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## **Biomaterials and osteoradionecrosis of the jaw: review of the literature according to the SWiM methodology**

Prescillia Lagarrigue<sup>1,2</sup>, Jérémy Soulié<sup>1</sup>, Emilien Chabrilac<sup>3</sup>, Vincent Darcos<sup>2</sup>, David Grossin<sup>1</sup>, Sébastien Vergez<sup>4</sup>, Christèle Combes<sup>1</sup>, Agnès Dupret-Bories<sup>1,3\*</sup>

1. CIRIMAT, Université de Toulouse, CNRS, Toulouse INP - ENSIACET  
4 Allée Emile Monso - CS 44362 - 31030 Toulouse Cedex 4, France

2. IBMM - Université de Montpellier - CNRS – ENSCM  
15 Avenue Charles Flahaut, 34093 Montpellier Cedex 5, France

3. Chirurgie ORL et Cervico-Faciale, IUCT Toulouse Oncopole, Institut Claudius Regaud,  
1 Avenue Irène Joliot Curie, 31059 Toulouse Cedex 9, France

4. Chirurgie ORL et Cervico-Faciale, CHU Toulouse, Hôpital Rangueil-Larrey, 31000  
Toulouse, France

### **\* Corresponding author:**

E-mail: Dupret-Bories.Agnes@iuct-oncopole.fr (Agnès Dupret-Bories)

Chirurgie ORL et Cervico-Faciale, Institut Universitaire du Cancer de Toulouse Oncopole,  
Institut Claudius Regaud, 1 Avenue Irène Joliot-Curie, 31059 Toulouse, France

## **Abstract**

**Objectives:** To systematically present and interpret the current literature on research and treatment perspectives for mandibular osteoradionecrosis (mORN) in the field of biomaterials.

**Material and methods:** A systematic review of the literature using the "Synthesis without meta-analysis" (SWiM) methodology was performed on PubMed, Embase and Cochrane, focusing on the implantation of synthetic biomaterials for bone reconstruction in mORN in humans and/or animal models. The primary endpoints were the composition, efficacy on mORN and tolerance of the implanted synthetic biomaterials.

**Results:** Forty-seven references were obtained and evaluated in full-text by two assessors. Ten (8 in humans and 2 in animal models) met the eligibility criteria and were included for analysis. Materials most often comprised support plates or metal mesh (5 of 10 cases) in combination with grafts or synthetic materials (phosphocalcic ceramics, glutaraldehyde). Other ceramic/polymer composites were also implanted. In half of the selected reports, active compounds (molecules, growth factors, lysates) and/or cells were associated with the reconstruction material. The number of articles referring to implantation of biomaterials for the treatment of mORN was small, and the properties of the implanted biomaterials were generally poorly described, thus limiting a thorough understanding of their role.

**Conclusion:** In preventing the morbidity associated with some reconstructive surgeries, basic research has benefitted from recent advances in tissue engineering and biomaterials to repair limited bone loss.

**Key-words:** Osteoradionecrosis of the jaw, systematic review, bone reconstruction, biomaterials

## 1. Introduction

Mandibular osteoradionecrosis (mORN) is a severe complication of radiation therapy for head and neck cancer. In France, there are more than 17,000 new cases of head and neck cancer par year, with high mortality. It is the 5<sup>th</sup> main cause of death from cancer (INCA 2016). Seventy percent of patients are treated by radiation therapy, isolated or associated to another treatment (INCA 2016). Radiation therapy induces acute and late toxicity, such as mORN, and can have major impact on quality of life, functionally, esthetically and psychologically [1]. Prevention and treatment of mORN is a major challenge for physicians managing cancer treatment sequelae in potentially cured patients. Although mORN has been widely studied, few articles focused on the use of synthetic biomaterials, despite a wide range being available for bone regeneration in other indications, and there has been no review of the literature. The present study therefore aimed to systematically present and interpret the current literature on the efficacy of biomaterial implantation in bone defects induced by mORN, in humans or in animal models. The PICO (Population – Intervention – Comparison – Outcome) approach was adopted: i) study of mORN patients or animal models (population); ii) study of defect reconstruction by biomaterials (intervention); iii) comparison between biomaterial implantation and autologous graft (comparison); iv) assessment of improvement in bone reconstruction (outcome).

