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Segmental Mandibular Reconstruction Using Tissue Engineering Strategies: A Systematic Review of Individual Patient Data

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Abstract

Objective: The aim of the systematic review was to analyze the current clinical evidence concerning the use of tissue engineering as a treatment strategy for reconstruction of segmental defects of the mandible and their clinical outcomes using individual patient data.

Methods: A systematic review of the literature was conducted using PubMed and Cochrane Library on May 21, 2019. The eligibility criteria included patients in whom segmental mandibular reconstruction was carried out using tissue engineering as the primary treatment strategy. After screening and checking for eligibility, individual patient data were extracted to the extent it was available. Data extraction included the type of tissue engineering strategy, demographics, and indication for treatment, and outcomes included clinical and radiographic outcome measures, vitality of engineered bone, dental rehabilitation, and patient-reported outcome measures and complications.

Results: Out of a total of 408 articles identified, 44 articles reporting on 285 patients were included, of which 179 patients fulfilled the inclusion criteria. The different tissue engineering treatment strategies could be broadly classified into 5 groups: "prefabrication," "cell culture," "bone morphogenetic protein (BMP) without autografts," "BMP with autografts," and "scaffolds containing autografts." Most included studies were case reports or case series. A wide variety of components were used as scaffolds, cells, and biological substances. There was not a single outcome measure that was both objective and consistently reported, although most studies reported successful outcome.

Discussion: A wide variety of tissue engineering strategies were used for segmental mandibular reconstruction that could be classified into 5 groups. Due to the low number of treated patients, lack of standardized and consistent reporting outcomes, lack of comparative studies, and low evidence of reported literature, there is insufficient evidence to recommend any particular tissue engineering strategy.

Keywords

tissue engineering, mandible reconstruction, segmental mandibular reconstruction, systematic review, scaffold, growth factor

Introduction

Mandibular resection is the curative treatment of choice for many diseases ranging from benign to malignant tumors, chronic infections, necrotic conditions, and large avulsive trauma. Mandibular resections can result in functional impairment of mastication and speech. They can also lead to aesthetic deformities with a decrease in health-related

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quality of life. The treatment goals for patients requiring reconstruction of segmental defects of the mandible have evolved from purely closing the defect to providing better aesthetic and functional outcomes leading to a better quality of life. At the same time, efforts are being made to provide solutions that decrease patient morbidity associated with treatment.[1]

Currently, the most commonly used treatment method for large reconstruction of mandibular segmental defects is vascularized bone containing free flaps (fibular, scapular, or deep circumflex iliac artery–based composite flap, etc).[2] Smaller resection defects are reconstructed using nonvascularized free bone grafts, most commonly from the iliac crest. Other methods such as transport distraction osteogenesis have also been described for the reconstruction of segmental defects.[3]

Autogenous bone transfer has been the gold standard for reconstruction of segmental defects.[4] Autogenous tissues have the capability to provide all factors critical for bone defect reconstruction: viable bone cells for osteogenesis, growth factors, and proteins for osteoinduction and a scaffold for bone regeneration[5] without the risk of incompatibility. However, the use of autogenous bone often results in donor site morbidity. Many patients are unable to go through the long and irksome procedure of free flap transfer. In addition, the anatomical and functional complexity of the mandible cannot be easily replicated with the existing autogenous tissue transfer and mere reconstruction of continuity of the resulting mandibular defects will not solve functional impairments caused by the resection.

Due to these reasons, mandibular reconstruction is still a clinical challenge and tissue engineering has been envisaged as a strategy to overcome the problems of current treatment methods. Tissue engineering has been defined as "an interdisciplinary field that applies principles of engineering and life sciences toward the development of biological substitutes, which restore, maintain, or improve tissue function (p.920)."[6] It is based on the use of 3 principal components: scaffolds, bioactive substances, and cells.[6,7] Preclinical animal studies have shown promising results after reconstructing segmental defects of the mandible; however, there is a clear lack of evidence in clinical applications.[5] This systematic review was undertaken to analyze the current clinical evidence concerning the use of tissue engineering as a treatment strategy for reconstruction of segmental defects of the mandible and their clinical outcomes.

Materials and Methods

A systematic review of the literature was conducted according to the PRISMA-IPD (Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Individual Patient Data) statement.[8-10] Electronic searches were conducted in PubMed and the Cochrane Library on May 21, 2019, to find the evidence related to the use of tissue engineering for mandibular reconstruction, defined as any combination of scaffolds, bioactive substances, and/or cells.

Table 1. Search Criteria.

#1	tissue scaffold OR stem cell OR bone morphogenetic protein OR BMP OR "bone marrow" or "growth factor" OR tissue engineering OR bioreactor OR bioimplant OR culture OR "in vitro" OR bioengineering OR "cell engineering" OR "cell culture" OR culture
#2	mandibular reconstruction OR mandibular reconstructive surgery OR segmental mandibulectomy OR hemimandibulectomy OR mandibulotomy OR mandibulectomies OR mandible reconstruction
#3	#1 AND #2
#4	sheep OR goat OR pig OR swine OR rabbit OR minipig OR rat OR mouse OR dog OR murine alveolus OR alveolar ridge OR atrophy OR socket OR extraction OR ridge resorption
#5	#3 NOT #4

Search Strategy

The search strategy is described in Table 1. Additional articles were identified by hand searching the reference lists of relevant articles (hand search). The available evidence consisted almost exclusively of case series and case reports, which, in most cases, presented information on an individual patient level. The eligibility criteria for this systematic review were as follows:

Inclusion criteria.

- Original clinical reports and studies with human subjects
- Any age
- Reconstruction of segmental defects of the mandible with tissue engineering as primary treatment
- Description of any outcome measure: radiological, clinical, functional, or bone vitality
- Minimum follow-up of 3 months
- Providing IPD on at least 1 parameter of interest
- Articles in English language
- Published within the last 20 years (1999 onward)

Exclusion criteria.

- Noncontinuity defects of the mandible
- Continuity defects secondary to fracture malunion or nonunion
- Gunshot injuries and resection defects without specification of defect size
- Isolated condylar or temporomandibular joint reconstruction
- Tissue engineering used as adjunct to vascularized bone free flaps
- Use of distraction osteogenesis alone.

Study Selection

Screening and eligibility assessment was performed by the first author (V.V.K.) who is a maxillofacial reconstructive surgeon. Individual Patient Data from eligible patients was extracted from each publication to the extent it was available. Whenever no IPD was available, the respective author was contacted per mail, requesting the missing information. Duplicate patient details were identified by comparing recruitment dates/treatment time/time frame during which patients were treated, comparing defect and reconstruction characteristics of the described patients and similarity in the author/institution details.

