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Bisphosphonate therapy in the management of diffuse sclerosing osteomyelitis of the mandible: a systematic review and narrative synthesis

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Background: Diffuse sclerosing osteomyelitis (DSO) affecting the mandible is an uncommon condition characterised by recurrent pain and functional disturbances. Traditional treatments involving antibiotics, steroids, and analgesics have generally yielded unsatisfactory results. Numerous articles have proposed the utilisation of bisphosphonate therapy as an alternative approach to achieve sustained symptom relief. This study aims to consolidate the available evidence on the effectiveness of bisphosphonate therapy in managing DSO.

Methods: A systematic review protocol was registered with PROSPERO and reported in accordance with the Preferred Reporting for Items for Systematic Reviews and Meta-Analyses. Comprehensive electronic search strategies were devised, and studies were screened based on predefined inclusion and exclusion criteria.

Results: Ten articles met the eligibility criteria, encompassing a total of 135 patients diagnosed with DSO who received bisphosphonate treatment. All included studies consistently reported a reduction in pain levels and swelling, along with a decrease in the cumulative use of analgesics. The majority of patients reported long-lasting symptom improvement with bisphosphonate therapy. Notably, four studies documented improvements in maximal mouth opening, with one study reporting a mean increase of 9.6mm. Furthermore, six studies observed improvements in panoramic radiographs and cone beam computed tomography scans, with one publication describing two patients exhibiting near-normal bone architecture. Importantly, all studies reported the absence of long-term complications.

Conclusions: Bisphosphonate therapy emerges as a promising treatment modality for DSO, exhibiting efficacy in symptom alleviation and radiological enhancement while conferring lasting benefits. Nevertheless, further prospective studies are warranted to refine treatment protocols and substantiate these findings.

Keywords: bisphosphonate, diffuse sclerosing osteomyelitis, oral and maxillofacial surgery

Introduction

Diffuse sclerosing osteomyelitis of the mandible (DSOM) is a rare, nonsuppurative condition. It is characterised by inflammation, recurrent severe pain, swelling of the cheek, and functional disturbances such as trismus[1]. The aetiology of DSOM remains unclear, and is often a diagnosis of exclusion. Some authors believe that the condition is a response to a microbial stimulus, while other authors believe that it is a result of chronic periostitis[2–4]. It is also suggested within the literature that DSOM is part of systemic spectrum with syndromes such as chronic recurrent multifocal osteomyelitis (CRMO), and synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome[5,6]. In the early stages, radiographic findings of DSOM are diffuse, however, in the chronic stages radiographs demonstrate a mixed pattern with osteolytic areas surrounded by sclerosis of cancellous bone and the destruction of cortical bone[7,8]. Technetium-scans (Tc-scans) demonstrate an increase in uptake in the involved area, likely due to increased bone turnover[9].

HIGHLIGHTS

- Of the 135 patients treated with bisphosphonate therapy, 57 patients reported no pain post-treatment.
- Four studies reported improvements in maximal mouth opening, with one study reporting a mean increase of 9.6 mm.
- Bone scintigraphy results post-bisphosphonate therapy varied.
- Several patients did experience a relapse of pain, requiring subsequent cycles of bisphosphonate therapy.
- The most common complication post-treatment was the development of flu-like symptoms.

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The management of DSOM is challenging, with various conservative treatment modalities trialled such as antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), and glucocorticoids. An alternative suggested treatment option is muscle relaxation therapy due to the hypothesis that DSOM is caused by the overuse of masticatory muscles which lead to the development of chronic tendoperiostitis (TP). However, the aforementioned treatment options were not able to achieve long-term effectiveness and as a result no standard treatment protocol is recommended for cases of DSOM[10–14]. Bisphosphonates have been trialled as a treatment modality in recent studies as it is hypothesised they inhibit osteoclast mediated bone remodelling which decreases the inflammatory response, and as a result, a long-term reduction in pain and swelling is observed[15–18]. This may be due to the fact that bisphosphonates are similar in structure to the naturally occurring pyrophosphate molecules, which play a role in regulating bone metabolism[19]. Currently, there are several different types of bisphosphonates available including alendronate, ibandronate, risedronate, and zoledronate. Bisphosphonates can be taken orally, but are also available in intravenous formulations[20].

