Bone antiresorptive or antiangiogenic medication and dental implant treatment in osteoporotic patients
– A systematic review

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ABSTRACT

Aim: The overall aim is to (i) analyze the prognosis of dental implant treatment concerning marginal bone loss (MBL) in patients undergoing or have undergone treatment with bone antiresorptive or antiangiogenic medication for osteoporosis (ii) and additional purpose to assess the available scientific literature in the first aim concerning the risk of getting medication-related osteonecrosis of the jaw (MRONJ) associated with dental implant installation.

Material and methods: A systematic literature search was conducted in October 2021 in the following three databases; MEDLINE/PubMed, Cochrane Library and Web of Science. PRISMA 2009 Flow Diagram were used for the selection process, whereas the included studies were evaluated for quality assessment using Newcastle Ottawa Scale (NOS).

Results: The search resulted in four included studies considering the eligibility criteria. The studies evaluated MBL in osteoporotic patients undergoing or have undergone oral bisphosphonate (BP) treatment before and/or during implant placement. MRONJ was also assessed in all four articles.

Conclusions: The results of this present study do not indicate that patients undergoing or have undergone antiresorptive or antiangiogenic medication for osteoporosis are at an increased risk of MBL in dental implants during follow-up periods. The present data assessing the risk for developing MRONJ remains low for osteoporotic patients. Therefore, dental implant surgery is considered possible with success in osteoporotic patients receiving earlier mentioned medications. However additional studies are required to evaluate the effects on this patient group concerning osseointegration of dental implant regarding MBL.

Keywords: Bisphosphonate, bone antiresorptive and antiangiogenic medication, denosumab, dental implant, marginal bone loss.
SAMMANFATTNING

Syfte: Syftet med denna studie är att analysera prognosen för implantatbehandling avseende marginell benförlust (MBL) hos patienter som genomgår eller har genomgått behandling med benantiresorptiv eller antiangiogen medicin för osteoporos. Ytterligare utförs en bedömning av tillgänglig vetenskaplig litteratur gällande risken för läkemedelsrelaterad käkbensnekros (MRONJ) associerat med implantatininstallation hos patienter som genomgår eller har genomgått behandling med benantiresorptiv eller antiangiogen medicin.

Material och metod: En systematisk elektronisk litteratursökning genomfördes i oktober 2021 i följande tre databaser; MEDLINE/PubMed, Cochrane Library och Web of Science. PRISMA 2009 Flow Diagram användes för urvalsprocessen, varav de inkluderande studierna kvalitetsgranskades enligt Newcastle Ottawa Scale (NOS).

Resultat: Sökningen resulterade i fyra studier, enligt inklusions- och exklusionskriterier. Studierna utvärderade MBL hos osteoporospatienter som går eller har gått behandling med orala bisfosfonater före eller under implantatininstallationen. MRONJ fastställdes i alla fyra artiklar.


Nyckelord: Benantiresorptiv och antiangiogen läkemedel, bisfosfonat, denosumab, dentala implantat, marginalbenförlust.
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1. INTRODUCTION

1.1 Background

**Bone**
The body’s skeletal system constitutes an entire framework of bones, cartilages, ligaments, and tendons, all collaborating to accommodate and maintain this system. Bone consists of organic compounds (collagen fibers and bone cells) and inorganic compounds (extracellular matrix of crystallized mineral salts). The combination of the respective compounds forms a cortical and cancellous bone, each with different composition and structure. Compact bone forms the outer part of the bone whereas cancellous bone forms the inner part of the bone (1).

Compact bone tissue is the strongest and densest part of bone tissue; hence it provides protection, support and resists forces generated by weight and movement. Compact bone consists of "Haversian systems", also known as osteons, which are repeating structural units surrounded by a small network of blood vessels and nerves running through central canals. Cancellous bone also referred to as “spongy bone” or “trabecular bone” is a significantly weaker bone tissue due to spaces filled with bone marrow containing blood vessels to provide nutrition to the bone cells (2).

As mineralization of the bone occurs through secretion of mineral salts by the bone-building cells “osteoblasts”, some cells get trapped and reside along the way in the matrix, known as "osteocytes". Osteocytes are mature bone cells embedded within the mineralized bone matrix forming a network of cytoplasmic processes to exchange nutrients and wastes with the blood, thereby maintaining the bone tissues’ daily metabolism (3). The osteocyte network is an extra- and intracellular communication channel enabling transmission of mechanical loading to other bone cells to further maintain their functions (4).

**Bone remodelling**
As we age our entire skeletal system requires simultaneous construction and deconstruction of bone tissues, a process known as "remodelling". For remodelling to occur there are four types of specialized bone cells carrying out a mission of bone formation and resorption: osteoprogenitor cells, osteoblasts, osteocytes, and osteoclasts (1).

The remodelling process constitutes of various bone cells with different functions being recruited to attain resorption and/or deposition of minerals. The cycle starts with the recruitment of osteoclast precursor cells, bone cells specialized in the breakdown of bone extracellular matrix. This recruitment is achieved by osteoblasts which expresses a type II transmembrane protein, Receptor Activator of Nuclear factor kappa B-Ligand (RANKL) by stimulation of certain hormones and cytokines. An interaction with RANKL and a specific receptor, Receptor Activator of Nuclear factor kappa B (RANK) on the osteoclast precursor cell membrane take place, inducing it to differentiate into multinucleated and mature osteoclasts (5).
Resorption of collagen and minerals occurs as osteoclasts attach tightly to the bone surface by forming a seal using its deeply folded plasma membrane, “ruffle ended border”. This seal enables osteoclasts to create an environment with lower pH at the bone surface by releasing hydrogen ions (H⁺), thereby initiating the breakdown of minerals, primarily hydroxyapatite crystals and collagen.

In the process of physiologic bone remodelling, various cytokines, i.e., transforming growth factor (TGF) and insulin-like growth factor (IGF-1) are gradually being released to recruit and activate osteoblasts to initiate new bone formation. There is also an inhibition mechanism to downregulate resorption by inactivating osteoclasts. Inactivation of osteoclasts is achieved by an inhibitor, osteoprotegerin (OPG) which binds to RANKL, thereby preventing RANKL-RANK interaction. Both the stimulating and inhibiting mechanisms are important to maintain the amount of bone resorption by controlling the activation of osteoclasts (6).

Osteoporosis
Osteoporosis is a skeletal disease that reduces bone strength and increases the risk of bone fracture. It is caused by the reduction of the quantity of bone tissues and deterioration of microstructure in the bone (7). There are two types of osteoporosis: primary and secondary. Primary osteoporosis is associated with ageing, menopause, and lifestyle factors such as smoking, alcohol, diet, and physical inactivity. Secondary osteoporosis is caused by certain diseases and treatments (8,9). Osteoporosis in older women is mainly caused by normal ageing and general morbidity. Osteoporosis is a common medical condition in Sweden. It has been reported that one-third of Swedish women aged 70–79 years are estimated to have osteoporosis when measuring the bone density of the hip. The consequences of osteoporosis are fractures that can occur after insignificant strain. In recent decades, the number of hip fractures has increased, mainly because life expectancy is increasing (7).

