



Medical treatment of chronic non-infectious osteomyelitis in the jaws

A systematic review

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ABSTRACT

Aim: To systematically review the literature of medical treatment alternatives of non-infectious chronic osteomyelitis in the jaws regarding bone healing and pain relief.

Methods: A systematic literature search has been made in four databases; PubMed, Cochrane Library, Web of Science and Scopus. The review was performed with directions from the PRISMA checklist and CRD's guidance. A quality assessment was made of the included studies.

Results: The search resulted in 2 100 articles and after the selection process, only three articles were included in this review. The studies evaluated different types of bisphosphonates - ibandronate, pamidronate and disodium clodronate. The reduction of pain was evaluated in all three articles and the bone healing was assessed in two of the articles.

Conclusion: Treatment of non-infectious osteomyelitis with bisphosphonates shows a reduction in pain. However, the pain-relieving effect is most probably dependent on the type of bisphosphonates. The results of bone healing assessed from Tc-scans are ambiguous and therefore no conclusion can be made. Only one article in this review was considered to have high quality in the quality assessment. To enable clear guidelines regarding treatment of non-infectious osteomyelitis, more clinical trials with high quality is desirable. In summary, bisphosphonates seem to be a good alternative in treatment of non-infectious osteomyelitis. An alternative to bisphosphonates might be treatment with denosumab, which have a similar mechanism of action but shorter half-life. However, further research is needed.

SAMMANFATTNING

Syfte: Att systematiskt sammanfatta litteraturen inom området för medicinska behandlingsalternativ för icke-infektiös, kronisk osteomyelit i käkarna, utvärderat genom utläkning i ben och smärtlindring.

Metod: En systematisk litteraturoversikt gjordes i fyra databaser; PubMed, Cochrane Library, Web of Science och Scopus. Översikten utfördes enligt instruktioner från ”PRISMA checklist” och ”CRD’s guidance”. En kvalitetsbedömning gjordes av samtliga inkluderade publikationer.

Resultat: Sökningen resulterade i 2 100 artiklar. Efter urvalsprocessen återstod tre artiklar som inkluderades i denna systematiska litteraturoversikt. Samtliga studier utvärderade olika typer av bisfosfonatbehandlingar – ibandronat, pamidronat och disodium clodronat. Den smärtlindrande effekten utvärderades i alla tre studierna och utläkningen av benet utvärderades i två av artiklarna.

Konklusion: Behandling av icke-infektiös osteomyelit med bisfosfonater visar en reduktion av smärta. Dock är den smärtlindrande effekten beroende på typen av bisfosfonat. Resultaten gällande utläkningen av ben är tvetydiga och därför kan ingen konklusion gällande detta göras. Endast en artikel ansågs i kvalitetsgranskningen ha hög kvalitet. För att kunna ta fram tydliga, evidensbaserade riktlinjer gällande behandling av icke-infektiös osteomyelit behövs fler kliniska studier som håller hög kvalitet. Bisfosfonater verkar vara ett bra behandlingsalternativ av icke-infektiös osteomyelit. Ett alternativ till bisfosfonater, skulle kunna vara behandling med denosumab, som har liknande verkningsmekanism men kortare halveringstid. Dock krävs fortsatta studier inom detta område.

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INTRODUCTION

Background

Bone structure

Bone tissue consists of cortical and cancellous bone and differs in composition and structure depending on the demands of function (1). Cortical bone tissue is found under the periosteum and is the densest part of the bone. It is composed of osteons, which are concentric structures arranged around a central canal, called Haversian canal, that contain nerves, blood- and lymphatic vessels (1,2). The cancellous bone, also referred to as spongy or trabecular bone, is always located in the inner part of the bone and is covered by cortical bone (1). Instead of osteons, the cancellous bone tissue has interconnecting rods arranged in thin structures called trabeculae (1,2). Between the trabeculae there are spaces filled with bone marrow that contains various blood vessels that is providing nutrition to the osteocytes (1).

Bone remodeling

Wolff formulated a law of bone remodeling: “Every change in the form and the function of a bone or of their function alone is followed by certain definite changes in their internal architecture, and equally definite secondary alterations in their external confirmation, in accordance with mathematic laws” (3). After bone is formed, it is continuously renewed by remodeling of the bone. The process includes breakdown and resorption of minerals and collagen fibers by osteoclasts and deposition of new minerals and collagen fibers by osteoblasts (1,4). The renewal rate every year is around 4 % in the cortical bone and around 20 % in the cancellous bone. The remodeling rate differs in different bones in the body (1).

The remodeling cycle starts with recruitment of osteoclast precursor cells, i.e. monocytes. The osteoclast becomes activated and multinuclear in the presence of osteoblasts. Certain hormones and cytokines are stimulating the osteoblast to express a type II transmembrane protein, Receptor Activator of Nuclear factor Kappa B-Ligand (RANKL) on the surface (4,5). Interaction between RANKL and a receptor on the pre-osteoclast, Receptor Activator of Nuclear factor Kappa B (RANK), are causing differentiation and activation of the cells into mature osteoclasts (5).

In response to anabolic agents such as bone morphogenetic proteins (BMPs) and transforming growth factor- β (TGF), the osteoblasts secrete various amount of osteoprotegerin (OPG). OPG acts as a decoy receptor since it binds to RANKL and prevents the ligand from binding to RANK. The expression of RANKL and OPG affect the degree of activated osteoclasts and is therefore balanced to control the amount of bone resorption (4).

Several of the mature osteoclasts are fusing together to form a huge multinuclear, bone-resorbing cell that adheres to the bone surface (5). The multinucleated osteoclasts undergo internal changes such as formation of tight junctions between basal membranes and the bone surface as well as rearrangement of the actin cytoskeleton (4). The cell also develops a ruffle border on the area attached to the bone, which enables secretion of hydrogen ions and enzymes. This leads to breakdown of minerals and proteins of the underlying bone matrix and the process is termed resorption. Embedded cytokines such as insulin-like growth factor (IGF-1) and TGF- β are gradually released from the bone during the resorption. The release of these cytokines leads to recruitment and activation of osteoblasts and is therefore also initiating new bone formation. The osteoblasts invade the area and secrete new organic bone matrix as well as IGF-1 and TGF- β . The cytokines and some of the osteoblasts are getting embedded in the

osteoid. The non-embedded osteoblasts are activating new osteoclast precursor cells and the remodeling cycle starts over again (5). The bone remodeling process is illustrated in *Figure 1*.

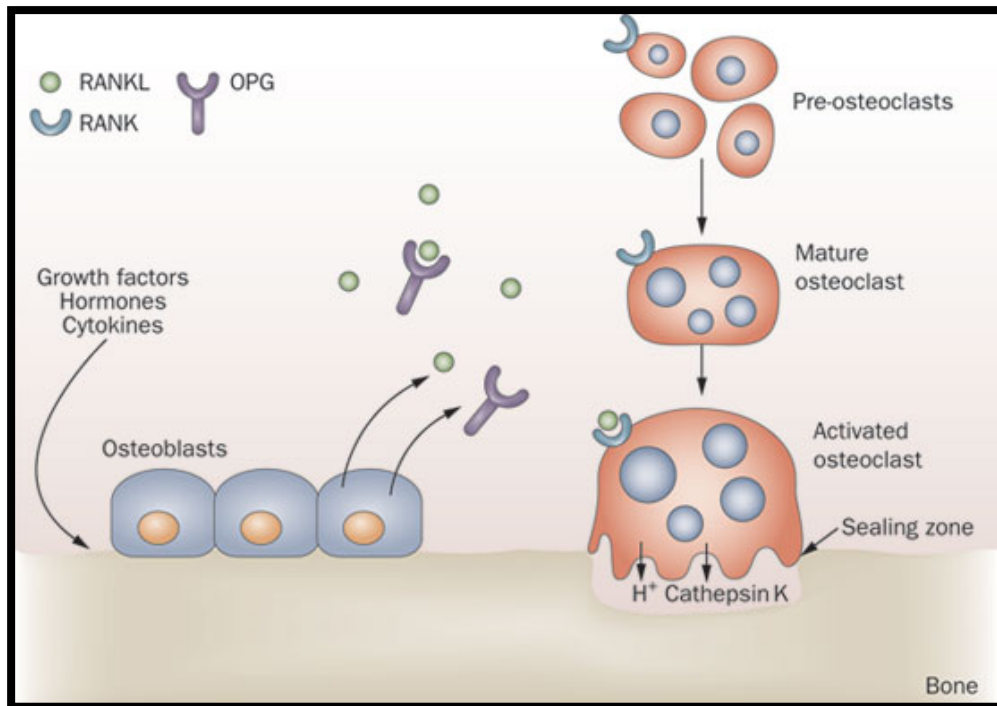


Fig. 1. The process of bone remodeling (6).

