Brazilian Dental Journal (2019) 30(2): 77-95
http://dx.doi.org/10.1590/0103-6440201902053
Review Article

ISSN 0103-6440

Bone, Periodontal and Dental Pulp Regeneration in Dentistry: A Systematic Scoping Review

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The aim of presented systematic scoping review was to investigate the actual and future clinical possibilities of regenerative therapies and their ability to regenerate bone, periodontal and pulp with histological confirmation of the nature of formed tissue. Electronic search was conducted using a combination between Keywords and MeSH terms in PubMed, Scopus, ISI-Web of Science and Cochrane library databases up to January 2016. Two reviewers conducted independently the papers judgment. Screened studies were read following the predetermined inclusion criteria. The included studies were evaluated in accordance with Arksey and O'Malley's modified framework. From 1349 papers, 168 completed inclusion criteria. Several characterized and uncharacterized cells used in Cell Therapy have provided bone regeneration, demonstrating bone gain in quantity and quality, even as accelerators for bone and periodontal regeneration. Synthetic and natural scaffolds presented good cell maintenance, however polyglycolid–polylactid presented faster resorption and consequently poor bone gain. The Growth Factor–Mediated Therapy was able to regenerate bone and all features of a periodontal tissue in bone defects. Teeth submitted to Revascularization presented an increase of length and width of root canal. However, formed tissues not seem able to deposit dentin, characterizing a repaired tissue. Both PRP and PRF presented benefits when applied in regenerative therapies as natural scaffolds. Therefore, most studies that applied regenerative therapies have provided promising results being possible to regenerate bone and periodontal tissue with histological confirmation. However, pulp regeneration was not reported. These results should be interpreted with caution due to the short follow-up periods.

Key Words: Regenerative therapy, mesenchymal stem cell, tissue engineering, revascularization root canal, scaffolds, cell therapy, platelet-rich fibrin, platelet-rich plasm.

Introduction

Conventional treatments performed on clinical dental practice can restore aesthetic and function after disease or injury, although these treatments do not promote the regeneration of affected structures. In this context, regenerative approaches based on tissue engineering principles aims to restore the natural biological apparatus, which synthetic materials cannot promote (1). Since the discovery of mesenchymal stem cells (MSC) in several orals tissues (2-5), regenerative approaches have been investigated aiming to improve the translational potential of regenerative therapies (6). Dental MSC are easily available and more accessible when compared to bone marrow mesenchymal stem cells (BMMSC) or embryonic stem cells. MSC from the dental pulp (DPSC) of exfoliated deciduous teeth (SHED) rise as an option which could contribute to the development of tooth banks for future clinical applications (7,8). Such MSC are able to originate mesodermal-derived cell line (9) providing, osteoblastic (6), odontoblastic (10,11) and periodontal cell lineages (12).

Regenerative therapies can be classified in three distinctive approaches that are often used together; the first one relies on the implantation of previously isolated and expanded MSC, which are seeded on scaffolds. This approach is named "stem cell-based therapies" (SC-BT) or just Cell-Based Therapies (C-BT), when differentiated cells are implanted (11). The second one, named "Growth Factor-Mediated Therapies" (GF-MT), relies on the ability of scaffolds and implanted growth factors (GF) to attract MSC to the damaged site (13-16). The third one, is based in the bioactivity of scaffolds charged (or not) with biomolecules able to provide appropriate adhesion and proliferation of implanted or recruited cells (7,11).

Venous blood derivatives such as Platelet-Rich Plasma (PRP) and Platelet-Rich Fibrin (PRF), contains high concentrations of transforming growth factor-beta (TGF-β), vascular endothelial growth factor (VEGF), epithelial growth factor (EGF) and insulin-like growth factor I (17). Besides, PRP and PRF application as scaffolds have shown promising clinical results (18,19). PRP comprises the first generation of platelet concentrates; although its inherent biological activity, the need for many centrifugation steps

and the addition of xenogeneic thrombin for platelet activation are viewed as hurdles for PRP clinical application (17). Choukroun et al. (20) developed the PRF, a second generation of platelet concentrates which requires only one centrifugation step without biochemical blood handling. PRF exhibits a natural support to immunity, guide to angiogenesis and recruitment of MSC (21,22). PRP and PRF have been largely used in both, surgeries for bone repair and root canal revascularization (RCR) in immature permanent teeth with necrotic pulp (23,24). RCR is based on blood clot formation into the root canal, previously decontaminated with a triple antibiotic paste (23,25). Therefore, stem cells present in the apical papilla can migrate to scaffold formed by blood clot and, thus, restore the pulp or perform the tissue's maturation (25,26).

Despite regenerative therapies being a new field in dentistry, this knowledge remains far away from clinical practice. Thus, the aim of this study was to perform a systematic scoping review exploring the actual and future clinical application of regenerative therapies emphasizing bone, periodontal and pulp regeneration with histological confirmation of formed-tissue's nature.

Material and Methodos

Study Design

The present scoping study was conducted following the modified five-stage framework suggested by Arksey and O'Malley (27) named Scoping Review. Newly, numerous papers use Scoping Review to state the actual knowledge in a particular area to provide a concise qualitative analysis (25,28). About the search strategy, the scoping study is indistinguishable to systematic reviews, directing a systematic and reproducible search. Yet, the main of scoping study is frequently address a wide topic or area and analyze individually the methodological quality in the included papers seeking from different methodologies wide generalizations. Thus, providing an overview of the current knowledge founding conclusions and tendencies from the general data. In addition, other objective of scoping reviews is to identify the literature gaps directing future researches.

Conceptual Definition

According to MeSH database, cell-and tissue-based therapy was defined in 2014 as "Therapies that involve the transplantation of cells or tissues developed for the purpose of restoring the function of diseased or dysfunctional cells or tissues". Hence, several tissues and cell lineages have been used for this propose being introduced into a patient. Their origin for cell therapy can be autogenic or allogeneic. Although the Growth factor-Mediated therapy is not described in the MeSH terms, this therapy can be described as the therapy that aims to employ growth factors to modulate and control the cells and tissues presents in the patient, being the location and the delivery key points of the therapy (29). Root Canal Revascularization can be defined as regenerative procedure aiming to re-vascularize the pulp tissue and it's structure with the recruitment of stem cells from apical papilla (25). This procedure is a new treatment option for necrotic immature permanent teeth based on the formation of blood clot into the root canal space. Thus, forming a natural scaffold for anchorage of stem cells, able to promote and contribute to the continuation of root development (25).

Search strategy: The structured research was conducted in PubMed, Scopus, Web of Science and Cochrane Library up to January 2016. Mesh terms, commonly used terms, and synonyms were included as part of the search (S1). An extensive combination of keywords was performed to include all the studies of interest (S2). The keywords were selected based on the pre-specified question formulated using the P.I.C.O. principle:

Are regenerative therapies in dentistry able to provide bone, periodontal and dental pulp regeneration in human?

Can the regeneration of bone periodontal and dental pulp be confirmed by histological analysis?