The deficiency of estrogen which is a sex hormone plays an important role in the pathogenesis of osteoporosis. It is reported that estrogen increases OPG which prevents RANKL-RANK interaction and therefore inhibits RANKL-induced osteoclast differentiation. It is also evident that estrogen is involved in vitamin D₃ metabolism which is required for healthy bones (10). At the time of menopause, i.e., when women lose the ability to menstruate, the production of estrogen reduces and will eventually cease completely, leading to increased breakdown of bone tissues. In older ages, both in men and women, the formation of active vitamin D₃ in the kidneys decreases. In addition, the physical activity and nutrient intake deteriorate which leads to increased loss of bone tissue and lower bone quality in the elderly (7).

Lifestyle interventions are a strategy for the prevention of osteoporosis but there are also pharmacological agents for treatment by preventing fractures and maintaining bone strength (10). Bone antiresorptive and antiangiogenic drugs are agents prescribed for different medical conditions such as osteoporosis, Paget’s disease, multiple myeloma etc. They have different mechanisms but similar objectives; to increase bone density by inhibiting bone resorption and initiating new blood vessel formation, a process known as “angiogenesis” (11,12). Angiogenesis is the formation of new blood vessels from existing ones through the growth, migration and differentiation of endothelial cells (12). In need of
inhibiting this process for instance to restrict tumor vascularization, antiangiogenic drugs exist. The majority of such drugs consist of monoclonal antibodies or inhibitors. Bevacizumab, pazopanib and ramucirumab are all antiangiogenics used for malignant tumors (13).

Antiresorptive drugs inhibit bone resorption by affecting osteoclast development and function (11). The most widely known antiresorptive drugs are Bisphosphonates (BPs) (14) and more recently Denosumab, which is based on monoclonal antibodies (15). Antiresorptive drugs are indicated for the treatment of various diseases, among other multiple myeloma, Paget’s disease, hypercalcemia, osteogenesis imperfecta, and osteoporosis (14).

Denosumab
Denosumab is a recombinant human IgG2 monoclonal antibody. Antibodies are molecules that are produced by the body to interact with our immune cells to fight infections. Monoclonal antibodies are obtained from cells grown in the laboratory that are specific to their intended target. They are used to deliver therapeutic agents to malignant cells in the human body (16). Denosumab inhibits RANKL by binding to it with high affinity preventing it from activating RANK. This inhibition mechanism decreases bone resorption by preventing osteoclast formation, function and survival (17).

Osteoclasts resume their normal functions approximately 12 months after ceasing denosumab treatment (18). The mean half-life of denosumab is 26 days. No traces of measurable denosumab are detected 6 months after administration in 53% of patients (19). Denosumab is administered as subcutaneous injections every 6 months depending on the disease and its degree of complexity. It can lead to altered bowel habits, hypocalcemia, hypophosphatasemia and MRONJ (17).

Bisphosphonates
BP is an antiresorptive drug that functions as an inhibitor of osteoclastic bone resorption, thereby reducing the rate of bone turnover. BPs are grouped into two categories: nitrogen-containing and non-nitrogen-containing (17). According to a study by Beaudart et al. (14), the antiresorptive potency increases by tenfold in the presence of nitrogen side chains, hence it is primarily associated with the development of MRONJ. The non-nitrogen containing BPs (e.g., etidronate, clodronate etc.) are simple compounds promoting osteoclast apoptosis. The nitrogen-containing BPs (e.g. alendronate, zoledronate etc.) are potent inhibitors preventing osteoclast attachment to the bone by interfering with cell surface proteins (17).

BPs bind with high affinity to bones with high turn-over rates and are only liberated again from the bone when it undergoes resorption. The systemically available BPs disappear rapidly from plasma and are excreted by the kidney which is the only route of elimination found yet. Thus, the mean half-life of BPs highly depends on the rate of bone turnover, nevertheless, it is within 1-10 years range (20).

Some BPs are administered intravenously (e.g., zoledronate, ibandronate) others orally on an empty stomach to prevent impaired absorption. Depending on the administration pathway it offers various degrees of unwanted side effects. Orally administered BPs will lead to gastrointestinal disturbances and occasional bone
pain. Whilst intravenously administered BPs can cause osteonecrosis of the jaw which mainly occurs in patients with malignant diseases undergoing procedures (17).

**Medical Related Osteonecrosis of the Jaw**

Different terms will be encountered in literature for osteonecrosis of the jaw (ONJ) and BRONJ (bisphosphonate-related osteonecrosis of the jaw). The most common term, which will be used in the present review, is MRONJ (medical related osteonecrosis of the jaw). MRONJ is the most discussed possible side effect during treatment with bone antiresorptive and antiangiogenic medication (21). A greater debated question is how great the risk of MRONJ is during treatment of osteoporosis and whether the risk is greater in intravenous compared to oral treatment (22).

The American Association of Oral and Maxillofacial Surgeons (AAOMS) developed diagnostic criteria for MRONJ based on pharmacological history and clinical- and radiographic findings (21). MRONJ staging system is presented below in table 1.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>At-risk category</td>
<td>No apparent necrotic bone in patients who have been treated with either oral or iv. BPs.</td>
</tr>
<tr>
<td>Stage 0</td>
<td>No clinical evidence of necrotic bone, but non-specific clinical findings, radiographic changes, and symptoms.</td>
</tr>
<tr>
<td>Stage 1</td>
<td>Exposed and necrotic bone or fistulae that probes to the bone in patients who are asymptomatic and have no evidence of infection.</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Exposed and necrotic bone or fistulae that probes to the bone, associated with infection as evidenced by pain and erythema in the region of the exposed bone, with or without purulent drainage.</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Exposed and necrotic bone or a fistula that probes to the bone in patients with pain, infection and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone (i.e., inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla) resulting in pathologic fracture, extra-oral fistula, oral-antral/oral-nasal communication or osteolysis extending to the inferior border of the mandible or sinus floor.</td>
</tr>
</tbody>
</table>

A survey study by Lo et.al (23) reviewed more than 13 000 Kaiser Permanente members during the treatment of osteoporosis with oral BP therapy. The authors reported a prevalence of MRONJ in patients undergoing long-term oral BP therapy at 0,1% and an increasing number to 0,21% after four years of treatment. Whilst a thesis by Hallmer (24) estimated the prevalence of MRONJ for osteoporosis patients on oral BPs to be 0,043% during the period 2012-2015 in Region Skåne, Sweden. There are no available epidemiological data that have evaluated the risk of MRONJ in patients who have undergone orally or intravenously administered BPs (22). Studies published so far suggest that it is not a common side effect but rather a very rare one (21).

