Review

Outcome of different treatments for chronic diffuse sclerosing osteomyelitis of the mandible: a systematic review of published papers

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Abstract

Treating chronic diffuse sclerosing osteomyelitis (DSO) is challenging and many treatments have been reported. However, we know of no standard protocol or guidelines. In this systematic review of relevant publications we provide an overview of the different treatments used. We made an electronic search of PubMed, Medline, Embase, Web of Science, and the Cochrane Library databases, for papers that described the treatment of DSO of the mandible. The search yielded 48 papers that applied to all inclusion criteria, resulting in 16 case reports, 13 case series, 18 retrospective clinical cohort studies, and one randomised controlled trial. Reported treatment options included different operations; the use of antibiotics, anti-inflammatories, and antiresorptive medication; conservative treatment; and hyperbaric oxygen. Surgical treatment resulted in a low success rate and was associated with higher morbidity than other treatments. Conservative treatment, and that of bisphosphonates, yielded more promising results, so conservative treatment and bisphosphonates seem to be the most promising therapeutic options. However, because of the high risk of bias, no firm conclusions can be drawn, and larger studies with clear inclusion criteria and specified endpoints are needed.

Introduction

Chronic diffuse sclerosing osteomyelitis (DSO) of the mandible is a relatively rare disease with an estimated prevalence of 1/200.000.[1] It is a form of chronic sterile osteomyelitis that has been described using many synonymous terms, including primary chronic osteomyelitis, chronic sclerosing osteomyelitis, and non-suppurative osteomyelitis.[2–4] Patients typically present with recurrent pain and swelling of the cheek or trismus, progressive mandibular deformity, or all three.[1,5]

Various hypotheses have been postulated about its aetiology, including a response to an unknown microbacterial noxa, a manifestation of a single autoimmune process, or as part of a more systemic syndrome, such as sternocostoclavicular hyperostosis, chronic recurrent multifocal osteomyelitis, or SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome.[1,6–10] The concept of chronic tendoperiostitis as a result of hyperactivity of the masticatory muscles has also been proposed as a possible aetiological factor.[11–14] As a reflection of the different hypotheses on the aetiology of the disease, different treatments have

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Table 1
Treatment options reported in the literature.

Antibiotics	Conservative treatment
β-lactam	Occlusal splint
Macrolide	Physiotherapy
Fluoroquinolone	Myofeedback therapy
Nitroimidazole	**Hyperbaric oxygen treatment**
Lincosamide	**Surgical options**
Analgesics	Curettage
Acetaminophen	Saucerization
NSAIDs*	Decortication
Muscle relaxants	Excision
Diazepam	Resection
Mefenoxalon	Hemimandibulectomy with reconstruction
Anti-inflammatory medication	Recontouring
NSAIDs	**Other**
Corticosteroids	Anti-rheumatics
Antiresorptive medication	Dental implants
Bisphosphonates	Radiation therapy
Denosumab	
Calcitonine	

* Non-steroidal anti-inflammatory drugs.

been reported (Table 1). Invasive surgical interventions, such as decortication, saucerisation, and segmental resections of the mandible have all been described.[1,2,4,5,13,15–40] Non-surgical treatments include long-term analgesic drugs, non-steroidal anti-inflammatory drugs (NSAID), antibiotics, corticosteroids, hyperbaric oxygen, bisphosphonates, and conservative measures.[1,2,4,5,13–50]

The aim of this systematic review of relevant published papers was to provide an overview of the treatments given to patients with DSO of the mandible. Different treatments – medical and surgical –are discussed, and the outcomes of different ones evaluated.

Material and methods

This systematic review was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and was registered on http://www.crd.york.ac.uk/PROSPERO as CRD42018110052.[51]

Selection of studies

We made an electronic search of PubMed, Medline, Embase, Web of Science, and Cochrane Library databases with the help of a trained librarian (Appendix A: Supplemental data). Papers published before 1 February 2019 were eligible for inclusion, without restriction of the year of publication.

All original papers, including case reports, case series, observational studies, and randomised controlled trials (RCT), that described treatments for patients with DSO of the mandible were included. Based on these we defined DSO of the mandible as a non-bacterial form of osteomyelitis of the mandible, with characteristic clinical symptoms of recurrent pain and swelling of the cheek, trismus, and absence of

pus or fistulas, or both, as originally reported by Jacobsson.[1] The radiographic appearance shows diffuse sclerosis, or a mixed sclerotic and lytic lesion with subperiosteal formation of bone in many cases,[5,52] which eventually may lead to mandibular deformity. All studies that reported patients with DSO (either defined as sclerotic osteomyelitis, primary chronic osteomyelitis, or non-suppurative osteomyelitis) were included. Studies that were not clear about their diagnostic criteria were not included. Studies that described other forms of osteomyelitis (such as acute or suppurative osteomyelitis, osteoradionecrosis, medication-related osteonecrosis, or a mandibular manifestation of SCCH, CRMO or SAPHO) were not included. Only articles in English, for which full-texts were available, were included. There were no restrictions on the outcome variables. All articles that were eligible for inclusion were collected in an EndNote database and duplicates removed. Two authors (MM and SP) independently carried out the selection of studies based on the title and abstract. Differences were solved by consultation with a third author (RM). Key articles were checked for additional references.