Osteomyelitis

Osteomyelitis is an inflammation in the bone marrow that may also include other soft tissues of the bone such as the periosteum and the Haversian system of the cortical bone (7-9). The most common localisation of osteomyelitis is in the long skeletal bones, but the vertebral bodies and the discs are also commonly affected. The incidence of osteomyelitis in children is estimated to be 13 per 100 000 individuals/year (10). In adults the incidence was suggested to be 21,8 per 100 000 individuals/year (11). The infection causing the inflammation is mostly carried haematogenous and can be a result of surgery or by trauma (12).

Predisposing factors

Reduced immunologic defence is a common factor contributing to the development and progression of osteomyelitis. Both medication and diseases that act immunosuppressive might cause a reduced immunologic defence (7,9). Diseases associated with osteomyelitis are for example leukaemia, human immunodeficiency virus infection (HIV), diabetes, autoimmune diseases and malnutrition (7). Radiation therapy reduces the blood supply in local areas and is therefore also a predisposing factor for developing an infection in the bone (9). Trauma to the bone might also lead to chronic osteomyelitis, because of the risk of infection (7).

Pathogenesis

Entry of bacteria into the bone results in an inflammatory response. Most often, this is a normal part of the healing process. Although occasionally, especially in patients that exhibit a predisposing factor, this process is not interrupted and becomes pathological. When inflammation occurs, there is an increase in blood flow, which leads to an increase of leukocytes in the local area. When the immunologic defence is not able to eliminate all of the debris created by the bacteria, pus is formed. The pus and inflammatory exudate will

accumulate in the bone marrow and thereby increase the pressure on the local vessels leading to less blood supply in the area (9). When the blood supply is reduced, host immunologic defence is not capable of preventing the progression of the infection. This leads to proliferation of bacteria and the inflammatory response can spread into the surrounding bone tissue and cause necrosis (8). Infectious osteomyelitis is the most common form of the disease and is always of multi-microbial aetiology, i.e. it is numerous of different bacteria causing the infection (9).

Osteomyelitis of the jaw

The prevalence of osteomyelitis differs between the mandible and the maxilla, with a higher prevalence in the mandible. This might be due to the high density and quantity of the cortical bone in the mandible, which reduces penetration of periosteal blood vessels. In combination with a reduced and less oxygenated blood flow to the mandible, this makes the mandible more sensitive for infections (7-9). Before the introduction of antibiotics, the prevalence of the disease was much higher than today, but the infection can still lead to severe morbidity with loss of function and aesthetics (8,9). In adults the osteomyelitis is often caused primarily of bacteria colonizing the jawbone due to odontogenic infections, for example, after extraction or endodontic treatment (7-9). If the condition is caused by an odontogenic infection, the involved teeth may be tender to pressure and often becomes mobile (7,8). Sometimes the inferior alveolar nerve is affected by the inflammation, which can lead to paraesthesia in the lower lip (7-9). Radiographs are used to detect pathological changes in the bone. When it comes to detecting osteomyelitis in the jaw, computerized tomography (CT) scans is mostly used since it provides a three-dimensional image (8,9,13). Magnetic Resonance Imaging (MRI) can detect osteomyelitis in the early stage, when the bone marrow is replaced by leukocytes and inflammatory exudate (8). Additionally, scintigraphy seems to be important in the diagnosis and assessment of disease activity in osteomyelitis (14). This is due to the effect of the radionuclide examination, which visualises bone remodeling. The method is also termed Tc-scan (15).

Classification

There is no uniform terminology of classifying osteomyelitis. A common and often used classification is to divide the disease into two subgroups; acute and chronic osteomyelitis (13). What classification the osteomyelitis is categorized as, depends on symptoms and clinical findings (7,9). In the acute phase, the osteomyelitis often is suppurative and occurs short after a predisposing event (5,9). An abrupt onset of systemic symptoms such as fever and intense pain is characterizing for the acute phase (8). Acute osteomyelitis, left untreated may progress and become chronic (7,8). Chronic osteomyelitis is a persistent and relapsing infectious condition that can take months to years to develop. Characteristics of the chronic inflammation are sequestrum and fistula formation (16). The patient normally has no fever in the chronic phase, although symptoms such as pain, swelling and loosening of teeth often occurs in the infected area (8). In chronic osteomyelitis, it is possible to detect a change of the trabecular structure on radiographs since necrotic parts tend to appear more radiolucent and irregular, due to a reduced density (7). Often, it also stimulates apposition of new periosteal bone. This can be seen as radiopaque lines parallel to the surface of the cortical bone in the images, see *Figure 2* (13).



Fig. 2. Radiographs demonstrating periosteal bone apposition (13).

Non-infectious osteomyelitis:

Non-infectious osteomyelitis is a chronic osteomyelitis with unknown aetiology (17). This means, when probing for microbiological cultures, there are usually no bacteria found (18). In cases where bacteria are detected, it has not been possible to exclude contamination, which might support the theory that this form of osteomyelitis has a non-infectious aetiology (18,19). There is no uniform term to classify this condition and therefore many diagnoses have been used. One commonly used term is diffuse sclerosing osteomyelitis (DSO) (17). It is a chronic, non-suppurative, inflammatory response, common in all ages and the symptoms, which includes pain and swelling persists for several years. On radiographs, the condition appears to be both radiolucent and radiopaque. The radiopaque areas are sclerotized bone, which is a characterization for DSO (7,8). In DSO, the balance of bone remodeling has shifted toward an increase in bone formation, which leads to a sclerotic bone pattern on radiographs (13). Another term that is used as a synonym for DSO is primary chronic osteomyelitis (17). Primary chronic osteomyelitis describes the clinical characteristics of the disease, while the term DSO is taking the radiological findings into account (20). Several authors have also reported similarities between primary chronic osteomyelitis and chronic recurrent multifocal osteomyelitis, which suggests that this is another term describing the same condition (21,22). In this study the term non-infectious osteomyelitis will be used.

Treatment of osteomyelitis in the jaws

Chronic infectious osteomyelitis is generally first treated with antibiotic therapy, administered intravenously in high doses for several weeks after culture testing. The choice of type, dose and duration of the antibiotic therapy varies in each case (8). The antibiotic treatment is followed by surgical therapy including drainage and debridement. If necessary, decortication of the affected jaw is performed (7). Surgery is a traditional way of treating osteomyelitis and with the aim to remove the infected bone, to improve healing and increase the blood supply to the area (8,9). The teeth adjacent to the infected area are quite often extracted. Removal of teeth and bone structures makes the jaw weaker and leads to an increased risk of fractures (9).

Hyperbaric oxygen treatment increases the amount of oxygenation in the tissue and thereby eliminates the anaerobic bacteria causing the infection (8,9). The patient breathes one hundred percent of oxygen at a higher pressure than the atmosphere, which leads to a higher amount of oxygen in the blood (8).

Treatment of non-infectious osteomyelitis

In non-infectious osteomyelitis, the previous mentioned treatment alternatives are insufficient and do not achieve a reduction in pain and swelling in the long term. It does not exist any well-defined guidelines for treatment of non-infectious osteomyelitis, which makes the treatment challenging (23,24). The treatment often consists of reducing the symptoms with non-steroidal anti-inflammatory drugs (NSAID), bisphosphonates or corticosteroids (8,25).

NSAID is an anti-inflammatory, analgesic and antipyretic drug and all therapeutic actions depend on inhibition of cyclo-oxygenase-2 (COX-2), which leads to less amount of prostaglandin in the tissues (5). NSAIDs have in combination with other treatments showed an additional therapeutic effect and can effectively be used both to prevent and during attacks in patients with chronic recurrent multifocal osteomyelitis in the jaws (17,26).

