ORIGINAL ARTICLE

The Prevention of Medication-related Osteonecrosis of the Jaw

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SUMMARY

Background: Medication-related osteonecrosis of the jaw (MRONJ) is a preventable complication of antiresorptive treatment. It arises in 1–20% of patients with bone metastases of solid tumors and hematologic malignancies and in 0.1–2% of patients being treated for osteoporosis with bisphosphonates. Depending on the underlying disease and medication dosage, the risk of MRONJ can be elevated even in the first year of antiresorptive treatment. The treatment of MRONJ is difficult and often involves surgery of the jaw.

Methods: We systematically reviewed publications retrieved by a selective search for literature on the prevention of MRONJ in the PubMed and Cochrane Library databases and with the aid of the Google Scholar search engine.

Results: 15 of 559 retrieved publications were included in the analysis. The quality of the evidence in the studies was generally moderate to low, with most of them being case series. In one case series of over 1200 patients with multiple myeloma, the incidence of MRONJ was lowered from 4.6% to 0.8% through regular dental checkups and improved oral hygiene. Tooth extraction, in particular, is associated with a high risk of MRONJ. In a retrospective study, 57% of patients who underwent tooth extraction without antibiotic prophylaxis developed MRONJ, compared to 0% with antibiotic prophylaxis.

Conclusion: Before antiresorptive medication is begun, oral hygiene should be improved. Moreover, it seems that perioperative antibiotic prophylaxis and adequate plastic wound closure can often prevent MRONJ. In view of the fact that bisphosphonates can persist in bone for more than 15 years, patients should be thoroughly informed of the risk that antiresorptive treatment can cause MRONJ, and the measures discussed should be initiated.

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In Germany, 1.7 million of patients with osteoporosis are taking antiresorptive medication. Patients with multiple myeloma (MM) and underlying malignant diseases resulting in bone metastases are also treated with bisphosphonates (BP) or other antiresorptive medications (1, 2).

If the medication is administered orally, esophagitis is observed in many cases; if it is given intravenously, acute-phase reactions may occasionally be observed after the first administration. Furthermore, hypocalcemia and hypomagnesemia have been described, as has, in rare cases, acute renal failure (3). Severe adverse effects are less common, such as medication-related osteonecrosis of the jaw (MRONJ)—which can affect especially patients with malignancies in 1–20% of cases—or, rather more rarely, atypical femoral fractures (4–7). In addition to bisphosphonates, other drugs—for example, denosumab—can cause MRONJ (Tables 1 and 2).

The clinical finding in MRONJ is exposed bone in the oral cavity for a period of more than 8 weeks after prior therapy with bisphosphonates or other drugs that affect the bone metabolism (8) (Figure a–c, Box 1). Progression of the condition can lead to tooth loss and necrosis of entire sections of the jaw bone, including pathological fractures of the mandible.

Structurally, bisphosphonates resemble inorganic pyrophosphate and bind covalently to hydroxyapatite. They have different potencies and can be administered orally or intravenously (Table 1). Amino- and nitrogen-free bisphosphonates are taken up by osteoclasts during the bone resorption process and inhibit osteoclast-mediated bone resorption by means of toxic ATP analogues or through inhibition of farnesyl pyrophosphate synthase. Their tight binding and the release and redeposition in the context of bone remodeling mean that they often remain in the bone for more than 15 years (9, 10).

The pathomechanism of the development of necrosis remains ultimately unexplained. The pH value, which is lowered as a result of the inflammatory response, triggers and biologically activates the bisphosphonate and results in a raised, locally toxic molecule concentration. The extent of the risk depends on:

- The indication for antiresorptive therapy (malignancy or osteoporosis)
- The administration route (intravenous or oral)
- The duration of the treatment.

