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Systematic Review

Role of Stem Cells in Augmenting Dental Implant Osseointegration: A Systematic Review

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Abstract: Dental implants are a widely used treatment modality for oral rehabilitation. Implant failures can be a result of many factors, with poor osseointegration being the main culprit. The present systematic review aimed to assess the effect of stem cells on the osseointegration of dental implants. An electronic search of the MEDLINE, LILACS, and EMBASE databases was conducted. We examined quantitative preclinical studies that reported on the effect of mesenchymal stem cells on bone healing after implant insertion. Eighteen studies that fulfilled the inclusion criteria were included. Various surface modification strategies, sites of placement, and cell origins were analyzed. The majority of the selected studies showed a high risk of bias, indicating that caution must be exercised in their interpretation. All the included studies reported that the stem cells used with graft material and scaffolds promoted osseointegration with higher levels of new bone formation. The mesenchymal cells attached to the implant surface facilitated the expression of bio-functionalized biomaterial surfaces, to boost bone formation and osseointegration at the bone–implant interfaces. There was a promotion of osteogenic differentiation of human mesenchymal cells and osseointegration of biomaterial implants, both in vitro and in vivo. These results highlight the significance of biomodified implant surfaces that can enhance osseointegration. These innovations can improve the stability and success rate of the implants used for oral rehabilitation.

Keywords: dental implant; osseointegration; mesenchymal stem cells; stem cells

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1. Introduction

Dental implants are an effective treatment strategy for the replacement of missing teeth, enhancing function and aesthetics [1]. Although implant therapy is associated with a success rate, several factors can influence the prognosis of the treatment, such as the experience of the operator [2], the site of the implant placement [3], and the bone quantity

and quality [4]. It is even possible to place implants in cases where there is reduced bone volume or inadequate bone support. However, a surgical bone grafting procedure to augment the bone would be necessary before placement. This would improve the prognosis, and enhance the stability and success [5].

Bone regeneration after grafting is a complex process that is an interplay of a variety of specialized cells and polypeptide growth factors to recreate the lost bone [6]. Osteoimmunology is a new area of study that examines the vital role that immune cells play in bone recovery [7]. Traditional bone-substitute materials were believed to guide osteoblastic lineage cells for osteogenesis, aiding in bone regeneration. However, there are discrepancies between the in vitro and in vivo results. The materials that aided in in vitro bone formation were not as effective in vivo. This may be due to the immune responses evoked by the material. While it may be unfeasible to look for biomaterials that trigger no immune response, it may be possible to modify existing materials to elicit a beneficial immune reaction. It is important to examine a bone biomaterial's immunogenicity, along with its osteogenic and osseointegrative capabilities [8–10].

A lack of adequate bone support is a contraindication for implant placement [11]. Demetriades et al. [12] reported that alveolar bone with a diameter of 5 mm has to be augmented before implant placement. There are many bone manipulation methods used to attain predictable effectiveness for dental implants in the long term, with autologous bone grafts being the gold standard. Autologous bone shows superior osteoconductive and immunogenic properties, and osteogenic and osteoinductive properties [13,14].

Various metallic, ceramic, and hybrid scaffolds have been used to enhance the osseointegration of load-bearing implants. However, implant malfunction studies reveal a high rate of interfacial failure, due to impaired implant tissue integration and osteolysis, combined with modulus mismatch. Recently, stem cells are being considered for the augmentation of implant sites. Stem cells are multipotent cells with the properties of self-renewal [15] and the capacity to differentiate into many different cell types, such as neurons [16], hepatocytes [17], chondrocytes [18], and osteoblasts [19]. Stem cells are found in the human body in various ecological niches, such as the blood, bone marrow, umbilical cord, dental pulp, apical papilla, and periodontal ligament [20]. Stem cells can be classified, based on surface markers, into hematopoietic or mesenchymal types [21]. A wealth of data supports the use of stem cells in regenerative medicine. Research has focused on using live cells, scaffolds, and growth factors for the regeneration of lost tissue parts [22]. Stem cells have potential applications in dental implantology. Implant dentistry already uses a plethora of scaffolds and growth factors that were developed via recombinant techniques, to improve stability and osseointegrations [23]. A few animal model studies have examined the use of stem cells for implant osseointegration [24–41]. The most recent review of available studies was published half a decade ago, by Misawa et al. They did not consider studies examining the role of stem cells in sinus augmentation for implant placement [42]. This systematic review aimed to qualitatively assess the animal studies available in the literature, on dental implants coated with stem cells to enhance osseointegration.

