



# Replacing one evil with another: Is the fibula really a dispensable spare part available for transfer in patients with medication-related osteonecrosis of the jaws?

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Because of the long-term and consecutive use of different causative agents, clinicians are increasingly encountering patients needing restoration of the stomatognathic system after surgical resection of highly advanced necroses of the jaw. For plastic restoration in these cases, microvascular reconstruction seems to represent the most viable option. According to the limited data available, the risks of this operation are considered comparable with those faced by other patient cohorts. We report here the case of a patient who suffered 2 successive pathologic fractures of the tibia after microsurgical reconstruction of the mandible with a free fibula flap. This exemplifies a general problem, especially because the patient also suffered from a treatment-refractory infection of the transplanted bone. Although the present literature indicates otherwise, fibula transplants might not be the gold standard in these cases. Therefore, alternatives to transplants from the weight-bearing parts of the body need to be considered until more data are available. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;129:e257–e263)

After the first case of “phosphorimus chronicus” (phosphorus necrosis or “phossy jaw”) was published 185 years ago, osteonecrosis of the mandibula and maxilla is widely accepted as a complication related to antiresorptive drugs.<sup>1–3</sup> The first reports about bisphosphonate-related osteonecrosis of the jaw were published as late as 2003.<sup>4</sup> Since then, the number of cases reported in the literature is continuously increasing, and osteonecrosis remains an unresolved challenge faced on a daily basis by maxillofacial surgeons.<sup>4–7</sup> As Marx has shown, the mechanisms of phosphorus necrosis of the jaw resemble those of bisphosphonate-related necrosis of the jaw because phosphorus fumes can undergo conversion to bisphosphonates.<sup>1,4,8</sup> These bisphosphonates form non-hydrolyzable and stable analogues of pyrophosphate phosphorus-carbon-phosphorus bindings, which mimic physiologic phosphorus-oxygen-phosphorus bindings.<sup>9</sup> Clinically used bisphosphonates generally comprise nitrogen side chains (aminobisphosphonates), which enable them to act as inhibitors of the cholesterol pathway, decreasing cytoskeletal rearrangement and vesicular trafficking in osteoclasts and, thus, causing cytotoxicity and cell death.<sup>5,9,10</sup> Because of a growing number of patients suffering from osteonecrosis caused by other antiresorptive drugs, the American Association of Oral and Maxillofacial Surgeons (AAOMS)

recommended changing the nomenclature to medication-related osteonecrosis of the jaw (MRONJ).<sup>11</sup> These drugs include denosumab, an antibody targeting the receptor activator of nuclear factor kappa-B ligand (RANKL), and a variety of antiangiogenic agents antagonizing the effects of the vascular endothelial growth factor in the form of antibodies (bevacizumab) or small molecules, such as sunitinib, sorafenib, and cabozantinib.<sup>9</sup> In the case of rapamycin (a mammalian target of rapamycin [mTOR] inhibitor), its association with MRONJ has been clinically documented and published.<sup>9,12,13</sup> General indications for antiresorptive therapy are osteoporosis, tumor-associated hypercalcemia or osteolysis, and Paget disease.<sup>9</sup> Antiangiogenic agents are used to treat glioblastoma, as well as multiple metastatic cancers originating from breast, prostate, renal, lung, and colorectal tissues.<sup>9</sup>

## CLINICAL CASE PRESENTATION

### Anything that can go wrong will go wrong

To the best of our knowledge and based on the current literature, we present the first case of recurrent tibial fractures after long-term antiresorptive treatment with zoledronic acid and denosumab in a patient who had undergone mandibular reconstruction with a free fibula flap following extensive resection of severe medica-

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Received for publication Jun 6, 2019; returned for revision Jul 18, 2019; accepted for publication Oct 15, 2019.

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2212-4403/\$-see front matter

<https://doi.org/10.1016/j.oooo.2019.10.008>

## Statement of Clinical Relevance

Patients with medication-related osteonecrosis of the jaws have a disadvantageous risk profile for orofacial reconstruction. Transplants from non-weight-bearing bones must be considered because of the potentially compromised quality of other bones. Concomitant antimicrobial treatment may be a decisive factor in treatment success.

tion-related necrosis of the lower jaw. This report may serve as springboard for future reviews.