Risk factors for developing MRONJ include operative treatment, anatomical factors, concomitant oral diseases, genetic factors, demographic, and systemic medication factors. Regarding operative treatment, the development of MRONJ is
usually initiated by dentists and oral- and maxillofacial surgeons during surgical interventions such as tooth extraction and implant installations. Thus, it is essential to make a risk assessment beforehand, regarding patients’ medical condition and medication history as well as to evaluate methods to prevent and eventually treat the condition (25,26).

**Dental implants and osseointegration**
A common method for the replacement of missing teeth is treatment with implant-supported prosthetics (27). The birth of modern dental implant treatment took place in the 1960s, pioneered by Per-Ingvar Brånemark, professor at the University of Gothenburg in Sweden, who discovered an intraosseous anchorage between living bone and titanium implants (28). Relying on this anchorage, the concept of osseointegrated implants was introduced in a 1969 report of 10-year clinical trials by Brånemark (29).

Osseointegration is a dynamic interaction between the dental implant surface and bone tissue. It was first defined by Brånemark as “a direct connection between living bone and a load-carrying endosseous implant at the light microscopic level” (p.24). Osseointegration is a structural and functional connection between the surface of alloplastic materials and organized, living bone without intervening soft tissue (30).

Dental implants are constructed of alloplastic material, primarily titanium. It is a biologically inert material because of its titanium oxide surface and does not set off a foreign body rejection reaction from host tissue (5). This biologically inert surface enables bone cells in the alveolar bone to attach to it without any interposing collagen and fibroblastic matrix making a clinically asymptomatic rigid fixation (30). Implant immobility, ankylosis occurs due to an absence of periodontal ligament and is an indirect sign of osseointegration which is a measure of implant stability (31). Osseointegration has been stated to be an immune-driven process that leads to new bone formation between the living bone and the surface of a dental implant by initiating an inflammatory reaction (32). A healing phase is later achieved which increases the strength of the interface by bone remodelling within 6-12 weeks after implant placement (4).

**Success rates**
There is still a lack of consensus regarding the criteria to define success rates in implant dentistry. Albrektsson et al. (33) proposed well-defined criteria of success stating that the absence of mobility and radiolucency around the implant as well as an absence of pain and infection after an implant treatment should be considered successful (33,34).

The following factors are also required for a successful outcome of any dental implant procedure (5):
1. Biocompatibility and macro/microscopic surface of the implant material.
2. Surgical technique, atraumatic surgery to minimize tissue damage.
3. Osseointegrated implant placement.
4. Immobility of the implant, relative to the bone, during the healing phase.

**Marginal bone loss**
MBL around dental implants after the placement has been subject to constant debate, whether it should be regarded as a success criterion or not. In certain
classifications and consensus statements including Albrektsson et al. (33), the loss of 0.2 mm MBL during the first year of so-called "physiological vertical marginal bone loss" of functional loading has been considered a successful outcome. Studies on titanium implants, the Brånemark system has shown that there is bone resorption of 0.9-1.6 mm during the first year after the distance surgery. The annual bone loss should after the first year lie at < 0.2 mm (35).

A published study by Galindo-Moreno et al. (35) has established the difference between physiological vertical MBL around dental implants and MBL due to peri-implantitis (inflammation of the soft and hard tissues surrounding dental implants). The study concluded that in cases where MBL is higher than 0.44 mm/year is an indication of peri-implant bone loss progression, therefore an increased risk of implant failure occurs at higher MBL. However, Galindo-Morena believes that a new success criterion should be developed based on MBL rates.

Survival rates
All treatments tend to inevitably propose survival- and failure rates. As in the case of dental implant treatment, a review of 14 prospective studies observed the survival rates for dental implants with follow-up periods of 10+ years. The review established survival rates averaging 94.6%, with mean MBL values of 1.3 mm (36). Although a high implant survival rate is presented, it is still of major importance to determine potential risk factors such as the influence of BPs on MBL around osseointegrated implants which has been evaluated by Zahid et al. (37). The retrospective study was conducted to determine the relationship between implant failure and BPs. The result revealed a relationship between BPs and MBL around dental implants, and that there might be a greater risk of MBL in patients taking BPs. However, there is no statistically significant relationship between BPs and implant failure (37).

A study by Mashiba et al. (38) demonstrated that increasing bone resorption may be due to the suppression of bone turnover by BPs. It was further reported by Komatsubara et al. (39) that long-term treatment with BPs increased microdamage accumulation which was studied using the cortical bone of dog rib. Microdamage accumulation is the amount of damage versus the amount of repair that is produced which might elevate by BPs due to the suppression of bone remodelling (36).

The available literature contains insufficient reports on osteoporotic patients on bone antiresorptive or antiangiogenic medication and dental implant treatment. Previous studies included all patients with several medical conditions such as malignities receiving bone antiresorptive and antiangiogenic medications. However, there were no systematic reviews with an aim focusing on only osteoporosis patients receiving these medications. In recent years it has been difficult to present actual evidence of how this specific medical condition, osteoporosis affect dental implant treatment. This is partly due to great heterogeneity in the patient material from the included examinations and partly because it is complex to assess in isolation as there are many confounders. Thus, it is important to systematize all available literature and primary studies from a clinical point of view as to whether osteoporotic patients on bone antiresorptive or antiangiogenic medication affects the procedure or is a contraindication for dental
1.2 Aim
The overall aim of this systematic review was to (i) to analyze the prognosis of dental implant treatment concerning MBL in patients undergoing or have undergone treatment with bone antiresorptive or antiangiogenic medication for osteoporosis (ii) and additional purpose to assess the available scientific literature in the first aim concerning the risk of developing MRONJ associated with dental implant installation.

1.3 Hypothesis
The scientific evidence currently available has revealed that patients with a history of bone antiresorptive and antiangiogenic medications are not at a higher risk of dental implant failure or MBL compared to healthy patients (35). A study by Zahid et al., could not suggest a statistically significant relationship between BP and implant failure (37). Thus, our hypothesis is that patients that have undergone or are undergoing treatment with bone antiresorptive or antiangiogenic medication for osteoporosis do not have impaired success of dental implant installation compared to patients without medication treatment.
2. MATERIAL AND METHODS
PICO Model (P = population, I = intervention, C = comparison, O = outcome) was used (shown in table 2) to form the focused question in this study which was as follows:

In patients who are undergoing or have undergone bone antiresorptive or antiangiogenic medication for osteoporosis, does the prognosis of dental implant treatment during or after medication concerning MBL deteriorate and if there is a risk of getting MRONJ associated with dental implant placement?

<table>
<thead>
<tr>
<th>Table 2. PICO</th>
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<tbody>
<tr>
<td><strong>Component</strong></td>
</tr>
<tr>
<td>Population (P)</td>
</tr>
<tr>
<td>Intervention (I)</td>
</tr>
<tr>
<td>Comparison (C)</td>
</tr>
<tr>
<td>Outcome (O)</td>
</tr>
</tbody>
</table>

The established inclusion- and exclusion criteria are as follows:

2.1 Inclusion criteria
Eligibility criteria included; human studies with age limitation (18+); administration of bone antiresorptive or antiangiogenic medication for osteoporosis before and during dental implant placement; a minimum of 1 implant/jaw/patient; retrospective-, prospective-, cohort studies, randomized controlled trials (RCTs), case series, single case reports > 5 cases; full text and electronically available publications for students at Malmö University, Sweden; studies should include evaluation of MBL or prognosis assessment, also an analysis of successful implant and risk for MRONJ in relation to fixture installation where MBL is evaluated.