2. Materials and Methods

Search strategy: The international prospective register of systematic reviews (PROSPERO) was searched for systematic reviews related to the role of stem cells in the osseointegration of dental implants. The preferred reporting items for systematic reviews and meta-analysis protocols (PRISMA) criteria were adopted [41].

Focus question: "Does the application of stem cells augment osseointegration of dental implants?" [41].

The clinical question in "PICO" format in our study was as follows:

Animal model eligibility criteria (P): all healthy in vivo animal models that can undergo extraction of teeth and implant treatment closely mimicking some aspects of tooth replacement by implants in humans.

Intervention (I): application of stem cells on implant surface before, or simultaneous or post-implant placement.

Comparison (C): comparison with negative control or graft material without stem cells (the control groups differed based on the intervention type in each study).

Outcome (O): osseointegration and new bone formation.

2.1. Search Strategy

The following steps were performed for conducting the review:

(I) A broad electronic search was conducted of the MEDLINE, Scopus, and Web of Science databases using the keyword combination "Stem Cell" AND "Dental Implant Osseointegration". The electronic search was complemented by a manual search of the references in the selected full articles.

(II) Titles and abstracts were independently screened by two calibrated reviewers to remove irrelevant articles and duplicates.

(III) Selection of the full-text articles was conducted manually by the same two reviewers with the inclusion and exclusion criteria in the following section.

2.2. Inclusion Criteria

In vivo animal model studies using stem cells (derived from humans, autologous stem cells, stem cells derived from another animal of the same species) to augment dental implant osseointegration, treatment of peri implant–bone defects, and sinus augmentation for implant placement published in the English language were eligible for this review.

2.3. Exclusion Criteria

In vitro studies, studies that used commercially available stem cells, reviews, short articles (commentary, letters, correspondence), case reports, and studies conducted without control groups were excluded from the review. Figure 1 depicts the PRISMA flow chart.