The retrieved records were uploaded into Mendeley™, to delete duplicated studies. Two reviewers (LAC and MCMC) conducted independently the initial evaluation of titles and abstracts under the following inclusion criteria:

- Studies: Clinical studies in humans, without language restriction;
- Follow-up time: not limited;
- Therapies: SC-BT, Cell-Based Therapy (C-BT) and GF-MT for bone, periodontal or pulp regeneration. The therapies aiming Root Canal Revascularization or applying PRP and PRF for tissue regeneration were also included;
- Study design:
- For SC-BT, C-BT and GF-MT: all clinical study design;
- Root Canal Revascularization: all clinical design that that induced
- Blood clotting or used PRP/PRF for RCR;
- Regeneration applying PRP and PRF: only randomized clinical trial;
- Reviews were excluded.

To confirm if the selected studies met the predefined inclusion criteria, full-text papers were read by the same reviewers. Persistent disagreement on inclusion, were resolved by intervention from a third reviewer (FFD). All studies included were assessed and data analysis was performed. After that, MCMC and LAC evaluated manually all references reported in each selected study to identify additional records. Gray literature was evaluated manually

in Google Scholar and ResearchGate (researchgate.net).

Results

The initial search yielded 2207 articles (39 papers from gray literature or from references of included studies), being 1349 of them considered unique studies (Fig. 1). After title and abstract evaluation, 173 studies were selected for full-text assessment, from which 168 completed inclusion criteria. Detailed reasons for studies' exclusion (30-35) are presented in Table 1. Four accompaniments studies were identified (6,36-38). Figure 2 shows the distribution of included studies per years.

Cell and Stem Cell-Based Therapies

Forty-nine studies reported C-BT or SC-BT providing periodontal and bone regeneration (Table 2 and 3). BMMSC were the most applied stem cells for SC-BT (39-56) (Fig. 3). Besides, Adipose Stem Cells (ASC) (57), DPSC (6,12,36,58,59) and periodontal ligament stem cell (PDLSC) (60,61) were employed. In addition, some studies did not report the tissue of MSC origin (56,62-64). Periosteal cells (65-68), osteoblastic (56,68-73), concentrate of monocytes (74), Mononuclear Cells (MNC) (75,76) and Bone Marrow Aspirate Concentrates (BMAC) (77-85) were used also in Cell-based therapy (Fig. 3).

Bone regeneration based on SC-BT and C-BT provided increase of bone deposition when combined with xenogeneic and alloplastic materials (39,40,44,46,48,54,57,63,65,68,69,79). Synthetic poly (lactic-co-glycolic acid) (PLGA) presented fast resorption rates in the postoperative

Table 1. Excluded studies and reasons for exclusion

Studies	Reason
Iwaia 2001(30); Iwaia 2011(31); Bose 2009 (32);	Not realized bleeding in the root canal
Okuda 2013 (33)	Not SC-BT
Yang 2010 (34)	Not Human
Peck 2012 (35)	Not growth-factor applying

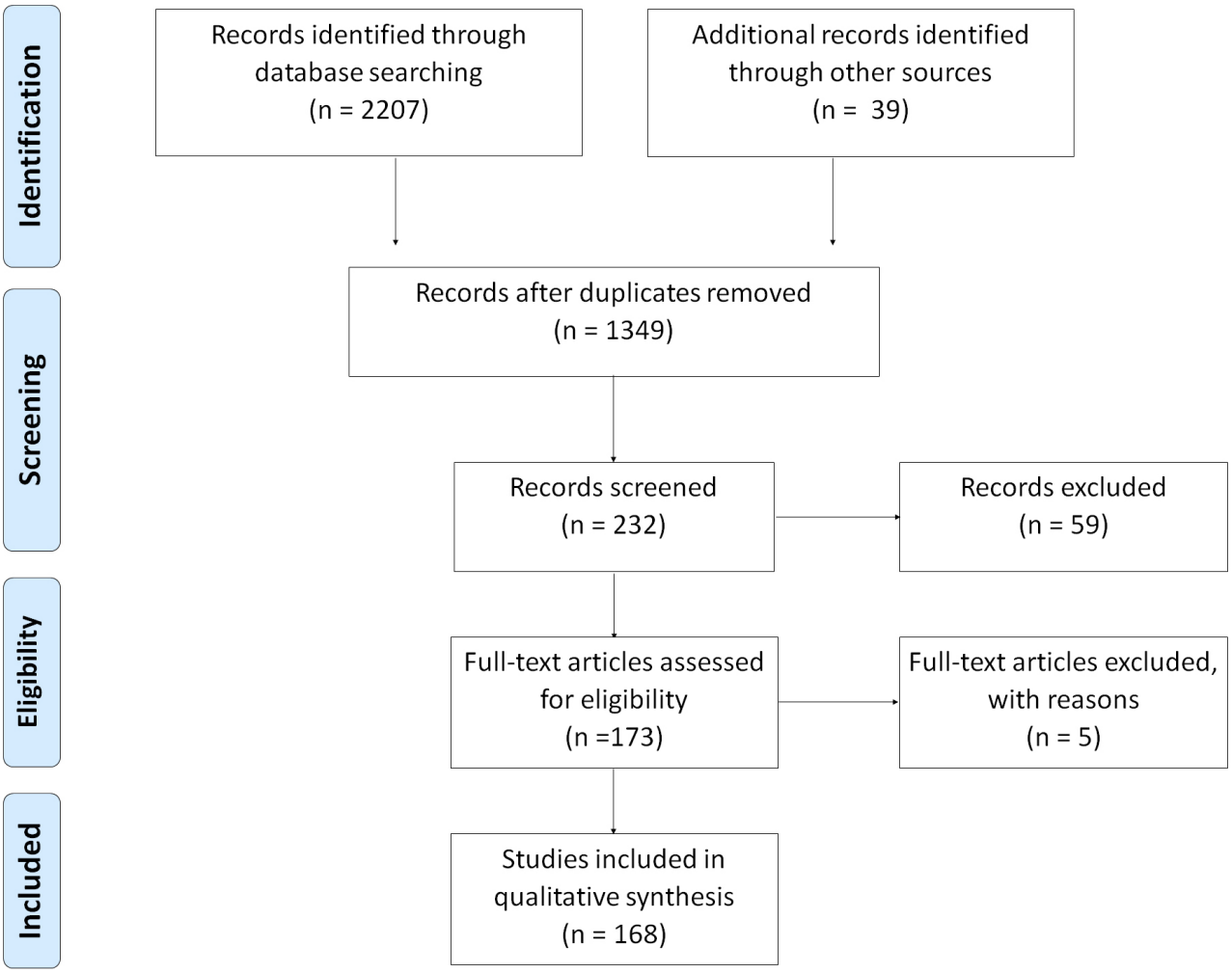

Fig.1 Prisma Flowchart

first weeks (71,73). Autografts (41,42,45,46,52,53) and allografts (47,52, 70,74,75,78,84) were successfully applied providing cell maintenance and mineral deposition. The Figure 4 illustrates the main scaffolds used and their classification. *De novo* bone tissue was histologically described generally as being compact without signs of inflammatory reaction. Bone remodeling, with gradual substitution of scaffolds by new-formed bone matrix, was frequently observed (49,77). Autologous bone without cell implantation also presented bone regeneration, however, the bone quality and vitality trend toward less when compared with SC-BT (54,73). Reported follow-ups ranged from three (63) to 75 months (41).