2.2 Exclusion criteria
Exclusion criteria were animal studies; studies with a follow-up < 1 year; no history of osteoporosis; systematic reviews; studies published in languages other than English; studies without a major focus on the relationship between the dental implant and bone antiresorptive or antiangiogenic medication; patients previously treated with radiation in the neck and head region.

2.3 Literature Search
In October 2021 an initial electronic systematic literature search was conducted in the following three databases: MEDLINE/PubMed, Cochrane Library and Web of Science. The search was performed by two authors, A.K. and T.A. independently and consisted of two search blocks. Both search blocks included free-terms and Medical Subject Headings (MeSH) terms in MEDLINE/PubMed and Cochrane Library. MeSH are controlled terms and phrases designed by the National Library of Medicine to search in biomedical and health-related databases such as
MEDLINE/PubMed (40). Boolean operators are terms used to combine and specify two or more concepts in a search (41). The two search blocks were combined using the Boolean Operators “OR” and “AND” resulting in more focused and productive results for the literature search strategy.

The following search strings were used in the search strategy in all three databases applying the filter “English publications only”: ((((((bone antiresorptive medication [all fields]) OR (bone antiangiogenic medication [all fields])) OR (bone antiresorptive drugs [all fields])) OR (bone antiangiogenic drugs [all fields])) OR (denosumab [MeSH Terms])) OR (bisphosphonate [all fields])) OR (diphosphonates [MeSH Terms])) AND (((((dental implant treatment [all fields]) OR (oral implant [all fields])) OR (dental implants [MeSH Terms])) OR (dental implant failure [all fields])) OR (dental implant success [all fields])).

2.4 Study selection
The screening and selection process of the literature search was carried out following the criteria of Preferred Reporting Items for Systematic Reviews and Meta-analyses, PRISMA guidelines. PRISMA 2009 Flow Diagram (shown in figure 1) aims to improve the reporting of systematic reviews and meta-analyses (42).

Identified publications from the conducted searches in MEDLINE/PubMed, Cochrane Library and Web of Science were transferred into Mendeley, a free reference manager to aid with a collection of references, organize citations, create bibliographies, and remove duplicates. The titles and abstracts of all studies were identified through Mendeley (43).

The publications were read, excluded, and included according to the exclusion-and inclusion criteria. Publications that met the included criteria were obtained for further investigation and screening of their abstracts. Abstracts meeting the eligibility criteria were included for further investigation in a full-text screening. Publications that did not meet the criteria after a full-text screening were excluded. The remaining publications that met the eligibility criteria were included for quality assessment. The quality of all identified publications was assessed by A.K. and T.A. independently to minimize the risk of bias during evaluation. Disagreements between the two authors were resolved by discussion.

2.5 Quality assessment
All included publications were evaluated for the quality assessment using New Castle Ottawa Scale (NOS) guidelines (44). It is a comprehensive quality assessment of nonrandomized studies to be used in a systematic review and a biased assessment tool for observational studies. NOS provides flaws that may or have emerged from the review's poor conduct. It calculates the study quality based on three parameters and generates an overall rating scale based on a “star system” which assigns maximum stars or scores per parameter.

1. The selection of the study groups (maximum of 4 stars).
2. The comparability of the study groups (maximum of 2 stars).
3. The outcome for cohort studies (maximum of 3 stars).
NOS does not state criteria for high, moderate or low quality, however, a review by Chrcanovic et al. (27) states that a study of the highest quality represents a maximum of 9 stars, where \( \geq 6 \) stars were considered high quality and studies with \( \leq 6 \) were considered moderate to low quality.

### 2.6 Data extraction

The following data were extracted from included publications and documented independently by A.K. and T.A.: authors, year of publication, study design, focused questions, and conclusions. The following collected data are presented in tables 3 and 4.
3. RESULTS

3.1 Literature search
The literature search in all three databases resulted in 1167 studies. A total of 292 were duplicates that were removed using Mendeley. The remaining 872 studies were screened by titles and a total of 716 studies did not meet the eligibility criteria (e.g., animal studies, systematic reviews, case reports etc.) and were therefore excluded. A total of 156 records remained for screening of abstract whereas 125 studies were excluded. A total of 31 full-text studies were assessed for eligibility criteria and out of these, 27 were excluded because of different reasons.

A total of 152 studies were excluded after a screening of abstracts and full-text for not meeting the inclusions criteria. The studies were excluded due to for example absence of an evaluation of MBL as a focus question, consensus guidelines for the use of BPs, topical BPs application of the surface of dental implants, in vitro- and histological studies, reviews, and electronically unavailable publications for students at Malmö University, Sweden (further details are available on APPENDIX II).

As a result, a total of four studies were included in this systematic review and further quality was assessed using NOS. PRISMA flow diagram illustrates the screening and selection process in figure 1.
Figure 1. PRISMA 2009 Flow Diagram were used in the screening and selection process of the literature search.
3.2 Included studies

All four included studies (37,45–47) were retrospective. They were conducted on osteoporotic patients that are undergoing or have undergone oral BPs therapy before or during dental implant treatment. Detailed data of the included studies are presented in tables 3 and 4. Table 3 and 4 describes each of the included studies in terms of study design, aim (focused questions), study population, follow-up, methodology, outcome, and conclusions.

Shabestari et al., 2010 (45) evaluated the success outcome of dental implant treatment between 1998-2006 in postmenopausal osteoporotic patients submitted to long-term oral BP treatment. The study population consisted of patients with a mean age of 53 years who received weekly treatment with oral BPs (Fosamax, 35-70mg) during a minimum of 2 months continuously, and a mean duration of 20,5 months. A total of seven patients were on BP therapy before implant placement. The study did state a follow-up period ranging from 0,6-8,1 years for postsurgical clinical and radiographic examination to assess changes in marginal bone. The study did not state implant success or failure criteria.

Zahid et al., 2011 (37) examined if there is a greater risk of implant failure in osteoporotic patients on oral BPs than patients not using BPs. A total of 26 patients on oral BP therapy (with varied BPs duration and dosage) with a mean age of 56 years had their implants placed by postgraduate residents following a surgical protocol. Implant success was defined as clinical osseointegration without radiolucency and MBL less than 0,2mm/year after the first year of function. Postoperative follow-up was conducted after 26 months, ranging from 2 months to 78 months.

Bell & Bell 2008 (46) investigated if patients on oral BPs are at greater risk of bone graft and implant failure than patients not using BPs. A total of 42 patients, predominantly females (95%) were undergoing oral BP therapy in varying durations, ranging from 3 months to 5 years. A follow-up averaging 3,1 years month (ranging from 4 months to 7,5 years) was conducted. The study did not state implant success or failure criteria.