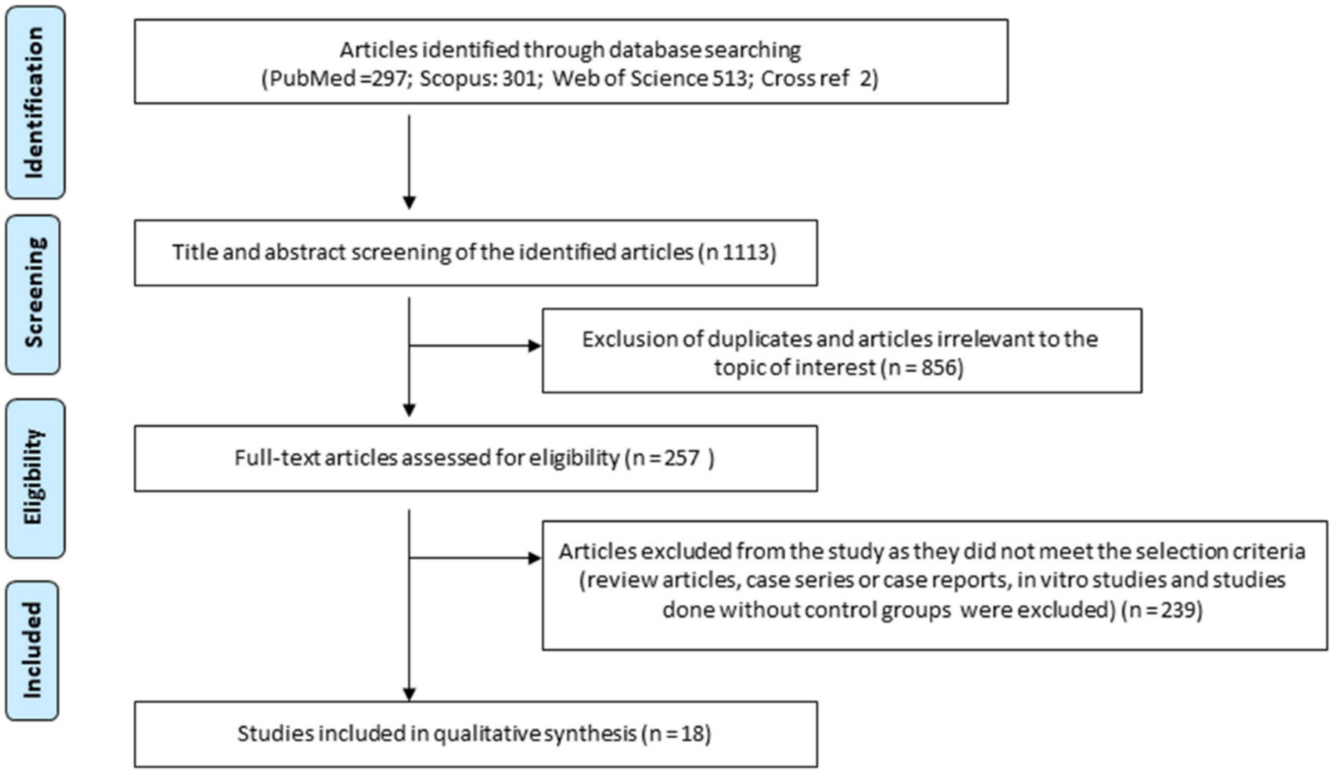

Figure 1. PRISMA flow chart.

2.4. Data Extraction

All studies fulfilling the inclusion criteria underwent a validity evaluation. Reasons rejected were recorded for each study. Kappa coefficient describes an agreement between reviewers. Both reviewers have extracted the data independently with disagreements resolved by discussion with a third reviewer. Authors were also contacted to provide missing information and clarify data. The following data were extracted and recorded: number of patients, number of defects per group, defect size and type, stem cell characterization, stem cell origin, defect location, length of follow-up, and treatment.

2.5. Quality Assessment and Data Synthesis

Both reviewers were blinded to the authors, journal titles, and institutions. The reviewers independently performed the quality assessment of included studies. Any conflicts were solved by a discussion with a third reviewer.

2.6. Risk of Bias Assessment

The studies were assessed based on 10 parameters sequence generation, baseline characteristics, allocation concealment, random housing, blinding of investigators/caregivers, random outcome assessment, blinding of assessor, incomplete outcome data, selective outcome reporting, and other sources of bias based on SYRCLE's risk of bias tool for animal studies. The risk of bias was categorized as low when 70% of the parameters were fulfilled, moderate when 50 to 69% of the parameters were fulfilled and high when <49% of parameters were fulfilled [42].

3. Results

3.1. Selection of Articles

A total of 1113 articles, including 297 from PubMed, 301 from Scopus, and 513 from Web of Science, were retrieved using the keywords. Title and abstract screening of the identified articles revealed that 856 articles were either duplicate or irrelevant to the topic of interest, and hence were excluded. Out of the 257 full-text articles that were screened for eligibility, only 18 met the inclusion criteria, and hence were included in the present review. The kappa score was 0.99. Figure 1 is a schematic representation of the search strategy used in the present review. Table 1 reports the characteristics of the final 18 retained articles.

3.2. Characteristics of the Included Studies

Geographical distribution: of the 18 included studies, 7 were from China, 3 each from Japan and Korea, 2 each from Italy and Brazil, and one from Egypt.

The source of the stem cells: 14 studies used bone marrow-derived stem cells. A few studies used other sources, such as amniotic fluid, umbilical cord, hematopoietic, dental pulp, SHED, adipose-derived, and periodontal ligament, and compared the differences between the different stem cell types [24–41].

Table 1. Summary of the data extracted from the included studies.