Data extraction

Demographic data of patients were recorded, including the number of patients included in the study, and their mean (SD) age (range) at the onset of the disease.

Tables were established according to type of study for those including five patients or more. Outcomes were recorded, including the treatment documented in the study, its clinical success, and mean (range) follow-up period (months). The clinical success was classified into three categories: complete response (CR), partial response (PR), and no response (NR). Complete response was defined as complete resolution of clinical symptoms (no pain or swelling, no need for pain relief, and no other complaints). Partial response was defined as an improvement of clinical symptoms or recurrent but improved symptoms (decreased pain scores or less need for pain relief). No response was defined as persistent or recurrent unchanged symptoms (similar or increased pain scores, persistent swelling or trismus, or both, and persisting need for pain relief). If no clinical success was reported, it was described as not specified (NS).

A separate description was made for the studies in children with DSO of the mandible.

Quality evaluation of the studies and risk of bias

The CAse REport (CARE) Guidelines were used for the assessment of the quality of case reports and case series.[53] The CARE checklist consists of 13 items scored as either yes or no: yes indicated that the item was reported in the paper, and no indicated that the item was not reported in the paper.

The methodological index for non-randomised studies (MINORS) guideline was used to assess the quality of non-randomised clinical studies.[54] MINORS is a tool comprising
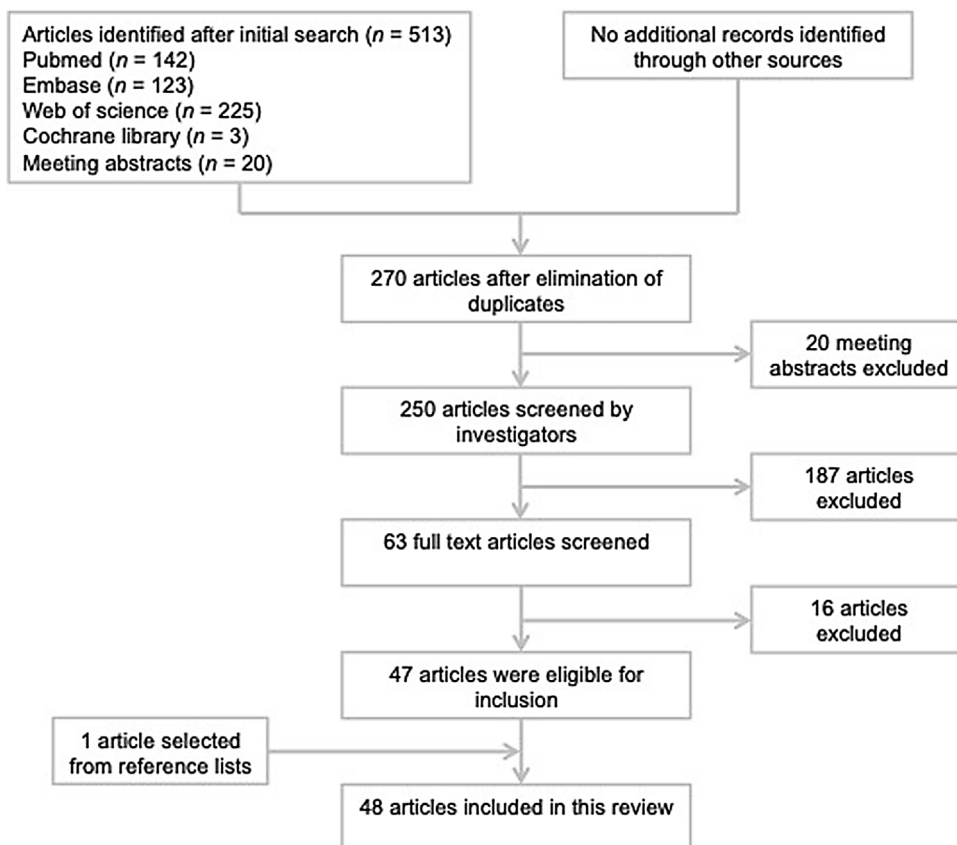
Fig. 1. Flowchart summarising the approach followed in the search for studies that described treatments for chronic diffuse sclerosing osteomyelitis (DSO) of the mandible.

