entry is here through the paradontal gap, (D) open fracture communicating with the oral cavity.

Am häufigsten ist der Unterkiefer und hier insbesondere das Corpus mandibulae betroffen, gefolgt von Symphyse, Kieferwinkel, aufsteigender Ast und Kondylus (22). Eitrige Osteomyelitiden kommen in jeder Altersgruppe vor, gehäuft aber bei Männern im mittleren Lebensabschnitt (17).

Auch ohne dentogenen Fokus können eitrige Entzündungen des Kiefers auftreten. Beispielsweise posttraumatisch bei offenen Kieferbrüchen oder nach eingebrachtem Fremdmaterial (z. B. Osteosythesematerial, Implantate).

Bestimmte Erkrankungen und Lebensumstände können eitrige Osteomyelitiden begünstigen. Zu diesen zählen besonders die Immunabwehr einschränkenden Erkrankungen wie Autoimmunerkrankungen, insbesondere begleitet von steroid- oder anderer immunsuppressiver Therapie, AIDS und Leukämie. Laufende Chemotherapien stellen ein großes Risiko dar, aber auch Mangelernährung, Virusinfektionen (HSV, CMV), Alkohol-, Drogen- und Nikotinabusus, Tumorerkrankungen, Sichelzellanämie oder vorausgegangene Traumata und Operationen (23). Diabetes mellitus setzt nicht nur die Immunabwehr herunter, sondern bekanntermaßen auch die Mikrozirkulation, so auch im Bereich der Kieferknochen (24).

Eine Sonderform der infektiösen Osteomyelitiden im Kieferbereich stellt die Osteomyelitis des Säuglings dar. Hier wird häufig ein hämatogener Streuungsprozess angenommen, wobei ein lokales (perinatales) Trauma der Gingiva nicht ausgeschlossen werden kann. Der Haupterreger ist hier wieder *Staphylococcus aureus*. Hauptmanifestationsort ist die Maxilla, Hauptmanifestationszeit die Wochen nach der Geburt (25–27).

Spezifische infektiöse Osteomyelitiden können auch durch *Mycobacterium tuberculosis* oder durch den Syphiliserreger *Treponema pallidum* hervorgerufen werden. (28–30). Glücklicherweise ist letzteres in Deutschland durch die schnelle und einfache antibiotische Therapieeinleitung mit Penicillin sehr selten geworden (kaum noch ein Erreichen von Stadium II oder III in Europa). Die Möglichkeit einer Tuberkuloseinfektion sollte im Zweifel differenzialdiagnostisch aber nicht außer Acht gelassen werden.

Die klinische Symptomatik eitriger Osteomyelitiden umfasst Schmerzen, Schwellung (je nach Ausmaß und Fortschritt der Entzündung: knochenhart, weich oder fluktuierend) sowie zervikale Lymphadenitis. Es können Fistelungen, aber auch freiliegender Knochen und Sequesterbildung vorliegen (▶Abb. 3) (31). Durch Zahnlockerungen kann es zu Okklusionsstörung oder Zahnverlust kommen. Sensibilitätsstörungen oder Trismus (Einschränkung der Kieferöffnung) können zu Funktionsstörungen führen. Ein unangenehmer bis fauliger Foetor ex ore liegt ebenfalls oft vor. Manchmal kommt es zu allgemeinen Begleitreaktionen wie Fieber und Anstieg der Entzündungsparameter im Labor (32, 33). Radiologisch (OPG, DVT, CT) ist ohne klare Abgrenzung eines Sequesters häufig keine eindeutige Diagnose zu stellen. Veränderungen in der Knochendichte/Radioopazität, Osteolysen, lokale Mehrsklerosierungen können Hinweise auf eine Osteomyelitis geben, aber auch anderer Genese sein. Eine MRT-Untersuchung stellt eine etwas sensitivere radiologische Diagnostik dar. Am besten, insbesondere auch für frühe Formen von Osteomyelitiden, ist die Knochenszintigrafie mit ^{99m}Technetium. Hier kann man schon frühzeitig eine Mehrspeicherung in entzündeten Arealen erkennen (34).

Primär chronische Osteomyelitis, diffus sklerosierende Osteomyelitis

Der Begriff diffus sklerosierende Osteomyelitis (DSO) entstammte eigentlich der Beschreibung eines radiologischen Bildes, welches klinisch durch unterschiedliche Ursachen hervorgerufen werden kann. Die

Knochentextur insbesondere des Unterkieferknochens zeigt sich hierbei in radiologischen Bildgebungen diffus sklerosiert, also mit unregelmäßigen teils klaren, teils verwaschenen Aufhellungen und ohne eindeutige Begrenzung dieser Veränderung. Heute wird sie teilweise der primär chronischen Osteomyelitis gleichgesetzt oder als Erscheinungsbild zumindest ihr zugeordnet. Was bei der akuten oder sekundär chronischen Osteomyelitis das charakteristische Bild ausmacht – Pus- und Fistelbildung sowie Knochenexposition – fehlt typischerweise bei der primär chronischen Osteomyelitis. Typisch hingegen sind Schwellung, Schmerz und Trismus, die im Intervall auftreten und oft auf eine Seite des Unterkiefers beschränkt sind (▶Abb. 4). Oft haben Patienten in der akuten Phase über Tage oder Wochen einen enormen Leidensdruck, aber können auch zwischenzeitlich über einen geraumen Zeitraum symptomfrei sein (35).

Die primär chronische Osteomyelitis wird von Baltensperger (16) in drei Subtypen unterteilt: Je nach Alter der Erstmanifestation in eine „early onset" (vor dem 20. Lebensjahr) und eine „adult onset" (nach dem 20. Lebensjahr) Osteomyelitis und eine syndromassoziierte Form (▶Abb. 1).

Die Ätiologie ist noch unbekannt und wird kontrovers diskutiert. Neben einer Reaktion auf ein primär infektiöses Geschehen gibt es auch Hypothesen, dass es sich um eine chronische Periostitis als Folge von Parafunktionen handeln kann (37, 38).

Oft gelingt kein direkter mikrobiologischer Erregernachweis. Ist ein Abstrich oder eine Probe dennoch positiv, handelt es sich meist um eine Kontamination mit den Keimen der Mundflora. Ein ausbleibender Effekt von Antibiotika ist dadurch nicht verwunderlich. Neuere Erkenntnisse stellen eine infektiöse Pathogenese zusätzlich in Frage und geben Hinweise auf eine Störung der Osteoklasten- und Osteoblastenfunktion und Kommunikation (36).

Frauen sind häufiger betroffen. Bei der Sonderform CRMO treten multifokale Osteomyelitisläsionen, bevorzugt in langen Röhrenknochen, auf (39). Aber auch die Kieferknochen können hierbei betroffen sein. Insbesondere trifft dieses Krankheitsbild Mädchen um das zehnte Lebensjahr. Die Symptome verschwinden in der Regel während der Pubertät (7).

Im Rahmen des bereits erwähnten SAPHO-Syndroms kann es zusätzlich zu Hautmanifestationen wie Akne oder Pustulosis der palmaren Hand- bzw. plantaren Fußflächen oder arthritischen Beschwerden kommen. Abgesehen von lokalen Schmerzen und Schwellungszeichen befinden sich die meisten Patienten in einem guten Allgemeinzustand. Im Unterschied zu der eitrigen Osteomyelitis sind die laborchemischen Infektionsparameter in der Regel bei primär chronischen Osteomyelitiden im Normbereich (7).

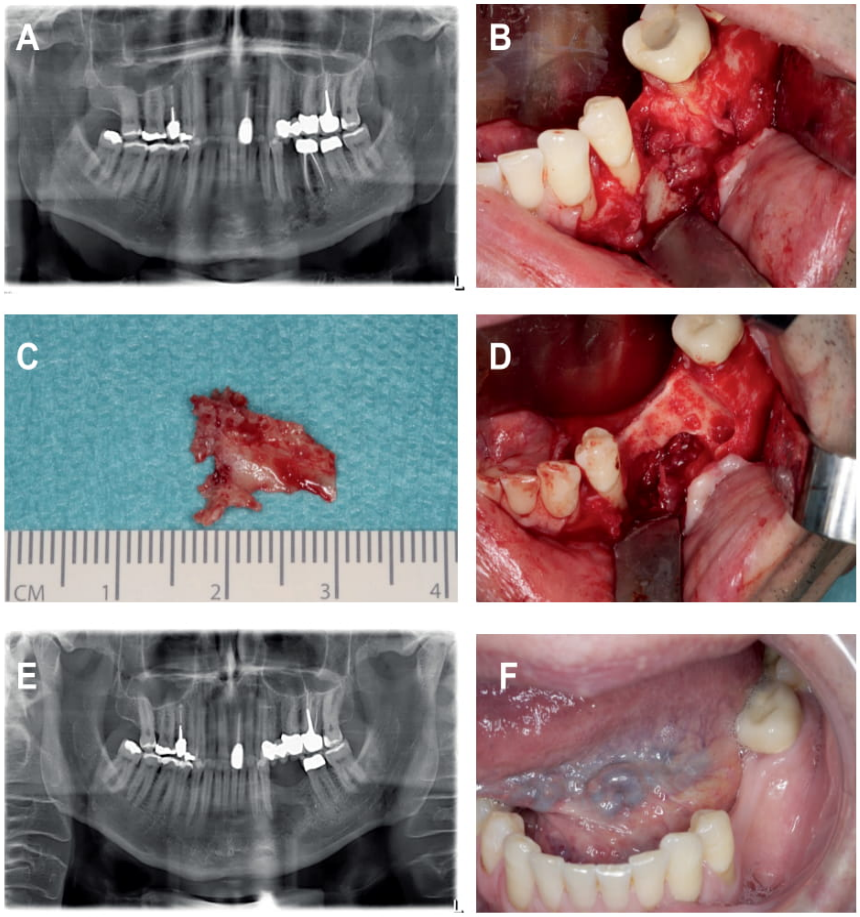

Abb. 3 Eitrige Osteomyelitis: (A) Inhomogener, teils osteolytischer Knochen im Bereich des Unterkiefers links bei Z. n. Wurzelkanalbehandlung Zahn 36; (B) intraoperativer Befund; (C) Sequester; (D) Z. n. chirurgischer Abtragung des nekrotischen Knochens und Entfernung Zahn 36 (E, F) Röntgenkontrolle und klinisches Bild nach vier Monaten

