

Review

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# The use of bone morphogenic protein and related therapies in the management of medication-related osteonecrosis of the jaw: a scoping review

Pranav A. Patel<sup>#</sup>, Sami I. Nassar<sup>#</sup>, Shaun A. Nguyen, Byung J. Lee, Alexandra E. Kejner 

Department of Otolaryngology Head and Neck Surgery, Medical University of South Carolina, Charleston, SC 29425, USA.

<sup>#</sup>Authors contributed equally.

**Correspondence to:** Prof. Shaun A. Nguyen, Department of Otolaryngology Head and Neck Surgery, Medical University of South Carolina, 135 Rutledge Avenue, Room 1133, MSC 550, Charleston, SC 29425, USA. E-mail: nguyensh@musc.edu

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## Abstract

Medication-related osteonecrosis of the jaw (MRONJ) is an uncommon adverse event of antiresorptive and antiangiogenic medications that can result in severe bony complications. Pentoxifylline and tocopherol (PENTOCO) and bone morphogenic protein (BMP) have shown promise as two therapies that could be effective in the management of MRONJ. The present paper reviews the findings of a total of 12 studies investigating the effectiveness of PENTOCO and BMP in the management of 417 patients with MRONJ. Additionally, three patient cases that were managed at our institution are discussed to supplement the findings of the review. While the available literature on the efficacy of PENTOCO and BMP use in the management of MRONJ is limited, the present study's findings support the potential effectiveness of these therapies as supplements to medical and surgical interventions currently employed.

**Keywords:** Medication-related osteonecrosis of the jaw, pentoxifylline, tocopherol, bone-morphogenic protein

## INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is a rare but major complication of antiresorptive or



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antiangiogenic medications and can result in the exposure of bone or the formation of non-healing intra- or extra-oral fistulae<sup>[1]</sup>. Per the American Association of Oral and Maxillofacial Surgeons (AAOMS), a diagnosis of MRONJ meets the following criteria: (a) grossly exposed bone or bone probed through an intra- or extra-oral fistula of the maxillofacial region with persistence for over 8 weeks in patients who (b) are currently taking or have previously been treated with antiresorptive or antiangiogenic agents, and (c) have not undergone radiation therapy or do not have any obvious metastatic disease of the jaw.

Antiresorptive medications, such as bisphosphonates, are the main risk factors for the development of MRONJ<sup>[2]</sup>. Bisphosphonates bind to hydroxyapatite on the surface of bones and are internalized by osteoclasts during active remodeling, subsequent to which they cause the downstream inhibition of osteoclast functioning<sup>[3]</sup>. Osteoclast inhibition is secondary to the blockade of significant metabolic pathways and the induction of cellular apoptosis<sup>[4]</sup>. Denosumab, an antiresorptive monoclonal antibody, has a similar mechanism of action. It operates through the direct inhibition of NF- $\kappa$ B, a receptor activation ligand of RANKL, which inhibits signaling pathways, thus decreasing osteoclastic division and activity<sup>[5]</sup>. These medications are clinically used to prevent excessive resorption of bone, such as in the treatment and management of osteoporosis<sup>[4,5]</sup>.

For many years following Marx *et al.*'s initial description of MRONJ, its pathophysiology was not fully understood<sup>[1]</sup>. More recently published literature suggests that MRONJ results from periodontal inflammation in conjunction with osteoclast inhibition caused by antiresorptive therapy<sup>[6]</sup>. This leads to persistent exposure of the bone to proinflammatory mediators that catalyze a feedback loop, resulting in osteocyte death and subsequent necrosis of the bone<sup>[6]</sup>. Clinically, MRONJ is classified into four distinct stages, ranging from stage 0 to stage 3. The current staging system was developed by Ruggiero *et al.* and has since been adopted by AAOMS as the diagnostic standard<sup>[7]</sup>.

Pentoxifylline and tocopherol (PENTOCO) and bone morphogenic protein (BMP) are two emerging medical therapies for the management and treatment of MRONJ, which can be used in lieu of or in conjunction with surgical interventions. PENTOCO has previously been described as a potential therapy, albeit with limited evidence, for the management of osteoradionecrosis and MRONJ. Its efficacy is believed to depend on its improvement of peripheral vascular blood flow, anti-inflammatory effects, and antioxidant effects<sup>[8]</sup>.

BMPs are a heterogeneous class of receptor ligands with osteoinductive properties capable of promoting bone formation. Originally named for their inductive role in the formation of ectopic bone, BMPs have since been found to be integral in the development and functioning of other types of tissue and organs. Due to their role in osteogenesis, BMPs have recently been proposed as a potential alternative or adjunctive therapy to PENTOCO<sup>[9,10]</sup>.

Since their initial discovery, BMPs have been subclassified into various subgroups. These subgroups include the BMP-2/-4 subgroup, the BMP-5/-6/-7/-8 subgroup, the BMP-9/-10 subgroup, and the BMP-12/-13/-14 subgroup. The BMP-2/-4 subgroup, which is the most clinically relevant subgroup, is part of the transforming growth factor  $\beta$  (TGF- $\beta$ ) family. Another notable BMP subtype is BMP-7, which, in addition to BMP-2/-4, has been shown to significantly induce osteoblast differentiation and subsequent bony growth<sup>[11-13]</sup>. As the other subtypes' clinical use and relevance are currently questionable, the BMP-2/-4 and BMP-7 subgroup and subtype, respectively, will be the focus of the present review.

In view of the limited literature on the efficacy of BMP and PENTOCO therapies in the treatment of MRONJ, the present scoping review aims to synthesize and analyze the currently available data on their clinical application, while also aiming to identify aspects of their use that warrant further investigation. The review portion of the present study will be supplemented by a case series of patients with MRONJ who were managed with BMP and PENTOCO regimens.

## METHODS

A comprehensive systematic scoping review methodology, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines, was implemented to identify relevant literature on the use of BMP and PENTOCO therapies in conjunction with locoregional reconstruction in the management and treatment of MRONJ<sup>[14]</sup>. Arksey and O'Malley's five-stage framework for performing scoping reviews was followed in the present study<sup>[15]</sup>. Preliminary searches of PubMed (US National Library of Medicine, National Institutes of Health), Scopus (Elsevier), CINAHL (EBSCO), and Cochrane databases did not identify any previously published reviews on the topic. There are no deviations from this methodology to report.

### Stage 1: Research question formulation

Initially, the primary objective of the present review was to discuss and identify future avenues for investigation of BMP's clinical utility in conjunction with locoregional reconstruction in the management and treatment of patients with MRONJ. Given the sparsity of literature on BMP's use in the MRONJ patient population, previous publications examining the use of PENTOCO therapy in MRONJ treatment and management were also identified and their findings were evaluated. Thus, the present review aims to provide an overview of the clinical utility of BMP and PENTOCO therapies in treating and managing MRONJ and, subsequently, delineate aspects of these therapies' use that warrant further scientific investigation.