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TABLE 1

Bisphosphonates: Groups of substances, effective substances, potency

Groups of substances	Effective substance	Potency*
Oral bisphosphonates	Etidronate	1
	Clodronate	10
	Pamidronate	100
	Ibandronate	1000–10 000
	Risedronate	1000–10 000
Intravenous bisphosphonates	Pamidronate	100
	Ibandronate	1000–10 000
	Zoledronate	>10 000

*Relative potency of bisphosphonates compared with etidronate (e1)

The mean duration of treatment until MRONJ develops is 20 months in patients with malignant disease and 4.4 years in patients receiving oral treatment for osteoporosis (11, 12). Further risk factors include odontogenic infections and periodontal diseases, which are present in 71–84% of cases. Pressure sores from dentures double the risk ratio; in 62% of cases, dental extractions are the trigger (8, 13–15).

The treatment of MRONJ is complex and often associated with inpatient stays and surgery.

Material and method

Our research question was formulated on the basis of the PRISMA guidelines: which available, scientifically-based approaches exist for the prevention of medication-related osteonecrosis of the jaw? In order to find an answer to this question, two of the authors (PP and PV) conducted a systematic literature search using the databases PubMed and the Cochrane Library, as well as the search engine Google Scholar. Because of the initial description of the disorder in 2003 (16) we restricted our search period to the time between January 2000 and November 2015. We used the following search terms: “Bisphosphonates OR Medication, OR Antiresorptive AND osteonecrosis AND jaw AND prevention”. We also searched for the MeSH term “Bisphosphonate-related osteonecrosis of the jaw AND prevention & control”. We included in our study publications on prevention strategies for MRONJ in patients with metastases originating from solid tumors and with osteoporosis. We did not include in the study articles that were in languages other than English or German, mere review articles, and animal models. We excluded studies in which medication-related osteonecrosis of the jaw had already occurred or been treated. The aim of our study was to identify approaches to preventing the disease. We excluded studies with fewer than 5 patients.

TABLE 2

Overview of further antiresorptive medications, mechanisms of action, indications, and incidence rates of MRONJ

Effective substance	Mechanism of action	Indications	MRONJ incidence
Denosumab	Antibodies to receptor activator of NF-κB ligand (RANKL) with half-life of 25–32 days	<ul style="list-style-type: none"> Prevention of skeletal related events in tumors with bone metastases Postmenopausal osteoporosis and osteoporosis in hormone ablation 	<ul style="list-style-type: none"> Incidence in denosumab 1.8% versus zoledronate 1.3% in underlying malignancy and MM (15) Osteoporosis: the same incidence as BP (e2–e4)
Bevacizumab	Antibodies to anti-vascular endothelial growth factor (VEGF)	<ul style="list-style-type: none"> Metastatic colon cancer Glioblastoma Metastatic non-small cell bronchial cancer Metastatic renal cell cancer Triple negative breast cancer Ovarian cancer Age-related macular degeneration 	<ul style="list-style-type: none"> Meta-analysis: 30 times higher incidence in BP co-medication, MRONJ rate in total 0.4%, only bevacizumab, without BP co-medication 0.06% (e5) 11 case reports in PubMed (e2)
Sunitinib	Tyrosine kinase inhibitors inhibit VEGF, c-Kit, and PDGRF	<ul style="list-style-type: none"> Metastatic renal cell cancer Gastrointestinal stromal tumors 	<ul style="list-style-type: none"> Incidence of 29% in BP co-medication (e6) 4 case reports in PubMed (e2)
Everolimus, sirolimus, temsirolimus	Mechanistic target of rapamycin (mTOR) inhibitors intervene in signal transduction pathways of growth factors and protein transcription	<ul style="list-style-type: none"> Metastatic renal cell cancer Hormone positive breast cancer Neuroendocrine tumors of the pancreas Immunosuppression in organ transplantation 	<ul style="list-style-type: none"> 2 case reports for everolimus, both in BP co-medication (e7, e8)

BP, bisphosphonates; c-Kit, tyrosine kinase KIT; MM, multiple myeloma; MRONJ, medication-related osteonecrosis of the jaw; mTOR, mechanistic target of rapamycin; PDGRF, platelet derived growth factor; RANKL, receptor activator of NF-κB Ligand; VEGF, „vascular endothelial growth-factor“

Figure: Typical clinical presentation of medication-related osteonecrosis of the jaw

- a) Medication-related osteonecrosis of the jaw (MRONJ) in the region of the lower jaw; the arrow points at an exposed area on the bone;
 b) Widely exposed bone after dental extraction in the lower right jaw;
 c) Extensive exposed bone areas in the upper jaw subsequent to pressure sores/mucosal ulcers caused by prostheses

We extracted the following parameters from each article:

- Study design
- Number of patients
- Preventive method
- Success rate
- Mean follow-up period.