Data Extraction

Data extraction was done by the first author (V.V.K.), which included study design, direction of study (prospective/ retrospective), number of patients reported in the article, and number of patients eligible according to the inclusion/exclusion criteria of our review, demographics, indication for mandibular resection, use of radiotherapy, defect location, and length of defect. Indications for mandibular resection were categorized as benign pathologies (odontogenic cysts, tumors, developmental cysts, and tumors), malignant pathologies (carcinomas, osteosarcomas), infective (osteomyelitis), osteoradionecrosis, and trauma (road traffic accidents, gunshot injuries, ballistic injuries). The length of defect was collected in centimeters, whereas the defect location was described according to the affected structure(s) as high (H) if the condyle was affected, lateral (L) if the ascending ramus and/or body were affected, and central (C) if the symphysis was affected (modified from Jewer et al[11]). Data related to the mandibular defect treatment included the type of reconstruction (primary or secondary), use of maxillomandibular fixation (MMF), and additional grafts and surgical treatments.

Data Synthesis

Data were synthesized in a qualitative manner. For a better overview, outcomes were summarized in separate tables for each type of tissue engineering strategy, categorized as follows:

1. *Prefabrication:* Entails the construction of a tissue-engineered mandible inside the body of the patient but that is away from the target site of segmental mandible reconstruction. It considers the patient as a "bioreactor." Typically, a scaffold with or without bioactive substances and autogenous bone with or without bone substitutes is implanted in a vascularized region of the patient's own body. This construct remains embedded until the fabricated tissue is viable. The construct is then transferred onto the mandibular defect and anastomosed by microvascular techniques or following flap delays.[12-15]
2. *Cell culture:* Mesenchymal stem cells and/or progenitors harvested from the patient's bone marrow or adipose tissue are isolated in the laboratory, cultured under preferential conditions over a few passages, concentrated and transferred into the defect.
3. *Bone morphogenetic protein without autografts:* Bone morphogenetic protein (BMP) alone is placed in an absorbable carrier and into the defect to promote bone regeneration.
4. *Bone morphogenetic protein with autografts:* In addition to BMP, varying amounts and types of autogenous tissues were used for reconstruction: bone marrow aspirates, platelet-rich plasma (PRP), and/or corticocancellous bone grafts.
5. *Scaffolds containing autografts:* Scaffolds that have anatomic similarity to the segmental reconstruction defect, additionally filled with autogenous bone graft and placed in the defect.

Treatment Data

Treatment data were extracted based on the individual tissue engineering strategy and included the type of scaffold, bioactive substance (eg, BMP-2, BMP-7), cell type (mesenchymal, adipose, bone marrow, stem cells, autologous bone chips, PRP), region/flap of prefabrication, time taken for prefabrication, origin and type of cells used for cell culture, time in culture, and additional treatments (additional use of flaps, use of hyperbaric oxygen, etc).

Outcome Measures

Outcomes were recorded according to the following categories: (a) clinical and radiological (b) vitality of the engineered bone assessed by scintigraphy or histology, (c) dental rehabilitation with dental implants or dentures, (d) patient-reported outcome measures, and (e) complications and additional surgical procedures. Patient-reported outcome measures were only extracted if validated questionnaires were used. Reports merely stating "patients were doing well/patients were happy with the outcome" without using well-defined questionnaires were not included.

When parameters of interest were not provided as IPD, the summarized data given in the original article were reported in this review. Due to the study design and quality of the articles included in the systematic review, a meta-analysis of pooled data was not possible. Risk of bias assessment across studies, quantitative synthesis of results, summary measures, treatment effect, heterogeneity assessment, and publication bias could not be performed. A formal quality assessment was not considered to be necessary as all included studies were of a similarly low level of evidence.

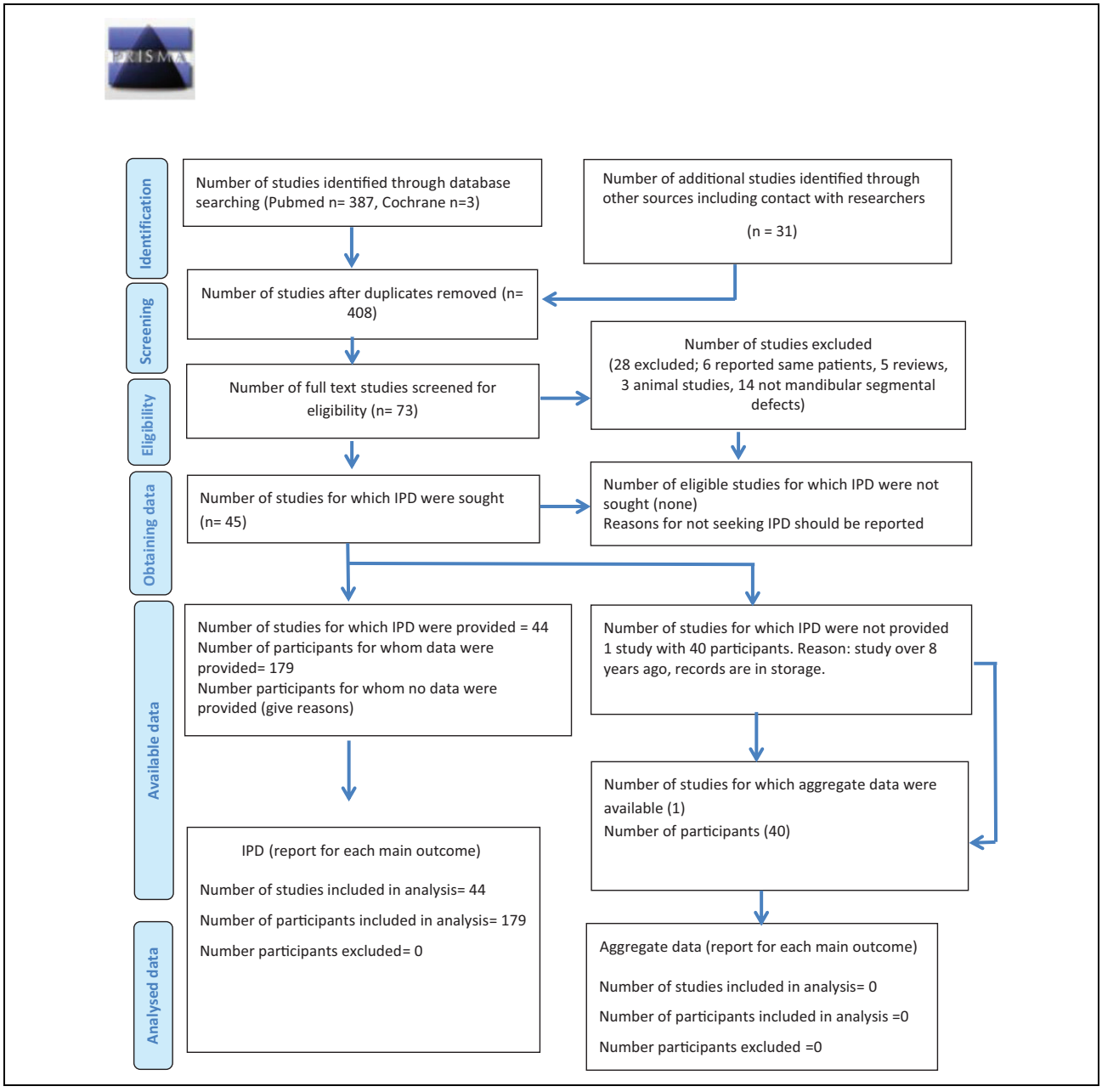


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Individual Patient Data flow diagram.