12 items, scored from 0 to 2 in which 0 indicates that the item was not reported in the paper, 1 indicates that the item was reported but not adequately, and 2 indicates that the item was reported adequately. The ideal score is 16 for observational studies, and 24 for clinical studies.

Lastly, the Cochrane Risk of Bias Tool as described in the *Cochrane Handbook for Systematic Reviews of Interventions* was used to assess the risk of bias of the clinical studies.[55] Studies were classified as having a high risk of bias if they did not meet two or more of the criteria; a moderate risk if they did not meet one of the criteria; and a low risk of bias if they met all criteria.

Statistical analysis

Descriptive statistics were used; data are presented as mean (SD) unless otherwise stated. No statistical meta-analysis was made.

Results

Search for papers and demographic data

The initial database search identified 270 papers, of which 20 were abstracts given at meetings. From these papers, 187 could be excluded based on the title or abstract, and 63 full texts were evaluated for eligibility. After evaluation of the full text, 47 papers were included. All lists of references from the included studies were screened, resulting in one additional inclusion. In total, 48 studies were included in this study (Fig. 1).

In total, 16 case reports were included, of which five were of men and 10 of women.[13,15–21,41–43,46,56–59] In one patient the sex was not mentioned.[21] Ages ranged between 6-67 years, mean (SD) 42 (18) years. Thirteen case series were included, reporting 49 cases (12 men and 37 women, mean (SD) age 20 (19) (range 3-72) years) (Table 2).[4,22–31,44,60] In addition, 18 retrospective clinical cohort studies were identified (Table 3).[1,2,5,11,14,32–40,45,47–49] Because it was highly likely that overlapping cohorts were being described, it was not possible to include demographic characteristics. One study presented data of children with bony lesions distributed throughout the body.[61] No further analysis of the results of this study was made, because it was not clear which patients were specifically diagnosed with DSO of the mandible. We identified one RCT with 10 patients – two men and eight women, with a mean age of 48 years (range 31-77 years) (Table 4).[50]

Table 2
Characteristics and outcome of case series.

First author, year, and reference	Study size (n)	Mean (range) age[a]	Treatment	Total No.	Clinical success (No.)	Mean (range) follow up (months)
Eyrich 2003[25]	11[b]	12 (4-17)	Surgical	8/10	CR (7), PR (2), NR (1)	65 (24-180)
			Antibiotics	10/10		
			Anti-inflammatory	3/10		
			Anti-resorptive	1/10		
			Conservative	2/10		
			HBO	3/10		
Heggie 2003[26]	8	11 (7-12)	Surgical	3/8	CR (1), PR (4), NS (3)	63 (60-66)[c]
			Anti-inflammatory	8/8		
Theologie-Lygidakis 2011[4]	5	7 (3-9)	Surgical	5/5	CR (2), PR (3)	27 (4-60)
			Antibiotics	5/5		
			Anti-inflammatory	5/5		

HBO = hyperbaric oxygen treatment; CR = complete response; PR = partial response; NR = no response; NS = no specification.
When a combination of treatment options was used, each individual treatment strategy was scored. Tables were established for studies including ≥5 patients.
  [a] Age at onset in years.
  [b] 1 patient was excluded because of a combination with CRMO.
  [c] 6 patients not reported.

Quality assessment and risk of bias

According to the CARE guidelines, none of the case reports satisfied all the criteria of the CARE checklist (Appendix B: Supplemental data).[53] All case reports therefore qualified as low. All non-randomised clinical studies were observational, and scored 3-11 points out of a possible 16 points according to the MINORS checklist (Appendix B: Supplemental data[54]). According to the Cochrane risk of bias tool, the estimated potential risk of bias was high in all clinical studies (Appendix C: Supplemental data).[55]

Surgical treatment

In total 34 studies reported on different surgical interventions, and 18 papers described multiple surgical techniques.[1,2,4,5,13,15–40,48,57,59]

In total seven studies described curettage of the DSO lesion, comprising 13 patients.[17,21–23,28,32,37] Three of these patients lost their symptoms after treatment with curettage combined with antibiotics.[32] In 10 out of 13 patients no improvement in complaints was reported.[17,21–23,28,32,37]

