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Review article

Induced pluripotent stem cells in periodontal reconstructive therapy: A narrative review of pre-clinical studies

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ABSTRACT

Background: *Regenerative periodontal surgical therapy faces significant challenges due to the limited ability of the body to regenerate damaged periodontal tissue. One of the primary goals in regenerative periodontal therapy is regaining periodontal tissue attachment after destruction by periodontal disease. Currently, stem cells, harnessing three pivotal components—cells, biomaterials, and growth factors—are widely used in periodontal regeneration. Stem cells can be obtained from various sources, either by isolating cells from bone marrow, teeth, and muscles or through the somatic cell programming method (reprogramming) known as induced pluripotent stem cells (iPSCs).* **Purpose:** *This review aims to describe the potential use of iPSCs in the treatment of periodontal defects.* **Review:** *Search strategies were developed using the PubMed, LILACS, Scielo, and Wiley online databases during the period of 2012–2022. Ten articles met the inclusion criteria. iPSCs were obtained by inducing somatic cells from both dental and non-dental sources with factors Oct3/4, Sox2, Klf4, and c-Myc. Periodontal tissue regeneration procedures can be augmented with iPSCs. Unlike tooth-based stem cells, iPSCs offer several advantages, such as unlimited cell sources and the capability to differentiate into any cell type, including periodontal tissue. The potential of iPSCs extends to correcting periodontal bone defects and forming new periodontal tissues, such as alveolar bone, cementum, and periodontal ligament. However, iPSCs do have limitations, including the need for clinical trials, cell programming production facilities, and optimization of differentiated-cell functionality.* **Conclusion:** *The combined use of iPSCs in cell-based tissue engineering holds vast potential for future periodontal treatment strategies.*

Keywords: *induced pluripotent stem cells (iPSCs); periodontal defect; periodontal regeneration; dentistry; medicine*
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INTRODUCTION

Therapies for treating periodontal disease are constantly evolving. Periodontal disease is an inflammatory condition that affects the periodontium, including the supporting bone, leading to aesthetic and functional disturbances. The goal of periodontal therapy is to ensure the complete biological restoration of all periodontal components—cementum, gingiva, alveolar bone, and periodontal ligament (PDL)—in both architectural and functional aspects.[1] Nowadays, therapy with conventional techniques for repairing periodontal defects still faces limitations in regenerating the periodontal structure as a whole.[2]

Since three decades ago, the principle of periodontium regeneration has been developed.[3] Regenerating a periodontal part can be achieved by substituting alveolar bone defects with bone graft biomaterials, the use of barrier membranes for guided tissue regeneration, and the use of bioactive molecules.[4–6] The emergence of the concept of tissue regeneration came with the functioning of one biological component, such as cells. This has led to the claim that cell-based therapy in periodontal regeneration can potentially repair and regenerate periodontal defects.[7] Cell-based therapy using stem cells has been utilized in tissue regeneration due to their ability to form new periodontal tissues.[8] However, the limited sources of these cells and the technological

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investment required for patient application make this therapy complicated.[9]

Stem cells are undifferentiated cells capable of self-renewal and differentiation into multiple lineages.[10] These cells can proliferate and produce daughter stem cells, while their progeny has the potential to differentiate into a wider variety of specific cell types.[9] Currently, stem cells have been isolated from various tissues and have been characterized accordingly.[11]

Generally, there are three categories of stem cells: embryonic stem cells (ESCs), adult stem cells, and induced pluripotent stem cells (iPSCs).[9] The iPSCs are developed through the genetic manipulation of somatic cells.[12] Compared to ESCs, iPSCs are relatively safe to use and do not pose ethical concerns in their application.[13] Promising in their potential, iPSCs are considered safe stem cell sources with characteristics akin to other stem cell types.[12] Through reprogramming, somatic cells can revert to their pluripotent state. This reprogramming results in the generation of iPSCs that are functionally similar to ESCs. iPSCs demonstrate ESC-like properties, exhibiting the expression of markers such as SSEA-4, TRA-1-60, Nanog, Oct4, and Sox2.[14] Additionally, Yan et al. found that the source of iPSCs could also be achieved by reprogramming other stem cell/progenitor types like stem cells from apical papilla (SCAP), stem cells exfoliated deciduous (SHED) teeth, and dental pulp stem cells (DPSCs).[14]

