Extraction Socket Preservation Using Growth Factors and Stem Cells: a Systematic Review

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ABSTRACT

Objectives: To evaluate the reported literature on the use of stem cells or growth factors for post extraction treatment of the alveolar bone.
Material and Methods: A NCBI PubMed and PubMed Central databases search was conducted between September 2010 and August 2018, to identify animal or clinical studies reporting the clinical, radiographical and/or histological outcomes of socket preservation techniques after applying mesenchymal stem cells or growth factors. Only studies published in English language in the last 10 years were included in the study.
Results: Eleven studies were identified fulfilling the inclusion criteria. They evaluate a total of 386 post extraction sockets. The main tested materials identified in the current review were bone morphogenetic protein-2 - 3 studies and mesenchymal stem cells - 3 studies. Other comparators were bone morphogenetic protein-9, platelet-derived growth factor-BB homodimers and bone marrow. Overall evaluation indicate positive results for all test groups showing differences in final socket width between 0.64 and 1.28 mm favouring the test groups. Histologically, no particular differences are detected between test and control groups. Most of the studies present low risk of bias.
Conclusions: In general, the use of mesenchymal stem cells or bioactive osteogenic molecules favours bone regeneration after tooth extraction, as evaluated clinically, radiographically and histologically. However, specific differences that support particular recommendations are still unclear in light of the current published evidence. Future studies should include the standardization of the mesenchymal stem cells selection and purification as well as dosage and delivery methods of bioactive molecules.

Keywords: alveolar bone atrophy; alveolar bone grafting; bone remodeling; mesenchymal stem cells; stem cell transplantation; transforming growth factors.

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INTRODUCTION

Tooth extraction is possibly the most commonly performed surgical procedure in dentistry. Following the extraction of teeth, the alveolar bone losses its supportive function. As a consequence, it is progressively resorbed [1]. Thus, in many cases, remaining bone volume may not be sufficient to properly support the placement of a dental implant in the correct three-dimensional position. Because of this, in recent years, filling of the socket with different biomaterials has been promoted [2]. Also, in cases when alveolar bone is lost, its reconstruction after the extraction of the tooth has been investigated. Regardless of the method and the biomaterial used, some level of volume loss should be expected [3]. Thus, better materials and techniques should be investigated.

Bone regeneration, as previously reviewed [4], "requires the migration of specific cells to the healing area to proliferate and provide the biological substrate for the new tissue to grow". Cell migration, proliferation and differentiation is regulated by a number of soluble factors in coordination with extracellular signals, three-dimensional support and scaffolds and with the correct blood supply. A number of scaffolds have been proposed in the literature. However, the bioactive molecules and cells with differentiation potential are still more un-used [4].

Stem cells have the capacity to self-renew and, under the adequate stimuli, to differentiate into multiple cell-types, depending on their potential. In the particular case of mesenchymal stem cells (MSC), they have the potential to differentiate into adipo-, chondro- and osteo-genic tissues [5]. Thus, they have been studied for a great number of regenerative cell-based therapies. This includes regeneration of maxillofacial bone. MSC can be obtained from a number of different adult tissues, including many in the oral cavity [6], mainly the bone marrow, dental pulp and periodontal ligament [7-9]. MSC from the oral cavity have demonstrated all the characteristics to consider a cell population as a MSC: growth kinetics, cumulative population doubling, total number of passages, clonogenicity, expression of surface markers and stemness genes and multilineage differentiation potential [6]. Because of this, they have gained interest from the scientific community to be used locally in maxillofacial defects. Although Sonoyama et al. [10] discussed the different differentiation potential of MSC from different origins, it must be noted that most properties are similar among MSC [11].

It should also be noted that before MSCs were proposed to be used for bone regeneration, growth factors and other bioactive molecules had been suggested [12], including platelet derived growth factor (PDGF), fibroblast growth factor, insulin-growth factor and bone morphogenetic proteins (BMPs) [4]. Moreover, around the use of bioactive molecules, a plethora of techniques have been developed in order to reduce the dosage of the drug while improving its timely delivery [13,14].