Decortication of the affected mandibular side was reported in 27 papers, comprising 156 cases.[1,2,4,5,13,15–18,20,23–27,29–36,38,40,48,57] In 54 cases only the treatment was described without mention of the outcome of treatment or clinical follow-up.[1,5,38,48] Of the remaining 102 cases, 37 patients (36%) reported complete cure without remaining symptoms. Thirty-two of these patients (31%) were treated with a combined approach, which consisted of decortication and partial resection; saucerisation; and antibiotics, with or without hyperbaric oxygen treatment.[1,2,20,25,30,32–35,40,57] Twenty-four patients (24%) reported a decrease of symptoms, of which 15 (15%) were treated with a combination of the above-mentioned treatments.[2,4,13,16,24–26,30,31,40] However,

in 40% of the cases no improvement in complaints was observed.[4,15,17,18,25–27,29–33,35,36,40]

Excision of the mandibular lesion (such as saucerisation, debulking, or other types of excision) was described in nine studies, including 29 patients.[22,23,26,27,30,37–40] In 10 of these 29 patients only the procedure was described and no outcome or clinical follow-up was reported.[22,38,39] Of the remaining 19 patients, 11 became asymptomatic, of whom six (were treated with saucerisation (three combined with particulate cancellous bone and marrow grafting), two with excision with reconstruction with hydroxyapatite, two with partial resection of the lesion, and one patient had a condylotomy and reconstruction with an interpositional silastic implant.[22,23,30,37,40] After these treatments six patients reported improvement in their symptoms, of whom four were treated with saucerisation (three combined with particulate cancellous bone and marrow grafting), one patient was treated with coronoidectomy combined with decortication and recontouring of the mandible, and one patient had the mandibular lesion debulked.[23,26,37] In two patients no improvement was reported after debulking combined with decortication and partial myomectomy, or after mandibular condylectomy with reconstruction with an arthroplasty and temporalis flap.[26,27]

A segmental resection or hemimandibulectomy followed by reconstruction was reported in six studies including 11 patients.[19,26,36,37,48,59] For three patients only the procedure was described and no outcome or clinical follow-up reported.[48] For the remaining eight patients, four had a reconstruction with a fibular free flap, two had a vascularised free graft from the iliac crest, and two had a titanium plate.[19,26,36,48,59] Of the eight patients, two lost their symptoms.[19,26] In six patients the symptoms improved, and two patients developed complaints on the contralateral side.[36,37,59]

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Table 3
Characteristics and outcome of retrospective clinical cohort studies.

First author, year, and reference	Study size (No.)	Mean (range) age[a]	Treatment	Total No.	Clinical success (No.)	Mean (range) follow up (months)
Hjørting-Hansen 1970[32]	6[b]	NS	Surgical	6/6	CR (4), NR (2)	NS
			Antibiotics	5/6		
Jacobsson 1979[33]	20	NS (2-73)	Surgical	6/20	CR (3), PR (11), NS (6)	NS
			Antibiotics	NS		
			Anti-inflammatory	6/20		
Jacobsson 1980, 1984[1,2]	16	27 (8-53)	Surgical	7/27	CR (3), NS (13)	NS
			Antibiotics	27/27		
			Anti-inflammatory	7/27		
			Other (rt)	1/27		
Van Merkesteyn 1984, 1988, 1990[5,11,34]	27	41 (6-72)	Surgical	12/27	CR (4), PR (7), NR (2), NS (14)	16 (11-24)
			Antibiotics	15/27		
			Anti-inflammatory	4/27		
			Conservative	22/27		
			HBO	13/27		
Montonen (1993[35]	41[c]	33 (5-69)	Surgical	34/34	CR (18), NR (16)	80 (18-259)
			Antibiotics	33/34		
Ogawa 2001[37]	9[d]	30 (13-60)	Surgical	6/6	CR (3), PR (3)	109 (36-232)
			HBO	6/6		
Yoshii 2001[45]	9	41 (19-70)	Antibiotics	9/9	CR (7), PR (2)	26 (15-53)
Baltensperger 2004[38]	30	35 (5-75)	Surgical	27/30	CR (11), PR (14), NR (5)	76 (12-228)
			Antibiotics	30/30		
			Anti-inflammatory	17/30		
			Anti-resorptive	1/30		
			Conservative	2/30		
			HBO	12/30		
Kuijpers 2010[47]	7	44 (12-78)	Anti-inflammatory	1/7	CR (3), PR (4)	30 (18-46)
			Anti-resorptive	7/7		
Otto 2015[49]	11	44 (17-76)	Anti-resorptive	11/11	CR (6), PR (4), NR (1)	27 (17-39)
Renapurkar 2016[40]	12	11 (3-14)	Surgical	12/12	CR (6), PR (5), NR (1)	45 (12-132)
			Antibiotics	12/12		
Julien Saint Amand 2017[48]	10	33 (7-58)	Surgical	10/10	CR (5), PR (4), NR (1)	66 (6-144)
			Antibiotics	10/10		
			Anti-inflammatory	8/10		
Van de Meent 2017[14]	11	12 (8-15)	Anti-inflammatory	9/11	CR (5), PR (6)	12 (12-12)
			Anti-resorptive	5/11		
			Conservative	11/11		

HBO = hyperbaric oxygen treatment, CR = complete response, PR = partial response, NR = no response, NS = no specification.
When a combination of treatment options was used, each individual treatment strategy was scored. Tables were established for studies including ≥5 patients.
[a] Age at onset in years.
[b] this report contained 28 patients, of whom 6 were diagnosed with DSO.
[c] 7 patients were excluded because of insufficient follow-up data.
[d] 3 patients were excluded because of deaths unrelated to DSO.

