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THÈSE POUR LE

DIPLÔME D'ÉTAT DE DOCTEUR EN CHIRURGIE DENTAIRE

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Ostéonécrose des maxillaires liée aux médicaments en contexte péri-implantaire : conséquence de la chirurgie ou de la présence de l'implant ? Une revue systématique de la littérature

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Table des abréviations

Abreviations	*Anglais*	*Français*
BRONJ	Bisphosphonate-Related Osteonecrosis of the Jaw	Ostéonécrose des mâchoires liée aux bisphosphonates
IPTO	Implant presence-triggered osteonecrosis of the jaw	Ostéonécrose des mâchoires déclenchée par la présence d'un implant
IV	Intravenous	Intraveineux
MRONJ	Medication related osteonecrosis of the jaws	Ostéonécrose des mâchoires liée à la prise de médicaments
ONJ	Osteonecrosis of the jaw	Ostéonécrose des machoires
OP	Osteoporosis	Ostéoporose
SC	Subcutaneous	Sous-cutané

Abstract

Introduction

Medication related osteonecrosis of the jaws (MRONJ) is a rare complication associated with antiresorptive therapies such as bisphosphonates and denosumab. Dental implants may involve a risk, either due to the surgical procedure or the long-term presence of the implant. Recent studies suggest that peri-implant infections and mechanical stress may contribute to implant-related MRONJ. This review aims to evaluate whether implants constitute a direct risk factor and to distinguish between surgery-induced and implant-related MRONJ in patients under antiresorptive treatment.

Methods

A bibliographic search was conducted in the PubMed, Embase, Web of Science, and Cochrane Library databases to identify relevant studies published between 2014 and 2024. The inclusion criteria encompassed retrospective and prospective studies, as well as case series, involving patients treated with bone resorption inhibitors who had received dental implants. The studies were evaluated based on their level of evidence, using the GRADE system.

Results

Out of 301 patients included, 185 developed peri-implant MRONJ, representing 61% of the cases. Among these patients, 222 were treated with low-dose bisphosphonates, and 78 received high doses (a case with no details provided about the type of treatment). In most cases, MRONJ develops more than 6 to 12 months after implant placement, whether the implant was inserted before or after the initiation of antiresorptive therapy. This suggests that the long-term presence of the implant may represent a greater risk factor than the surgical procedure itself, consistent with the 6- to 12-month threshold commonly cited in the literature.

I- Introduction

Medications-related osteonecrosis of the jaws (MRONJ) is a rare condition characterized by bone necrosis in the maxillary regions, often associated with severe degradation of bone structure and significant clinical symptoms such as pain and infections. It presents as one or more necrotic bone lesions that may be exposed or probed through an intraoral or extraoral fistula in the maxillofacial region, persisting for at least 8 weeks [1–3]. American Association of Oral and Maxillofacial Surgeons (AAOMS) in 2014 suggested a nomenclature change from BRONJ (Bisphosphonate-Related Osteonecris of the Jaw) to MRONJ (Medication Related Osteonecrosis of the Jaw) [3]. It is recognized as a complication of treatments with bone resorption inhibitors, such as bisphosphonates and denosumab, which are used to treat bone disorders like osteoporosis and bone metastases resulting from malignant conditions [4,5]. Anti-angiogenics may also be involved, but they are often used in combination with other treatments.

Since the first cases of MRONJ associated with the use of anti-resorptive agents were described by Marx in 2003 [1,3,6], the MRONJ has become a significant concern for dental surgeons. Maxillary osteonecrosis leads to irreversible consequences for patient's oral health. It has long been known that the risk of MRONJ is correlated with the indication for treatment, being higher in oncological cases, as well as with cumulative dosage (duration and dosage of the treatment). For denosumab, the timing of surgery should be as far as possible from the last dose of medication. Among the most important risk factors for triggering osteonecrosis in patients on bisphosphonates are surgical procedures, such as dental extractions [3,7,8]. This has led to a certain caution among dental surgeons when performing surgical procedures on these patients [3]. That is why is ongoing controversy about whether it is safe to proceed with surgical implants procedure in patients taking bisphosphonates for bone diseases. However, implants are the gold standard for replacing lost teeth, providing a fixed, comfortable, and aesthetic solution while restoring masticatory efficiency [9].

