

# Application of Adipose Tissue Stem Cells in Regenerative Dentistry: A Systematic Review

Sumit Gaur<sup>1</sup>, Rupali Agnihotri<sup>2</sup>

<sup>1</sup>Department of Pedodontics and Preventive Dentistry, <sup>2</sup>Department of Periodontology, Manipal College of Dental Sciences, Manipal Academy of Higher Education (MAHE), Manipal, Karnataka, India

Received : 06-02-21  
Revised : 28-02-21  
Accepted : 26-03-21  
Published : 10-06-21

ABSTRACT

**Aim:** The aim of this study was to systematically review the applications of adipose tissue stem cells (ADSCs) in regenerative dentistry. **Materials and Methods:** An electronic search was conducted in Medline (PubMed) and Scopus databases. The original research associated with the role of ADSCs in regeneration of alveolar bone, periodontal ligament (PDL), cementum as well as the dental pulp was evaluated. Among the included studies, three animal studies and one human study had low risk of bias. **Results:** A total of 33 relevant studies were included in the review. The animal models, *in vivo* human, and *in vitro* studies revealed that ADSCs had a significant osteogenic differentiation potential. Besides, they had potential to differentiate into PDL, cementum, and dental pulp tissue. **Conclusion:** The ADSCs may be specifically applied for bone tissue engineering in the management of alveolar bone defects, specifically in dental implants and periodontal disease. However, their role in regeneration of PDL, cementum, and dental pulp requires further investigations. Overall, their applications in regenerative dentistry needs further verification through human clinical trials.

**KEYWORDS:** Adipose tissue stem cells, bone, cementum, periodontal ligament, pulp, regeneration, tissue engineering

## INTRODUCTION

Regenerative dentistry is a branch of regenerative medicine that involves the understanding of “cell and molecular biology to design dental therapies that aim to restore, repair, rejuvenate and regenerate the dental tissues.”<sup>[1]</sup>

Adipose tissue stem cells (ADSCs) are a type of mesenchymal stem cells (MSCs) which are isolated from the fat tissues enzymatically.<sup>[2]</sup> They express the characteristic surface markers and have potential to differentiate into multiple lineages of MSCs. They contain 100–500 times more stem cells (SCs) than bone marrow (BM).<sup>[2]</sup> They can be isolated from the adipose tissues and injected or encapsulated in biomaterials to be implanted into the wounds.<sup>[2]</sup> They increase the healing rate and can directly differentiate into specific cell lineages.<sup>[2]</sup> They have been successfully applied for

repairing critical-sized bone defects and constructing engineered bone grafts. They are an excellent alternative to BMSCs.<sup>[3]</sup>

In regenerative dentistry, the ADSCs have been evaluated for their ability to regenerate alveolar bone, periodontal ligament (PDL), cementum, and dental pulp in animal models.<sup>[4-6]</sup> Some *in vivo* clinical studies investigated their efficacy in treating bone deficiencies arising due to trauma, tumor resection, or congenital disorders.<sup>[7]</sup> Although the BMSCs have been successfully applied in these situations, the ADSCs are more lucrative owing to the quantity of tissue and less invasive procedures

**Address for correspondence:** Dr. Rupali Agnihotri, Department of Periodontology, Manipal College of Dental Sciences, Manipal Academy of Higher Education (MAHE), Manipal, Karnataka 576104, India.  
E-mail: get2rupali\_agnihotri@yahoo.co.in, rupali.a@manipal.edu

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

**For reprints contact:** reprints@medknow.com

**How to cite this article:** Gaur S, Agnihotri R. Application of adipose tissue stem cells in regenerative dentistry: A systematic review. J Int Soc Prevent Communit Dent 2021;11:266-71.

Access this article online	
<b>Quick Response Code:</b> 	<b>Website:</b> www.jispcd.org
	<b>DOI:</b> 10.4103/jispcd.JISPCD_43_21

involved in their harvesting, isolation, and culture.<sup>[8]</sup> With this background, the present review focusses on the applications of ADSCs in regenerative dentistry.