Table 4
Characteristics and outcome of randomised controlled trials.

First author, year, reference	Study size (No.)	Mean (range) age[a]	Treatment	Total No.	Clinical success (No.)	Mean (range) follow up (months)
Montonen 2001[50]	10	48 (31-77)	Anti-resorptive	6/10	CR (3), PR (3), NR (4)	12 (12-12)
			Placebo	4/10		

CR = complete response; PR = partial response; NR = no response.
When a combination of treatment options was used, each individual treatment was scored. Tables were established for studies including ≥5 patients.
  [a] Age at onset in years.

Overall, a solitary surgical approach yielded a complete response rate of 8%, and a combined surgical approach yielded a complete response rate in 29% of cases.

Antibiotics

The use of different types of antibiotics was reported in 39 studies comprising 216 patients.[1,2,4,5,13,15–25,27–36,38–46,48,57,58,60] Treatments with β-lactam, macrolide, fluoroquinolone, nitroimidazole, and lincosamide antibiotics were reported.

In 122 patients only the treatment regimen was described without outcome or clinical follow-up.[1,2,5,22,31,33,35,38,48,60] Of the remaining 94 patients, 43 were free of symptoms after treatment, of whom 25 patients were treated with a combination of surgery, or hyperbaric oxygen, or both.[1,2,4,17,20,22–25,29,30,32,34,40,43,45] In 23 cases the symptoms improved, of whom 17 were treated with a combination of surgery, corticosteroids, NSAID, or hyperbaric oxygen.[4,16,23–25,27,30,34,40,45,46,57] Overall, of the 216 patients treated with antibiotics, 43 became free of complaints. In 122/216 cases no outcome was reported, and in 28 (30%) no improvement was detected.[13,15,18,19,21,25,28,30–32,34,36,39–42,44,58,60]

Anti-inflammatory medication

The use of anti-inflammatory medication, such as NSAID or corticosteroids, or both, was reported in 24 studies, including 94 patients.[1,2,4,5,13,14,17,18,24–26,28,30,31,33,34,38,39,41,42,44,47,48,60]

Sixty-three patients were treated with different types of NSAID such as piroxicam, indomethacin, ibuprofen, naproxen, and rofecoxib.[4,14,18,24–26,28,30,31,38,39,41,42,44,48] In 35 cases only the treatment was described and no outcome or clinical follow-up were reported.[14,26,38,48] Of the remaining 28 patients, four patients became free of symptoms, of whom three were treated with a combination of methotrexate, infliximab, antibiotics, or hyperbaric oxygen.[25,39,42,44] In 15 patients the symptoms improved, of whom six were treated with a combination of surgery, corticosteroids and antibiotics.[4,24–26,30,39,44] In nine patients treatment with NSAID was unsuccessful.[18,25,26,28,31,41,60]

Forty-nine patients were treated with corticosteroids, mostly prednisolone.[1,2,4,5,13,14,17,28,31,33,34,38,44,47,48,60] Of 19 cases, only the treatment was described and no outcome or clinical follow-up was reported.[5,14,31,38,47,48] Of the remaining 30 patients, 21 showed improvement in their symptoms, of which one was treated with a combination of corticosteroids and NSAID.[1,2,33,34,44] In nine patients the symptoms did not improve.[1,2,4,13,17,28,31,60]

In conclusion, solitary anti-inflammatory medication showed a complete response rate in 2%, and combined with other treatments it gave a complete response rate in 5% of cases.

Antiresorptive medication

Thirteen studies reported treatment in 40 cases with antiresorptive medication, such as bisphosphonates, denosumab, and calcitonin.[14,18,21,25,27,28,38,41,47,49,50,58,60]

Thirty-six patients were treated with bisphosphonates such as pamidronate, alendronate, zoledronic acid, olpadronate, ibandronate, and disodium clodronate.[14,18,21,25,28,38,41,47,49,50,58] Eighteen patients became free of symptoms after treatment with bisphosphonates,[14,18,21,28,41,47,49,50] in 16 the symptoms improved,[14,25,38,47,49,50,58] and in two there was no improvement.[49,50]

One randomised, placebo-controlled, double-blind trial was published by Montonen et al, who treated six patients with disodium clodronate and four patients with a placebo intravenously,[50] which resulted in a reduction in pain in both groups, but only after six months did the pain scores differ significantly between the groups. No significant differences were found at the other times of measurement. In total, seven patients needed a second infusion because of pain (five of the six patients in the clodronate group, and two of the four in the placebo group). The follow-up period was 12 months.