## 2. Material and method

A systematic literature review was performed with the main aim of inventorying the synthetic biomaterials used in the treatment of mORN. The main endpoints were biomaterial composition, efficacy in mORN, and tolerance. The review was conducted using a dedicated

protocol: mORN-related bone defect reconstruction by biomaterials (PICO, intervention) in mORN patients or animal models (PICO, population), if possible with comparison between biomaterials and autologous graft (PICO, comparison), to assess improvement in reconstruction (PICO, outcome). The literature search concerned articles in French or English, available in full text, without date limits, in the PubMed, Embase and Cochrane databases, following SWiM (Synthesis Without Meta-analysis) guidelines. The search-terms were: *(mandibular OR jaw) AND (osteoradionecrosis) AND (biomaterials OR scaffolds)*, and *(mandibular OR jaw) AND (reconstruction) AND (biomaterials) AND (osteoradionecrosis OR irradiated)*. Articles responding to these keywords were then sorted according to inclusion and exclusion criteria. Reference lists were also searched manually to ensure exhaustiveness. Figure 1 shows the search flowchart.

Studies were selected for full-text analysis on the following inclusion criteria: synthetic biomaterials (organic, inorganic or composite) implanted for treatment of mORN, in humans or animal models. Articles not available in French or English or in full text were excluded. No meta-analysis was feasible, due to lack and variability of data for statistical treatment. The selected articles were analyzed on double reading using pre-established forms detailing type of population (human or animal), number of cases, biomaterial characteristics (composition, market name, association with auto- or allo-grafts, bioactive compounds or cells, and form), and results following implantation (see Tables 1 and 2).

### 3. Results

#### 3.1. Articles, patients and animal models

The search of the PubMed, Embase and Cochrane databases in December 2020 identified 82 articles. After elimination of doubles, 47 remained, 10 of which addressed the

study question and met the inclusion criteria (Figure 1). Tables 1 and 2 show the data extracted from the selected articles. Eight of the 10 concerned mORN patients and 2 concerned animal models. Numbers were too small for statistical study, but the results confirmed the relevance of the present review. None of the human studies had a control group. Five focused on specific cases of mORN treatment [2–6] and 3 reported long-term or retrospective studies [7–9]. Table 1 shows the main data. In the particular case of the article by Zwetyenga et al., a preliminary study was conducted on mandibular bone defect in rabbits before translation to humans, but in a non-irradiated region not modeling mORN. The 2 animal studies were conducted in rats, with post-radiation extraction of mandibular molars [10,11] (Table 2).

### 3.2. Main objective

The main objective of the review was to inventory synthetic biomaterials used in the treatment of mORN. There were 4 main families: metals (6 cases) [3,4,6–9], polymers (3 cases) [3,10,11], ceramics (3 cases) [4–6], and composites of at least 2 materials (3 cases) [2,5,7]: in 1 case, polymers (PMMA and pHEMA) and a ceramic (calcium hydroxide) [2], in another metal (titanium) and ceramic (HA) [7], and in the third autograft (iliac cancellous bone) and ceramic (biphasic calcium phosphate) [5].

The biomaterials came in various forms. Composite titanium/HA meshes [7] or titanium support plates [3,4,6,8,9] were used in 4 ways: in association with bone auto- or allo-graft or with synthetic materials, to ensure stability and the mechanical solidity of the assembly. In the case study by Horta et al., the ceramic was stabilized in the defect using a collagen membrane (TissuDura®), an anterolateral thigh flap and a titanium plate [4]. The defect was filled by powdered (2 cases) [4,5] or solid ceramics (2 cases) [2,6]. Zwetyenga et al. reported mandibular reconstruction using the induced membrane technique, filling the defect first with PMMA cement to induce a synovial membrane, and then with an autograft-ceramic composite [5]. Lastly, hydrogels [10,11] or porous composites known as scaffolds [3] were used in 3 cases.