Fig. 3 Suppurating osteomyelitis: (A) condition after root canal treatment of tooth 36: inhomogeneous, partly osteolytic bone of the left mandible; (B) intraoperative view; (C) sequestra; (D) after surgical debridement and extraction of tooth 36; (E, F) postoperative X-ray control and clinical presentation after four months

Sonderformen

Medikamentenassoziierte Osteonekrose

In den vergangenen Jahren haben insbesondere medikamentenassoziierte Kiefernekrosen (Medication-related osteonecrosis of the jaw, MRONJ) an Bedeutung gewonnen (40). Sie sind definiert als exponierter Knochen bzw. Knochen, der sondiert werden kann, bei aktueller oder stattgehabter Therapie mit antiresorptiven (Bisphosphonate bzw. Denosumab) oder antiangiogenetischen Medikamenten bei nicht vorangegangener Strahlentherapie oder offensichtlicher Metastasierung im Kieferbereich (41) (▶Abb. 5). Neben dem Leitsymptom der Erkrankung, dem nekro-

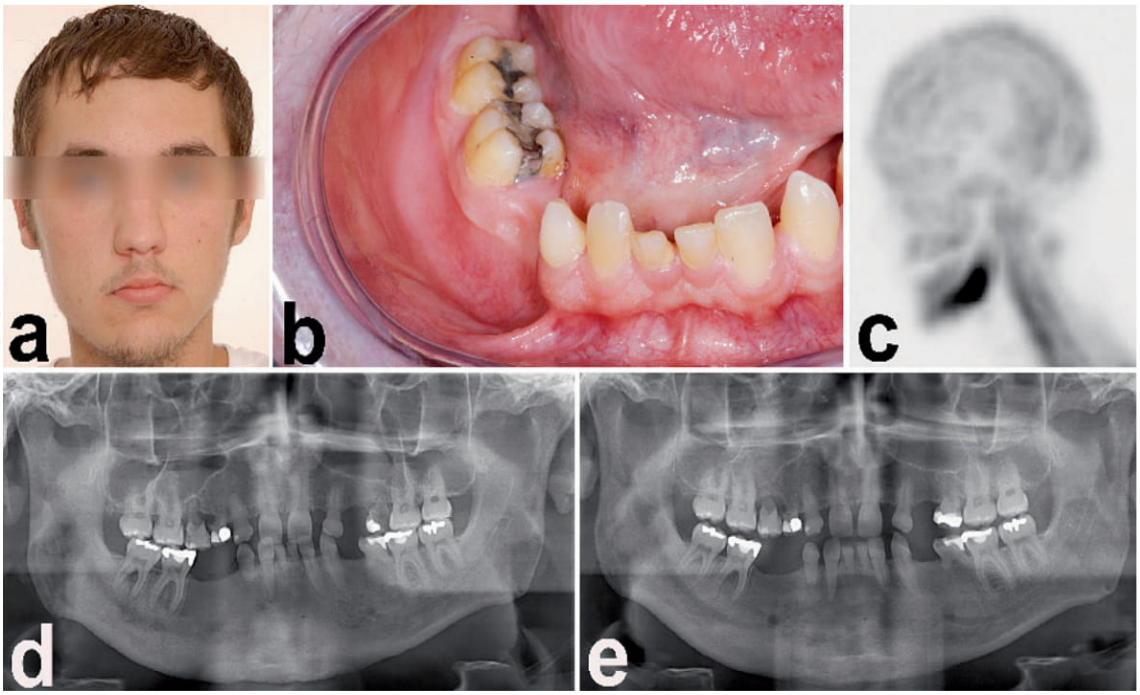

Abb. 4 Diffus sklerosierende Osteomyelitis: (a) 20-jähriger Patient mit Schmerzen und Schwellung im Bereich des Unterkiefers rechts und eingeschränkter Kieferöffnung; (b) intraoraler Befund; (c) Skelettszintigrafie mit deutlicher Mehranreicherung im Bereich des Unterkiefers. Die Symptomatik bestand bereits sechs Jahre und wurde mit der Gabe von Steroiden, nichtsteroidalen Antirheumatika und sogar Opioiden therapiert. Bei Aufnahme wurden Schmerzen auf einer visuellen Analogskala von 8–10 angegeben. Es erfolgte die intravenöse Einmalgabe von 6 mg Ibandronat. 48 Stunden danach war der Patient schmerzfrei und Analgetika konnten gänzlich abgesetzt werden. (d) Radiologisches Bild einer diffus sklerosierenden Osteomyelitis; (e) Kontrollbild neun Monate nach Bisphophonatgabe. Beachte insbesondere die homogenere Knochentextur und die klare Abgrenzung des Nervkanals.

Fig. 4 Diffuse sclerosing osteomyelitis: 20-year-old male patient who presented with severe and almost intractable pain in his right lower jaw, accompanied by a para-mandibular swelling and limited jaw opening. Extraoral and intraoral views are given in (a) and (b). Scintigraphy results (c). At the time of presentation, the patient reported that he had recurrent episodes of severe pain and swelling of his right lower jaw for the last 6 years. The clinical, radiological (panoramic radiograph, and CT scan) and histological diagnosis of DSO had already been made, and he was treated with anti-steroidal drugs and corticosteroids in case of exacerbation. At the time of admission the patient reported to have a pain level of 8e10, according to the visual analogue scale (VAS), which could not be sufficiently treated with NSAIDs and even treatment with opioids. After extensive information regarding the treatment options, the patient received 6 mg ibandronate intravenously. Forty-eight hours after infusion, the patient had a VAS score of 0 and stopped use of painkillers 2 days later. Panoramic radiograph prior to ibandronate infusion (d) and 9 months after infusion (e). There has also been a change in the radiological appearance including a less pronounced sclerosis, and a clearer visibility of the inferior alveolar channel resembling overall clinical improvement. These changes have also been seen in other patients when a panoramic radiograph was taken within the first year after infusion. However, this has not been done regularly.

tischen exponierten Knochen, können zahlreiche weitere Symptome wie Schwellungen, Schmerzen, Fistelbildungen (intra- und extraoral), entzündliche Infiltrate und Abszesse auftreten. Als Komplikationen wurden im Bereich des Unterkiefers auch Beeinträchtigungen der Funktion des Nervus alveolaris inferior und pathologische Frakturen des Unterkiefers beschrieben, im Oberkiefer können sich Beteiligungen der Kieferhöhle im Sinne einer Sinusitis maxillaris bzw. im Sinne von Mund-Antrum-Verbindungen manifestieren (42–44).

Als Risikofaktoren gelten neben malignen Grunderkrankungen (Mammakarzinom, Prostatakarzinom und multiples Myelom), Immunsuppression, Diabetes mellitus und eine Komedikation mit Steroiden. Die Mehrzahl der Fälle trat unter der onkologischen Dosierung von stickstoffhaltigen Bisphosphonaten und Denosumab auf. Als wesentliche lokale Risikofaktoren gelten insbesondere dentogene Infektionen, schlechte Mundhygiene, Prothesendruckstellen und lokale dentoalveoläre chirurgische Eingriffe (43, 45).

Hinsichtlich der Pathogenese der MRONJ scheint sich mehr und mehr die entzündliche Ätiologie durchzusetzen (46, 47). Daher ist es nicht verwunderlich, dass prophylaktische Maßnahmen, welche insbesondere auf die Beseitigung bzw. adäquate Therapie dentogener Infektionen abzielen, sowohl vor als auch unter bereits laufender Therapie mit antiresorptiven Medikamenten zu einer signifikanten Verminderung des MRONJ-Risikos führen.

Die MRONJ ist dennoch ein relativ junges Forschungsgebiet und zahlreiche Fragen sind noch unbeantwortet, insbesondere wird aktuell die Frage nach dem Nutzen eines sogenannten „drug holiday" kontrovers diskutiert, aber auch hinsichtlich der dentalen Rehabilitation von Patienten unter antiresorptiver Therapie und vor allem nach MRONJ bestehen noch Unsicherheiten.