Results

The electronic database search yielded 195 entries from PubMed, 148 entries from the PubMed MeSH term search, and 2 entries from the search of the Cochrane Library. The search with Google Scholar identified 214 sources. After eliminating duplicate entries, we excluded 105 review articles, animal models, and case reports, which left us with 67 potentially relevant publications. Of these, we excluded 28 as they contained existing or previously treated MRONJ. A further 13 publications were excluded after scanning the full text versions of the articles, because they did not pursue a preventive approach, or because the success rate or follow-up periods were not shown. Eventually we included 15 studies in our evaluation (*eFigure, eTable 1*) (17–30). We found no randomized controlled trials but case series with a high risk of bias. The evidence level of most of the studies was moderate because of the lack of randomization in most of them and therefore corresponded to level IIb, according to the classification system of the AWMF (*Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften* [Association of the Scientific Medical Societies in Germany]) and the ÄZQ (*Ärztliches Zentrum für Qualität in der Medizin* [Medical Center for Quality in Medicine]). The evidence level of the described new preventive approaches was low at a value of III (*eTable 2*).

In a case series in which the risk was explained in detail, a dental exam took place before the start of treatment, oral hygiene was improved, and with 6-monthly checkups were performed in patients with multiple myeloma and solid tumors with bone metastases, the

incidence of MRONJ in 1243 patients fell from 4.6% to 0.8% (28). Risk factors were detected by using radiographs, teeth that were beyond salvaging were extracted, conservative/restorative dental treatment was undertaken, and patients were informed about the importance of good oral hygiene.

General risk factors, such as smoking (odds ratio [OR] 3.0; 95% confidence interval [CI]: [0.8; 10.4]), alcohol consumption, or poorly controlled diabetes (OR 2.78; 95% CI [1.27; 6.07]) were also treated.

After the initial examination, bisphosphonate therapy was started immediately in 36–48% of patients. Dental surgical measures delayed the start of treatment by 6–8 weeks. Patients receiving bisphosphonate therapy underwent professional dental hygiene treatments at regular intervals, with 6-monthly professional dental examinations, and annual x-ray exams. The recommendations in *Box 2* are derived from these measures (18, 31–33).

Where teeth had been extracted, the exposure of bone in the oral cavity led to bacterial colonization of the modified bone. In 57% of patients receiving bisphosphonate treatment, MRONJ developed after dental extraction without perioperative antibiotic prophylaxis, whereas if such prophylaxis was given, no cases of MRONJ were seen (34).

Extending the antibiotic treatment to three days before dental extraction until 17 days afterwards did not confer any additional effect in terms of the development of MRONJ (20, 21). The extraction wound was covered with a mucoperiosteal flap in order to protect the bone from pathogens inside the oral cavity (19). Professional dental hygiene treatments, in which oral microorganisms may concentrate in the periodontal space, did not lead to an increase in MRONJ (34).

Atraumatic methods have been described as alternatives to surgical tooth extraction, in order to reduce pathogen load. Orthodontic elastic ligatures will eventually result in dental exfoliation, but the mean duration of treatment is 6 weeks (23). In one study, low

BOX 1

Definition of medication associated osteonecrosis of the jaw*

- Current or previous antiresorptive or antiangiogenic therapy
- Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks
- No history of radiation therapy to the jaws or obvious metastatic disease to the jaws

*According to the US specialty society (AAOMS, American Association of Oral and Maxillofacial Surgeons)

level laser therapy during and after the extraction led to postoperative MRONJ in 2.5% of interventions, which healed when the laser treatment was continued (26). In another study, treatment with autologous plasma-rich growth factor in the setting of the tooth extraction as a means of covering the defect, without using plastic surgical wound closure, led to MRONJ in 2.3% of cases (*eTable 1*).