Three patients were treated with subcutaneous injections of denosumab and the symptoms were well-controlled with regular injections.[58,60] In one patient no follow-up period was described, whereas in the other two the follow-up period ranged from 12-20 months after starting the denosumab.

Treatment with subcutaneous calcitonin was described in two patients.[27] One patient was free of symptoms with a maintenance dose of 25 units every two weeks, and the other showed improvement of her symptoms with a maintenance dose of between 20-50 units twice a week. Both patients were followed-up for three years.

In conclusion, antiresorptive treatments yielded a mixed response, being successful with complete response in just over half of the cases treated.

Conservative treatment

Six studies described conservative treatment in 29 patients that consisted of an occlusal splint; physiotherapy with habit-reversal training; myofeedback or relaxation, or both; counselling, or muscle relaxant drugs (diazepam and mephenoxalone).[11,13,14,17,25,38]

For only one patient the treatment was described but no outcome or clinical follow-up was reported.[38] Of the remaining 28, nine were cured after treatment with different types of conservative treatment,[11,13,14,25] and 11 showed improvement of their symptoms.[11,14] Eight patients showed no improvement at all.[11,14,17] The follow-up period ranged from 12-180 months.

Hyperbaric oxygen

Nine studies reported treatment with hyperbaric oxygen in 57 patients.[5,13,16,19,22,25,27,29,30,34,37,38] Of 25 patients only the treatment was described and no outcome or clinical follow-up was reported.[5,38] Of the remaining 32 patients, 11 patients became asymptomatic, all of them were treated with a combination of saucerisation, decortication, surgical excision, antibiotics, and/or NSAID.[22,25,29,34,37] In 11 cases the symptoms improved, of which nine patients (28%) were treated with a combination of saucerisation, decortication, hemimandibulectomy, and/or antibiotics.[16,25,27,34,37] In 10 patients treatment with hyperbaric oxygen was not successful.[13,19,25,30,34,37]

Hyperbaric oxygen was in almost all cases not used as a single treatment, but as an additional option.

Other

Four studies described the treatment of four patients with DSO of the mandible with other agents.[1,39,42,56] One patient was treated with a combination of a tumour necrosis factor-α inhibitor (infliximab) and methotrexate, which resulted in improvement in their symptoms.[42] Another patient was treated with antirheumatics (the type of medication was not specified) and had no symptoms after one year of treatment.[39] Dental implants were also used to improve the masticatory function as a treatment, but no results were reported.[56] One patient was accidentally treated with radiotherapy, as the disease was initially mistaken for Ewing's sarcoma.[1] Unexpectedly, the patient reported improvement of complaints, but the follow-up period lasted only two months.

Specific treatments in children

Twenty-five studies described treatment of 81 children with DSO of the mandible.[2,4,5,11,14,23,25,26,28–31,33,35,37–40,42,44,47–49,57,60] In three studies no clear distinction was made between the age of the patient and the treatment, so these studies were not included.[33,35,38]

Forty-seven children were treated surgically.[2,4,5,23,25,26,28,30,31,37,39,40,48,57] One was treated with curettage of the DSO lesion and showed improvement in symptoms.[28] Thirty-eight children were treated with decortication of the mandibular lesion, but in seven cases only the procedure was described and no outcome or clinical follow-up was reported.[2,4,5,25,26,30,31,40,48,57] Of the remaining 31 cases, 14 patients reported complete cure, 12 cases reported a reduction in symptoms, and in five children no improvement was observed.[2,4,5,25,26,30,31,40,48,57] Seven children were treated with excision (saucerisation, debulking, or other types of excision) of the mandibular lesion, and in one patient only the procedure was described and no outcome or clinical follow-up were reported.[23,26,30,37,39,40] Of the remaining six children, five reported complete cure, and one reported a reduction of symptoms.[23,26,30,37,40] Two children were treated with a hemimandibulectomy followed by reconstruction, of which one reported complete cure. In one patient the symptoms improved, but this child developed complaints on the contralateral side.[26,37]

Fifty-three children were treated with antibiotics.[2,4,5,23,25,28–31,39,40,42,44,48,57,60] Of the 42 children for whom follow-up was reported, 21 were free of symptoms after treatment, of whom 18 were treated with a combination of antibiotics, and surgery or hyperbaric oxygen or both.[4,23,25,29,30,39,40] In 13 cases the symptoms improved, of whom six patients were treated with a combination of antibiotics and surgery.[4,25,30,39,40,57] Eight patients reported no improvement of symptoms.[25,28,31,39,42,44]

