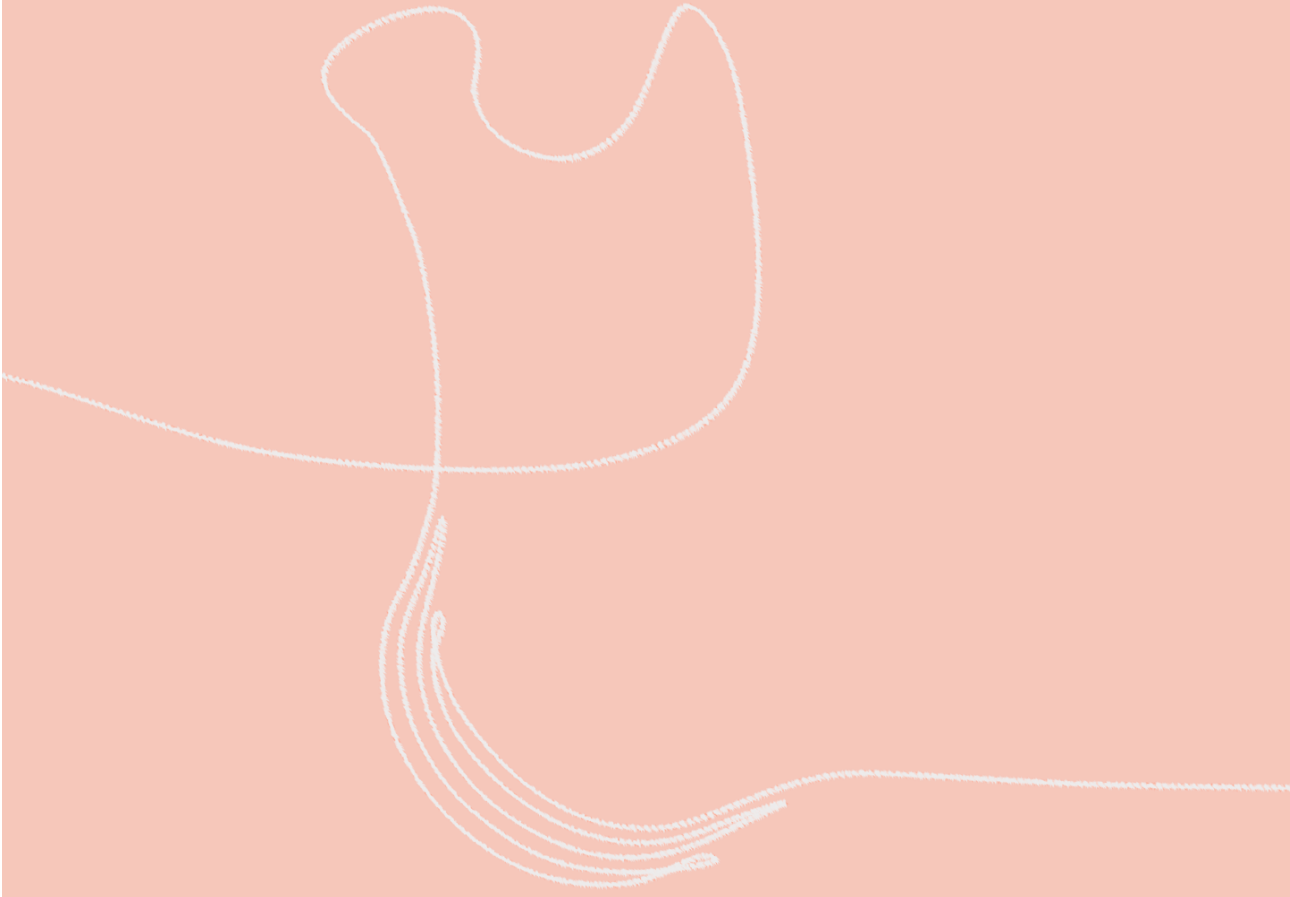
Chronic diffuse sclerosing osteomyelitis/tendoperiostitis of the mandible: standard of care

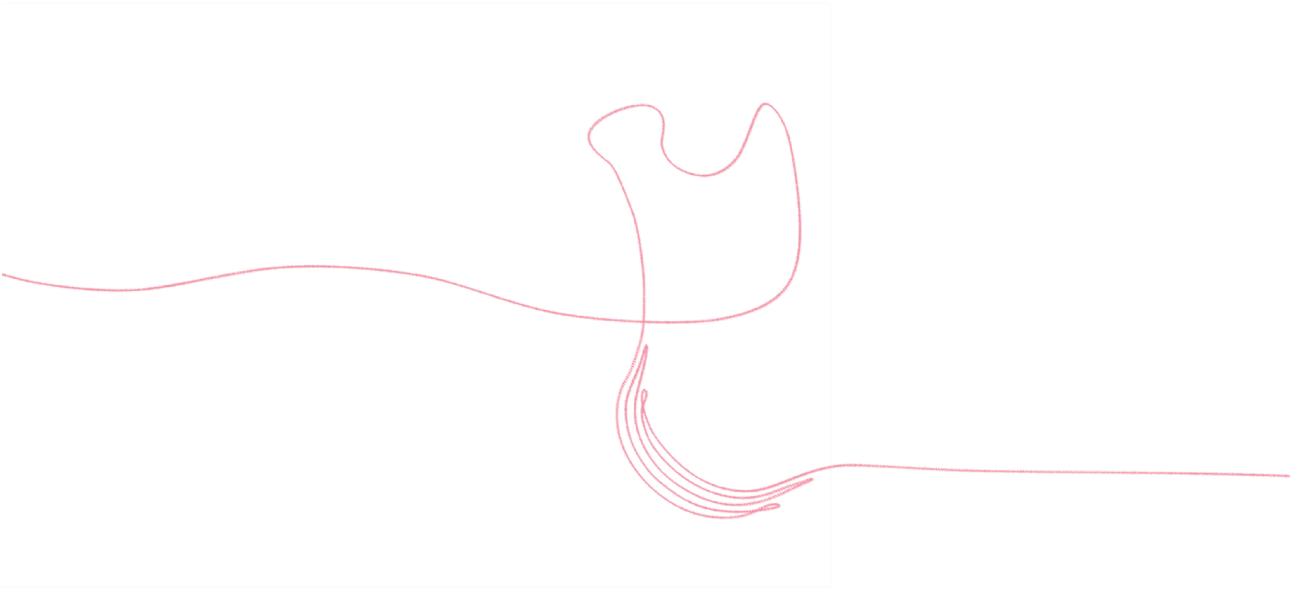
Meent, M.M. van de

PART ONE
GENERAL INTRODUCTION



Chapter 1

Introduction and aims of this thesis



THIS THESIS

General introduction

Osteomyelitis is an inflammation of bone, bone marrow and/or periosteum.[1-13] The word is derived from the Greek word ὀστέον (osteon; bone), μυελοσ (myelos; marrow), and the word-forming element -ιτισ (-itis), which denotes inflammation.[15] It may present in all bones of the body. This thesis studies osteomyelitis of the maxillofacial bone structures, with focus on a specific type of osteomyelitis: chronic diffuse sclerosing osteomyelitis (DSO) of the mandible.