## MATERIALS AND METHODS

### SEARCH STRATEGY

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed to identify the research publications on the applications of ADSCs in regenerative dentistry. The databases searched were Medline (PubMed) and Scopus till 25 January 2021. A combination of keywords like “Adipose” AND “stem” AND “cells” AND “dental” AND “regeneration” AND “pulp” OR “periodontal” OR “alveolar” AND “bone” OR “tooth” were used. They were verified in the titles, abstracts, or keywords during the initial search. It resulted in a total of 182 articles [Figure 1]. The data were screened for duplicates which resulted in 148 articles wherein the titles and abstracts were read.

### INCLUSION AND EXCLUSION CRITERIA

The eligibility criteria included free full text of original studies in English related to the applications of ADSCs in regenerative dentistry. Any kind of recommendations, expert statements, reviews, technical reports, case reports, and non-original papers were excluded.

This resulted in 51 original research articles of which 18 were excluded after reading the full text. Finally, 33 original studies were reviewed.<sup>[4-7,9-37]</sup>

### DATA EXTRACTION

The type of study, aims and objectives, source of ADSCs, methods of isolation, culture and differentiation, cell surface markers, type of tissue regenerated, results, and conclusions were recorded.

### RISK OF BIAS ASSESSMENT

Two independent review authors (S. G. and R. A.) assessed the risk of bias for animal studies according to the SYRCLE tool and for human studies according to the Cochrane guidelines.<sup>[38,39]</sup> The disagreements were resolved by a discussion.

## RESULTS

Among the studies included in the review, three animal studies<sup>[9,14,21]</sup> and one human study<sup>[30]</sup> had low risk of bias, whereas all other studies had unclear risk of bias [Figure 2].

The results obtained from different studies may be summarized as follows:

- Types of studies:* Of the 33 included studies, 23 involved the animal models<sup>[4-6,9-28]</sup> whereas three trials were done on humans<sup>[7,29,30]</sup> and seven studies were conducted *in vitro*<sup>[31-37]</sup> [Table 1].
- Sources of ADSCs:* The animal studies utilized ADSCs obtained from omentum, inguinal fat pad, epididymis, subcutaneous adipose tissue, abdominal fat tissue, fat deposits at the hip region, subcutaneous scapular and interscapular sites and buccal fat

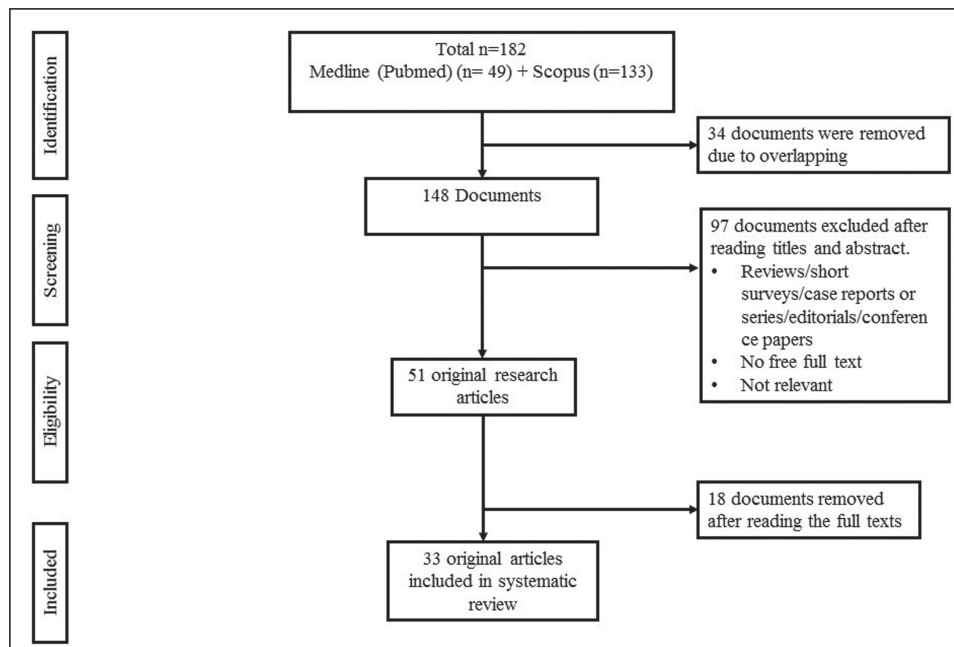


Figure 1: Evidence search on the applications of ADSCs in regenerative dentistry as per the PRISMA guidelines