Corticosteroids are anti-inflammatory and immunosuppressive drugs (5). In previous studies, treatment with corticosteroids has shown to be effective in decreasing and mitigate the symptoms in patients with DSO (27,28). Since corticosteroids have several undesirable side effects such as; suppression of the immunologic response, Cushing's syndrome, osteoporosis and hyperglycaemia, it should only be used in a limited amount of time and dosage (5,29).

Bisphosphonates are commonly used for treating osteoporosis, skeletal metastasis, multiple myeloma and hypercalcemia (30). The mechanism of action is based on bisphosphonates high affinity for hydroxyapatite crystals of the bone (30,31). Exactly how it affects the osteoclasts is still unknown (32). One possible mechanism of action is that bisphosphonates bind to the hydroxyapatite crystals and is thereby absorbed by the osteoclasts during bone remodeling. In the osteoclast, the molecule is interfering with its metabolism and causes apoptosis and consequently a reduction of resorption (31). Another theory is that bisphosphonates anchor to proteins on osteoclasts' cell surface. These proteins are necessary for the attachment to the bone surface and therefore also prevent bone resorption (5). Around 50% of the given dose is absorbed in the skeleton and the time remaining in the bone tissue depends on host factors, dose and the bisphosphonate's affinity for bone matrix etc. (30). Bisphosphonates have a half-life of approximately eleven years or longer in bone, due to an irreversible binding to the hydroxyapatite crystals (33,34). If patients are treated with high doses during a long period of time, it may lead to osteonecrosis. This is due to the reduced turnover of the bone, as a result of both diminished blood supply and reduced osteoclast activity. Osteonecrosis related to bisphosphonate-treatment are supposed to be triggered by bone invasive treatments and infection (7,8). The possible pathomechanisms are characterized by osteolysis and new bone formation in a randomized manner. This might be explained by the crucial role of osteoclasts and/or the balance between osteoclasts and osteoblasts with an imbalance of osteolysis and osteogenesis. In this respect, the RANK/RANKL/OPG system, which is essential for the communication between osteoclasts and osteoblasts, might play a key role in the progression of non-infectious osteomyelitis. Bisphosphonates act mainly on osteoclasts, but also have effects on osteoblasts. It is hypothesized that this might be of an important role in the disease process itself or in the development of concomitant pain (35).

Non-infectious osteomyelitis of the jaw is a challenging and painful disease that can induce severe morbidity. Today there are several different surgical and medical treatment alternatives, such as decortication and medical therapy with antibiotics, cortisone and bisphosphonates. Surgery is an invasive treatment method and is therefore the last choice of treatment for non-infectious osteomyelitis in the jaws. During the last two decades, several studies have been published regarding treatment with bisphosphonates of DSO. Most of these studies are case reports and smaller case series, but all of them show promising results (25,36-

38). To the best of our knowledge there is no systematic literature review made to evaluate medical treatment of non-infectious chronic osteomyelitis in the jaws. This leads to the purpose and problem statement of this review.

Purpose

The aim of this study was to systematically review the literature of medical treatment alternatives of non-infectious chronic osteomyelitis in the jaws regarding bone healing and pain relief.

Problem statement

What drug therapeutic alternatives for non-infectious chronic osteomyelitis in the jaws are available today? What is the result for each treatment method in terms of bone healing and pain relief?

MATERIAL & METHODS

This systematic literature review is performed with directions from the “PRISMA checklist” (39) and “systematic reviews – CRD’s guidance for undertaking reviews in health care” (40), consisting of the following steps: problem specification, formulation of inclusion and exclusion criteria, literature search, publication retrieval, data extraction, quality assessment and data synthesis.

Problem Specification

What drug therapeutic alternatives for non-infectious chronic osteomyelitis in the jaws are available today? What is the result for each treatment method in the terms of bone healing and pain relief?

To form a clear and distinct problem statement the PICOS-method was used. PICOS stands for Participant, Interventions, Comparisons, Outcome and Study design. It is a way to clarify important components of the problem statement (39). Following parts, seen in *Table 1*, were of interest when forming the problem statement of this review.

Table 1. PICOS

PICOS	
<i>Participants</i>	Humans with chronic, non-infectious osteomyelitis in the jaws
<i>Intervention</i>	Medical treatment of chronic non-infectious osteomyelitis in the jaws
<i>Comparison</i>	Not applicable
<i>Outcome</i>	Subjective pain relieving effect and/or bone healing detected on radiographs (intraoral, panoramic, CBCT/CT, MRI or scintigraphy)
<i>Study design</i>	<ul style="list-style-type: none"> - RCT - Retrospective observational studies - Prospective observational studies - Systematic reviews according to CRD’s guidance

In this context, formal definitions for the following elements were sought prior to the literature search:

- “Chronic disease” – a condition that requires a long period of supervision and care or leaves residual disability (MeSH term),
- “Osteomyelitis” – an inflammation of the bone as a result of infection (MeSH term),
- “Drug therapy” – use of drugs to treat a disease or its symptoms (MeSH term),
- “Pain relief” – the alleviation of pain (41).

Formulation of inclusion and exclusion criteria

PICOS elements of the review question were then refined in order to determine inclusion and exclusion criteria, which are shown in *Table 2*.

Table 2. Inclusion and exclusion criteria

	Inclusion	Exclusion
Population	<ul style="list-style-type: none"> • Humans with non-infectious chronic osteomyelitis (DSO, primary osteomyelitis (PCO) and RMCO) in the jaws 	<ul style="list-style-type: none"> • Animal studies • Garré’s osteomyelitis • Osteomyelitis caused by radiation or bisphosphonate treatment • Osteomyelitis treated with surgery alone or in combination with the

		evaluated drug <ul style="list-style-type: none"> • Osteomyelitis treated with combinations of more than one drug except NSAID • Osteomyelitis caused by lifestyle (alcohol abuse, drug abuse) • Patients treated with Hyperbar Oxygen therapy alone or in combination with the evaluated drug • Patients with syndromes or immunosuppressive diseases • A history of malignant disease with metastasis to the jaws
Study design	<ul style="list-style-type: none"> • Original articles • Literature reviews according to CRD's guidance with similar problem specification 	<ul style="list-style-type: none"> • Case reports • Case series <5 cases • Book chapters • Letters • Reviews
Intervention	<ul style="list-style-type: none"> • Drug therapy 	
Outcome	<ul style="list-style-type: none"> • Pain relieving effect subjectively • Bone healing seen on radiographs; intraoral, panoramic, CBCT/CT, MRI or scintigraphy 	
Language	<ul style="list-style-type: none"> • Articles in English or Swedish • Articles with an abstract in English 	<ul style="list-style-type: none"> • Articles without available abstracts in the respective databases

Literature search

A literature search was made in four different databases. PubMed was used as the primary database and Scopus, Cochrane Library and Web of Science were used additionally. In PubMed and Cochrane Library both MESH-terms and free search terms were used. They were combined in different search-blocks summarized in *Table 3*. In Web of Science and Scopus, only free search terms corresponding to MeSH-terms were used since these databases don't cooperate with MeSH-terms.

The search strategy in PubMed is summarized in *Table 4* and the same search strategy was used in Cochrane Library. The strategy used in Web of Science and Scopus is summarized in *Table 5*.