So, implant placement, like any surgical procedure, is considered a potential trigger for MRONJ. However, there is little information in the literature regarding the actual risk associated with implant surgery or the presence of implants in patients treated with bisphosphonates or denosumab.

Recently, Yong et al. suggested that implant presence-triggered osteonecrosis of the jaw (IPTO) is the consequence of combined peri-implant infectious and mechanical damage [43]. Thus, the

mere presence of the implant itself may interfere with local blood circulation, leading to bone necrosis. Furthermore, occlusal trauma, such as bruxism or excessive masticatory forces, may induce bone loss around the implant. In addition, peri-implant periodontal disease (peri-implantitis) can lead to progressive bone injury and evolve into osteonecrosis. Given the delayed onset of MRONJ, it is sometimes difficult to distinguish between cases caused by the surgical procedure itself and those related to the long-term presence of the implant. Various authors have proposed different timelines for this differentiation. According to Giovannacci et al. [44], the threshold appears to be 12 months post-implant surgery, whereas Kwon et al. [11] and Yong et al. [43] suggest a shorter period of 6 months.

The aim of this systematic literature review was to examine the available studies on dental implant placement in patients undergoing treatment with antiresorptive agents, in order to determine whether dental implants represent a direct risk factor for MRONJ, and to distinguish whether this risk is more closely associated with the surgical procedure itself or with the prolonged presence of the implant in patients treated with antiresorptive drugs.

II- Material and methods

A literature review was conducted in accordance with the PRISMA statement. The clinical question in 'PICO' format (population, intervention, comparison, outcome) for our study was:

'Are dental implant osteointegration or implant placement risk factors for peri-implant osteonecrosis in patients treated with bone resorption inhibitors ?'

a- Search strategy

A bibliographic search was conducted in the databases PubMed, Embase, Web of Science, and Cochrane Library. Article selection was based on their relevance, initially assessed through their titles, followed by their abstracts, and finally their full texts.

The following MeSH (Medical Subject Headings) terms: 'osteonecrosis', 'medication-related osteonecrosis', 'MRONJ', 'BRONJ', 'jaw' 'maxilla' or 'mandible' and their associated entry terms were used in various combinations with the Boolean operators 'AND' and 'OR' for the search.

Table 1 : Search strategies used on PubMed, Cochrane Library, Embase, and Web of Science

PubMed **From 2014 to 2024**	((osteonecrosis OR "medication-related osteonecrosis" OR MRONJ OR BRONJ) AND (jaw OR maxilla OR mandible)) AND (bisphosphonate OR denosumab OR antiresorptive OR anti-angiogenic OR sunitinib OR bevacizumab) AND (dental implant OR oral implant)
Cochrane Library **From 2014 to 2024**	((osteonecrosis OR "medication-related osteonecrosis" OR MRONJ OR BRONJ) AND (jaw OR maxilla OR mandible)) AND (bisphosphonate OR denosumab OR antiresorptive OR anti-angiogenic OR sunitinib OR bevacizumab) AND (dental implant OR oral implant)
Embase **From 2014 to 2024**	('jaw osteonecrosis'/exp OR 'medication related osteonecrosis of the jaw'/exp) AND ('bisphosphonate'/exp OR 'denosumab'/exp OR 'antiresorptive agent'/exp OR 'angiogenesis inhibitor'/exp) AND ('dental implant'/exp)
Web Of Science **From 2014 to 2024**	((osteonecrosis OR "medication-related osteonecrosis" OR MRONJ OR BRONJ) AND (jaw OR maxilla OR mandible)) AND (bisphosphonate OR denosumab OR antiresorptive OR anti-angiogenic OR sunitinib OR bevacizumab) AND (dental implant OR oral implant)

b- Data extraction

Study and reference management was performed using the Zotero software. Data were extracted and organized into predefined tables.

c- Selection criteria

To be included, studies had to be published in English between 2014 and 2024, covering a relatively recent and broad period in scientific publications. The studies had to involve patients with a history of treatment with bone resorption inhibitors and implant surgery or those who were about to begin one of these treatments. Accepted study types were: prospective studies, retrospective studies, and case series.