S. No.	Reference Number	Origin of Stem Cells	Animal Model Used	Type and Size of Implants Used	Differentiation/Characterization/ Application of Stem Cells	Site of Implant	Type of Defect	Total Period of Observation	Results and Conclusion
1.	[24]	Human amniotic mesenchymal stem cells	Twelve New Zealand white rabbits	Mini implant 1.5 mm × 5 mm (Bioconcept Co., Ltd., China)	Insertion of hAMSC-gel (AMSCs re-suspended in fibrin solution) into the maxillary sinus before implant placement and only fibrin in the control group	Maxillary sinus	Maxillary sinus floor elevation	4 and 12 weeks	Bone volume, bone volume/tissue volume, bone-to-implant contact ratio, and vessel-like structures were better in the Bio OSS hAMSC group in comparison with other groups. ALP was higher in hAMSC and hAMSC/BioOSS group
2.	[25]	Adipose-derived stem cells derived from dog's Bichat bulla	Six beagle dogs	10 × 3.3 mm Premium TM, Sweden and Martina	HA-based scaffolds previously seeded with ADSCs	Mandibular premolars and the first molars	Peri-implant–bone defect	1 month	ADSCs increased bone regeneration new vessels, osteoblasts, and new bone matrix, absence of inflammation
3.	[26]	UCMSCs (Lifeline Cell Technology, FC0020)	Eight male beagle dogs	SuperLine implants (Dentium Biomaterial Co., Ltd., Korea), 3.6 × 8 mm	Injection of UCMSCs with PRF into the peri-implant bone defect	Second, third, and fourth mandibular premolars	Peri-implant– bone defect	2, 4 and 8 weeks	A significantly higher percentage of new bone formation in the case group in comparison with the control
4.	[27]	Human clonal bone marrow mesenchymal stem cells	Four male adult mongrel dogs	GSII, Osstem, Korea 4 × 8.5 mm	Placement of cells with graft material randomly placed at the mesial bone defect area	Mandibular first molars and premolars	Peri-implant– bone defect	6 and 12 weeks	Highest level of bone density and bone–implant contact in HA, stem cells, and PRP group (no statistical significance)
5.	[28]	Canine BMMSCs (cBMMSCs), canine DPSCs (cDPSCs), puppy DTSCs (pDTSCs),	Adult hybrid dogs, sample size not mentioned	3.7 × 7 mm HA-coated JMM implants (POI = Finatite, Japan MedicalMaterials Corporation, Osaka, Japan)	Injection of the PRP, cBMMSCs PRP, cDPSCs PRP, and pDTSCs PRP admixtures into the bone defect before implant placement	1st molar, 1st, 2nd and 3rd and third premolars	Peri-implant– bone defect	16 weeks	Well-formed mature bone and neovascularization in all the three groups in comparison with control. Bone implant contact was highest in pDTSCs = PRP group > cDPSCs = PRP group, cBMMSCs = PRP group. PRP group. Control (statistically significant)
6.	[29]	Autologous periodontal ligament stem cells (PDLSCs) and bone marrow SCs (BMSCs)	Four adults, male beagle dogs	3.3 × 10 mm implant (brand not mentioned)	Placement of the graft material onto the defect after implant placement	Bilateral all mandibular premolars and first molars	Peri-implant–bone defect	8 and 16 weeks	Highest new bone formation in BMSC group > PDLSC > control group
7.	[30]	Dog mesenchymal stem cells (dMSCs) from bone marrow	Twelve adult hybrid dogs	3.75 × 7 mm Branemark implants	Simultaneous placement of implant and graft material	First molar, premolars, and the second and third premolars	Peri-implant– bone defect	2, 4 and 8 weeks	Natural margin bone level in dMSCs/PRP/fibrin and dMSCs/fibrin with no exposure if implant thread in comparison with only fibrin and control group. Bone implant contact dMSCs/PRP/fibrin > dMSCs/fibrin > fibrin > control
8.	[31]	Autologous bone marrow mesenchymal stem cells	Six male adult labrador dogs	3.75 × 10 mm implants (pure titanium, Cibei Medical Devices Co., Ltd. Zhejiang, Shanghai, China)	Placement of graft material following implant placement	Bilateral first, second, third, and fourth mandibular premolar teeth	Peri-implant– bone defects	3, 6, 9 weeks	Osseointegration highest in rhPDGF-BB/BMSCs/ β -TCP constructs > rhPDGF-BB/ β -TCP constructs > BMSCs/ β TCP constructs > TCP particles alone. No significant differences in bone–implant contact although rhPDGF-BB/BMSCs/ β -TCP constructs had the highest value
9.	[32]	Dog iliac bone marrow mesenchymal stem cells (I-BMSCs) and alveolar bone marrow mesenchymal stem cells (Al-BMSCs)	Four labrador dogs	4.1 × 10.0 mm Beijing Leiden Biomaterial implant	Placement of graft material following implant placement	Mandibular premolar region	Peri-implant– bone defects	12 weeks	Greater new bone formation and high bone–implant contact in Al-BMSC and I-BMSC group in comparison with the other groups and no significant difference between Al-BMSC and I-BMSC groups
10.	[33]	Autologous bone marrow mesenchymal stem cells from the iliac crest	Four Brazilian male adult miniature pigs	3.5 × 11 mm (ConeMor- se; Neodent, Curitiba, Brazil)	Placement of graft with cells before implant placement	Bilateral third and fourth mandibular premolar region	Peri-implant–bone defect	90 days	Although statistically insignificant lesser implant loss rate (ILR), greater bone–implant contact (BIC), and bone density within the threads (BDWT) in the test group in comparison with the control
11.	[34]	Dog hematopoietic mesenchymal progenitor cells (dBMPC)	Four adult male mongrel dogs	3 × 10 mm Ti-24Nb-4Zr7.9Sn (T2448)1	Placement of implants followed by graft in the same procedure	Bilateral second, third, and fourth mandibular premolars	Peri-implant–bone defect	12 weeks	More bone formation in dBMPC + nHAC/CSH g than other groups. Significantly high bone–implant contact and bone density in dBMPC + nHAC/CSH g > nHAC/CSH > control
12.	[35]	Autologous bone marrow stem cells from the iliac crest	27 mature New Zealand rabbits	1.4 × 6 mm implant	Placement of graft and implant in the same procedure	Maxillary sinus	Maxillary sinus augmentation	2, 4 and 8 weeks	At 2 and 4 weeks, greater new bone formation and bone–implant contact in the BMP-2 transduced BMSC group in comparison with other 2 groups and at 8 weeks no significant difference between all the three groups although BMP-2 BMSC > non-transduced BMSC > control
13.	[36]	Autologous bone marrow stem cells from the iliac crest	Nine healthy female goats	3.3 × 12 ITI-SLA; Strauman AG	Simultaneous placement of implant and graft	The maxillary second and third premolar	Maxillary sinus floor elevation	12 weeks/3 months	Bone formation and bone–implant contact highest in BMSCs/CPC > autogenous bone group > CPC alone group (statistically significant)