Five articles reported associating active compounds (molecules, growth factors, lysates) and/or cells to a material. Gallego et al. formed a scaffold by reticulating autologous serum with glutaraldehyde, supported by a titanium plate [3]. Jin et al. compared hydrogels of hyaluronic acid alone or with a growth factor (BMP-2) and/or mesenchymal stem cells as bone substitute [10]. Park et al. also studied mesenchymal stem cells in bone defect reconstruction using a commercial hydrogel based on extracellular matrix (Matrigel®) as filler and cell vector [11]. Mendonça et al. created a bioactive matrix using a blend of  $\beta$ -TCP-HA and blood plasma (platelet rich and poor) and bone marrow cells cultivated in vitro [6]. Carl et al. associated a blend of blood and tetracycline to a polymer-ceramic composite so as to obtain a dense material by coagulation [2].

#### 4. Discussion

##### 4.1. Pathophysiology

mORN mainly arises after radiation therapy for oral cavity or oropharynx cancer [12]. There are several clinical classifications, of which Table 3 presents the best-known. Onset depends on several factors. The main risk factors are: primary tumor site and local extension, dental status and tooth extractions, radiation dose, irradiated mandible volume, and chemotherapy [13].

As mORN is difficult to treat, prevention is primordial. Radiation therapy should be preceded by oro-dental care, including extraction of any teeth within the radiation field that are unlikely to survive in the long term, and improvement to oro-dental health status. Prophylactic extraction should be performed at least 14 to 21 days ahead of the radiation therapy, to allow for healing [14,15]. Even so, efficacy in preventing mORN is unproven: extraction may even be associated with higher incidence of mORN [16].

Prevention after radiation therapy involves optimal oral hygiene and close dental monitoring. A recent meta-analysis found no benefit for fluoride [17]. Extraction in mandible regions that received > 35 Gy radiation is to be avoided if possible; otherwise, perioperative antibiotic therapy and hyperbaric oxygen therapy both demonstrated efficacy [13,17]. Despite preventive measures and the use of intensity-modulated radiation therapy, mORN rates remained high in recent studies, at 5-10% over a 2-year period [13].

In 2002, Schwartz and Kagan described mORN pathophysiology as a complex interaction of several etiologic factors, the main one of which is healing defect [18]. The vascularization defect in mORN is mainly due to radiation-related sclerosis of the terminal branches of the inferior alveolar artery. The angular and horizontal regions of the mandible, which are most affected by mORN, have what is known as “terminal” vascularization, without any back-up network, which is why the mandibular bone is more affected than the maxillary [14]. This lack of blood supply then leads to mucosal and osseous tissue necrosis. Radiation therapy moreover damages cells in the irradiated tissue, impairing function. Together, these two factors impair the normal cycle of tissue regeneration: degradation exceeds renewal, preventing healing and inducing osteonecrosis [14]. Dental extraction, surgery and trauma thus constitute the main risk factor for mORN, as tissue healing is impaired by the radiation therapy and trauma can lead to decompensation in already fragile vascularization [13,18].

Although according to Schwartz and Kagan bone healing defect is the main cause of mORN [18], bacterial infection probably plays a major role in progression. The necrotic bone exposed in the oral cavity is colonized by a variety of oral bacteria. Moreover, irradiation of the salivary glands acidifies the saliva, from pH 7 to 5, favoring acidogens such as *Streptococcus mutans*, *Lactobacillus* and *Candida* [19]. This highly septic environment is probably the main obstacle in implantation, requiring antibacterial biomaterials.

#### 4.2. Main objective and discussion of selected studies



Only 10 studies published to date focused on synthetic implants in mORN. The present review found that, in humans, a key point in the treatment of mORN-induced bone defects is the stability and fixation of the filling material. In 6 of the 8 selected articles, the authors used titanium plates or meshes to ensure conservation of mechanical properties, and in 5 cases these were associated to a biomaterial or a bone graft (Table 1). The other 2 studies used composites: either polymer/ceramic associated to the patient's own blood, or ceramic/bone graft. Overall, the clinical results testified to successful osseointegration in more than half the cases, except in the study by Kämmerer et al. [8], where results for mORN patients were not specified, and that by Probst et al. [9], where the success rate was lower (5/11). The 2 studies in rats validated the development of an mORN model (Table 2); the results showed that hydrogels loaded with growth factors and/or mesenchymal stem cells improved reconstruction and bone regrowth. The results further suggested that introducing growth factors and/or mesenchymal stem cells immediately after tooth extraction limited mORN onset [44].

