Journal of Research in Medical and Dental Science
2018, Volume 6, Issue 1, Page No: 179-183

Available Online at: www.jrmds.in
eISSN No. 2347-2367: pISSN No. 2347-2545

Periodontal Stem Cells for Bone Regeneration in Clinical Use: A Review of Literature

Shireen Shidfar[1], Ahad Khoshzaban[2], Razieh Nejhadi[3], Zahra Zohri[3], Mohammad Taghi Baghani[4]*

[1]Postgraduate Student of Periodontics, Department of Periodontics, School of Dentistry, Shahed University, Tehran, Iran
[2]Dental Biomaterials Department Tehran University of Medical Sciences Stem Cell Preparation Unit, Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran
[3]Periodontist, Private Practice
[4]Postgraduate Student of Prosthodontics, Department of Prosthodontics, School of Dentistry, Shahed University, Tehran, Iran

DOI: 10.24896/jrmds.20186129

ABSTRACT

Human periodontal stem cells were proved as a source of mesenchymal stem cells due to the presence of mesenchymal stem cell surface markers. This review of literature was aimed to assess clinical experiments, which have evaluated the efficacy of human periodontal stem cells for bone regeneration. The search strategy was based on the search strategy developed for MEDLINE (OVID) but revised appropriately for each database. We searched MEDLINE and EMBASE via OVID (1990 to October 2017) and no restrictions were placed on the language or date of publication when searching the electronic databases. Later all the references lists of the included studies would have been checked manually to identify any additional studies. None of the studies fulfilled our inclusion criteria and therefore no data analysis was conducted. There is little evidence relevant to this subject. There would appear to be a need for robust clinical trials to assess the efficacy of periodontal stem cells for regeneration.

Keywords: Stem Cells, Periodontal Ligament, Bone Regeneration

HOW TO CITE THIS ARTICLE: Shireen Shidfar, Ahad Khoshzaban, Razieh Nejhadi, Zahra Zohri, Mohammad Taghi Baghani, Periodontal Stem Cells for Bone Regeneration in Clinical Use: A Review of Literature, J Res Med Dent Sci, 2018, 6 (1): 179-183, DOI: 10.24896/jrmds.20186129

Corresponding author: Mohammad Taghi Baghani
e-mail✉ mtbaghani@gmail.com
Received: 22/08/2017
Accepted: 17/01/2018

INTRODUCTION

Bone and tissue loss are common results of various clinical conditions such as trauma, periodontal diseases, tumors, malformations and atrophy of alveolar ridges following tooth extraction which need intervention to promote repair [1, 2]. Periodontal ligament (PDL) is a is a specialized, vascular, and highly cellular connective tissue [3] which takes response in attaching cementum to the inner wall of alveolar bone [4] and it is constructed by different cell types, including fibroblasts, osteoblasts, neuronal, and endothelial cells [5]. The PDL plays important roles in maintaining homeostasis, repairing damaged tissue in response to disease or mechanical trauma and particularly supporting tooth function [5]. According to the recent studies, PDL cells, as well as stem cells, express stem cell markers and have pluripotent and colony-forming abilities.(4, 6-8) Several in vivo studies showed that, PDL cells have the potential to induce cementum and PDL-like regeneration in periodontal defects, thus they may be useful for treatment of periodontal diseases [4, 9-11].

Tissue engineering as a new frontier in the regeneration of lost tissues have developed during the recent years first by Langer and Vacanti in 1993 [12]. Trilogy of Bone tissue engineering

consists of key elements such as osteogenic cells, scaffolds and signaling factors in order for a mature bone structure to be created [13-15]. Stem cells have self-renewal abilities and are capable of colony-forming efficiency, self-renewal, and multilineage differentiation [13, 16-18]. Obtaining stem cells with confined morbidity and more availability was achievable by deriving adult stem cells from adipose, dental and periodontal tissues instead of bone mesenchymal stem cells [11]. Human periodontal stem cells were proved as a source of mesenchymal stem cells due to the presence of mesenchymal stem cell surface markers. Studies have provided the evidence to suggest that these cells are capable of osteogenic, dentinogenic, adipogenic, chondrogenic, myogenic, and neurogenic differentiation [4, 11, 19].

The existence of PDL stem cells has been reported [10] but the characterization of those cells has been less issued in the literature. A high rate of positivity for human periodontal mesenchymal stem cell marker proteins such as CD44, CD73, CD90, CD105, CD106(VCAM-1), CD146(MUC-18) and STRO-1 and lack of hematopoietic markers like CD31, CD34 and CD45 have been illustrated in hPDLSC [20-22]. Further identification of more stem cell specific markers are desired in order to obtain pure populations of stem cells [23].