Exclusion criteria were: in vitro studies, systematic reviews, meta-analyses, studies published in languages other than English, patients with a history of facial radiation therapy, and those without bone metastases in the maxillary region.

III- Results

The initial search resulted in 430 articles (Figure 1). After removing duplicates, 227 articles were identified. Following a review of the titles and abstracts, 28 articles were retained, and finally, 17 articles were included after reading the full texts. No articles showing the role of antiangiogenic treatments were found in the search.

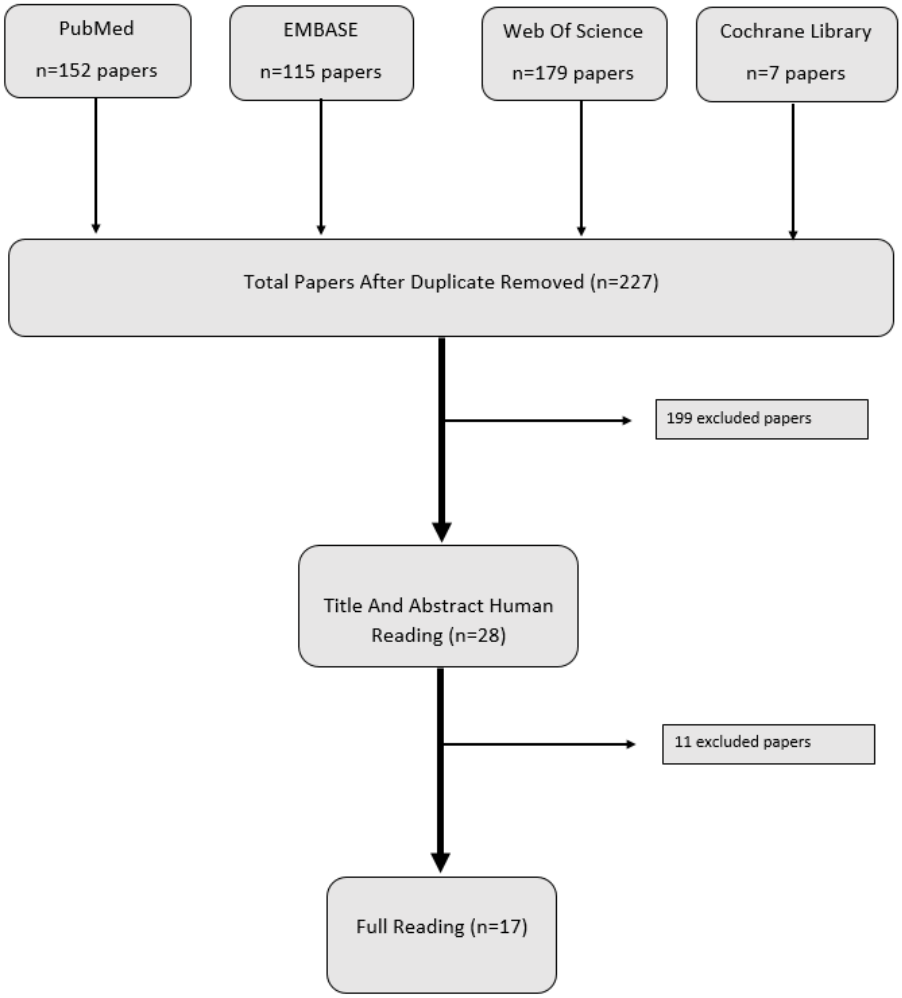

Fig 1. Flowchart of studies selection

In total, there were 5 retrospectives studies [11–15], 3 prospectives studies [16–18] and 9 case series [19–27] included. The average sample size was 17.7. A total of 301 patients treated with bone resorption inhibitors were included in this study (Table 3). In total, 597 implants were analyzed. Among the 301 patients, 222 were treated with low-dose bisphosphonates (for osteoporosis), and 78 were treated with high-dose bone antiresorptive agents (denosumab and bisphosphonates) for cancer or myeloma. None of the patients were receiving an anti-angiogenic agent in addition to their treatment.