Five studies evaluated the influence of Bone Morphogenetic Protein (BMP) 2 (57,84), BMP-7 (77,83) or Platelet Derived Growth Factor (PDGF) (63) for constructs (MSC+Scaffolds) showing an improved potential of regeneration. Large reconstruction of bone defect – six (83), six to eight (84), seven (77), ten (57), 14 (53) and 15 cm (42) – were successful conducted employing BMAC, ASC or BMMSC.

Growth Factor–Mediated Treatment (GF-MT)

Twenty-four studies identified used GF-MT, from which nineteen (Table 4) did not combine them with cellular therapies. The GF applied in the selected studies includes PDGF (15,16,37,63,86-93) BMP-2 (13,14,57,84,91,94-96), Plasma Rich in Growth Factors (PRGF) (97-99) and BMP-7 (65,83). Such GF were reported as safe and effective in the treatment of periodontal and bone defects (87,88,92). Besides, the regeneration provided by these GF seems not to be dose dependent, thus a specific GF concentration must be defined since high GF concentration could be harmful for MSC (87). Wide bone mandible defects (5 to 12 cm) were regenerated by applying BMP-2 and beta-tricalcium phosphate (β-TCP) scaffolds (96). Histological analysis showed that density of blood vessels seems to be higher in tissues that utilize GF (13).

Root Canal Revascularization

Increase in length and width of root dentin walls and resolution of periapical lesion in immature permanent teeth with necrotic pulp were reported (23,100-109). Besides, tooth under revascularization could respond positively to thermal and electrical sensibility tests (110). Hoshino's triple antibiotic paste (TAP), containing ciprofloxacin, metronidazole and minocycline, was the most applied intracanal medication (24,110-143), providing good infection control (144). However, TAP possess an inherent potential for tooth discoloration as drawback. Tooth discoloration is unleashed by the contact of minocycline with the root walls during time needed for infection eradication (25). Thus, some studies have been investigating the substitution of minocycline by amoxicillin (100,145,146), cefaclor (23,147-152), clindamycin (153), tetracycline (154) and doxycycline (155-157) or utilization of $Ca(OH)_2$ (158-168). Besides, some studies did not use intracanal medication (169-

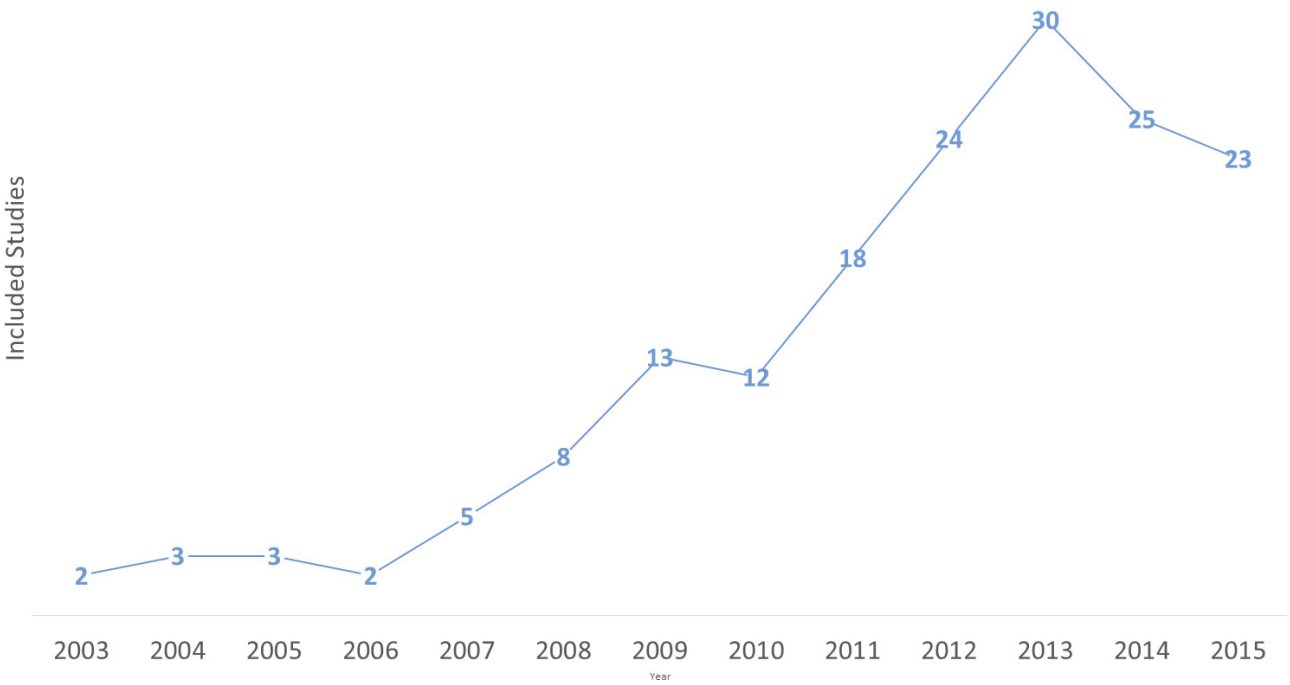

Figure 2. Studies included in the systematic scoping review according to year of publication

171). Although revascularization have been indicated for immature permanent teeth, recent studies demonstrated to be possible to perform revascularization in necrotic mature teeth (105,172). Few failures have been reported for teeth under revascularization, mainly due to crown fractures (131,165), root canal reinfection (102,173) and impossibility to induce the initial periapical bleeding (110). The tissue formed through revascularization

