

Use of Stem Cells in Periodontal Regeneration and Periodontal Disease

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Abstract

Periodontal disease (PD) is a disease of the gingiva, supporting tissue and alveolar bone caused by chronic inflammation of the gingiva due to long-term plaque and bacteria build-up. PD is the most common cause of tooth loss in adults and plagues public health worldwide. Two distinctions in PD are gingivitis and periodontitis. Gingivitis is mild and reversible whereas periodontitis affects underlying gingival tissue and connective structures, causing significant irreversible damage to your teeth and alveolar bone resulting in tooth loss. While the most common method of treatment for periodontitis is management, gingival regeneration methods have been experimented with. Current regenerative treatments of periodontitis have proven to show moderate improvement but incomplete management of the condition despite extensive experimentation and research efforts. Emerging stem cell research has suggested that stem cell-based therapies can holistically treat periodontitis. Mesenchymal stem cells are multipotent and highly variable with strong differentiation potential. Dental pulp stem cells (DPSCs) and periodontal ligament derived stem cells (PLDSCs) are mesenchymal stem cells and can differentiate into various cell types efficacious for regeneration. Pre-clinical and clinical studies have shown growth and promise in the use of stem cells for periodontal regeneration, providing positive outcomes and improvement of regenerative capacity in multiple facets. Although, there are significant obstacles in the development of stem cell-based therapies in terms of ethical considerations and safety that need to be addressed. Stem cell research is rapidly advancing, proving to have a promising future in oral and public health.

Keywords

Periodontal disease; Periodontal regeneration; Mesenchymal stem cells; Stem cell therapy; Regenerative dentistry.

Abbreviations

- Cementum derived stem cells (CDCs)
- Dental pulp stem cells (DPSCs)

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- Guided tissue regeneration (GTR)
- Mesenchymal stem cells (MSCs)
- Periodontal disease – (PD)
- Periodontal ligament derived stem cells (PDLSCs)
- Photodynamic therapy (PDT)
- Superoxide dismutase (SOD)

Introduction

Periodontal disease is one of the most prevalent oral health conditions in the world and can affect up to 90% of the adult population worldwide, posing significant public health concerns and risks [1]. Periodontal disease has been plaguing the human population for centuries, with evidence in ancient Chinese and Egyptian writings [2].

Periodontal disease is a generalized term for disease characterized by chronic inflammation of the gingiva, supporting tissue, and the alveolar bone. It is the leading cause of tooth loss in adults [2]. Two forms of periodontal disease are gingivitis and periodontitis. Gingivitis can be acute or chronic and is the mildest form of periodontal disease that precedes periodontitis [1]. It is generally characterized by gingival inflammation and caused by bacterial accumulation on the teeth and surface of the gums. A key distinction between gingivitis and periodontitis is gingivitis does not affect underlying supporting structures of the gingiva and teeth or the alveolar bone. It's due to this surface-confined inflammation that gingivitis is considered reversible and treatable [1]. Common gingivitis symptoms include increased redness, swelling, gingival bleeding during oral care such as teeth brushing or flossing and a change in the position of the gingival margin [2]. These symptoms are due to the bacteria plaque and biofilm formation on the surface of the teeth and gingiva. This build-up is specifically located towards the gingival sulcus, the space between the gingiva and the tooth. Plaque build-up is most associated with poor oral hygiene habits. This can be due to lack of patient knowledge on proper technique, crowding of teeth or unusual dental anatomy making it difficult to remove plaque in certain areas. As well as nutritional deficiencies and hormonal changes or imbalances [3]. The disease can be visually diagnosed by a dentist. The common plan of action obtaining regularity in dental visits to reduce inflammation, this is done by scaling and root planning. Depending on the severity of the condition and cause (nutritional deficiencies, hormonal changes, lack of hygienic habits) the treatment plan may vary [3]. Lack of treatment or action to prevent and manage gingivitis may worsen the condition causing progression to periodontitis. Although gingivitis precedes periodontitis it may never progress to the severity of periodontitis in all patients, if managed properly [4].