pads (BFPs) of Sprague Dawley rats, beagle dogs, micromini pigs, rabbit, porcine, and sheep.<sup>[4-6,9-15,18-22,24-26,32,34]</sup> Some studies obtained ADSCs from human liposuction aspirates, infrapatellar or BFP, and commercial cell lines.<sup>[7,17,23,27,29,30,37]</sup>

- c. *Isolation and culture of ADSCs obtained from different sources:* In most of the studies, ADSCs were isolated via an enzymatic process which involved the final digestion of the harvested fat tissue with the collagenase<sup>[4,5,7,9,11-14,16-18,20,22-25,27,30-36]</sup> [Figure 3]. An automated system was also used in a study.<sup>[29]</sup>
- d. *Cell surface markers expressed by ADSCs:* The cell surface markers like CD73, CD90, CD105, CD29 and CD44, CD166, CD54 and CD13 were expressed by ADSCs.<sup>[6,7,9,11,13,14,16,17,20,23,24,27-36]</sup> However, they did not express hematopoietic antigens like CD34, CD45, CD146, CD31, CD271, CD117, CD106, CD133, CD144, CD309, and HLA-DR.<sup>[6,7,9,11,14,16,17,20,23,24,27-36]</sup> The expression of stemness genes like SOX2, OCT4, NANOG, and KLF4 was also reported.<sup>[17]</sup>
- e. *Differentiation of ADSCs:* The following section discusses the differentiation of ADSCs into the tooth supporting dental tissues.

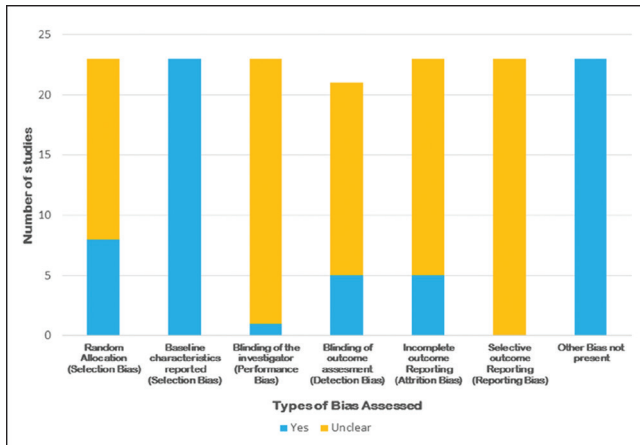


Figure 2: Risk of bias summary for animal studies

**DIFFERENTIATION INTO THE BONE**

The ADSCs differentiated into osteoblast-like cells and regenerated bone around the titanium discs and peri-implantitis defects in animals.<sup>[16,21]</sup> The ADSCs isolated from swine BFP and micromini pigs showed osteodifferentiation with synthetic supports and in periodontal defect models.<sup>[26,32]</sup> Their combination with inorganic bovine bone increased the bone volume in calvarial defects in rats with type 2 diabetes.<sup>[14]</sup> Furthermore, a dose-response relationship was observed between bone regeneration and quantity of ADSCs.<sup>[9]</sup> They regenerated alveolar bone in dehiscence-type defects when combined with platelet-rich plasma (PRP) or fibrin (PRF), hydroxyapatite (HA), or  $\beta$ -tricalcium phosphate ( $\beta$ -TCP) granules.<sup>[10,23]</sup>