Statistical Analysis

Individual patient data were aggregated according to treatment received and descriptive statistics were performed using Microsoft Excel (MS Excel 2016).

Results

The search identified 387 articles in PubMed and 3 articles in Cochrane (Figure 1). Hand search of relevant articles identified 21 additional references. Once duplicates were removed, the abstracts of 408 articles were screened and 335 were considered ineligible. After reading the full text of 73 articles, 28 were excluded. Out of the remaining 45 articles, one study did not report on individual patient data of any parameter (neither baseline data nor outcome measures[16]) and the attempt to procure the respective IPD directly from the author remained fruitless. Therefore, 44 articles reporting on a total of 285 patients were included. Of these, 179 patients fulfilled the eligibility criteria.[13,15,17-58]

In instances where the same patient data had been reported in another publication,[12,14,22,59-61] the article that reported on longer term follow-up was included,[13,15,22,38] except for Sandor et al[59] and Wolff et al,[33] because the articles with shorter follow-up provided more detailed information. Several reports did not provide IPD on all

parameters of interest,[18,24,32,39,56,59,62] While baseline characteristics were mostly given as IPD, the outcomes were often summarized for the whole study population included in the study.

Current Tissue Engineering Strategies

Due to the broad definition, a large number of treatment options qualified as "tissue engineering." As described above, these treatment strategies were classified into 5 major treatment groups: prefabrication, cell culture, BMP without autografts, BMP with autografts, and scaffolds containing autografts. The number of studies and patients per treatment group are described in Table 2, whereas information on study design and treatment details ("individual treatment characteristics") along with outcome parameters is given in Tables 3-7.

Included Study Characteristics

Overall and irrespective of treatment group, most studies included were case reports or case series (Table 2). Most reports were retrospective except for 2 prospective case series[24,32] and 4 studies in which the direction was either not mentioned or unclear.[31,51,53,56] The highest number of patients was in the group "scaffolds containing autografts" with 115 patients, and the smallest number of patients was in the group "prefabrication" with 10 patients. The "cell culture" group consisted of 12 patients, "BMP without autografts" had 23 patients, and "BMP with autografts" had 19 patients.

Thirteen out of the 44 articles reported on series of patients with heterogenous defect characteristics, some of them not fulfilling the eligibility criteria.[19,22,32,34,39,47-51,56,59,60] For these articles, individual patient data were examined and data from eligible patients were included in this review.

Baseline Patient and Defect Characteristics

Table 2 shows baseline characteristics of each treatment group. In general, patients in the "prefabrication" and the "scaffolds containing autografts" group had a higher median age compared to the other treatment modalities.

Treatment indications. The "prefabrication" group had the highest proportion of patients with malignant pathologies, followed by "scaffolds containing autografts" group, whereas the "cell culture," "BMP with autografts," and "BMP without autografts" groups contained mostly patients with benign tumors. Consequently, 8 of 10 patients in the "prefabrication" group and 32 of 115 patients in the "scaffolds containing autografts" group underwent therapeutic radiation.

Defect location and size. The most common defect location was the lateral aspect (body and ramus) of the mandible, but the distribution varied widely. The median defect size was similar in all treatment groups; however, IPD was provided only for 40 of 179 patients.

General Treatment Information

Timing of reconstruction. All patients in the prefabrication group and most patients in the cell culture group underwent secondary reconstruction, whereas the remaining patients underwent primary reconstruction. *The use of MMF* was only mentioned in a few reports with a higher proportion of use in patients treated with "BMP with autografts" and "scaffolds with autografts" compared with other treatment groups.[20,21,29,32,37,39,51-53]

Group-Specific Treatment Characteristics

There was a high degree of variability in the treatment strategies even within the same treatment group. The individual treatment characteristics as well as the outcome measures according to treatment group are summarized for each of the studies in Tables 2-6.

In the "prefabrication" group (Table 3), the donor area of prefabrication was gastrocolic omentum, latissimus dorsi, radial forearm, pectoralis major, and scapular fascia. Titanium mesh was the most commonly used scaffold, packed with bone substitute materials such as deproteinized bovine bone, beta tricalcium phosphate, hydroxyapatite, and/or autografts. Almost all cases treated by this method used BMP (either as BMP-2 or BMP-7). The time for prefabrication varied from 4 weeks to 6 months. All reports employed scintigraphy to check for viability of the construct before it was transplanted to the defect site; however, only 2 reports described scintigraphy as a measure to check viability of the reconstruction after flap transfer.[13,52]

In the "cell culture" group (Table 4), the most common type of cells used were mesenchymal stem cells from the bone marrow of the iliac crest and adipose tissue. The time of culture varied from 3 days to 4 weeks. The scaffolds used in this treatment group were biologically active bovine graft covered with decellularized human amnion/chorion membrane, fresh frozen cadaver mandible, and autogenous freeze-dried resected mandible.

In the "BMP without autografts" group (Table 5), the scaffolds used were diverse, from bovine bone blocks, titanium mesh, and allogenic bone. The most commonly used BMP was recombinant human bone morphogenetic protein 2 (rhBMP-2). The amount of BMP used varied from 2 to 16 mg and seemed to depend on the size of the defect in most cases, although many reports did not mention the criteria for choosing a particular amount.

In the "BMP with autografts" group (Table 6), the scaffolds used were bovine bone blocks, titanium mesh, allogenic bone, resorbable polylactide mesh, and fresh frozen cadaver mandible cribs. Recombinant human bone morphogenetic protein 2 was the most commonly used BMP and the amount used seemed to vary depending upon the

Table 2. Publication Details and Baseline Characteristics According to Treatment Groups.[a]