### Stage 2: Relevant literature identification

PubMed, Scopus, CINAHL, and Cochrane databases were systematically reviewed from the date of inception through September 19, 2024, for the identification of peer-reviewed, English-language articles exploring BMP and PENTOCO therapy use in the MRONJ patient population. Keywords used in the search strategy included "medication related osteonecrosis of the jaw", "MRONJ", "bone morphogenetic protein", "BMP", "locoregional reconstruction", and "pentoxifylline". Detailed search strategies and the number of results per database are outlined in [Supplementary Materials](#).

### Stage 3: Study selection

Using Covidence (Veritas Health Innovation Ltd., Melbourne, Australia), an online article review program that permits collaboration between reviewers, two authors (P.A.P. and S.I.N.) independently screened records identified from the reviewed databases by title and abstract. Articles deemed relevant to the present review based on title and abstract subsequently underwent full-text review. Any disagreements or conflicts were resolved through discussion between P.A.P., S.I.N., and S.A.N. The inclusion criteria were as follows: (1) full-text articles were available; (2) investigations were primary studies; (3) articles were written in the English language; (4) articles were published in peer-reviewed journals; (5) patients included were adults aged 18 or above with a diagnosis of MRONJ; and (6) patients in the studies underwent BMP, PENTOCO, or teriparatide therapy in their MRONJ treatment and management regimen. Articles were excluded if they (1) were not published in peer-reviewed articles; (2) were not available in the English language; (3) did not have an available full-text manuscript; (4) included non-human subjects; (5) were not primary clinical studies; and (6) did not report outcomes of patients who underwent either BMP or PENTOCO therapy.

#### Stage 4: Data charting

Two authors (P.A.P and S.I.N.) independently extracted data from the included studies, which were organized in a common Microsoft Excel spreadsheet. Disagreements and conflicts were resolved by discussion between P.A.P., S.I.N., and S.A.N. Data extracted from the articles included study characteristics, patient demographics, patient comorbidities and MRONJ risk factors, surgical and medical therapies employed, and characteristics of MRONJ.

The included studies were appraised independently by P.A.P. and S.I.N. using the Oxford Centre for Evidence-Based Medicine (OCEBM) criteria<sup>[16]</sup>. Disagreements and conflicts in the articles' level of evidence were resolved through discussion between P.A.P., S.I.N., and S.A.N.

#### Stage 5: Collating, summarizing, and reporting the results

Relevant information from the included studies was synthesized per the guidelines set out by the Cochrane Handbook<sup>[17]</sup>. Analysis of the results of the included studies is presented through descriptive statistics examining both categorical and continuous variables. To assess the robustness of our findings, we performed a sensitivity analysis using the one-study removal technique, which systematically excludes one study at a time to evaluate the impact of individual studies on the pooled results. Qualitative data were synthesized and are presented in a narrative format. When possible, the results of the statistical analyses were stratified by treatment employed.

## RESULTS

### Studies included

A review of PubMed, Scopus, EBSCO, and Cochrane databases yielded 50 unique articles, from which 12 were included in the present scoping review. [Figure 1](#) outlines the selection of articles. A summary of the included studies is presented in [Table 1](#). Included studies were conducted in Italy (2/12), Brazil (1/12), South Korea (4/12), Germany (1/12), the United Kingdom (2/12), the United States (1/12), and Poland (1/12), and the articles from which data were collected were published between the years of 2015 and 2024. Of the studies included, one was a retrospective chart review, four were prospective clinical studies, and seven were case reports or case series.

Risk of appraisal per ROBINS-I criteria found an overall acceptably low risk of bias across all seven domains<sup>[29]</sup>. Unclear risk of bias was most frequently observed due to confounding variables and deviations from intended interventions, which were ultimately the greatest potential contributors to included study bias [[Figure 2](#)]. Low publication bias was suggested per the funnel plot [[Figure 3](#)] with Kendall's tau (0.146;  $P = 0.47$ ), as all studies were within the funnel and exhibited little asymmetry relative to the midpoint.

### BMP study patient characteristics

Of the studies examining the efficacy of BMP in the treatment of MRONJ, 140 patients were included. Characteristics of the treatment and control groups of BMP studies are presented in [Tables 2](#) and [3](#).

Among patients who received BMP treatment, the mean age was 76.32 years (range: 60-85) and the mean duration of treatment was 74.14 months (95%CI: 37.98-110.30). Females comprised 94.79% (95%CI: 85.89-98.84) of the BMP cohort. Stage 2 MRONJ [61.59% (95%CI: 47.76-74.17)] was more common than stage 1 [17.34% (95%CI: 8.60-29.67)] and stage 3 MRONJ [22.39% (95%CI: 3.64-50.84)], with mandibular lesions being more common than maxillary lesions [78.53% (95%CI: 66.14-88.01) vs. 26.29% (95%CI: 15.52-39.63)]. The most common causative agent was alendronic acid [43.79% (95%CI: 30.68-57.57)]. The most commonly performed surgical procedure was sequestrectomy [98.80% (95%CI: 87.80-100.00)]. At the time of follow-up, 94.84% (95%CI: 81.05-99.52) of patients receiving BMP exhibited signs of healing.

**Table 1. Characteristics of included studies**

Study	Country	Study design	OCEBM level of evidence	Primary therapy	Patients (n)
<b>PENTOCO</b>					
Colapinto et al., 2023 <sup>[18]</sup>	Italy	Prospective randomized control trial	2	PENTOCO	202
Fernandes et al., 2024 <sup>[19]</sup>	Brazil	Case series	4	PENTOCO	11
Magalhães et al., 2023 <sup>[20]</sup>	Germany	Case series	4	PENTOCO	17
Martin et al., 2018 <sup>[21]</sup>	United Kingdom	Case series	4	PENTOCO	3
Owosho et al., 2016 <sup>[22]</sup>	USA	Case series	4	PENTOCO	7
Słowik et al., 2024 <sup>[23]</sup>	Poland	Case series	4	PENTOCO	2
Varoni et al., 2021 <sup>[24]</sup>	Italy	Retrospective cohort study (chart review)	3	PENTOCO	35
<b>BMP</b>					
Jung et al., 2017 <sup>[25]</sup>	Korea	Prospective study	3	BMP-2	17
Kim et al., 2020 <sup>[26]</sup>	Korea	Retrospective case series	4	BMP-2	3
Kim et al., 2024 <sup>[9]</sup>	Korea	Prospective study	3	BMP-2	64
Park et al., 2017 <sup>[27]</sup>	South Korea	Prospective case control study	3	BMP-2	55
Rahim et al., 2015 <sup>[28]</sup>	United Kingdom	Case report	4	BMP-7	1

OCEBM: Oxford Centre for Evidence-Based Medicine; BMP: bone morphogenic protein; PENTOCO: pentoxifylline and tocopherol.