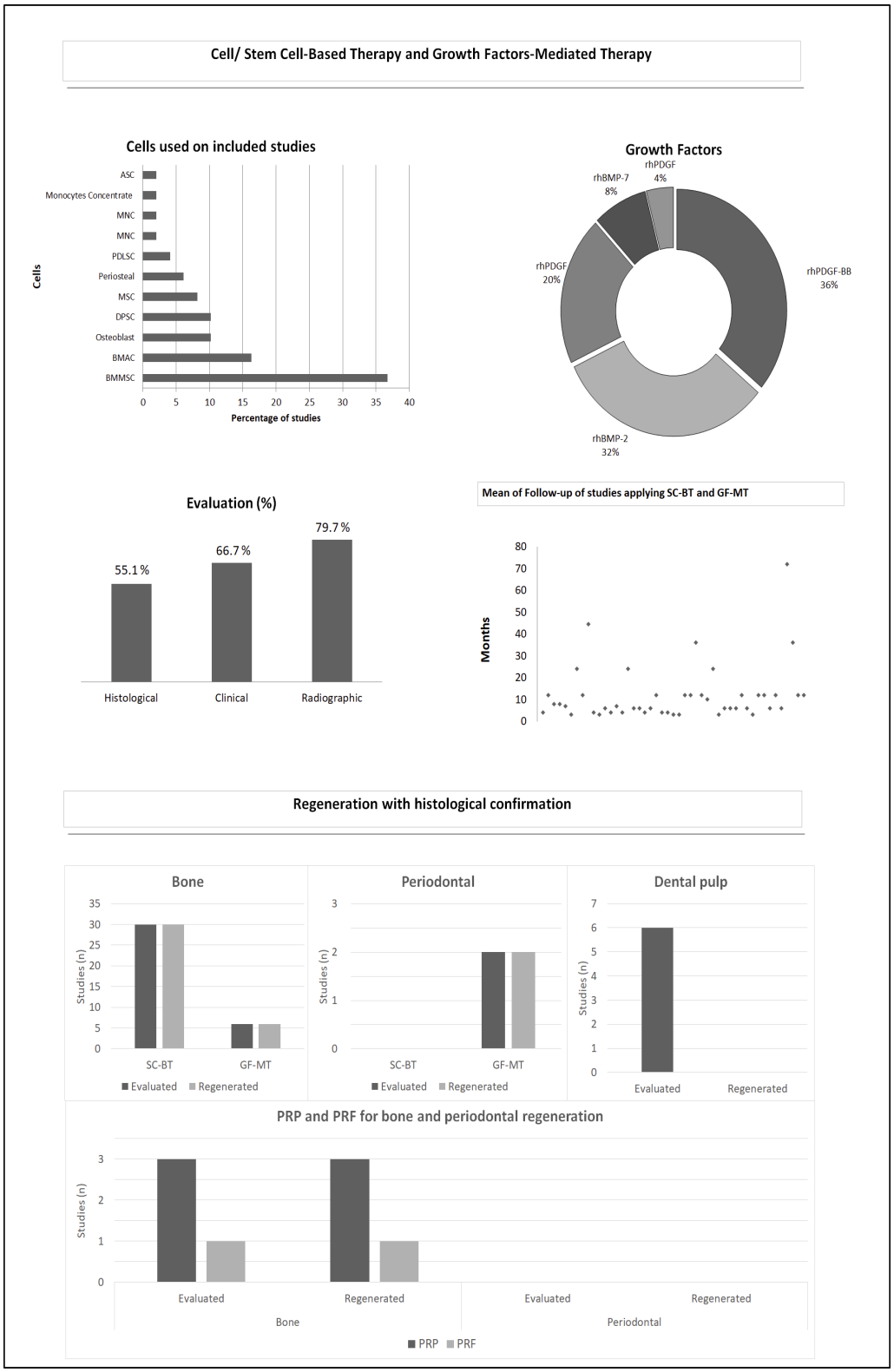

Figure 3. Pooling of main results

Table 2. Studies applying SC-BT for bone regeneration

Year	Author	Cell	Scaffold	Growth Factor	Patients	Follow-up	Parameters	Outcome
2003	Schmelzeisen et al. (65)	Periosteal	Polymer fleece		2	4 months	Histologic and clinical	Mineralized tissue formed
2004	Warnke et al. (77)	BMAC	BioOss	rhBMP7	1		Clinical and radiographic	Mineralized tissue formed
2005	Ueda et al. (39)	BMMSC	PRP–β-TCP injectable		6	12 months	Radiographic	Mineralized tissue formed (7.3 ± 4.6 mm)
2007	Cerruti et al. (75)	MNC	PRP and Bone scaffod		32	8 months	CT, histologic and clinical	Mineralized tissue formed
2007	Soltan et al. (78)	BMAC	Allograft bone block		5	8 months	Histologic and histomorphometry	Mineralized tissue formed (54%)
2007	Smiler et al. (79)	BMAC	PepGen Putty or C-Graft		5	7 months	Clinical and histologic	Mineralized tissue formed; (45%)
2007	Zizelmann et al. (71)	Osteoblast	PLGA		10	3 months	CT	Mineralized tissue formed; High resorption of scaffolds
2008	Pradel et al. (72)	Osteoblast	Demineralized bovine bone matrix or from solvent-dehydrated mineralized bovine bone; and graft		6	1 year	Histologic	Mineralized tissue formed. Inflammation and some scaffold resorption was found in 5 months
2008	Shayesteh et al. (40)	BMMSC	β-TCP/hydroxyapatite		6	12 months	Clinical, radiographic and histologic	Mineralized tissue formed (41.3%)
2008	Yamada et al. (41)	BMMSC	PRP Injectable		12	2-6.3 years: 6.3/ 6.3/ 5.3/ 4.9/ 4.3/ 4.3/ 3.3/ 3.5/ 3.0/ 3.3/ 2.1/ 2.1/ 3.8/ 2.5/ 2.5/ 2.0	Orthopantomograms, histologic, CT	Mineralized tissue formed; increases of 8.8 ± 1.6 mm
2009	Behnia et al. (62)	MSC	Demineralized bone mineral and calcium sulfate (Osteoset)		2	4 months	CT	Mineralized tissue formed (34.5%)
2009	D'Aquino et al. (58)	DPSC	Collagen sponge		7	3 months	Histologic and radiographic	Mineralized tissue formed
2009	Mangano et al. (73)	Osteoblasts	PLGA		5	6 months	Clinical, histologic and CT	Mineralized tissue formed; fast resorption of scaffold
2009	McAllister et al. (70)	MSC and osteoprogenitor cells	Bone graft		5	4.1 months	Clinical, radiographic and histologic	Mineralized tissue formed; (vital bone content of 33% - 22% to 40%-)
2010	Lee et al. (42)	BMMSC	Freeze-dried autobone tray and fibrin glue		1	7 months	Histological, clinical and radiographic	Mineralized tissue formed
2010	Sauerbier et al. (43)	BMMSC	FICOLL		4	4,1 months; clinical 2 years	Histologic and clinical	Mineralized tissue formed (19.9% Confidence interval 945% 10.9 to 29%)
2010	Soltan et al. (80)	BMMAC	Resorbable hydroxylapatite OR Allograft		2	4-6 months	Histologic and radiographic	Mineralized tissue formed (34% to 45%)
2010	Mangano et al. (69)	Osteoblasts	PLGA		1	6 months	Histologic and CT	Mineralized tissue formed (28.89% bone and 71.11% medullary spaces)
2011	Brunelli et al. (59)	DPSC	Collagen sponge		1	4 months	Clinical, radiographic and histologic	Mineralized tissue formed
2011	Graziano et al. (36)	DPSC	Collagen sponge		1	6 months	Clinical and radiographic	Mineralized tissue formed
2011	Montesani et al. (68)	osteoblast and periosteal cells	nonwoven polyglactin-910 fibers connected by poly-p-dioxanon bonding		2	12 months	Clinical and radiographic	Mineralized tissue formed