Classification of different types of osteomyelitis

Many different (sub)classifications of osteomyelitis have been introduced in the literature in the last decades. Proposed classifications are based on clinical course, aetiology, histopathological- and/or radiological features.[1,3,5,7,8,12,14,16-21] Many of these classifications still overlap in the description of different types of osteomyelitis and in nomenclature. In this thesis, the classification of osteomyelitis of the jaws is based on the Zurich classification, in which acute osteomyelitis can progress to secondary chronic osteomyelitis.[14] Chronic Diffuse Sclerosing Osteomyelitis (DSO), proliferative periostitis, and osteoradionecrosis are other entities (Figure 1).[14]

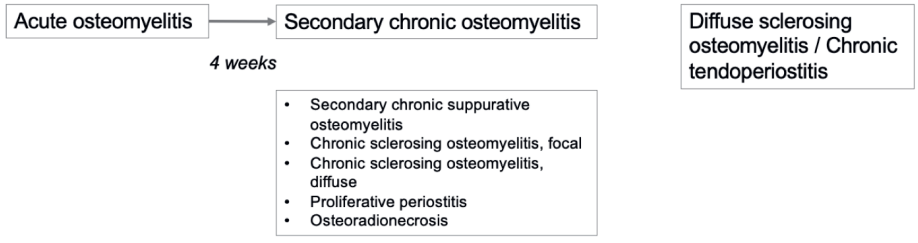


Figure 1. Based on the Zurich classification of osteomyelitis of the jaws.[14]

Acute (suppurative) osteomyelitis

In acute osteomyelitis patients present with acute pain, swelling of the cheek, fever, sometimes with intra- and extra-oral fistulas and/or neurosensory disturbances.[9,11,20,22] This type of osteomyelitis is usually caused by prolonged odontogenic infections, poor fracture healing after trauma, infections of internal fixation material, or infections of dental implants. Bone fragments can become necrotic and sequestration occurs, due to the

acute inflammatory process and compromised blood supply.[11,14] On panoramic radiographs osteolysis and sequestration will be visible after 2-3 weeks of disease duration.[9,10,23] The treatment of acute osteomyelitis is focused on surgical removal or treatment of the primary cause, drainage of pus, and antibiotic therapy.[9,17,20,22]

Secondary chronic (suppurative) osteomyelitis

Secondary chronic suppurative osteomyelitis, also known as chronic purulent osteomyelitis or chronic suppurative osteomyelitis develops following acute osteomyelitis after a disease duration of more than four weeks.[1-12,14,20,22,24] It is caused by the same infectious factors as acute osteomyelitis and clinical symptoms are the same, although less pronounced. Due to progressive bone resorption, fistula formation may be present, and pathological fractures may occur.[7,12,23] Treatment is focused on removal of the source of infection, purulent drainage, and removal of sequesters to establish contact between well-vascularised soft tissue and the osseous defect to promote revascularisation and healing.[9,20,22] The surgical procedure is combined with long-term antibiotic therapy.

Chronic sclerosing osteomyelitis, focal

Chronic focal sclerosing osteomyelitis is also known as chronic non-suppurative osteomyelitis or condensing osteitis.[22,23,25-28] It is usually caused by a mild odontogenic infection, that causes infection of the pulp and subsequent complaints of the tooth involved. The condensed bone lesion itself is asymptomatic. A radiograph shows a radiopaque area surrounding the apex of the tooth involved, with a maximum diameter of 2cm.[20] Endodontic therapy or extraction of the tooth involved should be performed.[14,27] In some cases, curettage of the inflammatory tissue is necessary.[23] The lesion disappears or residual sclerosis remains as a bone scar.[14,23]

Chronic sclerosing osteomyelitis, diffuse

One of the most confusing terms in medical literature is chronic diffuse sclerosing osteomyelitis (DSO), a variety of denominations can be found, such as primary chronic osteomyelitis, juvenile mandibular chronic osteomyelitis, chronic sclerosing osteomyelitis, and non-suppurative osteomyelitis. The true DSO is a rare disease with high morbidity and abundant use of painkillers.[27,29] Characteristics of the disease are recurrent pain and swelling of the cheek, often accompanied by trismus, and progressive mandibular deformity.[1,3,5-7,11-13,19,24,26-69] There is an absence of pus, fistulae, growth of microorganisms in cultures or other symptoms of bacterial infection.[2,7,8,11,12,27,33,39,41-43,46,52,55,60,65-68] The radiographic characteristics are osteosclerosis or a combination of osteolysis and -

sclerosis.[1,2,4,6,8,9,11-13,19,24,26-29,32,33,35-42,44-56,58-60,62,64,66-69] In patients with chronic diffuse sclerosing osteomyelitis no infectious cause can be found, and the aetiology and treatment are still uncertain.[7,8,12,17,24,27-30,32,33,36,39-46,48,49,51-56,58,59,61-68,70] This type of osteomyelitis will be discussed in more detail in this thesis.

Proliferative periostitis

This type of osteomyelitis is also known as periostitis ossificans, and Garré's sclerosing osteomyelitis, because it was first described by the Swiss surgeon Carl Garré in 1893.[9,14,20,23,27] The disease usually appears in children and young adults and is clinically characterised by a nontender, unilateral bony swelling, which is localized in the latero-inferior parts of the mandible.[5,6,10] Proliferative osteomyelitis is associated with a response to a low-grade infection, usually a carious lower first molar, which causes a periosteal inflammatory reaction, resulting in formation of immature new bone outside the normal cortical layer. Radiographically this can be seen as a focal osteosclerotic lesion with an 'onion skin' appearance, with a radiolucency around the apices of the involved tooth.[9,71] Treatment of the tooth involved should be performed with extraction or endodontic therapy.[9,14]

Osteoradionecrosis

All patients with osteoradionecrosis have a history of radiotherapy of the head and neck region.[5,6,8,9,11,14,53,71-79] It occurs because of decreased vascularisation of the bone and the surrounding tissues after radiation therapy, and mostly after trauma, such as tooth extraction, denture sores, and periodontal disease.[11,71-73,75,77] Patients have pain and clinically exposed bone can be seen, often combined with intra- or extraoral fistulae.[9,71,73-79] Radiographically osteosclerosis and -lysis with sequestrum formation and in advanced cases pathological fracture can be seen.[72-74] In treatment, surgery with removal of sequestra and primary closure of soft tissues, combined with intravenous antibiotic therapy is recommended.[71,73,77,79]

Chronic diffuse sclerosing osteomyelitis/tendoperiostitis; the current situation

Chronic diffuse sclerosing osteomyelitis (DSO) of the mandible is a rare disease with an estimated prevalence of 1/200.000.[27,29] In the literature, it is also known as primary chronic osteomyelitis, juvenile mandibular chronic osteomyelitis, chronic sclerosing osteomyelitis, and non-suppurative osteomyelitis.