Anti-inflammatory drugs were used in 28 children.[2,4,25,26,28,30,31,44,48,60] Twenty-six were treated with different types of NSAID, and in five patients only the treatment was described without mentioning follow-up.[4,25,26,28,30,31,44,48] Of the remaining 21 children, two became symptom-free, in 11 the symptoms improved, and in eight no improvement was observed.[4,25,26,28,30,31,44,60] Eleven children were treated with corticosteroids.[2,4,28,31,44,48,60] In two children the symptoms improved, and four reported no improvement.[4,28,31,44,60]

Bisphosphonates were used in nine children.[14,25,28,47,49] In eight cases follow-up was described as showing improvement in all cases, and four children became symptom-free.[14,25,28,47] One child was treated with subcutaneous injections of denosumab and the symptoms were well-controlled with regular injections.[60]

Fourteen children were treated conservatively, and in one case only the treatment was described and no outcome or clinical follow-up was reported.[11,14,25] Of the remaining 13 patients, four were cured after conservative treatment, four children reported improvement of their symptoms, and five reported no improvement.[14,25]

Discussion

Treating DSO of the mandible is challenging. Many treatments have been described, and because of the recurring nature of the disease it is difficult to prove long-term therapeutic responses to the clinical signs. However, this review could help in providing an overview of the treatment options.

Invasive surgical techniques have been described, and include curettage of the lesion, decortication, forms of marginal excisions (such as saucerisation, debulking, and other types of excision), segmental resection, and hemimandibulectomy.[1,2,4,5,13,15–40,48,57,59] In these papers the purpose of the operation was the removal of necrotic and avascular bone, and to establish contact between well-vascularised soft tissue and the surgical defect to promote revascularisation and osseous healing.[1,2,4,15,19,23,31,32,34,57] Decortication is one of the more common surgical techniques used in patients with DSO of the mandible. In this review we found that 36% of the patients showed complete cure after treatment with decortication, and 24% of the patients showed reduction in the severity of symptoms.[1,2,4,13,16,20,24–26,30–35,40] However, in 35% of cases follow-up was not mentioned. Some cases improved after repeated decortication, but other cases developed recurrences even after multiple procedures.[2,35] Some authors attributed recurrences to inadequate margins or the presence of devitalised teeth, and advised a more aggressive form of decortication, removal of all non-vital teeth, or (partial) resection of the diseased area.[1,2,15,26,35,36,44,50] However, even after partial or marginal resections recurrences were still common, particularly around resection margins.[36,44] Some patients were treated with hemimandibulectomy followed by reconstruction, of which two patients developed complaints on the contralateral side.[37,59] Surgery, and particularly mandibular resection, is associated with severe morbidity, such as damage of the inferior alveolar nerve, deformity, problems with mandibular reconstruction, and (in children) problems with mandibular growth. Advanced surgery should therefore be done only on severe, treatment-resistant cases, where all other therapeutic regimens have failed.[2,4,29,31,35–37,50]

Many patients were treated with antibiotics, although in most cases the antibiotics were prescribed before the diagnosis of DSO of the mandible had been made and were often combined with other treatments.[1,4,13,16,18,19,23–25,27,29–31,33,34,40,42,44,57,60] In more than half of the patients treated with antibiotics the results were not clearly reported and no conclusion can be drawn. It has been postulated that a moderate response could be attributed to impaired vascularisation resulting in low concentrations of the antibiotic, but the origin of DSO of the mandible is non-infective, and therefore antibiotics are unlikely to work.[15,23,26,34]

Anti-inflammatory drugs (such as NSAID and corticosteroids) block the inflammatory pathway at different levels, which could result in the suppression of inflammatory responses and an analgesic action.[26,62] This review shows that 68% of the patients treated with NSAID and 70% of the patients treated with corticosteroids had no symptoms or improvement in symptoms after initiation of treatment. Anti-inflammatory medication could be useful to stabilise and improve symptoms without the risk of severe side effects. Accordingly, anti-inflammatory drugs should certainly be recommended for control of symptoms during exacerbations.[1,2,23,26,33,34,36,39,41,44]