Treatment Groups; Number of Articles per Group (N)	Studies Included; Year (Prospective [P]/ Retrospective [R])	Number of Eligible Patients (Total Number of Patients) per Article	Total Number of Patients in Analysis	Demographics; Sex M/F (ND[1]); Age (Median, Q1; Q3)[2]; Follow-Up (FU) Months (Min-Max)	Indication	Radiotherapy Y/N (ND[1])	Defect Location[3]	Length of Defect, Median (Q1; Q3)[2]	Type of Reconstruction, Primary/ Secondary	MMF: Yes/No (ND[1])
Prefabrication (N = 6)	Naukojat et al, 2018 Kokemueller et al[41] (R) Leonhardt et al[43] (R) Warnke et al[13] (R) Heliotis et al[52] (R) Orringer et al[58] (R)	1 (1) 1 (1) 5 (5) 1 (1) 1 (1) 1 (1)	10	Sex: 4/1 (5); age: 53 (57; 61); FU: 5-48	Benign tumor: 1 Malignant tumor: 9 Infection: 0 Trauma: 0 ND: 0	8/2 (0)	HL +/− C = 1 L = 3 LC = 3 LCL = 3	8.5 (7.75; 10.25) ND = 4	0/10	1/2 (7)
Cell culture (N = 5)	Kakabadze et al[24] (P) Park et al[27] (R) Zamiri et al[31] (nm) Wolff et al[33] (R) Lee et al[40] (R)	4 (4) 1 (1) 3 (3) 3 (3) 1 (1)	12	7/5 (0); age 35.5 (30; 48); FU: 6-51	Benign tumor: 8 Malignant tumor: 0 Infection: 0 Trauma: 0 ND: 4	0/11 (4)	HL +/− C = 7 L = 3 LC = 0 LCL = 2	8.1 (6; 10) ND = 9	3/9	0/3 (9)
BMP without autograft (N = 11)	Lustosa et al[28] (R) Ciccu et al, 2014 (R) Desai et al[34] (R) Ciccu, 2013 (R) Herford, 2012 (R) Herford and Boyne[45] (R) Clokie and Sandor[48] (R) Herford et al[50] (R) Chao et al[53] (nm) Ferretti et al[56] (nm) Moghadam et al[57] (R)	1 (1) 1 (1) 3 (6) 1 (1) 2 (2) 3 (14) 7 (10) 1 (6) 1 (1) 2 (13) 1 (1)	23	12/11 (0); age 40 (20; 55); FU: 6-48	Benign tumor: 23 Malignant tumor: 0 Infection: 0 Trauma: 0 ND: 0	0/19 (0)	HL +/− C = 4 L = 14 LC = 2 LCL = 3	7.0 (5.75; 11.25) ND = 9	21/2	2/16 (5)
BMP with autograft (N = 12)	Stoor et al[18,b] (R) Oliviera et al, 2017 (R) Melville et al, 2017 (R) Johnson et al[21] (R) Melville et al, 2016 (R) Rahim et al[26] (R) Balaji[30] (R) Hernandez-Alfaro et al[35] (R) Zetola et al[37] (R) Herford and Ciccu[42] (R) Balaji, 2019 (R) Carter et al[49] (R)	4 (14) 1 (3) 1 (1) 1 (1) 5 (5) 1 (1) 1 (1) 1 (1) 1 (1) 1 (1) 1 (1) 1 (5)	19	9/10 (0); age 35 (16-60); FU: 5-60	Benign tumor: 16 Malignant tumor: 1 Infection: 2 Trauma: 0 ND: 0	0/10 (0)	HL +/− C = 5 L = 7 LC = 3 LCL = 3	5.7 (3.9; 7.5) ND = 10	13/6	16/6 (7)

(continued)

Table 2. (continued)

Treatment Groups; Number of Articles per Group (N)	Studies Included; Year (Prospective [P]/ Retrospective [R])	Number of Eligible Patients (Total Number of Patients) per Article	Total Number of Patients in Analysis	Demographics; Sex M/F (ND[1]); Age (Median, Q1; Q3)[2]; Follow-Up (FU) Months (Min-Max)	Indication	Radiotherapy Y/N (ND[1])	Defect Location[3]	Length of Defect, Median (Q1; Q3)[2]	Type of Reconstruction, Primary/ Secondary	MMF: Yes/No (ND[1])
Scaffold containing autograft (N = 11)	Rodrigues Arantes[17] (R) Stoor et al[18,b] (R) Yamada et al[22] (R) Ikawa et al[25] (R) Yagihara et al[32] (P) Matsuo et al, 2011 (R) Mooren et al[39] (R) Iino et al, 2010 (R) Simon et al[51] (nm) Rochanawutanon et al[54] (R) Kiyokawa et al[55] (R)	1 (1) 10 (14) 19 (21) 1 (1) 34 (62) 5 (18) 17 (20) 15 (15) 6 (11) 4 (4) 2 (2)	115	67/ 47 (0); age 53 (33-65); FU: 6-200	Benign tumor: 56 Malignant tumor: 57 Infection: 0 Trauma: 1 ND: 0	32/83(0)	HL +/− C = 6 L = 63 LC = 13 LCL = 16 ND = 17	5.65 (5.5; 7.5) ND = 107	58/57	57/25 (33)

Abbreviations: BMP, bone morphogenetic protein; F, female; M, male; MMF, maxillomandibular fixation; N, no; ND, not documented; Q1; Q3, first quartile, third quartile; Y, yes.

[a]Defect location defined as: H = high defect that includes condyle, L = lateral aspect of mandible including body and ramus, C = central defect crossing midline, +/− = with or without, LCL = bilateral defects crossing the midline.

[b]Stoor et al[18] describe patients who belong to both group 3b and 4.

Table 3. Treatment Characteristics and Outcomes of Prefabrication Group.

Author, Year, Study Design, Eligible Patients (Number of Patients in Article), Follow-Up (FU)	Treatment Description, Area of Prefabrication (A), Scaffold (S), Cells (C), Biomolecule (B), Time for Prefabrication (T)	Clinical and Radiologic Outcomes	Viability Assessment, Histology/SPECT/ Scintigraphy	Dental Rehabilitation With Dental Implants and/or Dentures	Complications and Additional Surgical Treatment
Naujokat et al,[15] case report, 1 (1), FU: 18 months	A = gastrocolic omentum, S = Ti mesh + DBB blocks, C = iliac crest cancellous bone + BMA, B = rhBMP2, T = 3 months	Bone formation: incomplete Bone healing seen on CT with partial resorption Bone density: higher in engineered bone Aesthetic outcome: patient satisfied QoL of patient increased	Histology: vital mineralized bone seen	Dental rehabilitation not carried out	Intraoral dehiscence, treated surgically 2 times Extra oral fistula formation treated by surgical debridement Recurrent extra oral fistula treated by removal of titanium cage at 9 months Bone formation not continuous, treated with scapula bone transfer
Kokemueller et al,[41] case report with preclinical, 1 (1), FU: 12 months	A = latissimus dorsi, S = Ti mesh + ßTCP, C = iliac crest cancellous bone, T = 6 months	Bone healing seen on CT		Dental rehabilitation not carried out	No complications No signs of infection or rejection No complaints of pain or discomfort at the site of prefabrication
Leonhardt et al,[43] case series, 5 (5), FU: 8-48 months	A = radial forearm, S + C = iliac crest bone cylinders, T = 4 weeks	Bone healing: CT scan revealed sufficient healing No fracture Bony union seen Aesthetic result: pleasing		1 patient received dental rehab with implant placed in native bone	1 mini recon plate fractured in 1 (out of 5) patient due to fall. In 1 patient, free cancellous bone from iliac crest between mandibular bone stump and engineered bone was necessary
Warnke et al,[13] case report, 1 (1), FU: 15 months	A = latissimus dorsi, S = Ti mesh + HA blocks, C = BMMSC, M = rhBMP-2, T = 7 weeks	Bony healing seen on CT scan QoL: Patient-reported improvement. Took part in family functions. Body weight raised from 60 to 65 kg. "Patient regained full masticatory function"	Scintigraphy showed viability	Dental rehabilitation not carried out	7 to 13 months following recon, fracture of titanium mesh leading to infection Curettage followed by iliac autogenous bone graft done but was unsuccessful. Patient died due to cardiac arrest 15 months after
Heliotis et al,[52] case report, 1 (1), FU: 5 months	A = pectoralis muscle, S = HA blocks, B = rhBMP-7, T = 4 weeks[a]	Bone union and healing clinically[b]	Scintigraphy and histology showed viable bone	Dental rehabilitation not carried out	Five month after apparently good take, infection occurred due to MRSA, and bone flap had to be removed
Orringer et al,[58] case report, 1 (1), FU: 18 months	A = scapular fascia, S = Dacron polyurethane tray, C = iliac crest cancellous bone, B = hBMP with insoluble noncollagenous protein, T = not documented[c]	Bone healing seen on surgical reentry		Dental implants were placed and integrated successfully	Tensor fascia lata sling for lip competence Osteotomy for correction of jaw relation Patient developed metastasis and succumbed to disseminated disease after approximately 2 years