2011	Rickert et al. (49)	BMMSC	BioOsss and autogenous stem cells (Test); BioOsss mixed with autogenous bone (Control)		12	14.8 weeks 3-4 months	Histologic	Mineralized tissue formed; test group presented more bone formation than control
2011	Sauerbier et al. (81)	BMAS	Autogenous bone combination with a bovine bone mineral		26	biopsies 3-4 month	Histologic	Mineralized tissue formed (12.6% ± 1.7%)
2011	Schmelzeisen et al. (82)	BMAC	FICOLL		1	3 months	Histologic	Mineralized tissue formed (26.9%); no signs of inflammation
2012	Behnia et al. (63)	MSC	Synthetic biphasic bone substitute	PDGF	3	3 months	CT	Mineralized tissue formed (51.3%)
2012	Hernández-Alfaro et al. (83)	BMAC	Bovine HA	rhBMP-7	1	1 year	Histologic, clinical and radiographic	Mineralized tissue formed
2012	Soltan et al. (74)	Concentrated of monocytes	Demineralized allograft material		2	1 year	Radiographic and histologic	Mineralized tissue formed
2012	Nagata et al. (67)	Periosteal	Autogenous bone and PRP		25	1 year	CT	Mineralized tissue formed
2013	Giuliani et al. (6)	DPSC	Collagen sponge		7	3 years	Histologic and radiographic	Mineralized tissue formed
2013	Kaigler et al. (44)	BMMSC	Absorbable gelatin sponge		N=12 Control=12	1 year	Clinical, radiographic, CT and histologic	Mineralized tissue formed; therapy accelerated alveolar bone regeneration
2013	Sandor et al. (57)	ASC	β-TCP	rhBMP-2	1	10 months	Histological	Mineralized tissue formed
2013	Yamada et al. (46)	BMMSC	Membran + PRP Injetável		1	24 months	Histological, CT and radiographic	Mineralized tissue formed
2013	Yamada et al. (45)	BMMSC	PRP Injectable			3 months	Clinical	Mineralized tissue formed.; all patients improved bone tissue
2013	Zamiri et al. (47)	BMMSC	Bone Human cadavers (allograft)		3	6 months	CT	Mineralized tissue formed
2014	Marx et al. (84)	BMAC	Collagen sponge	rhBMP-2	40	6 months	Clinical, CT, radiographic and histologic	Mineralized tissue formed; Patients that received cells presented more bone formation
2014	Rajan et al. (48)	BMMSC	β-TCP		1	biopsy 4 months; and 6 months follow-up	CT and histologic	Mineralized tissue formed; 80% of the original jawbone
2014	Rickert et al. (50)	BMMSC	BioOss + MSCs and BioOss + autogenous bone		12	1 year	Clinical and radiographic	Mineralized tissue formed; 3 implant (91%) failed in osteointegration
2014	Wildburger et al. (51)	BMMSC	Bio-Oss		7	3 and 6 months	Histological and CT	Mineralized tissue formed (13.5%)
2015	Bertolai et al. (52)	BMMSC	PRP and corticocancellous freeze-dried bone chips		20	3 months	Histological and clinical	Mineralized tissue formed
2015	Park et al. (53)	BMMSC	Bone from the iliac crest; collagenous membrane		1	1 year	Clinical and radiographic	Mineralized tissue formed
2015	Kaigler et al. (54)	BMMSC	β-TCP		Test=13; Control=13	1 year	Clinical, radiographic, and histologic	Mineralized tissue formed (12.2% ±3.3)
2015	Pasquali et al. (85)	BMAC	Bio-Oss		8	6 months	Histologic	Mineralized tissue formed (55.15 ± 20.91)

beta-tricalcium phosphate (ββ-TCP); polyglycolid–polylactid (PLGA); Synthetic polysaccharide (FICOLL); bovine bone mineral (BioOsss); hydroxyapatite (HA); Bone Morphogenetic Protein (rhBMP); Platelet Derived Growth Factor (PDGF); Computed Tomography (CT); Bone Marrow Mesenchymal Stem Cells (BMMSC); Bone Marrow Aspirate Concentrates (BMAC); Adipose stem cells (ASC); Dental Pulp Stem Cells (DPSC); Periodontal Ligament Stem Cells (PDLSC); Mesenchymal Stem Cells (MSC); Mononuclear Cells (MNC); Platelet-Rich Plasma (PRP); Platelet-Rich fibrin (PRF)

presented blood vessels (131,174,175) with fibrous connective tissue (175) and areas with deposition of a cementum/bone-like tissue (131,165,173,175) without presence of dentin (175) or fibrous nerves (174). This way, the tissue presented more characteristics of a repair than regenerated tissue (175).

PRP and PRF in Tissue Reparation

Venous blood derivatives presented benefits when applied for bone, periodontal and pulp regeneration (18,19,24,128,144,155,176-194). In this way, few studies did not observe improvement of regeneration results after PRP and PRF application (195-198). 60% of selected clinical trials (Table 5) evaluated regeneration induced by PRP-based therapies, while 28% evaluated PRF and 12% both.

The higher follow-up reported was 4 years (187). Benefits of PRP (182) or PRF (190) for bone regeneration seems to provide better results when combined with autologous bone instead of PRP/PRF alone. Although PRF possess higher GF amounts than PRP, studies comparing both venous blood derivatives found similar results for bone and periodontal regeneration (188,189). Thus, PRP and PRF provided significant improvement, clinically and radiographically, in 3-wall periodontal intrabony defects (184,188). On the other hand, one study performing revascularization reported best results for PRF (144).

Regeneration with Histological Confirmation

In Figure 3 is displayed the pooled of regeneration data, which shows that all studies employing cell and SC-BT were able to promote regeneration of bone with histological confirmation of tissue nature. Periodontal regeneration with SC-BT did not performed histological analysis. GF-MT promote bone and periodontal regeneration in all included studies. However, the papers that evaluated histologically the features of revascularization of root canal did not observe regeneration of dental pulp. PRP and PRF improved the regeneration of bone with histological features. Periodontal regeneration using PRP and PRF did not confirm with histological analysis.

P*ossibilities and Perspectives of Clinical Transition*

Injectable scaffolds appear as an interesting option facilitating the clinical application of regenerative therapies (39,41,45,55,64) even as the use of PRP, when combined with biomaterials can facilitate the clinical manipulation of the materials for graft (182,198). Other possibility related, the replacement of xenogeneic fetal bovine serum by autologous human serum, has been reported as an option to reduce exogenous agents to ex vivo cell expansion (28,62,63).

Discussion

The presented systematic scoping review showed that

Table 3 – Studies applying SC-BT for periodontal regeneration

Year	Author	Cells	Scaffold	Growth factor	Patients	Follow-up	Parameters	Outcome
2006	Yamada et al. (55)	BMMSC	PRP Injectable	-	1	1 year	Clinical and Radiographic	Bone defects reduced; Reduction on probing depths and gain on clinical attachment
2009	Okuda et al. (66)	Periosteal	PRP with HA granules	-	3	6 months	Clinical and Radiographic	Radiographic deposition of bone, clinical attachment gain
2010	Feng et al. (60)	PDLP	Bone Grafting material Calcitite	-	3	32–72 month	Clinical	Decrease in tooth movement and probing depth and attachment gain
2011	McAllister et al. (56)	MMSC and osteoblast	Allograft bone matrix from cadavers	-	2	6 months	Clinical and radiographic	Radiographic bone deposition and decrease of probing depth
2013	Sankaranar et al. (76)	MNC	Thermo-reversible gelation polymer	-	1	36 months	Clinical and Radiographic	Bone height was observed radiographically. Reduction of probing pocket depth, improve of clinical attachment
2014	Aimetti et al. (12)	DPSC	Collagen sponge	-	1	1 year	Clinical and radiographic	Bone increase was observed by radiographic
2015	Yamada et al. (64)	MSC	PRP and Hyaluronic Acid	-	1		Clinical	Volume of papilla increase

beta-tricalcium phosphate (β-TCP); polyglycolid–polylactid (PLGA); Synthetic polysaccharide (FICOLL); bovine bone mineral (BioOsss); hydroxyapatite (HA); Bone Morphogenetic Protein (rhBMP); Platelet Derived Growth Factor (PDGF); Computed Tomography (CT); Bone Marrow Mesenchymal Stem Cells (BMMSC); Bone Marrow Aspirate Concentrates (BMAC); Adipose stem cells (ASC); Dental Pulp Stem Cells (DPSC); Periodontal Ligament Stem Cells (PDLSC); Mesenchymal Stem Cells (MSC); Mononuclear Cells (MNC); Platelet-Rich Plasma (PRP); Platelet-Rich fibrin (PRF).

bone and periodontal regeneration can be successfully achieved, presenting histological confirmations of new regenerate tissue. Dental pulp regeneration was not achieved by revascularization; such therapy provided just repaired pulp-like tissue. Clinical, radiographic, histological and immunohistochemical data confirmed the nature of regenerated tissues by SC-BT and GF-MT (58,73). Besides, PRP and PRF were able to improve bone deposition (198).