Table 3. Terms and blocks. PubMed and Cochrane Library 2017-03-20

Disease	Site of infection	Treatment
Osteomyelitis (MESH)	Jaw (MeSH)	Treatment*
Osteomyelitides	Jaw*	Treatment outcome (MeSH)
Osteomyelitis	Mandible (MeSH)	Therapy*
	Maxilla (MeSH)	Therapeutics (MeSH)
	Maxilla*	Drug Therapy (MeSH)
	Mandib*	Therapeutic*
	Jaw diseases (MeSH)	Cortisone (MeSH)
		Cortisone*
		Corticosteroid*
		Antibiotic*
		Antibacterial agent*
		Antibacterial agents (MeSH)

Table 4. Searching strategy in PubMed 2017-03-20

Search	Query	Items found
#26	Search: #23 AND #24 AND #25	1345
#25	Search: Treatment* OR Treatment outcome (MeSH Terms) OR Therapy* OR Therapeutics (MeSH Terms) OR Therapeutic* OR Drug Therapy (MeSH Terms) OR Cortisone (MeSH Terms) OR Cortisone* OR Corticosteroid* OR Antibiotic* OR Antibacterial agent* OR Antibacterial agents (MeSH Terms)	8 737 286
#24	Search: Jaw (MeSH Terms) OR Jaw* OR Mandible (MeSH Terms) OR Maxilla (MeSH Terms) OR Maxilla* OR Mandib* OR Jaw diseases (MeSH Terms)	256 352
#23	Search: Osteomyelitis (MeSH Terms) OR Osteomyelitides OR Osteomyelitis	27 492
#22	Search: Antibacterial agents (MeSH Terms)	316 380
#21	Search: Antibacterial agent*	6 770
#20	Search: Antibiotic*	313 339
#19	Search: Corticosteroid*	88 131
#18	Search: Cortisone*	22 914
#17	Search: Cortisone (MeSH Terms)	19 430
#16	Search: Drug Therapy (MeSH Terms)	1 179 385
#15	Search: Therapeutic*	2 705 706
#14	Search: Therapeutics (MeSH Terms)	3 778 329
#13	Search: Therapy*	4 397 509
#12	Search: Treatment outcome (MeSH Terms)	795 530
#11	Search: Treatment*	4 109 646
#10	Search: Jaw diseases (MeSH Terms)	90 350
#9	Search: Mandib*	103 103
#8	Search: Maxilla*	77 395
#7	Search: Maxilla (MeSH Terms)	26 601
#6	Search: Mandible (MeSH Terms)	50 333
#5	Search: Jaw*	71 284
#4	Search: Jaw (MeSH Terms)	95 441
#3	Search: Osteomyelitis	27 490
#2	Search: Osteomyelitides	27 492
#1	Search: Osteomyelitis (MeSH Terms)	20 956

Table 5. Searching strategy in Web of Science 2017-03-20. The same search was made in Scopus.

Search	Query	Items found
#16	Search: #15 AND #14 AND #13	544
#15	Search: #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6	5 273 252
#14	Search: #5 OR #4 OR #3	119 900
#13	Search: #2 OR #1	18 157
#12	Search: Antibacterial agent*	25 355
#11	Search: Antibiotic*	267 706
#10	Search: Corticosteroid*	83 694
#9	Search: Cortisone*	10 161
#8	Search: Therapeutic*	724 101
#7	Search: Therapy*	1 681 689
#6	Search: Treatment*	3 763 398
#5	Search: Mandib*	63 153

#4	Search: Maxilla*	43 838
#3	Search: Jaw*	33 605
#2	Search: Osteomyelitides	7
#1	Search: Osteomyelitis	18 152

Publication retrieval

After the search was made in the four databases, the search results were checked for duplicates. All duplicates were removed. With aid of the inclusion and exclusion criteria, two calibrated readers independently reviewed retrieved titles and abstracts. When at least one reader identified a publication as matching the problem specification, it was ordered and read in full text. A protocol was made to meet the requirements of the study (Appendix 1). Articles that were read in full text were assessed according to the protocol. It resulted in those articles that were included in this systematic literature review. In cases of inconsistency between the readers, a third reader who is a specialist within the area was consulted.

The reference lists of the articles read in full text were screened for additional, relevant articles. To include articles in this hand search, the title had to contain the words “chronic osteomyelitis” or “PCO” or “DSO” or “RMCO” in combination with “medical treatment” or the name of the medical treatment evaluated, for example “ibandronate”. A duplicate control was made towards the main search. The hand search articles were screened in full text by the same protocol as the other articles (Appendix 1).

Quality Assessment

Two readers made a quality assessment of the included studies and a quality assessment protocol was made (Appendix 2). This protocol was composed of questions that could only be answered by “yes”, “no” and unsure. The questions and the criteria used for assessing the quality were a modification of STROBE checklist (42). If all questions were answered with a “yes”, the study was assessed to have a high quality. The article was considered to have moderate quality if few of the questions were answered “no”. Low quality was achieved if the study had many questions with the answer “no”. The criteria for different levels of quality can be seen in *Table 6*.

Table 6. The criteria for quality assessment

High quality	<i>The study was considered to have a high quality if following criteria were achieved:</i>
	<ul style="list-style-type: none"> - The objective was clearly specified - The method was clearly presented - Relevant settings were described, such as location, relevant dates, doses etc. - The method described the selection criteria for included participants - Factors such as predictors and effect modifiers were defined - Diagnostic criteria were defined - Each variable of interest was described in detail, for example method of measurement - Potential bias was described - If statistical methods were used, they were described in detail - Numbers of individuals were reported in each stage of the study - Reasons for loss of follow-up were addressed - Characteristics of the participants were described (age, gender etc.) - Follow-up time was summarized (average and total amount) - Measurements from the outcome were reported - The key results were summarized and referenced to the study object - Limitations of the study were discussed - An overall interpretation of the study results was made
Moderate quality	<i>The study was considered to have moderate quality if any of the above-mentioned criteria was not achieved. Although the study did not show any shortcomings described</i>

	<i>below.</i>
Low quality	<i>The study was considered to have a low quality if following criteria were present:</i>
	<ul style="list-style-type: none">- Risk of bias- Study design (case report, letter, cross sectional study and case control study)- The variability from different results were not explained- No clearly specified objective- The method was not clearly described- Selection criteria for included participants was not clearly described- Diagnostic criteria were not defined- No reason for loss of follow-up was addressed

RESULTS

Literature Search

The literature search resulted in 1345 articles from PubMed, 544 articles from Web of Science, 12 articles from Cochrane and 1620 articles from Scopus, see *Figure 3*. In total 2100 articles were found. Screening was made based on titles and abstracts, which resulted in 17 articles for full text screening. The flowchart is a modification of the PRISMA flow diagram, illustrated in *Figure 3*. Additionally, eight articles were identified as relevant when screening the reference lists of the 17 articles included in full text reading. The most common causes for exclusion of articles in this stage of the selection process were that the osteomyelitis was infectious and that the studies were case series with less than five cases. When reading articles in full text, only three of them fulfilled the selection criteria and therefore were included in this systematic literature review.