Abbreviations: BMA, bone marrow aspirate; BMMSCs, bone marrow–derived mesenchymal stem cells; ßTCP, beta tricalcium phosphate; CT, computed tomography; DBBM, deproteinized bovine bone; HA, hydroxyapatite; hBMP, human bone morphogenetic protein; MRSA, Methicillin-resistant *Staphylococcus aureus*; QoL, quality of life; rhBMP, recombinant human bone morphogenetic protein; SPECT, single-photon emission computed tomography.

a Additional 6 weeks for division of pedicle.

b Clinically there appeared to be union as there was no movement between engineered and native bone.

c The reconstruction was carried out with 2 flap delays.

Table 4. Treatment Characteristics and Outcome Measures for Patients Treated by Cell Cultures.

Author, Year, Study Design, Eligible Patients (Number of Patients in Article), Follow-Up (FU)	Treatment Description, Type of Cells Used for Culture (C), Scaffold (S), Bioactive Molecule (B), Culture time (T)	Clinical and Radiologic Outcomes	Viability Assessment: Histology or Scintigraphy	Dental Rehabilitation With Dental Implants and/or Dentures	Complications and Additional Treatment
Kakabadze et al,[24] Experimental laboratory study + case series, 4 (4), FU: ND	C = BMMSC, S = biologically active bovine graft + decellularized human amnion/chorion membrane, B = none, T = 3 days. Additionally, thoracodorsal flap was used to cover the defect	Bone formation: "Bone volume maintenance" seen in X-ray	ND	ND	None
Lee, 2015, case report, 1 (1), FU: 48 months	C = BMMSC + differentiated autologous osteoblasts, S = hollowed out autologous cortical graft, B = none, T = 4 weeks	Bone formation: "effective healing process"	ND	Implant supported fixed partial dentures	None
Zamiri et al,[31] case series, 4 (4), FU: 6 months	C = BMMSC, S = allogenic fresh frozen cadaver mandible, B = fibrin glue, T = not mentioned	Bone formation: "Normal bone healing" by clinical and radiographic examination. Bone density: Lesser density of engineered bone as compared to native by CT	Scintigraphy: Viable bone done for 2/4 patients, at 1 month postop	ND	1 reconstruction failed and was removed after 4 months
Wolff et al,[33] case series, 3 (3), FU: 19-43 months	C = ASC, S = Ti mesh, ßTCP, B = rhBMP-2, T = 21 days culture + 2 days incubation with scaffold	Bone formation: "successful"	ND	Implants: 7 implants in 2/3 patients; dentures: 3/3 patients	1/7 dental implants failed
Lee et al,[40] case report, 1 (1), FU: 9 months	C = BMMSC + osteoblastic differentiated MSCs, S = autogenous freeze-dried resected mandible, B = fibrin glue, T = second passage cells used[a]	Bone formation: "Excellent clinical and radiographic evidence of bone regeneration but insufficient to place implants without additional procedures"; aesthetics: improvement of facial aesthetics	Histology: Remodeled bone with abundant viable osteocytes	Prosthesis with 3 implants	Preprosthetic distraction osteogenesis and GBR

Abbreviations: ASC, adipose-derived stem cells; BMMSC, bone marrow–derived mesenchymal stem cells; ßTCP, beta tricalcium phosphate; GBR, guided bone regeneration; MSC, mesenchymal stem cells; ND, not documented; rhBMP-2, recombinant human bone morphogenetic protein 2.
[a]Time of culture not reported.

Table 5. Treatment Characteristics and Outcome Measures of Patients Treated With BMP Without Autograft.

Author, Year, Study Design, Eligible Patients (Number of Patients in Article), Follow-Up (FU)	Treatment Description, Scaffold (S), Molecule (M), Cells (C)	Clinical and Radiologic Outcomes	Viability Assessment: Histology/Scintigraphy	Outcome Assessment in Relation to Functional Dental Rehabilitation	Complications and Additional Treatment, Maximum Reported Follow-Up
Lustosa et al,[28] case report, 1 (1), FU: 18 months	S = bovine bone, M = rhBMP-2, C = none	Bone formation: "satisfactory," function: "regained normal function"	ND	Dental rehabilitation with 4 implants	None
Ciccu et al, 2014, case report, 1 (1), FU: 18 months	S = Ti mesh + allogenic bone, M = rhBMP-2 in ACS, C = none	Bone formation: Seen clinically and radiographically; palpation: hard induration	ND	ND	Severe postoperative swelling
Desai et al,[34] case series, 3 (6), FU: 12-39 months	S = demineralized allogenic bone, BTCP, M = rhBMP-2 in ACS, C = none	Bone formation: "good" in 2/3 patients	Scintigraphy: viable bone[a]	ND	Poor wound healing, osteomyelitis, orocutaneous fistula, failed reconstruction in 1/3 patients
Ciccu et al, 2012, case report, 1 (1), FU: 9 months	S = Ti mesh, M = rhBMP2 in ACS, C = none	Bone formation: seen clinically and radiographically; palpation: hard induration	ND	4 dental implants placed	None
Herford,[45] case series, 2 (2), FU: 8-9 months	S = Ti mesh + demineralized allogenic bone, M = rhBMP2 in ACS, C = none	Bone formation: "complete" clinically and radiographically in 2/2	ND	Dental implants placed in 1/2 patients	None
Herford and Boyne,[47] case series, 3 (14), FU: 6-9 months	S = none, M = rhBMP2 in ACS, C = none	Bone formation: "complete" clinically and radiographically in 3/3	ND	Prosthetic rehabilitation done, dental implants in 1/3 patients	Exposure of titanium mesh in 1/3 patient
Clokie and Sandor,[48] case series, 7 (10), FU: 9 months	S = allogenic demineralized bone, M = BMP 7, C = none	Bone formation: seen clinically and radiographically in 7/7	ND	Dental implants in 4/10	None
Herford et al,[50] case series, 1 (6), FU: 12 months	S = none, M = rhBMP2 in ACS, C = none	Bone formation: seen clinically and radiographically	ND	ND	Minor plate exposure
Chao et al,[53] case report, 1 (1), FU: 14 months	S = ßTCP and HA blocks, M = rhBMP-2 in ACS, C = none	Bone formation: "insufficient"	ND	ND	Insufficient height of regenerated bone so distraction osteogenesis done
Ferretti et al,[56] case series, 2 (13), FU: 13-48 months	S = Ti mesh + demineralized allogenic bone, M = bovine BMP, C = none	Bone formation: "adequate"	Histology: new bone formation[b]	Prosthetic rehabilitation in 2/2	None
Moghadam et al,[57] case report, 1 (1), FU: 9 months	S = poloxamer-based gel, M = native human BMP, C = none	Bone formation: "Adequate"	Histology: viable bone	ND	None

Abbreviations: ACS, absorbable collagen sponge; BMP, bone morphogenetic proteins; ßTCP, beta tricalcium phosphate; HA, hydroxyapatite; rhBMP, recombinant human bone morphogenetic protein.
[a]Scintigraphy was done in all cases, but result shown only in 1 case.
[b]Seven out of 13 patients had histologic evidence of new bone formation and the remaining 6 out of 13 patients showed no osteogenic activity.