In fact, SC-BT or GF-MT comprise important strategies to improve bone regeneration. 30 studies employed SC-BT and confirmed regeneration by histological analysis. All included papers showed a new regenerated tissue with better characteristics than control groups without use of cells. A clinical trial regarding bone regeneration by SC-BT reported excellent results for sinus floor elevation after 3-4 months applying MSC with bovine bone mineral (49). Histological analysis showed 17.7% of bone formation in SC-BT group while in control group, just 12% of new bone was formed. Similarly, bone tissue regenerated by applying an inorganic bone scaffold charged with PRGF, exhibited more blood vessels than those tissues regenerated with scaffolds alone (98). Autologous bone without cell implantation also provided bone regeneration – due to osteoconductive properties. However, the bone quality is smaller when compared with cell and stem cell-based therapies (54,73). Therefore, the bone regeneration can be achieved without use of SC-BT, although its use increases bone deposition and maturation of bone tissue.

Likewise, GF-MT has been used to induce recruitment and differentiation of stem cells located in the target tissue (7). Thus, the use of GF-MT was effective in 100% of studies that confirmed the regeneration through histological analysis, being able to increase the regenerative potential to periodontal tissue. *De novo* tissue showed new compact bone without signs of inflammatory reaction. Bone remodeling (77) with gradually substitution of scaffolds for bone was frequently observed (36,49). Similarly, complete periodontal regeneration was reported with deposition of new cement, alveolar bone and connective tissue using PDGF-BB in demineralized freeze-dried bone allograft or β-TCP + bioresorbable collagen (86,93). In contrast, no signs of periodontal regeneration were detected in control group (93). Periodontal ligament and gingival tissue present stem cells able to deposit bone and cement. Such cell population can be recruited by growth factors to induce tissue regeneration (4,199). GF-MT is considered easier to apply than SC-BT (7). GF-MT reduces costs since there is no need for an additional intervention for cell isolation. Furthermore, GF-MT presents insignificant risk of contamination since does not require the addition of xenogeneic substances as medium culture and its supplementation (28,200).

PRP and PRF have been reported as extracellular matrix mimetics being both able to guide cell behavior showing interesting results combined with SC-BT and C-BT therapy (41,46,52,55,64,66,67,75). In addition, the use of PRP and PRF provided bone regeneration confirmed by histological analysis. In a recent case series, the bone formed as of a combination of MSC and PRP exhibited better histological results, suggesting this combination can significantly improve bone formation (52). The use of PRP seems to increase the histological features proving good osteoconductive properties (180,191). Bone formation in sinus lifting was more efficient in group treated with PRP than in the control group (with inorganic bovine bone alone) (180). Combination of autologous BMMSC with PRP and cancellous freeze-dried bone chips also provided good results by exhibiting more cellular components than group BMMSC-PRP free (52). In the same way, PRF alone presented a propensity to regenerate higher bone volume and quality, even as PRF combined with socket filling (190). Thus, the application of both generations of blood concentrated can be used for periodontal defects treatment, alone or combined with conventional open flap debridement providing goods results (18,186,188).

Regarding scaffolds, the major part of studies report good properties in relationship to the ability of maintenance the cell adherence and maintenance the structure to promote the regeneration process, however, some points have been highlighted regarding the PLGA (71,73). Two studies evaluated the potential of osteoblastic cells seeded on PLGA scaffolds for bone regeneration, reported unfavorable results (71,73). This was due to fast bone resorption observed after 3 months in sinus augmentation, which was significantly higher in PLGA (90%) than that observed for autologous iliac crest bone implants (29%) (71). Polymeric scaffolds should be incorporated in metabolic routes to be replaced by cell-secreted extracellular matrix. However, this process should not be so fast (7). After adhesion and osteoblastic differentiation, bone remodeling is expected to happen parallel to new extracellular matrix formation (201). Histological analysis revealed high medullar spaces with few amount of regenerated bone (73). Therefore, the fast PLGA resorption rate seems to hamper proper bone regeneration (71,73). In contrast, collagen sponges, hydroxyapatite (HA) and β-TCP, as well as allogenic or xenogeneic bone has provided suitable bone stability (43,54,58,80,85). It can be justified by the fact that these scaffolds possess components derived from natural bone tissue.

Although the studies demonstrate that it is possible to regenerate bone and periodontal tissue, the same is not true regarding pulp tissue. Thus, some points should be highlight and discussed about the characteristics of

dental pulp to understood this fact. The blood supply in the pulp chamber is practically insignificant due the dimensions of the apical foramen that do not allow an adequate revascularization of the constructs; hence, it makes the regeneration of this tissue more difficult. In this sense, it is seems not yet possible regenerate a pulp-like tissue able to deposit dentin, following revascularization (38,131,165,173-175). Conventional revascularization did not apply expanded MSC or GF; solely underlies on stem cell from apical papilla migration towards the formed blood clot inside root canal (25). In this way, the biological mechanisms coordinating migration and differentiation of stem cell from apical papilla are not clearly understood, as well as the real harm provided by pulp necrosis above these cells (25). Real-time polymerase chain reaction analysis showed that blood collected from root canal during revascularization, presented higher expression of MSC markers CD73 and CD105 (up to 600-fold) than systemic blood (202). However, the increase of MSC markers was selective, since there wasn't any change in expression of mRNA transcripts encoding dentin sialophosphoprotein and alkaline phosphatase (molecules considered as odontoblast markers) (202). In fact, after performing revascularization, mineral deposition is observed into the root canal characterized as cementum/bone-like tissue, but not dentin (174). Thus, considering that application of SC-BT or GF-MT improves the quality of bone and periodontal formed (57,93), the use of these therapies (SC-BT and GF-MT) could be combined with revascularization to increase the quality of the formed tissue. Although none study was identified employing cells or growth factors in revascularization, we can hypothesize that use of these therapies could comprise interesting strategies for pulp regeneration. Moreover, the increase observed in length and width of root canal has been provided by a repaired tissue, this mineral deposition can be responsible for good longevity rates in teeth submitted to revascularization, justifying the use of this therapy (25). A recent review evaluating 75 studies (367 teeth) corroborated with presents results showing a success rate of 94.3% in teeth submitted to revascularization with a mean of follow-up 17.6 months (25). Although these results are provided from case reports and case of series studies, the authors suggest that revascularization should be considered as treatment option in cases of necrosis of immature permanent teeth (25). Moreover, revascularization does not requires the instrumentation of root canal , since bacteriological control is chemically achieved, reducing the tooth structure loss cooperating with the increase on survival rate (26).