Aetiology

The exact underlying pathophysiological mechanism of DSO of the mandible is controversial.[7,8,12,17,24,27-30,32,33,36,39-46,48,49,51-56,58,59,61-68,70] Various hypotheses have been postulated; such as an endogenic infection or an immunological overshoot, that it is part of a syndrome, or that hyperactivity of the masticatory muscles is the underlying problem.[2-4,6-8,11,12,20,23,24,26-29,32-37,39,41-53,55-67,70,80-89]

One hypothesis is that of a low virulent infection which causes periosteal and endosteal reactions.[11,12,26-29,37,39,42,43,46,49-53,55,58,61,62,64-67,70,80,81] However, it has proven difficult to find micro-organisms in biopsy or culture material other than contamination of the oral flora.[3-6,14,27,29,32-34,41,42,48,55,59,80,90] Therefore, it is thought that it is a local endogenic infection, which causes vasculitis with a decrease of circulation, resulting in a perfect environment for an anaerobic infection to arise.[5,28,29]

Another hypothesis is a hyperactive or hypoactive humoral immune response in patients with chronic diffuse sclerosing osteomyelitis of the mandible.[7,8,12,27,37,39,43,49,50,64-66,82,83] However, a significant defect in (auto-)immune response is never proven in patients with DSO of the mandible.[82]

Some authors suggest DSO of the mandible to be part of a spectrum of diseases with different types of chronic, non-infectious inflammatory osteomyelitis. Sternocostoclavicular hyperostosis (SCCH), chronic recurrent multifocal osteomyelitis (CRMO), and synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome are also part of this spectrum.[2-4,6-8,11,12,20,24,29,32-35,39,41,43-45,47,50,52,55-57,59,62-65,81,84-89] CRMO is a condition mainly in children with osteomyelitic lesions, occurring in one or more bones in the body, particularly in the long bones.[35,57,88,91-93] In SCCH, patients complain of intermittent mild pain and swelling of the anterior chest wall, and changes of osteitis are seen on imaging, comparable to DSO and CRMO.[86,94] SAPHO syndrome is characterised by chronic non-bacterial osteomyelitis, in combination with one of the following: synovitis, acne, and/or pustulosis palmoplantaris.[35,45,47,84,87,95]

Groot *et al*. stated in his dissertation that DSO/tendoperiostitis is caused by overuse of the masticatory muscles.[3,7,8,11,12,23,24,29,33,36,37,39,41,43,46,48,55,60,64-66,81] They suggest a non-infectious origin for DSO of the mandible, because of the chronic recurrent character of the disease, the bacteriologic findings do not support an infectious origin, and the poor results of infectious treatment.[7,8,13,23,36,37,41,48,60,64,66,67] They showed that specific parts

corresponding with the attachment-site of masticatory muscles of the mandible were involved in DSO/tendoperiostitis and that patients with DSO/tendoperiostitis of the mandible showed excessive activity of the masseter muscle.[23,36,64,66,67] Also, treatment of DSO/tendoperiostitis of the mandible based on relaxation of the masticatory muscles has been shown effective.[23,37,60,64,66,81,89] All arguments that overuse of the masticatory muscles could be the cause of DSO/tendoperiostitis.

Clinical features

DSO of the mandible can appear at any age, however there is a peak in adolescents/young adults and another after the age of 50.[2-7,11,12,26,27,29,34,39-41,44,48,57,62,96] It occurs more in females than in males.[12,19,26,27,29,30,32,34,39,48,56,57,59,62]

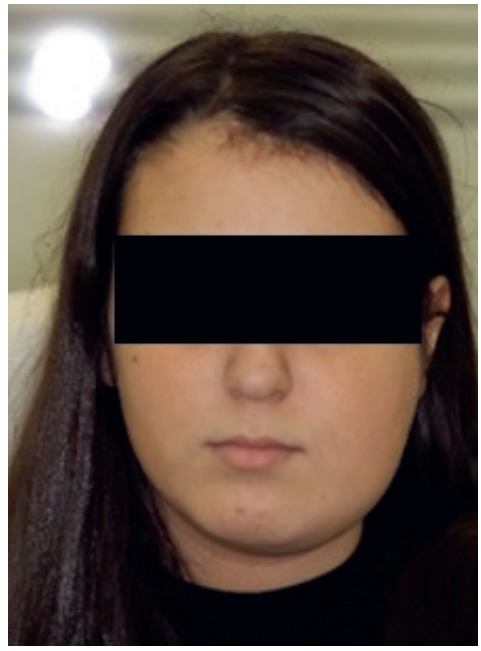


Figure 2. A 13-year-old patient with a swelling of the cheek at the left side, due to DSO/TP of the left mandible.

Diffuse sclerosing osteomyelitis typically occurs in the mandible, and not in other facial bones.[7,12,14,19,27-29,39-41,44,47,48,50,52,58,62,80,96] It usually occurs unilaterally, but bilateral involvement is possible as well.[12,19,27,39,44,47,67] Patients present with intermittent episodes of pain in the region of the affected mandible and also swelling of the cheek at the same side (Table 1, Figure 2).[1,3,5-7,11-13,19,24,26-69] In some cases, the complaints are accompanied

by trismus. On physical examination, patients report tenderness on palpation in the affected area, tenderness of masticatory muscles, and signs of parafunctional habits and tooth wear could be seen.[37,66] Facial asymmetry can occur, due to high periosteal activity with growth of the involved mandibular area.[52] No fistulae or signs of infection are seen, and even no odontogenic origin of the disease.[2,7,8,11,12,27,33,39,41-43,46,52,55,60,65-68] Typically, patients do not present signs of inflammation, like fever or elevated infection parameters, although sometimes a mild elevation in erythrocyte sedimentation rate or C-reactive protein level is found.[2-4,6,7,11,12,27,28,32,39,48,50,53,56,59,60,62,64,66,67]