Regarding the control cohort, the mean age was 77.92 years (range: 59-97). Patients were mostly female [95.18% (95%CI: 76.11-99.54)]. Stage 2 MRONJ was more common than stage 1 and 3 lesions [69.02% (95%CI: 28.75-96.94) vs. 16.17% (95%CI: 8.26-27.30) and 16.70% (95%CI: 0.55-48.22), respectively]. The majority of lesions were localized to the mandible [60.61% (95%CI: 47.82-72.43)], with alendronic acid being the most common causative agent [48.37% (95%CI: 28.53-68.47)].

When considering the BMP and control cohorts together, the average age was 75.51 years (range: 59-97) and the average time to follow-up was 0.15 years (95%CI: 0.10-0.20). Most patients were female [94.95% (95%CI: 90.01-97.89)]. Systemic arterial hypertension and diabetes mellitus were reported by 36.30% (95%CI: 8.51 -70.55) and 29.97% (95%CI: 22.10-38.81) of patients, respectively. Regarding staging, 16.50% (95%CI: 10.38-24.33) of patients had stage 1 MRONJ, 64.36% (95%CI: 36.00-88.10) of patients had stage 2 MRONJ, and 18.98% (95%CI: 1.72-48.46) of patients had stage 3 MRONJ. Sequestrectomy and marginal resection were performed on 99.36% (95%CI: 92.82-100.00) and 99.39% (95%CI: 92.68-100.00) of patients, respectively.

### PENTOCO study patient characteristics

Of the studies examining the efficacy of PENTOCO in the treatment of MRONJ, 251 patients were included. Characteristics of the treatment and control groups of PENTOCO studies are presented in [Tables 2](#) and [3](#).

When considering patients in the PENTOCO cohort, the mean age was 65.01 years (range: 43-93), the average time to follow-up was 1.37 years (95%CI: 0.87-1.87), and the mean duration of treatment was 44.76 months (95%CI: 1.77-87.75). Most patients were female [79.81% (95%CI: 52.26-97.16)]. Most patients had stage 2 MRONJ [70.13% (95%CI: 36.90-94.42) vs. 28.91% (95%CI: 0.17-78.97) and 42.70% (95%CI: 21.69-65.84) for stage 1 and stage 3 MRONJ, respectively]. The most common causative agent was zoledronic acid [69.68% (95%CI: 49.90-85.25)] and most patients underwent sequestrectomy [58.47% (95%CI: 13.07-96.07)].

**Table 2. Patient characteristics from BMP studies**

Variable	BMP cohort, % (95%CI)	Control cohort, % (95%CI)	Total, % (95%CI)
Sex			
Male	5.111 (1.033-14.408)	4.823 (0.460-23.892)	5.053 (2.108-9.986)
Female	94.791 (85.887-98.844)	95.177 (76.108-99.540)	94.947 (90.014-97.892)
Comorbidities			
Systemic arterial hypertension	- <sup>*</sup>	-	36.299 (8.511-70.552)
Diabetes mellitus	-	-	29.967 (22.102-38.807)
MRONJ stage			
Stage 0	-	-	-
Stage 1	17.340 (8.599-29.671)	16.174 (8.260-27.297)	16.501 (10.376-24.335)
Stage 2	61.587 ( 47.760-74.168)	69.015 (28.749-96.942)	64.360 (36.002-88.098)
Stage 3	22.391 (3.641-50.844)	16.696 (0.550-48.224)	18.983 (1.722-48.463)
Causative agent			
Alendronic acid	43.794 (30.681-57.574)	48.366 (28.533-68.472)	-
Ibandronic acid	13.854 (6.136-25.579)	12.060 (5.339-22.420)	-
Risedronic acid	17.508 (8.721- 29.865)	10.539 (4.328-20.556)	-
Zoledronic acid	12.973 (0.489-38.265)	7.531 (0.407-33.742)	-
Treatment			
Sequestrectomy	98.797 (87.801-100.00)	-	99.361 (92.823-100.00)
Marginal resection	-	-	99.389 (92.675-100.00)
Anatomical location of MRONJ liufangyuanesion			
Maxilla	26.287 (15.516-39.632)	39.387 (27.575-52.184)	-
Mandible	78.529 (66.141-88.011)	60.613 (47.816-72.425)	-
Outcome			
Healing	94.84 (81.05-99.52)	-	-

<sup>\*</sup>Hyphen denotes lack of data. BMP: Bone morphogenic protein; MRONJ: medication-related osteonecrosis of the jaw.

Maxillary lesions were present in 57.31% (95%CI: 48.31-65.98) of patients and mandibular lesions were present in 77.38% (95%CI: 55.33-92.00) of patients. At the time of follow-up, 25.63% (95%CI: 19.17-99.69) of patients had a complication, 39.74% (95%CI: 31.17-48.80) of patients exhibited either treatment failure or no improvement in their MRONJ, and 77.89% (95%CI: 36.58-99.67) of patients exhibited signs of healing.

Due to concern that the inclusion of Fernandes *et al.* biased the result of the meta-analysis examining the proportion of patients exhibiting healing in the PENTOCO cohort, a sensitivity analysis was performed. The exclusion of Fernandes *et al.* resulted in 89.80% (95%CI: 67.07-99.85) of patients exhibiting healing at the time of follow-up compared to 77.89% (95%CI: 36.58-99.67) when its findings were included in the analysis. A comparison of proportions comparing the results of the sensitivity analysis to the original findings demonstrated that the results of the sensitivity analysis were significantly greater by 11.91% ( $P < 0.0085$ ), suggesting that the inclusion of Fernandes *et al.* biased the overall analysis<sup>[19]</sup>.

**Table 3. Patient characteristics from PENTOCO studies**

Variable	PENTOCO cohort, % (95%CI)	Control cohort, % (95%CI)	Total, % (95%CI)
Sex			
Male	22.940 (2.661-54.957)	0.490 (0.00112-4.038)	14.218 (1.585-36.339)
Female	79.809 (52.258-97.163)	99.510 (95.962-99.999)	86.884 (67.396-98.230)
Comorbidities			
Tobacco smoking	- <sup>*</sup>	9.048 (4.416-16.031)	10.377 (6.688-15.172)
MRONJ stage			
Stage 0	-	-	53.528 (26.912-79.101)
Stage 1	28.907 (0.167-78.968)	2.505 (0.196-12.549)	29.709 (11.438-52.252)
Stage 2	70.126 (36.898-94.416)	-	51.447 (4.220-96.866)
Stage 3	42.699 (21.693-65.836)	-	36.755 (19.178-57.356)
Causative agent			
Alendronic acid	49.838 (23.698-76.025)	48.039 (38.039-58.156)	-
Ibandronic acid	29.706 (0.664-77.054)	12.645 (6.888-20.690)	-
Zoledronic acid	69.676 (49.900-85.250)	75.364 (6.931-93.109)	-
Denosumab	18.335 (3.349-41.596)	4.960 (3.355-35.035)	-
Pamidronic acid	53.504 (22.580-82.532)	-	-
Treatment			
Sequestrectomy	58.468 (13.069-96.065)	-	52.359 (15.746-87.535)
Debridement	2.364 (0.438-7.077)	-	-
Anatomical location of MRONJ lesion			
Maxilla	57.313 (48.306-65.978)	58.048 (24.770-87.639)	-
Mandible	77.379 (55.327-91.997)	-	-
Outcome			
Healing	89.800 (67.070-99.848)**	88.292 (73.780-97.435)	-
Stable/Failure	39.738 (31.166-48.800)	-	-
Any complication	25.625 (19.170-99.686)	53.027 (6.333-90.403)	-

<sup>\*</sup>Hyphen denotes lack of data; <sup>\*\*</sup>Results of sensitivity analysis. PENTOCO: Pentoxifylline and tocopherol; MRONJ: medication-related osteonecrosis of the jaw.