Similar effects were seen when ADSCs were combined with mediators like semaphorin-3A,  $\beta$ -TCP, and bone morphogenetic protein-2 (BMP-2).<sup>[18,19]</sup> The ADSC extracellular vesicles (exo) significantly increased the levels of newly formed tissues.<sup>[24]</sup> The 3T3L1-exo enhanced preadipocyte osteogenic differentiation *in vitro* owing to reduced miR-223 expression.<sup>[37]</sup> Additionally, different types of scaffolds like poly lactic-co-glycolic acid (PLGA), Gelfoam, amniotic membrane, HA/ $\beta$ -TCA, and the bovine bone teeth enhanced the osteogenic potential of ADSCs.<sup>[4,5,7,9,14,17,28,29,36]</sup>

An *in vitro* comparative evaluation of ADSCs, BMSCs, and dental pulp SCs showed that addition of dentine matrix components (DMCs) to the SCs promoted mineralization and dentinogenic differentiation of ADSCs in cultures.<sup>[34]</sup> Both ADSCs and periodontal ligament stem cells (PDLSCs) showed similar calcification potential in another *in vitro* study.<sup>[35]</sup> The ADSCs isolated from Bichat’s fat pad expressed the stemness features that enabled osteodifferentiation.<sup>[31]</sup> Moreover, ADSCs isolated from swine BFP and interscapular subcutaneous adipose tissue increased the calcified ECM.<sup>[32]</sup>

**Table 1: Studies to evaluate the role of adipose stem cells in regenerative dentistry**

Source of adipose tissue stem cells	Type of tissue regenerated	Scaffolds and bioactive mediators	Applications in dentistry
<ul style="list-style-type: none"> <li>• Animal source<sup>[4-6,9-15,18-22,24-26,32,34]</sup></li> <li>• Human adipose tissue cells<sup>[7,17,23,27,29,30]</sup></li> <li>• Commercial cell lines<sup>[37]</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Bone<sup>[4,5,7,9,10,13,14,16-21,23-37]</sup></li> <li>• Periodontal ligament and cementum<sup>[4,12,20,22,33]</sup></li> <li>• Pulp<sup>[6]</sup></li> </ul>	<ul style="list-style-type: none"> <li>• PLGA<sup>[4,5]</sup></li> <li>• Gelfoam<sup>[28]</sup></li> <li>• Amniotic membrane<sup>[7,17]</sup></li> <li>• Bovine bone<sup>[9,14,36]</sup></li> <li>• Hydroxyapatite/<math>\beta</math>-tricalcium phosphate<sup>[23,29]</sup></li> <li>• BMP-2<sup>[19]</sup></li> <li>• PRF/PRP<sup>[23,25]</sup></li> <li>• Semaphorin-A<sup>[18]</sup></li> <li>• Dentine matrix components<sup>[34]</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Peri-implantitis<sup>[19,25]</sup></li> <li>• Periodontal disease<sup>[4,5,12,22,33]</sup></li> <li>• Pulp regeneration<sup>[6]</sup></li> <li>• Tooth avulsion<sup>[20]</sup></li> <li>• Tooth<sup>[11]</sup></li> </ul>