Osteoradionekrose

Eine gefürchtete Komplikation einer Bestrahlungstherapie im Kopf-Hals-Bereich ist die Osteoradionekrose (ORN). Nach

Marx et al (48) wird der Effekt einer Radiatio auf bestrahlte Gewebe mit den „3 H's" beschrieben: Hypoxie, Hypozellularität, Hypovaskularität. Die genaue Entstehungsweise einer ORN ist noch ungeklärt. Man nimmt an, dass durch eine stark verminderte Durchblutung und die lokal resultierende Hypoxie ein Absterben des Knochens begünstigt wird (49) (▶Abb. 6). Ob eine Infektion dabei mitwirkt oder erst sekundär das Krankheitsbild verschlimmert, ist nicht geklärt. Neun Prozent der mit über 6000 cGy bestrahlten Patienten entwickeln eine ORN, die sich nach Monaten, nach Jahren oder gar Jahrzehnten manifestiert (49). Zum Teil geht der Manifestation der ORN eine Zahnextraktion voraus. Das Risiko für bezahnte Kiefer ist größer als für unbezahnte (50). Deswegen ist eine zahnärztliche Sanierung vor Beginn der Bestrahlung obligat, um Zahnextraktion oder Behandlungen während und nach der Bestrahlung zu vermeiden. Individuelle Strahlenschutzschienen sollten während der Bestrahlung getragen werden und Fluoridierungsschienen zur Nacht. Regelmäßige Kontrollen und eine gute Zahnpflege müssen auch nach der Bestrahlung fortgeführt werden.

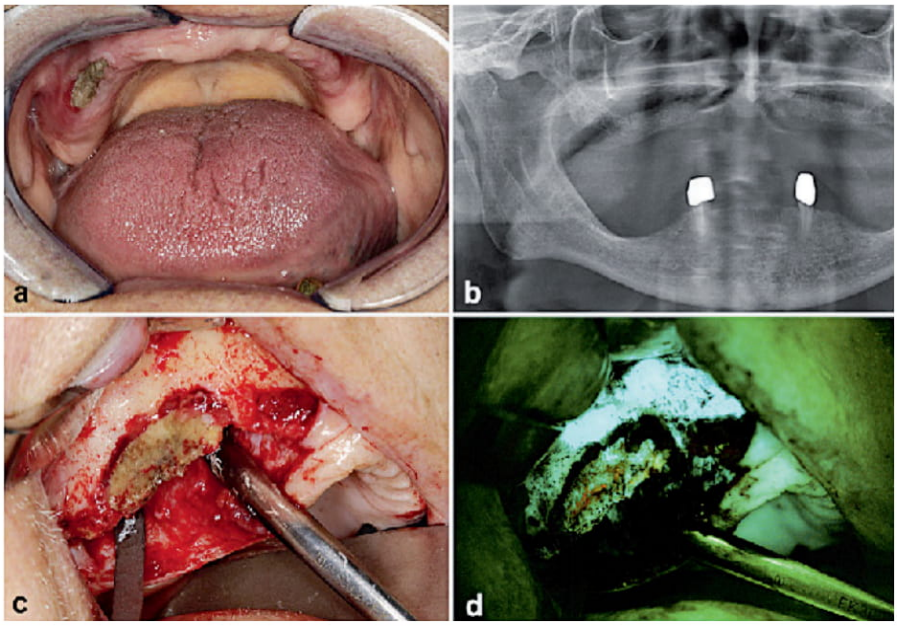

Abb. 5 MRONJ: 79-jähriger Patient mit Z. n. Chemotherapie und intravenöser Bisphophonatgabe (4 mg Zolendronat alle vier Wochen) aufgrund eines metastasierten Mammakarzinoms: (a) Freiliegender Knochen im Bereich des rechten Oberkiefers. (b) Im konventionellen Röntgenbild sieht man meist keine Auffälligkeiten. (c) Das eigentliche Ausmaß ist häufig erst intraoperativ zu sehen. (d) Fluoreszenzgestützte Chirurgie: Vitaler Knochen wird grün dargestellt, dunkel ist der nekrotische Knochen sichtbar, rot sind Bakterienbesiedlungen.

Fig. 5 MRONJ: A 79-year-old man presented with pain and a non-healing wound in the right upper jaw. The patient suffered from prostate cancer with metastatic bone disease and had received chemotherapy and intravenous bisphosphonate administrations (zoledronate 4 mg every 4 weeks). Clinically, exposed necrotic bone (a) in the right upper jaw was present e the hallmark of bisphosphonate-related osteonecrosis of the jaw. Conventional radiology often lacks major pathological findings (b). The patient was treated surgically (c) with using fluorescence-guided bone resection e a novel technique to objectify the margins of the osteonecrosis intra-operatively (d): green: living bone; dark dead bone; red: bacteria).

Therapie der Osteomyelitiden im Kieferbereich

Je nach Entität der Osteomyelitis differiert die Wahl der Therapie. Bei infektiöser Genese und bei freiliegendem Kieferknochen sollte in jedem Fall auf eine ausreichend lange und suffiziente Antibiotikagabe geachtet werden (bestenfalls Antibiogramm!). Erste Wahl sind Aminopenicilline mit beta-Lactamasehemmern. Ausweichpräparate sind Lincosamide (Clindamycin), Cephalosporine und Makrolide. Carbapeneme können als Reserveantibiotika hergenommen werden. Eine intravenöse Antibiotikatherapie ist bei schweren Verlaufsformen und zusätzlichen Risikofaktoren zu empfehlen.

Zusätzlich zur antibiotischen Therapie kann oft eine chirurgische Intervention nicht umgangen werden. Die anatomischen Besonderheiten im Bereich des Gesichtschädels begrenzen bzw. erschweren die chirurgischen Therapieoptionen, insbesondere bezogen auf ästhetische und funktionelle Aspekte.

Akute Abszessformationen müssen inzidiert und drainiert werden, avitaler Knochen mittels Debridement, Dekortikation oder Sequestrotomie abgetragen werden. In extremen Fällen kann es zu einer partiellen Resektion oder Kontinuitätsresektion des Unterkiefers kommen mit anschließender Eingliederung einer Rekonstruktionsplatte zur Stabilisierung oder sogar direkte oder zweizeitige Rekonstruktion mittels (mikrovaskulärem) Knochentransplantat. Auf die Entfernung scharfer Knochenkanten muss akribisch geachtet werden.

Unterstützende Maßnahmen zur lokalen Desinfektion sind die Softlaser- und photodynamische Therapie. Eine fluoreszenzorientierte Knochenabtragung unterstützt durch die optische Unterscheidung von nekrotischem und vitalem Knochen eine ausreichende Entfernung des erkrankten Knochens bei weitest möglicher Substanzschonung des gesunden Knochens (52).

Um eine Barriere für das erneute Eindringen von Bakterien zu minimieren, sollte bei chirurgischen Eingriffen abschließend ein dichter Wundverschluss, meist in Form einer lokalen plastischen Deckung, erfolgen. Da Anaerobier häufig Verursacher einer Osteomyelitis im Kieferbereich sind, wird teilweise auch eine hyperbare Sauerstofftherapie empfohlen.

Zur Therapie der MRONJ wurden sowohl konservative als auch chirurgische Methoden beschrieben. Die konservative Therapie beinhaltet in der Regel eine systemische Antibiose und lokal desinfizierende Spülungen (sowie oft auch die Pausierung des Antiresorptivums), wobei sie oft zur Symptombesserung führt, aber nur selten zur vollständigen schleimhäutigen Abheilung. In den vergangenen Jahren haben sich daher zunehmend chirurgische Thera-

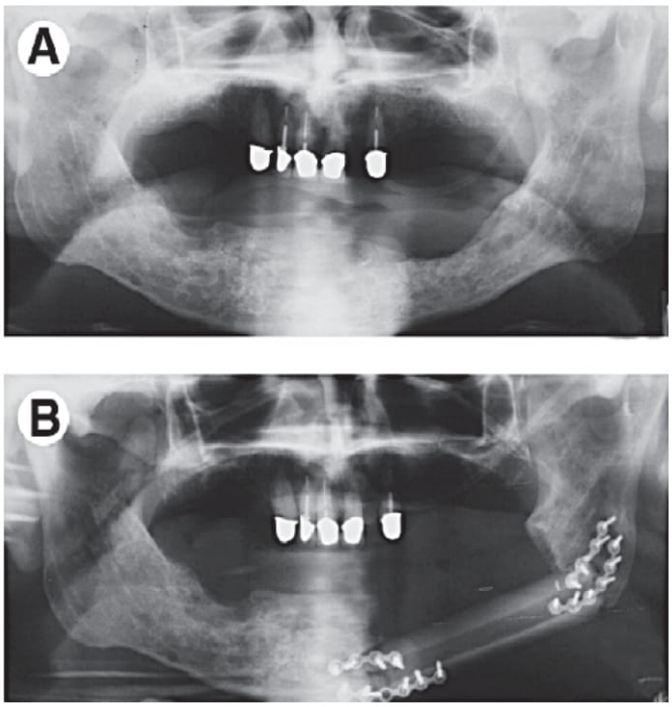

Abb. 6 Patient mit ORN: (A) Z. n. zweimaliger Nekroseabtragung ohne Kontinuitätsresektion. Beachte: Die Nekrosenränder sind nicht klar abgrenzbar; (B) Z. n. partieller Mandibulektomie und Rekonstruktion mittel freiem mikrovakulärem Fibulatransplantat.