Table 6. Treatment Characteristics and Outcome Measures of Patients Treated by BMP With Autograft.

Author, Year, Study Design, Eligible Patients (Number of Patients in Article), Follow-Up (FU)	Treatment Description, Scaffold (S), Biomolecule (B), C = Cells, A = Additional Procedures	Clinical and Radiologic Outcomes	Bone Viability Assessment	Dental Rehabilitation With Dental Implants and/or Dentures	Complications and Additional Treatment(s)
Stoor et al,[18] case series, 4 (14), FU: 6-49 months	S = Ti tray+ ßTCP, B = rhBMP-2, C = autogenous bone, A = soft tissue free flap (radial forearm, ALT)	Bone formation: "satisfactory," "full recovery"; function: "normal"	Histology: viable bone formation (done in 4/14 patients)	Sufficient bone to place implants/ support prosthesis (in 2/4)	Flap loss and death: 1/4; intraoral perforation:1 patient
Oliviera et al, 2017, case series, 1 (3), FU: 12 months	S = autogenous bone block from iliac crest; B = rhBMP-2 in ACS, C = autogenous bone	Bone formation: "good" as shown in CT	ND	ND	None
Melville et al, 2016, case report, 1 (1), FU: 12 months	S = cadaver mandible crib + allogenic bone chips, B = rhBMP-2 in ACS, C = platelet-rich plasma	Bone formation: "Consolidation and remodeling" seen on CBCT; function: normal mouth opening; normal mandibular growth	ND	Not applicable (bone defect distal to second molar)	None
Johnson et al,[21] case report, 1 (1), FU: 12 months	S = resorbable poly lactide mesh + allogenic corticocancellous bone, B = rhBMP-2, C = bone marrow aspirate	Bone formation: "adequate bone with excellent height, width, and arch coordination" as seen in 1-year CBCT	ND	Sufficient bone to place implants	Excess bone formation (recontouring planned)
Melville et al, 2016, case series, 5 (5), FU: 12-14 months	S = freeze dried cortical and cancellous cadaver bone; B = rhBMP2; C = bone marrow aspirate	Bone formation: "complete bone union"[a]	Histology: normal reactive bone with regular trabecular pattern (done in 1/5 patients)	Sufficient bone to place implants or prosthetics in all patients; implant placement: 2/5 patients	None
Rahim et al,[26] case report, 1 (1), FU: 60 months	S = cortical bone from iliac crest, B = rhBMP-7 + type I collagen, C = cancellous bone from iliac crest	Bone formation: "clinical and radiologic signs of bone regeneration"	ND	Implant supported denture	None
Balaji,[30] case report, 1/1, FU: 18 months	S = autologous costochondral graft, B = rhBMP2 in ACS, C = autologous costochondral graft	Bone formation: "radiologic evidence of bone continuity"; 'normal quality' upon retrieving bone during implant placement	ND	Implant supported denture	Postoperative inflammatory swelling necessitating tracheostomy
Hernandez-Alfaro et al,[35] case "report, 1 (1), FU: 21 months	S = Ti mesh + DBB blocks, B = BMP 7 + collagen membrane, C = bone marrow aspirate	Bone formation: "adequate reconstruction of the defect" seen in CBCT	Histology: new bone formation	Implant supported prosthesis	None
Zetola et al,[37] case report, 1 (1), FU: 7 months	S = Ti mesh + HA-ßTCP, B = rhBMP2 in ACS, C = autologous bone chips	Bone formation: "bone repair" (by palpation) and "with good bone formation" (by CT)	ND	ND	None
Herford and Cicciu,[42] case report, 1 (1), FU: 12 months	S = ßTCP and HA blocks, B = rhBMP-2 in ACS, C = iliac crest graft	Bone formation: bone repair (by palpation) and with good bone formation (by CT); mandibular continuity (clinical and radiographical)	ND	Removable prosthesis; sufficient bone to place implants	ND
Balaji,[46] case report, 1 (1), FU: 12 months	S = rib graft, B = rhBMP-2 in ACS, C = autologous rib bone	Bone formation: adequate[b]	ND	Sufficient bone to place implants	Severe postoperative swelling
Carter et al,[49] case series, 2 (5), FU: 5 months	S = allogenic cancellous bone, B = rhBMP-2 in ACS, C = autogenous bone marrow	Bone formation: bridging of the defect with regenerated bone 1/2 patients; failure of reconstruction" (unspecified reasons) 1/2	ND	ND	Reoperation with autogenous bone graft due to "failure of reconstruction"; swelling above expectation: 2/2 patients

Abbreviations: ACS, acellular collagen sponge; ALT, anterolateral thigh flap; BMP, bone morphogenetic protein; ßTCP, beta tricalcium phosphate; CBCT, cone beam computed tomography; CT, computed tomography; DBB, demineralized bovine bone; HA, hydroxyapatite; rhBMP, recombinant human bone morphogenetic protein.

[a]Defined as complete bone union at the site of the defect; minimum of 2 cm height and 1 cm width of reconstructed mandible.

[b]Described as reconstructed segment of the mandible approximately resembled that of the normal side, the height at the center being 13.4 mm, and breadth being 9.3 mm. Coronal, axial, and sagittal sections revealed homogenous bone formation.

Table 7. Treatment Characteristics and Outcome Measures for Treatment Group "Scaffolds Containing Autograft."