Periodontitis is a severe form of periodontal disease occurring mostly in adults as a slowly progressive chronic disease. However, rapid progression can be seen in children or older patients dependent on environmental factors, hygiene and treatment. Periodontitis is characterized by a loss of supporting connective tissue and alveolar bone due to a build-up of pathogenic bacteria and biofilm formation. This resulting in a deepened gingival sulcus and increased pocket depth between the gingiva and root of the tooth leading to pain, discomfort, loosening and loss of teeth [1]. Most commonly periodontitis results from harmful microbiota; additional factors such as genetics, lifestyle and habits like alcohol and tobacco

use, HIV, poor nutrition and osteoporosis play a role in disease development. With a significant number of oral bacteria, pathogenic plaque build-up plays a sizable role in disease progression and development and implicates periodontitis in several systemic diseases. Notable conditions include diabetes mellitus, cardiovascular diseases, respiratory conditions, and harmful pregnancy outcomes.

Periodontitis pathophysiology is extremely complex but imperative to understanding the progression and implications of the disease. The oral cavity harbors a diverse population of microbiota that facilitate colonization and can favor bacterial growth and development of disease. In periodontitis specifically, oral bacteria colonize and form a biofilm - a protective matrix composed of polysaccharides and glycoproteins. Biofilms protect microbes, allowing them to thrive and providing them resistance to 1000-1500x more microbial agents than the microbiota itself [5]. Initially, an acquired pellicle is laid on the surface of the teeth consisting of saliva containing proteins and peptides and is bacteria-free [6]. Primary bacterial colonizers form an attachment to the pellicle via interactions between adhesin receptors and proline-rich pellicle proteins forming the biofilm. Coaggregation persists and layers of bacterial deposition form, decreasing the available oxygen and allowing for the colonization of anaerobic bacterial species [5]. This progression is a key indicator of the development of periodontal disease from gingivitis to periodontitis and irreversible oral damage [5]. Innate immune responses are initiated because of the infection and are indicative of the inflammation, bleeding, and swelling seen as periodontal disease symptoms. This immune response provides an explanation for the association between periodontitis and systemic disease, as elevated systemic inflammation and oral inflammation can facilitate bacterial entry into the bloodstream [4].

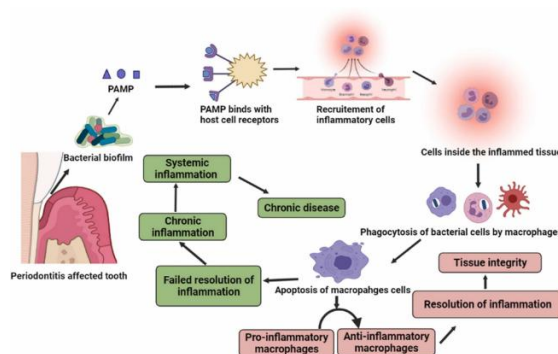


Figure 1: A schematic representation of the inflammatory cascade of periodontal disease progression.

Pathogen associated molecular patterns (PAMP) derived from biofilms, recruit inflammatory cells, triggering an inflammatory response. Bacterial cell phagocytosis occurs as a result. Macrophage apoptosis contributes to pro-inflammatory or anti-inflammatory responses, potentially leading to chronic inflammation and systemic disease.

Source: Jain et al. (2021).

The periodontium is comprised of cementum, the periodontal ligament, alveolar bone and the gingiva [7]. All these structures support the tooth and promote oral health, safety and proper mastication. The gingiva is a soft tissue that covers the alveolar bone and the tooth root to protect function, against mechanical damage and harmful microbiota. Three anatomical distinctions are the marginal, attached and interdental gingiva. The marginal gingiva represents the border surrounding the teeth that forms a collar around the

teeth and the gingival sulcus. The marginal gingiva is useful in periodontitis diagnoses as it can be separated from the tooth using a probe to indicate infection [8]. In healthy human gingiva, the probing depth of the sulcus is 2-3 mm, if the gingiva permits probing deeper than this point it can be an indicator of infection and connective tissue damage due to periodontitis [8]. The attached gingiva is tightly bound to alveolar bone, and its width can be another indication of the presence of periodontal disease. Interdental gingiva refers to the gingiva in the interproximal space, or between two teeth. Structurally, the gingiva consists of epithelial and connective tissue and is differentiated into three components - gingival, sulcular, and junctional. All these components play their own crucial role in oral health and periodontium structure, although junctional epithelium integrity is vital to preserve the periodontium. The junctional epithelium forms a seal to the tooth, protecting it from pathogens and disruptions in the oral cavity [7]. Uniquely, the junctional epithelium is supported by connective tissue containing a significant vascular plexus. The vascular proximity allows inflammatory cells to migrate into the junctional epithelium in case of infection and to the gingival sulcus or place of infection [7]. This proximity may suggest an explanation for the association between systemic disease and periodontal disease.