Thus, it is the aim of the current review to evaluate the use of mesenchymal stem cells and bioactive molecules for bone regeneration after tooth extraction.

MATERIAL AND METHODS

Protocol and registration

This systematic literature reviews adheres to the PRISMA Statement [15].

The review protocol was registered before any search was conducted in an international prospective register of systematic reviews (PROSPERO) in which the methodology and inclusion and exclusion criteria were specified and documented in advance. The protocol can be accessed at: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=136092 with the registration number: CRD42019136092.

Focus question

The following focus question was developed according to the problem, intervention, comparison, and outcome (PICO) design (Table 1).

What biomaterials in combination with stem cells and growth factors are used for socket preservation after the tooth extraction and which of those show the best results regarding alveolar dimensional changes and quality of newly formed bone?

Types of publications

Studies on humans or animals that had been published in the English language were included in the review. Other type of reports, such as abstracts, PhD theses, literature reviews, editorials and letters were excluded. Publication time was established between April 7, 2010 and January 27, 2018.

Types of studies

The review included clinical, comparative, prospective, cohort and case series studies on various extraction socket preservation procedures using

Table 1. The focus question development according to the PICOS study design

Component	Description
Problem (P)	Bone resorption after tooth extraction
Intervention (I)	Filling alveolar socket with regenerative biomaterial
Comparison (C)	Comparison between efficiency of different biomaterials
Outcome (O)	Different dimensional changes of alveolar bone
Study design (S)	Random controlled trial
Focus question	What biomaterials in combination with stem cells and growth factors are used for socket preservation after the tooth extraction and which of those show the best results regarding alveolar dimensional changes and quality of newly formed bone?

growth factors and stem cells. Case reports were excluded.

Information sources

The search strategy was introduced into electronic databases (NCBI PMC and PubMed) and supplemented by hand searches in dental implant related journals, particularly "Clinical Oral Implants Research", "International Journal of Oral and Maxillofacial Surgery", "European Journal of Oral Implantology", "Journal of Clinical Periodontology", "Journal of Oral and Maxillofacial Implants", "Journal of Periodontology", "Journal of Oral and Maxillofacial Surgery", and "The International Journal of Periodontics and Restorative Dentistry". In addition, the references of the included relevant studies were screened to find potential relevant publications not included in the previous search to improve the sensitivity.

Search

The databases were explored through advanced searches. The following search inquiries were used: "extraction socket" OR ''extraction socket'' AND ''growth factors'' OR ''extraction socket'' AND ''stem cells'' OR ''extraction socket'' AND ''mesenchymal stem cells'' OR ''alveolar ridge preservation'' OR ''alveolar ridge preservation'' AND ''stem cells'' OR ''alveolar ridge preservation'' AND ''mesenchymal stem cells'' OR ''socket preservation'' OR ''socket preservation'' AND ''stem cells'' OR ''socket preservation'' AND ''mesenchymal stem cells''. These keywords were selected in order to collect as much relevant references as possible.

Selection of studies

Two reviewers (MP and MP-M) evaluated the resulting articles according to clear criteria for inclusion and exclusion. The reviewers made decisions and set differences through discussion. If consensus about inclusion or exclusion could not be reached, a third party (an experienced senior reviewer, PG-M) was consulted and his decision adopted.

Inclusion and exclusion criteria

Studies were included if they fulfil the following criteria as follows:

- Investigated changes of bone dimensions or quality after preservation, regeneration or tissue formation using stem cells and/or growth factors after tooth extraction;
- Human or animal studies and clinical trials, comparative studies, prospective studies, feasibility trials, cohort studies and case series studies;
- At least 1 month of follow-up after the extraction and following procedure;
- If before careful reading the study could not be excluded.