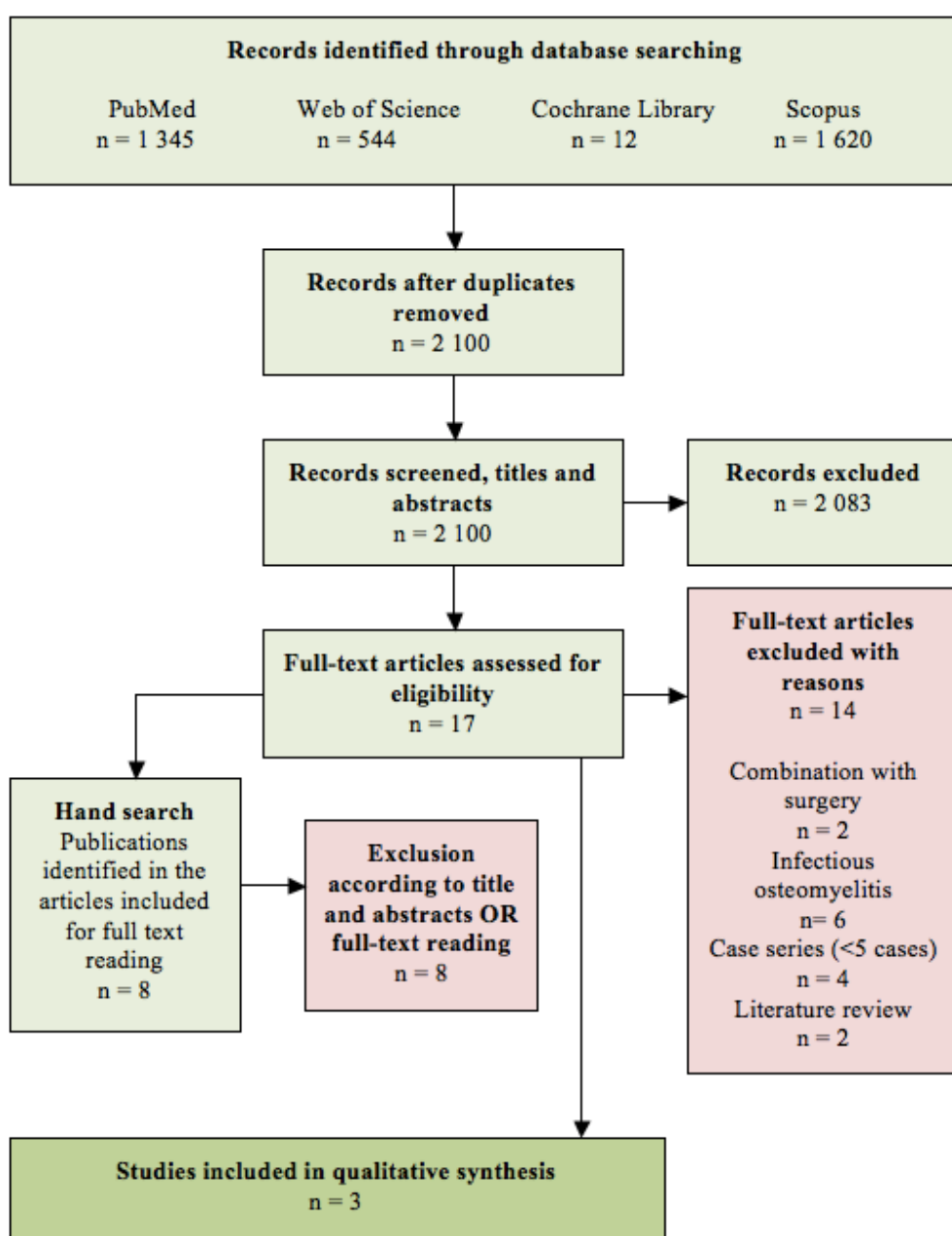


Figure 3. The flowchart of the selection process

Included studies

All three included studies were clinical trials (43-45). Of these, only one was a double-blinded randomized clinical trial (RCT) study (44). The other two were cohort studies (43,45). The studies were performed in Germany, Finland and The Netherlands (43-45).

The total numbers of participants in the three studies was 28 patients and varied from seven to eleven patients. All studies evaluated the effect of different bisphosphonates as a treatment method for DSO (43-45).

Medical treatment

Kuijpers et al. evaluated treatment with pamidronate of seven patients diagnosed with DSO. The given dose was 15 mg pamidronate intravenously every day, for three to five consecutive days. Depending on if the patients showed improvement or not, this treatment procedure was repeated after three months (43).

Montonen et al. assessed the effectiveness of disodium clodronate in ten patients with DSO. This study was a double-blinded RCT, with six patients in the trial group and four patients in the placebo group. Either a dose of 300-900 mg disodium clodronate (trial group) or non-pyrogenic, sterile 0,9% sodium chloride (placebo group) was given intravenously during a time period of three hours. Likewise, the first mentioned study, a second infusion was made if symptoms remained. During the treatment period, prescription of diclofenac 50-150 mg/day was allowed if the patient was still in pain after the medical infusion (44).

The third included study evaluated treatment with ibandronate in eleven patients with DSO. The ibandronate was given in doses of 6 mg intravenously. The infusion was repeated in four cases with recurrent pain (45).

Follow-up

In the study that evaluated treatment with pamidronate, one Tc-scan was taken before starting the treatment and another one was taken after a year. The follow-up time in this study was 18-46 months (mean 30 months). However, it was only after a year that the same treatment was evaluated for all seven patients, after that the continued treatment varied (43).

In the study that evaluated treatment with disodium clodronate, different methods were used to assess the outcome. To evaluate the level of pain, both a Visual Analogue Scale (VAS) and McGill Pain Questionnaire (MPQ) were used. Regular follow-ups were performed 1 week, 1 month, 3 months, 6 and 12 months after treatment. At each visit the patients also reported the amount of used diclofenac. In addition, the bone healing was assessed using Tc-scans. One Tc-scan was taken before treatment and one was taken a year after treatment (44).

The third article also measured the level of pain by using a VAS. Every day, ten days prior to treatment and ten days after treatment, the patients filled in the scale (45).

Main results

Two out of three articles assessed disease activity by the use of Tc-scans (43,44). Kuijpers et al. reported a decrease in disease activity after treatment with pamidronate (43). In the study where disodium clodronate was assessed, the Tc-scans showed no difference in disease activity between the trial and the placebo-group (44).

Pain was assessed in all three articles, although it was measured by different methods (43-45). After treatment with pamidronate, all patients showed a decrease in pain after 1-2 days. Three of seven patients were free of pain after the treatment period. The other four patients experienced pain a few weeks before every infusion cycle (43). In the double-blinded study where disodium clodronate was evaluated, both the trial group and the placebo group showed a reduction of pain one week after infusion. Although after six months there was a statistically significant decrease in pain in the trial group. A second infusion was needed in the both groups, 5/6 patients in the disodium clodronate group and 2/4 patients in the placebo group. Numbers of exacerbations were also reported, with higher prevalence in the placebo group, although this result was not statistically significant (44). Otto et al. reported a reduction of pain in 10/11 patients, 2-3 days after infusion with ibandronate. This result was considered statistically significant. 4/11 patients needed further treatment with a meantime of 245 days between the ibandronate infusions. The patients experienced a better quality of life and could eliminate the pain by using Ibuprofen 600 mg (45).

The patients in all three studies were monitored for eventual side effects from the treatment with bisphosphonates. No severe side effects, such as osteonecrosis, were reported in any of the articles during the time of assessment (43-45). In *Table 7*, all included studies are summarized.

Table 7. Summarize of the included articles.

First author	Sophie C.C. Kuijpers et al. 2010	M. Montonen et al. 2001	Sven Otto et al. 2015
Study design	Prospective cohort study	Double-blinded RCT	Retrospective cohort study
Purpose	To make a more extensive study since earlier available studies only are case reports and smaller case series.	To assess the effectiveness of disodium clodronate for relieving pain in patients with DSO.	To determine whether there is a beneficial role of infusions with nitrogen-containing bisphosphonates (ibandronate) in acute conditions of DSO
Time of symptoms	Mean 78 month (20 months-14 years)	> 1 year	Mean 6,3 years (1-20 years)
Participants	Total: 7 (6 female, 1 male)	Total: 10 (8 female, 2 male). 6 in the clodronate group and 4 in the placebo group	11 (9 female, 2 men)
Medical treatment	Pamidronate 15mg/day intravenously during 3-5 days	Disodium clodronate 300-900mg intravenously	Ibandronate 6mg intravenously
Method of assessment: bone healing	Tc-scan	Tc-scan	
Method of assessment: pain relief		VAS and MPQ.	VAS
Follow-up time	1 year after treatment	1 week, 1 month, 3 months, 6 months, 12 months after leaving hospital.	Mean = 27 months (17-39) (does not apply to the levels of pain)
Main results	<ul style="list-style-type: none"> • A decrease in disease activity after treatment in Tc-scans • 1-2 days after infusion, all patients showed a decrease in pain • 3 patients became pain free after treatment, 4 patients had pain a few 	<ul style="list-style-type: none"> • 5/6 patients in the trial group and 2/4 patients in the placebo group needed a second infusion • 1 week after infusion - reduction of pain in both groups • 6 months after infusion 	<ul style="list-style-type: none"> • 2-3 days after infusion, 10 patients experienced a reduction in pain • One patient did not improve in pain • Statistically significant reduction of pain level • 4 patients retrieved

	weeks before every new cycle	<ul style="list-style-type: none"> - statistically significant less pain in the trial group • The average of exacerbations was 1,5 (trial) vs 6,0 (placebo), not statistically significant. • No difference on Tc-scans between the groups after 12 months 	further infusions (mean time between infusions was 245 days)
Conclusion	Long-lasting relief of symptoms.	Pain relieving effect for 3-6 months. Does not result in immediate pain relief.	Beneficial effects of single-shot administrations
Quality	Low	High	Moderate

Quality Assessment

The quality assessment of the studies resulted in one study with low quality (43), one study with moderate quality (45) and one study with high quality (44). The study that evaluated pamidronate did not have a clearly described objective and the method of assessment was inadequately described as well. Due to these factors the study was considered to have a low quality (43). The study assessed to have a moderate quality met all the criteria for high quality, although it was a retrospective cohort study and there was a potential bias that was not mentioned in the study. These factors downgraded the study to a moderate level (45).