Discussion

Since bisphosphonates were introduced to the market for the treatment of osteoporosis, a reduction in the rate of femoral head fractures of 24.5% has been documented (35). In patients with malignant disease, treatment with bisphosphonates prolongs the time interval before bone metastases develop, reduces the risk of skeletal related events (SRE) and bone pain, and improves quality of life. However, because of the higher dosage and frequency of application, treatment with bisphosphonates is associated with an increased risk for MRONJ (7, 36, 37).

In 2003, Marx et al. were the first to report occurrences of osteonecrosis of the jaw after intravenous administration of zoledronate and pamidronate in patients with multiple myeloma and metastatic breast cancer (16).

The German S3 guideline distinguishes different risk profiles in MRONJ. Patients with primary osteoporosis, who receive bisphosphonates orally or intravenously, have a low risk profile (prevalence 0.1%). The risk in therapy-induced osteoporosis, which is treated by means of 6-monthly intravenous bisphosphonate applications, is 2%. Patients who receive intravenous bisphosphonates on a monthly basis because of bone metastases or multiple myeloma are at high risk (prevalence 1–20%) (38).

Before initiating antiresorptive therapy, a systematic examination of the oral cavity by a dentist is a compulsory requirement. Patients should be informed about the risk of MRONJ. While undergoing antiresorptive treatment, patients need to maintain good oral hygiene, and regular checkups should be conducted at 6-monthly intervals (18). Before starting antiresorptive therapy, teeth and implants that are beyond salvaging should be removed, and pericoronal infections and entry points for pathogens should be eliminated. In this way, necroses can successfully be prevented from recurring (17, 38). If the underlying disorder permits this, the antiresorptive therapy should be delayed by 2–3 weeks until the extraction wounds have healed. However, MRONJ can also develop spontaneously or after small trauma. For this reason, it is important to ensure that dentures with mucosa contact are well fitted, in order to avoid pressure sores/mucosal ulcers. Surgical interventions should be undertaken in all patients receiving systemic antibiotic treatment at least one day before and 3 days after the intervention. Antiresorptive therapy should be restarted only once the bone has healed completely (8, 37) (*Box 2*).

BOX 2

Strategies for the prevention of medication-related osteonecrosis of the jaw in patients receiving antiresorptive therapy in the setting of malignancies and osteoporosis (e9)

- Clear explanation of the risk of medication-related osteonecrosis of the jaw and the need for effective oral hygiene (e9)
- Thorough dental examination, including x-rays, before the start of the treatment (18, 25, 27)
- If possible, conservative dentistry, and surgical and prosthetic interventions should precede the start of antiresorptive treatment (8)
- Checking for pressure sores and relining of poorly fitting prostheses with mucosa contact—or fitting a newly made prosthesis (8)
- Dental extractions, only where absolutely necessary and accompanied by perioperative antibiotic prophylaxis with plastic wound closure by plastic surgery (8, 22)
- Prophylactic antibiotic treatment before, during, and after invasive oral surgery (19–21, 25)
- Professional dental cleaning and dental checkups at regular (half yearly) intervals during and after antiresorptive therapy (25, 27, e9)
- Smoking cessation and treatment of general disorders (for example, diabetes mellitus) (e9)
- Checking the indication for continuing antiresorptive therapy at regular intervals (36)

TABLE 3

Recommendations for therapeutic intervals for bisphosphonates in osteoporosis, and antiresorptive medication risk (36)