This review of literature was aimed to assess clinical experiments, which have evaluated the efficacy of human periodontal stem cells for bone regeneration and analyzing the method of characterizing of those cells.

MATERIALS AND METHODS

Procedure

Criteria for considering studies for this review

Table 1: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Only randomized controlled clinical trials (RCTs) were included in this review. • Humans with defects of alveolar bone • Periodontal stem cell transplantation derived from periodontal ligament into human alveolar bone defects in clinical studies	• Articles Which has been written in language other than English • Data that has been Published more than once • In Vitro Studies and Animal Studies

We intended to report on any adverse effects related to periodontal stem cell transplantation.

Search methods for identification of studies

The search strategy was based on the methodology produced for MEDLINE (OVID) yet overhauled suitably for every database. We searched MEDLINE and EMBASE via OVID (1990 to October 2015) and no restrictions were placed on the language or date of publication when searching the electronic databases. Later every one of the references arrangements of the included investigations would have been checked physically to recognize any extra examinations

Data collection and analysis

Selection of studies

Two authors, Shireen Shidfar (SS) and Ahad Khoshzaban (AK), autonomously assessed the titles and the abstracts of studies detected in the searches. Full texts of all potentially relevant studied were acquired. The full-text papers were evaluated individualistically and any disagreement on the suitability of trials was settled through discussion and dialog, or if vital through an outsider, Mohammad Taghi Baghani (MTB).

Table 2: Extracted Data

The Following Data has been Extracted:
(a) method of allocation
(b) masking of participants and outcome assessors
(c) exclusion of participants after randomization and proportion of losses at follow-up
(d) demographic characteristics including symptoms of bony lesions, country of origin, sample size, age, sex
(e) type of intervention
(f) follow-up duration
(g) type of control or placebo
(h) Follow-up duration in the control group.
(i) primary and secondary outcomes

Data extraction and management

Although no investigations were incorporated into this survey, if future examinations are recognized and incorporated into updates, the accompanying strategies for information extraction and administration is recommended. Study subtle elements will be gathered utilizing a pre-destinated form intended for this reasin and went into the Characteristics of included examination table. Two review authors (SH and MTB) will independently remove the applicable information. Any variations will be forestalled by consulting with a third author (Zahra Zohri (ZZ)) (Table 2).

This data will be utilized to assess heterogeneity and the external validity of the trials.

Assessment of risk of bias in included studies
In spite of the fact that we didn't identify any relevant randomized controlled trials, we plan to apply the following methods for assessing risk of bias if further studies are distinguished in future updates. Two review authors (SH and AK) will evaluate the selected studies. The assessment will be linked and any disagreements between the reviewers will be discussed. The following fields will be assessed as low, high or unclear risk of bias:
1. Sequence generation;
2. Allocation concealment;
3. Blinding (of participants, personnel and outcome assessors);
4. Incomplete outcome data;
5. Selective outcome reporting;
6. Other sources of bias.
After evaluation of the involved studies, the articles will be labeled suitably as mentioned below
(A) Low risk of bias (plausible bias unlikely to seriously alter the results)
(B) Unclear risk of bias (plausible bias that raises some doubt about the results)
(C) High risk of bias (plausible bias that seriously weakens confidence in the results)

Measures of treatment effect
The data would have been analysed by SH and AK using Review Manager (RevMan) 5 and reported.

Assessment of reporting biases
If a sufficient number of randomized controlled trials had been found, we would have assessed bias by a funnel plot.

RESULTS

Our search strategy pointd out studies, which were autonomously assessed for relevance by two of the authors (Shireen Shidfar (SS) and Ahad Khoshzaban (AK)). We also conduct a free-text search on Google Scholar for any potentially qualified trials, which resulted in the finding of publications. Full-text copies of these studies were obtained. Then the bibliographical references of these papers were searched for any relevant studies and related studies were found. Handsearching of the Iranian dental journals did not include any related studies.

Included studies
We did not find any suitable study.

Risk of bias in included studies
No trials were included.

Effects of interventions
None of the studies fulfilled our inclusion criteria and therefore no data analysis was conducted.

DISCUSSION

The aim of this systematic review was to assess the effect of periodontal ligament stem cells for bone regeneration in clinical usage. For this purpose, clinical studies using periodontal stem cells were detected according to a described list of criteria to determine suitability for the review. None of them could successfully fulfill the criteria. Therefore, no meta-analysis of the data could be accomplished.