Fig. 6 Orthopantomographs of a patient suffering from ORN in the left mandible (A) after 2 conservative resections. Note that the margins of the necrosis are not visible by conventional radiology and (B) after partial mandibulectomy and reconstruction with a free microvascular osteomyocutaneous fibula flap.

piekonzepte durchgesetzt, welche vor allem auf die vollständige Entfernung des nekrotischen und infizierten Knochens, die Knochenglättung und den sicheren Verschluss des Weichgewebes abzielen, durchgesetzt. In der Kombination mit einer perioperativen antibiotischen Therapie führen diese chirurgischen Konzepte konsistent zu hohen Abheilungsraten der Schleimhäute. Die innovative Methode der fluoreszenzorientierten Nekroseabtragung kann auch hierbei intraoperativ zur Visualisierung des Ausmaßes der Nekrose herangezogen werden (53, 54).

Osteoradionekrosen zählen zu den am schwierigsten zu behandelnden entzündlichen Erkrankungen des Kiefers. Durch die häufig stark herabgesetzte Durchblutung großer Kieferabschnitte und die geringe lokale Immunabwehr sowie die zusätzliche Beeinträchtigung der umgebenden Weichgewebe sind Rezidive sehr häufig und eine komplette Heilung oft nicht möglich. Die oben genannten Therapieoptionen gelten aber auch hier.

Die diffus sklerosierende Osteomyelitis wurde häufig symptomatisch mit Steroiden oder Analgetika behandelt. Auch Dekortikationen bis hin zu Kontinuitätsresektionen des Unterkiefers wurden beschrieben (55). Ein neuer erfolgsversprechender Therapieansatz ist die Gabe von stickstoffhaltigen Bisphosphonaten (36). In der Rheumatologie werden sie im Rahmen der Behandlung des SAPHO-Syndroms bereits erfolgreich eingesetzt (56).

Diskussion und Fazit

Eitrige Osteomyelitiden der Kiefer wurden im Zeitalter, bevor Antibiotika zur Verfügung standen, häufiger und mit fulminanteren Verläufen gesehen. Dennoch darf man ihre Präsenz heutzutage auch in unseren Breitengraden nicht unterschätzen. Insbesondere stellt hier der immunsupprimierte Patient eine große Herausforderung dar, aber auch die Besonderheiten der MRONJ und ORN. Trotz Einsatz von Antibiotika sind Osteomyelitiden und Osteonekrosen hartnäckige Erkrankungen, die oft einen langwierigen bzw. wiederkehrenden Verlauf zeigen. Komplikationen wie pathologische Unterkieferfrakturen, Mund-Antrum-Verbindungen, Zahnlockerungen und Zahnverlust, ästhetische Beeinträchtigungen im Gesicht, schmerzbedingte Sprech- und Essprobleme, Gewichtsverlust und Abgeschlagenheit belasten die Patienten mit ohnehin meist schweren Grunderkrankungen und schränken stark ihre Lebensqualität ein. Dies zeigt wie wichtig hier die Prävention ist.

Vor Chemo- und Radiotherapie und auch vor dem Einsatz von Bisphosphonaten und Denosumab sollte eine zahnärztliche oder mund-, kiefer-, gesichtschirurgische Untersuchung und Beratung erfolgen, um mögliche entzündliche Läsionen frühzeitig zu identifizieren und zu beseitigen. Die Indikation zur Zahnextraktion wird hier oft großzügiger gestellt. Aber auch zahnerhaltende Behandlungen brauchen ihre Zeit. Deswegen ist es wichtig, den Patienten über das Risiko aufzuklären und rechtzeitig vor Therapiebeginn vorzustellen. Hierbei können auch Infobroschüren helfen, wie die von der Bundeszahnärztekammer und der kassenzahnärztlichen Bundesvereinigung zum kostenlosen Download zur Verfügung gestellten: „Als Krebspatient zum Zahnarzt".

Zahnärzte und Mund-, Kiefer-, Gesichtschirurgen müssen wissen, was sie zur Prophylaxe und zur Behandlung einer Osteomyelitis des Kiefers zu tun haben. Andere Ärzte sollten das Krankheitsbild mit seinen Symptomen und Gefahren kennen, um rechtzeitig reagieren und auch das Risiko vor Einleiten ihrer spezifischen Therapie berücksichtigen zu können.

Die nicht eitrige, diffus sklerosierende Osteomyelitis muss in ihrer Pathogenese und ihren Therapiemöglichkeiten noch weiter erforscht und besser verstanden werden.

Interessenkonflikt

SO hat Honorare für wissenschaftliche Vorträge von Amgen erhalten. Bei TKK, SA, GK und ME bestehen keine Interessenkonflikte bezüglich des Artikels.

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PUBLICATION 4

Surgical Treatment of Medication-Related Osteonecrosis of The Upper Jaw: Case Series.

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Oral Diseases, available online October 2018

Received: 1 March 2018 | Revised: 21 September 2018 | Accepted: 10 October 2018

DOI: 10.1111/odi.12992

ORIGINAL ARTICLE

WILEY ORAL DISEASES

Surgical treatment of medication-related osteonecrosis of the upper jaw: Case series

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Funding information
AO foundation, Grant/Award Number: AOCMF 14-070 and AOCMF 64-210; Friedrich-Bauer and Curt-Bohnewand foundations

Abstract

Purpose: The management of maxillary medication-related osteonecrosis of the jaw (MRONJ) is challenging. Therefore, identifying the proper treatment is important. This study aimed to evaluate the surgical treatment of maxillary MRONJ using single-layer closure with mucoperiosteal flap and double-layer closure with buccal fat pad flap (BFPF) and mucoperiosteal flap and to find the outcomes after rehabilitation with obturators.

Methods: A retrospective analysis was conducted and included all surgically treated and followed-up maxillary MRONJ cases in a single center. Demographics and clinical data, stage of MRONJ, surgical treatment, and treatment outcome were collected.

Results: Seventy-nine lesions were included. Removal of necrotic bone was followed by coverage with mucoperiosteal flap in 60 lesions and BFPF in 14 lesions. Seven lesions (five primarily and two following unsuccessful treatment with BFPF) underwent necrectomy and were reconstructed with obturators. Complete mucosal healing was achieved in 76.7% of the lesions covered with mucoperiosteal flap. BFPF led to complete mucosal healing in 85.7% of the lesions. No complications were observed in the defects rehabilitated with obturators.

Conclusion: Removal of necrotic bone followed by closure with mucoperiosteal flap is reliable for MRONJ treatment. BFPF is effective for closure of MRONJ-related oroantral communications (OACs).

KEYWORDS
jaw osteonecrosis, maxilla, medication-related osteonecrosis of the jaw, osteonecrosis of the jaw

1 | INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is more common in the mandible than in the maxilla in a ratio of 3:1 (Otto et al., 2012; Saad et al., 2012). The clinical presentation of MRONJ can vary from a mild to a severe lesion. In the maxilla, MRONJ can extend into the maxillary sinus, resulting in oroantral communications (OACs) and sinusitis. Maxillary sinus involvement was reported in 35.8% of the maxillary lesions (Mast et al., 2012). Wasserzug et al. (2017) reported the presence of oroantral fistula and oronasal fistula in 32% and 10% of the patients, respectively. Sinus pain is one of the symptoms of MRONJ that indicates maxillary sinus involvement (Ruggiero et al., 2014). However, some cases might remain totally asymptomatic and can be detected only through careful clinical and radiographic examinations (Wasserzug et al., 2017).

Effective management of maxillary lesions is particularly important as the lesion can extend further and lead to nasal septal abscess, orbital cellulitis, skull base necrosis, and brain abscess (Khan & Sindwani, 2009; Maeda, Matsunobu, Kurioka, Kurita, & Shiotani, 2016; Malik, Fernando, Laitt, & Leatherbarrow, 2014; Matsushita, Kamigaki, & Nakamura, 2013; Yamada, Takahata, Nakagawa, Yamamoto, & Kogo, 2016). The same principles of treatment apply to maxillary and mandibular MRONJ, namely complete removal of non-vital bone followed by meticulous wound closure. Nevertheless, OACs associated with maxillary MRONJ can represent an additional challenge to the oral surgeon. The closure of these defects is essential to improve the functionality and long-term quality of life. This closure can be established by reconstruction using regional or distant flaps or rehabilitation with a prosthetic obturator.

Egyedi (1977) was the first to report the use of the buccal fat pad flap (BFPF) for closure of oroantral and oronasal communications. It has been proven to be effective for the closure of small- to medium-sized OACs secondary to dental extractions and oncologic resections (Amin, Bailey, Swinson, & Witherow, 2005; Chaudhary et al., 2014). BFPF is a valuable technique characterized by its sufficient blood supply, easy mobilization, and long-term post-surgical stability. The use of BFPF was reported to be successful in closing OACs related to MRONJ (Duarte, Alonso, Basso, & Dib, 2015; Gallego, Junquera, Pelaz, Hernando, & Megias, 2012; Melville et al., 2016; Rotaru, Kim, Kim, & Park, 2015).