Patients	Recommendation	Comment
High risk – T-score of hip ≤ -2.5 – previous fracture of femoral neck or vertebra – Long-term, high dose glucocorticoid therapy	No break in therapy (e12, e13)	Evaluation of therapeutic indication at regular intervals
Medium risk – T-score of hip >-2.5 and – no previous hip or spinal fracture	Therapeutic break should be considered after 3–5 years for alendronate, risedronate, or zoledronate treatment (e14, e15)	Individual decision, after balancing risk and benefit (36)
Low risk No current therapeutic indication given	Pause therapy (e16)	Re-start therapy if the therapeutic indication is given once more (e11, e16)

For manifest osteonecrosis of the jaw, the guidelines of the American Association of Oral and Maxillofacial Surgeons (AAOMS) recommend a stage-appropriate approach, using primarily conservative therapeutic measures (8). Cure rates are 23% for exclusively conservative therapy using antibiotics and antibacterial rinses (39).

The German guideline of the AWMF favors early surgical intervention, so as to prevent progression of the lesion and in order to achieve cure rates of higher than 90% (38). In the context of surgical therapy, patients received prophylactic intravenous antibiotics perioperatively two days before and—depending on the extent of the necrosis—up to five days after the procedure. Under general anesthesia, the entire necrotically altered bone is ablated, sharp edges are smoothed, and the soft tissue is closed over the bone by plastic surgical techniques, using multiple-layer sutures (40). In order to be able to assess the extent of the necrosis during the operation, fluorescent marking can be used to expose non-vital bone (e10). To help the wound to heal, patients should ingest only liquid foods through a nasogastric tube (38).

Because of its relatively short half-life, the therapeutic effect of the receptor activator of NF- κ B Ligand (RANKL) antibody denosumab ceases within 6 months after administration of the substance has ended. By contrast, the covalent binding of bisphosphonates to hydroxyapatite ensures a half-life of several years' duration in the bone, which leads to an extended therapeutic effect in spite of a treatment break (37, e11). The decision regarding a break from bisphosphonate treatment should be made individually for each patient after assessing their fracture risk (Table 3). There are currently no data on when antiresorptive therapy should be restarted. Bone density measurements or serum markers 2–3 years after the start of the break may provide indications of the residual activity of the bisphosphonate (36, e16).

As other substances—such as denosumab, which is also used to prevent fractures in malignancy and osteo-

porosis—are also associated with the occurrence of osteonecrosis of the jaw, the term bisphosphonate-associated osteonecrosis of the jaw was substituted by medication-related osteonecrosis of the jaw (8, e2). The incidence of MRONJ for denosumab in phase II and III clinical trials in patients with metastatic solid tumors is 2.0%, compared with 1.4% for zoledronate.

In the setting of osteoporosis treatment, similar incidence rates have been described for denosumab as for bisphosphonates (e17). The vascular endothelial growth-factor (VEGF) antibody bevacizumab, which is also used in tumor therapy, has also been associated with the occurrence of osteonecrosis of the jaw. So far, 11 case reports have been published for sole administration of bevacizumab. Combination treatment with bisphosphonates is associated with a 30-fold increase in the risk for developing MRONJ (e3, e5, e18). Four case reports are currently available for the tyrosine kinase inhibitor sunitinib, and the mechanistic target of rapamycin (mTOR) inhibitors everolimus und temsirolimus (2 case reports) are associated with a minimally increased risk for developing MRONJ; however, this risk rises substantially when the bisphosphonates are given as combination treatment (e5) (Table 2).

As the understanding of its pathogenesis is incomplete and biomarkers for identifying patients at risk of developing MRONJ are lacking, options for preventing and treating MRONJ are limited. Early dental examination and preventive treatment are crucial for preventing MRONJ. No scientific basis currently exists for a positive effect of interrupting antiresorptive therapy in tooth extractions or other procedures. Specialist societies recommend in high-risk patients a therapeutic break of 2 months before the planned procedure, as well as continuation of treatment only once wound healing is complete (8). In patients receiving intravenous bisphosphonate treatment, the preventive measures should have been taken before the treatment even starts. The short (compared with bisphosphonates) half-life of denosumab can be used to minimize risk. Denosumab is completely excreted by the body after 6