A 75-year-old female patient presented to our outpatient clinic with severe MRONJ, including a pathologic fracture and extraoral fistulas (AAOMS stage 3) of the lower jaw. The patient had received antiresorptive therapy for 4 years for metastasized mammary carcinoma. After 3 years of intravenous application of zoledronic acid, the treatment regime was changed intermittently to subcutaneous denosumab, followed by another shorter period of zoledronic acid therapy, which ended about 5 years before the patient's first presentation to our clinic. During the typical clinical course of this disease, the patient underwent various reductive osteotomies, with unsatisfactory long-term results. The main complaints were swelling, pain, and a persisting extraoral fistula with ongoing putrid secretion in the left submandibular area. Computed tomography (CT) revealed a major defect involving the entire right corpus and ramus of the mandible ranging from region 33 to 38 (Figures 1 and 2). Because of the major defect size and in the wake of a therapy-refractory MRONJ infection, a continuity resection became necessary. Plastic reconstruction was performed via a microvascular free osseomusculocutaneous fibula flap (Figure 3).

Two months after transplantation, the patient suffered a tibial fracture without relevant trauma, which, according to the Arbeitsgemeinschaft für Osteosynthesefragen (AO Foundation) principles, had to be treated with open surgery with open reduction and internal fixation, and the surgery was performed in a hospital close to the patient's place of residence (Figure 4). About another 2 months later, the patient suffered a second pathologic fracture of the right medial malleolus, distant to the first fracture, and again the patient did not experience any trauma to the lower leg (Figure 5). Because of the questionable prognosis of a second surgical intervention and mild impairment (the patient was mobile with a rollator and suffered little to no pain), the patient agreed to conservative treatment with supporting bandages and custom-made orthopedic footwear. We were not aware of any other bone-debilitating disease in this patient, and the patient presented normal



Fig. 1. Preoperative orthopantomogram before the last attempt of "conservative" reductive osteotomy.

vitamin D values in blood samples (25-OH-vitamin D3: 140.9 nmol/L; 1.25-OH-vitamin D3: 49.3 pmol/L).

Besides the complications at the donor site, the patient developed therapy-refractory putrid infections at the primary surgical site 9 months after the free fibular reconstruction of the mandibula, despite osseous consolidation.

After attempts at conservative antibiotic treatment, the reconstruction plate was removed, followed by a meticulous surgical debridement to control the infection, as well as collection of histopathologic and microbiologic specimens. The intervention was accompanied by long-term antibiotic treatment (a combination of intravenous meropenem 1 g,  $\times$  3 per day, and intravenous vancomycin 0.5 g,  $\times$  2 per day, for 10 days, followed by oral antibiotic therapy with doxycycline 100 mg,  $\times$  2 per day, and cotrimoxazole 960 mg,  $\times$  2 per day, over a period of 3 months), based on the microbiologic and histologic results as well as the recommendation by the Department of Infectiology and Septic Surgery. Follow-up examination revealed persisting but clinically inapparent submental fistulas in the area of the transplanted bone.

## DISCUSSION

### Only the jaws?

Long-term antiresorptive therapy is capable of severely compromising bones as well as soft tissues, eventually leading to impairment of mechanical and biologic properties.<sup>9,14</sup> There is ongoing debate about why the complications of antiresorptive drugs are mainly related to the jaws despite the systemic effects of these drugs. Several reasons can be put forth to explain why the jaws, especially the mandible, are the most affected bones in the body: thin soft tissue coverage, teeth perforating the epithelial barrier, microtrauma caused by mastication, a high turnover rate, and the peculiar embryologic origin and development.<sup>9,15,16</sup> Although bisphosphonates are effective in preventing osteoporotic fractures during the first 3 to 5 years of treatment, there are strong indications that long-term treatment could elevate the risk of atypical femoral fractures (AFFs) resulting from low-impact trauma to the shaft and subtrochanteric areas.<sup>17,18</sup> These fractures are generally rare, but Lee et al. recently found that in approximately 80% of these cases, the fractures were related to bisphosphonate therapy.<sup>14,19</sup>