DISCUSSION

Methodology of the literature search and data interpretation

To ensure the retrieval of many publications, the search strategies comprised for databases – PubMed, Cochrane Library, Web of Science and Scopus. The search of at least two electronic sources is regarded as improving the methodological quality of a systematic review (46). Medical Subject Headings (MeSH) is a controlled vocabulary designed by the National Library of Medicine to search PubMed and other health science databases. This review used it primarily to establish the formal definition of the element problems. Pain relief is not a MeSH term, instead a well-known dictionary was consulted for definition of this element (41).

In the literature search it was desirable to include all articles within the relevant area. For this reason, both MeSH-terms and free search terms were combined. PubMed was the primary database and additionally three databases were used to ensure that all relevant articles were included and that a systematic working strategy was accomplished. The search resulted in a large number of articles, which indicates that the search had a wide spectrum. An even wider search would probably only have led to more irrelevant articles.

The reason why the term “bisphosphonates” was not included in the search blocks was because it resulted in too many irrelevant articles such as osteomyelitis caused by treatment with bisphosphonates. Excluding the term “bisphosphonates” from the search probably did not lead to any loss of relevant articles, even though this might be a source of error in finding relevant articles. The hand search of the reference lists of included publications has, however, been regarded as the most effective method of identifying additional relevant publications (47).

Predetermined protocols with topics related to the problem specifications were used to standardize data extraction. This facilitated the structuring of the publications into groups.

The difficulty in making a systematic review about non-infectious osteomyelitis was that many terms are used for the condition (17,21,22). DSO, PCO and CRMO are common terms found in the literature and are probably used to describe the same condition. Although the definitions for these terms are not used in a uniform way and there is a risk that non-infectious osteomyelitis have been termed differently and have therefore not been included in our search. To overcome the difficulty with different terms, it was decided that the only thing of importance was that the osteomyelitis should be non-infectious, no matter which term that was used for diagnosis.

In the criteria it was specified that only original articles should be included. This enabled the reviewers to assess the articles by themselves instead of reading conclusions from other authors. In this way risk of bias were avoided. Case reports were excluded, but case series that contained more than five cases were included to minimize the risk of coincidental results.

Another exclusion criterion was patients treated with the evaluated drug in combination with contemporary surgical treatment, another drug therapy, or hyperbaric oxygen treatment. This exclusion also aimed at enabling evaluation of the medical treatment of interest. One exception was the contemporary treatment with NSAIDs, which was commonly used to assess the level of pain (44).

A protocol of quality assessment was made as a modification of the STROBE checklist for cohort studies (42). Since articles with different study designs were included, there was a difficulty in adjusting the protocol to suit both cohort and RCT studies. One benefit was the consistency of using the same protocol for all included studies. Another checklist for quality assessments could have been used for the RCT study (Consort 2010), however, a modified checklist according to STROBE was considered to suit the requirements.

The main reason that only three articles were included in this systematic review is that most available studies are case reports. Montonen et al. presented a well-made double-blinded RCT (44), which is desirable to achieve a study with high quality. Non-infectious osteomyelitis is a rare condition, thereby making it difficult to provide sufficient material to perform a blinded RCT. To enable a more extensive and trustworthy study design, it would probably be useful to merge different centres to be able to include a greater number of cases. Another difficulty in making studies within this area is the ethical considerations. A double-blinded study with placebo as control would imply that some of the patients would not receive any treatment at all and this might lead to a large loss of participants due to symptoms. Further on, it would also be desirable that no other contemporary medication, such as NSAID, was used, since this could be a source of error when analysing the results. This might also be difficult due to ethical reasons while patients endure pain and progressive appearance of the condition.

Results

The search resulted in three studies to be included for quality assessment. All the included studies evaluated the effect of treatment with bisphosphonates in patients with DSO (43-45). Three different types of bisphosphonates were used, pamidronate (43), ibandronate (45) and disodium clodronate (44). Since, different types, dosage and treatment protocols were used, it was not possible to make a comparison between the outcomes of the studies.

In the blinded RCT study by Montonen et al., the patients received 300-900 mg disodium clodronate at one point. The precise infused dose was not specified ranging from 300-900 mg, which makes it hard to conclude the exact dose needed for effective treatment of non-infectious osteomyelitis (44). The effects of bisphosphonates are suggested to be dose dependent (45). Therefore, it would have been interesting to know how the specific dose was chosen in each case, since it might have affected the outcome.

Otto et al. reports that ten out of eleven patients showed a decrease in pain after 2-3 days. The patient that did not respond to the treatment with ibandronate had had symptoms for 12 years and experienced many unsuccessful treatments before the treatment with bisphosphonates (45). The long duration of complaints or the unsuccessful previous treatments could be possible explanations why the bisphosphonate treatment did not succeed. Montonen et al. showed a statistically significant reduction of pain in the trial group, which included six patients, six months after infusion (44). Although it was not specified for how long time the symptoms of the disease had been present before the treatment was started, respectively in each group. In future studies, investigation of the relationship between duration of symptoms and efficiency of treatment of non-infectious osteomyelitis could be of interest.

The included studies in this review allowed contemporary use of analgesics during the evaluation time (43-45). Montonen et al. prescribed diclofenac when necessary and used it for measuring the level of pain (44). In the other two studies (43,45), analgesics was also used contemporary, but not specified. It did not emerge what kind of drug that was used by the different patients and to what extent. Several studies have reported that NSAIDs have a

therapeutic effect in cases with non-infectious osteomyelitis (17,48). Therefore, contemporary treatment with analgesics could be a potential source of error. It would have been desirable to evaluate a medical treatment of non-infectious osteomyelitis with bisphosphonates without any other contemporary treatment, but this could be difficult to achieve due to ethical considerations.

The aim of this study was to evaluate the pain-relieving effect and bone healing after medical treatment of non-infectious osteomyelitis. The methods of assessment varied between the included studies. Montonen et al. and Otto et al. both evaluated the level of pain by using VAS (44,45). Kuijpers et al., on the other hand, reported a decrease in pain (43) but did not describe how it was measured (43). Yet, this is another difference between the studies, which makes it difficult to compare the results. An advantage of the study by Montonen et al. was that both VAS and MPQ were used in combination (44). VAS is an organizing way of ranking the level of pain (49) and MPQ measures the quality and intensity of pain (50).

Tc-scans have proved to be a very good method of assessing bone healing in osteomyelitis. The scintigraphy is a valuable tool in all stages of osteomyelitis. It is useful for detection, treatment planning and for evaluating treatment outcome, since it shows both the extension of the lesion and the disease activity (14). It is advantageous that two of the articles have used Tc-scans (43,44), since this is an objective evaluation method. Unlike these studies, Otto et al. only measured the outcome subjectively in form of VAS (45) and not the objective extension of the disease. The follow up time used in all studies were approximately one year (43,44). It would be of interest with more extended follow up times to evaluate the long-lasting effect of the medical treatment of non-infectious osteomyelitis.

All the three articles included, report a decrease in pain as a result of treatment where bisphosphonates were used (43-45). However, the time-span between treatment start and pain relief varied. Treatment with pamidronate and ibandronate resulted in a major decrease in pain 1-3 days after the first infusion (43,45). The study evaluating disodium clodronate showed a prolonged onset before the pain relief effect emerged (44). The difference in pain relief onset between different bisphosphonates could be explained by the variation in the chemical structure of the drug. Pamidronate and ibandronate are both high-potency nitrogen-containing bisphosphonates and disodium clodronate is a non-nitrogen-containing bisphosphonate and considered to be a first generation of bisphosphonates which might play a role when treating non-infectious osteomyelitis. One advantage of the nitrogen-containing bisphosphonates could be the additional nitrogen-group that increases the anti-resorptive capability of the drug and might make a difference (51).

There are advantages with a bisphosphonate that result in rapid onset, not only the reduction of patients' suffering, but also the better cost-efficiency. On a societal basis, it will decrease the symptoms and enable people to work or go to school. Clear guidelines for treatment of non-infectious osteomyelitis will also be cost-efficient since many inadequate and insufficient examinations and treatments will be avoided. On a personal basis, this would lead to reduced pain and avoidance of progression and invasive surgery, which in turn would lead to better function and aesthetics. This would give the patients a better quality of life.