While promising results have been observed applying regenerative therapies in dentistry, these results are mostly based in clinical cases and small clinical trials, which limits the extrapolation of the data. Thus, this should be interpreted with caution. Besides, literature presents short follow-ups, generally under 1 year. Therefore, it is important to keep researching and publishing initial clinical

Autogenous	Allogeneic	Alloplastic		Xenogeneic
Cancellous bone (mandible) (44)	Bone from tissue bank + PRP (54, 76)	HAP/TCP	Kasios™ (42)	Bio-Oss™ (Bone matrix) (78, 85)
Cancellous bone (iliac crest) (55)	Bone from tissue bank + rhBMP-2 (17)	HAP/TCP	Reprobone™ (64)	Bio-Oss™ (Bone-Blocks) (78)
Rehydrated (PRP) lyophilized bone (54)	Bone from tissue bank (49, 75, 79)	β-TCP	Cerasorb™ (50, 56, 80)	Bio-Oss™ + Autogenous bone (51, 52, 82, 84)
PRP (43, 47, 48)	Bone block – ACE Surgical (79)	β-TCP	VitOss™ (80)	PepGenTM (80)
PRF (205, 206)	AllOss™ (79)	β-TCP	CronOSS™ (18)	
	Osteocel™ (71)	β-TCP	β-TCP +PRP (41)	
		Polymers	PLGA (70, 72)	
		Polymers	Polymer Fleece (66, 69)	
		Polymers	GelFoam™ (46)	

Figure 4. Main scaffolds reported in the included studies by origin classification.

Table 4. Studies applying growth factor–mediated therapy

Year	Author	Scaffold	Growth Factor	Patients	Follow-up	Parameters	Outcome
2003	Nevins et al. (86)	Demineralized freeze-dried bone allograft	rhPDGF-BB	9	9 mths	Clinical, radiographic and histologic	Probing depth reduction (6.42 mm), clinical attachment level gain 6.17 mm, radiographic fill 2.14 mm; Histological evaluation show periodontal regeneration
2005	Nevins et al. (87)	β-TCP	rhPDGF-BB	180	6 mths	Clinical and radiographic	Improve bone fill, clinical attachment level and reduce gingival retraction
2006	McGuire et al. (92)	β-TCP and collagen membrane	rhPDGF	7	6 mths	Clinical	Favorable clinical results in all cases
2009	Mcguire et al. (93)	β-TCP with a bioabsorbable collagen	rhPDGF-BB	30	6 mths	Clinical, radiographic and Histologic	Recession depth reduction (-2.9 mm), root coverage (90.8%), recession width reduction. Regeneration of periodontal regeneration, cementum and bone.
2009	Schuckert et al. (94)	Polycaprolactone and PRP	rhBMP-2	1	6 mths	Radiographic and histologic	Radiographic evidence of bone confirmed by biopsy
2010	Schuckert et al. (95)	β-TCP and PRP	rhBMP-2	1	1 yr	CT and histologic	
2011	Jayakumar et al. (88)	β-TCP	rhPDGFBB	54	6 mths	Clinical, radiographic	Bone gain radiographic, clinical attachment gain and reduction on probing depth
2011	Nevins et al. (89)	β-TCP	rhPDGF-BB	3	5 mths	Clinical, radiographic and histologic	Bone gain radiograph and histologic
2011	Nevins et al. (90)	Mineral collagen bone substitute	rhPDGF-BB	16	5 mths	Clinical, radiographic and Histologic	Histological bone; histomorphometric shown more new bone with growth-factor
2011	Sohn et al. (97)	Fibrin-rich blocks	PRGF	53	10 mths	Clinical, radiographic and Histologic	Histological evidence of bone regeneration
2012	Anitua et al. (98)	Bovine anorganic bone	PRGF	5	5 mths	Clinical, radiographic and histologic	More vital bone was observed in growth factor group (21.4%) than control (8.4%) even less inflammation. Immunohistochemical show blood vessels
2012	Taschieri et al. (99)	Deproteinized bovine bone matrix	PRGF	8	6 mths	Clinical and radiographic	Less complication were observed in group treated with PRGF
2013	Desai et al. (96)	β-TCP	rhBMP-2	6	12/ 39/ 36/ 50/ 51/ 28 mths	Clinical and radiographic	From 6 patient one develop infection requiring new intervention
2013	Jensen et al. (91)	Absorbable collagen sponge OR bone autograft/ xenograft	rhBMP-2 OR PDGF-bb	4	3 yrs/ 4 mths/ 4 mths/ 6 mths	Clinical and radiographic	Bone gain major than 13 mm in all patients
2013	Marx et al. (13)	Collagen sponge; cancellous freeze-dried allogeneic bone; PRP	rhBMP-2	20	6 mths	Clinical, radiographic and histologic	Bone formation (54%) and histological bone regeneration
2013	Nevins et al. (37)	β-TCP	PDGF-BB	83	36 mths	Clinical and radiographic	Long-term stable clinical and radiographic improvements;
2013	Sclar et al. (14)	Collagen sponge, autogenous bone graft, bovine bone mineral, PRP, and guided bone regeneration	rhBMP-2	1	1 yr	Clinical, radiographic and CT	Increase in bone deposition
2014	Maroo et al. (15)	β-TCP	rhPDGF	1	9 mths	Clinical and radiographic	Pocket defect was totally filled by mineral tissue
2014	Maroo et al. (16)	β-TCP	rhPDGF-BB	15	9 mths	Clinical and radiographic	Pocket depth reduction, clinical attachment gain, alveolar crest gain

beta-tricalcium phosphate (β-TCP); polyglycolid–polylactid (PLGA); Synthetic polysaccharide (FICOLL); bovine bone mineral (BioOsss); hydroxyapatite (HA); Bone Morphogenetic Protein (rhBMP); Platelet Derived Growth Factor (PDGF); Computed Tomography (CT); Bone Marrow Mesenchymal Stem Cells (BMMSC); Bone Marrow Aspirate Concentrates (BMAC); Adipose stem cells (ASC); Dental Pulp Stem Cells (DPSC); Periodontal Ligament Stem Cells (PDLSC); Mesenchymal Stem Cells (MSC); Mononuclear Cells (MNC); Platelet-Rich Plasma (PRP); Platelet-Rich fibrin (PRF)

Table 5. Clinical trials applying PRP and PRF for bone pulp and periodontal regeneration