Table 3: summary of studies providing data on medication-related osteonecrosis of the jaws

Author / year	*Number of cases/controls*	*Number of implant*	*Type of medication*	*Indication of medication*	*Route of administation*	*Treatment duration (months)*	*Ratio of peri-implant MRONJ to the number of implants*	*Time between implantation and MRONJ*	*Location of péri-implant MRONJ*
Kwon and al.	33	47	Alendronate Ibandronate Zoledronate Risedronate Denosumab	32 osteoporosis 1 breast cancer	Oral and IV	61.37	33 47 implants	51.03 +/- (39.75) months	31 mandible 2 maxillary
Pichardo and al.	18	47	Zoledronate Alendronate Risedronate Denosumab (Xgeva)	11 osteoporosis 7 breast/prostate cancer	Oral and IV	OP = 60 Cancer = 18	18 30 implants	24 months (osteointegrated implants before medication) 6 months (implant during medication)	12 Mandible 6 Maxila
Troeltzsh and al.	34	117	Zoledronate Pamidronate Ibandronate Denosumab	5 osteoporosis 29 oncology	Oral and IV	39.8	19 62 implants	45.4 months	13 mandible 2 maxilla 4 no data
Massaad and al.	6	43	Zoledronate Alendronate Denosumab	4 osteoporosis 1 Breast cancer 1 prostate cancer	Oral and IV and Sc	36	6 17 implants	12.5 years (implant before antiresorptive drugs) 4.6 years (antiresorptive drug before implant)	11 maxilla 6 mandible
Suvarna and al.	112	140	Alendronate Ibandronate Risedronate	112 osteoporosis	oral	/	0	/	/
Siebert and al.	24 12 with OP	?	?	24 osteoporosis	?	?	0	/	/
Tallarico and al.	32	98	Alendronate	32 osteoporosis	Oral	>36	0	/	/
Andersen and al.	27	49	Zoledronate Pamidronate Alendronate Denosumab	27 metastasis and myeloma	Oral and IV	25.3	0	/	/
Pogrel and al.	11	>11	Alendronate Zoledronate Xgeva	8 osteoporosis 3 metastasis	Oral and IV	57.6	11	/	/
Park and al.	4	10	Alendronate	4 osteoporosis	Oral	>24	4 9 implants	2 and 5 years	mandible
Bayani and al.	1	1	Zoledronate	Myeloma	IV	22	0	/	/
Ottesen and al.	1	4	Denosumab	Prostate Cancer	IV	11	1 2 implants	8.5 months	maxilla
Rawal and al.	1	2	Alendronate	osteoporosis	Oral	120	1 2 implants	18 months	maxila
Storelli and al.	1	8	Alendronate	osteoporosis	oral	36	1 2 implants	3 months	maxilla
Miniello and al.	1	2	Zoledronate	osteoporosis	oral	60	1 2 implants	24-36 months	mandible
Ferreira and al.	1	3	Risedronate Ibandronate	osteoporosis	oral	24	0	0	/
Tam and al.	6	15	Alendronate Zoledronate	4 osteoporosis 1 myeloma 1 metastasis prevention	Oral and IV	41	6 12 implants	2 months and 12 months	6 maxilla 6 mandible

A total of 185 cases of medication-related osteonecrosis of the jaws (MRONJ) around implants were recorded, accounting for 61% of the included patients. However, some studies only included patients who already had MRONJ around implants.

The evaluation of the level of evidence helps establish the strength of the results obtained in the reviewed studies, ensuring the credibility and relevance of the conclusions drawn. This step is essential for guiding practical recommendations and informed decision-making.

In this review, we used the GRADE system (Grading of Recommendations Assessment, Development and Evaluation) to assess the certainty of the evidence [10]. This system considers several criteria, such as the type of study, the consistency of results, the effect size, and the risk of bias. Four levels are assigned to classify the certainty: high, moderate, low, and very low. Randomized controlled trials start with a "high" level of certainty, while observational studies begin with a "low" level of certainty. The different studies were categorized in Table 3.