Patients in the control cohort had an average age of 67.43 years (range: 43-85), an average time to follow-up of 1.64 years (95%CI: 0.50-2.78), and a mean duration of treatment of 46.13 months (95%CI: -4.38-96.63). The cohort was overwhelmingly female [99.51% (95%CI: 95.96-100.00)] and 9.05% (95%CI: 4.42-16.03) of patients reported smoking tobacco. Patients with stage 1 MRONJ comprised 2.51% (95%CI: 0.20-12.55) of the cohort. The most common causative agent was zoledronic acid [75.36% (95%CI: 6.93-93.11)]. Maxillary lesions were present in 58.05% (95%CI: 24.77-87.64) of patients. At the time of follow-up, 53.03% (95%CI:

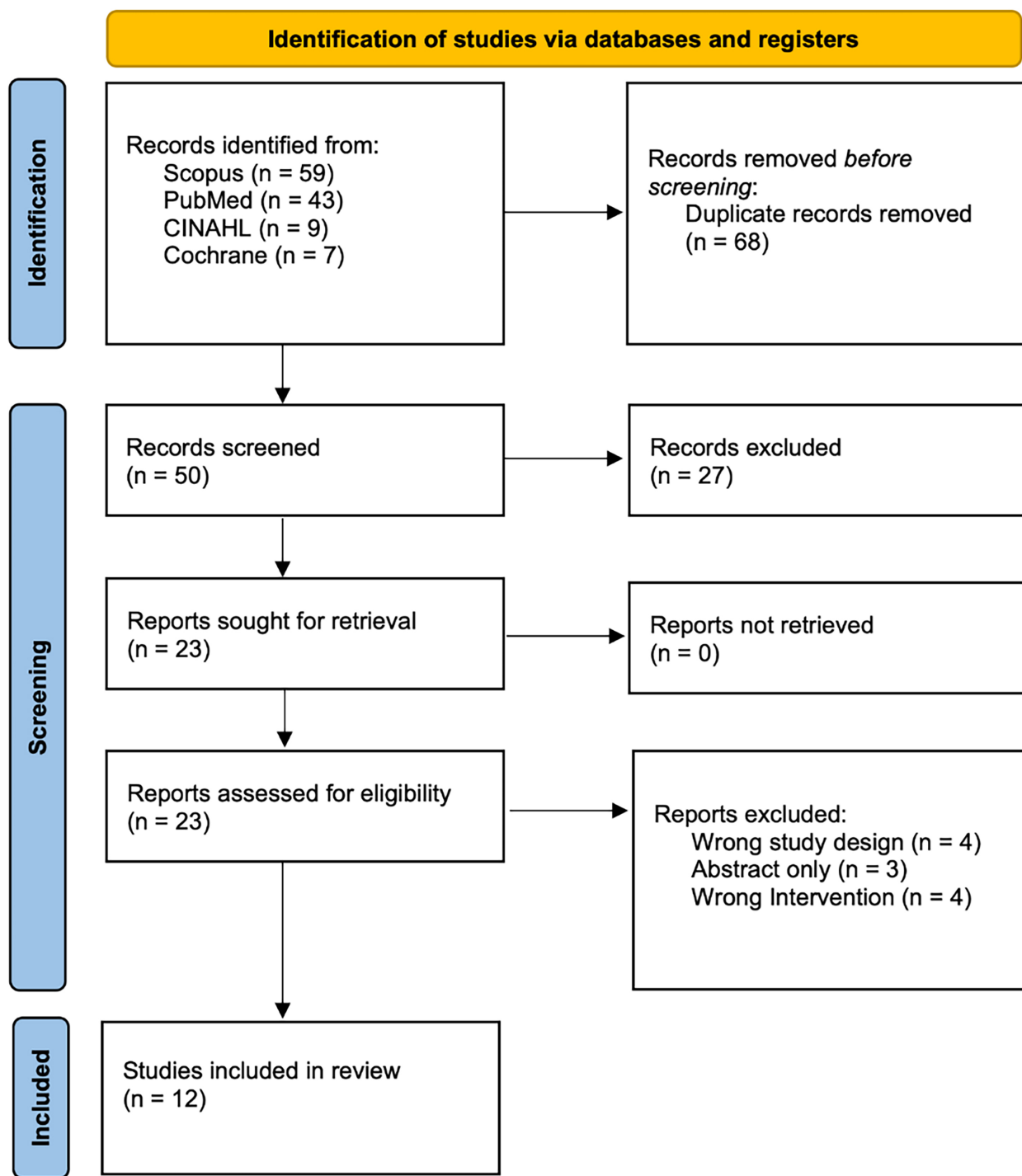


Figure 1. PRISMA diagram outlining the study selection process.

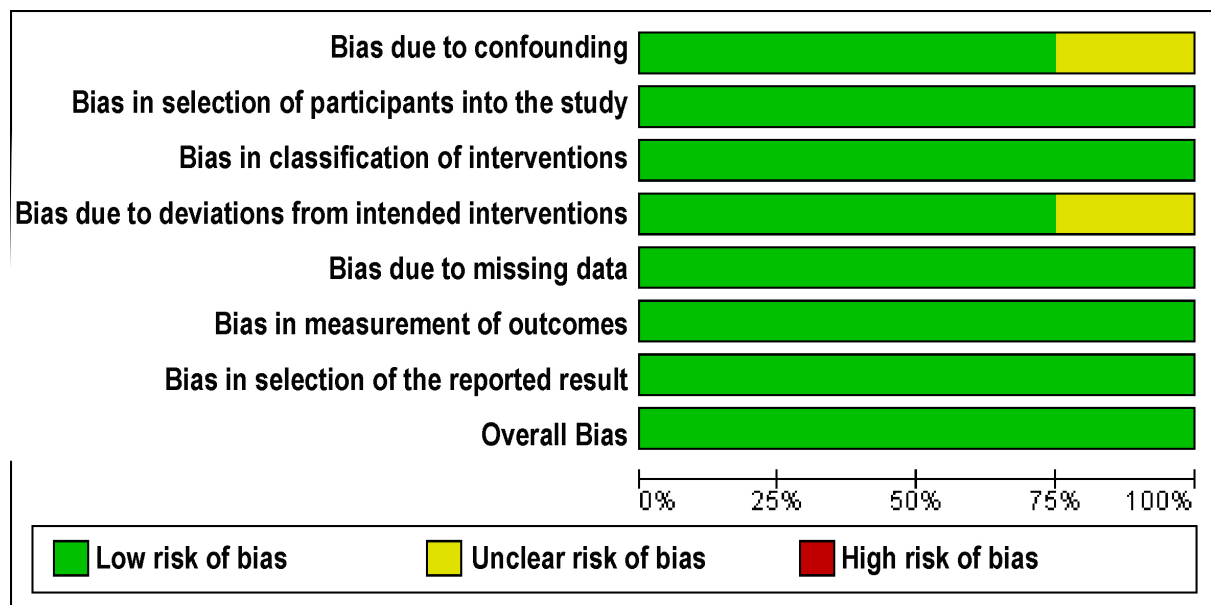


Figure 2. Risk of bias by ROBINS-I domain.