Currently, autologous grafts are favored for mORN-related bone defect, and there are few studies of filling by biomaterials [20,21]. In the 34 excluded articles, human studies mainly concerned mandibular reconstruction by autograft, mostly in non-irradiated locations, and/or the impact of radiation therapy on bone regrowth and implant fixation. The excluded animal studies reporting synthetic biomaterials mainly concerned models of ORN in the tibia or femur rather than the mandible, being easier to implement, with simpler surgery, lower risk of early animal death, the possibility of having 4 defects per animal, etc. Although these articles were not included in the present review focusing on mORN, they nevertheless presented useful progress in the use of different synthetic materials with or without bioactive compounds or cells for radiation-related bone defect reconstruction [22–28].

#### 4.3. Critical analysis and biases

Methodologically, the main bias in the selected articles was a failure to identify and characterize the biomaterials being used, so that the effects of the materials could not be determined. Moreover, the human studies had no control group to confirm the findings. Reconstruction efficacy was analyzed, depending on the study, as percentage successful outcome or successful implantation. Studies differed widely, and results could be pooled only as regards type of material. Bias was assessed per study, according to the number of cases.

Scientifically, the present systematic review found few studies of biomaterials in mORN. There are more studies of defect reconstruction in non-irradiated bone, but even there the range of types of biomaterials is small. 75% of materials used in humans were titanium alloys in the form of meshes or plates (Table 2). As well as being highly biocompatible, titanium ensures mechanical support throughout bone regrowth. Kämmerer's statistical study assessed the effect of implant length and of manufacturer [8]. Despite their undeniable usefulness for mechanical support, titanium alloys by no means meet the charge-book for bone defect reconstruction in mORN.

## 5. Perspectives

The discussion of the results of the present SWiM review highlighted the limits of synthetic biomaterials for the treatment of mORN. Thus the wealth of biomaterials being developed in fundamental research is of particular interest.

Apart from the classical mechanical properties of commercially available biomaterials, the ideal bone substitute should meet the following criteria: 1) to stimulate regrowth in critical bone defects by cell differentiation and proliferation; 2) to be osteoconductive and favor cell adhesion; 3) to have angiogenic and antibacterial properties; and 4) to be highly porous in terms of pore size and total porosity, so as to favor the cell colonization and angiogenesis required by bone regrowth.

The first two properties are classically related to the composition and degradation rate of so-called “bioactive” materials, and notably of inorganic materials composed of calcium and phosphate ions, constituting apatite, which is the mineral phase of bone. Engineering enables the reactivity of these materials after implantation to be controlled, releasing the active ions that stimulate osteoblasts and promote differentiation, and are thus locally “recycled” in the mineralization processes involved in bone regrowth. However, a balance needs to be struck so that degradation is not too fast, to allow osteoconduction or cell colonization.

By their composition and physicochemical properties, two families of materials meet the first two criteria: phosphocalcic materials, and bioactive glass. Loading, forming and/or association to polymers and/or biologically active agents can confer on them porosity and architecture and additional angiogenic and antibacterial properties, thus meeting the third and fourth criteria of the specifications for an ideal biomaterial for use in mORN.

Calcium phosphate (CaP) bioceramics, and especially those based on stoichiometric hydroxyapatite (HA:  $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ ) and/or  $\beta$  tricalcium phosphate ( $\beta$ -TCP:  $\text{Ca}_3(\text{PO}_4)_2$ ) obtained by high-temperature sintering of synthetic powder (Cerapatite®, Biosorb®, Calciresorb®, Ceraform®, etc.) or biological tissue (Endobon®, Bio-Oss®), are the most widely implanted bioactive ceramics, especially in orthopedic and maxillofacial surgery [29,30]. They are able to bind chemically to bone tissue and induce a stable interface on contact, enabling apatite to nucleate from biological fluids on their surface. They can take the form of solid materials, either dense or microporous (interconnected porosity: 200-500  $\mu\text{m}$  pores to allow cell rehabilitation), coatings on metal implants, injectable cements, and mineral-organic composite scaffolds for tissue engineering [31,32]. Hydroxyapatite can vary greatly in composition, with ions incorporated via a variety of cationic (strontium, silver, copper, zinc, etc.) or anionic substitutions (hydrogen phosphate, carbonate, silicate, etc.) affecting its physicochemical properties and conferring additional biological properties (antibacterial,