We found promising results for the treatment of DSO of the mandible with antiresorptive medication. Of the cases treated with bisphosphonates, 94% showed improvement of which half lost their symptoms, meaning that only 6% showed no response. Bisphosphonates are strong inhibitors of osteoclast-mediated bone resorption.[18,21,49,50,62,63] In patients with mandibular DSO the rationale for treatment is based on the fact that the local increased bony turnover causes an inflammatory response that induces swelling and pain. Treating this locally increased bony turnover with antiresorptive medication will lead to a reduction in bony remodelling and therefore a reduction in pain.[14,18,21,31,41,49] Various types of bisphosphonates, such as those that contain nitrogen (pamidronate, olpadronate, alendronate, ibandronate, and zoledronate), and those that do not (disodium clodronate), have different routes of administration, and different doses have been reported.[14,18,21,25,28,38,41,47,49,50] The only randomised, placebo-controlled, double-blinded trial enrolled 10 patients who were given the non-nitrogen-containing bisphosphonate, disodium clodronate or a placebo intravenously.[50] This resulted in a significant reduction in pain at six months in patients compared with those given placebo, but no difference at 12 months. Five of the six patients in the disodium clodronate group, and two of the four patients in the placebo group, needed a second infusion for persistent or recurrent pain. A possible explanation could be that disodium clodronate has a low affinity for bone and so wears out. The currently available nitrogen-containing bisphosphonates have greater potency and better bioavailability and therefore a prolonged duration of action.[49] Long-term side effects, such as medication-related osteonecrosis of the jaw have not been reported in patients with DSO of the mandible.

Conservative measures consisting of physiotherapy with habit-reversal training; myofeedback or relaxation, or both; occlusal splint; disease counselling; and (in some patients) muscle relaxant drugs, are non-invasive treatments for patients with mandibular DSO.[11,13,14,17,25,38] This treatment improved symptoms in 71% of the patients, of whom 32% lost their symptoms. Conservative treatment was based on the hypothesis that chronic tendoperiostitis caused by hyperactivity of the masticatory muscles is an aetiological factor for DSO of the mandible.[11–14]

Hyperbaric oxygen, which is often used as an addition to surgery and antibiotics, was described as a possible alternative in the treatment for DSO of the mandible.[29,34] The patient

inhales 100% oxygen in a pressure chamber and this increases oxygen uptake and results in augmentation of angiogenesis, improvement in osteogenesis, increased leucocyte activity, and stimulation of growth factors.[15,16,29,31,34,39] The efficacy of hyperbaric oxygenation is difficult to establish, as almost all patients who benefited from the treatment were given combination treatment with surgery, or antibiotics, or both. The use of hyperbaric oxygen has important disadvantages, because periods of treatment are long, ranging from 10-320 hours, and require multiple visits.[23,34]

The results of the use of treatments in children were comparable to those described in adults. Conservative measures and antiresorptive medication showed the most promising results, with improvement of symptoms in 62% (of whom 31% were symptom-free), and 100% (of which half lost their symptoms), respectively. Considering the morbidity of surgery, (problems with mandibular growth in children with DSO of the mandible) surgery should be avoided.

One limitation of this review is that most published treatments provide only short-term improvement with short or unspecified follow-up times. It is difficult to conclude, therefore, whether the improvements are the result of the treatment or can be attributed to the relapsing-remitting nature of the disease. In many reported cases, no outcome or clinical follow-up was described. These reports could therefore not be used to evaluate the prognosis of treatment.

Another limitation of this review is our inability to conduct a meta-analysis, because measurements of treatments and outcome varied widely, and most cases were given multiple combinations of treatments, which hindered valid comparisons among the outcome data. It must also be stressed that the papers studied were of poor quality, and all clinical studies were at high risk of bias when screened for selection, performance, detection, attrition, and reporting bias, according to the Cochrane Risk of Bias Tool.[55] The findings are based on a small number of case reports, case series, and clinical cohort studies, with low levels of evidence as well as potential publication bias. This emphasises the need for well-designed research, preferably randomised controlled trials, for assessment of the best treatments for DSO of the mandible. However, as it is a relatively rare disease, it is difficult to obtain large samples.

Conclusions

In conclusion, many treatments for DSO of the mandible, including surgery, antibiotics, anti-inflammatory drugs, antiresorptive drugs, conservative treatment, and hyperbaric oxygen have been reported. This systematic review of relevant published papers found a relatively low rate of success after (invasive) surgical treatment or (impractical) treatment with hyperbaric oxygen. Non-invasive conservative treatment and antiresorptive drugs showed more promising results. Because these treatments are less invasive, we advise considering them as the first choice for treatment of DSO of the

mandible. Nevertheless, the studies in this review all had a high risk of bias, and further well-designed research is necessary to evaluate the best treatment strategy for DSO of the mandible further.

Conflict of interest

We have no conflicts of interest.

Ethics statement/confirmation of patients' permission

No ethics committee approval or exemption, or patients' consent, required.

Appendix A, B, and C Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.bjoms.2020.01.012.

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