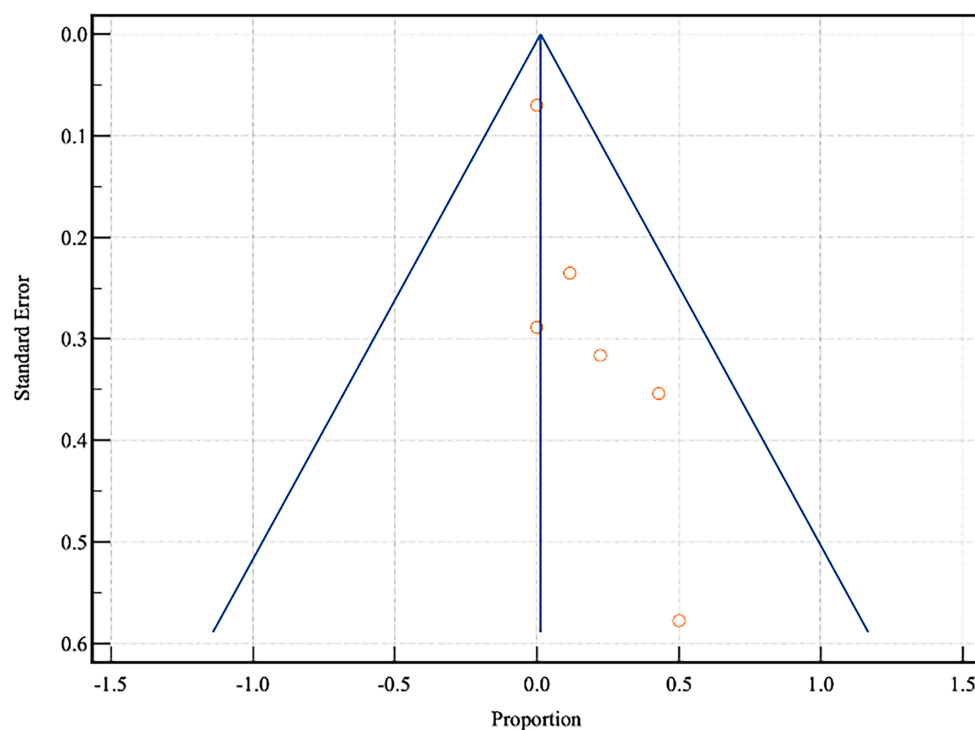


Figure 3. Funnel plot of included studies.

6.33-90.40) of patients had complications due to the progression of MRONJ and 88.29% (95%CI: 73.78-97.44) exhibited signs of healing. The complication rate was significantly greater in the control cohort compared to the PENTOCO cohort by 27.40% ( $P < 0.0001$ ), whereas healing rates were not significantly different between the two cohorts (1.51%;  $P = 0.70$ ).

When considering PENTOCO and control cohorts in totality, the mean age was 66.27 years (range: 41-93), and the mean time to follow-up was 1.42 years (95%CI: 0.97-1.87). Females comprised 86.88% (95%CI: 67.40-98.23) of the patients and 10.38% (95%CI: 6.69-15.17) of patients smoked tobacco. In terms of MRONJ stage, 53.53% (95%CI: 26.91-79.10) had stage 0 MRONJ, 29.71% (95%CI: 11.44-52.25) had stage 1 MRONJ, 51.45% (95%CI: 4.22-96.87) had stage 2 MRONJ, and 36.76% (95%CI: 19.18-57.36) had stage 3 MRONJ. Sequestrectomy was undertaken in 52.36% (95%CI: 15.75-87.54) of patients.