angiogenic, etc.) [33–35]. Ceramics based on biomimetic nanocrystalline non-stoichiometric apatites ( $\text{Ca}_{10-x}(\text{PO}_4)_{6-x}(\text{HPO}_4, \text{CO}_3)_x(\text{OH})_{2-x}$  with  $0 \leq x \leq 2$ ) deserve particular attention, having a specific structure associating a core of non-stoichiometric apatite and a hydrated surface layer rich in relatively labile bivalent ions ( $\text{Ca}^{2+}$ ,  $\text{HPO}_4^{2-}$ ,  $\text{CO}_3^{2-}$ ) conferring exceptional properties on the biomimetic apatites: ionic exchange, molecule adsorption, protein interaction, and variable solubility [36–39]. Given their similarity to bone mineral in terms of composition and reactivity, biomimetic nanocrystalline apatites certainly have a role of choice to play in the development of bioactive bone substitutes in various forms (powder, dense or porous ceramic, cement, composite, coating) requiring low-temperature processing methods to conserve the hydrated layer that ensures their exceptional bioactivity [40–43].

Biomimetic apatite cements and coatings show properties suited for the treatment of mORN. The main advantage of apatite cements ( $\alpha$ -BSM®,  $\beta$ -BSM®, Hydroset®, etc.) is their ability to fill precisely the shapes of the most complex bone defects. Their consistency allows them to be implanted by minimally invasive procedures such as trocar-syringe injection. After resorption, they leave room for newly formed bone, and they can be loaded with patient-specific biologically active agents such as antibiotics, bisphosphonates, growth factors, platelets, ions, etc. [44–48]. They harden at body temperature ( $37^\circ\text{C}$ ), unlike acrylic cements with relatively exothermal polymerization which may degrade the active principles. Low-temperature CaP coatings are processed under wet conditions using a solution or suspension on the surface of the metal implant (notably titanium or titanium alloy), or more rarely on ceramic. They usually provide a nanocrystalline apatite coating or other phosphocalcic phases that can be hydrolyzed into apatite (brushite, octacalcium phosphate) [49–53]. Wet coating techniques, such as precipitation, SBF solution, sol-gel, electrodeposition, hydrothermal deposit, cold spray, etc., provide coatings of adjustable thickness, from a few to tens of micrometers [42,49–55].

Bioactive glasses [56] are the other great family of inorganic bone substitutes. These amorphous materials are principally composed of a silica network and also contain calcium, phosphorus and sodium. When implanted, they dissolve and release silicic acid ( $\text{Si}(\text{OH})_4$ ), which stimulates formation of collagen I and osteoblast differentiation [57]. Bioactivity also involves surface formation of a biomimetic apatite layer after implantation, including  $\text{Ca}^{2+}$  and  $\text{PO}_4^{3-}$  ions released by the glass [56]. Apart from their involvement in extracellular membrane mineralization, they also promote osteoblast proliferation and differentiation and increase the expression of growth factors (IGF-I or IGF-II) and matrix Gla protein, which is a key regulator of bone growth [58]. The properties of the first bioactive glasses, produced by fusion, were closely dependent on their speed of degradation and thus exclusively on their composition. They are marketed and implemented in various applications as bone substitutes. They enhance bone regrowth, whatever their form (granules, putty, etc.) [59]. To our knowledge, these commercial products have never been used in mORN, but seem especially indicated in association to classic treatments. An alternative sol-gel synthesis route allows precise control of composition ( $\text{SiO}_2\text{-CaO}$  and  $\text{SiO}_2\text{-CaO-P}_2\text{O}_5$ ), morphology (nano/microparticles [60]) and porosity [61]. Loading with active ions [62,63] confers specific biological properties. Ions such as  $\text{Cu}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Sr}^{2+}$  and  $\text{Mg}^{2+}$  may induce antibacterial, angiogenic and/or anti-inflammatory properties [64]. Porous materials can also be obtained, such as mesoporous glass [65,66] with nanometric pore diameter and large surface area ( $> 500 \text{ m}^2/\text{g}$ ) to encapsulate (bio)molecular active principles such as BMP-2 [67]. This allows prolonged modulated release of the compounds that can be adapted to applications in mORN.