There exists biological evidence that regeneration can happen in human model, however there is not consensus on predictability of this method as a final complete treatment.

The first step in determining the potential of stem cells to recapitulate periodontal development is to develop studies in preclinical animal models. The concept of stem cells locating in periodontal tissues was first proposed by Melcher in 1985 [24]. Periodontal ligament stem cells had been discussed in literature for almost two decades but there existed little evidence to fully support their usage [25-27]. The most potent evidence that these cells were residing in the periodontal tissues was proposed by McCulloch *et al.,* in an in-vivo and histological study [28].

The isolation of periodontal ligament stem cells was first performed in 2004 [4] and there were proved to have mesenchymal stem cell-like features such as: plastic adherence; expression of verified mesenchymal stem cell markers; formation of clonogenic clusters resembling fibroblasts; and the capacity to differentiate into adipocytes and osteoblast and cementoblast-like cells in vitro [29]. Surprisingly these cells were qualified to produce cementum- and other periodontal ligament-like tissues in vivo. In addition, Periodontal ligament stem cells can express some cementoblast and osteoblast markers [30].

The studies have illustrated the possibility and feasibility usage of periodontal-derived stem cells for periodontal and tooth regeneration in vivo and in vitro.

The findings from previous systematic reviews [27] indicate that in different animal models the implantation of periodontal ligament stem cells has a positive outcome in improving periodontal regeneration. As a consequence of these promising animal studies, the clinical application of periodontal stem cells for the regeneration of periodontal tissue may be considered.

To date, only one clinical human study has been performed with the objective of assessing the potential of periodontal ligament progenitors for the reconstruction of periodontal intrabony defects [31]. Autologous periodontal ligament stem cells, in combination with bone grafting material, were transplanted into periodontal defects of three patients. In two patients, additional gain in periodontal attachment was detected. This study demonstrated that utilization of autologous periodontal ligament cells in cell-based surgical treatment for periodontitis may enhance regenerative dentistry.

There is lots of work to be done to come to a conclusion for outcomes of stem cell-based periodontal regeneration but its future seems very promising. According to excellent body of evidence to support the notion that periodontal ligament stem cells can be used for periodontal regeneration in animals, it is time to progress to human clinical trials.

CONCLUSION

Implications for practice

There is little evidence relevant to this subject, only a case report study exists. In the absence of any randomized controlled trials, clinicians should base their decisions on clinical experience in conjunction with patients situation.

Implications for research

Although there would appear to be a need for robust clinical trials to assess the efficacy of periodontal stem cells for regeneration, future randomized controlled trials might emphasize more closely on type of used scaffolds and method of isolation and characterization of stem cells. Any further trials that are carried out should be well designed and reported according to the CONSORT statement (www.consort-statement.org/).

REFERENCES

1. Yamada Y, Ito K, Nakamura S, Ueda M, Nagasaka T. Promising cell-based therapy for bone regeneration using stem cells from deciduous teeth, dental pulp, and bone marrow. Cell Transplantation. 2011; 20(7):1003-13.
2. Esposito M, Grusovin MG, Felice P, Karatzopoulos G, Worthington HV, Coulthard P. The efficacy of horizontal and vertical bone augmentation procedures for dental implants-a Cochrane systematic review. Eur J Oral Implantol. 2009; 2(3):167-84.
3. Gronthos S, Mrozik K, Shi S, Bartold P. Ovine periodontal ligament stem cells: isolation, characterization, and differentiation potential. Calcified Tissue International. 2006; 79(5):310-17.
4. Seo BM, Miura M, Gronthos S, Bartold PM, Batouli S, Brahim J, Young M, Robey PG, Wang CY, Shi S. Investigation of multipotent postnatal stem cells from human periodontal ligament. The Lancet. 2004; 364(9429):149-55.
5. Beertsen W, McCulloch CAG, Sodek J. The periodontal ligament: a unique, multifunctional connective tissue. Periodontology. 2000. 1997; 13(1):20-40.
6. Xu J, Wang W, Kapila Y, Lotz J, Kapila S. Multiple differentiation capacity of STRO-1+/CD146+ PDL mesenchymal progenitor cells. Stem Cells and Development. 2008; 18(3):487-96.
7. Nagatomo K, Komaki M, Sekiya I, Sakaguchi Y, Noguchi K, Oda S, Muneta T, Ishikawa I. Stem cell properties of human periodontal ligament cells. Journal of Periodontal Research. 2006; 41(4):303-10.
8. Gay IC, Chen S, MacDougall M. Isolation and characterization of multipotent human periodontal ligament stem cells. Orthodontics & Craniofacial Research. 2007; 10(3):149-60.
9. Volponi AA, Pang Y, Sharpe PT. Stem cell-based biological tooth repair and regeneration. Trends in Cell Biology. 2010; 20(12):715-22.
10. Park J-Y, Jeon SH, Choung P-H. Efficacy of periodontal stem cell transplantation in the treatment of advanced periodontitis. Cell transplantation. 2011; 20(2):271-85.