Author, Year, Study Design, Eligible Patients/Number of Patients in Article), Follow-Up (FU)	Treatment Description, Scaffold (S), Molecule (M), C = Cells, A = Additional Procedures	Clinical and Radiologic Outcomes	Viability Assessment: Histology/Scintigraphy	Functional and Dental Rehabilitation	PROM	Complications and Additional Treatment
Rodrigues Arantes,[17] case report, FU: 28 months	S = Ti mesh + allogenic graft, M = none, C = autogenous bone graft + PRP + BMMSC	"Good clinical and radiologic outcomes"	ND	Implants placed: 3	ND	None
Stoor et al,[18] case series, 10 (14), FU: 7-48 months	S = PSI + βTCP, M = none, C = autogenous bone, A = soft tissue free flap RFA, ALT	Bone formation: "satisfactory"; function: normal; fit of PSI: excellent	Histology 4/14 patients, showed viable bone formation	ND	ND	4 patients needed removal of PSI and 3 of them underwent DCIA flap; 4/10 patients died; 1 intraoral perforation; 1 slight disturbance of occlusion
Yamada et al,[22] case series, 19 (21), FU: 9-62 months	S = Ti sheet, M = none, C = particulate bone marrow from iliac bone	Bone formation: "sufficient"	ND	Prosthesis: 10/21, out of which implant-supported prosthesis: 5/21		3 cases of infection; 2 cases of mesh fracture
Ikawa et al,[25] case report, 1 (1), FU: 6 months	S = Ti mesh, M = none, C = autogenous bone	Bone formation: "sufficient"	ND	"Dental rehabilitation provided"	ND	None
Yagihara et al,[32] case series, 34 (62), FU: 9-200 months	S = polylactide mesh, M = none, C = autogenous particulate cancellous bone and marrow, A = 2 cases of pedicled soft tissue flap, 5 cases of soft tissue free flap	Bone formation: "excellent"[a] = 35/62 cases; "good"[b] = 17/62 cases; "poor": 10/62 cases	ND	Dentures: 28/62, out of which implant supported: 5/62	ND	Mesh exposure: 1 patient
Matsuo et al, 2011, case series, 5 (18), FU: ND	S = Ti mesh, M = none, C = PRP with autologous thrombin	Bone formation: "satisfactory" in 17/18 patients	ND	ND	ND	Mesh exposure: 3/18 patients; infection leading to part bone removal = 1/18
Mooren et al,[39] case series, 17 (20), FU: 12-72 months	S = autogenous cortical bone plate, M = none, C = cancellous bone from iliac crest + PRP with thrombin	Bone formation: "good clinically and radiographically": 17/17 patients	ND	Implants 17/17 patients	Patients assessment of reconstruction: good 10/20 satisfactory 9/20[c]	Additional bone grafting: 3/15
Iino et al,[44] case series, 15 (15), FU: 29-108 months	S = Ti mesh, M = none, C = autogenous particulate cancellous bone marrow, A = HBO in 5 patients, 10 patients with PRP, RFA in 2 patient, PMMC in 6, LD in 2	Bone formation: "successful" in 13/15 patients	ND	Implants: 10/15 patients; prosthesis: 7/15 patients	ND	Major infection and graft failure: 1/15; mild infection: 2/15; partial wound dehiscence: 1/15; death due to metastasis:1/15; implant failure: 1/15
Simon et al,[51] case series, 11 (6), FU: 12 months	S = excised mandible removed from tumor cells, irradiated to 50 Gy, B = none, C = PRP, autogenous cancellous bone chips	Bone formation: "good": 3/6	ND	ND	EORTC QLQ questionnaire: Main improvement gained in appearance and diminished pain	Fracture of scaffold: 2/6; breakdown of oral mucosa: 1/6; death due to pulmonary tuberculosis = 1; second operation due to pathology recurrence = 1; loss of reconstruction = 1; plates traumatizing soft tissues = 1; no complications seen = 2

(continued)

Table 7. (continued)

Author, Year, Study Design, Eligible Patients/Number of Patients in Article), Follow-Up (FU)	Treatment Description, Scaffold (S), Molecule (M), C = Cells, A = Additional Procedures	Clinical and Radiologic Outcomes	Viability Assessment: Histology/Scintigraphy	Functional and Dental Rehabilitation	PROM	Complications and Additional Treatment
Rochanawutanon et al,[54] case series, 4 (4), FU: 48-144 months	S = fresh frozen cadaver mandible hollowed out, M = none membrane, C = particulate cancellous bone marrow+ PRP	Facial contour: "excellent' 4/4; function: mastication "satisfactory" 4/4; pronunciation: "satisfactory" 4/4	Histology: normal bone formation (1/4); presence of vessels and cells indicating surviving graft (1/4)	Removable dental prosthesis: 4/4 patients	ND	Preprosthetic surgery to improve denture seating: 1/4
Kiyokawa et al,[55] case series, 2 (2), FU: 8-28 months	S = resected mandible hollowed out to 1-2 mm and boiled in physiologic saline solution at 100 °C for 30 minutes, M = none, C = cancellous bone from iliac bone, A = PMMC flap wrap around	Bone formation: "good bone formation, no resorption" 2/2; good shape of reconstructed bone 2/2; mouth opening: no problem 2/2	Bone scintigraphy: viable bone (done in 1/2 patients at 2 months after surgery)	ND	ND	None

Abbreviations: ALT, anterolateral thigh flap; BMMSC, bone marrow–derived mesenchymal stem cells; ßTCP, beta tricalcium phosphate; DCIA, deep circumflex iliac artery; HBO, hyperbaric oxygen therapy; LD, latissimus dorsi flap; PMMC, pectoralis major myocutaneous flap; PRP, platelet-rich plasma; PROM, patient-reported outcome measures; PSI, patient-specific implant: rapid prototyped titanium implant; RFA, radial forearm flap; Ti, titanium.

[a]Defined as more than two-third of radiographic bone fill.

[b]Defined as less than two-third, but no further recon required.

[c]One patient lost to follow-up.

size of the defect, although many reports did not mention criteria for choosing a particular amount. Autografts were harvested from the costochondral region as well as from the iliac crest region and PRP was also used in some reports.

In the "scaffolds containing autografts" group (Table 7), the scaffolds used included titanium trays, either stock or patient-specific fabricated by electron beam melting technology, titanium meshes, polylactide meshes, autogenous cortical bone plates, and allogenic or autologous mandibles.

Outcomes

Outcome measures for individual patients are provided in Tables 2 to 6 for the respective treatment groups. There was not a single outcome measure that was both objective and consistently reported across all eligible studies.

Clinical and radiographic outcomes were not uniformly reported in ways that enabled comparison between groups or between patients within the same group. The most commonly reported radiologic outcome measures were "bone formation" and "bone healing," but only one study performed a quantitative assessment.[32] Other radiologic outcome measures included "sufficient continuity of reconstructed bone" and amount of bone resorption. Clinical outcome measures included mandibular range of motion, functional outcomes such as eating, social interaction, ability to attend work, "sufficient wound healing," bone resorption, and recurrence of pathology.

Histology and scintigraphy were additionally used to assess bone viability. Histology was reported for only 15 patients in total[15,18,19,33,35,56,57] and scintigraphy for 19 patients in total.[13,15,30-32,34,51,52,55] In contrast to other groups, all reports in the prefabrication group used scintigraphy to assess the vitality of the construct prior to flap harvest but not as an outcome measure of the reconstructed mandible. All reports on histology and/or scintigraphy as an outcome measure for reconstruction showed vital bone.

Dental rehabilitation with dental implants and/or restoration with prostheses was reported for 2 of 10 patients in the "prefabrication" group, 4 of 12 in the "cell culture" group, 9 of 23 in the "BMP without autografts" group, 11 of 19 in the "BMP with autografts" group, and 71 of 115 in the "scaffolds containing autografts" group. There was only one report of implant failure in 1 patient.[44] Dental prosthetic rehabilitation (either with or without the use of dental implants) was successfully done in 1 of 10 patients in the "prefabrication" group, 5 of 12 patients in the "cell culture" group, 6 of 23 patients in the "BMP without autografts" group, 4 of 19 patients in the "BMP with autografts" group, and 50 of 115 patients in the "scaffold with autografts" group.