The results assessed from Tc-scanning are inconsistent. Kuijpers et al. showed a decrease in disease activity one year after infusion (43), while Montonen et al. did not see any difference regarding bone healing between the placebo and trial groups (44). These ambiguous results

based on two different types of bisphosphonates are insufficient to make any conclusions and further research is necessary.

Free discussion

Even though previous studies have shown good results with treatment of DSO with bisphosphonates, it is still not a standard treatment of the condition (45). The reason might be the fear of severe unwanted side effects that bisphosphonates might lead to, such as medication-related osteonecrosis of the jaw. The studies included in this systematic review monitored the patients for unwanted side effects and no severe complications were reported. Long-term intravenous administration of bisphosphonates has in earlier studies been implicated as the highest risk factor for development of osteonecrosis of the jaw (52). Consequently, it is important to have longer follow-ups after treatment of non-infectious osteomyelitis with bisphosphonates. Some nitrogen-containing bisphosphonates have also shown a higher risk to develop osteonecrosis than other types, for example pamidronate (53).

This study shows that there is a lack of studies with high quality within this area. In the future, it would be of interest to perform larger double-blinded RCT-studies regarding medical treatment of non-infectious osteomyelitis. Ideally, no other medication such as NSAID should be used contemporary and it would also be desirable with more extended follow-up times to evaluate the long-lasting effect of the drug therapy.

Otto et al. suggested that denosumab might be an alternative for treatment of DSO. denosumab has a similar mechanism of action as bisphosphonates. It is a monoclonal human antibody that inhibits RANKL and prevents the ligand from binding to RANK. This interaction is essential for activation of osteoclasts and for them to resorb bone. The use of denosumab therefore leads to a reduced bone resorption (31,54). The effects are fully reversible and the medicine is not stored in the skeletal bones (55), which shortens the half-life of elimination (54) and therefore decreases the risk of severe side effects.

CONCLUSION

According to this systematic literature review, treatment of non-infectious osteomyelitis with bisphosphonates demonstrates a reduction in pain. However, the pain-relieving effect is most probably dependent on the type of bisphosphonate. The results of bone healing assessed from Tc-scans are ambiguous and therefore no conclusion can be made. Only one article in this review was considered to have high quality in the quality assessment. To enable clear guidelines regarding treatment of non-infectious osteomyelitis, more clinical trials with high quality is desirable.

In summary, bisphosphonates seem to be a good alternative in treatment of non-infectious osteomyelitis. An alternative to bisphosphonates might be treatment with denosumab, which have a similar mechanism of action but shorter half-life. However, further research is needed.

REFERENCES

- (1) Tortora GJ, Derrickson Be. Principles of anatomy & physiology. 13th ed. New York: Wiley, 2011: 182-188, 194.
- (2) VanPutte CL, Seeley RR. Seeley's anatomy & physiology. 10th ed. New York: McGraw-Hill, 2014: 165-172.
- (3) Ross Ethier C, A. Simmons C. Introductory Biomechanics: From Cells to Organisms. 1st ed. New York: Cambridge University Press, 2007: 11.
- (4) Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. *Nature* 2003; 05/15;423(6937):337.
- (5) Rang HP, Dale MM. Rang and Dale's pharmacology. 7th ed. Edinburgh: Churchill Livingstone, 2011: 402-406, 438.
- (6) Lewiecki EM. New targets for intervention in the treatment of postmenopausal osteoporosis. *Nat Rev Rheumatol* 2011 Sep 20;7(11):631-638.
- (7) Pogrel MA, Kahnberg K, Andersson L. Essentials of Oral and Maxillofacial Surgery. [electronic resource]. Hoboken: Wiley, 2014.
- (8) Andersson L, Kahnberg K, Pogrel MA. Oral and Maxillofacial Surgery. 1st ed. Hoboken: Wiley, 2011: 519-528.
- (9) Miloro Me, Ghali GE, Larsen PEe, Waite PDe, Peterson LJe. Peterson's principles of oral and maxillofacial surgery. 2nd ed. Hamilton, Ont.: B C Decker, 2004;. / editor, Michael Miloro / associate editors, G.E. Ghali, Peter E. Larsen, Peter D. Waite; 2004.
- (10) Riise OR, Kirkhus E, Handeland KS, Flato B, Reiser T, Cvancarova M, et al. Childhood osteomyelitis-incidence and differentiation from other acute onset musculoskeletal features in a population-based study. *BMC Pediatr* 2008 Oct 20;8:45-2431-8-45.
- (11) Kremers HM, Nwojo ME, Ransom JE, Wood-Wentz CM, Melton LJ,3rd, Huddleston PM,3rd. Trends in the epidemiology of osteomyelitis: a population-based study, 1969 to 2009. *J Bone Joint Surg Am* 2015 May 20;97(10):837-845.
- (12) Christensson B. Osteomyelit och spondylit. 2016; Available at: <http://www.internetmedicin.se/page.aspx?id=178>. Accessed 09/27, 2016.
- (13) White SCe, Pharoah MJe. Oral radiology: principles and interpretation. 7th ed. St. Louis, Mo. : Mosby/Elsevier, cop. 2014: 318-324.
- (14) Rohlin M. Diagnostic value of bone scintigraphy in osteomyelitis of the mandible. *Oral Surg Oral Med Oral Pathol* 1993 May;75(5):650-657.
- (15) Buckley O, O'Keeffe S, Geoghegan T, Lyburn ID, Munk PL, Worsley D, et al. 99mTc bone scintigraphy superscans: a review. *Nucl Med Commun* 2007 Jul;28(7):521-527.

- (16) 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 Feb;32(1):43-50.
- (17) 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 Nov;28(10):456-464.
- (18) 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 Oct;70(4):414-419.
- (19) Turlington EG. Chronic sclerosing nonsuppurative osteomyelitis. *Trans Int Conf Oral Surg* 1973;4:120-124.
- (20) 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 May;61(5):561-573.
- (21) Flygare L, Norderyd J, Kubista J, Ohlsson J, Vallo-Christiansen J, Magnusson B. Chronic recurrent multifocal osteomyelitis involving both jaws: report of a case including magnetic resonance correlation. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997 Feb;83(2):300-305.
- (22) Sueti Y, Tanimoto K, Taguchi A, Yamada T, Yoshiga K, Ishikawa T, 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 Oct;80(4):401-408.
- (23) 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 Nov;74(5):557-560.
- (24) 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 Oct;46(10):825-829.
- (25) 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 Dec;92(6):637-640.
- (26) Abril JC, Ramirez A. Successful treatment of chronic recurrent multifocal osteomyelitis with indomethacin: a preliminary report of five cases. *J Pediatr Orthop* 2007 Jul-Aug;27(5):587-591.
- (27) Jacobsson S, Hollender L. Treatment and prognosis of diffuse sclerosing osteomyelitis (DSO) of the mandible. *Oral Surg Oral Med Oral Pathol* 1980;49(1):7-14.
- (28) Jacobsson S. Diffuse sclerosing osteomyelitis of the mandible. *Int J Oral Surg* 1984 Oct;13(5):363-385.
- (29) Wipff J, Adamsbaum C, Kahan A, Job-Deslandre C. Chronic recurrent multifocal osteomyelitis. *Joint Bone Spine* 2011 Dec;78(6):555-560.
- (30) Drake MT, Clarke BL, Khosla S. REVIEW: Bisphosphonates: Mechanism of Action and Role in Clinical Practice. *Mayo Clin Proc* 2008;83:1032-1045.