Radiography

The diagnosis diffuse sclerosing osteomyelitis is made on clinical and radiological findings, and can be supported by histopathological examination. For radiological examination, panoramic radiographs, (cone beam) computed tomography ((CB)CT) imaging, and in some cases magnetic resonance (MR) imaging can be performed.[1,4,7,9,11,13,32,35,39,44,48,50,53,56,58,96]

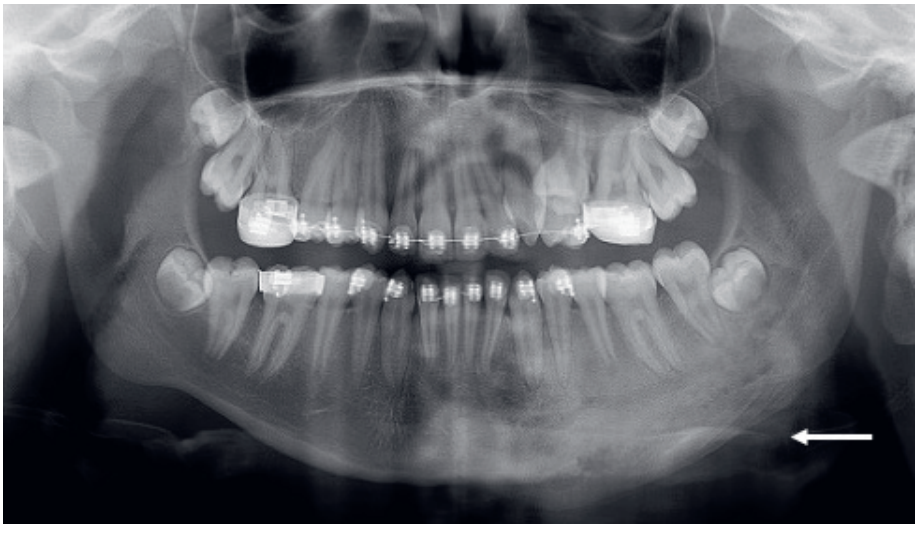


Figure 3. Panoramic radiograph of a patient with DSO/TP of the left side of the mandible, which shows asymmetry, excessive subperiosteal bone formation, and diffuse sclerosis of the ramus, angle, and body.

The radiological abnormalities are mostly seen unilateral in the anterior region of the mandibular angle and posterior part of the mandibular body, but it can also arise from angle to angle.[13,48,58,66,67] Depending on the stage of the disease, radiographs typically

show intermingled sclerosis and osteolysis often combined with subperiosteal bone formation of the mandible (Table 1, Figure 3).[1,2,4,6,8,9,11-13,19,24,26-29,32,33,35-42,44-56,58-60,62,64,66-69] This periosteal reaction can lead to an onion skin appearance on CT-imaging, on which the original cortex is still visible (Table 1, Figure 4).[19,24,44,64] A shift towards a more sclerotic pattern with normalisation of the cortical bone can be seen after clinical improvement.[2,3,6,12,14,24,27,28,33,35,44,51,54,55,60,62] Nevertheless, mandibular asymmetry can remain.

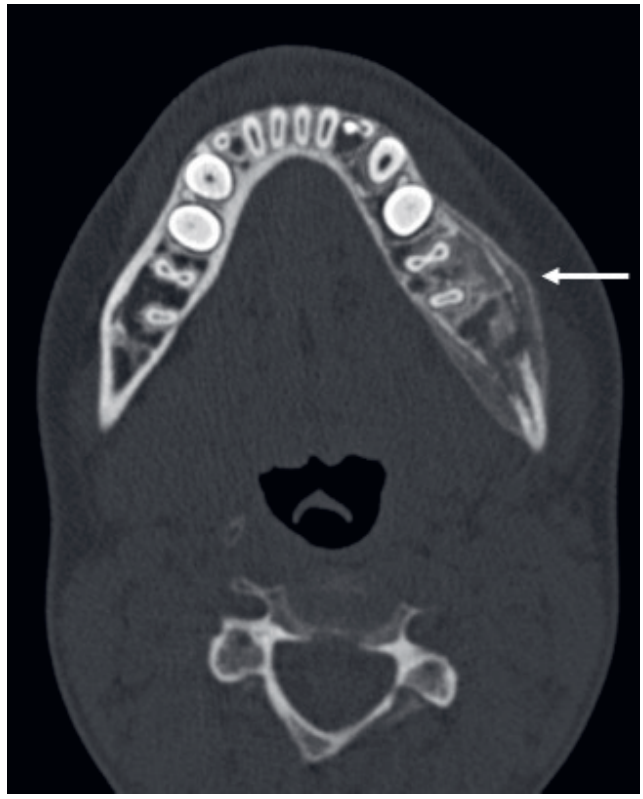


Figure 4. CT-image of a patient with DSO/TP of the left side of the mandible with subperiosteal bone formation which led to an onion skin appearance.

Soft tissue changes can be examined on CT- and MR imaging, which could show hypertrophic and oedematous changes in the masticatory muscles surrounding the osseous abnormalities.[11,44,47,59]

Disease activity can also be examined on bone scintigraphy.[1,4,7,11,13,19,27,29,32,39,40,44,45,48-53,58,60,62,66,67,80,96] Bone scintigraphy is furthermore used to screen patients for extra-oral lesions in cases of CRMO, SCCH, or SAPHO syndrome (Table 1, Figure 5).[52]

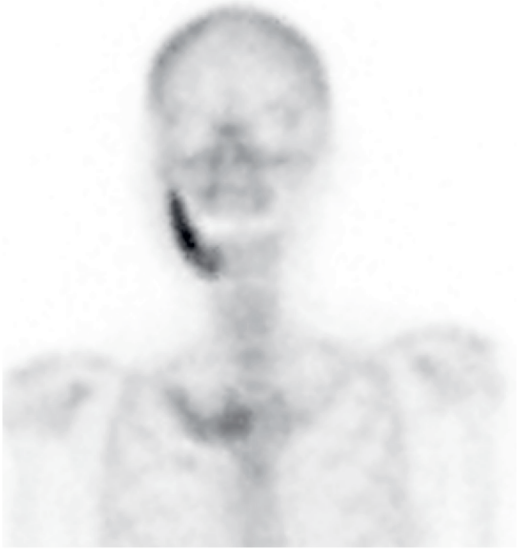


Figure 5. Bone scintigraphy of a patient with DSO/TP of the mandible on the right side with an extra-oral lesion of the sternocostoclavicular joint (SCCH).