Several studies suggest that iPSCs have properties comparable to ESCs in terms of gene expression profile, cell morphology, proliferation ability, and differentiation capacity.[12] However, their behaviors can be unpredictable due to genetic manipulation. Furthermore, iPSCs may exhibit tumorigenic properties and malignant transformation, posing safety challenges in their use for regenerative therapy.[15,16]

In various studies, iPSCs have been demonstrated to be capable of producing periodontal tissues such as cementum, periodontal ligament, alveolar bone, and gingiva.[8,17–19] Periodontal tissue regeneration is a complex healing cascade that stems from coordinated interactions between stem cells, biomaterials, and the host immune system.[20] Due to their unlimited source from somatic cells, fewer ethical implications compared to ESCs, and vast differentiation potential, iPSCs present a promising avenue for regeneration. This scoping review aims to describe the potential of iPSCs in assisting periodontal tissue regeneration at the pre-clinical stage, positioning them as one of the most important interaction components in periodontium regeneration therapy.

REVIEW

Searching Protocol Through Academic Databases

The search for article data was carried out comprehensively, limiting the search period to a range of 10 years (2012–2022). Data searches were conducted using the PubMed, LILACS, Scielo, and Wiley Online Library electronic databases (Table 1). Access was obtained by entering search terms using keywords from MeSH. The initial search on the online databases yielded 580 publications from Wiley, 47 articles from PubMed, 13 publications from LILACS, and 7 articles from Scielo.

Table 1. Keywords and synonyms for database searching

Database Sources	MeSH/Keywords	Synonym	MeSH/Keywords	Synonym	MeSH/Keywords	Synonym
Pubmed	Induced Pluripotent Stem Cell	Human Induced Pluripotent Stem Cells hiPSC IPS Cell Induced Pluripotent Stem Cell	Periodontal tissue	Periodontal ligaments Alveolodental Membrane Alveolar bone Cementum Gingiva	Periodontal tissue engineering Periodontal-guided tissue regeneration	-
Wiley	Induced Pluripotent Stem Cell	Human Induced Pluripotent Stem Cells hiPSC IPS cell	Periodontal tissue	Periodontal ligaments Alveolar bone Cementum Gingiva	Periodontal tissue engineering Periodontal-guided tissue regeneration	-
LILLAC	Induced Pluripotent Stem Cell	-	Periodontal tissue	Periodontal ligaments Alveolar bone Cementum Gingiva	Periodontal tissue engineering Periodontal-guided tissue regeneration	-
Scielo	Induced Pluripotent Stem Cell	Human induced pluripotent stem cell Human iPSC iPS cell	Periodontal tissue	Periodontal ligaments Alveolar bone Cementum Gingiva	Periodontal-guided tissue regeneration	-

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Inclusion Criteria

The database search results were manually selected based on downloadable full-text publications, eliminating duplicates and book chapters. The obtained manuscripts were further analyzed to identify research that aligned with the inclusion criteria. The inclusion criteria for this narrative review were as follows: first, articles available in full text and in English; second, pre-clinical research published in journals from January 2012 to March 2022; third, articles (both prospective and retrospective studies) that discussed periodontal tissue regeneration; fourth, research articles using cell cultures (in vitro) and experiments on animals (in vivo). The total search yielded 647 articles. After sorting based on the inclusion criteria, 10 studies remained (Figure 1).

Exclusion Criteria

Exclusion criteria encompassed all studies that did not meet the inclusion criteria. This included research conducted on humans or in clinical phases, narrative review articles, article reviews, meta-analyses, books, and chapters. After selecting articles based on the inclusion criteria, all abstracts and full texts were downloaded, evaluated, and identified to serve as material for this narrative review. The recorded data from the selected articles included the title, author, year of publication, and types of periodontal cells. These data were then incorporated into this review.