Although rare, DSOM can have a significant impact on a patient's quality of life. Bisphosphonate therapy shows promise as a non-invasive treatment option, and may offer hope for improved outcomes in patients with this challenging condition. Therefore, the aim of this systematic review is to summarise the clinical effectiveness of bisphosphonate treatment on patients with diffuse sclerosing osteomyelitis of the mandible.

Methods

Search strategy and selection criteria

This systematic review was first registered on PROSPERO (CRD42022380476). This review is reported in accordance with Preferred Reporting for Items for Systematic Reviews and Meta-Analyses (PRISMA)[21]. Search strategies were developed for all databases searched using the key words in the title. A total of 6 databases were searched through which includes (MEDLINE, EMBASE, Cochrane, CINAHL, EMCARE, KLHub). The search strategy was modified so that the index headings relevant to each specific database were selected. The search strategy was peer-reviewed by information specialists at the London North West Hospital Library.

Duplicate papers were identified and removed on Rayyan, before screening commenced.

Three independent reviewers screened titles and abstracts according to the inclusion and exclusion criteria (Table 1). The full text of the remaining papers left were then downloaded and screened. Conflicts were resolved through a discussion with the senior author. Target population of this study included patients with diffuse sclerosing osteomyelitis of the mandible undergoing bisphosphate therapy. Outcomes of interest included mouth opening, radiographic changes, and improvements in pain and analgesia use.

Data extraction

After selection of papers relevant to the review, data was extracted onto a customised Microsoft Excel spreadsheet. Data included: (1) Study Characteristics including author, year of publication, sample size, country, study design, study timeframe, and the assessment tools used; (2) Patient Demographics; (3) Name of bisphosphonate administered; (4) Outcomes of treatment; and (5) Side-Effects.

Table 1

Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Primary research papers investigating the efficacy of bisphosphonate therapy in treating diffuse sclerosing osteomyelitis of the mandible	Systematic/narrative reviews, case reports, book chapters, abstracts, comments or notes
Human subjects	Animal studies
English language	Non-English language

Synthesis

A meta-analysis was not considered for this review because of the wide variability of the studies in relation to research design, study population, cohort size, inconsistency in the reporting of outcomes, and the diversity of treatment protocols. A narrative synthesis was performed to synthesise the findings of the different studies. The results of the studies were discussed and structured into themes, depending on the common outcomes reported within the included articles. These outcomes formed the framework for our narrative synthesis. All articles that were included in this review were published before. The quality and risk of bias of the studies eligible for inclusion were evaluated using the Joanna Briggs Institute (JBI) critical appraisal tool for Case Series and for randomised trials[22–24].

The methodological quality of this systematic review was evaluated by our team by utilising A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR-2)[25]. This tool is comprised of 16 items, with 7 critical items, and 9 non-critical items. For non-critical items, we assigned 1 point for "Yes", 0.5 for "Partial Yes", and 0 for "No". For critical items, the score was double. The total AMSTAR-2 score was 23 points[26,27]. This study was registered with the Research Registry.

Results

Four hundred and four published articles were identified following a comprehensive literature search. These articles were filtered for relevance and duplication, resulting in 58 articles. A subsequent full-text assessment reduced the number of articles suitable for inclusion to ten[14,28–36]. No additional articles were identified through searching bibliographies. With regards to the quality and risk of bias of the studies eligible for inclusion, the JBI score for the case series included within our review ranged from 6 to 10, with a mean of 7.8 points. The only randomised trial within our study received a score of 8 out of 13. This is due to the authors not describing the randomisation and allocation process. The AMSTAR-2 score for this systematic review was 14.5 points. Table 2 summarises the studies included in this study. The PRISMA flow diagram is summarised in Figure 1.