Extended OACs can be observed after complete removal of necrotic bone of stage 3 MRONJ. In these cases, primary defect closure can be complicated and might result in unfavorable prosthetic outcome. Rehabilitation with free flap can potentially increase morbidity especially in elderly and terminally ill patients. Using prosthetic obturators is a well-established method for the reconstruction of maxillary defects and OACs and was reported to improve nasal leakage, speech, and esthetics (Kornblith et al., 1996). Marx (2009) suggested obturators after maxillary MRONJ resection as used after primary cancer surgery. It can be argued that such a reconstruction modality might increase the risk of MRONJ recurrence as denture trauma is considered an important cofactor in its onset. However, the few reported cases so far have shown that conservative prosthetic rehabilitation with obturators was well tolerated with no recurrence of MRONJ (Troeltzsch, Probst, Troeltzsch, Ehrenfeld, & Otto, 2015).

Due to the more frequent occurrence of MRONJ in the mandible, most of the published case series focused on the treatment of mandibular MRONJ. Compared to the mandibular bone stock, the reduced bone volume of the maxilla with its proximity to the sinus makes the management of upper jaw lesions more critical. Therefore, we aim to present our experience in the management of maxillary MRONJ and to review the outcomes of single-layer closure with mucoperiosteal closure and double-layer closure with BFPF. Another aim is to evaluate the outcomes of obturator prostheses in extensive upper jaw lesions.

2 | MATERIALS AND METHODS

2.1 | Patient selection

A retrospective review of all the patients diagnosed with MRONJ of the maxilla, treated surgically, and followed up between 2008 and 2017 was conducted in the Oral and Maxillofacial Department of Ludwig Maximilians University, Munich, Germany. The criteria for inclusion in the study were as follows:

1. Diagnosis of MRONJ according to the American Association of Oral and Maxillofacial Surgeons (AAOMS) guidelines (Ruggiero et al., 2014), which necessitates the presence of: current or previous intake of ARDs, exposed bone or bone that can be probed through intra- or extraoral fistula in the maxillofacial region which persisted more than 8 weeks, and no history of radiotherapy or obvious metastasis to the jaws. The diagnosis was confirmed by dental panoramic tomograms (when appropriate CBCT or CT) and histopathological analysis of representative bone biopsies.
2. MRONJ located in the upper jaw.
3. Surgical treatment was performed.
4. A minimum postoperative follow-up period of 3 months.

Only patients with the required data were included in the study. The exclusion criteria were presence of a history of radiotherapy in the head and neck, presence of metastasis to the jaws, and a management limited to conservative approach. This study was conducted in compliance with the Declaration of Helsinki and approved by the local institutional review (18-691, Ludwig Maximilians University). The recruitment of the patients was consecutive. All patients signed informed consent for medical treatment and use of their clinical information and images for research purposes.

2.2 | Surgical procedure

All patients started oral antibiotics 3–5 days before admission to the hospital. Amoxicillin/clavulanic acid (875 mg/125 mg), three times daily, was routinely prescribed. Clindamycin 600 mg, four times daily, was prescribed for patients allergic to penicillin.

After admission, intravenous antibiotics had been started at least 1 day before surgery for duration of 3–5 days. IV ampicillin/sulbactam (2 g/1 g), three times daily, was the most frequently prescribed antibiotic. For patients with penicillin allergy, clindamycin was administered in a dose of 1,800 mg/day. Microbiological smears from the lesion were taken intraoperatively, and antibiotics were adjusted if sensitivity dictates. After discharge, oral antibiotics were prescribed (same as the pre-admission antibiotics) for at least 10 days.

All patients were operated under general anesthesia except one patient who was operated under local anesthesia. A second surgical intervention was carried out for some of the unhealed lesions after the first surgery.

For all lesions, a mucoperiosteal flap was raised. After that, a careful removal of osteonecrosis followed by smoothening of sharp bony edges was performed. Some operations were performed according to fluorescence-guided surgery technique as described before by our group (Otto et al., 2016; Otto, Baumann, Ehrenfeld, & Pautke, 2013; Pautke, Bauer, et al., 2011). Bone biopsies were routinely taken for histological and microbiological assessment. All teeth within the necrotic bone were removed.

If OAC was present, a thorough rinsing of the sinus with antiseptic solution was performed. The maxillary sinus was opened in absence of evident OAC only in presence of clear signs of sinus empyema or in case of suspected malignancy. Even then, only a small incision (3–5 mm) was made with a scalpel for drainage or biopsy taking via endoscope. In general, intentional opening of the maxillary sinus mucosa was avoided even in the presence of mild-to-moderate local reaction or swelling in correlation with MRONJ lesion to prevent the development of OAC.

For the defects covered by mucoperiosteal flap only, meticulous suturing using multiple back stitches to attain tension-free, watertight closure of the wound was performed (Figure 1).

Buccal fat pad flap was harvested after incision in the posterolateral region of the maxilla. The fat pad was mobilized to the defect with extreme caution to avoid disruption. After that, tension-free fixation with few transmucosal sutures was established. All BFPFs were additionally covered with mucoperiosteal flaps (Figure 2).

In case of extremely extended OAC (combined bone and soft tissue defect of more than 10 mm in diameter), the sinus was packed with a gauze which was changed at least once per week. After 4–6 weeks, impressions were taken for manufacturing of obturator prosthesis.

2.3 | Data collection

Medical charts of the patients who fulfilled the entry criteria were reviewed. The data on demographics, medical and dental comorbidities, type and duration of ARD use, site and stage of the lesion, the presence of OAC, surgical treatment technique, and the treatment outcomes were recorded. Lesions were classified into four stages (0–3) according to the AAOMS last position paper (Ruggiero et al., 2014).

2.4 | Primary and secondary outcomes

The primary outcome was complete epithelialization of the surgical site in absence of inflammation and pain after single-layer closure with mucoperiosteal flap and double-layer closure with BFPF for MRONJ lesions with or without OAC. These outcomes were evaluated after the first and second surgical interventions. The secondary outcome was absence of signs of infection and absence of disease-defining clinical signs for lesions reconstructed with obturators.

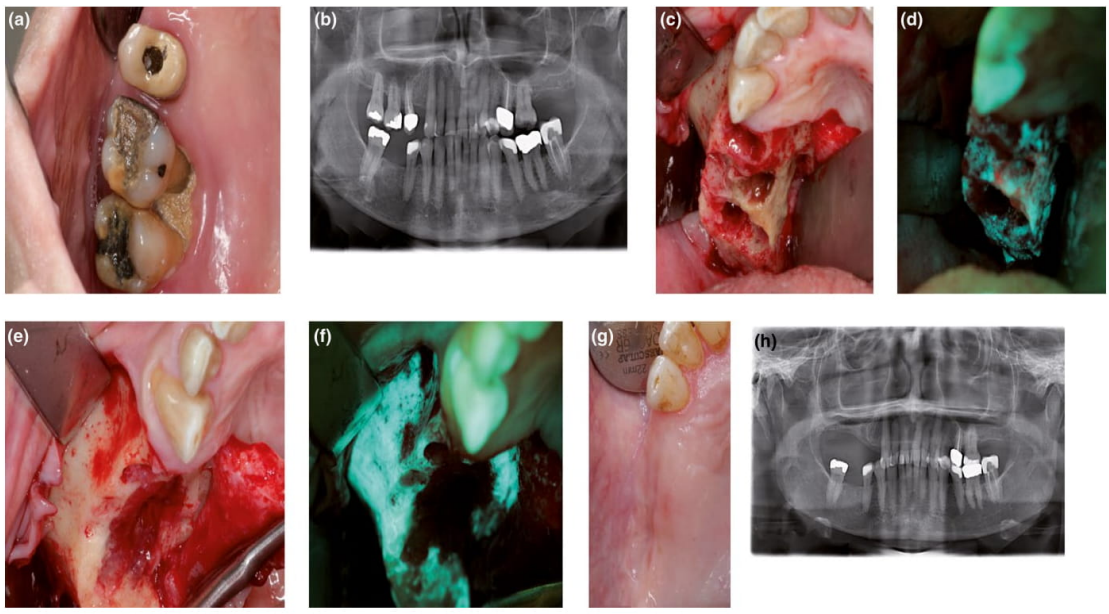

FIGURE 1 Eighty-year-old female patient with medication-related osteonecrosis of the jaw: (a) The clinical picture shows right maxillary lesion (stage 2). (b) The radiograph shows area of reduced bone density of right maxilla associated and widening of the apical part of the periodontal ligament space of the endodontically treated right upper second premolar. (c) During surgery and upon reflection of mucoperiosteal flap, a large area of necrotic bone was evident. (d) Diminished fluorescence prior to removal of the necrotic bone. (e) The intraoperative picture after removal of the necrotic bone using fluorescence-guided surgery and smoothening of sharp bony edges. (f) The resulting homogenous greenish fluorescence indicated complete necrotic bone removal, after that, a tensionless primary wound closure was achieved with proper suturing. (g) and (h) Complete healing was evident 1 year after the surgery