DISCUSSION

For regeneration therapy in periodontal defects, iPSCs serve as a sophisticated stem cell source. These cells boast a vast capacity to differentiate into a wide array of tissue types. The preference for stem cells over other cell types is based on their ability to have a high rate of re-application in order to achieve a specific tissue volume and the differentiation of cells into the desired type, making them especially suitable for targeted application purposes.[9] Several studies have indicated that mesenchymal cells derived from iPSCs are capable of addressing periodontal defects.[8,18,19] Indeed, these cells have demonstrated the potential to develop into dental tissue structures.[21–23] As a result, iPSCs can be used in cell-based therapy, undergoing transdifferentiation towards specific target cells.

Source of iPSCs

Differentiated cells can be reprogrammed into iPSCs that share many properties with ESCs.[24] Subsequently, certain markers were identified as potential variables for the reprogramming of cells to produce iPSCs. By transducing somatic cells with a variety of transcription factors, including Sox2 (sex-determining region Y), Oct4/3 (octamer-binding transcription factor 4/3), c-Myc (Avian Myelocytomatosis), and Klf4 (Kruppel-like factor 4), iPSCs are generated.[12] At the cellular level, iPSCs are similar to

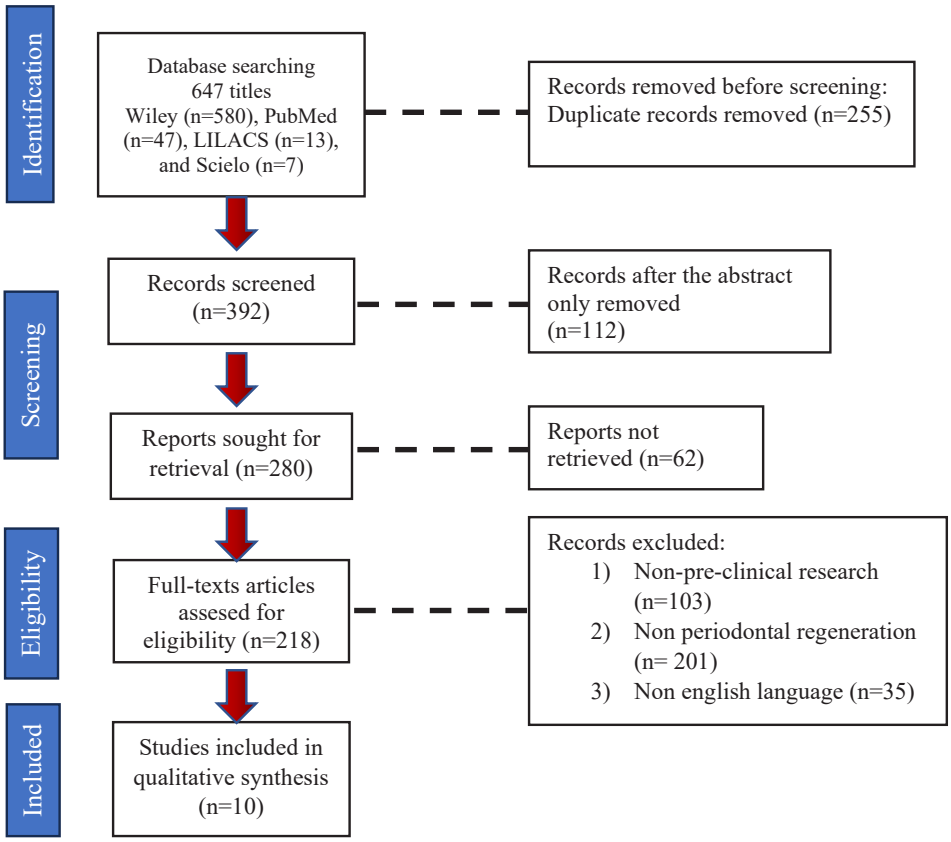

Figure 1. PRISMA flow diagram showing the process of study search, selection, inclusion, and exclusion. This illustrates the mechanism of searching for article data through PubMed, Wiley, LILACS, and Scielo databases.