Pain and analgesia use post-bisphosphonate therapy

Various reporting tools were utilised within the studies which commented on pain, such as visual analogue scale (VAS), and Likert scores. Of the 135 patients treated with bisphosphonate therapy, 57 patients reported no pain post-treatment. Number of

Table 2

Summary of studies included within systematic narrative synthesis

Paper title (year)	Study design	No. patients (male: female)	Bisphosphonate therapy (route of administration)	Follow-up
Application of pamidronate disodium for the treatment of diffuse sclerosing osteomyelitis of the mandible: A clinical study (2020)	Case series	43 (13:30)	Pamidronate Disodium (intravenous)	6–18 months
Bisphosphonate therapy in chronic diffuse sclerosing osteomyelitis/tendoperiostitis of the mandible: Retrospective case series (2021)	Case series	18 (6:12)	Pamidronate (intravenous) Olpadronate (intravenous/oral) Zoledronic acid (intravenous) Risedronate (oral)	
Bisphosphonates in treatment of chronic aseptic sclerotizing osteomyelitis in the mandible (2021)	Case series	8 (1:7)	Pamidronate (intravenous)	> 1 year
Conservative treatment of children with chronic diffuse sclerosing osteomyelitis/tendoperiostitis of the mandible (2017)	Case series	5 (2:3)	Pamidronate (intravenous)	1 year
Diffuse Sclerosing Osteomyelitis: A Case Series and Literature Review (2020)	Case series	11 (8:3)	Alendronic acid (unspecified route)	1 month after commencement of bisphosphonates and then at 3-month intervals for the first year and 6-month intervals in the subsequent years;
Disodium clodronate in the treatment of diffuse sclerosing osteomyelitis (DSO) of the mandible (2001)	Prospective, randomized, double-blind and placebo-controlled.	10 (2:8)	Disodium clodronate (intravenous)	12 months
Ibandronate treatment of diffuse sclerosing osteomyelitis of the mandible: Pain relief and insight into pathogenesis (2015)	Case series	11 (2:9)	Ibandronate (intravenous)	
Initial results of the treatment of diffuse sclerosing osteomyelitis of the mandible with bisphosphonates (2011)	Case series	7 (6:1)	Pamidronate (intravenous)	Mean: 30 months Range: 18–46 months
Non-surgical treatment of adults with chronic diffuse sclerosing osteomyelitis/tendoperiostitis of the mandible (2019)	Case series	16 (5:11)	Pamidronate (intravenous) Zoledronic acid (intravenous)	
Pediatric chronic nonbacterial osteomyelitis of the mandible: Seattle Children's hospital 22-patient experience (2020)	Case series	6 (4:2)	Pamidronate (unspecified route)	Range: 12–58 months

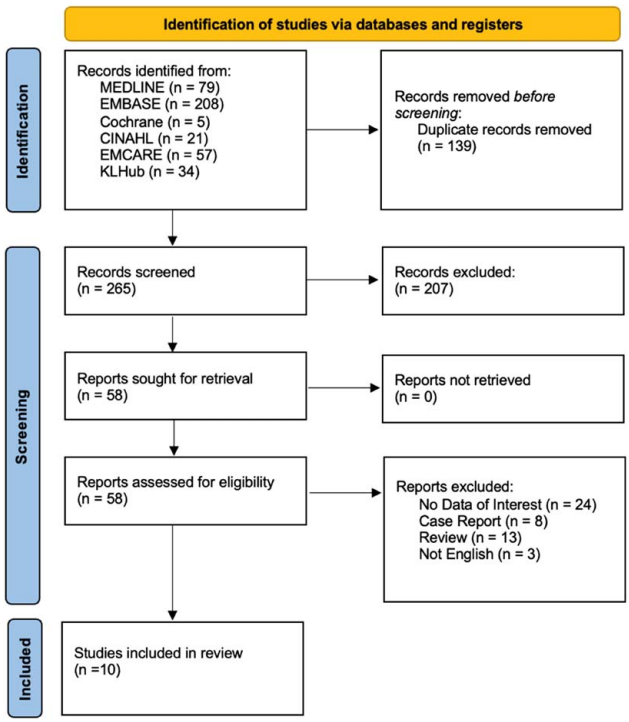

Figure 1. PRISMA flow diagram.

treatment cycles ranged from 1 to 11 cycles of bisphosphonate treatment.