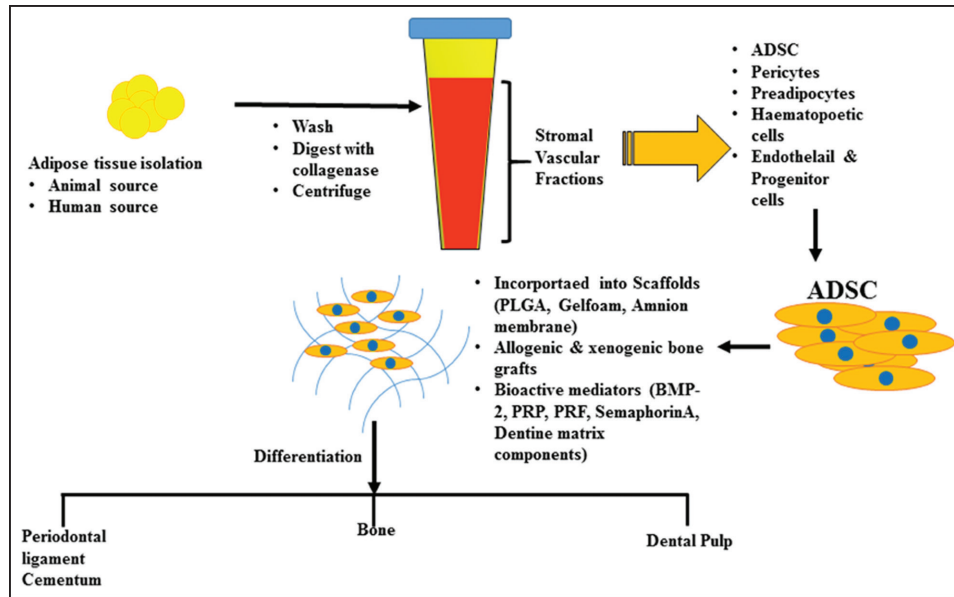


Figure 3: Isolation, culture, differentiation, and applications of ADSCs in regenerative dentistry

#### DIFFERENTIATION INTO THE PDL AND CEMENTUM

ADSCs combined with PLGA scaffolds resulted in increased bone, PDL, and cementum growth in animal models.<sup>[4]</sup> In combination with fibrin sealant, they reduced inflammatory resorption, increased PDL formation, and reduced ankylosis in avulsed tooth.<sup>[20]</sup> It was suggested that implantation of ADSCs increased cementum and PDL fibers regeneration due to improved periodontal microenvironment.<sup>[22]</sup> Another study reported that the ADSCs cultured in dental follicle conditioned medium (DFC-CM) supplemented with DKK-1 promoted cementogenic differentiation.<sup>[33]</sup> Further, a combination of autologous ADSCs and PRP promoted periodontal tissue regeneration.<sup>[12]</sup>

#### DIFFERENTIATION INTO THE DENTAL PULP

A study suggested that adipose CD31 side population cells yielded the same amount of regenerated pulp tissue as dental pulp derived cells in the pulpectomized root canals of dogs.<sup>[6]</sup> This tissue had similar qualitative and quantitative patterns of mRNA expression characteristic of dental pulp.

#### TOOTH REGENERATIVE POTENTIAL OF ADSCS

We found only one animal study in which *in vivo* and *in vitro* comparisons showed that both ADSCs than dental pulp SCs regenerated the tooth with nerves and vascular system similar to a normal tooth.<sup>[11]</sup>

## DISCUSSION

The results from the included studies indicate that ADSCs have the potential to regenerate the bone, PDL, cementum, and pulp. The bone was the most common tissue regenerated in the included studies. Different

scaffolds in combination with ADSCs resulted in greater osteogenic differentiation. The PLGA scaffold had interconnected pores and larger pore size that promoted cell ingrowth.<sup>[4]</sup> Likewise, Gelfoam seeded with ADSCs created a three-dimensional environment that favored bone formation.<sup>[28]</sup> The scaffold of human amniotic membrane had inherent growth factors that enhanced bone regeneration.<sup>[7,17]</sup> The bovine bone and biphasic HA/ $\beta$ -TCP ADSCs were osteoconductive.<sup>[9,23,29]</sup> Furthermore, ADSC-derived exo produced greater osteogenesis due to reduced miR-223 expression.<sup>[24,37]</sup>

Besides the scaffold, the DMCs and bioactives like BMP-2, PRF, and semaphoring-A increased the osteogenic differentiation of ADSCs.<sup>[18,19,25,34]</sup> The BMP-2 is osteoinductive, and PRF is rich in various growth factors, whereas semaphorin A is osteoprotective protein which promotes osteogenesis.<sup>[18,19,25]</sup> The property of ADSCs to differentiate into the bone may be successfully applied in the management of fenestration around the implants and periodontal disease defects.<sup>[19,25]</sup> Their ability to regenerate cementum was related to the Wnt/ $\beta$ -catenin signaling in DFC-CM microenvironment.<sup>[33]</sup> The addition of DMC to the ADSCs increased the expression levels of the dentinogenic markers like dentine sialophosphoprotein and dentine matrix protein-1.<sup>[34]</sup> They also showed tooth and pulp regeneration ability in animal models.<sup>[6,11]</sup>

Although the present review reinstates the role of ADSCs in regeneration of alveolar bone, PDL, cementum, and pulp, the outcomes cannot be generalized as most of these studies involved animal models with unclear risk of bias. Therefore, further well-designed human trials

are recommended to verify the roles of ADSCs in regenerative dentistry.