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ESCs due to their propensity for self-renewal and extensive differentiation potential. Furthermore, both Takahashi et al. and Nakagawa et al. made attempts to generate human fibroblast-derived iPSCs. While iPSCs present significant potential for cell therapy, their genetic stability remains a concern.

Several types of adult cells can be used to obtain iPSCs, with the majority being derived from fibroblasts from both animals and humans (Table 2). Research has shown that iPSCs derived from dental cells (specifically dental-derived mesenchymal-like stem cells) are more effective than somatic cells such as skin fibroblasts and adult MSCs.[14] At present, human gingival fibroblasts (hGFs) are considered a promising source of iPSCs and are expected to be a valuable cell source for regenerative therapies in dentistry.[29]

Apart from mature fibroblast cells, iPSCs can also be obtained from other types of stem cells, such as SHED, SCAP, and DPSCs. Human blood cells offer an alternative source of iPSCs through the isolation of peripheral blood mononuclear cells (PBMCs).[28] Takahashi et al.[12] reported

Table 2. Sources of iPSCs derived from somatic cells and dental stem cells

Authors	iPSC Sources	Methods of Reprogramming	Methods	Results
Choi et al.[25]	Human gingival fibroblasts (hGFS)	Reprogramming by factor transduction using Sendai virus	In Vitro	hGF-iPSCs express pluripotent cell markers, and their characteristics and morphology are similar to human embryonic stem cells (ESCs).
Okawa et al.[26]	Mouse Gingival Fibroblast	Retroviral using Oct3/4, Sox2, and Klf4 factors (without c-Myc)	In Vitro	Mouse GF-iPSCs can act as osteoinductive scaffold-free in 3D cell constructs.
Egusa et al.[27]	Mouse gingival fibroblasts Human gingival fibroblasts (hGFs)	Using factors Oct3/4, Sox2, Klf4 (without c-Myc)	In Vitro	iPSC cells have features and morphology similar to human embryonic stem cells (hESCs) and express ES-specific genes.
Yan et al.[14]	Stem cells from exfoliated deciduous (SHED) teeth Stem cells from apical papilla (SCAP) Dental pulp stem cells (DPSCs)	Reprogramming using viral vector	In Vitro	iPSCs formed express markers SSEA-4, TRA-1-60, TRA-1-80, TRA-2-49, Nanog, Oct4, and Sox2. They resemble hESCs but can form embryoid bodies in vitro and teratomas in vivo.
Vlahos et al.[28]	Peripheral blood mononuclear cells (PBMCs)	Reprogramming factors POU5F1 (Oct4), Sox2, Klf4, and Myc by Sendai viruses	In Vitro	iPSCs exhibit a normal karyotype and express pluripotent markers.

Table 3. iPSCs used in periodontal regeneration

Authors	Description	Part of Periodontal Restoration	Methods
Duan et al.[8]	The combination of mouse iPSC with EMD can improve the healing of periodontal defects.	Cementum Alveolar bone Periodontal ligament	In Vivo (Mouse model)
Hamano et al.[19]	Periodontal ligaments derived from iPS-Neural Crest (iPS-NC) cultures express typical markers of PDL. iPS-PDL-NC is highly proliferative and multipotent.	Periodontal ligament	In Vitro (Inducing iPS-NC with ligament-like cells)
Yin et al.[17]	iPSC-MSCs demonstrate a high ability to differentiate into periodontal tissues using recombinant growth/differentiation factor-5 GDF-5 (rhGDF-5). Increased expression of Osteocalcin, periostin, and cementum attachment protein (CAP).	Potential for periodontal differentiation, namely cementum, alveolar bone, periodontal ligament	In vitro and in vivo (Inducing iPSC-MSCs with ECM from primary human PDL cells)
Sheyn et al.[34]	MSCs produced from iPSCs are more effective at regenerating bone defects in mice than MSCs derived from bone marrow. iPSC-derived MSCs have a self-renewal capacity without being tumorigenic.	Bone	In Vivo (Radial defect in mice)
Chien et al.[18]	The synergistic effect of iPSCs and BMP-6 increases bone and cementum formation. Hydrogels with iPSCs-BMP-6 show bone formation, periodontal ligament, and reduced inflammatory cytokines.	Alveolar bone Periodontal ligament cementum	In vitro (by using Hydrogel) and In vivo (rat periodontal defect)
Liu et al.[35]	Bone tissue engineering technique with iPSC-MSCs on calcium phosphate cement (CPC) immobilized with RGD.	Enhancement of bone matrix mineralization and osteogenic differentiation	In Vitro (iPSC-MSC seeding on RGD-CPC scaffold)