Table 3: Level of evidence

Author, Year	*Type of study*	*Levels of evidence, GRADE*
Kwon and al.	Retrospective	2
Pichardo and al.	Retrospective	2
Troeltzsh and al.	Retrospective	2
Massaad and al.	Retrospective	2
Suvarna and al.	Retrospective	2
Siebert and al.	Prospective comparative	2
Tallarico and al.	Prospective Observational	2
Andersen and a.	Prospective interventional feasibility	2
Pogrel and al.	Case report	1
Park and al.	Case report	1
Bayani and al.	Case report	1
Ottesen and al.	Case report	1
Rawal and al.	Case report	1
Storelli and al.	Case report	1
Miniello and al.	Case report	1
Ferreira and al.	Case report	1
Tam and al.	Case report	1

Some studies did not provide details regarding the localization of peri-implant MRONJ. Among the articles that reference the location, the mandible was more affected than the maxilla. Indeed, 71 patients developed MRONJ around implants in the mandible, while 29 had it in the maxilla. MRONJ occurred around implants in 33 patients who had already been treated with bisphosphonates, and 64 patients who had received implants before starting bisphosphonate treatment developed MRONJ after undergoing bone antiresorptive agent therapy following implant osseointegration [11–13]. The onset of peri-implant MRONJ appears to be faster, on average, in patients who received their implants either during or after treatment with bone

resorption inhibitors 21.80 months versus 80.09 months on average in patients who received implants after bisphosphonate therapy (Table 4). However, studies involving patients with osseointegrated implants only included those who had already developed MRONJ.

Table 4: Outcome in patients with MRONJ who received implants after or during antiresorptive therapy

ARTICLE	***NUMBER OF PATIENTS***	***NUMBER OF IMPLANT PLACED***	***LOCATION***	***TIME BETWEEN IMPLANTATION AND MRONJ***	***TIME BETWEEN TREATMENT AND MRONJ***	***INDICATION OF MEDICATION***
KWON AND AL.	*18*	*18*	*No data*	*37.33 (+/-26.67)*	*No data*	*No data*
PICHARDO AND AL.	*4*	*14*	*No data*	*6*	*No data*	*No data*
MASSAAD AND AL.	*1*	*6*	*6 maxilla*	*55.2*	*132*	*OP*
OTTESEN AND AL.	*1*	*2*	*2 maxilla*	*8.5*	*No data*	*Prostate Cancer*
RAWAL AND AL	*1*	*2*	*2 maxilla*	*18*	*120*	*OP*
TAM AND AL.	*6*	*12*	*6 mandible* *6 maxilla*	*3.5*	*No data*	*4 OP* *1 myeloma* *1 metastasis prevention*
MINIELLO AND AL.	*1*	*2*	*2 mandible*	*24-36*	*48-72*	*OP*
STORELLI AND AL.	*1*	*2*	*2 maxilla*	*3*	*24*	*OP*
MEAN	***33***	***43***	*/*	***21.80***	*/*	*/*

OP : osteoporosis

It is observed that, in the vast majority of cases included in the study, when MRONJ is triggered, there is a delay of more than 6 to 12 months between implant placement and the onset of MRONJ whether the patients were implanted before or after the initiation of antiresorptive therapy (Tables 4 and 5). This suggests that the presence of the implant may represent a greater risk factor for MRONJ than the surgical procedure itself. This assumption is based on the 6- or 12-month threshold commonly cited in the literature.

Among the 78 patients treated with high doses of bone antiresorptive drugs (for malignant conditions), 32 developed peri-implant MRONJ, representing 41%. Therefore, at least 68 patients treated with low-dose antiresorptive agents (for osteoporosis) developed MRONJ around an implant out of 222 patients, accounting for 29%. Some cases of MRONJ occurred in patients treated with denosumab for both benign and oncological purposes. However, it is not possible to draw any definitive conclusions regarding a real difference in MRONJ occurrence between denosumab and bisphosphonates. Studies that included both treatments did not distinguish between these patient groups in their results. Out of the 185 implants associated with MRONJ, 86 appear to be linked to peri-implantitis, accounting for 47% of the peri-implant

MRONJ cases [12,15,20,22]. Peri-implantitis appears to be a significant risk factor. When available, most patients who developed peri-implant MRONJ also had other comorbidities, such as hypertension, diabetes, and long-term corticosteroid use [13,22–24].