Histopathology

The diagnosis of diffuse sclerosing osteomyelitis can be supported by histopathological examination. This is indicated if the diagnosis is not clear on the basis of clinical and radiological findings and/or to exclude other disorders (i.e. bacterial osteomyelitis or malignancy).[1,3,4,6,27,29,34,50,52,56,59,66,67,80] Histological examination usually shows remodelling of the buccal cortical plate, with subperiosteal bone formation and an increase of subcortical bone volume (Table 1).[12,19,26-29,33,36,41,42,45,48,50,53,56,58,59,62,64,66-68] Focal chronic inflammatory responses are seen, which could be caused by tissue breakdown.

Microbiology

In most cases no growth of microorganisms is found in cultures of bone biopsies (Table 1).[6,8,12,19,24,27,29,33,34,39,42,48,52,53,55,59,62,66,67,70,90] Only three studies report growth of bacteria in cultures of tissue specimens in patients with diffuse sclerosing osteomyelitis (species of *Actinomyces*, *Eikenella corrodens*, *Escherichia coli*, *Propionibacterium acne*, *Staphylococcus epidermidis*, and a mixed oral flora).[9,19,27,28,34,39,41,42,45,48,50,52,58,62,67,80]

However, other papers have reported that these positive cultures could be caused by skin- or oral flora contamination, depending on how the biopsies were obtained.[3-6,14,27,29,32-34,41,42,48,50,53,55,59,67,80]

Table 1
Disease characteristics of diffuse sclerosing osteomyelitis of the mandible

Symptoms	- Recurrent pain and swelling of the cheek - Trismus - Mandibular deformity
Radiographic characteristics	- (Mixed) sclerosis (and lysis), subperiosteal bone formation, and/or condylar process deformation of the mandibular bone on panoramic radiograph and/or CT - Masticatory muscle changes on CT and/or MRI - Elevated uptake in the mandibular bone on bone scintigraphy
Histopathological findings	- Reactive bone with subperiosteal bone formation - Increase of subcortical bone volume - Small focal collection of inflammatory cells - No sign of infection with micro-organisms
Microbiological findings	- No growth of microorganisms - In case of growth, contamination of skin- or oral flora

CT = computed tomography, MRI = magnetic resonance imaging

Treatment

Various hypotheses have been reported about the aetiology of diffuse sclerosing osteomyelitis of the mandible. Likewise, many different treatment modalities have been reported as well. Non-surgical therapy, such as analgesic drugs, non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, corticosteroids, hyperbaric oxygen, bisphosphonates, and conservative treatment are reported in literature.[1-9,12,19,24,26-30,32,33,35,37-41,43,44,46,48-52,54-56,58-65,67-70,80,81,89,90,96] Surgical interventions, with minor and more invasive surgery are reported as well, such as decortication, saucerisation, and even segmental resections of the mandible.[2-9,12,17,19,24,26-31,33,35,37-41,43,46,49,50,52,54,55,58-63,65-70,80,81,89,90,96] The treatment of diffuse sclerosing osteomyelitis will be further explored in this thesis.

Aims of this thesis

Despite decades of research, the cause of chronic diffuse sclerosing osteomyelitis/tendoperiostitis of the mandible remains unclear. Many different treatment options have been reported, all without proof of long-term therapeutic effect. In 1995 Groot *et al.* reported a thesis called "*Diffuse sclerosing osteomyelitis of the mandible:*

infection or traction?", in which the hypothesis arose that DSO/tendoperiostitis could be caused by overuse of the masticatory muscles (chronic tendoperiostitis; TP) and that it should be treated accordingly based on relaxation of these muscles.[23] In this thesis, the hypothesis of a mechanical cause of DSO is further explored. Hereby, this thesis attempts to evaluate the diagnostic examination and long-term therapeutic effect of treatment in patients with diffuse sclerosing osteomyelitis/tendoperiostitis of the mandible and to propose a standard of care protocol for clinicians. This could potentially prevent unnecessary diagnostic examination and harmful extensive (surgical) treatments.

Outline of the thesis

Part I (this part) of the thesis focuses on the general introduction of DSO/tendoperiostitis of the mandible, classification of different types of osteomyelitis, and the current situation of DSO of the mandible.

Part II of this thesis will focus on the diagnostic examination of DSO/tendoperiostitis of the mandible, with CHAPTER 2 describing an evaluation of the diagnostic examination, in particular the radiographic characteristics of patients with DSO/tendoperiostitis of the mandible.

Part III focuses on the treatment of DSO/tendoperiostitis of the mandible with a special emphasis on conservative treatment of these patients.

- A systematic review of the literature, in which all different treatment strategies are being described and evaluated (CHAPTER 3);
- Evaluation of conservative or non-surgical therapy in children and adult patients with diffuse sclerosing osteomyelitis/tendoperiostitis of the mandible (CHAPTER 4 and 5);
- Evaluation of bisphosphonate therapy in patients with diffuse sclerosing osteomyelitis/tendoperiostitis of the mandible (CHAPTER 6);
- The results of remodelling surgery with three-dimensional designed- and -printed patient specific surgical guides for patients with diffuse sclerosing osteomyelitis/tendoperiostitis of the mandible, who had complaints about facial asymmetry caused by mandibular deformity (CHAPTER 7).

Part IV includes a general discussion and summaries in English and Dutch (CHAPTER 8, 9, and 10).