Mozzati et al., 2015 (47) assessed the risks of implant failure and BRONJ in osteoporotic patients receiving dental implant treatment with topical application of the dental surface by plasma rich in growth factor (PRGF) so-called Endoret® PRGF®. It enhances tissue vascularization and accelerates bone regeneration which stimulates bone and tissue healing. A large cohort of patients was studied, a total of 235 and undergoing dental implant placement with Endoret® PRGF® from 2004-2011. The minimum follow-up of the study was 24 months but ranged up to 120 months. This study has stated the following implant survival criteria: immobile at clinical examination and connected to a fixed prosthesis providing functional service, absence of signs or symptoms of pain or infection and an absence of peri-implant radiolucency in radiographic images.

Methodology of all studies

All four studies conducted a clinical and radiographic examination. Clinical parameters included bleeding on probing (BoP), probing depth (PD) and mobility to assess the clinical outcome of dental implants. Radiographic examination was conducted concerning changes in marginal bone by measuring thread exposure (TE), baseline and postoperative images were obtained at follow-up. Only
Mozzati et al. (47) stated that a yearly collection of panoramic and periapical images were obtained for determining changes in marginal bone.

Table 3. Extracted data of the included studies.

<table>
<thead>
<tr>
<th>No.</th>
<th>Author, year published</th>
<th>Study design</th>
<th>Aim</th>
<th>Patients (n)</th>
<th>Implants (n)</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Shabestari et al., 2010 (45)</td>
<td>Case series</td>
<td>To report the successful implant treatments in patients submitted to long-term treatments with oral BPs owing to postmenopausal osteoporosis.</td>
<td>7 patients</td>
<td>46</td>
<td>Average: 4.2 years (range: 0.6-8.1 years)</td>
</tr>
<tr>
<td>2</td>
<td>Zahid et al., 2011 (37)</td>
<td>Retrospective study</td>
<td>To examine whether patients who take BPs are at greater risk of implant failure than patients not using those agents.</td>
<td>26 patients</td>
<td>51</td>
<td>Average: 26 months (ranging: 2-78 months)</td>
</tr>
<tr>
<td>3</td>
<td>Bell &amp; Bell 2008 (46)</td>
<td>Retrospective study</td>
<td>To examine whether patients who take medications containing BPs are at greater risk of bone graft and implant failure than other patients.</td>
<td>42 patients</td>
<td>101</td>
<td>Average: 3.1 years (range: 4 months to 7.5 years)</td>
</tr>
<tr>
<td>4</td>
<td>Mozzati et al., 2015 (47)</td>
<td>Retrospective study</td>
<td>To assess the risk level as related to adverse events such as implant failure and BRONJ in a large cohort of osteoporotic patients submitted to implant placement and concomitant application of plasma rich in growth factor Endoret® PRGF®.</td>
<td>235 patients</td>
<td>1267</td>
<td>Average: 120 months (minimum 24 months)</td>
</tr>
<tr>
<td>No.</td>
<td>Author, year published</td>
<td>Methodology</td>
<td>Outcome (MBL)</td>
<td>Conclusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----</td>
<td>------------------------</td>
<td>-------------</td>
<td>---------------</td>
<td>------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Shabestari et al., 2010 (45)</td>
<td>Clinical examination: - BoP - PD - Mobility Periapical radiographic examination: - TE</td>
<td>No TE in 29,66% of all kinds of prosthetic options. 6,3% showed three TE</td>
<td>BP therapy showed no statistically significant influence on PD, BoP, and TE (P &gt; 0,05) Not enough data is available to prove a causal link between the use of oral BPs and ONJ.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Zahid et al., 2011 (37)</td>
<td>Clinical examination: - Mobility Radiographic examination by a collection of panoramic and/or periapical radiographs.</td>
<td>Implant success criteria: clinical osseointegration without radiolucency and MBL &gt;0,2mm/year after the first year of service Implant success rate: 94% Implant failure criteria: mobility and absence of implant in the oral cavity. Three implants failed, yielding success rates of 94,11% and 88,46% for implant-based and subject-based analyses.</td>
<td>Statistically significant relationship (P=0,001) association between the use of BPs and TE. No statistically significant relationship between BP and implant failure. No cases of MRONJ were observed. Patients taking BP may be at higher risk for implant TE.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Bell &amp; Bell 2008 (46)</td>
<td>Clinical examination: - BoP - PD Panoramic and periapical radiographic examination: - Height of the ridge</td>
<td>5 implants failed Implant success rate: 95% 1 patient experienced 2mm MBL (stopped using BPs 1 year before follow-up appointment, but 2 years after implant placement) No other patients had clinical or radiographic signs of MBL</td>
<td>Patients on BPs are at no more risk of an implant or bone graft failure than other patients. No patients showed signs of MRONJ.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.3 Quality assessment

All four included studies were further quality assessed using NOS. Two studies were estimated “high quality”, one was of “moderate quality” and the other of “low quality”. The scores are summarized in table 5.

Table 5. Quality assessment of the included studies by NOS.

<table>
<thead>
<tr>
<th>No.</th>
<th>Author, year published</th>
<th>Selection</th>
<th>Comparability</th>
<th>Exposure/Outcome</th>
<th>Total stars (max. 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Shabestari et al., 2010 (45)</td>
<td>★★★</td>
<td>-</td>
<td>★</td>
<td>★★★★ 3/9</td>
</tr>
<tr>
<td>2</td>
<td>Zahid et al., 2011 (37)</td>
<td>★★★★</td>
<td>-</td>
<td>★★</td>
<td>★★★★★ 5/9</td>
</tr>
<tr>
<td>3</td>
<td>Bell &amp; Bell 2008 (46)</td>
<td>★★★★</td>
<td>-</td>
<td>★★★</td>
<td>★★★★★★ 6/9</td>
</tr>
<tr>
<td>4</td>
<td>Mozzati et al., 2015 (47)</td>
<td>★★★★</td>
<td>-</td>
<td>★★★</td>
<td>★★★★★★ 6/9</td>
</tr>
</tbody>
</table>

* BoP = bleeding on probing
† BP = bisphosphonate
* PD = probing depth
+ TE = thread exposure

No cases of BRONJ were reported. Neither oral BP therapy nor osteoporosis seem to affect dental implant survival.
4. DISCUSSION

4.1 Method discussion

**Literature search**

Three databases were used for the literature search: MEDLINE/PubMed, Cochrane Library and Web of science. It is advisable to use multiple databases for optimal searches in a systematic review, a minimum of three databases should be included. According to “Cochrane Handbook for Systematic Reviews of Intervention” (48) and “Developing NICE guidelines” (49) it is not considered enough to conduct a literature search in one database. To avoid the risk of distortion of the results of the overview results by articles being missed, several databases should be searched (50,51).