Year	Author	PRP/PRF	Regeneration	Scaffold /intervention	Control	Patients	Follow-up	Parameters	Outcome
2004	Hanna et al. (176)	PRP	Periodontal	Bovine derived xenograft	Bone graft	30	6 mths	Clinical and radiographic	PRP improve the results: CAL and PD
2005	Okuda et al. (177)	PRP	Periodontal	HA	HA	35	12 mths	Clinical and radiographic	Group with PRP show better results
2008	Keceli et al. (195)	PRP	Periodontal	Connective tissue graft	Connective tissue graft	40	12 mths	Clinical	No differences with addiction of PRP
2008	Piemontese et al. (178)	PRP	Periodontal	Demineralized freeze-dried bone allograft	Demineralized freeze-dried bone allograft	30	12 mths	Clinical and radiographic	Greater changes in PD reduction and CAL
2009	Harnack et al. (196)	PRP	Periodontal	β-TCP	β-TCP	22	6 mths	Clinical and radiographic	PRP did not improve the results
2009	Pradeep et al. (18)	PRP	Periodontal	PRP alone	Open flap debridement	20	6 mths	Clinical and radiographic	PRP improve the results: CAL and PD
2009	Torres et al. (180)	PRP	Bone	Anorganic bovine bone	Anorganic bovine bone	87	24 mths	Clinical, radiographic and histologic	No differences; graft resorption was similar treatment and control
2009	Markou et al. (179)	PRP	Periodontal	Demineralized freeze-dried bone allograft	PRP alone	24	6 mths	Clinical and radiographic	PRP not improve significantly the treatment
2010	Alissa et al. (181)	PRP	Bone	PRP	-	20	3 mths	Clinical and radiographic	PRP show better bone trabecular pattern
2010	Arenaz-Búa et al. (182)	PRP	Bone	Synthetic calcium HA or autologous bone OR PRP alone OR allogeneic demineralized bone matrix	Anny material or PRP alone	82	6 mths	Clinical and radiographic	Greatest bone formation was observed in PRP + autologous bone
2010	Badr et al. (197)	PRP	Bone	Bone graft	Bone graft	22	5-6 mths	Clinical	Improve in the results was not observed with use of PRP
2011	Sharma et al. (184)	PRF	Periodontal	PRF with conventional open-flap debridement	Conventional open-flap debridement alone	42	9 mths	Clinical and radiographic	Highest percentage of bone fill was found in PRF group
2011	Yilmaz et al. (185)	PRP	Periodontal	PRP	PPP with Bovine-derived xenograft	20	12 mths	Clinical and radiographic	PPP demonstrated similar efficacy to PRP
2011	Thorat et al. (186)	PRF	Periodontal	PRF	Conventional open flap debridement alone	40	9 mths	Clinical and radiographic	PRF was better in all clinical and radiographic parameters
2012	Menezes et al. (187)	PRP	Periodontal	Porous HA and PRP	Porous HA	60	4 yrs	Clinical and radiographic	PRP improve the results

2012	Pradeep et al. (188)	PRP and PRF	Periodontal	PRP or PRF with open-flap debridement or autologous	Open-flap debridement alone	54	9 mths	Clinical and Radiographic	PD and CAL were better in PRF followed by PRP. Bone fill was more observed in PRF group
2013	Bajaj et al. (189)	PRP and PRF	Periodontal	PRP or PRF with open-flap debridement	Open-flap debridement alone	42	9 mths	Clinical and radiographic	CAL were better in PRF and PRP. No differences were observed among PRP and PRF
2013	Khairy et al. (198)	PRP	Bone	PRP with autogenous bone	Autogenous bone	15	6 mths	Clinical, radiographic and histologic	PRP group show more bone density
2013	Hauser et al. (190)	PRF	Bone	PRF or PRF and socket filling	Extraction alone	23	2 mths	Clinical, radiographic and histologic	PRF group shown better results
2014	Eskan et al. (191)	PRP	Bone	PRP and resorbable polylactide membrane	Resorbable polylactide without PRP	28	4 mths	Clinical, radiographic and histologic	PRP shown more bone gain
2015	Angelo et al. (192)	PRF	Bone	Biphasic (60% HA/40% β-TCP) or monophasic (100% β-TCP)	Bi or monophasic without PRF	82	8.3 mths	Clinical, radiographic and histologic	PRF shown superior mechanical stability to restored alveolar bone
2015	Narang et al. (144)	PRP and PRF	Pulp	PRP and PRF revascularization	Blood Clot revascularization	15	18 mths	Clinical and radiographic	PRF was superior that PRP. PRF and PRF were better than control group
2015	Pradeep et al. (19)	PRF	Bone and Periodontal	PRF OR PRF with Metformin 1% OR Open-flap debridement with PRF plus 1% metformin	Open-flap debridement alone	120	9 mths	Clinical and radiographic	PRF + 1% MF group showed greater improvements in clinical parameters
2015	Shah et al. (194)	PRF	Periodontal	Open flap debridement and PRF	Open-flap debridement + Demineralized freeze-dried bone allograft	20	6 mths	Clinical and radiographic	Better result observed in PRF group
2015	Kumar et al. (193)	PRF	Bone	PRF		31	3 mths	Clinical and radiographic	Bone density was more in PRF group

beta-tricalcium phosphate (β-TCP); polyglycolid–polylactid (PLGA); Synthetic polysaccharide (FICOLL); bovine bone mineral (BioOsss); hydroxyapatite (HA); Bone Morphogenetic Protein (rhBMP); Platelet Derived Growth Factor (PDGF); Computed Tomography (CT); Bone Marrow Mesenchymal Stem Cells (BMMSC); Bone Marrow Aspirate Concentrates (BMAC); Adipose stem cells (ASC); Dental Pulp Stem Cells (DPSC); Periodontal Ligament Stem Cells (PDLSC); Mesenchymal Stem Cells (MSC); Mononuclear Cells (MNC); Platelet-Rich Plasma (PRP); Platelet-Rich fibrin (PRF); probing depth (PD), Clinical Attachment Level (CAL)

cases as well as reporting the possible failures that may happen. Moreover, large randomized clinical trials should be conducted primarily investigating different scaffolds, cells and growth factors and their interactions with different regenerated tissues.

In conclusion, the regenerative therapies in dentistry are able to regenerate bone and periodontal tissue. No evidence of dental pulp regeneration was observed. Stem Cell-Based Therapy provide histological evidence to bone regeneration while GF-MT regenerate bone and periodontal tissues. PRP and PRF were able to promote bone regeneration with histological confirmation.

Resumo

O objetivo da presente Scoping review foi investigar as possibilidades clínicas atuais e futuras das terapias regenerativas e sua capacidade de regenerar tecido ósseo, periodontal e polpar em humanos com confirmação histológica da natureza do tecido formado. Uma busca eletrônica foi realizada utilizando uma combinação entre as palavras-chave e termos MeSH nos bancos de dados PubMed, Scopus, ISI-web of Science e Cochrane library até janeiro de 2016. Dois revisores realizaram de forma independente o julgamento dos documentos. Os estudos selecionados foram lidos seguindo os critérios de inclusão predeterminados. Os estudos incluídos foram avaliados de acordo com a estrutura modificada de Arksey e O'Malley. Dos 1349 artigos, 168 preencheram os critérios de inclusão. Várias células caracterizadas e não caracterizadas promoveram regeneração óssea utilizada em terapias celulares, demonstrando ganho ósseo em quantidade e qualidade, de forma rápida para regeneração óssea e periodontal. Os scaffolds sintéticos e naturais apresentaram boa manutenção celular, no entanto o poliglicol-polilácido apresentou uma reabsorção rápida e, consequentemente, pequeno ganho ósseo. A terapia mediada por fatores de crescimento foi capaz de regenerar tecido ósseo e todas as características de um tecido periodontal. Dentes submetidos à revascularização apresentaram aumento do comprimento e largura do canal radicular. No entanto, os tecidos formados não foram capazes de depositar dentina, caracterizando um tecido reparado. Tanto o PRP quanto o PRF parecem apresentar benefícios quando aplicados em terapias regenerativas sendo um bom scaffold natural. Portanto, a maioria dos estudos que aplicaram terapias regenerativas forneceram resultados promissores sendo possível regenerar tecido ósseo e periodontal com confirmação histológica. No entanto, não foi observada regeneração de polpa dental. Estes resultados devem ser interpretados com cautela.

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Received Mach 17, 2018
Accepted July 2, 2018