It is obvious that the risks are even greater after invasive intervention (e.g., harvest of free bone flaps or orthopedic surgical intervention) at previously unaffected bones of the skeleton, especially when bacterial contamination or infection occurs in the postoperative phase. Our patient did not suffer from other bone diseases. Vitamin D levels were in the upper normal range. This raises questions regarding the reason for this type of unexpected pathologic fracture and whether it is associated with earlier cancer treatment. Schilcher et al. investigated 8

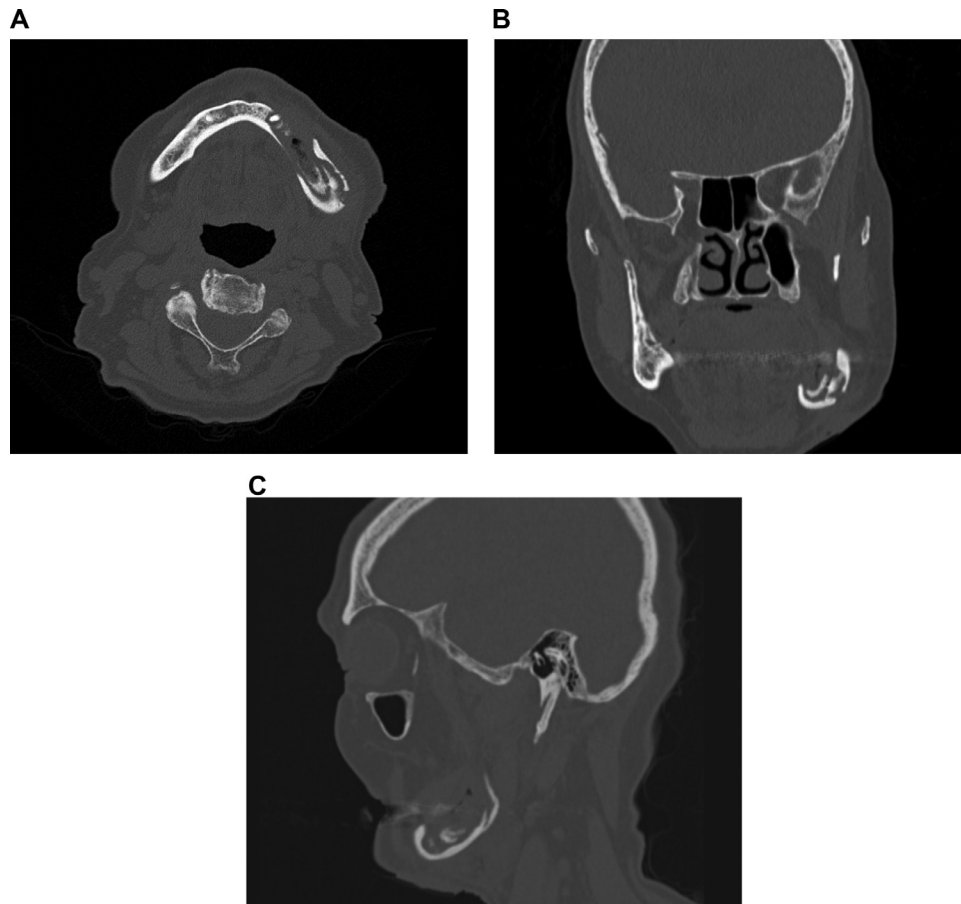


Fig. 2. Preoperative computed tomography (CT) scan before a continuity resection and reconstruction with a free fibula flap. **A**, Coronal plane. **B**, Axial plane. **C**, Angulated view of the sagittal plane.

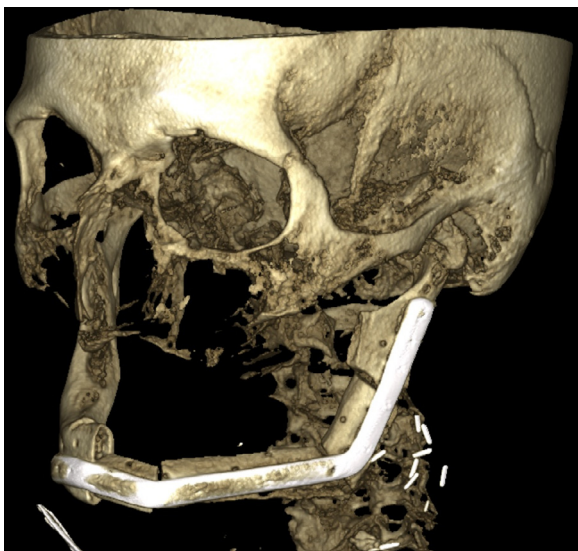


Fig. 3. Postoperative situation after reconstruction of the left mandible with a free fibula transplant and CAD-CAM (computer-assisted design/computer-assisted manufacturing)–manufactured osteosynthesis plates.