REFERENCES

1. Abdalla-Aslan R, Nadler C, Benoliel R, Sharav Y, Haviv Y. Periodic persistent orofacial pain due to osteomyelitis of the mandible: A case report. Quintessence International 2016;47:609-15.
2. Agarwal A, Kumar N, Tyagi A, De N. Primary chronic osteomyelitis in the mandible: a conservative approach. BMJ Case Rep 2014;2014.
3. Baltensperger M, Gratz K, Bruder E, Lebeda R, Makek M, Eyrich G. Is primary chronic osteomyelitis a uniform disease? Proposal of a classification based on a retrospective analysis of patients treated in the past 30 years. J Craniomaxillofac Surg 2004;32:43-50.
4. Berglund C, Ekstromer K, Abtahi J. Primary Chronic Osteomyelitis of the Jaws in Children: An Update on Pathophysiology, Radiological Findings, Treatment Strategies, and Prospective Analysis of Two Cases. Case Rep Dent 2015;2015:152717.
5. Carmony B, Bobbitt TD, Rafetto L, Cooper EP. Recurrent mandibular pain and swelling in a 37-year-old man. J Oral Maxillofac Surg 2000;58:1029-33.
6. Eyrich GK, Baltensperger MM, Bruder E, Graetz KW. Primary chronic osteomyelitis in childhood and adolescence: a retrospective analysis of 11 cases and review of the literature. J Oral Maxillofac Surg 2003;61:561-73.
7. Haverals L, Mattheij M, Hoppenreijs E, Berge S, van der Weij A. A boy with recurrent swelling of the jaw. Pediatr Rep 2017;9:7489.
8. Julien Saint Amand M, Sigaux N, Gleizal A, Bouletreau P, Breton P. Chronic osteomyelitis of the mandible: A comparative study of 10 cases with primary chronic osteomyelitis and 12 cases with secondary chronic osteomyelitis. J Stomatol Oral Maxillofac Surg 2017;118:342-8.
9. Koorbusch GF, Deatherage JR, Cure JK. How can we diagnose and treat osteomyelitis of the jaws as early as possible? Oral Maxillofac Surg Clin North Am 2011;23:557-67, vii.
10. Schuknecht BF, Carls FR, Valavanis A, Sailer H. Mandibular osteomyelitis: Evaluation and staging in 18 patients, using magnetic resonance imaging, computed tomography and conventional radiographs. Journal of Cranio-Maxillofacial Surgery 1997;25:24-33.
11. Schuknecht B, Valavanis A. Osteomyelitis of the mandible. Neuroimaging Clinics of North America 2003;13:605-+.
12. Theologie-Lygidakis N, Schoinohoriti O, Iatrou I. Surgical management of primary chronic osteomyelitis of the jaws in children: a prospective analysis of five cases and review of the literature. Oral Maxillofac Surg 2011;15:41-50.
13. Yoshiura K, Hijiya T, Ariji E, et al. Radiographic patterns of osteomyelitis in the mandible. Plain film/CT correlation. Oral Surg Oral Med Oral Pathol 1994;78:116-24.
14. Baltensperger M, Eyrich G. Osteomyelitis of the jaws. Berlin Heidelberg: Springer-Verlag; 2009.
15. Pinkhof H. Geneeskundig woordenboek. Houten/Diegem: Bohn Stafleu van Loghum; 1998.
16. Panders AK, Hadders HN. Chronic sclerosing inflammations of the jaw. Osteomyelitis sicca (Garre), chronic sclerosing osteomyelitis with fine-meshed trabecular structure, and very dense sclerosing osteomyelitis. Oral Surg Oral Med Oral Pathol 1970;30:396-412.
17. Hjorting-Hansen E. Decortication in treatment of osteomyelitis of the mandible. Oral Surg Oral Med Oral Pathol 1970;29:641-55.
18. Hudson JW. Osteomyelitis of the jaws: a 50-year perspective. J Oral Maxillofac Surg 1993;51:1294-301.
19. Grime PD, Bowerman JE, Weller PJ. Gentamicin impregnated

polymethylmethacrylate (PMMA) beads in the treatment of primary chronic osteomyelitis of the mandible. Br J Oral Maxillofac Surg 1990;28:367-74.
20. Suei Y, Taguchi A, Tanimoto K. Diagnosis and classification of mandibular osteomyelitis. Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontics 2005;100:207-14.
21. Termaat MF, Raijmakers PG, Scholten HJ, Bakker FC, Patka P, Haarman HJ. The accuracy of diagnostic imaging for the assessment of chronic osteomyelitis: a systematic review and meta-analysis. J Bone Joint Surg Am 2005;87:2464-71.
22. Stegenga B, Vissink A, de Bont LGM, Spijkervet FKL. Mondziekten, kaak- en aangezichtschirurgie. Assen: Van Gorcum; 2013.
23. Groot RH. Diffuse sclerosing osteomyelitis of the mandible: infection or traction? [Dissertation]. Helmond: University of Amsterdam; 1995.
24. Bevin CR, Inwards CY, Keller EE. Surgical management of primary chronic osteomyelitis: a long-term retrospective analysis. J Oral Maxillofac Surg 2008;66:2073-85.
25. Baart JA, van der Waal I. Mondziekten, kaak- en aangezichtschirurgie. Houten: Bohn Stafleu van Loghum; 2009.
26. Elbagoury EF, Fayed NA, Abd el Lattif ZA. Diffuse sclerosing osteomyelitis of maxilla and mandible: review of the literature and case report. Egypt Dent J 1988;34:297-308.
27. Jacobsson S. Diffuse sclerosing osteomyelitis of the mandible. Int J Oral Surg 1984;13:363-85.
28. Jacobsson S, Hollender L. Treatment and prognosis of diffuse sclerosing osteomyelitis (DSO) of the mandible. Oral Surg Oral Med Oral Pathol 1980;49:7-14.
29. Garcia-Marin F, Iriarte-Ortabe JI, Reychler H. Chronic diffuse sclerosing osteomyelitis of the mandible or mandibular location of S.A.P.H.O. syndrome. Acta Stomatol Belg 1996;93:65-71.
30. Armstrong DJ, Wright SA, Coward SM, Finch MB. Bone marker response in chronic diffuse sclerosing osteomyelitis treated with intravenous ibandronate. Ann Rheum Dis 2006;65:976-7.
31. Block MS, Zide MF, Kent JN. Excision of sclerosing osteomyelitis and reconstruction with particulate hydroxylapatite. J Oral Maxillofac Surg 1986;44:244-6.
32. Borzutzky A, Stern S, Reiff A, et al. Pediatric Chronic Nonbacterial Osteomyelitis. Pediatrics 2012;130:E1190-E7.
33. Creo Martínez T, Salazar Fernández C, Rosario Regalado R, Rollón Mayordomo A, Marín Lapeira Y. Tratamiento de la osteomielitis esclerosante difusa con roxitromicina a largo plazo: a propósito de un caso. Rev Esp Cir Oral y Maxilofac 2005;27:368-74.
34. Frid P, Tornes K, Nielsen O, Skaug N. Primary chronic osteomyelitis of the jaw-a microbial investigation using cultivation and DNA analysis: a pilot study. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology 2009;107:641-7.
35. Compeyrot-Lacassagne S, Rosenberg AM, Babyn P, Laxer RM. Pamidronate treatment of chronic noninfectious inflammatory lesions of the mandible in children. J Rheumatol 2007;34:1585-9.
36. Groot RH, Ongerboer de Visser BW, van Merkesteyn JP, Speelman JD, Bras J. Changes in masseter inhibitory reflex responses in patients with diffuse sclerosing osteomyelitis of the mandible. Oral Surg Oral Med Oral Pathol 1992;74:727-32.
37. Groot RH, van Merkesteyn JP, van Soest JJ, Bras J. Diffuse sclerosing osteomyelitis (chronic tendoperiostitis) of the mandible. An 11-year follow-up report. Oral Surg Oral Med Oral Pathol 1992;74:557-60.
38. Hallmer F, Korduner M, Moystad A, Bjornland T. Treatment of diffuse sclerosing osteomyelitis of the jaw with denosumab