CaP-based bioactive ceramics or bioactive glasses were associated to polymers in the quest for an ideal bone-substitute material in terms of composition (bone being a mineral-organic composite), microstructure (notably porosity), mechanical properties, and ease of use in surgery (cutting before implantation). These composite materials can form the basis of

natural polymer matrices (collagen [68,69], chitosan [70,71], alginate [72,73]), synthetic matrices (poly(methyl methacrylate) [74], polyesters [75]) or inorganic matrices (CaP [43,76]). Aliphatic polyesters such as poly(lactic acid) (PLA) or poly( $\epsilon$ -caprolactone) (PCL) play a role of choice due to their biodegradability, biocompatibility and potential as vectors for active principles [77–79]. Their mechanical properties are better than those of the polymer alone, and degradation can be controlled [80], limiting risk of inflammatory reaction. Very recently, associating inorganic nanoparticles to polymers at molecular level has opened up new perspectives for the spatial homogeneity of the properties of these nanocomposites [81].

It is also possible to control the “macroporosity” ( $> 150 \mu\text{m}$ ) of these materials, which is especially suited to bone regrowth (colonization, angiogenesis) in defects following mORN and to mimicking mandibular trabecular bone. This has 70-80% porosity with 300-400  $\mu\text{m}$  pores in a partially anisotropic porosity/trabecula orientation [82,83]. Porous composite scaffolds can be produced in various ways: electrospinning [84], hard template methods [85], 3D printing [86], supercritical  $\text{CO}_2$  [87], or freeze-casting [88]. Associating tissue engineering to these scaffolds has shown benefit in maxillofacial surgery [89], and may be considered to promote cell colonization and proliferation, which are sometimes limited by mandibular hypovascularization.

In mORN, lower local stress in a non-load-bearing region means that dense injection-molded composites [84] are not necessary as they are in load-bearing sites in orthopedic surgery. This is in line with the need for open microporosity to promote cell colonization and angiogenesis. In our opinion, a major field for optimization lies in associating titanium alloy plates and meshes, as classically used in maxillofacial surgery to ensure mechanical stability, to macroporous bioactive composite scaffolds; the present authors are currently developing a macroporous composite scaffold for mORN based on poly(lactic acid) and bioglass particles.

With a wide range of bone substitutes on the market or under research and development, complete physicochemical characterization is a major issue. As described above, biological properties are closely related to composition, crystallinity, porosity and particle diameter. In preclinical and clinical cellular studies, more systematic details of the characteristics of the material used (never given in the articles reviewed here) would enable better understanding of the various factors involved in an integrative approach. The lack of characterization of the implanted biomaterials was the main bias in the articles presented here.

## 6. Conclusions

Incidence of mORN is high, despite well-conducted prevention based on solid knowledge of pathophysiology and risk factors. To avoid the morbidity associated with certain surgical repair procedures, fundamental research is founded on promising recent progress in tissue engineering and biomaterials for filling limited bone defects.

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*Figure 1. Flowchart*

Table 3. Main clinical classifications of mORN progression

Reference	Factors taken into account	Grades
Marx [14] 1983	Treatment response (surgery and hyperbaric oxygen therapy)	<b>I</b> Complete mucosal cover with 60 HOT sessions
		<b>II</b> Complete mucosal cover with sequestrectomy and 60 HOT sessions
		<b>III</b> Cure with 30-50 HOT sessions and mandibulectomy (if pathologic fracture, orostoma, radiographic proof of inferior cortical lysis)
Epstein et al. [90] 1987	Imaging and clinical findings	<b>I</b> mORN resolved or cured
		<b>II</b> Chronic (> 3 months), persistent, non-progressive mORN
		<b>III</b> Progressive active mORN
Schwartz and Kagan [18] 2002	Imaging and clinical findings	<b>I</b> Isolated superficial mandibular involvement
		<b>II</b> Localized mandibular involvement
		<b>III</b> Diffuse mandibular involvement
Notani et al. [91] 2003	Imaging and clinical findings	<b>I</b> mORN limited to alveolar bone
		<b>II</b> mORN limited to alveolar bone and/or mandible above dental canal
		<b>III</b> mORN extending to mandible below dental canal, mORN with cutaneous fistula or pathologic fracture