atypical femoral fractures histologically and found amorphous acellular material in the fracture gap of incomplete atypical fractures.<sup>20,21</sup> Especially in cases with prolonged bisphosphonate use, dead osteocytes have been found at a distance from the fracture line.<sup>20</sup> Via in vivo microindentation, Guerri-Fernandez et al. compared stress resistance of the tibial bone between patients with typical and atypical femoral fractures and between those with and without bisphosphonate therapy.<sup>21,22</sup> In this study, the tibias of patients with bisphosphonate-related AFFs showed greater indentation to applied forces, leading to the assumption of a lower resilience to crack propagation.<sup>21,22</sup> In a study by Brock et al., 4-point bending in the femurs of osteoporotic sheep treated with alendronic acid showed reduced fatigue life and reduced tendency to bend.<sup>21,23</sup> The thicker tissue coating of bones other than the jaws might be a reason for medication-associated osteonecrosis being a problem predominantly of the oral cavity.<sup>9</sup>

#### Treatment options for severe MRONJ

Because of lack of long-term studies investigating the treatment modalities for MRONJ, the extent of surgical



Fig. 4. **A, B**, Pathologic tibial fracture 2 months after transplantation of the right fibula.



Fig. 5. Second pathologic fracture of the medial malleolus 2 months after open reduction internal fixation of the tibial fracture.

procedures continues to be a controversial topic, even though surgical debridement appears to be superior compared with conservative management in cases of acute inflammation and exposed bone.<sup>24-26</sup> There is

broad consensus that surgical procedures should include complete removal of necrotic bone, as well as thorough wound closure with tight and thick soft tissue coverage, to improve local wound healing.<sup>11,25,27-30</sup> In severe cases of MRONJ, surgical removal of necrosis can result in total or subtotal resection of the affected bone, leaving insufficient or no load-carrying bone. In many cases, even when it exists, the remaining bone with compromised mechanical resilience is functionally deficient, so adequate reconstruction is required.

In a retrospective review, Caldrony et al. investigated 11 cases of advanced mandibular MRONJ after microvascular reconstruction with either fibula or scapula transplants, and they concluded that after a mean follow-up of 25 months, this type of treatment was not associated with a higher risk of surgery-related or general complications compared with those in other patient populations.<sup>25</sup> In a systematic review, Sacco et al. came to the same conclusion, but they emphasized that limited data are available at present.<sup>31</sup> Marx et al., in contrast, advocated bone reconstruction of continuity defects only in cases where fixation with reconstruction plates and adequate soft tissue coverage or a plate by itself would be insufficient.<sup>30</sup> Radical approaches are controversial, especially in medically compromised patients, but Ehrl et al. showed that even in patients in whom general anesthesia poses a high risk, such as those with American Society of Anesthesiologists physical status III and IV, no significantly higher rate of complications with microsurgical reconstruction could be found.<sup>32</sup> Nevertheless, these procedures should be performed in high-volume centers to optimize flap outcomes.<sup>33</sup>

**Is superinfection of freshly transplanted bone a major problem?**

Whether bone exposure is a consequence of infections following necrosis, or vice versa, is still not clear and remains a topic of scientific discussion.<sup>9,34-36</sup> Irrespective of the cause of bone exposure, invasion of the exposed necrotic bone by oral microorganisms and development of biofilms are frequently observed.<sup>9,37,38</sup> Interestingly, the most commonly encountered species appears to be *Actinomyces* in approximately 69% of the cases.<sup>39</sup>

*Actinomyces*, in contrast to other bacteria of the oral cavity, seems overrepresented in MRONJ lesions and is known to be part of polymicrobial biofilms.<sup>39-41</sup> Because of the slow growth of *Actinomyces*, it is possible that prior antibiotic treatment leads to the preselection of this bacterial genus.<sup>42,43</sup>