To ensure the retrieval of all relevant studies within the relevant topic a combination of free-terms and MeSH terms were used. This generated a large number of results which indicated a broad search spectrum hence will most likely produce multiple irrelevant articles. The search strategy was therefore narrowed to increase the sensitivity and therefore produce greater accuracy of relevant articles by excluding the following terms from the search blocks; "orally", "osteoporosis", "marginal bone loss" and "prognosis". The search result displayed all pharmacological treatments administered orally and all osteoporosis patients with or without dental implants. "Marginal bone loss" and "prognosis" were not used due to a wide spectrum of all cases with MBL and prognosis not related to dental implants. Nevertheless, it is of great importance to have in mind that with a narrower search, a loss of relevant literature is inevitable (52). Booth et al., 2016 (53) described in their book "Systematic approaches to a successful literature review" the design of literature searches with different purposes. Andrew states that a search with two combined search blocks applying the Boolean operators "AND" gives a narrow search spectrum with a higher percentage of relevant articles.

**Inclusion- and exclusion criteria**

Single case reports >5 cases were included to minimize the risk of outcome regarding MBL and MRONJ, which can occur spontaneously. Follow-up less than one year is an exclusion criterion as we wanted to make sure that MBL is not a result of biological bone resorption around dental implants' so-called "biological width"(54). The most used criterion for implant success is an allowance of 0,2mm vertical bone loss around osseointegrated dental implants the first year. Another exclusion criteria were patients that had previously been treated with radiation in the neck and head region. This exclusion aimed to remove these patients because they already have a risk factor that could affect the results by inducing MRONJ (55).

**Full-text assessment**

The main reason only four articles were included was that most available studies did not answer our first aim and were therefore excluded. A range of studies (67, 70, 71, 76, 79, 81) were not electronically available for students at Malmö University. Different methodologies were conducted in three other studies (66, 73, 75) relying on questionnaire and satisfaction parameters regarding dental implant
survival. During the full-text assessment of two studies (68, 86) it was later mentioned that patients received high doses of intravenous BPs. Four studies (69, 82, 83, 88) evaluated dental implant treatment outcomes in patients on antiresorptive medication, nevertheless they did not state the patients’ medical diagnosis. There were four studies (56–59) that evaluated the risk of developing MRONJ in patients on BP therapy associated with dental implant installation but did not analyze the prognosis of MBL in patients undergoing or have undergone treatment with bone antiresorptive or antiangiogenic medication for osteoporosis. Therefore, all the previously mentioned studies (shown in APPENDIX II) were not included in the quality assessment.

**Quality assessment**

The quality assessment protocol was made of a modified version of the NOS checklist for assessing both case-control studies and cohort studies. This systematic review included one case-control study and three cohort studies, making it beneficial to use the NOS quality assessment protocol for all included studies. There was a difficulty in adjusting other protocols to suit all our included study designs (one case-control study and three cohort studies). Other protocols could have been used such as STROBE but a modified version of NOS made it easier and relatively quick to adapt the questions to our outcomes and was therefore considered to suit our systematic review. Though by modifying the protocol some cred may be lost and lead to alteration of the quality assessment. This is noted in Shabestari et al. (45) who included only 7 patients but still received a high score on NOS. In addition, NOS did not specify the number of stars considered to be of high/moderate/low quality.

**Study design**

Due to a limited number of included studies in this systematic review, additional studies are required to evaluate the effects on this patient group concerning osseointegration of dental implant regarding MBL. Three of the included studies (37, 46, 47) were retrospective which are more efficient for diseases with a long latency period. Weaknesses with retrospective studies are that records used are not designed for the study and the available data is of poor quality (61). Therefore, some prospective studies should have been included to enable a more trustworthy study but there were none in the literature search that answered our aims. In particular, RCTs which are globally perceived as “gold standard” in the hierarchy of evidence for the evaluation of health care outcomes. Nonetheless it is impractical for the evaluation of MBL in osteoporotic patients on bone antiresorptive or antiangiogenic medication which will be further discussed in the “Ethical consideration” section.

One included study by Shabestari et al. (45) were a case study. Case studies are descriptive by illustrating atypical features in patients in medical practice therefore providing multiple cases as a beneficial tool and learning experience among researchers. However, case studies display a lack of clinical implications, and the presented cases are not generalizable. This study by Shabestari et al. is an observational one that reports data from a subject group, in this case osteoporotic patient receiving oral BP treatment, without a comparison population hence it is prone to selection bias (90, 91). Nevertheless, data collections were randomly selected as the included patients which were provided written informed consent, were treated with dental implants during the period of 1998 and 2006 in Tehran,
Iran. A random selection of data ensures that results obtained from the included studies are impartial.

4.2 Result discussion
The result of the present study cannot suggest a significant relationship between BPs and implant failure, regarding MBL as well as no cases of MRONJ were observed. Shabestari et al. (45) reported that not enough data were available to prove the causal relationship between MRONJ and the use of oral BPs in patients with a history of osteoporosis. These results are in line with a systematic review and meta-analysis by Stavropolous et al. (62) reporting that patients taking BPs treatment for osteoporosis does not have a higher risk of implant failure or complications compared to patients without oral BPs. Another meta-analysis by Chrcanovic et al. (27) concluded that due to a limited number of studies it cannot yet be suggested that BPs affect the MBL of dental implants.

To analyze appropriately the survival and failure of dental implants there is a need for consensus regarding the criteria. To ensure that the result of each study is interpreted accordingly, it is essential to be clear about the definition of what every author considers as an implant survival or success versus failure rate. The following studies by G. Shabestari, B. Bell and T. Zahid (37, 45, 46) have not stated a definition regarding implant survival. On the other hand, Zahid et al. defined implant success as clinical osseointegration of implants without radiolucency and an annual bone loss to be less than 0.2 mm after the first year of function. Bell and Bell (46) do not state a definition regarding implant success. Implant mobility or implant which was no longer present in the mouth were considered an implant failure. In a study by Mozzati et al. (47) implant survival was defined by T. Albrektsson et.al (32) whereas an implant must be immobile and connected to a fixed prosthesis providing functionality. The clinical findings should indicate an absence of signs or symptoms of pain or infection as well as the radiological evaluation should not show peri-implant radiolucency.

The lack of defining implant survival and failure makes it difficult for reviewers to interpret the result and outcome. In some way, it will increase the risk of bias due to the lack of objective judgment of the authors during the assessment of the result and outcome. This in turn leads to an alteration of our result and conclusion. Studies have reported success rates of dental implants over a 10-year course to be 90-95% (93) and failure rates 5-10% (94). An interpretation of the success rates will deceive the reader into believing that such rates are exclusively of significant value, meanwhile an interpretation of the failure rates changes one’s perception of this treatment of choice. Thus, presented rates of dental implant treatment should be interpreted with caution to avoid distortion of data in research.

Methodology
The 4 included studies used clinical and radiographic examination as the methodology. The clinical examination contained the following parameters: BoP, PPD and mobility. In addition to the clinical examinations, T. Zahid conducted a periapical radiographic examination.