shows remarkable results-A report of two cases. Clin Case Rep 2018;6:2434-7.
39. Heggie AA, Shand JM, Aldred MJ, Talacko AA. Juvenile mandibular chronic osteomyelitis: a distinct clinical entity. Int J Oral Maxillofac Surg 2003;32:459-68.
40. Hino S, Murase R, Terakado N, Shintani S, Hamakawa H. Response of diffuse sclerosing osteomyelitis of the mandible to alendronate: follow-up study by 99mTc scintigraphy. Int J Oral Maxillofac Surg 2005;34:576-8.
41. Idahosa CN, Boggess WJ, Levin LM, Alawi F. Unilateral enlargement of the mandible in a child. Oral Surg Oral Med Oral Pathol Oral Radiol 2015;120:424-8.
42. Jacobsson S, Dahlen G, Moller AJ. Bacteriologic and serologic investigation in diffuse sclerosing osteomyelitis (DSO) of the mandible. Oral Surg Oral Med Oral Pathol 1982;54:506-12.
43. Jones J, Amess TR, Robinson PD. Treatment of chronic sclerosing osteomyelitis of the mandible with calcitonin: a report of two cases. Br J Oral Maxillofac Surg 2005;43:173-6.
44. Kadom N, Egloff A, Obeid G, Bandarkar A, Vezina G. Juvenile mandibular chronic osteomyelitis: multimodality imaging findings. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;111:e38-43.
45. Kahn MF, Hayem F, Hayem G, Grossin M. Is diffuse sclerosing osteomyelitis of the mandible part of the synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome? Analysis of seven cases. Oral Surg Oral Med Oral Pathol 1994;78:594-8.
46. Kuijpers SC, de JE, Hamdy NA, van Merkesteyn JP. Initial results of the treatment of diffuse sclerosing osteomyelitis of the mandible with bisphosphonates. J Craniomaxillofac Surg 2011;39:65-8.
47. Mari A, Morla A, Melero M, Schiavone R, Rodriguez J. Diffuse sclerosing osteomyelitis (DSO) of the mandible in SAPHO syndrome: a novel approach with anti-TNF therapy. Systematic review. J Craniomaxillofac Surg 2014;42:1990-6.
48. Marx RE, Carlson ER, Smith BR, Toraya N. Isolation of Actinomyces species and Eikenella corrodens from patients with chronic diffuse sclerosing osteomyelitis. J Oral Maxillofac Surg 1994;52:26-33; discussion -4.
49. Montonen M, Iizuka T, Hallikainen D, Lindqvist C. Decortication in the treatment of diffuse sclerosing osteomyelitis of the mandible. Retrospective analysis of 41 cases between 1969 and 1990. Oral Surg Oral Med Oral Pathol 1993;75:5-11.
50. Montonen M, Lindqvist C. Diagnosis and treatment of diffuse sclerosing osteomyelitis of the jaws. Oral Maxillofac Surg Clin North Am 2003;15:69-78.
51. Montonen M, Kalso E, Pylkkaren L, Lindstrorm BM, Lindqvist C. Disodium clodronate in the treatment of diffuse sclerosing osteomyelitis (DSO) of the mandible. Int J Oral Maxillofac Surg 2001;30:313-7.
52. Obel G, Krogdahl A, Thygesen T, Godballe C. Juvenile mandibular chronic osteomyelitis: 3 cases and a literature review. J Oral Maxillofac Surg 2013;71:305-9.
53. Orpe EC, Lee L, Pharoah MJ. A radiological analysis of chronic sclerosing osteomyelitis of the mandible. Dentomaxillofac Radiol 1996;25:125-9.
54. Otto S, Burian E, Troeltzsch M, Kaeppler G, Ehrenfeld M. Denosumab as a potential treatment alternative for patients suffering from diffuse sclerosing osteomyelitis of the mandible-A rapid communication. J Craniomaxillofac Surg 2018;46:534-7.
55. Otto S, Troeltzsch M, Burian E, et al. Ibandronate treatment of diffuse sclerosing osteomyelitis of the mandible: Pain relief and insight into pathogenesis. J Craniomaxillofac Surg 2015;43:1837-42.
56. Padwa BL, Dentino K, Robson CD, Woo SB, Kurek K, Resnick CM. Pediatric Chronic Nonbacterial Osteomyelitis of the Jaw: Clinical, Radiographic, and Histopathologic Features. J Oral Maxillofac Surg 2016;74:2393-402.

