Medication related osteonecrosis of the jaws (MRONJ): Diagnosis and treatment

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Dental implants as a Risk Factor for Medication Related Osteonecrosis of the Jaws (MRONJ)

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ABSTRACT

INTRODUCTION

Recently, an increasing number of cases of medication related osteonecrosis of the jaws (MRONJ) have been reported. It is still debated whether the presence or placement of dental implants can lead to MRONJ. The aim of this study is to investigate whether dental implants are a risk factor for MRONJ.

METHODS

From January 2003-January 2019 180 patients with MRONJ were seen at the Leiden University Medical Center. Retrospectively, luxating moments for the onset of MRONJ were determined. Clinical data and details of anti-resorptive medication use were collected; 22 patients with dental implants and MRONJ were found. In 18 patients the implants were located in the region of the MRONJ.

RESULTS

18 patients were included in this study. 77.8% received dental implants prior to anti-resorptive drug use and 22.2% had anti-resorptive drug use before or at the time of implant placement. The median time between the placement of implants and the diagnosis of MRONJ in these two groups was 24 months and 6 months respectively. Among 47 implants present in these patients, 30 were located in the necrotic region. All these 30 implants were either lost spontaneously or had to be removed during treatment of MRONJ.

DISCUSSION

This cohort study shows an increased risk for developing MRONJ in patients with dental implants. Both peri-implantitis around previously placed implants and insertion of dental implants can be seen as risk factors. Therefore, prevention of peri-implantitis and caution when indicating dental implants in patients that use anti-resorptive medication are important.

INTRODUCTION

Bisphosphonates and denosumab have become very common in the oncologic field, both as anti-resorptive medication and as neoadjuvant therapy. They are also still the drugs of choice in the treatment of osteoporosis. Although the exact mechanism of action differs, bisphosphonates as well as denosumab are responsible for a direct and strong decrease in osteoclast activity and thus in bone resorption. One of the most debated side-effects of this type of anti-resorptive medication is medication related osteonecrosis of the jaws (MRONJ). MRONJ can be difficult to treat and further insight in its cause and approach to treatment are needed. Ever since the first publication on MRONJ there has been discussion on its origin[1-4], especially whether it is spontaneous or related to dental procedures and/or pathology. There have been reports showing that the presence or the placement of dental implants can initiate MRONJ, especially in patients with intravenous bisphosphonate use[4-10]. Studies have been published that describe MRONJ in patients who use oral bisphosphonates[6, 7, 10]. Several authors[9, 11-16] however found no increased risk for implant failure in patients with oral bisphosphonate use.

The association between MRONJ and dental implants is still unknown. It is not yet clear whether the use of anti-resorptive medication is a contra-indication for the placement of dental implants. The aim of this study was to investigate implants as a possible risk factor for MRONJ in patients seen in our center. All MRONJ patients in this study were surgically treated according to our previously reported protocol[17-19].

METHODS

180 consecutive patients presenting with MRONJ at the department of Oral and Maxillofacial Surgery of the Leiden University Medical Center between January 2003 and January 2019 were studied.

For inclusion in this study a diagnosis of MRONJ according to the criteria of the American Association of Oral and Maxillofacial Surgeons (AAOMS) was a required. MRONJ was diagnosed when there was exposed bone present for more than 8 weeks, current or previous anti-resorptive drug use and no history of radiation therapy in the head and neck region[20].

Patients

All patients with dental implants and MRONJ from our cohort were collected. Only patients with one or more dental implants in the necrotic region were included. Their implant history was studied and protocolled clinical and radiographic analysis was performed. Possible peri-implantitis was studied. This was described as local gingivitis, an infrabony pocket and an angular bony defect around the implant.

The following patients characteristics were analyzed as well: sex, age, medication use, co-morbidity, type and duration of anti-resorptive medication and the type of treatment of MRONJ prior to referral of the patient to our department.

Treatment

The patients were treated following our previously reported[17-19] protocol with a combination of surgery and antibiotics. The surgical outcomes were studied. Healing was defined as a closed mucosa without a fistula or pain.