Table 1. *Cont.*

S. No.	Reference Number	Origin of Stem Cells	Animal Model Used	Type and Size of Implants Used	Differentiation/Characterization/ Application of Stem Cells	Site of Implant	Type of Defect	Total Period of Observation	Results and Conclusion
14.	[37]	Goat bone marrow-derived mesenchymal stem cells from femur	Five goats	Titanium fixture not mentioned	Placement of implant and graft material simultaneously	Mandibular canine	Peri-implant–bone formation	10 days and 4 weeks	More bone formation and PDL tissue regeneration in the case group in comparison with control.
15.	[38]	Dog dental pulp stem cells (dDPSC), dog bone marrow stem cells (dBMSC), and dog periosteal cells (dPC)	3 dogs	3.7 × 8 mm (POI-EX(FINATITE) Japan Medical Materials	Placement of graft with or without cells and placement of implants 8 weeks after graft placement	Mandibular all premolars and first molar	Peri-implant–bone defect	8 weeks after implant placement	Bone implant contact highest in dDPSC/PRP > dBMSC/PRP > dPC/PRP > control
16.	[39]	Bone marrow mesenchymal cells from the iliac origin	8 adult minipigs	3.8 × 1 mm implantXiVE; Dentsply-Friadent	Placement of graft followed by implant simultaneously	Maxillary sinus region	Maxillary sinus augmentation	12 weeks (3 months)	Significant increase in bone formation and high BIC in the test group (with MSC and PRP)
17.	[39]	Bone marrow mesenchymal cells from the iliac origin	Eight beagle dogs	4 × 8.5 mm (Biomet-3iTM do Brasil LTDA, São Paulo, SP, Brazil)	Placement of implant followed by graft material in the same procedure	3rd and 4th mandibular premolar	Peri-implant–bone defect	12 weeks (months)	Statistically significant higher bone fill in BMSC and BMSC-guided bone regeneration with control. No significant difference in bone fill in BMSC and BMSC + guided none regeneration. Statistically significant new bone area, bone-to-implant contact, new bone height, and new bone weight in BMSC-guided bone regeneration in comparison with control
18.	[41]	Autologous bone marrow-derived mesenchymal stem cells	Five beagle dogs	3.75 × 10 mm Brånemarks dental implant (Nobel Biocare, Göteborg, Sweden	Placement of implant followed by graft in the same procedure	Not clear	Peri-implant–bone defect	12 weeks	Statistically significant mineral apposition in BMP + FGF + BMSCs + CPC > BMP + BMSCs + CPC > FGF + BMSCs + CPC > BMSC + CPC > control