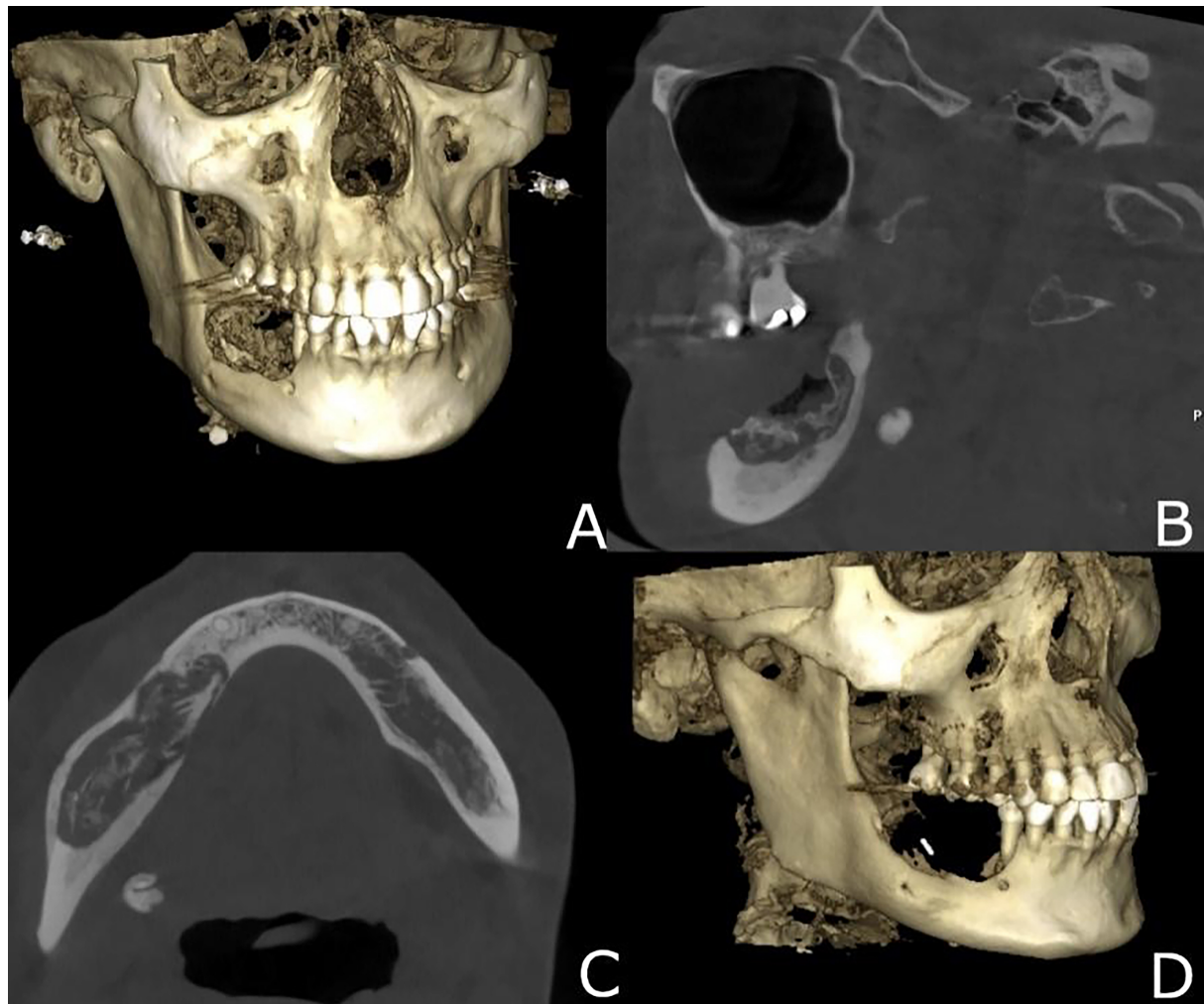
## CASE SERIES

### Case 1

The first patient is a 64-year-old female with a history significant for clear cell carcinoma of the kidney and unspecified bone and lung cancers. She had been started on risedronic acid due to her bone cancer, but this was discontinued when she developed right-sided mandibular osteonecrosis following the removal of a tooth [Figure 4]. She was subsequently referred to our care for surgical intervention following failed initial debridement of the necrotic tissue. On presentation, the patient was not able to chew on the right side of her mouth due to mastication-related pain that was only relieved by oxycodone. In addition to the right-sided mandibular pain, physical examination was significant for drainage and odor from an oral wound located at the posterior lower right mandible. An incidental large obstructive sialolith of the right submandibular gland was also noted. Two weeks prior to surgery, she was managed with 400 mg pentoxifylline, 1,000 U of over-the-counter vitamin E, and oral timolol drops to the open wound. At the time of surgery, a 3 cm × 2 cm section of necrotic bone was surgically debrided in the operating room until healthy bone was identified. Following debridement, BMP-soaked cellulose was placed in the wound bed and a buccinator myomucosal flap with a facial artery pedicle was used for the reconstruction of the surgical defect [Figure 5]. Excision of the submandibular gland was performed as transoral sialolithotomy was unsuccessful. At the time of her two-month follow-up appointment, the patient exhibited healing of the mandibular outer cortex with improvement in her medullary loss noted on cone beam CT (CBCT) scan. There was no evidence of a pathologic mandibular fracture. Her pain significantly improved along the mandible and the flap was completely healed. She did note some mild tongue paresthesia, likely related to the sialolithotomy, but this was successfully managed with topical medication.

### Case 2

The second patient is a 74-year-old male with a history significant for recurrent stage IV papillary thyroid cancer with metastasis to the right tenth rib. He had been started on zoledronic acid due to his bony metastasis, but this was discontinued when his medical oncologist noticed bilateral exposure of the posterior mandible [Figure 6]. He was subsequently referred to our care for surgical intervention after debridement that failed to achieve complete resolution. At the time of presentation, there was resolution of the left-sided foci of exposed posterior mandible. The patient reported experiencing pain localized to the right posterior mandible upon mastication. Physical examination of the oral cavity was notable for a nontender sub-centimeter locus of the exposed right posterior mandible, from which purulence was expressed. Two weeks prior to surgery, the patient was started on 400 mg of pentoxifylline twice daily, 1,000 U of tocopherol daily, and twice daily chlorhexidine (Peridex) mouthwash with a monojet syringe to the area of exposed bone. The necrotic bone was subsequently surgically debrided in the operating room until healthy bone was reached. Intraoperatively, given the relatively improved appearance of the bone on the PENTOCO regimen, it was decided to defer the placement of BMP. At the time of the first follow-up seven weeks following surgery, the locus of bony exposure and purulence had resolved, and an alveolus granuloma was noted to have developed on the lingual surface of the right posterior mandible. The patient was advised to continue his PENTOCO regimen. Three weeks later, at the second follow-up, the granuloma had decreased to 1 mm in size. At the time of the subsequent and most recent follow-up, six months postoperatively, the patient exhibited complete resolution of the granuloma with no evidence of mandibular exposure.



**Figure 4.** (A-C) Showcase the locus of osteonecrosis in the right body of the mandible at the time of referral; (D) Exhibits the patient's mandible at the post-surgical two-month follow-up appointment.

### Case 3

The third patient is a 72-year-old female with a history of metastatic lung cancer and multiple myeloma for which she had been taking zoledronic acid. After having had two lower teeth pulled by her dentist, her zoledronic acid therapy was discontinued. Subsequently, she saw an oral surgeon, who ordered a CT scan of her jaw, which was significant for a mandibular fracture and osteomyelitis with associated soft tissue swelling. The patient subsequently underwent incision and drainage in conjunction with a six-week course of intravenous ertapenem. The patient was then referred to our care for further management and treatment. Upon examination of the oral cavity, the patient was missing teeth along the right mandible and two foci of exposed bone were noted with purulent drainage. She was started on a regimen of PENTOCO and chlorhexidine (Peridex) via Monojet syringe and a follow-up CT showed healing of the mandibular fracture. At the time of the next visit, the patient had a 3 cm × 1.5 cm area of exposed anterior mandible that was deemed necrotic on examination. The patient was advised to continue the PENTOCO regimen and subsequently underwent partial mandibulectomy with excision of the necrotic bone and BMP graft to fill the bony defect. A rotational buccinator flap with a facial artery pedicle was laid over the exposed mandible. At the time of the first follow-up, the patient was healing well with slight mucosal graft loss but with improved cortical bone by CBCT. She continued her PENTOCO treatment regimen and healed without evidence of redeveloping bony exposure.