If articles presented any of the following, they were excluded from the current review:

- Studies that evaluated bone lateral augmentation, sinus lifts or other type of bone grafting or regeneration;
- Studies where the effect of stem cells and growth factors influence in post extraction socket regeneration could not be analysed from the data;
- Studies that presented unclear data;
- Studies older than 10 years;
- Articles written not in English language.

Sequential search strategy

After the initial literature search, case reports, review articles and other irrelevant publications were eliminated by reading the titles of the studies. Then, abstracts of the pre-selected studies were evaluated to further exclude irrelevant publications. The final stage of article selection involved reading the full texts [16-43], and based on the inclusion and exclusion criteria

defined above, confirm each study's eligibility.

Data extraction

The data from different studies were registered from studies according to the interests of the current review, as listed below.

Data items

Data from the included articles were collected and organised in in columns with the following information: author and year, sample size for this outcome/measure, defect location/defect type, measuring method (clinical, histological, radiography), test groups, surgical protocol, results, and outcome.

Assessment of methodological quality

As part of the data extraction process, two review authors assessed the risk of bias of the included studies. To do so, the recommended approach for assessing risk of bias in studies included in Cochrane reviews was used [44].

Synthesis of results

As mentioned, tables were prepared with the fields included as data items.

Statistical analysis

Due to the high heterogeneity between the studies, no meta-analysis could be performed. Thus, only a descriptive evaluation is presented.

RESULTS

Study selection

Article review, selection and data extraction were conducted as shown in the PRISMA flow diagram (Figure 1). As it can be observed, the initial search located a total of 2342 articles. Of those, 408 were identified as potentially relevant articles by the screening of the article titles. The abstracts were read and from there, 39 publications were selected for possible inclusion. Finally, these 39 publications were evaluated in full-text. After applying the inclusion and exclusion criteria, 11 articles fulfil the predefined criteria and were, therefore, incorporated in the systematic review.
There are no reasons for exclusion. Excluded full text articles should be included into references list. If it is big number, so show most often reasons and numbers how much for each reason excluded.
Eight of them are clinical trials (extraction sockets number: 295), two animal studies (extraction sockets number: 44), one prospective pilot clinical study (extraction sockets number: 47). Total extraction sockets number: 386.

Study characteristics

The included studies compared ridge dimension changes and bone formation considering the number of extraction sockets and clinical, radiological or histological parameters.

Influence of MSC and growth factors for extraction socket preservation

Clinical/radiographical measurements

Changes of post extraction sockets dimensions were metered in six studies. Three of them for sockets preservation as test group used BMP-2 [45-47] and collagen sponge [46], demineralized bone [45] or hydroxyapatite [47] as matrix. One study used MSC [48] and collagen membrane as a matrix, another one used BMP-9 [49] and collagen membrane, and in one study sockets were filled with bone marrow without any matrix [50]. The difference of socket width between test and control groups varies from 0.64 to 1.279 mm. Despite the heterogeneity of studies, all test groups showed statistically significant better results comparing to control groups or unassisted healing (Table 1).

Histological measurements

The percentage of new bone or connective tissue that had invaded the former space of the root was examined in five articles [51-55]. In these studies platelet-derived growth factor-BB homodimers (PDGF-BB) [51], BMP-2 [52], bovine bone + poly (L-lactide-coE-caprolactone), PDGF-BB [53], and MSC [55] were used as test groups. Collagen sponge (Collaplug®; Zimmer DentaI Inc., Carlsbad, CA, USA) [51,52] (Bio-Oss® Collagen; Geistlich Pharma AG, Wolhusen, Switzerland) [54] and gelatine sponge (Gelfoam®; Pfizer Inc, New York, USA) [55], were used as comparator. New bone formation in test groups varies between 28 and 49.6%. Connective tissue percentage in test groups varies between 19.6 and 50.4%. Otherwise than in clinical/radiological measurements two of these five studies showed no significant difference between test and control groups.