Table 5: Outcome in patients with MRONJ who received implants before antiresorptive therapy

ARTICLE	***NUMBER OF PATIENTS WITH MRONJ***	***NUMBER OF IMPLANT***	***LOCATION***	***TIME BETWEEN IMPLANTATION AND MRONJ MONTHS***	***TIME BETWEEN TREATMENT AND MRONJ***	***INDICATION OF MEDICATION***
KWON AND AL.	*15*	*15*	*No data*	*80.87 (+/-51.81)*	*No data*	*No data*
PICHARDO AND AL.	*14*	*4*	*No data*	*45.4*	*32*	*No data*
MASSAAD AND AL.	*5*	*11*	*5 maxilla* *6 mandible*	*24*	*No data*	*3 OP* *1 breast cancer* *1 prostate cancer*
PARK AND AL.	*4*	*4*	*4 mandible*	*24-60*	*33*	*4 OP*
TROELTZSH AND AL.	*15*	*15*	*13 mandible* *2 maxila*	*150*	*51.24*	*5 OP* *29 oncology*
POGREL AND AL	*11*	*11*	*No data*	*No data*	*No data*	*8 OP* *3 oncology*
MEAN	***64***	***60***	*/*	***80.09***	*/*	*/*

OP : osteoporosis

IV- Discussion

Given the widespread use of bisphosphonates, the significant rise in implant surgeries for edentulism, and the increasing cases of MRONJ associated with these medications, the question of whether dental implants can be considered a risk factor for the development of MRONJ remains a topic of debate within the scientific community. While some studies show an increased risk of MRONJ in patients undergoing drug therapy, others have failed to establish a significant link between implant placement and the onset of this condition.

Previous literature reviews have presented conflicting results, with some suggesting a strong association between dental implants and MRONJ, while others, did not find any conclusive evidence. Among risk factors, Granate-Marques and all assert that therapeutic duration increase MRONJ occurrence and they noticed that in patients treated with bone antiresorptive treatment for more than 36 months for benign conditions, there is a higher risk of developing peri-implant MRONJ [28]. In their literature review, they emphasize that prolonged use of these medications, particularly when combined with surgical procedures such as implant placement, significantly increases the risk of peri-implant osteonecrosis in this patient population. Considering administration route, Mínguez-Serra et al [29] argue that it is preferable to avoid implant procedures in patients receiving intravenous bisphosphonates, aligning with other studies such as that of Scully et al. [30]. On the contrary, Mendes and al [31] and Stavropoulos and al. [32] et Koka and al. [33] argue that implant placement does not pose an additional risk of bone loss, MRONJ, or implant failure in patients treated with these medications. Moreover, some authors consider that bisphosphonates could help for a better osteointegration as Javed and Almas' literature review that conclude the dental implants can osseointegrate and remain stable over time in patients treated with bisphosphonates [34]. They assert that the risk of MRONJ is still present in implanted patients, however, the proportion of necrosis significantly decreases when considering only patients treated with low-dose boneantiresorptive agents.

The prevalence of MRONJ following tooth extraction reported in the literature ranges from 0.8% to 1.6% in patients treated with bisphosphonates for more than four years [35]. In our study, we observe a significantly higher prevalence related to implant surgery compared to tooth extractions. However, these figures may be skewed by the limited number of included participants and the fact that they were selected solely due to the development of MRONJ. Additionally, there may be a bias, as we specifically targeted studies reporting osteonecrosis -

an adverse outcome - rather than a representative sample of all implant procedures. These results should therefore be interpreted with caution. Considering here dental implants as a direct risk factor for MRONJ, due to lack information among patients about time-course between implant placement and peri-implant MRONJ at the time of inclusion, it was not possible to determine the prevalence of MRONJ specifically caused by implant surgery or by the long-term presence of the implant. Moreover, available data on this subject in the literature remain limited. However, it was observed that the mandible was more frequently affected than the maxilla, likely due to its denser bone structure and terminal vascularization. The mandible as a more common site for MRONJ has been consistently reported in numerous publications [36,37].