57. Patel R, Jacob R, Lee K, Booth TN. Parotid swelling and chronic recurrent multifocal osteomyelitis of mandible in children. International Journal of Pediatric Otorhinolaryngology 2015;79:47-52.
58. Penna KJ, Sadoff RS, Dfex JC. Diffuse sclerosing osteomyelitis. A case report. N Y State Dent J 2004;70:36-9.
59. Renapurkar S, Pasternack MS, Nielsen GP, Kaban LB. Juvenile Mandibular Chronic Osteomyelitis: Role of Surgical Debridement and Antibiotics. J Oral Maxillofac Surg 2016;74:1368-82.
60. Shuren SL. The use of implant therapy in diffuse sclerosing osteomyelitis. J Oral Implantol 1994;20:60-2.
61. Singh S, Graham ME, Bullock M, et al. Chronic Sclerosing Osteomyelitis of the Mandible Treated with Hemimandibulectomy and Fibular Free Flap Reconstruction. Plast Reconstr Surg Glob Open 2015;3:e580.
62. Soubrier M, Dubost JJ, Ristori JM, Sauvezie B, Bussiere JL. Pamidronate in the treatment of diffuse sclerosing osteomyelitis of the mandible. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;92:637-40.
63. Suei Y, Tanimoto K, Taguchi A, et al. Possible identity of diffuse sclerosing osteomyelitis and chronic recurrent multifocal osteomyelitis. One entity or two. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1995;80:401-8.
64. Suei Y, Taguchi A, Tanimoto K. Radiographic evaluation of possible etiology of diffuse sclerosing osteomyelitis of the mandible. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997;84:571-7.
65. Urade M, Noguchi K, Takaoka K, Moridera K, Kishimoto H. Diffuse sclerosing osteomyelitis of the mandible successfully treated with pamidronate: a long-term follow-up report. Oral Surg Oral Med Oral Pathol Oral Radiol 2012;114:e9-12.
66. van Merkesteyn JP, Groot RH, Bras J, McCarroll RS, Bakker DJ. Diffuse sclerosing osteomyelitis of the mandible: a new concept of its etiology. Oral Surg Oral Med Oral Pathol 1990;70:414-9.
67. van Merkesteyn JP, Groot RH, Bras J, Bakker DJ. Diffuse sclerosing osteomyelitis of the mandible: clinical radiographic and histologic findings in twenty-seven patients. J Oral Maxillofac Surg 1988;46:825-9.
68. Yamazaki Y, Satoh C, Ishikawa M, Notani K, Nomura K, Kitagawa Y. Remarkable response of juvenile diffuse sclerosing osteomyelitis of mandible to pamidronate. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;104:67-71.
69. Yoshii T, Nishimura H, Yoshikawa T, et al. Therapeutic possibilities of long-term roxithromycin treatment for chronic diffuse sclerosing osteomyelitis of the mandible. J Antimicrob Chemother 2001;47:631-7.
70. Van Merkesteyn JP, Bakker DJ, Van der Waal I, et al. Hyperbaric oxygen treatment of chronic osteomyelitis of the jaws. Int J Oral Surg 1984;13:386-95.
71. Costa DA, Costa TP, Netto EC, et al. New perspectives on the conservative management of osteoradionecrosis of the mandible: A literature review. Head Neck 2016;38:1708-16.
72. Bachmann G, Rossler R, Klett R, Rau WS, Bauer R. The role of magnetic resonance imaging and scintigraphy in the diagnosis of pathologic changes of the mandible after radiation therapy. Int J Oral Maxillofac Surg 1996;25:189-95.
73. Hermans R, Fossion E, Ioannides C, Van den Bogaert W, Ghekiere J, Baert AL. CT findings in osteoradionecrosis of the mandible. Skeletal Radiol 1996;25:31-6.
74. Store G, Larheim TA. Mandibular osteoradionecrosis: a comparison of computed tomography with panoramic radiography. Dentomaxillofac Radiol 1999;28:295-300.
75. Store G, Smith HJ, Larheim TA. Dynamic MR imaging of mandibular osteoradionecrosis. Acta Radiol 2000;41:31-7.
76. Store G, Boysen M. Mandibular osteoradionecrosis: clinical behaviour and diagnostic aspects. Clin Otolaryngol Allied Sci 2000;25:378-84.

77. Hermans R. Imaging of mandibular osteoradionecrosis. Neuroimaging Clin N Am 2003;13:597-604.
78. Chong J, Hinckley LK, Ginsberg LE. Masticator space abnormalities associated with mandibular osteoradionecrosis: MR and CT findings in five patients. AJNR Am J Neuroradiol 2000;21:175-8.
79. Gevorgyan A, Wong K, Poon I, Blanas N, Enepekides DJ, Higgins KM. Osteoradionecrosis of the mandible: a case series at a single institution. J Otolaryngol Head Neck Surg 2013;42:46.
80. Jacobsson S. Diffuse sclerosing ostemyelitis of the mandible. Acta Otolaryngol Suppl 1979;360:61-3.
81. Ogawa A, Miyate H, Nakamura Y, Shimada M, Seki S, Kudo K. Treating chronic diffuse sclerosing osteomyelitis of the mandible with saucerization and autogenous bone grafting. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;91:390-4.
82. Malmstrom M, Fyhrquist F, Kosunen TU, Tasanen A. Immunological features of patients with chronic sclerosing osteomyelitis of the mandible. Int J Oral Surg 1983;12:6-13.
83. Montonen M, Li TF, Lukinmaa PL, et al. RANKL and cathepsin K in diffuse sclerosing osteomyelitis of the mandible. J Oral Pathol Med 2006;35:620-5.
84. Eyrich GK, Harder C, Sailer HF, Langenegger T, Bruder E, Michel BA. Primary chronic osteomyelitis associated with synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO syndrome). J Oral Pathol Med 1999;28:456-64.
85. Jurik AG, Moller BN. Chronic sclerosing osteomyelitis of the clavicle. A manifestation of chronic recurrent multifocal osteomyelitis. Arch Orthop Trauma Surg (1978) 1987;106:144-51.
86. Azouz EM, Jurik AG, Bernard C. Sternocostoclavicular hyperostosis in children: a report of eight cases. AJR Am J Roentgenol 1998;171:461-6.
87. Cianci F, Zoli A, Gremese E, Ferraccioli G. Clinical heterogeneity of SAPHO syndrome: challenging diagnose and treatment. Clin Rheumatol 2017;36:2151-8.
88. Otsuka K, Hamakawa H, Kayahara H, Tanioka H. Chronic recurrent multifocal osteomyelitis involving the mandible in a 4-year-old girl: a case report and a review of the literature. J Oral Maxillofac Surg 1999;57:1013-6.
89. Rustemeyer J, Siegmund BJ, Okcu Y, Busch A. Total mandibular reconstruction following diffuse sclerosing osteomyelitis. Oral Maxillofac Surg 2019;23:95-9.
90. Suei Y, Tanimoto K, Miyauchi M, Ishikawa T. Partial resection of the mandible for the treatment of diffuse sclerosing osteomyelitis: report of four cases. J Oral Maxillofac Surg 1997;55:410-4.
91. Suei Y, Tanimoto K, Taguchi A, Wada T, Ishikawa T. Chronic recurrent multifocal osteomyelitis involving the mandible. Oral Surg Oral Med Oral Pathol 1994;78:156-62.
92. Hofmann SR, Kapplusch F, Girschick HJ, et al. Chronic Recurrent Multifocal Osteomyelitis (CRMO): Presentation, Pathogenesis, and Treatment. Curr Osteoporos Rep 2017;15:542-54.
93. Taddio A, Zennaro F, Pastore S, Cimaz R. An Update on the Pathogenesis and Treatment of Chronic Recurrent Multifocal Osteomyelitis in Children. Paediatr Drugs 2017;19:165-72.
94. Yachoui R, Kreidy M, Parker BJ. Treatment-Refractory Sternocostoclavicular Hyperostosis. Clin Med Res 2017;15:37-40.
95. Aljuhani F, Tournadre A, Tatar Z, et al. The SAPHO syndrome: a single-center study of 41 adult patients. J Rheumatol 2015;42:329-34.
96. Lentrodt S, Lentrodt J, Kubler N, Modder U. Hyperbaric oxygen for adjuvant therapy for chronically recurrent mandibular osteomyelitis in childhood and adolescence. Journal of Oral and Maxillofacial Surgery 2007;65:186-91.