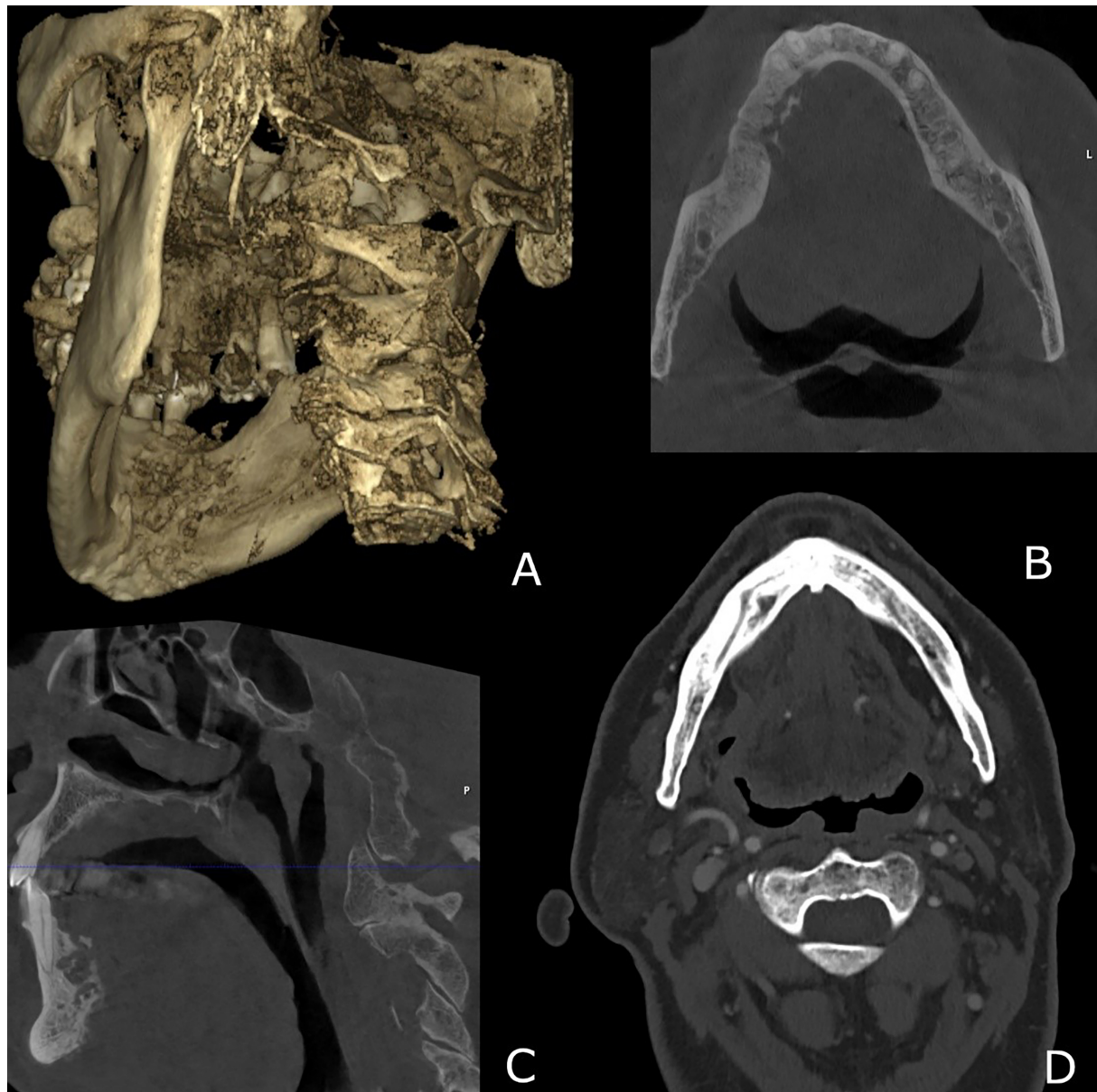


**Figure 5.** Healed buccinator myomucosal flap with a facial artery pedicle at the two-month follow-up postoperative appointment.

## DISCUSSION

The present study's findings highlight the limited nature of the literature exploring the etiology, treatment, and outcomes of MRONJ. A total of 12 studies were included, with 140 patients in the BMP group and 251 in the PENTOCO group. Of these patients, a majority were females and were taking bisphosphonate therapy. The delineation of such potential risk factors serves as a preliminary step in the identification of high-risk patient populations. For example, our findings may suggest that women taking bisphosphonates for the management of osteoporosis are at a higher risk of developing MRONJ, which is in line with previous findings that MRONJ has a pooled prevalence of approximately 19% among patients on bisphosphonate therapy<sup>[30]</sup>.

Given the elevated risk of developing MRONJ associated with antiresorptive or antiangiogenic agents, preventative measures should be considered prior to beginning patients on these therapies. Preventative steps include dental clearance prior to beginning medication regimens and the creation of drug schedules that take into consideration the intended duration of therapy, patient comorbidities, and other medications a patient might be taking<sup>[2]</sup>. Consideration of prophylactic pentoxifylline in patients deemed at higher risk may also be an option.



**Figure 6.** (A-C) Exhibit the locus of osteonecrosis on the posterior aspect of the mandible; (D) Showcases the status of the patient's mandible six months following surgical intervention.

The current management and treatment standards and paradigms for MRONJ were developed by the AAOMS to streamline patient evaluation and care<sup>[2]</sup>. According to these management and treatment algorithms, nonoperative management of stage 1 MRONJ typically involves chlorhexidine wound care and oral hygiene regimens, while more advanced disease stages may require antibiotics for treatment<sup>[2]</sup>. Patients with the most advanced cases of MRONJ may require further invasive interventions for comprehensive treatment of their disease, including surgical debridement and sequestrectomy<sup>[2]</sup>.

In contrast to the treatment of MRONJ, osteoradionecrosis of the jaw (ORN) is commonly managed through antibiotics, analgesics, hyperbaric oxygen therapy, and radical surgery<sup>[31]</sup>. ORN refers to bony necrosis of the mandible that develops secondary to radiation therapy to the head and neck and is

characterized by exposed necrotic bone in the irradiated region that persists for over three months and is often accompanied by pain, infection, and potential fractures<sup>[32]</sup>. While PENTOCO use has been more established via case series in the literature for the treatment of ORN, evidence for the therapeutic potential of BMPs remains limited. In addition to having differences in etiologies and treatments, there are marked variations in the oral microbiota that predominate in each condition. A previous study found that in patients with radiotherapy-treated head and neck cancer, ORN lesions had greater oral microbial abundance and diversity than healthy oral tissue<sup>[33]</sup>. When compared to healthy tissue at the species level, ORN lesions had higher levels of *endodontalis* and *intermedia* microbiota and lower levels of *parvula*, *fluorescens*, and *mucilaginosa* microbiota<sup>[33]</sup>. In a similar study done on MRONJ patients, MRONJ lesions exhibited higher levels of *F. fastidiosum*, *G. adiacens*, *P. micra*, *P. pisci*, *S. constellatus*, *T. forsythia*, *T. maltophilum*, and *T. socranskii* compared to healthy oral tissue<sup>[34]</sup>. Whether variations in the predominance of certain oral bacteria affect the effectiveness of therapeutic agents and patient outcomes should be considered in future studies on PENTOCO and BMP's utility in the management of MRONJ and ORN.