Even though this study included 78 patients treated with high doses of bone resorption inhibitors, the French SFCO 2013 and American AAOMS 2014 guidelines [3] recommend against, or even contraindicate, the placement of implants in patients treated with anti-resorptive medications for oncologic indication. However, Stavropoulos and al. [32] state that there is virtually no relevant information available on the potential effects of high-dose BP therapy or other widely used anti-resorptive drugs on implant therapy. However we found than nearly half of the patients treated with high-dose anti-resorptive medications developed peri-implant MRONJ. Although the small sample size does not allow for definitive conclusions, MRONJ appears to be more frequent in patients receiving high-dose antiresorptive therapy. This observation is consistent with official guidelines, which contraindicate implant placement in such patients.

It has been shown that patients with other comorbidities, such as hypertension or those treated with long-term corticosteroids or immunosuppressants, were more likely to develop peri-implant MRONJ. Indeed, the combination of anti-resorptive treatments with long-term corticosteroids or other immunosuppressants has been repeatedly described as a risk factor for developing MRONJ [3,38–41]. These results are also observed in the present study among many patients. However, in several of the included studies, there is no additional information regarding the comorbidities of the patients other than their anti-resorptive treatment.

In the review, 64 patients developed MRONJ while they had already received implants prior to anti-resorptive treatment, and 33 patients who were implanted during or after the anti-resorptive treatment reported MRONJ. However, studies involving patients with osseointegrated implants only included those who developed MRONJ. These results warrant further research, especially since several studies report differing outcomes. Holzinger and al. in their review conclude that

the placement of dental implants during or after BP treatment accelerates the development of MRONJ and that MRONJ occurs less frequently when implants are placed before the initiation of Bisphosphonates treatment [42].

In the vast majority of cases in our study, the onset of MRONJ occurred several months — or even years — after implant placement. This suggests that most MRONJ cases were likely caused by the continued presence of the implant, rather than the surgical procedure itself. This distinction has only recently been addressed in the literature, and various authors have proposed different perspectives regarding the time threshold that separates MRONJ triggered by implant surgery from that caused by the implant's long-term presence. According to Kwon and al. [11] et Yong and al. [43], it seems that this threshold is around 6 months after implant surgery, while Giovannacci and al. [44] suggest 12 months. In a 2024 review, Yong and al. [43], suggest that IPTO is the result of combined effects from infectious and mechanical peri-implant lesions. Peri-implantitis, described in several studies, as an infectious process, can lead to IPTO [32,45,46]. This is similar to the association between periodontitis and an increased risk of MRONJ. In both cases, oral dysbiosis leading to the release of cytokines, reactive oxygen species, and matrix metalloproteinases, against a backdrop of altered bone remodeling, has been implicated as a cause of IPTO. Any implant mobility should raise suspicion of MRONJ. If no sequestra are present, conservative treatment should be pursued to avoid an increased risk of MRONJ in case of surgical intervention. The presence of peri-implantitis was reported in several patients with peri-implant MRONJ which accounted for nearly half of the participants [12,15,20,22]. In the literature, there are no clearly defined figures regarding MRONJ cases specifically caused by periodontitis. However, patients with MRONJ appear to be more likely to have periodontal disease compared to those without MRONJ, with an odds ratio of 2.75 [95% CI: 1.67–4.52]. This raises the question of whether patients with MRONJ may also be more susceptible to developing peri-implantitis [45].

Regarding the mechanical lesions that may be responsible for IPTO, unlike natural teeth, implants lack periodontal ligaments to absorb occlusal forces. As a result, the forces transmitted to the peri-implant bone lead to the formation of microfractures. Due to the use of bone resorption inhibitors, the peri-implant bone's ability to remodel or recover is reduced, allowing for the accumulation of these microfractures. The loss of bone viability, reduced vascularization, and decreased number of cells increase the risk of peri-implant infection [43]. No information regarding the quality and adaptation of peri-implant structures, nor concerning

occlusal adjustment, was found in the studies included in our review. The role of peri-implantitis and its risk factors in the development of peri-implant MRONJ raises important questions. In our review, there is little to no information regarding specific risk factors or indicators (such as a history of periodontitis, smoking, follow-up protocols, treated or untreated periodontal disease, diabetes, design of the prosthetic suprastructure etc). Further studies are therefore needed to better understand the true role of peri-implantitis, to identify its risk factors, and to improve early detection and management strategies. Regular clinical and radiological follow-up is therefore recommended to detect as early as possible any loss of attachment, overloading, or other clinical signs that could lead to this phenomenon.