Of the studies which utilised VAS scores, bisphosphonate therapy demonstrated an improvement in pain symptoms. For example, in the study by Otto *et al.*[34] which utilised 6mg of ibandronate, all but one patient reported long-lasting complaint-free or minimal complaint intervals which could be handled by first-line analgesic medication. Although there was a significant reduction in pre- and post-infusion pain levels ($P < 0.01$), four patients did return for further infusions and received between three and six infusions of ibandronate, with mean time between infusions being ~245 days. The study by Li *et al.*[28] also utilised VAS to measure pain severity within their patient cohort. Thirty-three percent of their patient cohort reported moderate to severe pain prior to undergoing bisphosphonate therapy. Alleviation was evident on day two and day three. On follow-up, 90.7% of their patient cohort reported that their pain had disappeared. Table 3 demonstrates the VAS scores of their patients before and after treatment with pamidronate.

The study by Montonen *et al.*[35] was a prospective, randomized, double-blind and placebo-controlled study which utilised the VAS and the McGill Pain Questionnaire (MPQ). Their study reported that patients treated with disodium clodronate had a significantly greater change in VAS score between baseline and 6 months, in comparison to the placebo group ($P = 0.038$). There was also a significant decrease in the number of words chosen to describe the pain in the disodium clodronate group when compared to the placebo group between the beginning of the study and after 6 months of follow-up ($P = 0.007$). Furthermore, cumulative doses of analgesics were lower for patients on disodium clodronate. However, VAS scores did not differ statistically between treatment groups at any other time during the study period.

Effect of bisphosphonate therapy on mouth opening

Four studies commented on the effects of bisphosphonate therapy on mouth opening, either through evaluating the presence of trismus or measuring mouth opening directly. The study by van de Meent *et al.* took the former approach, identifying that no patient reported trismus following bisphosphonate therapy[29]. Similarly, Kuijpers *et al.*[33] also took the former approach and reported that within their study trismus diminished, although only briefly in some patients.

Li and colleagues and Montonen and colleagues both reported using quantitative measurements of the effect of bisphosphonate therapy on mouth opening[28,35]. Li and colleagues reported that within their population study of 43 patients, the mean mouth opening of patients before treatment was 28.5 mm and was observed to have increased to 38.1 mm during re-examination at 6 months after treatment. Figure 2 demonstrates the improvement in mouth opening over the 6-month follow-up period within their study. Montonen and colleagues observed that within the placebo group, the maximal mouth opening was marginally greater at the start of the trial ($P = 0.071$) and significantly greater at the time of the first infusion ($P = 0.024$) compared with the group receiving bisphosphonate therapy. However, median values for maximal mouth opening in the bisphosphonate group were significantly higher than in the placebo group 1 month ($P = 0.043$) and 6 months ($P = 0.033$) after treatment.

Radiographic findings after bisphosphonate therapy

Within this review, six studies utilised panoramic radiographs to assess the response to bisphosphonate therapy, two studies utilised computed tomography (CT) imaging, and three studies utilised bone scintigraphy[14,28–30,33,35].

Table 3

Visual Analogue Scale scores of patients with diffuse sclerosing osteomyelitis of the mandible before and after treatment in the study by Li *et al.*[28]

	No pain	Mild pain			Moderate pain			Severe pain				
	0	1	2	3	4	5	6	7	8	9	10	Total
Before treatment	0	0	0	4	5	2	7	9	16	0	0	43
After treatment	32	2	3	2	3	0	0	1	0	0	0	43
At 1 month	29	2	4	3	0	2	0	0	0	0	0	40
At 3 months	29	0	1	0	2	0	2	0	0	0	0	34
>6 months	39	0	1	0	0	0	1	2	0	0	0	43