The second soft tissue associated with the periodontium is the periodontal ligament, composed of specialized vascular connective tissue. The periodontal ligament connects the cementum of the tooth to the inner wall of alveolar bone [8]. The main function of the periodontal ligament is to support and protect teeth through the forces of mastication, reinforce them and maintain proper position through bone attachment. The periodontal ligament is composed of principal fibers in bundles, arranged differently throughout different areas of the ligament [8]. The periodontal ligament is composed of a multitude of cell types, those being osteoblasts and osteoclasts, fibroblasts, epithelial cells, mesenchymal stem cells, cementoblasts and odontoclasts. Most notably, the periodontal ligament contains mesenchymal stem cells, allowing the ligament to repair itself and restore lost bone and cementum [7]. These properties suggest that the periodontal ligament may be a candidate for stem cell transplantation if isolated.

The periodontium is also formed by hard tissue, one of which is the cementum. The cementum is the avascular connective tissue surrounding the tooth root. It functions in protection of the root and attachment to the periodontal ligament fibers. It is calcified and forms the outer covering of the root, consisting of acellular and cellular tissue. The acellular extrinsic cementum has a large amount of periodontal ligament fibers and functions largely in ligament-tooth attachment. The cellular intrinsic cementum functions as a repair tissue and contains cementoblasts that produce collagen. Intrinsic cementum is significantly less mineralized than extrinsic, making it a more dynamic tissue type. Cementum functions to protect the root surface from exposure to pathogens or harmful microbiota [7]. Specifically, the cemento-enamel junction is of clinical relevance. Ideally, the cementum and enamel should overlap - leaving no gap or vulnerability for infection or root exposure [8]. However, when cementum and enamel fail to meet it may expose dentin causing pain and infection. This can be due to gingival recession or genetics.

The final periodontium hard tissue is alveolar bone, which forms sockets for the teeth as they erupt to provide attachment for the periodontal ligament [8]. It consists of an outer cortical plate, the alveolar bone proper which is the inner socket wall and cancellous trabeculae which supports the bone. Like any

bone it is differentiated into the periosteum and endosteum. The periosteum is composed of osteoblasts and osteoprogenitor cells, and blood vessels and nerves with collagen fibers and fibroblasts. The endosteum is composed of a simple layer of osteoblasts [8]. Alveolar bone has a short turnover rate and diminishes to eventual loss if a tooth is lost [7]. So, in the case of periodontitis and tooth loss you are diminishing your alveolar bone in that area.

Periodontitis can diminish and affect each of these periodontium structures. The periodontium protects, supports and stabilizes the teeth, maintaining the necessary oral homeostasis. Its components function together and damage in a single area can jeopardize the integrity of the periodontium. Gingivitis begins in the gingiva. The build-up of plaque, biofilms and harmful bacteria causes inflammation and deepening of the gingival sulcus, that without treatment pockets characteristic of periodontitis. This deepening breaks the seal to the tooth formed by the marginal gingiva and junctional epithelium allowing the penetration of pathogens towards the tooth's root and underlying structures. While infection plays a large role here, the loss of the gingival seal to the tooth forces the periodontal ligament to do additional work to hold the tooth in place during mastication. This damages and degrades the ligament, reducing support and allowing loosening or loss of the tooth as a result. Alveolar bone diminishes because of tooth loss, eradicating a significant portion of the tissue. Bacterial penetration can lead to damaged cementum and an exposed root. Specifically, if the cemento-enamel junction does not meet properly due to gingival recession and exposes dentin to pathogens. The periodontium structures are integrated and interdependent, it is imperative that early infection intervention is sought out.

Clinical diagnosis of periodontitis is dependent on the severity. Diagnosis is generally based on visual observation and assessment. Visual observations assess gingival color, sensitivity, and visual bleeding. A comprehensive periodontal probing procedure is performed to assess pocket depth, the space between the tooth and gingiva or the gingival sulcus. Probing depth deeper than 3mm generally indicates a loss of connective tissue or bone [1]. Additionally, radiography is utilized to assess bone viability and confirm periodontal probing findings [2]. Periodontal disease can often be asymptomatic and will not cause pain but loosening of teeth and gingival bleeding are key indicators of disease development [2].