KEY MESSAGES

- Medication-related osteonecrosis of the jaw (MRONJ) is a potentially avoidable complication of antiresorptive and antiangiogenic therapies.
- In addition to bisphosphonates, antiresorptive and antiangiogenic drugs, such as denosumab, bevacizumab, sunitinib, and everolimus, are also associated with an increased risk of developing MRONJ.
- Before starting therapy, the oral cavity should be systematically examined and oral hygiene measures should be initiated.
- Dental extractions or other dental-surgical measures during and after the treatment should be accompanied by prophylactic administration of antibiotics.
- Especially in patients with osteoporosis, the indication for continuing treatment with bisphosphonates should be checked at regular intervals.

months. This is also the case for the substances bevacizumab and sunitinib, neither of which accumulates in the bone (8).

While antiresorptive medications improve patients' quality of life by reducing tumor-related complications, this quality of life can be impaired by pain, exposed bone areas, and maxillary sinusitis—which accompany MRONJ (e19). Because of their increasingly widespread use and the extended indication for antiresorptive drugs, as well as the longer life expectancy of the population and tumor patients, the number of affected patients will increase in future (e20). Prophylaxis and early detection before, during, and after therapy in the context of general practice can, however, rather successfully prevent MRONJ (38).

Conflict of interest statement

The authors declare that no conflict of interest exists.

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Supplementary material

For eReferences please refer to:
www.aerzteblatt-international.de/ref

eFigure, eTables:
www.aerzteblatt-international.de/17m0063

Supplementary material to:

The Prevention of Medication-related Osteonecrosis of the Jaw

by Philipp Poxleitner, Monika Engelhardt, Rainer Schmelzeisen, and Pit Voss

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Results of the literature search according to the PRISMA criteria;

Search terms:

“Bisphosphonates OR medication, OR Antiresorptive AND osteonecrosis AND jaw AND prevention”;

MeSH term: “Bisphosphonate-related osteonecrosis of the jaw AND prevention & control”;

MRONJ, medication-related osteonecrosis of the jaw; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

eTABLE 1

Study results on preventing MRONJ, for example, by means of improved oral hygiene and antibiotic prophylaxis, where surgical intervention was required

Method	Author/year (reference)	Patients/design	Study period (months)	Measure	Result
Improved oral hygiene	Dimopoulos et al. 2009 (18)	128 retrospective	17	Dental examination and restoration/treatment before starting ZOL therapy in patients with multiple myeloma	16 of 128 patients developed necroses, Control group: 23% necroses, intervention group: 7% necroses, Incidence ratio: 2.92 (95% CI [1.06; 8.03]; p = 0.0296)
	Ripamonti et al. 2009 (27)	966 pro- and retrospective	10	Dental examination and restoration/treatment before BP therapy	Control group: 3.2% necroses, Intervention group: 1.3% necroses, Incidence ratio: 0.30 (95% CI: [0.03; 1.26]; p = 0.048)
	Vandone et al. 2012 (25)	269 pro- and retrospective	47	Dental examination and restoration/treatment before BP therapy in bone metastases originating from solid tumors	Control group: 5.5% necroses, Intervention group: 2.8% necroses
	Bramati et al. 2015 (29)	212 pro- and retrospective	60	Dental examination and restoration/treatment before and during BP therapy in bone metastases	Control group: 8.6% necroses, Intervention group: no necroses, Risk reduction: 100% (95% CI: [86%; 100%], p < 0.0001)
	Bonacina et al. 2011 (17)	282 prospective	18	Dental examination and restoration/treatment before and during BP therapy	Control group: 10.8% necroses, Intervention group: no necroses
	Sim et al. 2015 (28)	1243 retrospective	33 and 16	Dental examination and restoration/treatment before and during BP treatment	Control group: 4.6% necroses, Intervention group: 0.8% necroses, Risk reduction: 0.24 (95% CI: [0.09; 0.61]; p < 0.004)
	Montefusco et al. 2008 (34)	178 retrospective	35	Dental treatment, antibiotic prophylaxis yes/no BP therapy in multiple myeloma	Without antibiotic prophylaxis: 57% With antibiotic prophylaxis: 0%
	Ferilio et al. 2010 (19)	34 prospective	12	Antibiotic prophylaxis before dental extraction, Amoxicillin and clavulanic acid for 2 days before and 5 days after extraction, wound closure using mucoperiosteal flap	71 extractions without occurrence of necroses
	Lodi et al. 2010 (21)	23 prospective	12	Improving oral hygiene before extraction, antibiotic prophylaxis for 3 days before and up to 17 days after extraction, wound closure using mucoperiosteal flap	31 extractions without occurrence of necroses, no control group
	Heufelder et al. 2014 (20)	68 prospective	12	Perioperative antibiotic therapy, wound closure using mucoperiosteal flap, removal of stitches 14 days after surgery at the earliest	117 extractions, 3% necroses after dental extraction, no control group
Changed surgical techniques, new approaches	Regev et al. 2008 (23)	10 prospective	9	Atraumatic extraction using orthodontic rubber ligatures	No occurrence of necroses, time to exfoliation circa 6 weeks, no control group
	Vescovi et al. 2013 (26)	217 prospective	15	Perioperative antibiotic therapy, dental extraction, and low-level laser treatment	2.3% necroses, no control group
	Mozzali et al. 2011 (22)	700 prospective, randomisiert	12–72	Dental extraction in patients receiving oral BP treatment, Intervention group: plastic surgical wound closure, Control group: no closure	No occurrence of necroses in either group
	Scoletta et al. 2013 (24), Scoletta et al. 2013 (e21)	64/63 prospective	At least 4	Dental extraction in patients receiving intravenous BP therapy, antibiotic therapy, application of platelet rich growth factor and wound closure	Follow-up period of at least 4 months, 2011: 2.3% necroses after dental extraction, 2013: 1% necroses after dental extraction