Ref.	Number of patients	Biomaterials				Bioactive compounds	Cells	Form	Comments	Results
		Type	Composition	Market name (Company name)	Autograft Allograft					
[2]	8	Composite (polymer/ceramic)	PMMA/pHEMA Ca(OH) <sub>2</sub>	Bioplant HTR (Bioplant, Inc.)	-	Blended blood / tetracycline	-	Densified matrix	Ceramic + tetracycline + blood blend	No prolonged pain, bone necrosis or infection
[63]	2	Polymer Metal	Glutaraldehyde Titanium	(Sigma Aldrich) (Orthoconcept)	-	Autologous serum	-	Scaffold	Serum reticulation by glutaraldehyde Titanium plate support	Success at 12 months
[4]	1	Ceramic Metal Polymer	60 % HA + 40% β-TCP Titanium Collagen	Repros® (JRI Orthopaedics)  TissuDura® (Baxter)	Anterolateral thigh flap	-	-	Powder Support plate Membrane	Ceramic filling maintained by membrane and tissue flap	Success at 3 months
[5]	4	Composite (ceramic/bone) Polymer	BCP (75% HA 25% β-TCP) PMMA	Kasios Surgical Simplex P (Stryker)	Autologous iliac cancellous bone	-	-	Powder (50%) + flap (50%) Cement	Induced membrane (PMMA) before composite implantation	50% success
[6]	3	Ceramic Metal	HA + β-TCP Titanium	-	-	Platelet-rich and –poor plasma	Bone marrow	Densified matrix	Ceramic + plasma + cells Support plate	100% success (mastication)

[7]	14 (79)	Composite (metal/ceramic)	Titanium Hydroxyapatite	-	Cancellous hip bone	-	-	HA- coated titanium mesh	-	11/14 success
[8]	4 (162)	Metal	Titanium	Medicon (Leibinger)	-	-	-	Support plate	Support plate without filling	73% success at 1 year (162) No detail on mORN patients
[0]	11 (71)	Metal	Titanium	MatrixMANDIBLE (Synthes)	Flap or allograft	-	-	Support plates	-	5/11 success