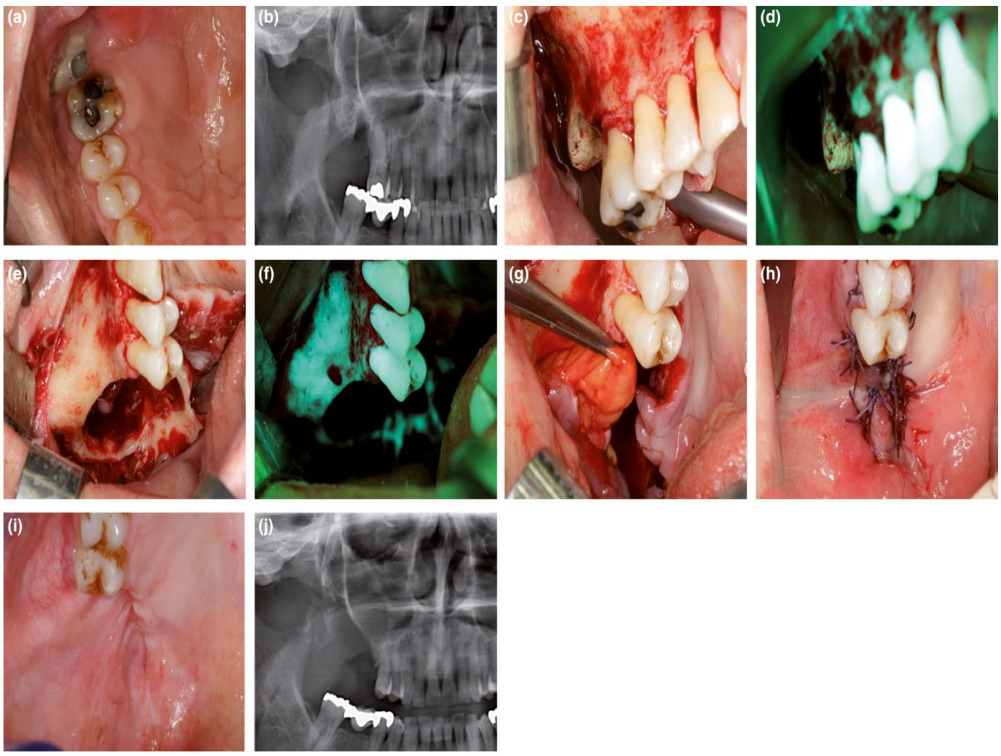

FIGURE 2 The clinical presentation of medication-related osteonecrosis of the jaw lesion in a 68-year-old female patient with metastatic breast cancer: (a) preoperative picture showing exposed bone surrounded by inflamed swollen mucosal tissue in the right posterior maxilla. (b) Panoramic radiograph showing sequestrum and opacification of the right maxillary sinus (stage 3 lesion). (c) and (d) Intraoperative view after mucoperiosteal flap elevation. (d) Diminished fluorescence prior to necrotic bone removal. (e) Oroantral fistula was evident after necrectomy. (f) Brighter homogenous greenish fluorescence after removal of the necrotic bone. (g) and (h) Double-layered wound closure was established using buccal fat pad flap and mucoperiosteal flap. (i) and (j) Complete healing 6 months postoperatively

2.5 | Statistical analysis

All analyses were conducted using SPSS version 24 (SPSS Inc., Chicago, IL, USA). Results were expressed as percentages, and mean or median values ± *SD* and/or range, where appropriate. Logistic regressions were used to evaluate the association between the different independent variables (stage of MRONJ, presence of OAC, age, chemotherapy, chronic corticosteroids, diabetes mellitus, type of primary disease, and the used surgical technique) and treatment outcomes. 95% confidence intervals (CIs) for estimated odds ratios (OR) were given. A p value <0.05 was considered statistically significant. The cases of a minimum follow-up of 6 months were extracted from the main cohort and evaluated using the same statistical methods.

3 | RESULTS

3.1 | Patients

From a pool of 158 patients with operated MRONJ in the maxilla, 72 patients (79 MRONJ lesions) met the inclusion criteria. Twenty-six patients were male and 46 were female with an average age of 72 ± 9.6 years. The most common primary indications of ARDs were breast cancer in 39% (28/72), multiple myeloma in 21% (15/72), prostate cancer in 14% (10/72), and osteoporosis in 8% of the cases (6/72). The remaining 13 patients (18%) suffered from other types of malignancies, including cancer of unknown primary origin, bladder carcinoma, anal carcinoma, Waldenstrom macroglobulinemia, lung adenocarcinoma, ovarian carcinoma in combination with osteoporosis, and breast cancer in combination with renal cancer. All patients had received ARDs with average duration of 39 ± 18 months. The clinical characteristics of the patients are described in Table 1.

3.2 | MRONJ location and severity

Fifty-one lesions had developed in the posterior maxillary segment, distal to the maxillary canine (n = 51, 64.6%), nine lesions in the anterior maxillary segment, mesial to the maxillary canine (11.4%), and 18 lesions in both segments (22.8%). Most the lesions were classified as stage 2 and stage 3 (33/79, 42% and 30/79, 38%, respectively).

TABLE 1 Summary of the clinical characteristics

	N (%)
Comorbidities	
Metastasis to the bone	49 (68)
Chemotherapy	50 (69.4)
Allergy	23 (32)
Cardiovascular disease	28 (39)
Osteoporosis as a comorbidity	17 (23.6)
Long-term corticosteroid therapy	13 (18)
Type 2 diabetes mellitus	12 (16.7)
Rheumatoid arthritis	7 (9.7)
Thalidomide	7 (9.7)
Current or previous smoking (up to 5 years prior to medication-related osteonecrosis of the jaw)	21 (29)
Characteristics of antiresorptive drugs	
Zoledronate	45 (62.5)
Pamidronate	1 (1.4)
Ibandronate	3 (4)
Combination of different bisphosphonates	10 (14)
Denosumab	4 (5.6)
Zoledronate and denosumab	7 (9.7)
Denosumab and ibandronate	1 (1.4)
Denosumab, zoledronate, pamidronate	1 (1.4)
Preceding oral event	
Tooth extraction	30 (41.7)
Apical periodontitis	9 (12.5)
Marginal periodontitis	7 (9.7)
Peri-implantitis	7 (9.7)
Unknown	5 (7)
Denture pressure sores	4 (5.6)
Tooth extraction and denture pressure spot	4 (5.6)
Extraction and endodontic treatment	3 (4.2)
Endodontic treatment due to apical infection	2 (2.8)
Ridge augmentation	1 (1.4)

Eleven lesions were classified as stage 1 (14%). The remaining five lesions were classified as stage 0 lesions (6%). OAC was evident at the time of MRONJ diagnosis in 38% of the lesions.

3.3 | Treatment

The median length of hospitalization after the first operation was 4.3 ± 0.91 days for the cases treated with mucoperiosteal flap, 4.5 ± 0.52 days for the cases reconstructed with BFPF, and 4 days for the cases rehabilitated with obturators.

The median duration of the whole antibiotic treatment was 19 days (ranges from 15 to 23 days).

Removal of necrotic bone and smoothening of sharp bony edges were carried out in all cases. Fluorescence-guided surgery was used for 29 lesions (36.7%). Plastic closure with mucoperiosteal flap was performed for 60 lesions (76%), while BFPF followed by mucoperiosteal wound closure was used for 14 lesions (17.7%). Seven lesions were closed with obturator prostheses (9%). Five of these seven lesions were too extended to be covered with local tissue, and two lesions failed to heal after initial closure with BFPF (two of the 14 BFPF-treated lesions mentioned above) (Table 2).

Ten lesions were operated twice due to lack of healing after the first surgery. The median follow-up period was 6 months (ranged from 3 to 48 months).

Forty lesions in 37 patients had a minimum follow-up period of 6 months. The median follow-up duration of this group was 13 months (ranged from 6 to 48 months).

3.4 | Treatment outcomes

Complete epithelialization of the surgical site in absence of inflammation and pain was achieved in 82.2% (65/79) of the lesions after the first operation and in 92.4% (73/79) after the second operation.

In lesions with a minimum follow-up period of 6 months, the healing rate was 82.5% (33/40) after the first operation and 87.5% (35/40) after the second operation.

3.4.1 | Outcomes of the different treatment modalities

Forty-six of the lesions that underwent coverage with mucoperiosteal flap healed completely (46/60, 76.6%). For patients who were followed up for at least 6 months, the healing rate was 80% (24/30).

On the other hand, all lesions underwent BFPF showed complete mucosal healing except two lesions (12/14, 85.7%). One of these lesions did not heal, and a long-term OAC was developed, and the second one was complicated by severe local hemorrhage and necessitated surgical revision after which wound dehiscence was evident (Figure 3). These two lesions were reconstructed eventually with obturators. For patients with a minimum follow-up period of 6 months, the healing rate after BFPF was 85.7% (6/7).

Five lesions underwent osteotomy followed by rehabilitation with obturator due to their large size. All the seven lesions were effectively managed with obturators and healed completely with no signs of inflammation or pain. Three cases were followed up for at least 6 months.

The treatment outcome was not found to correlate with the stage of MRONJ, the presence of OAC, the used treatment modality and chemotherapy (Table 3). The healing rate after the first operation done with fluorescence guidance was 93% while it was 79.6% for the cases treated without. However, statistical significance has not been seen between fluorescence guidance and healing ($p = 0.135$, OR = 3.375). Likewise, no statistically significant association was observed between healing and other variables in patients with a minimum follow-up period of 6 months (Table 4).