PENTOCO therapy refers to the use of pentoxifylline and tocopherol (vitamin E) in conjunction, which has been posited to carry clinical utility in the treatment of various disease states, including osteomyelitis and diabetic microangiopathy<sup>[35,36]</sup>. Independently, pentoxifylline has been approved by the Food and Drug Administration for the treatment of peripheral artery diseases and has also been used to manage pulmonary fibrosis for over 20 years<sup>[37]</sup>. Tocopherol has been thought to decrease tissue fibrosis and inflammation. In the context of MRONJ, PENTOCO has also been theorized to have therapeutic potential when used as an adjuvant therapy with other existing treatment options, although the exact mechanism of action of PENTOCO in this context remains unclear<sup>[38-40]</sup>. One review of 202 patients showed a relapse rate of 0% in patients treated with sequestrectomy with adjuvant PENTOCO therapy versus a 71% relapse rate in the control group, which was treated with sequestrectomy without any concomitant medical therapy<sup>[18]</sup>. It should be noted that this study only included patients with stage 1 MRONJ, thus limiting the applicability of its findings to patients with more advanced disease. Our findings support the relationship between PENTOCO use and positive outcomes in the MRONJ patient population, including patients with more advanced disease, as the PENTOCO treatment group was found to have significantly lower complication rates related to MRONJ progression compared to the control group at the time of patient follow-up. Further investigations are necessary to better delineate the proper and appropriate use of PENTOCO therapy in the clinical context.

BMP has also shown therapeutic potential in the treatment of MRONJ. Osteocytes in necrotic areas express lower endogenous levels of BMP-2 activity, and thus, supplementation of exogenous BMP-2 can augment local activity<sup>[41,42]</sup>. A study found that BMP-2 increased calcium deposition and, consequently, new bone formation in the test group compared to the control group, providing insight into its physiological mechanism of function<sup>[43]</sup>. Additionally, BMP-2 induces stem cell differentiation into osteocyte and chondrocyte lineages, thus restoring the natural trabecular structure and mechanical strength of the mandible or maxilla, which are adversely affected by the pathological sequelae of MRONJ<sup>[44]</sup>. In addition to increased calcium deposition, it was previously demonstrated that BMP-2 administration via a novel core-shell electrospun fiber delivery vector promoted osteogenic gene expression by bone marrow mesenchymal stem cells<sup>[45]</sup>. While the therapeutic technologies for the administration of BMP are currently being developed and refined, the literature supports its effectiveness of action across various modalities of administration.

The present review has included two prospective cohort studies discussing or evaluating the clinical implementation and efficacy of BMP<sup>[9,27]</sup>. While findings related to healing and complication rates were

explored in these studies, a meta-analysis of this data was not able to be performed in the present study due to a paucity of available data. Therefore, descriptive and narrative approaches were opted for in the present investigation, while also acknowledging this limitation and the necessity of future systematic reviews to be conducted on the topic once data from additional clinical trials become available. One study compared the treatment of MRONJ in four groups of patients receiving surgery with different adjuvant therapies<sup>[9]</sup>. The first group was treated with adjuvant BMP and teriparatide, which is an endogenous parathyroid hormone analog, for four weeks preoperatively<sup>[46]</sup>. The second group also received BMP and teriparatide, but teriparatide was taken for eight weeks instead of four. The third and fourth groups, which were considered the control groups, received either BMP alone or no treatment at all. While the group receiving solely BMP exhibited shorter healing times ( $14.40 \pm 6.08$  weeks) than the group receiving no treatment ( $15.79 \pm 9.79$  weeks), the group receiving both teriparatide and BMP therapies healed faster than both control groups ( $8.35 \pm 1.58$  weeks). Additionally, the findings showed that patients treated with teriparatide in conjunction with BMP were 4.80 times more likely to achieve complete resolution compared to the patients receiving no therapy. Another study compared 30 patients who were treated with BMP in conjunction with leukocyte-rich and platelet-rich fibrin (L-PRF) to 25 patients who received L-PRF alone at the one- and four-month postoperative time points. It was found that the patients receiving BMP therapy showed significantly greater rates of clinical improvement compared to the control group and that patients in the control group exhibited higher rates of delayed healing compared to the BMP group<sup>[27]</sup>.

Finally, teriparatide, widely used in osteoporosis management due to its anabolic effect on bone, has been proposed as another potential treatment for MRONJ<sup>[47]</sup>. Teriparatide is a biosynthetic human parathyroid hormone that stimulates osteoblast activity when taken intermittently<sup>[48]</sup>. Case studies have demonstrated superior outcomes among MRONJ patients managed with teriparatide compared to patients managed with BMP<sup>[9]</sup>. Additionally, a recent double-blinded, randomized controlled trial involving 34 patients found a significantly higher rate of healing with teriparatide compared to a placebo after 52 weeks<sup>[49]</sup>. Moreover, there is evidence suggesting that combining teriparatide with BMP may further enhance treatment outcomes, with a recent prospective study of 17 MRONJ patients reporting significantly higher levels of bone formation on CBCT when BMP was supplemented with teriparatide on a short-term basis<sup>[25]</sup>.

### Limitations

While our study provides an overview of the currently available literature on the use of PENTOCO and BMP therapies in the management and treatment of MRONJ, it has limitations in the conclusions that can be drawn from its findings. The sparsity of extant literature and reported findings limited a more rigorous statistical approach from being performed. While three cases of MRONJ treated at our institution were discussed in the present review, we acknowledge that overarching clinical conclusions cannot be drawn from them. Instead, they should be considered as supplements to the findings presented in the growing body of literature on MRONJ surveyed in the present study. Additionally, a lack of available patient outcome data or studies comparing PENTOCO and BMP's clinical efficacy prevented the generation of more substantive conclusions that would result from a direct comparative analysis of these two treatments.

While a broad literature search was conducted, the included studies were of a heterogeneous study design. Thus, several measures were undertaken to preserve the validity of the results in view of this limitation: Firstly, studies that were included in the present review were selected in adherence to PRISMA-ScR guidelines and clear inclusion and exclusion criteria as outlined in the Methods section. Secondly, the descriptive statistical analyses that were performed weighed the influence of each individual study's findings on the overall results in accordance with the study's respective sample size. Lastly, a risk of bias evaluation in accordance with ROBINS-I criteria was performed on each included study to ensure there was no excessive risk of bias on the overall review.

In conclusion, the present study highlights a knowledge gap in the implementation of PENTOCO and BMP therapies in the treatment of MRONJ. While the available literature, as well as our case series, suggests that both BMP and PENTOCO may carry therapeutic promise regarding MRONJ, further research on the broader MRONJ patient population, including patients with advanced stages of the disease, varying comorbidities, and differing MRONJ causative factors, will be required to draw more generalizable conclusions. Future studies should explore the efficacy of PENTOCO and BMP vis-à-vis one another, as well as how their combination with other therapeutic agents and treatment approaches can affect patient outcomes in the MRONJ patient population. Statistical analyses using the findings of investigations with larger study populations and, thus, with greater statistical power are also needed.

## DECLARATIONS

### Authors' contributions

Substantial contributions to the conception or design of the work and the acquisition, analysis, and interpretation of data for the work, drafting the work and reviewing it critically for important intellectual content, final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: Patel PA, Nassar SI, Nguyen SA, Lee BJ, Kejner AE

### Availability of data and materials

Not applicable.

### Financial support and sponsorship

None.

### Conflicts of interest

All authors declared that there are no conflicts of interest.

### Ethical approval and consent to participate

Ethical approval is not applicable to this study. All patients whose de-identified information presented above had been consented prior to publication via written informed consent, which may be available per request.

### Consent for publication

Not applicable.

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