The animals used: 12 studies used various species of dogs [25,26,28–32,34–38,40,41], 2 studies each used rabbits [24,27], and 2 studies used miniature pigs [33,39].

The site of the study: Of the 18 studies, 14 studies assessed the effect of stem cells on the peri-implant–bone defect, and 4 studies assessed the impact on maxillary sinus floor elevation [24,35,36,39].

The implant type: All the studies used titanium implants of varying sizes and brands. Twelve studies were in the mandibular premolar to the molar region [25–34,38,40], one study was in the mandibular canine region [37], 4 studies were in the maxillary sinus region [24,35,36,39], and in one study, the site was not mentioned [41].

The follow-up period: The period of follow-up ranged between 2 weeks and 16 weeks, approximately [24–41].

Outcome assessment: All 18 studies assessed osseointegration through histology and histomorphometry [24–41]. Three studies used sequential fluorescence labelling [24,36,41], and two each used micro CT [32,36] and radiography [33,37].

3.3. Risk of Bias

The studies were assessed based on 10 domains sequence generations, baseline characteristics, allocation concealment, random housing, blinding of investigators/caregivers, random outcome assessment, blinding of assessor, incomplete outcome data, selective outcome reporting, and other sources of bias, based on SYRCLE's risk of bias tool for animal studies (Table 2).

3.4. Qualitative Analysis of the Effect of Stem Cells on Osseointegration

All the included studies reported that the stem cells used with graft material and scaffolds promoted osseointegration with higher levels of new bone formation at the contacts. However, there was no homogeneity in the scaffolds used (Table 3).

Osseointegration determined by bone–implant contact: all the studies reported higher bone–implant contact in the study group with stem cells and the graft material. However, the results were not statistically significant in five of the included studies [27,31–33,35].

Table 2. Summary of the ROB analysis of the included studies.