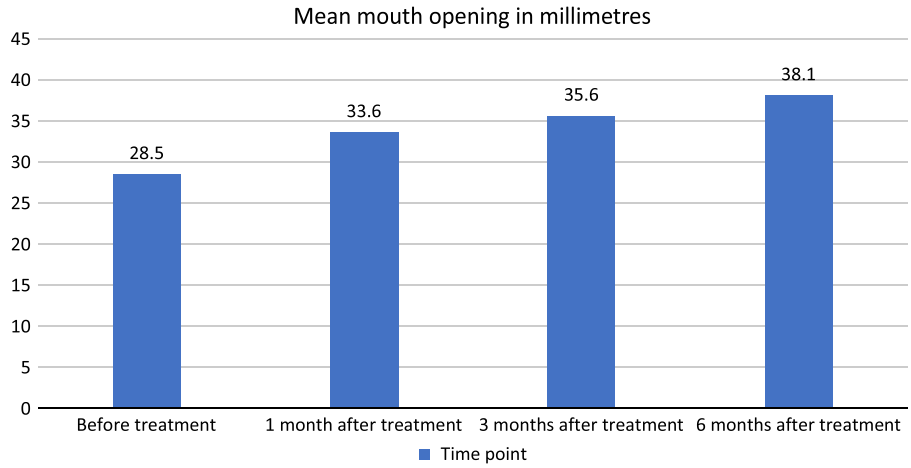

Figure 2. Mean mouth opening in millimetres in diffuse sclerosing osteomyelitis of the mandible before and after treatment[28].

In the study by Li *et al.*[28], prior to starting bisphosphonate therapy, thirty-two patients were found to have evidence of cortical bone destruction and unclear boundaries between the cortical bone and the medullary substance. At 1-month post-treatment, radiographs demonstrated bone reconstruction and remodelling. This remained present even at 6–12-months post-treatment. Furthermore, improvements in the bone structure were noted in the 11 patients that presented with sclerosis of the cancellous bone within their patient cohort at 6–12-months post-treatment. In the study by Van de Meent *et al.*[29], panoramic radiographs and cone beam computed tomography (CBCT) were performed on patients post-bisphosphonate therapy. On the panoramic radiographs post-bisphosphonate therapy, an almost normal bone architecture was described in two patients, an improvement was described in seven patients, and deterioration was described two patients in the form of increased lysis and/or extension of the disease. On CBCT, two patients demonstrated normalisation in bone architecture, six patients demonstrated an improvement, and 1 patient demonstrated a deterioration post-bisphosphonate therapy. In the second study by Van de Meent *et al.*[14], improvement was reported in all the five5 patients that received bisphosphonate therapy. However, no detailed description on how this improvement manifested was provided. Similarly in the study by Montonen *et al.*[35], the extent in which the radiographic findings improved were limited. The researchers reported a slight decrease in sclerosis between enrolment and 12 months for both treatment and placebo groups. The only study to report no improvements in their radiographic findings of their patient cohort post-bisphosphonate therapy was by Sælen *et al.*[30].

With regards to bone scintigraphy post-bisphosphonate therapy, this was performed in three studies with varying results reported. The only study to report a decrease in uptake in all their patients' 1-year post-therapy was by Kuijpers *et al.*[33]. In the study by Van de Meent *et al.*[29], a reduction in activity was noted in seven patients, no activity in two patients, no change in one patient, and an increase in activity in one patient post-bisphosphonate therapy. Finally, in the study by Montonen *et al.*[35], no differences in uptake were identified between the bisphosphonate treatment group and the placebo group post-therapy.

Side-effects and complications post-bisphosphonate therapy

Only five articles reported the occurrence of side-effects post-bisphosphonate therapy. A total of 47 patients developed what was described as flu-like symptoms. In the study by Li *et al.*[28], 90.7% of patients had developed a fever, typically 18–30 h after initial treatment with the highest temperature recorded at 40.2°C. Furthermore, 76.7% of patients developed hypocalcaemia which typically occurred on the second day of treatment, and 14% of patients developed hypokalaemia which typically occurred on day three of treatment. In the study by van de Meent *et al.*[29], six of the eighteen patients reported an acute phase reaction, with transient complaints of headache, fever, and flu-like symptoms. Sælen *et al.*[30] reported that only one out of the eight patients treated developed influenza like symptoms. Similarly, in the study by van de Meent *et al.*[32] 2019, only one patient reported flu-like symptoms. Matharu *et al.*[36] qualitively recorded their side-effects, reporting that three patients "felt unwell" and consequently decided to halt the treatment after 1 month. All three patients reported a near-immediate response and improvement in their DSO-related symptoms.