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generating iPSCs from adult human dermal fibroblasts by transfecting them with four pluripotent factors. These human-derived iPSCs share several characteristics with human ESCs, such as similar morphology, proliferation, surface antigens, gene expression, and telomerase activity.

iPSC Used in Periodontal Regeneration

The use of iPSCs in tissue creation enables new treatment methods in the field of regenerative dentistry (Table 3). Cells originating from teeth, gingival fibroblasts, skin fibroblasts, periodontal ligament fibroblasts, and other somatic cells can be used to generate iPSCs.[14,25,26,28] Additionally, when activated with certain stimuli, such as growth factors, iPSCs can develop into periodontal cells. Furthermore, whether combined with or without a scaffold, iPSCs can promote periodontal bone regeneration and the formation of new periodontal tissues, such as alveolar bone, cementum, and periodontal ligament.[8,18,19]

To achieve effective neo-periodontal tissue regeneration, it is essential to understand tissue engineering in clinical applications. Scaffolds are vital components that need to be combined with living cells and/or biologically active molecules. This combination results in 'tissue engineering constructs' that can promote tissue regeneration. The use of scaffolds is crucial for supporting various essential cellular processes and functions, including cell colonization, migration, growth, and differentiation.[30,31]

The regeneration of both tooth structure and its supporting periodontal tissues using stem cells is on the rise. A study conducted by Chai et al.[32] demonstrated success in creating tooth structures using human iPSCs. Tooth development and growth is a complex process involving reciprocal interactions between epithelial and mesenchymal cells originating from the cranial neural crest.[32,33] Research that has been conducted successfully produced iPSC-derived epithelium cells from ifHU (iPSC-ifHU).21 Beyond dental stem cells, there are also opportunities to maximize the use of alternative iPSC sources via DPSCs, SHED, DPSLC, and SCAP.

Another study revealed that periodontal tissue regeneration can be achieved by using MSCs derived from iPSCs. MSCs produced from these iPSCs have been shown to be capable of repairing periodontal deficiencies in mice. Implantation of the MSC cells resulted in a significant increase in mineralized tissue in the defect.[36] Additionally, the same researchers found that orally administered iPSC-MSCs can alleviate inflammation and further bone damage induced by *Porphyromonas gingivalis* in vivo.[37]

Another study found that when iPSCs are treated in a specific manner, they can lead to the generation of specific periodontal cells through growth/differentiation factor-5 (GDF-5).[17] Yin et al.[17] demonstrated the in vitro and in vivo differentiation of BMMSCs and iPSC-MSCs into periodontal tissue-specific lineages. GDF-5 promotes periodontal tissue regeneration and plays a pivotal role in the development of iPSCs into MSCs. In vivo, iPSC-MSCs encapsulated in a hydrogel of hyaluronic acid (HA) can promote periodontal-specific differentiation by expressing high levels of OCN, periostin, and CAP (cementogenesis). Periostin is a vital marker in the development of the periodontal ligament. Periostin (POSTN), a secretory matrix protein also known as osteoblast-specific factor-2 (Osf-2), plays an essential role in the rebuilding of PDL tissue.[38] Periostin has been demonstrated to enhance the migration, proliferation, and differentiation of Human Periodontal Ligament Mesenchymal Stem Cells (hPDL-MSC).[38] Yang et al.[39] determined another function of iPSCs, showing that the expression of iPSC-MSCs can mitigate inflammation in periodontitis and curtail alveolar bone resorption. BMP-6 and iPSC-hydrogel complex injections have been shown to repair periodontal tissue abnormalities in mice.[18]