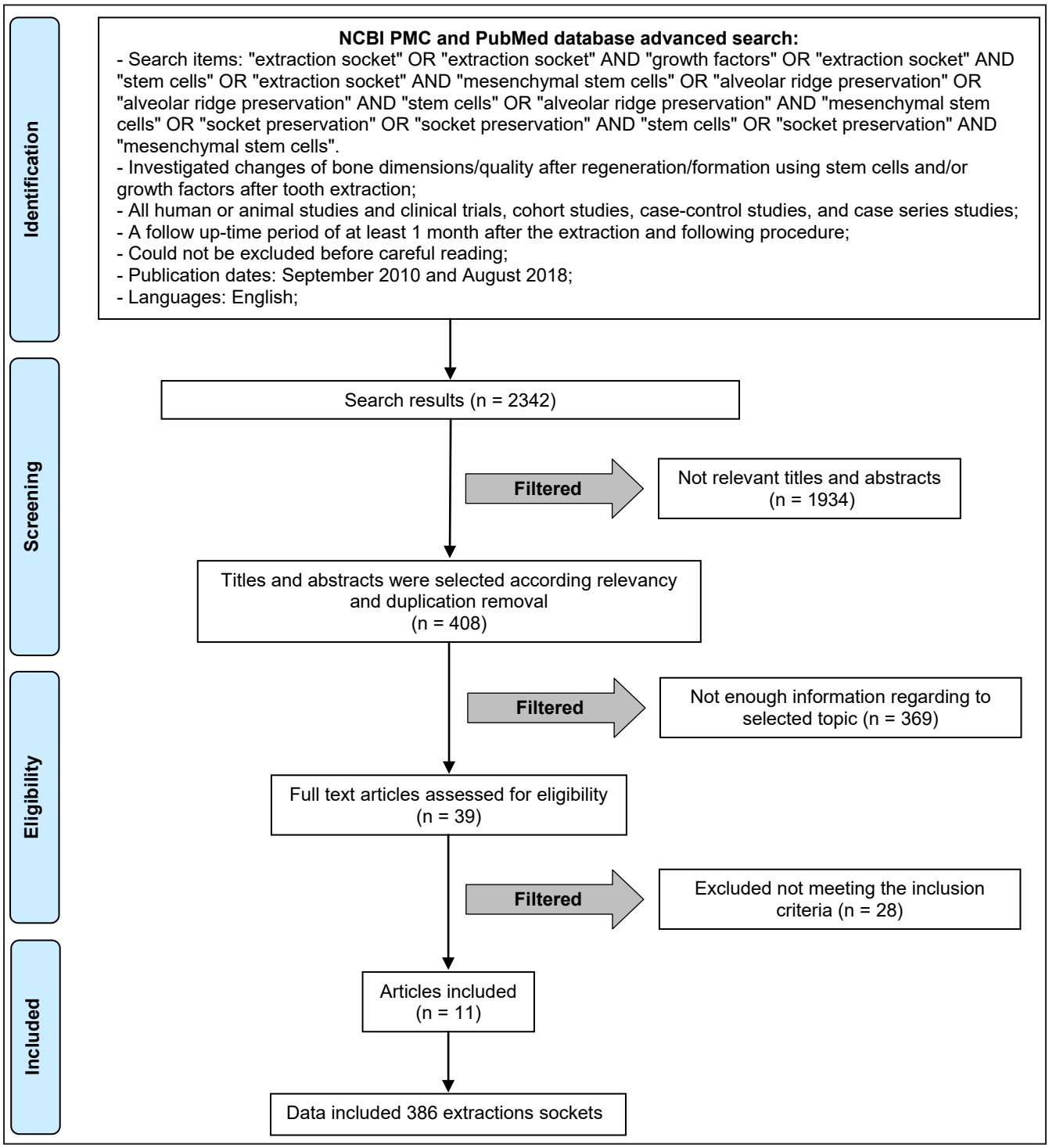

Figure 1. PRISMA flow diagram.

Moreover, one article demonstrates that usage of recombinant human PDGF-BB produced less residual bone graft material, indicating more rapid turnover of bone graft during early healing (8 weeks) [51] (Table 2).