- (31) Ljunggren Ö, Salminen H, Tørring O. Osteoporos och frakturprevention. 2015; Available at: https://lakemedelsboken.se/kapitel/endokrinologi/osteoporos_och_frakturprevention.html?id=k2a_1#k2a_1. Accessed 11/02, 2016.
- (32) Ibandronic acid Sandoz. 2014; Available at: <https://www.fass.se/LIF/product?nplId=20110105000028&userType=0>. Accessed 11/03, 2016.
- (33) Marx RE. A decade of bisphosphonate bone complications: what it has taught us about bone physiology. *Int J Oral Maxillofac Implants* 2014 Mar-Apr;29(2):e247-58.
- (34) Lassetter KC, Porras AG, Denker A, Santhanagopal A, Daifotis A. Pharmacokinetic considerations in determining the terminal elimination half-lives of bisphosphonates. *Clin Drug Investig* 2005;25(2):107-114.
- (35) Montonen M, Li TF, Lukinmaa PL, Sakai E, Hukkanen M, Sukura A, et al. RANKL and cathepsin K in diffuse sclerosing osteomyelitis of the mandible. *J Oral Pathol Med* 2006 Nov;35(10):620-625.
- (36) Kopterides P, Pikazis D, Koufos C. Successful treatment of SAPHO syndrome with zoledronic acid. *Arthritis Rheum* 2004 Sep;50(9):2970-2973.
- (37) Hino S, Murase R, Terakado N, Shintani S, Hamakawa H. Response of diffuse sclerosing osteomyelitis of the mandible to alendronate: follow-up study by ^{99m}Tc scintigraphy. *Int J Oral Maxillofac Surg* 2005 Jul;34(5):576-578.
- (38) 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 Jul;104(1):67-71.
- (39) Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol* 2009 Oct;62(10):e1-34.
- (40) Centre for Reviews and Dissemination. Systematic Reviews, CRD's Guidance For Undertaking Reviews in Health Care. 2009; Available at: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf. Accessed 02/20, 2017.
- (41) Lary MS. *New Oxford American Dictionary*, 3rd edition. *Libr J* 2010;135(20):136-136.
- (42) von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 2007 Oct 20;335(7624):806-808.
- (43) Kuijpers SC, de Jong E, Hamdy NA, van Merkesteyn JP. Initial results of the treatment of diffuse sclerosing osteomyelitis of the mandible with bisphosphonates. *J Craniomaxillofac Surg* 2011 Jan;39(1):65-68.
- (44) Montonen M, Kalso E, Pylkkaren L, Lindström BM, Lindqvist C. Disodium clodronate in the treatment of diffuse sclerosing osteomyelitis (DSO) of the mandible. *Int J Oral Maxillofac Surg* 2001 Aug;30(4):313-317.

- (45) Otto S, Troeltzsch M, Burian E, Mahaini S, Probst F, Pautke C, et al. Ibandronate treatment of diffuse sclerosing osteomyelitis of the mandible: Pain relief and insight into pathogenesis. *J Craniomaxillofac Surg* 2015 Nov;43(9):1837-1842.
- (46) Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* 2007 Feb 15;7:10-2288-7-10.
- (47) Whiting P, Harbord R, de Salis I, Egger M, Sterne J. Evidence-based diagnosis. *J Health Serv Res Policy* 2008 Oct;13 Suppl 3:57-63.
- (48) Huber AM, Lam PY, Duffy CM, Yeung RS, Ditchfield M, Laxer D, et al. Chronic recurrent multifocal osteomyelitis: clinical outcomes after more than five years of follow-up. *J Pediatr* 2002 Aug;141(2):198-203.
- (49) Ohnhaus EE, Adler R. Methodological problems in the measurement of pain: a comparison between the verbal rating scale and the visual analogue scale. *Pain* 1975 Dec;1(4):379-384.
- (50) Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. *Pain* 1975 Sep;1(3):277-299.
- (51) Russell RG. Bisphosphonates: from bench to bedside. *Ann N Y Acad Sci* 2006 Apr;1068:367-401.
- (52) Yuan H, Niu LN, Jiao K, Pei DD, Pramanik C, Li JY, et al. Revival of nitrogen-containing bisphosphonate-induced inhibition of osteoclastogenesis and osteoclast function by water-soluble microfibrinous borate glass. *Acta Biomater* 2016 Feb;31:312-325.
- (53) Bamias A, Kastiris E, Bania C, Mouloupoulos LA, Melakopoulos I, Bozas G, et al. Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. *J Clin Oncol* 2005 Dec 1;23(34):8580-8587.
- (54) XGEVA. 2016; Available at: <http://www.fass.se/LIF/product?userType=0&nplId=20100612000161>. Accessed 11/03, 2016.
- (55) Miller PD, Bolognese MA, Lewiecki EM, McClung MR, Ding B, Austin M, et al. Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinded phase 2 clinical trial. *Bone* 2008 Aug;43(2):222-229.

APPENDIX

Appendix 1. Protocol for full text reading

PROTOCOL FOR ASSESSMENT OF FULL-TEXT PUBLICATIONS ON MEDICAL TREATMENT OF CHRONIC OSTEOMYELITIS IN THE JAWS

Title:	
1 st Author:	Year:
Journal:	Article number:

PUBLICATION TYPE:

Original Study Systematic review Other Specify type: _____

AIM OF THE STUDY

IS THE OSTEOMYELITIS NON INFECTIOUS?

Yes No

Diagnosis: _____

No. of cases: _____

WHAT TREATMENT WAS EVALUATED?

TREATMENT OUTCOME?

Was treatment outcome described? Yes No

WAS THE LEVEL OF PAIN MEASURED?

Yes No How?: _____

WAS THE LESION EVALUATED ON RADIOGRAPHS?

Yes No How?: _____

RELEVANCE FOR THIS REVIEW: Include Exclude Uncertain

REASON FOR EXCLUSION:

- | |
|--|
| <ul style="list-style-type: none"><input type="checkbox"/> Case report<input type="checkbox"/> Case series (< 5 individuals)<input type="checkbox"/> Book chapter or letter<input type="checkbox"/> Review (not according to CRD's guidance and without similar problem specification)<input type="checkbox"/> Animal study<input type="checkbox"/> Article in other language than Swedish or English
<input type="checkbox"/> Infectious osteomyelitis |
|--|

- Osteomyelitis caused by radiation or bisphosphonate treatment
- Osteomyelitis caused by lifestyle (alcohol abuse, drug abuse)
- Patients with other systemic diseases
- Patients treated with immunosuppressive pharmacology

- Osteomyelitis treated with surgery alone or in combination with the evaluated drug
- Osteomyelitis treated with Hyperbar Oxygen treatment alone or in combination with the evaluated drug
- Osteomyelitis treated with combination of different drugs during the assessed treatment period

- Treatment outcome not defined
- Other (specify):

COMMENTS

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Evaluated by:	Date:
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Quality Assessment Protocol - STROBE

Introduction		Is the objective clearly specified?	
Method	Study design	Is the setup of the study procedure presented clearly in the method? (It should enable repeatability)	
	Setting	Are relevant settings described, such as location, relevant dates, doses, follow-up and data collection?	
	Participants	Does the method describe the selection criteria for included participants?	
	Variables	Are factors such as predictors and effect modifiers defined?	
		Are diagnostic criteria defined?	
	Measurement	Are each variable of interest described in detail, for example method of measurement?	
	Statistical methods	If statistical methods are used, are they described in detail?	
Results	Participants	Are numbers of individuals reported in each stage of the study?	
		Are reasons for loss of follow-up addressed?	
	Descriptive data	Are characteristics of study participants described (age, gender etc.)?	
		Is follow-up time summarized (average and total amount)?	
	Outcome data	Are measures from outcome reported?	
Discussion	Key results	Are the key results summarized with reference to the study object?	
	Limitations	Are limitations of the study discussed and are sources of potential bias taken into account?	
	Interpretations	Is there an overall interpretation of the study results?	
Other		If there is a source of funding, is the role of the funding neutral?	

GRADE

Study design	Ranking	
Systematic review	High	
RCT	High	
Cohort study	Moderate	
Case control study	Low	
Cross sectional study	Low	

Animal study or in vitro study	Low	
Case report, opinion paper, letter	Low	

Reason to downgrade
<p>Risk of bias:</p> <ul style="list-style-type: none"> - Lack of clearly randomized allocation sequence - Lack of blinding - Trial is cut short - Large losses to follow-up <p>Inconsistency:</p> <ul style="list-style-type: none"> - The variability from different results is not explained

Final GRADE ranking		
High	⊕ ⊕ ⊕	We are very confident that the effect of the study reflects the actual effect
Moderatae	⊕ ⊕	We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different
Low	⊕	The true effect may differ significantly from the estimated effect