Pre- or peri-implant surgeries, such as grafts, bone filling, or sinus lifts, are also potential factors that could explain the appearance of some MRONJ cases in the short term. However, in the present review, there were not enough patients who had undergone peri- or pre-implant surgeries to conclude that such surgeries are an additional risk factor for osteonecrosis beyond that of implant surgery alone. There is limited research in the literature on this topic. Hibi and Hideharu show that there is an increased risk of implant failure, but further studies are needed to prove a real risk [47].

One limitation of the study is the lack of clinical trials and high-quality evidence studies included in this review. Only one author participated in the selection and analysis of results, which may introduce errors and subjectivity at various stages of the review process. However, the large number of patients included and the analysis of implants in the study allowed for a better generalization of the studied population and supports the validity of the findings. Nevertheless, the small number of high-quality studies included, coupled with the divergent results across different studies, highlights the need for further research to apply these findings in clinical practice. Furthermore, the inclusion of studies focusing only on osteonecrosis cases may influence the results, leading to a higher prevalence of MRONJ. Therefore, it is not possible to determine a prevalence of MRONJ specifically due to implantation or the presence of implants, nor to extrapolate these findings to the general population.

V- Conclusion

Following current recommendations, it is contraindicated to place implants in patients undergoing high-dose bone resorption inhibitors (oncological indication) treatment for edentulism. However, implants can be placed in patients using these medications at low doses. Our study's results show that when patients are treated with low doses of bisphosphonates, the incidence of MRONJ decreases significantly, and the risk of its development is much lower than patients with high-dose of bone resorption inhibitors. Nevertheless, the risk still exists, and if MRONJ occurs, it generally appears several months or even years after implant placement or the initiation of bone treatment.

The majority of cases in the study developed peri-implant MRONJ more than six months after implant placement. The peri-implant MRONJ appears to be primarily triggered by the presence of the implant itself (IPTO), along with peri-implant infections or occlusal dysfunctions, rather than by the surgical procedure alone pointing to local infectious and mechanical cofactors. Evidence certainty remains low. Regular follow-up by an oral health professional is essential to detect early signs and symptoms for timely intervention.

Additional studies are needed to fully understand the real short- and long-term risks, to improve the management and care of these patients.

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Thèse d'exercice : Chir. Dent. : Lille : Année 2025 –

Ostéonécrose des maxillaires liée aux médicaments en contexte péri-implantaire : conséquence de la chirurgie ou de la présence de l'implant ? Une revue systématique de la littérature

Pierre PELABON. - p. 33 : ill. 6 ; réf. 47.

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Mots clés Libres : Ostéonécrose des maxillaires, biphosphonates, Dénosumab, implants dentaires

Résumé de la thèse en français

Cette revue systématique de la littérature porte sur l'apparition de l'ostéonécrose des maxillaires en contexte péri-implantaire. Elle rescence les études portant sur les patients traités par inhibiteurs de la résorption osseuse ayant reçu ou qui vont recevoir la pose d'un ou plusieurs implants dentaires.

L'objectif est d'examiner si la pose ou la présence d'implants dentaires chez les patients sous traitement par agents anti-résorptifs constitue un facteur de risque direct de l'ostéonécrose des maxillaires liée aux médicaments. Le délai d'apparition entre la pose implantaire et la survenue d'une ostéonécrose des maxillaires liée aux médicaments est évalué. Nous cherchons à distinguer si ce risque d'ostéonécrose est davantage lié à l'acte chirurgical lui-même ou à la présence prolongée de l'implant chez les patients traités par des médicaments anti-résorptifs.

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