Quality assessment

The majority of the included studies have an unknown risk of bias for one or more key domains [46,48-50,52,54]. Five studies [45,47,51,53,55] were classified as low risk of bias for all key domains (Table 3).

DISCUSSION

The current review has found a number of studies analysing the use of MSC and/or bioactive molecules for socket preservation/regeneration.

Table 2. Characteristics of studies determine alveolar ridge dimensions (quality, quantity) changes after different ridge preservation methods

Study	Year of publication	Sample size for this outcome/ measure	Defect location/ defect type	Measuring method (clinical, histological, radiography)	Test groups	Surgical protocol	Results	Outcome
Kim et al. [45]	2014	69 patients (69 extraction sockets)	Single rooted teeth	CBCT immediately and 3 months thereafter	1. DBM + rhBMP-2 (0.05 mg/mL; rhBMP-2/DBM) 2. DBM	Teeth were extracted atraumatically with full flap elevation and primary closure was performed.	Ridge width change: 1. -1.06 (SD 1.26) mm; 2. -1.21 (SD 1.31) mm; P > 0.05 Ridge high change: 1. -1.17 (SD 0.82) mm; 2. -1.5 (SD 1.07) mm; P > 0.05	The addition of rhBMP-2 did not induce significant differences in the radiographic changes of alveolar bone remodelling after tooth extraction
Commes et al. [46]	2014	39 patients (39 extraction sockets)	Sockets with ≥ 50% buccal dehiscence	CBCT immediately and 5 months thereafter	1. rhBMP-2 + absorbable collagen sponge; 2. Collagen sponge	Atraumatic extraction without flap elevation and primary closure.	Ridge width change: 1. -2.07 (SD 1.17) mm; 2. -3.4 (SD 1.73) mm; P < 0.05	The inclusion of rhBMP-2 in the collagen sponge applied in extraction socket with a buccal dehiscence improves the regeneration of the lost buccal plate
Huh et al. [47]	2011	72 patients (72 extraction sockets, molars/ premolars)	< 50% of localized alveolar vertical bone loss	CBCT scans were took before and 3 months after treatment	1. Escherichia coli-derived rhBMP-2, coated β-TCP and hydroxyapatite; 2. β-tricalcium phosphate and hydroxyapatite	Teeth were extracted atraumatically without flap elevation and no primary wound closure was performed.	Ridge width change at 25% extraction socket length: 1. 1.279 (SD 1.387) mm; 2. 0.006 (SD 1.149) mm; P < 0.01 Ridge height change: 1. -0.059 (SD 0.96) mm; 2. -1.087 (SD 1.413) mm; P < 0.01	β-TCP and hydroxyapatite bone grafts coated with Escherichia coli-derived rhBMP-2 were found to be useful in preserving alveolar bone and more effective than conventional β-TCP and hydroxyapatite alloplastic bone grafts
Jain et al. [48]	2016	10 bilateral symmetrical extraction sockets	Premolars	Radiography immediately, 3 and 6 months after extraction (CBCT). Widths (mesiodistal; buccolingual) measures at: 2, 5 and 8 mm below CEJ.	1. Collagen membrane; 2. MSCs seeded on collagen membrane	Teeth were extracted atraumatically. Extracted socket sides were closed primarily with nonresorbable sutures.	Mean difference (P < 0.05) After 3 months: 2 mm below CEJ: buccolingual -0.64 mm; mesiodistal -1.42 mm. 5 mm below CEJ: buccolingual -1.44 mm; mesiodistal -1.2 mm. 8 mm below CEJ: buccolingual -1.03 mm; mesiodistal -1.02 mm After 6 months: 2 mm below CEJ: buccolingual -1.26 mm; mesiodistal -1.07 mm. 5 mm below CEJ: buccolingual -1.13 mm; mesiodistal -0.69 mm. 8 mm below CEJ: buccolingual -0.81 mm; mesiodistal -1.21 mm	Using MSCs and collagen membrane was successful in maintaining the dimensions of the post extraction socket
Saulacic et al. [49]	2018	5 male Beagle dogs (20 premolars sockets)	Buccal bone of the sockets was removed	After 8 weeks of healing: micro-CT; histological analysis	All extraction sockets were filled with deproteinized bovine bone mineral and covered with collagen membrane loaded with: 1. sterile saline as a control; 2. 20 μg of rhBMP-9; 3. 4 μg of rhBMP-9; 4. rhBMP9	Premolars were hemi sected, and the distal roots were extracted. The canal of the mesial roots was then reamed and filled with gutta-percha. Full thickness flap was elevated, and the buccal bone was removed.	rhBMP-9 defects showed higher values of bone (P = 0.024), bone marrow (P = 0.044), and total augmentation volume (P = 0.033) than the rhBMP2 (20 μg) or control sites. Highest bone area was found in rhBMP-9 defects (P = 0.895)	rhBMP-9 demonstrated the highest density of bone substitute and lowest level of soft/connective tissue density