11. Wada N, Wang B, Lin NH, Laslett AL, Gronthos S, Bartold PM. Induced pluripotent stem cell lines derived from human gingival fibroblasts and periodontal ligament fibroblasts. Journal of periodontal research. 2011; 46(4):438-47.
12. Langer R, Vacanti J. Tissue engineering. Science. 1993; 260(5110):920-6.
13. Sedgley CM, Botero TM. Dental stem cells and their sources. Dental Clinics of North America. 2012; 56(3):549-61.
14. Khademhosseini A, Langer R, Borenstein J, Vacanti JP. Microscale technologies for tissue engineering and biology. Proceedings of the National Academy of Sciences of the United States of America. 2006; 103(8):2480-87.
15. Morad G, Kheiri L, Khojasteh A. Dental pulp stem cells for in vivo bone regeneration: a systematic review of literature. Archives of Oral Biology. 2013; 58(12):1818-27.
16. Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, et al. Multilineage potential of adult human mesenchymal stem cells. Science. 1999; 284(5411):143-47.
17. Tuan RS, Boland G, Tuli R. Adult mesenchymal stem cells and cell-based tissue engineering. Arthritis Research and Therapy. 2003; 5(1):32-45.
18. 18. Baksh D, Song L, Tuan R. Adult mesenchymal stem cells: characterization, differentiation, and application in cell and gene therapy. Journal of Cellular and Molecular Medicine. 2004; 8(3):301-16.
19. Pejcic A, Kojovic D, Mirkovic D, Minic I. Stem Cells for Periodontal Regeneration. Balkan Journal of Medical Genetics. 2013; 16(1):7-11.
20. Fujii S, Maeda H, Wada N, Tomokiyo A, Saito M, Akamine A. Investigating a clonal human periodontal ligament progenitor/stem cell line in vitro and in vivo. Journal of cellular physiology. 2008; 215(3):743-49.
21. Huang G-J, Gronthos S, Shi S. Mesenchymal stem cells derived from dental tissues vs. those from other sources: their biology and role in regenerative medicine. Journal of dental research. 2009; 88(9):792-806.
22. Wada N, Menicanin D, Shi S, Bartold PM, Gronthos S. Immunomodulatory properties of human periodontal ligament stem cells. Journal of Cellular Physiology. 2009; 219(3):667-76.
23. Shi S, Gronthos S. Perivascular niche of postnatal mesenchymal stem cells in human bone marrow and dental pulp. Journal of bone and mineral research. 2003; 18(4):696-704.
24. Melcher A. Cells of periodontium: their role in the healing of wounds. Annals of the Royal College of Surgeons of England. 1985; 67(2):130.
25. Amar S. Implications of cellular and molecular biology advances in periodontal regeneration. The Anatomical Record. 1996; 245(2):361-73.
26. Pitaru S, McCulloch C, Narayanan S. Cellular origins and differentiation control mechanisms during periodontal development and wound healing. Journal of Periodontal Research. 1994; 29(2):81-94.
27. Bright R, Hynes K, Gronthos S, Bartold P. Periodontal ligament-derived cells for periodontal regeneration in animal models: a systematic review. Journal of Periodontal Research. 2015; 50(2):160-72.
28. McCulloch C. Progenitor cell populations in the periodontal ligament of mice. The Anatomical Record. 1985; 211(3):258-62.
29. Dominici ML, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini FC, Krause DS, Deans RJ, Keating A, Prockop DJ, Horwitz EM. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy. 2006; 8(4):315-17.
30. Trubiani OD, Di Primio R, Traini T, Pizzicannella J, Scarano A, Piattelli A, Caputi S. Morphological and cytofluorimetric analysis of adult mesenchymal stem cells expanded ex vivo from periodontal ligament. International Journal of Immunopathology and Pharmacology. 2005; 18(2):213-21.
31. Feng F, Akiyama K, Liu Y, Yamaza T, Wang TM, Chen JH, Wang BB, Huang GJ, Wang S, Shi S. Utility of PDL progenitors for in vivo tissue regeneration: a report of 3 cases. Oral Diseases. 2010; 16(1):20-28.