S. No.	Author/Year	Selection Bias 1. Was the Allocation Sequence Adequately Generated and Applied?	Selection Bias 2. Were the Groups Similar at Baseline or Were They Adjusted for Confounders in the Analysis?	Selection Bias 3. Was the Allocation Adequately Concealed?	Performance Bias 4. Were the Animals Randomly Housed during the Experiment?	Performance Bias 5. Were the Caregivers and/or Investigators Blinded from Knowledge of Which Intervention Each Animal Received during the Experiment?	Detection Bias 6. Were Animals Selected at Random for Outcome Assessment?	Detection Bias 7. Was the Outcome Assessor Blinded?	Attrition Bias 8. Were Incomplete Outcome Data Adequately Addressed?	Reporting Bias 9. Are Reports of the Study Free of Selective Outcome Reporting?	Other Bias 10. Was the Study Apparently Free of Other Problems That Could Result in a High Risk of Bias?	Overall Score
1.	Yin/2019/China [24]	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Moderate
2.	Bressa.2015/Italy [25]	Unclear	Yes	Unclear	Not applicable (split-mouth design)	Not applicable (split-mouth design)	Unclear	Unclear	Yes	Yes	Yes	Moderate
3.	Hao et al./2014/China [26]	Unclear	Yes	Unclear	Not applicable (split-mouth design)	Not applicable (split-mouth design)	Unclear	Unclear	Yes	Yes	Yes	Moderate
4.	Yun/2019/Koreav [27]	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	High
5.	Yamada et al./2010/Japan [28]	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear	High
6.	Kim et al./2009/Korea [29]	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	High
7.	Ito et al./2005/Japan [30]	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	High
8.	Xu et al./2015/China [31]	Unclear	Yes	Unclear	Not applicable as each animal received one construct from each of the groups	Not applicable	Unclear	Unclear	Yes	Yes	Yes	High
9.	Wang et al./China/2018 [32]	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	High
10.	Zanicottiet al/2021/Brazil [33]	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	High
11.	Han et al./China/2011 [34]	Unclear	Yes	Unclear	Not applicable as each animal received one construct from each of the groups	Not applicable	Unclear	Yes	Yes	Yes	Yes	Moderate
12.	Jhin et al./2012/South Korea [35]	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	High
13.	Zhou et al./2012/China [36]	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	High
14.	Marei et al./2009/Egypt [37]	No	Yes	Unclear	Not applicable split-mouth design	Not applicable split-mouth design	Unclear	Unclear	Yes	Yes	Yes	High
15.	Ito et a;/2011/Japan [38]	Unclear	Yes	Unclear	Not applicable	Not applicable	Unclear	Unclear	Yes	Yes	Yes	High
16.	Pieri/2008/Italy [39]	Unclear	Yes	Unclear	Not applicable (split-mouth design)	Not applicable (split-mouth design)	Unclear	Unclear	Yes	Yes	Yes	High
17.	Ribeiro/2012/Brazil [40]	Yes	Yes	unclear	Not applicable (split-mouth design)	Not applicable (split-mouth design)	Unclear	Yes	Yes	Yes	Yes	Low
18.	Wang et al./2011/China [41]	Unclear	Yes	Unclear	Not applicable (split-mouth design)	Not applicable (split-mouth design)	Unclear	Unclear	Yes	Yes	Yes	High

Table 3. Characterization of scaffold used.

Number of Studies	Type of Scaffold Used
4	Platelet-rich plasma (PRP)
3	Tricalcium phosphate (TCP)
2	Hydroxyapatite
1	Bio OSS graft, platelet-rich fibrin (PRF), deproteinized bovine bone mineral, PRP and fluorohydroxyapatite (FH), BMP-2 with bFGF and CPC, guided bone regeneration, PLG scaffold, nHAC/CSH, and calcium phosphate cement

4. Discussion

The purpose of this systematic review was to analyze the effect of stem cell-coated dental implants on osseointegration in animal models. Animal model studies were chosen as few human studies are available [43,44].

Most of the animal studies on stem cell-coated dental implants were from Asia (n = 13), while the other five studies were from Africa, South America, and Europe, respectively [24–41]. This suggests that further global research, especially in North America and Oceania could help advance and unlock the benefits of stem cells in implantology.

All the included studies reported that the stem cells used with graft material and scaffolds promoted osseointegration with higher levels of new bone formation. Osteoblasts are necessary for bone formation; while mesenchymal stem cells may promote osseointegration [45], MSCs influence osteogenesis through their molecular signals that favor the osteoblastic differentiation of MSCs [31,37,46,47]. The application of stem cells along with scaffolds or graft material could promote osseointegration and bone formation through osteoblastic differentiation. The implant surface characteristics play a major role in osseointegration [48]. The studies that modified the surface of the implants, through the application of mesenchymal stem cells, reported enhanced osseointegration. This may be due to the various growth factors that enhance osteoblastic differentiation of the stem cells, and ensure new bone formation.

Many of the animal models used dogs in the studies [25,26,28–32,34–38,40,41]. Dogs are a reliable model for periodontal and peri-implant research [49]. They have tooth sizes that are comparable to humans, and they show a similar history of progression of periodontitis [48]. Testing and surgical procedures are more readily carried out in dogs, due to their size. Dogs have been used to examine the use of bone grafts and barrier materials in peri-implant regeneration. The data from previous research have been used with predictability on human subjects [49]. The data from this systematic review on safety and tolerability can be extrapolated for further research in human subjects.