## CONCLUSION

The ADSCs are promising SCs for regenerative dentistry. Their ability to regenerate the alveolar bone has been thoroughly investigated in the animal models, the human trials, and *in vitro* studies. However, there is a need to explore their role in regeneration of PDL and cementum. At present, the information is scarce and there is a need to investigate their effects through *in vivo* studies in humans.

## ACKNOWLEDGEMENTS

None.

## FINANCIAL SUPPORT AND SPONSORSHIP

Nil.

## CONFLICTS OF INTEREST

There are no conflicts of interest.

## AUTHORS CONTRIBUTIONS

Authors equally contributed to the paper.

## ETHICAL POLICY AND INSTITUTIONAL REVIEW BOARD STATEMENT

Not applicable.

## PATIENT DECLARATION OF CONSENT

Not applicable.

## DATA AVAILABILITY STATEMENT

Not applicable.

## REFERENCES

- Sharpe P. Regenerative dentistry. *Front Dent Med* 2020;1:3.
- Chu DT, Nguyen Thi Phuong T, Tien NLB, Tran DK, Minh LB, Thanh VV, *et al.* Adipose tissue stem cells for therapy: An update on the progress of isolation, culture, storage, and clinical application. *J Clin Med* 2019;8:917.
- Storti G, Sciola MG, Kim BS, Orlandi A, Cervelli V. Adipose-derived stem cells in bone tissue engineering: Useful tools with new applications. *Stem Cells Int* 2019;2019:3673857.
- Akita D, Morokuma M, Saito Y, Yamanaka K, Akiyama Y, Sato M, *et al.* Periodontal tissue regeneration by transplantation of rat adipose-derived stromal cells in combination with PLGA-based solid scaffolds. *Biomed Res* 2014;35:91-103.
- Akita D, Kano K, Saito-Tamura Y, Mashimo T, Sato-Shionome M, Tsurumachi N, *et al.* Use of rat mature adipocyte-derived dedifferentiated fat cells as a cell source for periodontal tissue regeneration. *Front Physiol* 2016;7:50.
- Ishizaka R, Iohara K, Murakami M, Fukuta O, Nakashima M. Regeneration of dental pulp following pulpectomy by fractionated stem/progenitor cells from bone marrow and adipose tissue. *Biomaterials* 2012;33:2109-18.
- Akhlaghi F, Hesami N, Rad MR, Nazeman P, Fahimipour F, Khojasteh A. Improved bone regeneration through amniotic membrane loaded with buccal fat pad-derived MSCs as an adjuvant in maxillo-mandibular reconstruction. *J Craniomaxillofac Surg* 2019;47:1266-73.
- Han Y, Li X, Zhang Y, Han Y, Chang F, Ding J. Mesenchymal stem cells for regenerative medicine. *Cells* 2019;8:886.
- Pieri F, Lucarelli E, Corinaldesi G, Aldini NN, Fini M, Parrilli A, *et al.* Dose-dependent effect of adipose-derived adult stem cells on vertical bone regeneration in rabbit calvarium. *Biomaterials* 2010;31:3527-35.
- Aziz Aly LA, El-Menoufy H, Hassan A, Ragae A, Atta HM, Roshdy NK, *et al.* Influence of autologous adipose derived stem cells and PRP on regeneration of dehiscence-type defects in alveolar bone: A comparative histochemical and histomorphometric study in dogs. *Int J Stem Cells* 2011;4:61-9.