Patient-reported outcome measures with standardized questionnaires were reported in 2 of 44 studies only,[39,51] with only one of them reporting on individual patient data.[51] *Complications* were not reported in many studies and were not documented as objective outcomes in a structured manner. A higher number of complications, flap failures, and deaths were reported in patients from the "prefabrication" group, followed by the "scaffolds containing autografts" group. A common complication reported in the groups using BMPs was "increased swelling" during the first 2 postoperative weeks, with 1 patient requiring tracheostomy due to the severity of the swelling.[30]

Discussion

This systematic review provides a comprehensive description and categorization of the use of tissue engineering strategies for the reconstruction of segmental mandibular defects and a synthesis of the currently available evidence. Our findings show that in this field, tissue engineering strategies are extremely diverse. They ranged from the relatively simple treatment strategy of rhBMP-2 in a collagen carrier to the extremely complex use of the patient as a bioreactor to prefabricate a segment of mandible at a distant site that was then harvested and transplanted into the defect. It also included the use of autogenous iliac crest cortical bone plates filled with cancellous bone, mixed with autogenous PRP and subsequently fixed onto a titanium plate, or the use of bone grafts with titanium carriers/scaffolds. Of note, this strategy is similar to autogenous bone grafting alone, which is not regarded as tissue engineering strategy. However, the data were included in this systematic review to provide comprehensive data. This decision may be debatable and actually relies on the generally accepted definition of tissue engineering. At the moment, this definition is rather broad and makes it difficult to distinguish tissue engineering from other reconstruction techniques.

Although we were able to fit all treatment strategies into one of the 5 categories, there was little homogeneity within these groups. A wide variety of scaffolds, cell types, and bioactive substances were used. Scaffolds showed the maximum diversity: diseased mandibles,[40,51,55] cadaveric mandibles,[31,54] allogenic bone, heterogenic bone, and polylactide and titanium meshes/plates (either stock or patient-specific).[63] The most commonly documented bioactive substances were BMPs, whereas the most commonly used cells were autologous bone chips, bone marrow–derived mesenchymal stem cells, and PRP (which also contains bioactive substances).

Heterogeneity was also present concerning the patient populations in several studies, which reported a single technique used in patients with different indications. In combination with the aforementioned scarcity of homogenous treatment modalities, interpreting the role or the usefulness of each of the individual treatment characteristics for segmental mandibular reconstruction is difficult.

Likewise, there was heterogeneity in the reported outcome measures in spite of their importance for evaluating the effectiveness of a specific treatment strategy. The most commonly reported outcome measures were related to bone formation. Nearly all authors reported "successful outcomes," irrespective of the treatment strategy, with

"sufficient bone formation" or "positive radiographic and clinical outcomes." However, these outcomes were hardly ever specified objectively. The lack of objective standardized outcomes precludes the valid comparison of results. Hence, we suggest caution in interpreting treatment outcomes based purely on subjective or arbitrary methods as successful.

At the same time, objective methods to evaluate segmental mandibular reconstruction are indeed scarce. Histology and scintigraphy are objective methods to assess respectively bone neogenesis and viability, but only few articles used this as an outcome measure. Successful reconstruction was reported in all instances and not a single publication mentioned cases of nonviable or unsuccessful bone regeneration. Since these results either come from case reports or from case series in which the outcome was reported for selected patients, it strongly suggests reporting bias.

The ability of reconstructed mandibles to support a dental prosthesis is an objective measure that shows that the reconstruction provides a sufficient foundation to support function. Although 97 out of the 197 eligible patients received dental implants, prosthodontic rehabilitation was reported for only 66 patients. There were no reports objectively specifying that reconstructed bone was of insufficient quality to support dental prostheses, so it is unclear what happened in the rest of the cases. Very few studies reported failure of dental implants. In interpreting these findings, one must keep in mind that dental implant placement is not required for all cases of segmental mandibular reconstruction. The use of dental implants in segmental reconstruction is well justified for adult patients but controversial prior to skeletal maturity. Additional scenarios where dental implants are not needed are patients who have defects posterior to the second molar, patients with sufficient remaining functional dentition, and patients who do not desire or cannot afford dental implant rehabilitation. These limitations should be considered when choosing dental prostheses as an outcome measure.

Patient-reported outcome measures using standardized questionnaires were reported in only 2 studies.[39,51] Even though these studies reported most patients having satisfactory treatment outcomes, the information is too sparse to generalize it.

In contrast to the rest of the outcomes, almost all studies reported specifically on the presence or absence of complications—if none were observed. There was a seemingly higher rate of complications, flap loss, and mortality in the "prefabrication" and "scaffolds with autografts" groups. However, the reason for this is likely related to the underlying disease rather than the reconstruction method. The "prefabrication" and "scaffolds with autografts" groups contained more patients with advanced recurrent diseases than the other groups and were often treated with adjuvant therapeutic radiation. Additionally, the "prefabrication" group primarily comprised patients who had recurrent malignant disease, and many of these patients died due to disease-related factors (not related to reconstruction) in the follow-up period. This is in stark contrast to most patients treated with BMP alone, who were young patients with benign tumors and in whom the resective and reconstructive therapy could be performed with preservation of the periosteum in most cases.

Strengths and Limitations

This is the first time an attempt to collate all available evidence on tissue engineering for reconstruction of segmental mandibular defect has been made. Here, we provide an overview of the current strategies with a functional categorization and a summary of the reported outcomes.

However, our study has several limitations. The level of evidence in the available publications was very low. Most of the included studies were retrospective case reports and case series; no comparative studies could be included. Moreover, several studies consisted of mixed patient populations of whom only a part was eligible for inclusion into our review. In many of these reports, the outcomes were not provided as IPD but as summary information, so it was not possible to draw any conclusions on our population of interest (segmental mandible reconstruction).[13,15,18,19,22,30-35,39,47-52,55-57,59] Objective or quantifiable outcome criteria were hardly ever used.[13,15,18,19,30-35,51,52,55-57] The low level of evidence, the variability in the patient population and in the treatments (even within the same treatment group), and the lack of objective outcome measures did not allow to perform a quantitative synthesis of results or a comparison among patients or treatment groups. The combination of selective reporting and the lack of standardized outcome reporting is an important methodological weakness seen in all studies and appears likely to have introduced bias. Finally, prognostic factors such as defect or patient characteristics could not be identified due to the scarcity of data.

Conclusion

A wide variety of tissue engineering strategies have been used for the reconstruction of segmental mandibular defects. After categorizing the most commonly used tissue engineering strategies into 5 treatment groups, a high variability of individual treatment strategies was seen. Currently, there is insufficient evidence to recommend any particular tissue engineering strategy for segmental mandibular reconstruction, given the low number of patients treated with any particular strategy and the low levels of evidence in the available literature. Future studies should report outcomes for segmental mandibular reconstruction in a more systematic, consistent, and objective manner.

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