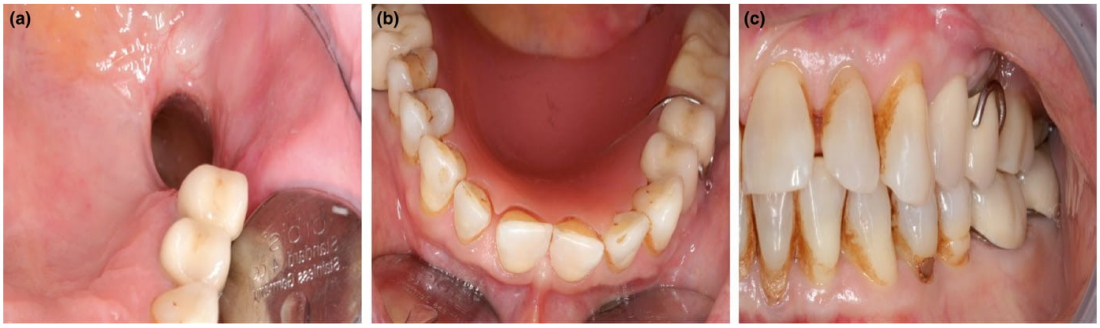

FIGURE 3 (a) The clinical presentation of oroantral fistula as a result of wound dehiscence after prior necrotic bone removal and closure with buccal fat pad in a 76-year-old female patient. (b) and (c) The fistula was sealed conservatively using obturator prosthesis

3.4.2 | Outcomes of the second surgical treatment

A second surgical intervention was performed in 10 lesions treated previously with mucoperiosteal coverage. The closures of these lesions were performed with mucoperiosteal flaps except for one lesion, which was covered by BFPF. Eight of those lesions healed completely, including the one covered by BFPF.

3.4.3 | Oroantral communications

Oroantral communication was evident before treatment in 30 lesions (38%) and occurred during the operative treatment in 16 lesions (20%). In total, 46 of 79 lesions showed OACs.

Of these OACs, 28 lesions were covered with mucoperiosteal flap (61%) and 13 lesions were covered using BFPF (28.3%). Of seven lesions with OACs, five lesions had been too extensive to be covered and two failed to be covered with BFPF, which were reconstructed few weeks after the operation using obturators (15%).

TABLE 2 Summary of the used surgical techniques

	N (%)
Plastic closure	
No OAC, conventional osteotomy, plastic closure	20 (25.3)
No OAC, fluorescence-guided osteotomy, plastic closure	12 (15.2)
OAC, osteotomy plastic closure	23 (29.1)
OAC, fluorescence-guided osteotomy, plastic closure	5 (6.3)
Buccal fat pad flap (BFPF)	
OAC, fluorescence-guided osteotomy, BFPF	6 (7.6)
OAC, conventional osteotomy, BFPF	5 (6.3)
In absence of OAC, fluorescence-guided osteotomy, BFPF	1 (1.3)
Obturator	
OAC, conventional osteotomy, BFPF (failed), obturator	2 (2.5)
OAC, fluorescence-guided osteotomy, obturator	5 (6.3)

The healing rate of OACs after the first surgical attempt was 75% after mucoperiosteal closure (21/28). Five recurrent lesions underwent a second surgery and healed completely except for one lesion. The healing rate after the second attempt was 89% after mucoperiosteal closure (25/28). The postoperative course after BFPF was uneventful for 84.6% of the OACs (11/13). No clinical or radiologic problems were noted in the seven defects that underwent prosthetic reconstruction.

Healing rate of OACs covered with mucoperiosteal flap with a minimum follow-up period of 6 months was 69.2% (9/13). Two of the unhealed OACs underwent a second surgical attempt using the same closure technique and healed. The healing rate after the second surgery was 84.6% (11/13). No signs and symptoms of relapse were evident for 85.7% of the OACs covered with BFPF (6/7).

4 | DISCUSSION

MRONJ of the maxilla is not as frequent as that of the mandible due to the better vascularization of the maxillary cancellous bone compared to the dense compact mandibular bone supplied by end arteries. Accordingly, one can assume that maxillary MRONJ has a better prognosis and can respond better to the conservative treatment. A recent prospective study evaluating the outcomes of MRONJ surgical treatment has reported that the stage of upper jaw MRONJ improved in 71% of the cases, while only 58% of the lower jaw cases improved (Klingelhoffer, Zeman, Meier, Reichert, & Ettl, 2016). However, it is important to keep in mind that proper and early management of upper jaw MRONJ is particularly important as the maxillary sinus can be involved. Owing to the hidden nature of maxillary MRONJ, detection of early stages is difficult. Accordingly, reported maxillary MRONJ tends to be at severe stage at their initial detection (Kim et al., 2017; Nisi et al., 2015). The clinicians need to be aware of the early clinical as well as radiographic manifestations of maxillary MRONJ and the corresponding maxillary sinus involvement to help in early diagnosis and treatment (Wasserzug et al., 2017). This study aimed to evaluate the surgical approaches for the upper jaw

TABLE 3 Results of logistic regression analysis examining the effect of different variables on the healing

Variable	Odds ratio	95% CI	*p* value*
Age	2.342	0.94–1.06	0.888
Primary disease	1.010	0.92–1.12	0.842
Chemotherapy	2.072	0.65–6.62	0.213
Diabetes mellitus	0.982	0.19–5.11	0.983
Chronic corticosteroids	2.648	0.31–22.39	0.371
Location	1.227	0.6–2.49	0.573
Treatment modality	1.010	0.63–8.77	0.842
Fluorescence-guided surgery	3.375	0.69–16.62	0.135
Stage	0.865	0.44–1.69	0.671
Oroantral communication	1.295	0.42–3.99	0.653

*$p < 0.05$ considered significant.

TABLE 4 Results of logistic regression analysis examining the effect of different variables on the treatment outcomes in 6-month follow-up group

Variable	Odds ratio	95% CI	*p* value*
Age	0.96	0.867–1.063	0.431
Primary disease	0.974	0.86–1.11	0.692
Chemotherapy	3.37	0.593–19.2	0.17
Diabetes mellitus	0.556	0.086–3.58	0.536
Chronic corticosteroids	0.36	0.34–1.85	0.39
Location	0.573	0.23–1.45	0.241
Treatment modality	0.833	0.61–1.13	0.244
Fluorescence-guided surgery	0.34	0.84–1.45	0.661
Stage	0.59	0.19–1.79	0.35
Oroantral communication	0.26	0.044–1.54	0.139

*$p < 0.05$ considered significant.

MRONJ (removal of necrotic bone followed by coverage with single-layer closure with mucoperiosteal flap or double-layer closure with BFPF and mucoperiosteal flap) performed in our institute over the last 10 years. In addition, it investigated the outcomes of the maxillary prosthetic reconstruction with obturators.

To the best of our knowledge, this study is the largest in investigating the outcomes of surgical treatment of maxillary MRONJ. The operated 79 lesions in this study had a healing rate of 82.2% after the first operation. The healing rate has increased to 92.4% after the second intervention. That is in line with other authors who found a success rate of over 80% after surgery (Carlson & Basile, 2009; Pautke, Bauer, et al., 2011; Stanton & Balasanian, 2009; Voss et al., 2012). Nevertheless, few similar studies specific to maxillary MRONJ with a limited number of patients have been reported so far (Berrone, Florindi, Carbone, Aldiano, & Pentenero, 2015; Gallego et al., 2012; Melville et al., 2016; Procacci et al., 2018; Rotaru et al., 2015; Voss et al., 2016). Most of these studies included stage 3 lesions and analyzed a single surgical technique. In contrast, the present study included different stages of maxillary MRONJ and evaluated different surgical techniques.

There are several surgical techniques proposed for wound closure of MRONJ. Among them, the mucoperiosteal flap is the most conventional and convenient technique. It can be considered for MRONJ lesions of stages 1 and 2 when the surrounding mucosa is not extremely altered. The healing rate of the presented 60 MRONJ lesions treated with mucoperiosteal flap was 76.6% after the first surgery and 88.3% after the second one. The healing rate of those with OACs was 75% after the first operation and 89% after the second. The healing rate was slightly higher for cases of at least 6 months of follow-up (80%, 24/30). Nonnenmuhlen et al. (2018) reported a comparable healing rate (75.86%, 22 of 29 patients) after surgical removal of avital bone followed by mucoperiosteal flap for mandibular and maxillary MRONJ lesions. Interestingly, the same study found a similar healing rate of the mucosal (epiperiosteal) coverage and the mucoperiosteal coverage. Nevertheless, mucosal coverage should be avoided in MRONJ treatment as the reflection of full-thickness mucoperiosteal flap is crucial to ensure complete removal of the necrotic bone.

Buccal fat pad flap was reported to be reliable in extended MRONJ lesions especially in association with OACs (Berrone et al., 2015). This surgical choice is characterized by its simplicity, low associated complications, mechanical stability, and good vascularization. Moreover, fat grafts contain stem cells which can differentiate into different cell types and therefore can promote tissue healing, including bone tissue healing (Burian et al., 2017; Farre-Guasch, Marti-Page, Hernadez-Alfaro, Klein-Nulend, & Casals, 2010). Melville et al.