In our case, microbiologic testing after partial removal of the reconstruction plate revealed evidence of only *Streptococcus constellatus* and *Escherichia*



*coli*, *Actinomyces* spp., which were found in the sample of the continuity resection, were not encountered after surgical revision of the infected area. Therefore, the abovementioned treatment protocols were chosen. Biofilms, with their complex biologic features, seem to play an important role in MRONJ and, thus, may be a major reason for the difficulty in obtaining stable and recurrence-free results. Biofilms require decisive antimicrobial treatment and, in advanced cases, thorough debridement of necrotic and, therefore, potentially contaminated bone.<sup>37,44,45</sup> This must be considered to avoid transplantation failure, especially when major reconstructive surgery is planned.

### Is the fibula dispensable?

As described in detail before, antiresorptive drugs have a huge impact on bone metabolism and turnover, resulting in serious impairment of the stability of not only the jaws but also other bones of the body.<sup>46</sup> It has even been suggested that the impact of antiresorptive medication on osteoimmunology indicates that the pathology of MRONJ resembles that of systemic rheumatoid arthritis.<sup>9</sup> This must be considered meticulously to avoid severe complications in medically compromised patients. Even though the fibula seems dispensable in other patients and overall donor site morbidity is low, compromised bone quality in patients with MRONJ may require thorough patient selection in cases of potential reconstruction with free fibula flaps.<sup>47-50</sup> In these cases, the tibial fractures may be analogous to the pathophysiology of atypical femoral fractures, according to Wolf's law, which states that bones in healthy patients adapt to load bearing and changes in mechanics and/or weight.<sup>51</sup> Lack of adequate bone remodeling is likely to lead to impaired bones that are insufficiently adapted to mechanical and physiologic requirements because of their higher porosity and lower resilience to stress.<sup>23,52</sup> Weight-loading experiments in autopsy specimens performed by Takebe et al. showed load distribution of 6.4% to the fibula in the neutral ankle joint position, increasing in dorsiflexion and when the tibia was strained laterally and posteriorly.<sup>52</sup> Yazdi et al. showed that partial fibulectomy resulted in increased pressure on the lateral compartment of the knee and decreased pressure on the medial one.<sup>53</sup> This emphasizes the adaptive process the remaining bones need to undergo to cope with the changing demands of body mechanics. Age-related differences in bone geometry indicate that inactivity resulting from aging and a poorer general condition seems to primarily affect weight-bearing bones, such as the tibia.<sup>54</sup> Furthermore, Loyson et al. found that MRONJ is more likely to occur in patients who switch from bisphosphonates to denosumab.<sup>55</sup> Consequently, greater damage and deterioration of the peripheral

bones is probable after treatment with 2 or more antiresorptive drugs. Therefore, alternatives, such as reconstruction plates with a soft tissue flap or free scapula flap, must be considered in the treatment of high-risk patients with severe MRONJ.

### CONCLUSIONS

Severe MRONJ is a challenge for patients, oncologists, dentists, and maxillofacial surgeons. The damage of other parts of the skeleton in serious cases of MRONJ is likely to be a concern also for other specialties, such as orthopedic and general surgeons. In advanced cases with severe clinical symptoms, there may be no alternatives to surgical intervention, including segmental resection. Even though free flap procedures, such as fibula transplantation, remain the gold standard for reconstruction in many head and neck cancer treatment centers and low postoperative morbidity has been shown in the majority of patients, we would like to draw attention to the likelihood of an increased risk of severe complications in this specific patient cohort. Even though direct as well as general conclusions from a single case are not possible, data on atypical femur fractures suggest compromised overall bone quality in these patients. Currently available publications have indicated and emphasized the relative safety of fibula transplants in MRONJ patients, our review should serve as a call for greater caution until more studies on this subject are available. When the reconstruction of continuity defects in this specific patient population is considered, careful evaluation is essential to avoid debilitating and tedious complications, as presented in this review. Furthermore, a decisive concomitant antimicrobial treatment based on the results of pathologic and microbial testing should be obligatory. Future research needs to address the long-term effects and risks of consecutive and/or long-term treatment with various antiresorptive and antiangiogenic agents.

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