- Hung CN, Mar K, Chang HC, Chiang YL, Hu HY, Lai CC, *et al.* A comparison between adipose tissue and dental pulp as sources of MSCs for tooth regeneration. *Biomaterials* 2011;32:6995-7005.
- Tobita M, Uysal CA, Guo X, Hyakusoku H, Mizuno H. Periodontal tissue regeneration by combined implantation of adipose tissue-derived stem cells and platelet-rich plasma in a canine model. *Cytotherapy* 2013;15:1517-26.
- Pourebahram N, Hashemibeni B, Shahnasari S, Torabinia N, Mousavi B, Adibi S, *et al.* A comparison of tissue-engineered bone from adipose-derived stem cell with autogenous bone repair in maxillary alveolar cleft model in dogs. *Int J Oral Maxillofac Surg* 2013;42:562-8.
- Liang L, Song Y, Li L, Li D, Qin M, Zhao J, *et al.* Adipose-derived stem cells combined with inorganic bovine bone in calvarial bone healing in rats with type 2 diabetes. *J Periodontol* 2014;85:601-9.
- Murakami M, Hayashi Y, Iohara K, Osako Y, Hirose Y, Nakashima M. Trophic effects and regenerative potential of mobilized mesenchymal stem cells from bone marrow and adipose tissue as alternative cell sources for pulp/dentin regeneration. *Cell Transpl* 2015;24:1753-65.
- Bressan E, Botticelli D, Sivolella S, Bengazi F, Guazzo R, Sbricoli L, *et al.* Adipose-derived stem cells as a tool for dental implant osseointegration: An experimental study in the dog. *Int J Mol Cell Med* 2015;4:197-208.
- Wu PH, Chung HY, Wang JH, Shih JC, Kuo MY, Chang PC, *et al.* Amniotic membrane and adipose-derived stem cell co-culture system enhances bone regeneration in a rat periodontal defect model. *J Formos Med Assoc* 2016;115:186-94.
- Fang K, Song W, Wang L, Xu X, Tan N, Zhang S, *et al.* Semaphorin 3A-modified adipose-derived stem cell sheet may improve osseointegration in a type 2 diabetes mellitus rat model. *Mol Med Rep* 2016;14:2449-56.
- Xu L, Sun X, Bai J, Jiang L, Wang S, Zhao J, *et al.* Reosseointegration following regenerative therapy of tissue-engineered bone in a canine model of experimental peri-implantitis. *Clin Implant Dent Relat Res* 2016;18:379-91.
- Demirel S, Yalvac ME, Tapsin S, Akyuz S, Ak E, Cetinel S, *et al.* Tooth replantation with adipose tissue stem cells and fibrin sealant: Microscopic analysis of rat's teeth. *SpringerPlus* 2016;5:656.
- Godoy Zanicotti D, Coates DE, Duncan WJ. In vivo bone regeneration on titanium devices using serum-free grown adipose-derived stem cells, in a sheep femur model. *Clin Oral Implants Res* 2017;28:64-75.
- Lemaitre M, Monsarrat P, Blasco-Baque V, Loubières P, Burcelin R, Casteilla L, *et al.* Periodontal tissue regeneration using syngeneic adipose-derived stromal cells in a mouse model. *Stem Cells Transl Med* 2017;6:656-65.
- Shafieian R, Matin MM, Rahpeyma A, Fazel A, Sedigh HS, Nabavi AS, *et al.* Effects of human adipose-derived stem cells