Statistics

For continuous variables median and range were recorded. Statistical analyses were performed in SPSS (Version 25; SPSS Inc., Chicago, IL, USA). Data are reported in median unless reported otherwise.

RESULTS

Among the 180 MRONJ patients, 22 patients had dental implants and 18 (10%) had implants in the necrotic area and were included in our study. The clinical characteristics for the 18 patients are listed in table I-III.

Clinical features

There were 15 female patients and 3 male. Age varied from 52-86 with a mean of 68,5±9 years.

Eleven patients (57,8%) used anti-resorptive drugs for osteoporosis and the remaining for cancer (42,2%). Five patients used anti-resorptive drugs for metastasized breast cancer, 2 for multiple myeloma and 2 for metastasized prostate cancer.

Stage II was seen in 50% (n=9) of the patients and no statistical difference was found between stage and indication (p=0.629), (see table I).

The median duration of use of anti-resorptive medication in the oral bisphosphonate group was 60 months (range 18-120). The intravenous bisphosphonate users and the denosumab users respectively had a median duration of 18 and 24 months. Oncologic patients seem to have a shorter time of anti-resorptive medication use until development of MRONJ. However, the data was not normally distributed, therefore further statistical analysis was not conducted. The specific durations can be seen in table III.

Duration of symptoms had a median of 6 months (3-48) for cancer patients and a median of 8 months (2-84) with osteoporosis patients.

Preservation of implants was found in 28,6% (n=2) in cancer patients and in 71,4% (n=5) in osteoporosis patients. The location of preserved implants was mostly seen in the mandible in

Table I Clinical features

	Cancer	Osteoporosis	Total	p-value
Gender				0.280[C]
Female	5	10	15	
Male	2	1	3	
	7	11	18	
Indication			18	
Osteoporosis		11	11	
Cancer	7		7	
Breast cancer	5			
Prostate cancer	2			
Anti-resorptive medication			18	
Bisphosphonates		15		
Intravenous use		5		
Zolendronic acid monthly		1		
Zolendronic acid yearly	1			
Pamidronic acid monthly		3		
Oral use		10		
Alendronic acid 70mg weekly		8		
Risedronic acid 35 mg weekly		2		
Denosumab-subcutaneous use			3	
Xgeva 120mg monthly	3			
Prolia 60mg every 6 months				
Stage[1]				0.629[C]
II	3	6	9	
III	4	5	9	
	7	11	18	
Duration of medication (months)	18 (7-24)	60 (18-168)		
Duration of symptoms (months)	6 (3-48)	8 (2-84)		
Preservation of implants				0.513[C]
Loss	5	6	11	
Survival	2	5	7	
	7	11	18	
Location of preserved implant				0.468[C]
Mandible	2	4	6	
Maxilla		1	1	
			7	
	2	5		

[C]=Chi-square-test, not statistically significant

[1]=staging according to definition MRONJ AAOMS (Ruggiero et al 2014)

Table II Patient characteristics

Nr	Indication	Location implants/MRONJ	Cause MRONJ	Lost implants (placed implants)
1	OP	Mand ant	P	4 (4)
2	MM	Mand ant	P	2 (2)
3	BC	Max post	P	2 (2)
4	OP	Mand ant	T	1 (2)
5	BC	Max ant	P	1 (1)
6	OP	Max post	T	1 (6)
7	OP	Max post	P	2 (2)
8	OP	Max ant	T	1 (1)
9	OP	Mand ant	P	2 (2)
10	PC	Mand post	P	1 (3)
11	OP	Mand ant	T	1 (4)
12	BC	Max post	P	1 (1)
13	OP	Mand ant	P	2 (2)
14	PC	Mand ant	P	1 (1)
15	OP	Mand ant	P	1 (4)
16	OP	Mand ant	P	2 (2)
17	OP	Mand ant	P	1 (4)
18	BC	Mand ant	P	4 (4)

Nr= Patient number,
Indication of anti-resorptive medication: OP= osteoporosis, MM= multiple pyeloma, BC= breastcancer, PC= prostate cancer
Location of implants/MRONJ, mand= mandible, max=maxilla, ant=anterior, post=posterior
Cause of MRONJ: P= peri-implantitis; T=traumatic with insertion of implants
Number of Lost and placed implants

85,7% (n=6), but also in osteoporosis patients in 71,4% (n=5). No statistical difference was found between the groups (see table I).