While the use of iPSCs has been confirmed to regenerate alveolar bone, cementum, and periodontal ligament, its application to gingival defects has not been extensively studied. Instead, gingival fibroblasts have emerged as a promising source for iPSC production. The potential of GMSCs offers an alternative to addressing periodontal defects, especially in gingival tissue.[40] In vivo, GMSCs contain precursor cells that can differentiate into gingival cells. Li et al.[40] found that transplanting human GMSCs into the gingival defects of mice led to the formation of new, normal gingival tissue during the healing process.

Periodontal Regenerative Therapy

Periodontium has a unique, complex architecture that supports the teeth. When performing artificial periodontal tissue regeneration therapy, there are still limitations that remain unpredictable, even with the aid of stem cell transplantation. Currently, there have not been many studies using combinations of stem cells, especially of the iPSC type, in the tissue engineering field to form neo-periodontal tissue. The concept of restoring periodontal tissue structure using stem cells has seen numerous developments.[41] Several approaches have been developed, such as periodontal tissue engineering through in vitro cell material design and the utilization of endogenous stem cells in in-vivo cell-material interaction.[1]

Numerous studies have demonstrated the potential for tissue regeneration when stem cells are combined with biomaterials. For instance, it is hypothesized that the tissue engineering approach using the "sandwich" technique can construct new periodontal structures.[42] Additionally, tests involving the use of composite sheets with cell implantation of periodontal ligament stem cells (PDLSC) and/or Bone marrow mesenchymal stem cells (BMMSC) have shown the capability to regenerate complex periodontium-like structures in vivo.[43]

In therapeutic settings, stem cell therapy can be combined with a variety of other techniques, including cell sheeting, spheroid culture, electrospinning, and 3D printing.[44–47] Each technique offers a number of pros and cons. Cell sheeting requires a longer culture time and is extremely costly, but its use can help sustain and decrease

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cell loss. Electrospinning has the advantage of producing an extracellular matrix-like structure, but it also expedites the decomposition of the material, which is challenging to manage. Advanced technology allows operators to incorporate 3D printing into biomedical applications where the scaffold created is tailored to the defect's needs. However, the reinforcement process, which generates relatively high temperatures in materials, restricts the use of 3D printing.[48] The clinical applicability of iPSCs remains a pressing question; for instance, achieving optimal neovascularization in fresh tissue is still elusive. Consequently, the approach for integrating iPSCs in periodontal regeneration applications needs refinement.

Periodontal therapy can also enhance cellular responses in the body by directing them to the injury site, a phenomenon termed cell homing. This process involves guiding endogenous cells to the defect site in response to biological cues like growth factors, cytokines, and cell-adhesive molecules.[49] Research by Li et al. highlighted stromal cell-derived factor-1α (SDF-1α) and stem cell factor as pivotal in mobilizing the patient's inherent stem cells for healing.[50]

Unfortunately, there are no studies that apply iPSCs in the human clinical phase. However, iPSCs, as the most advanced type of stem cell, are considered extremely promising for future clinical uses. An ideal source of cells, iPSCs are transgene-free and have a suitable human leukocyte antigen (HLA) sequence, potentially leading to minimal rejection by the recipient body.[51] Additionally, the ability of iPSCs to differentiate indefinitely is an attractive feature for tissue regeneration, particularly in the periodontium. In the future, it will be important to conduct further research into the parameters that govern the differentiation of iPSCs into periodontal cells, paving the way for their implementation in periodontal regeneration therapy.

In conclusion, while the potential for iPSCs to restore periodontal tissue defects is compelling, a better understanding of microenvironmental conditions is essential to optimize cell phenotypes for periodontal-specific cells. Before their clinical application, more research is needed to comprehend the growth properties and developmental potential of these cells. In the future, using iPSCs as a cell-based tissue engineering approach might serve as an alternative strategy for periodontal treatment.

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