Pelegrine et al. [50]	2010	13 patients (30 extraction sockets)	Upper anterior teeth	After 6 months: clinical (CEVM; CIVM; CHM); histological analysis (mineralized bone)	1. Test group - sockets grafted with an autologous bone marrow; 2. Control group - blood clot	Teeth were extracted and full thickness flap with two vertical incisions were elevated. Sutured using nonresorbable nylon 5-0 sutures.	CEVM: 1. -0.62 (SD 0.51) mm; 2. -1.17 (SD 0.26) mm CIVM: 1. -10.06 (SD 1.1) mm; 2. -10.44 (SD 0.84) mm CHM: 1. -1.14 (SD 0.87) mm; 2. -2.46 (SD 0.4) mm Mineralized bone: 1. 45.47 (SD 7.21)%; 2. 42.87 (SD 11.33)%	According to the results, the autologous bone marrow graft could contribute to alveolar bone regeneration after tooth extraction
Geurs et al. [51]	2014	41 extraction sockets	Premolars (n = 26), anterior teeth (n = 10) or canines (n = 5)	Histological analysis after 8 weeks: bone graft; new bone; organic matrix; artefact/air	1. Collagen plug (control); 2. FDBA/β-TCP/collagen plug; 3. FDBA/β-TCP/platelet-rich plasma/collagen plug; 4. FDBA/β-TCP/PDGF-BB/ collagen plug	Teeth were extracted atraumatically and without flap elevation. Sutured with 4.0 resorbable crossing mattress sutures.	1. Bone graft: 0 (SD 0)%[a]; new bone: 43 (SD 24)%; organic matrix: 45 (SD 23)%[a]; artefact/air: 10 (SD 10)%[a] 2. Bone graft: 35 (SD 13)%[a]; new bone: 27% (SD 7)%; organic matrix: 24% (SD 10)%[a]; artefact/air: 12% (SD 8)%[a] 3. Bone graft: 27 (SD 13)%[a]; new bone: 28 (SD 9)%; organic matrix: 28 (SD 12)%[a]; artefact/air: 25 (SD 12)%[a] 4. Bone graft: 17 (SD 10)%[a]; new bone: 28 (SD 9)%; organic matrix: 28 (SD 12)%[a]; artefact/air 25 (SD 12)%[a]	Inclusion PDGF-BB produced less residual bone graft material, indicating more rapid turnover of bone graft during early healing (8 weeks)
Wallace et al. [52]	2014	7 patients (10 extraction sockets)	Single rooted teeth with 4 intact walls and a minimum of 5 mm crestal bone height	Every 2 weeks - clinically; 4 weeks post extraction - CBCT; CBCT and histological analysis after 4 months of healing	rhBMP-2 + collagen membrane.	Teeth were extracted atraumatically and full-thickness flaps were released, advanced to achieve primary closure and sutured with polypropylene sutures	Bone: 49.6%; Marrow/fibrous tissue: 50.4%; Bone density: 562 Hounsfield units	rhBMP-2/absorbable collagen sponge could be used as substitute of the combination of barrier membranes over allografts, xenografts, and alloplasts
Mayer et al. [53]	2018	24 Sprague-Dawley rats	Two connected maxillae molars sockets	Histological analysis after 8 weeks of healing	1. BB-PLCL; 2. Bio-Oss®; 3. Unassisted healing	Maxillae molars were extracted, and the sockets were connected using a diamond bur. Flaps were coronally positioned and sutured using resorbable vicryl 5-0 sutures.	New bone formation: 1. Bovine bone: 39.1 (SD 14.3)%; 2. Bio-Oss®: 23.7 (SD 10.8)%; P = 0.096 Connective tissue: 1. Bovine bone: 49.6 (SD 13.7)%; 2. Bio-Oss®: 73.7 (SD 11.1)%; P = 0.018 Residual grafting martial: 1. Bovine bone: 11.34 (SD 4.18)%; 2. Bio-Oss®: 2.62 (SD 1.23)%; P = 0.011	Higher percentage of new bone and lower connective tissue portion were found in the BB-PLCL compared with Bio-Oss®
Heberer et al. [54]	2012	25 patients (47 extraction sockets)	All kind of teeth	Histological (immunohistochemical) analysis after 6 weeks	1. MSCs embedded in Bio-Oss collagen; 2. Unassisted healing	Teeth were extracted atraumatically without flap elevation and no primary wound closure was performed	1. Grafted sockets: Cbfa1/Runx2 73.3%; osteonectin 61.4%; osteocalcin 20.1% 2. Non-grafted sockets: Cbfa1/Runx2 72.3%; osteonectin 66.9%; osteocalcin 23.4%	The quantity of osteogenic cells in the post extraction socket was not influenced by grafting procedure
Kaigler et al. [55]	2013	24 patients (24 extraction sockets)	All kind of nonrestorable teeth was performed	6 or 12 weeks postsurgery micro-CT and histological analysis (bone mineral density [mg/cc]; bone volume fraction; bone area/tissue area)	1. Tissue repair cells (or ixmyelocel-T) suspension + absorbable gelatin sponge; 2. Guided bone regeneration-only absorbable gelatin sponge	Teeth were extracted with full flap elevation. In both groups, a bioabsorbable collagen barrier membrane was placed over the sponge and the tissues were closed.	Bone mineral density (6/12 weeks): 1. 195[a]/186.8; 2. 85.5[a]/146.6 Bone volume fraction (6 /12 weeks): 1. 0.28/0.3; 2. 0.13/0.24 Bone area/tissue area (6 /12 weeks): 1. 0.335/0.352; 2. 0.196/0.351	Cell therapy applied in post extraction sockets showed accelerated bone healing, demonstrated both by clinical and laboratory analyses