Discussion

DSOM is often a difficult to treat condition. It is characterised by recurrent pain, swelling, trismus, and local inflammatory changes within the mandible. Multiple theories regarding the aetiology of DSOM have been suggested within the literature. Examples include low-grade infection, hyperactive immunologic response, and chronic tendoperiostitis from muscle overuse[2,6,37,38]. Various treatment modalities have been suggested within the literature, such as antibiotics, corticosteroids and surgical intervention, however long-term effectiveness remains suboptimal. Bisphosphonate therapy has gained popularity over the last decades due to the promising results it has delivered within this patient cohort[10–14]. This systematic literature review was conducted to summarise the clinical effectiveness, and the potential side-effects which may ensue when administering bisphosphonates as a treatment option for DSOM.

Bisphosphonates are considered antiresorptive medications. They are able to decrease the rate of bone resorption by attaching to hydroxyapatite binding sites on the bone, particularly in areas with active resorption. They are then released when osteoclasts resorb bone, which subsequently impairs the osteoclast's ability to continue bone resorption[39–41]. As DSOM is hypothesised to result in osteoclast hyperactivity, bisphosphonates will likely reduce this activity and consequently result in the alleviation of symptoms of DSOM, such as pain, swelling, and even trismus. This was particularly true with regards to pain within our included studies. Of the 135 patients treated with bisphosphonate therapy, 57 patients reported no pain post-treatment. Additionally, in the study by Li *et al.*[28], 39 of the 43 patients within their study reported complete alleviation of pain during the 6–18-month follow-up. However, several patients did experience a relapse of pain, requiring subsequent cycles of bisphosphonate therapy. Number of bisphosphonate cycles ranged from only 1, to 11 within the included studies. This may be due to the increase in rate of bone turnover once the efficacy of the previously administered bisphosphonate expiring. For example, in the study by Otto *et al.*[34], four patients received between three and six infusions of ibandronate, with mean time between infusions ~245 days. Therefore, this should be taken into account by clinicians when choosing bisphosphonates as treatment options, as patients will likely require subsequent cycles.

Bisphosphonates can be broadly divided into two groups, nitrogen-containing, and non-nitrogen-containing. Nitrogen-containing bisphosphonates include risedronate, alendronate, pamidronate, ibandronate, and zoledronic acid. Non-nitrogen-containing bisphosphonates include clodronate, etidronate and tiludronate. As stated earlier, bisphosphonates decrease the rate of bone resorption by attaching to hydroxyapatite binding sites on the bone, however, the mechanism by which this is accomplished differs depending on the type of bisphosphonate. Nitrogen-containing bisphosphonates achieve this inhibiting farnesyl pyrophosphate synthase, which results in the detachment of osteoclasts from bone, consequently inhibiting bone resorption. Non-nitrogen-containing bisphosphonates achieve a reduction in bone resorption by initiating osteoclast apoptosis through forming a nonfunctional molecule that competes with adenosine triphosphate in the energy metabolism of the cell[39–41]. Nitrogen-containing bisphosphonates are considered to be more potent than their non-nitrogen counterparts, as they have a higher affinity for bone, a higher bioavailability and a possible longer duration of action[34]. This might explain the reason why patients within the study by Montonen and colleagues which was the only randomized, placebo-controlled, double blinded trial, only reported significant reduction in pain in the first 6 months in the disodium clodronate group (a non-nitrogen-containing bisphosphonate), but no differences in pain reduction at 12 months when compared to the placebo group. Furthermore, seven patients required a second infusion due to ongoing or recurrent pain[35]. The results might have been different if a nitrogen-containing bisphosphonate was utilised.