- and platelet-rich plasma on healing response of canine alveolar surgical bone defects. *Arch Bone Jt Surg* 2017;5:406-18.
24. Mohammed E, Khalil E, Sabry D. Effect of adipose-derived stem cells and their exo as adjunctive therapy to nonsurgical periodontal treatment: A histologic and histomorphometric study in rats. *Biomolecules* 2018;8:167.
  25. Ding L, Tang S, Liang P, Wang C, Zhou PF, Zheng L. Bone regeneration of canine peri-implant defects using cell sheets of adipose-derived mesenchymal stem cells and platelet-rich fibrin membranes. *J Oral Maxillofac Surg* 2019;77:499-514.
  26. Venkataiah VS, Handa K, Njuguna MM, Hasegawa T, Maruyama K, Nemoto E, *et al.* Periodontal regeneration by allogeneic transplantation of adipose tissue derived multi-lineage progenitor stem cells *in vivo*. *Sci Rep* 2019;9:921.
  27. Jin Q, Yuan K, Lin W, Niu C, Ma R, Huang Z. Comparative characterization of mesenchymal stem cells from human dental pulp and adipose tissue for bone regeneration potential. *Artif Cells Nanomed Biotechnol* 2019;47:1577-84.
  28. Wofford A, Bow A, Newby S, Brooks S, Rodriguez R, Masi T, *et al.* Human fat-derived mesenchymal stem cells xenogenically implanted in a rat model show enhanced new bone formation in maxillary alveolar tooth defects. *Stem Cells Int* 2020;2020:8142938.
  29. Prins HJ, Schulten EA, Ten Bruggenkate CM, Klein-Nulend J, Helder MN. Bone regeneration using the freshly isolated autologous stromal vascular fraction of adipose tissue in combination with calcium phosphate ceramics. *Stem Cells Transl Med* 2016;5:1362-74.
  30. Khojasteh A, Kheiri L, Behnia H, Tehranchi A, Nazeman P, Nadjmi N, *et al.* Lateral ramus cortical bone plate in alveolar cleft osteoplasty with concomitant use of buccal fat pad derived cells and autogenous bone: Phase I clinical trial. *Biomed Res Int* 2017;2017:6560234.
  31. Broccaioli E, Niada S, Rasperini G, Ferreira LM, Arrigoni E, Yenagi V, *et al.* Mesenchymal stem cells from bichat's fat pad: *In vitro* comparison with adipose-derived stem cells from subcutaneous tissue. *Biores Open Access* 2013;2:107-17.
  32. Niada S, Ferreira LM, Arrigoni E, Addis A, Campagnol M, Broccaioli E, *et al.* Porcine adipose-derived stem cells from buccal fat pad and subcutaneous adipose tissue for future preclinical studies in oral surgery. *Stem Cell Res Ther* 2013;4:148.
  33. Liu N, Gu B, Liu N, Nie X, Zhang B, Zhou X, *et al.* Wnt/ $\beta$ -catenin pathway regulates cementogenic differentiation of adipose tissue-deprived stem cells in dental follicle cell-conditioned medium. *PLoS One* 2014;9:e93364.
  34. Davies OG, Cooper PR, Shelton RM, Smith AJ, Scheven BA. A comparison of the *in vitro* mineralisation and dentinogenic potential of mesenchymal stem cells derived from adipose tissue, bone marrow and dental pulp. *J Bone Miner Metab* 2015;33:371-82.
  35. Szepesi Á, Matula Z, Szigeti A, Várady G, Szalma J, Szabó G, *et al.* *In vitro* characterization of human mesenchymal stem cells isolated from different tissues with a potential to promote complex bone regeneration. *Stem Cells Int* 2016;2016:3595941.
  36. Sari DS, Maduratna E, Latief FDE, Nugraha AP, Sudiana K, Rantam FA; Osteogenic differentiation and biocompatibility of bovine teeth scaffold with rat adipose-derived mesenchymal stem cells. *Eur J Dent* 2019;13:206-12.
  37. Du W, Su L, Zhang N, Wang H. Exosomes derived from preadipocytes improve osteogenic differentiation, potentially via reduced miR-223 expression. *Mol Med Rep* 2019;19:951-8.
  38. Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE'S risk of bias tool for animal studies. *BMC Med Res Methodol* 2014;14:43.
  39. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, *et al.* *Cochrane Handbook for Systematic Reviews of Interventions | Cochrane training [Internet]. Cochrane Handb Syst Rev Interv version 6.02019 [cited February 1, 2021]. Available from: <https://training.cochrane.org/handbook/current>.*