Implant features

Fourteen patients (77,8%) were implanted before the use of anti-resorptive drugs. These patients had osseointegrated and functioning dental implants before the onset of MRONJ. However, they developed peri-implantitis around the implants which evolved into MRONJ after some time of anti-resorptive drug use. The median time of onset of MRONJ in this group was 24 months (range 7-120) after the start of anti-resorptive medication. In some patients implants had already fallen out at presentation due to the extensive peri-implantitis and bone loss. Other patients had typical peri-implantitis with bleeding on probing, deep pockets and mobile implants.

Four patients (22.2%) received dental implants during anti-resorptive medication use. They developed MRONJ shortly after insertion of the implants. The median time of onset of MRONJ in this group was 6 months (range 3-6). The median use of anti-resorptive medication in this

Table III Characteristics risk factors MRONJ

Cause MRONJ	Administration manner	Duration of complaints	Duration of AR therapy
Peri-implantitis (n=14)	PO (n=6)	10 (2-84)	56 (18-120)
	IV (n=5)	20 (5-48)	18 (12-60)
	SC (n=3)	6 (3-6)	24 (7-24)
Total P	(n=14)	9 (2-84)	24 (7-120)
Trauma (n=4)	PO (n=4)	5 (3-13)	72 (36-168)
Total T	(n=4)	5 (3-13)	72 (36-168)

Risk factors MRONJ: P= peri-implantitis, T=Trauma due to insertion of implants
Administration manner: po=oral bisphosphonates, iv= intravenous bisphosphonates, sc=subcutaneous denosumab
Duration of complaints in months: median (range)
Duration of AR therapy until MRONJ in months: AR= anti-resorptive, median (range)

group was 72 months (range 36-168). The 18 patients in our study group initially had a total of 47 implants. 30 (64%) of the implants were lost. Most of the implants were already lost before referral. The remaining implants involved in the necrosis were removed during surgery.

Treatment outcome

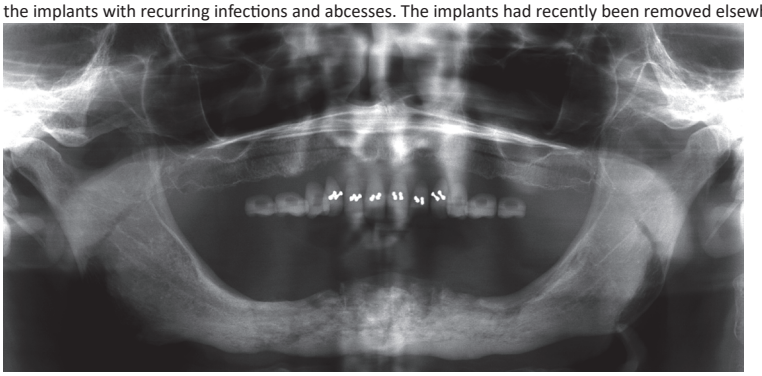
Fifteen patients were admitted to our hospital, underwent sequestrectomy and remained hospitalized for one week for intravenous antibiotic therapy followed by two weeks of oral antibiotics. Three patients were treated in the outpatient clinic. The period of follow-up was at least 3 months postoperatively. One case is shown in figures 1-3.

Seventeen patients had a closed and healed mucosa and were free of complaints after a minimum follow-up of 3 months. The follow-up had a median duration of 12,5 months (range 3-36). One patient died during follow-up after three months due to metastasized disease.