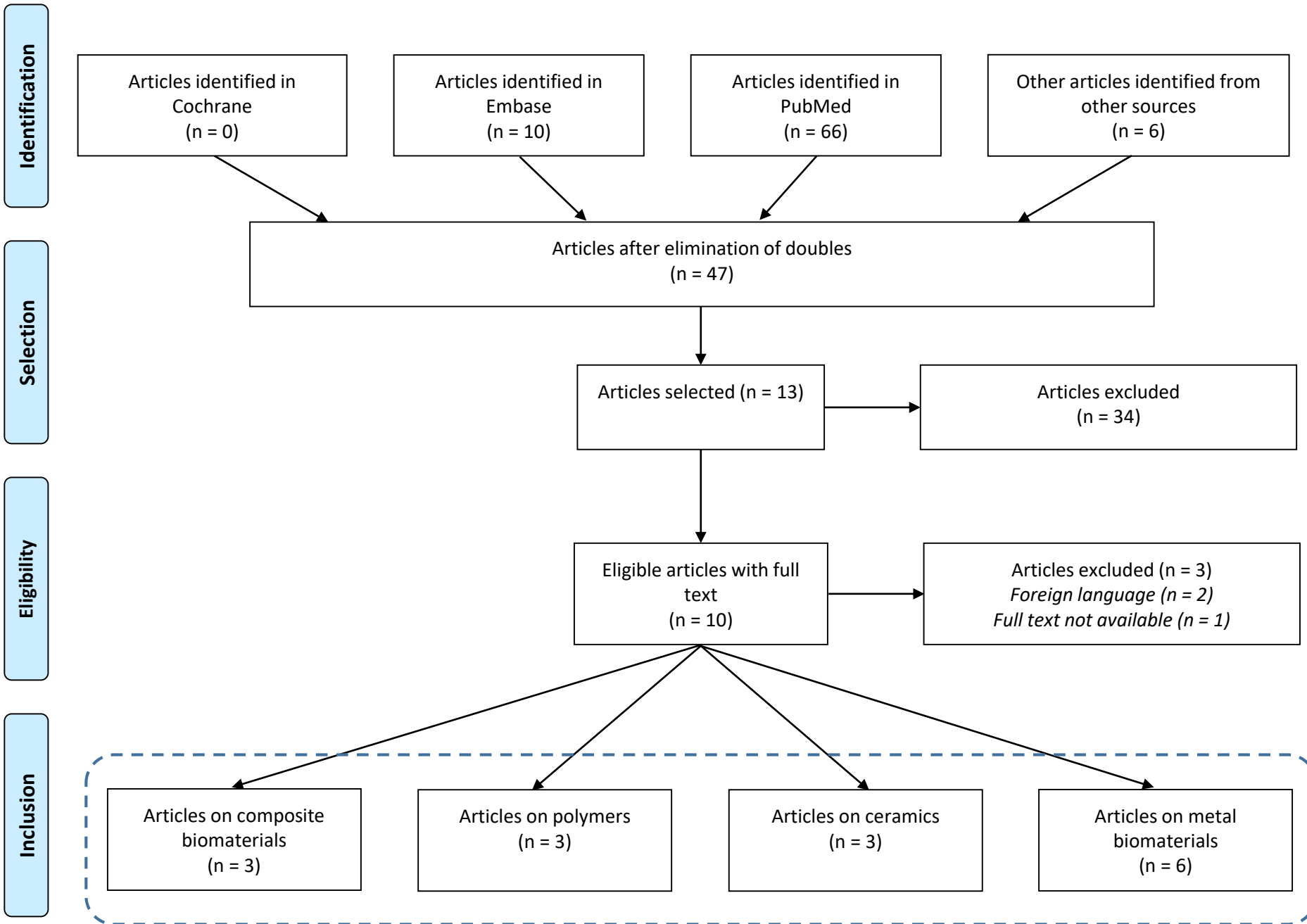
*Table 1. Main data from the 8 articles on mORN in humans treated using biomaterials*



Table 2. Main data from the 2 articles on rat models of mORN treated using biomaterials

Ref.	Number of rats	mORN model	Study	Biomaterials			Bioactive compounds	Cells	Form	Results
				Type	Composition	Company name				
[10]	50	Mandibular molar extraction 1 week after 30 Gy radiation	<p>2 groups :</p> <ol style="list-style-type: none"> <li>1. implantation after extraction (n=25)</li> <li>2. Implantation 4 weeks after extraction (n=25) :</li> </ol> <ul style="list-style-type: none"> <li>- Bone defect (n=5)</li> <li>- Hydrogel (n=5)</li> <li>- Hydrogel + cells (n=5)</li> <li>- Hydrogel + BMP-2 (n=5)</li> <li>- Hydrogel + cells + BMP-2 (n=5)</li> </ul>	Polymer	Hyaluronic acid	Lifecore Biomedical	BMP-2	Mesenchymal stem cells	Hydrogel	<p>Better results in group 1 : Hydrogel + BMP-2</p> <p>Better results in group 2 : hydrogel + cells + BMP-2</p>

[11]	44	Mandibular molar extraction 1 week after 20 Gy radiation	<ul style="list-style-type: none"> <li>- Negative control (n=3)</li> <li>- ORN (n=5)</li> <li>- Matrigel after extraction (n=9)</li> <li>- Cells after extraction (n=9)</li> <li>- Matrigel 4 weeks after extraction (n=9)</li> <li>- Cells 4 weeks after extraction (n=9)</li> </ul>	Polymer	Matrigel® matrix	BD Biosciences	-	Mesenchymal stem cells	Hydrogel	Immediate application of cells after extraction improved bone regrowth
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*Some articles used several biomaterials*