The selected studies showed heterogeneity in the implant site chosen. Most of the studies [13] placed implants coated with stem cells in the mandibular canine/premolar to the molar region [25–34,37,38,40]. A few studies [4] used the maxillary sinus region as the site of placement [24,35,36,39]. One study did not mention the site of placement [41]. Owing to the heterogeneity of the sites, the data are not comparable, as the bone quality varies with the site of placement. The amount of cancellous bone versus cortical bone varies in the maxilla versus the mandible. The mandible presents with more cortical bone than scant cancellous bone. This can contribute to increased implant stability and enhanced osseointegration [50]. However, since a control site with an uncoated implant was used in all of the studies, the bias induced by the jaw of choice and the bone quality could be eliminated.

Most studies (14) used bone marrow mesenchymal stem cells for coating the implant. A few studies used amniotic fluid, umbilical cord, hematopoietic, dental pulp, SHED, adipose-derived, and periodontal ligament [24–41]. Bone marrow represents a good source of mesenchymal stem cells, with distinct surface markers that differentiate them from hematopoietic lineage stem cells. These cells have good pluripotency and can differentiate

into osteoblasts in a favorable environment of induction factors, growth factors, and biological modifiers. The regenerative and differentiation potential of these cells is also reflected in the recruited studies. Many studies found good regeneration and osseointegration with the bone marrow mesenchymal stem cells. The only demerit that we recognize is the difficulty of sourcing these cells. Obtaining bone marrow tissue requires surgical aspiration, which is painful and can involve postoperative morbidity. Mesenchymal stem cells prove to be a viable alternative. Stem cells with adequate regenerative potential can be harvested from the teeth pulp, periodontal ligament, and gingiva. Further research is required to ascertain the potential of using dental pulp-derived stem cells for peri-implant regeneration.

Various scaffolds were used in the 18 studies. The most popular scaffold material used was platelet-rich plasma [4], followed by tricalcium phosphate [3], followed by hydroxyapatite [2]. The remaining studies used Bio OSS graft, platelet-rich fibrin (PRF), and deproteinized bovine bone mineral; fluorohydroxyapatite (FH), BMP-2 with bFGF, and CPC; PLG scaffold, nHAC/CSH, and calcium phosphate cement [25–42]. There was no uniformity in the type of carrier/scaffold used. The scaffolds had osteoconductive, osteoinductive, or osteogenic potential. An osteoinductive material is the most superior, as it has bone morphogenetic protein, which could differentiate the stem cells into osteoblasts. An osteoconductive material will only act as a scaffold and would serve as a bland carrier of the stem cells. The use of PRF and PRP prove advantageous, as they are autologous materials that are rich in platelets and also serve as a reservoir of growth factors, such as PDGF.

Of the 18 selected studies, many authors did not mention the details of blinding, which is not ideal [24–41]. All the studies used the histology and histomorphometry technique for assessing bone regeneration and osseointegration. Three of the studies used sequential fluorescence labelling [24,36,41]. Two studies used micro CT [32,36] and radiography [33,37]. None of the articles that were selected used MRI for imaging. However, recent research in dentistry has reported the use of this imaging modality [51,52].

A meta-analysis could not be performed based on the data available, due to a lack of homogeneity in the type of animal, stem cells, technique, carrier, and methodology used. Hence, this systematic review is presented as a qualitative analysis. The majority of the recruited studies [13] revealed a high risk of bias. A moderate risk of bias was observed in four studies and only one study had a low risk of bias. A note of caution is due here in the interpretation of these results, as there is a lack of homogeneity in the data. This indicates the urgent need for further well-designed, high-quality standardized animal studies. At present, only two preliminary human studies are available on this topic [45,46]. The data from high-quality standardized clinical trials in animals can be extrapolated into research in human test subjects, to establish the benefits of stem cell-coated dental implants.

5. Conclusions

The present systematic review examined 18 published studies that investigated the application of stem cells on implant surfaces. Our analysis of the results revealed that stem cells, when used with graft material and scaffolds, promoted osseointegration with higher levels of new bone formation. We observed heterogeneity in the scaffolds selected. These findings emphasize the role of bioactive molecules in the promotion of stability and osseointegration in implants. The major limitation of the present review is the lack of homogeneity of the data in the selected studies, along with a high risk of bias in the majority of the studies. Future animal model research in this topic must be well designed and clearly describe the method of sequence generation, allocation concealment, randomizing, and outcome assessment, to reduce the risk of bias. This systematic review illustrates the current state of the research into the effects of stem cell-coated dental implants, and provides a basis for future randomized control trials.

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