In seven patients a total of 17 implants, close to but not involved in the necrosis, could be preserved. There was a stage III MRONJ patient who developed a pathologic fracture after surgery where fixation was carried out and a pseudarthrosis could be achieved without further complaints.

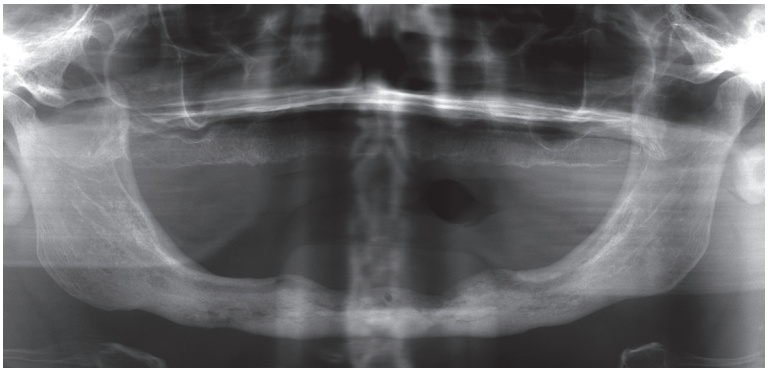
Figure 1 Patient with BRONJ of the mandible

Case Female 65 years old with osteoporosis and dental implants inserted in the region of the lower cuspids 8 years before and anti-resorptive medication use since 48 months. At presentation in our hospital she had a history of 4 years of complaints of the implants with recurring infections and abcesses. The implants had recently been removed elsewhere.



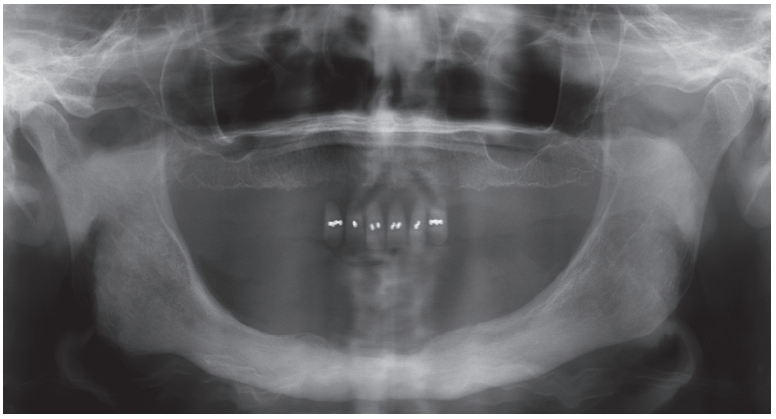
Pre-op panoramic radiograph shows osteolysis and sequestration in the mandibular symphysis

Figure 2 Panoramic radiographs of immediately postoperative from patient fig 1



Panoramic radiographs immediately postoperative after saucerization with visible smooth contours of the bone

Figure 3 Panoramic radiographs 2 years postoperative from patient fig 1



Panoramic radiograph shows smooth edges and healing of bone. There is a suggestion for regeneration of the bone in the mandible.

DISCUSSION

The purpose of this study was to establish whether dental implants could be a cause for MRONJ. The hypothesis is that dental implants can be related to MRONJ. Further clinical & implant features were studied and the treatment outcomes were analyzed.

The results of this study confirm the hypothesis that dental implants can be related to the development of MRONJ. We found 2 major risk factors: peri-implantitis (77.8%) and insertion of dental implants (as a surgical trauma) (22.2%). Peri-implantitis leading to MRONJ was observed with the anti-resorptive drug use after insertion of implants. With placement of implants MRONJ was seen during or after anti-resorptive therapy.

This study shows that osseointegrated and functioning dental implants, present at the start of anti-resorptive medication use may initiate the development of MRONJ when there is peri-implantitis. The insertion of dental implants during anti-resorptive medication use led even faster to the development of MRONJ.

More than sixty percent of the implants were lost. All lost implants were located in regions of MRONJ. In cases where not all implants were located in the region of osteonecrosis, early intervention seemed to save close implants. Based on these results, caution with placement of dental implants and a strict dental hygienic regiment and follow-up seems necessary, to prevent development of MRONJ.