[a]Indicates statistical significance.

CBCT = cone-beam computed tomography; CT = computed tomography; CEJ = cementoenamel junction; DBM = demineralized bone matrix; CEVM = clinical external vertical measurement; CIVM = clinical internal vertical measurement; CHM = clinical horizontal measurement; Cbfa1/Runx2 = core-binding factor a 1/runx-related protein 2; MSC = mesenchymal stem cells; β-TCP = β–tricalcium phosphate; PDGF-BB = platelet-derived growth factor-BB homodimers.

Table 3. Bias summary

Study	Random sequence generation	Allocation concealment	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias
Kim et al. [45]	+	+	+	+	+	+
Coomes et al. [46]	?	?	+	+	+	+
Huh et al. [47]	+	+	+	+	+	+
Jain et al. [48]	?	+	+	+	+	+
Saulacic et al. [49]	+	+	+	?	+	+
Pelegrine et al. [50]	?	?	+	+	+	+
Geurs et al. [51]	+	+	+	+	+	+
Wallace et al. [52]	?	?	+	+	+	+
Mayer et al. [53]	+	+	+	+	+	+
Heberer et al. [54]	?	?	+	+	+	+
Kaigler et al. [55]	+	+	+	+	+	+

+ = low risk; ? = unclear risk; - = high risk.