Possible adverse reactions which may occur during and after bisphosphonate therapy include systemic responses, and bisphosphonate-related osteonecrosis of the jaw (BRONJ). In this review, adverse drug responses included increase in body temperature, electrolyte imbalances, such as hypokalaemia and hypocalcaemia, and headache. Only five articles reported the occurrence of these side-effects, of which only one were symptoms so severe they had to halt the treatment. However, all adverse drug responses resolved within the studies. There was no incidence of BRONJ within the included studies. Risk factors for BRONJ include the use of high dose intravenous bisphosphonates, prolonged duration of exposure to bisphosphonates, pre-existing dental disease, dental implants, dental extraction, and poorly fitting dentures[42]. In the study by Gimsing *et al.*, BRONJ did not appear until the pamidronate dosed reached 480 mg. Although not all the studies within the review utilised pamidronate, all bisphosphonate doses were within normal range, and treatment time was short, therefore risk for BRONJ was relatively low. However, a comprehensive dental assessment should be completed, and any dental therapy or tooth extraction performed, prior to starting bisphosphonate therapy. This is to ensure safety, and reduce the risk of BRONJ.

An alternative therapeutic approach has been explored, further strengthening the argument and hypothesis that osteoclasts play a pivotal role in the pathogenesis and management of DSO. Denosumab, a human monoclonal antibody that effectively inhibits osteoclast activity and, consequently, bone resorption, has been the subject of recent investigations for the treatment of DSO and TP[43,44]. These studies have demonstrated the efficacy of denosumab, with patients' symptoms well-controlled through regular injections. Additionally, denosumab exhibits a shorter bone half-life in comparison to bisphosphonates. However, it is important to note that discontinuing denosumab treatment has been linked to adverse effects, such as vertebral fractures, a rebound in bone turnover, and hypercalcemia[45,46].

Limitations

We acknowledge the limitations in this study. The articles included within the review were heterogenous in nature. Of the most notable causes of variability between the studies was the type of bisphosphonate treatment administered. Different bisphosphonate treatments were administered following different protocols. Furthermore, the variability in assessed outcomes, and the lack of standardisation in measuring these outcomes increased the degree of clinical heterogeneity. This did not allow for a meta-analysis to be performed. Additionally, our sample size is relatively small despite our comprehensive search. This, along with the high degree of heterogeneity likely reduces the generalisability of our results. Finally, the majority of the studies included within our review were case series, rather than randomised controlled trials, thus increasing the risk of selection bias. Also, due to the lack of a comparator group within the case series, the degree of internal validity would likely be low. These factors further reduced the degree of generalisability of our results.

Conclusion

Bisphosphonate therapy does appear to be a promising treatment option for DSO, as it has shown to improve symptoms and radiological features, providing long-term benefits. Although there were some acute side-effects such as nausea, vomiting and fever reported by some patients, studies did not report major long-term complications. Larger studies are warranted, in the form of randomised control trials not only assessing the efficacy of bisphosphonate therapy, but potentially different dosing regimens, and different types of bisphosphonate drugs, and alternative therapies such as denosumab. The potential use of bisphosphonates within future studies in the treatment of DSO

may also provide insight into the pathogenesis of this disease, assisting clinicians in formulating suitable management plans for this patient cohort.

Ethical approval

No ethical approval was required for this project as it was a systematic review of the literature. Papers were retrieved from a literature search.

Consent

Not required as this was a systematic review of the literature. We did not have a cohort of patients we trialled treatment on. We incorporated data from other publications, where it is assumed that consent was provided by the patients for publication.

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

Author contribution

M.A.: design of study, supervisor, editing paper. S.N.E.: screening papers, data collection, writing paper. S.V.D.L.: screening papers, data collection, writing paper. N.H.: developing search strategy, data analysis, writing the paper. D.A.: developing search strategy, data analysis, writing the paper. H.A.: development of search strategy, screening papers, data analysis, writing the paper. L.L.: senior supervisor responsible for devising the search strategy, liaised with the London North West Hospital Library, ensuring search strategy was peer-reviewed and accurate.

Conflicts of interest disclosure

None.

Research registration unique identifying number (UIN)

The systematic review protocol was registered with PROSPERO (CRD42022380476).

This study was registered with the Research Registry, unique identifying number: reviewregistry1677.

Hyperlink: https://www.researchregistry.com/browse-the-registry#registryofsystematicreviewsmetaanalyses/registryofsystematicreviewsmeta-analysesdetails/64cbd78929cff30027d11667/.

Guarantor

Munir Abukhder.

Data availability statement

Datasets generated during and/or analysed during the current study are available upon reasonable request.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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