BP, bisphosphonates; CI, confidence interval; MRONJ, medication-related osteonecrosis of the jaw; ZOL, zoledronate

eTABLE 2

Validity of the included studies according to Cochrane Risk of Bias Tool and evidence level

Measures	Author/year (reference)	Randomization	Blinded group allocation	Blinding of participants and study personnel	Blinding of endpoint assessment	Incomplete endpoint data	Selective reporting of endpoints	Other causes of bias	Evidence level according to AWMF and AZQ modified according to GRADE
Improved oral hygiene	Dimopoulos et al. 2009 (18)	-	-	-	-	-	?	?	IIb
	Ripamonti et al. 2009 (27)	-	-	-	-	-	-	?	IIb
	Vandone et al. 2012 (25)	-	-	-	-	-	-	?	IIb
	Bramali et al. 2015 (29)	-	-	-	-	-	-	?	III
	Bonacina et al. 2011 (17)	+	-	-	-	-	-	?	IIb
	Sim et al. 2015 (28)	-	-	-	-	-	-	?	IIb
	Montefusco et al. 2008 (34)	-	-	-	-	-	?	?	IIb
Antibiotic treatment	Ferlito et al. 2010 (19)	-	-	-	-	-	-	?	III
	Lodi et al. 2010 (21)	-	-	-	-	-	?	?	III
	Heufelder et al. 2014 (20)	-	-	-	-	-	?	?	III
	Regev et al. 2008 (23)	-	-	-	-	-	-	?	III
	Vescovi et al. 2013 (26)	-	-	-	-	-	?	?	III
Changed surgical techniques, new approaches	Mozzati et al. 2011 (22)	+	-	-	-	-	?	?	III
	Scoletta et al. 2013 (24)	-	-	-	-	-	?	?	III
	Scoletta et al. 2013 (e21)	-	-	-	-	-	?	?	III

+ Low risk of bias

? Risk of bias not known

- High risk of bias

AWMF, Association of the Scientific Medical Societies in Germany; AZQ, Ärztliches Zentrum für Qualität in der Medizin [Medical Center for Quality in Medicine]; GRADE, Grading of Recommendations Assessment, Development and Evaluation