Most of them indicate, as it could be arguably expected, because of publication bias, a non-inferiority of the test group under study, regardless of the specific agent and the comparator control group. Post extraction sockets are usually self-contained and small defects. Thus, the potential advantages of additional products, beside those for maintaining the space (traditional particulated bone grafts) and excluding soft tissue invasion (guided tissue regeneration membranes), might be limited. This does not necessarily mean that they are not useful though. On the contrary, it reflects a lack of standardization in the clinical application of these methods. As previously reviewed [4], the application of MSCs for bone regeneration within the oral cavity varies tremendously in the observation period, specific therapeutic application, carrier, origin of the MSCs and method of purification of such cells. Because of this diversity, comparison among studies is complicated. Noteworthy, the current study found only three studies using MSC for bone regeneration after tooth extraction. In all three cases, MSC were obtained from the iliac crest. However, neither the carrier nor the processing method was standard in all cases: one used an automatic subculturing and purification process for 14 days and implanted the cells through a collagen sponge [55], other manually subcultured the cells during 10 days and implanted them in a collagen membrane [48] and the other extracted the bone marrow and applied it directly with no subculture nor purification [50]. Because of this, in addition to other differences in the evaluation method, specific differences in results might be explained. In any case, in all three cases, positive outcomes were reported.

On the other hand, bioactive molecules that regulate the process of MSC differentiation also report positive results in all cases under review in the current manuscript. The most analysed growth factor is a member of the transforming growth factor-ß superfamily, the bone morphogenetic proteins, particularly BMP-2 [14]. BMPs can induce angiogenesis, synthesis of the extracellular matrix, chondrogenesis and osteogenesis. BMP-2 is probably the most active inductor of bone formation, being able to compensate for the absence of other members of the family [56]. The natural activity of BMP-2 is initiated after bone resorption, when the resorptive activity of osteoclasts releases the BMP from the matrix [14]. However, the reported use of BMP-2 for bone regeneration also lacks from standardization among studies. One of the main issues identified in previous and current reports is the dosage of the recombinant protein and the delivery method. Either absorbable collagen sponges [46,52] or mineralized grafts [45,47,49] have been identified as carriers in the current review. In both cases, the addition of the protein seems to induce better outcomes. Similar results have been indicated in previous reviews, in which particular doses were recommended (1.5 mg/ml) [20]. In more recent years, another step has been taken into the use of this kind of active molecules. A protein is usually rapidly deactivated by denaturalization. Also, proper bioactivity requires the protein to be active at a specific time. Thus, protecting the activity of the protein by means of poly-lactic-co-glycolic acid nanoparticles has been proposed. Moreover, a controlled release may also be beneficial for the success of these techniques [13]. However, so far, these techniques have not yet been applied clinically.

Other bioactive molecules may also provide positive results, including but not limited to those identified

in the current review, such as PDGF-BB. PDGF activity had been initially analysed for periodontal tissue regeneration [57] for its capacity to induce not only cell differentiation but also, and mainly, new vascular development. Thus, its application for bone regeneration might also be useful. The current review has not found sufficient evidence to support clear indications about this molecule, but in turn, negative results from one of the studies in which it was evaluated [51].

In summary, the current review presented an overview of different studies showing the outcomes after using either MSC or regulatory molecules for bone regeneration in the context of after-tooth-extraction therapies. In view of the current review and according to previous reports [21], it must be concluded that beside the positive reported outcomes, no clear conclusion nor recommendation on the use of these techniques can be made because of the different methods applied in the studies under analysis.

CONCLUSIONS

Stem cells and growth factors usage for alveolar ridge preservation are promising for future daily clinical practice. Today, these methods need to be standardized and based on more scientific data. Recommendations for future studies should include the standardization of the mesenchymal stem cells selection and purification as well as a specific effort into conducting comparable studies in the current topic.

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