(2016) and Rotaru et al. (2015) reported 23 and 10 cases of MRONJ effectively treated with BFPF, respectively. Berrone et al. (2015) reported a healing rate of 100% after this procedure in five stage 3 MRONJ lesions. A recent case series reported successful BFPF in seven MRONJ patients (Procacci et al., 2018). Ristow et al. (2018) presented a retrospective case series with 29 lesions of different MRONJ stages managed with BFPF. The reported healing rate was 93.1% (27/29). In the present study, the healing rate of the MRONJ covered with BFPF was 85.7% (12/14) and 85.7% (6/7) for cases with a minimum follow-up period of 3 and 6 months, respectively. Healing rate specific to lesions with OACs was 84.6%. In the presence of MRONJ-related sinus involvement, BFPF is considered the best surgical choice due to its long-term stability (Melville et al., 2016).

Some other methods of surgical reconstruction were suggested. A limited number of studies proposed free flaps for MRONJ lesions, mostly mandibular lesions, with poor vascularization and large soft tissue defects (Hanasono, Militsakh, Richmon, Rosenthal, & Wax, 2013; Mucke et al., 2016; Seth, Futran, Alam, & Knott, 2010; Vercruysse, Backer, & Mommaerts, 2014). Mucke et al. (2016) reported successful reconstruction of four maxillary lesions reconstructed with radial forearm flap and one with anterolateral thigh flap. The limitations of these techniques include their complexity, long operative time, risk of donor site morbidity, and particularly the complexity of postoperative prosthetic rehabilitation. A case of histologically proven MRONJ in a microvascular iliac bone graft due to stage 3 MRONJ has been reported (Pautke, Otto, et al., 2011). Indeed, complex surgical reconstruction with free flaps seems to be unwarranted in MRONJ patients who often have incurable malignancies, poor medical status, and limited life expectancy. Thus, this approach must be preceded by a critical assessment of cost/benefit ratio and treatment efficacy. Free flaps might be reasonable in extremely extended bony lesions accompanied by extremely extended soft tissue lesions in patients with good general status.

Lemound et al. (2018) compared the outcomes of nasolabial flap and mucoperiosteal flap after decortication of MRONJ in the maxilla (13 lesions) and in the mandible (three lesions). In this study, 68% of 16 lesions treated with nasolabial flap healed, while only 18.7% of 16 lesions treated with mucoperiosteal flap (used as a control group) healed. Nevertheless, the selection criteria of the control group were not fully clarified. Another study has reported an uneventful healing in 93% of the oral defects reconstructed with nasolabial flaps (three out of 16 lesions were MRONJ) (Eckardt, Kokemuller, Tavassol, & Gellrich, 2011). This technique is simple and less time-consuming in comparison with free flaps. However, the bulkiness of this flap makes the postoperative dental prosthetic rehabilitation extremely challenging, if not impossible. Moreover, it can be complicated by scaring and intraoral growth of hair (Rai, Datarkar, & Rai, 2014).

It is well established that complete removal of necrotic bone and smoothening of sharp bony edges followed by tensionless wound closure are essential to achieve complete mucosal healing and to decrease relapse of MRONJ (Groetz, Piesold, & Al-Nawas, 2012; Otto et al., 2016; Pautke, Bauer, et al., 2011). Distinguishing the avital bone from the viable one is deemed as a clinical challenge. One of the used parameters is the color and texture of the bone as well as bone bleeding. However, these parameters are liable to mistake and largely subjective. In 2009, Pauthke et al. proposed fluorescence-guided MRONJ surgery as a reliable and reproducible technique for identification of necrotic bone. Several studies have evaluated this technique prospectively and reported a high success rate (over 85%) and complete removal of necrotic bone as verified by histological investigations (Otto et al., 2016; Pautke, Bauer, et al., 2011; Ristow et al., 2017). In this series, 93% of the maxillary lesions operated with fluorescence guidance and 79.6% of those operated without presented complete mucosal healing after the first surgical attempt.

Oroantral communications in MRONJ patients might occur before or during removal of necrotic bone. Their management can be critical particularly in this group of medically compromised patients. Poor health status and severe reduction in soft tissue are all obstacles to achieve a successful second surgical intervention after MRONJ relapse. Obturator prostheses can improve the quality of life of patients with maxillary defects by restoring mastication and speech functions, preventing nasal fluid leakage and enhancing esthetics (Kornblith et al., 1996). A recent systematic review indicated that the quality of life of patients who underwent reconstruction with obturators and that of patients free of tumors are similar (Brandao, Vechiato Filho, Batista, de Oliveira, & Santos-Silva, 2016). Only four cases of prosthetic rehabilitation of MRONJ were reported so far. Troeltzsch et al. (2015) proposed the use of obturators for MRONJ patients who had reopening of OACs without signs of pain and inflammation. Another study reported the use of obturator in a MRONJ patient with no complications for 4 years (de Almeida et al., 2014). This procedure can be considered for large defects, which might be difficult to be covered successfully with regional flaps, and for patients with poor general status. Within the limitations of small sample size, all the presented patients showed a favorable response and a high satisfaction with obturator prostheses. No recurrence of MRONJ occurred over a mean follow-up period of 7.3 months (ranged from 3 to 18 months).

In this case series, the various surgical techniques used for maxillary MRONJ reconstruction in a single center were investigated. We are aware of the limitation of the retrospective nature of this study. Only randomized clinical trials with a large sample size can evaluate the effects of these techniques precisely. Unfortunately, these studies are still lacking. Nevertheless, most of the studies in concern to MRONJ share this limitation due to the rarity of this disease. Another limitation was incomplete data or lack of access to some medical records.

In conclusion, this study demonstrated that surgical treatment of MRONJ can be effective to establish complete mucosal healing of upper jaw MRONJ. The mucoperiosteal flap is a fast and simple method suitable for stage 1 and 2 MRONJ lesions. For stage 3 MRONJ, BFPF appears to be very versatile and helpful in achieving a long-term covering of MRONJ-related OACs. Obturators can be suggested for extended stage 3 lesions, especially when accompanied by large soft tissue defects in critically or terminally ill patients.

ACKNOWLEDGEMENTS

Sven Otto acknowledges the financial support of AO foundation (AOCMF 14-070 and AOCMF 64-210) for the research of MRONJ. He also acknowledges the financial support of Friedrich-Bauer and Curt-Bohnewand foundations. Sven Otto has received honoraria for scientific talks from Nobel Biocare, CAMLOG, and AMGEN. Dr. Hafner has given scientific lectures about antimicrobial photodynamic therapy and medication-related osteonecrosis of the jaw sponsored by Bredent Medical GmbH. The authors would like to thank Dr. Ingrid Ricard and the Institute for Medical Information Processing, Biometry, and Epidemiology, LMU, for assistance in the statistical analysis of the data.

CONFLICT OF INTEREST

Suad Aljohani, Matthias Troeltzsch, Gabriele Kaeppler, and Gerson Mast declare that they have no conflict of interest.

AUTHOR CONTRIBUTION

Suad Aljohani drafted the manuscript and contributed to acquisition and analysis of the data. Matthias Troeltzsch, Sigurd Hafner, Gabriele Kaeppler, and Gerson Mast contributed to critical revision of the manuscript. Sven Otto contributed to the study design and critical revision of the manuscript.

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How to cite this article: Aljohani S, Troeltzsch M, Hafner S, Kaeppler G, Mast G, Otto S. Surgical treatment of medication-related osteonecrosis of the upper jaw: Case series. *Oral Dis*. 2018;00:1–11. https://doi.org/10.1111/odi.12992

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ACKNOWLEDGEMENTS

Special mention goes to my enthusiastic supervisor, Dr. Sven Otto. The door to Dr. Otto's office has been always open whenever I ran into a trouble spot or had a question about my research or writing. He never hesitated to support and advise me whenever I needed his support. I have been extremely lucky to have a supervisor who cared so much about my work, and who responded to my questions and queries so promptly. Actually, I quite simply cannot imagine a better adviser. It has been truly an honour and a privilege working as a part of his team over the last three years and I've really enjoyed it.

Similar, profound gratitude goes to Prof. Jan Kühnisch, who has been a truly dedicated mentor. He was keen to provide me with every bit of guidance, assistance, and expertise that I needed during my PhD. I am particularly indebted to his support and advise when everything seemed impossible.

I am also hugely appreciative to Dr. Matthias Tröltzsch for being so dedicated to his role as my secondary supervisor.

My thanks and appreciations also go to my colleagues and people who have willingly helped me with their abilities.

I recognize that this research would not have been possible without the financial assistance of King Abdulaziz University, the Department of Basic and Clinical Science (Graduate Research Scholarships) and the Ministry of Higher Education, Saudi Arabia, and I express my gratitude to those agencies.

Finally, I would like to express my very profound gratitude to my parents for the support they provided me through my entire life and in particular, during my PhD. A

very special thanks go to my sisters, Rajha and Salha, for almost unbelievable support. I also would like to thank my husband, Waleed, for providing me with unfailing support and continuous encouragement throughout my years of study and through the process of researching and writing this thesis. Last, but by no means least, I am grateful to my children; Taleen, Taliah and Taym, without whose love, kisses and hugs, I would not have finished this thesis. This accomplishment would not have been possible without all of them.