B. Bell and T. Zahid conducted a similar type of radiographic examination by collecting periapical as well as panoramic radiographs. Periapical radiographs have shown higher accuracy of marginal bone height (63) compared to panoramic...
radiographs. In a review by Rushton et al. (64) it was reported that panoramic radiographs have a low reliability and image quality to detect small-scale MBL. Therefore, there is higher uncertainty in the assessment of MBL and TE in dental implants.

**Number of patients**

There was a difference in the number of patients included in the 4 studies. G. Shabestari included 7 patients, T. Zahid 26, B. Bell 42 meanwhile M. Mozzati included a total of 235 patients. A low number of patients will not give a representative sample to accurately reflect the characteristics of a larger group taking oral BPs for osteoporosis. There is a higher risk of a random and spontaneous outcome and will most likely be false therefore not representative of the population. All four included studies reported MBL in dental implants at baseline by different types of x-rays (periapical and panoramic x-ray) and had follow-ups. However, they could not with certainty establish a relationship between MBL in osteoporotic patients on BP therapy. The studies did not observe MRONJ as an outcome during dental implant installation in osteoporotic patients on BP therapy.

**Risk factors**

In a retrospective study by M. Mozzati patients had risk factors such as smoking, diabetes, and chronic use of corticosteroids. The study mentions that implant failure may have been the result of the risk factors of the patient. In a thesis written by S. Sayardoust (65), it was concluded that the overall dental implant survival rate was lower in smokers compared to non-smokers. Smokers have higher MBL in dental implants during the healing stage and long-term (5 years) compared to non-smokers. M. Mozzati reported that complications of implant failure arose in the presence of combining two risk factors such as a history of diabetes, smoking and/or corticosteroids.

M. Mozzati also presented the use of Endoret® PRGF® as a topical application on dental implants which could have supported all healing stages by the stimulation and acceleration of tissue healing and bone regeneration, primarily in patients on BP therapy. No cases of MRONJ occurred throughout the observation period which is in line with another retrospective study by B. Bell.

B. Bell concluded that patients on oral BPs are not at a greater risk of implant failure than patients not using BPs. However, a total of 5 implant failures occurred of the 100 implant placement giving a 95% implant success. It is comparable to the success rate of 96,5% of implant placement by the same operation in patients not taking BPs. The authors have stated that implant failures are not related to BP treatment but to possible placement location and patients risk factors. The present data by M. Mozzati resulted in a total of 16 implant failures occurring in 16 patients, essentially where a strong association was confirmed in the maxilla requiring a sinus lift. It was noted that sinus lift is a factor with the heaviest impact on implant failure rate for patients receiving Endoret® PRGF® but the authors did not state any scientific evidence behind this relationship. The data by B. Bell showed to be consistent with the higher risk of implant failure in patients who smoke and the posterior maxilla, which is in line with the conclusion made by M. Mozzati.
Follow-up
It is of importance to point out the follow-up period for postsurgical clinical and radiographic examination to assess changes in marginal bone. It varied substantially between the studies; it was ranging from 2 months to 8 years. A longer follow-up period after dental implant installation leads to a higher chance of detecting implant failure.

4.3 Ethical consideration
In order to effectively help distinguish between the actual effects of oral BPs of osteoporotic patients regarding MBL around dental implants and those arising from other factors, there will be a need of control groups. It has been universally acclaimed by researchers that RCTs are regarded as “gold standard” providing the best evidence-based evaluations due to their potential of limiting all sorts of bias. Treatments and interventions are performed under very meticulous conditions ensuring that confounders are evenly distributed by the help of treatment- and control group. The lack of a control group leads to the difficulty of knowing if changes have arisen from the given treatments. A study by Brody et al. (60) concluded the case of placebo controls used in subjects with osteoporosis would be put at substantial risk of serious outcomes and are thereby not ethically permissible.

Ethical considerations have been emphasized by the Belmont Report (92), whereas researchers are required to follow the four principles of ethics; beneficence, nonmaleficence, autonomy, justice and are therefore expected to minimize the risk outcomes of human subjects’ participation. A control group of osteoporotic patients denied their best available medical treatment by not receiving bone antiresorptive or antiangiogenic medication will be exposed to some substantial risks. Increased fractures rendering patients unable to walk unassisted and elevate risk of premature death are few illustrations of multiple outcomes of such clinical research. Hence, a control group of this character contradicts the ethical principle of beneficence and nonmaleficence and will presumably be ethically disapproved by the regulatory bodies.

4.4 Dental and societal perspective
General dentists and oral- and maxillofacial surgeons need to be made aware of this important topic regarding osteoporotic patients on bone antiresorptive or antiangiogenic medication during surgical interventions such as dental implant installations. It is of importance to make a risk assessment beforehand, regarding patient’s medical condition and medication history to minimize the possibility of an increased negative MBL and occurrence of MRONJ with time which can eventually lead to implant loss. Furthermore, for optimal implant installation and other operative treatment it is crucial to evaluate methods to prevent and eventually treat the condition on a societal level and with regard to sociodemographic. On a societal level dental implants have a favorable impact on the quality of life which was evaluated in a research article by Sargolzaie et al. (95). According to our results replacement of missing teeth by the help of dental implants is considered possible in osteoporotic patients on bone antiresorptive or antiangiogenic medication. The physiological impact of tooth loss causing emotional distress will thereby be avoided.
5. CONCLUSIONS
The results of this present study cannot suggest that dental implant treatment in patients with osteoporosis undergoing or have undergone bone antiresorptive or antiangiogenic medication is at an increased risk of MBL during follow-up periods. The present data assessing the risk for developing MRONJ associated with dental implants remain low for osteoporotic patients receiving oral BPs. Therefore, dental implant surgery is considered possible in osteoporotic patients receiving bone antiresorptive or antiangiogenic medication. However due to a limited number of published studies characterized by a lack of proper control groups, an evaluation of the effects on this patient group concerning osseointegration of dental implant regarding MBL needs to be established through additional studies.
6. REFERENCES


27. Albrektsson T, Chrcanovic BR, Wennberg A. Bisphosphonates and


34. Aghaloo T, Moy P. Which hard tissue augmentation techniques are the most successful in furnishing bony support for implant placement?. Int J Oral Maxillofac Implants. 2007;22:49-73.