In literature there are several possible risk factors for implant failure. Implant loss is reported to be more often seen in the mandible[21-23], but our results could not confirm this. On the contrary, our results shows survival of implants in osteoporosis and the mandible. This suggests that when there is no peri-implantitis MRONJ will not develop spontaneously.

The time elapsing between implant insertion and the onset of MRONJ seemed more than 3 times longer in the osteoporosis patients than in the cancer patients. High doses of anti-resorptive medication is usually intravenously administered to oncologic patients. Together with the often compromised general medical condition of cancer patients it may explain the higher risk of MRONJ when dental implants are present or inserted.

The median time of anti-resorptive medication use in the peri-implantitis group reflects the time necessary for the bone to become susceptible or prone to MRONJ. This time is similar to the reported duration of medication use before development of MRONJ as stated by other authors[1, 3]. Patients with a shorter period of medication use may not have developed MRONJ yet and were therefore not seen with MRONJ. The period of time from insertion of the implant(s) to the initiation of the anti-resorptive drug therapy in the peri-implantitis group seems irrelevant, because implants were sometimes already functioning for more than 5 years in our patients before anti-resorptive medication was started.

Considering the increasing number of reports on implant related MRONJ an association between implants and the development of MRONJ becomes more evident[7, 8, 10, 21, 22, 24]. There is a tendency in the literature to focus on two main causes for MRONJ in relation to dental implants.

Firstly, MRONJ seems to be related to peri-implantitis around dental implants that were placed before anti-resorptive medication was started. Secondly, MRONJ seems related to the insertion of implants in patients with anti-resorptive medication use. These risk factors are confirmed in this study and in other reports[7, 8, 10, 12, 22]. It is still unclear which of these two factors are more associated to the risk of MRONJ. Further longitudinal research it is required to investigate whether peri-implantitis in patients that use anti-resorptive medication can be stabilized and so prevent development of MRONJ.

There is no consensus on placement of implants during bisphosphonate therapy. However, literature shows no hard contra-indications for placement of dental implants in combination with oral bisphosphonate use[10]. Several authors show good results of dental implants in combination with anti-resorptive therapy with even reports of large series of patients with oral bisphosphonate use and implant placement without or with just a few failed implants[5, 11-16, 25-27]. No increased risk was found for MRONJ in relation to dental implants. Madrid & Sanz (2009) report that it is safe to undergo dental procedures such as the insertion of dental implants with oral bisphosphonate use for a duration of less than 5 years[5]. In a few reports development of MRONJ in patients with implants after bisphosphonate use was not observed[28]. Due to the heterogeneity of the studies, however there is not enough evidence in literature to draw conclusions regarding implant insertion in patients with anti-resorptive medication or in relation to MRONJ[16]. This may suggest a possibly smaller risk for the development of MRONJ with oral bisphosphonate use than assumed earlier. The insertion of dental implants under the right circumstances and precaution measures seems justified.

This study among others[5, 6, 10, 24, 29, 30] also reports extensive failure of implants and development of MRONJ and possible loss of parts of the jaw(s) when anti-resorptive medication are used including users of oral bisphosphonates. In these “high risk” patients with anti-resorptive therapy reserve should be taken when planning dental implants and good dental hygiene and follow-up of dental implants is recommended. Early surgical intervention of MRONJ may save adjacent dental implants. Considering all the risks treatment in a specialised centre is advised.

CONCLUSION

There is an increased risk for development of MRONJ due to the insertion of dental implants and due to peri-implantitis. These two risk factors seem to contribute to the overall risk of MRONJ. Overall, the use of intravenous anti-resorptive medication is more likely to lead to implant failure and MRONJ than the use of oral anti-resorptive medication. MRONJ due to these two risk factors can lead to considerable morbidity including loss of parts of the jaw. Therefore prevention is important. Further research regarding dental implants as a risk factor for the development of MRONJ is recommended.

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