67. Famili P, S. Quigley, Mosher T. Survival of dental implants among post-


90. Sayre JW, Toklu HZ, Ye F, Mazza J, Yale S. Case reports, case series - From clinical practice to evidence-based medicine in graduate medical


APPENDIX I

Quality Assessment Protocol
Newcastle-Ottawa Quality Assessment Scale (NOS)

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

<table>
<thead>
<tr>
<th>No.</th>
<th>Criterion</th>
<th>Decision rule</th>
<th>Score: (<em>=1 no</em>=0)</th>
<th>Location in text</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>SELECTION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Is the case definition adequate?</td>
<td>a. Yes, with independent validation (&gt;1 person/record/time/process to extract information, or reference to primary record sources such as x-rays or structured injury data)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>b. Yes, based on self-reports</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>c. No description</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Representativeness of the cases</td>
<td>a. Consecutive or obviously representative series of cases*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>b. Not satisfying requirements in part (a), or not stated.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Selection of controls</td>
<td>a. Community controls (e.g. controls selected from the same source population as the cases*)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>b. Controls were selected from a different source population</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>c. No description</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Definition of controls</td>
<td>a. No history of BP therapy*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>b. No description of injury history</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>COMPARABILITY</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Comparability of cases and controls on the basis of the design or analysis</td>
<td>a. Study controls for marginal bone loss cases on BP therapy due to osteoporosis vs non-BP therapy*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>b. Study controls for additional factors* (e.g., MRONJ)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>EXPOSURE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Ascertainment of exposure</td>
<td>a. Structured injury data (e.g., record completed by medical/dental staff, x-rays)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>b. Structured interview was blinded to case/control status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>Criterion</td>
<td>Decision rule</td>
<td>Score (<em>=1, no</em>=0)</td>
<td>Location in text</td>
</tr>
<tr>
<td>-----</td>
<td>-----------</td>
<td>---------------</td>
<td>---------------------</td>
<td>-----------------</td>
</tr>
</tbody>
</table>
| 2   | Same method of ascertainment for cases and controls | a. Yes*  
b. No | | |
| 3   | Non-response rate | a. Same rate for both groups*  
b. Non-respondents described  
c. Rate different and no designation | | |

**SCORE:**

**COHORT STUDIES**

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability
|   | Demonstration that outcome* of interest was not present at the start of the study | a. Yes*  
b. No or not explicitly stated |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>*Outcome = marginal bone loss around the implant, MRONJ</td>
<td></td>
</tr>
</tbody>
</table>

**COMPARABILITY**

| 1 | Comparability of cohorts on the basis of the design or analysis | a. Study controls for cases on BP therapy due to osteoporosis vs non-BP therapy*  
b. Study controls for additional factor* (e.g., marginal bone loss and/or MRONJ) |

**OUTCOME**

| 1 | Assessment of outcome | a. Independent blind assessment stated*  
b. record linkage*  
c. Self-report  
d. No description |

| 2 | Was follow-up long enough for outcomes to occur? | a. Yes (≥1 year) *  
b. No (<1 year) |

*Note! The exclusion criteria are < 1 year.*

| 3 | Adequacy of follow up of cohorts | a. Complete follow-up – all subjects accounted for*  
b. Subjects lost to follow up unlikely to introduce bias - small number lost (<15% lost to follow up, or description provided of those lost*)  
c. Follow up rate <85% and no description of those lost provided  
d. No statement |

**SCORE:**
APPENDIX II

APPENDIX II: excluded studies from full-text assessment

<table>
<thead>
<tr>
<th>No.</th>
<th>Author, publication year</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Al-Sabbagh M et al., 2015 (66)</td>
<td>Patient interview and patient satisfaction parameters.</td>
</tr>
<tr>
<td>2</td>
<td>Dubey P et al., 2020 (56)</td>
<td>Absence of radiological follow-up of marginal bone loss.</td>
</tr>
<tr>
<td>3</td>
<td>Famili P et al., 2011 (67)</td>
<td>Study not electronically available for students at Malmö University.</td>
</tr>
<tr>
<td>4</td>
<td>Fugazzotto P et al., 2007 (68)</td>
<td>Intravenous administration of BPs.</td>
</tr>
<tr>
<td>5</td>
<td>Goss A et al., 2010 (69)</td>
<td>Does not specify the reason to BPs administration.</td>
</tr>
<tr>
<td>6</td>
<td>Jahan S et al., 2019 (70)</td>
<td>Study not electronically available for students at Malmö University.</td>
</tr>
<tr>
<td>7</td>
<td>Kasai T et al., 2009 (71)</td>
<td>Study not electronically available for students at Malmö University.</td>
</tr>
<tr>
<td>8</td>
<td>Kim J et al., 2020 (72)</td>
<td>Patients on antiresorptive after implant installation and already preexisting MBL.</td>
</tr>
<tr>
<td>9</td>
<td>Koka S et al., 2010 (73)</td>
<td>Questionnaire and no measurement of marginal bone loss.</td>
</tr>
<tr>
<td>10</td>
<td>Kwon T et al., 2014 (57)</td>
<td>Does not answer our first aim.</td>
</tr>
<tr>
<td>11</td>
<td>López-Cedrún J et al., 2013 (58)</td>
<td>Does not answer our first aim.</td>
</tr>
<tr>
<td>12</td>
<td>Lazarovici T et al., 2010 (74)</td>
<td>Survey and does not answer aim.</td>
</tr>
<tr>
<td>13</td>
<td>Martin D et al., 2010 (75)</td>
<td>Questionnaire and self-report of implant failure.</td>
</tr>
<tr>
<td>14</td>
<td>Memon S et al., 2012 (76)</td>
<td>Study not electronically available for students at Malmö University.</td>
</tr>
<tr>
<td>15</td>
<td>Pandey A et al., 2019 (77)</td>
<td>Does not answer our aims.</td>
</tr>
<tr>
<td>16</td>
<td>Pichardo S et al., 2020 (78)</td>
<td>&lt; 5 patients.</td>
</tr>
<tr>
<td>17</td>
<td>Ruocco-Vetucci V et al., 2019 (79)</td>
<td>Study not electronically available for students at Malmö University.</td>
</tr>
<tr>
<td>18</td>
<td>Ryu J et al., 2021 (59)</td>
<td>Does not answer our first aim.</td>
</tr>
<tr>
<td>19</td>
<td>Savoldelli C et al., 2007 (80)</td>
<td>Full text in Spanish, abstract in English.</td>
</tr>
<tr>
<td>20</td>
<td>Schmitt C et al., 2017 (81)</td>
<td>Study not electronically available for students at Malmö University.</td>
</tr>
<tr>
<td>21</td>
<td>Suvarna S et al., 2016 (82)</td>
<td>Patients do not have osteoporosis.</td>
</tr>
<tr>
<td>22</td>
<td>Tallarico M et al., 2016 (83)</td>
<td>Patients do not have osteoporosis.</td>
</tr>
<tr>
<td>23</td>
<td>Tam Y et al., 2014 (84)</td>
<td>&lt; 5 patients had osteoporosis, only 2 took oral BP.</td>
</tr>
<tr>
<td>24</td>
<td>Taxel P et al., 2014 (85)</td>
<td>Does not answer our aims.</td>
</tr>
<tr>
<td>25</td>
<td>Troeltzsch M et al., 2016 (86)</td>
<td>In the full text it is revealed the patients take i.v. BP.</td>
</tr>
<tr>
<td>26</td>
<td>Wagner F et al., 2017 (87)</td>
<td>Only 5 patients.</td>
</tr>
<tr>
<td>27</td>
<td>Yip J et al., 2012 (88)</td>
<td>Does not mention if the patients have osteoporosis.</td>
</tr>
</tbody>
</table>