Most current clinical treatments of periodontitis and periodontal disease are directed at disease management and reducing progression rather than regenerating lost periodontium structure. In mild periodontitis, scaling and planning is done to mechanically remove plaque and smooth the tooth's roots using curettes. If the condition has affected the cementum, scaling and root planning removes bacterially infected cementum. This is an adequate treatment for the disease combined with antibiotics and patient behavior and habitual adjustments if the condition is mild [2]. Open-flap debridement is a surgical approach using incisions allowing access to the tooth root to remove calculus and reduce pocket depth [2]. Photodynamic therapy (PDT) is an additional non-surgical option using a photosensitizing laser activator to eliminate harmful bacteria [10]. While most used treatments are for management purposes, there are some regenerative options using grafts and bioengineered substances. Bone grafts are commonly performed surgically, with multiple variations available using fabricated materials with properties that facilitate natural bone repair. Guided tissue regeneration (GTR) is a periodontal ligament reconstruction option using a polymer membrane to hinder the migration of harmful tissues and cells into

the lesion site. This therapy facilitates a necessary environment for the required regeneration cells to grow [11]. Additionally, autologous platelet concentrates are platelets removed from the patient's own blood. They are rich in growth factors, cytokines, and proteins to allow them to regulate cell proliferation and differentiation, proving a decent option for regenerative therapies [10]. The current treatments of periodontal disease, more specifically periodontitis, are limited by the incomplete management and lack of total regenerative outcomes. Many surgical procedures and treatments target one aspect of periodontal regeneration rather than addressing the total and holistic regeneration of the periodontium and its components.

Discussion

Emerging stem cell research proves to be promising in terms of oral regenerative therapies. Stem cells possess differentiation and self-renewal potential, two key regenerative characteristics. They are highly variable with a large capacity for plasticity. Mesenchymal stem cells (MSCs) specifically, are highly proliferative and can distinguish themselves into distinct cell types [12]. Mesenchymal stem cells originate during the embryonic period and form many oral structures. In many oral regenerative therapies dental pulp stem cells (DPSCs), a type of MSC is used as MSCs form dental pulp, dentin, cementum and the PDL [13]. Dental pulp stem cells are found in the dental pulp, the innermost living tissue of the tooth, meaning they are relatively easily accessible. They can differentiate into cementoblasts, collagen-forming cells and osteoblasts. Additionally, the periodontal ligament contains mesenchymal progenitor cells that have the same self-renewal and differentiation potential. In various pre-clinical studies, they have proven the ability to differentiate into osteogenic cells and precursors of the neural-crest cell. Periodontal ligament stem cells (PDLSCs) are not as easily identifiable as DPSCs, so they must be tested for specific antigenic markers to determine their viability [14]. Both DPSCs and PDLSCs show strong oral regeneration potential in periodontics as mesenchymal stem cells. This is due to their unique ability to differentiate into multiple tissue types, addressing the possibility of a holistic regenerative approach for the periodontium.

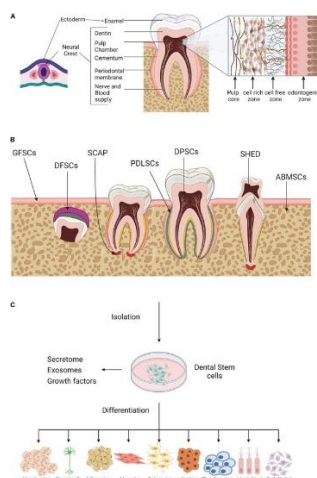


Figure 2: A schematic representation of the anatomical organization of the tooth, including the organization of the dental pulp. Major sources of dental and oral mesenchymal stem cells, and the isolation and differentiation of those stem cell types into varying cells. Source: from Al Madhoun et al. (2021), *Frontiers in Cell and Developmental Biology*, 9, 717624. Al Madhoun et al (2021).

In pre-clinical research regarding stem cells and periodontal regeneration, outcomes have been generally positive and shown improvement compared to current regenerative techniques. In a pre-clinical research trial in Spain, positive outcomes were observed using the implantation of cementum-derived stem cells (CDCs) and periodontal ligament stem cells (PDLSCs). The study involved four male beagles, aged 1 year old. Researchers isolated the healthy canine CDCs and PDLSCs prior to any manipulation of disease or infection, then cultured the cells. Using the same canines, manual intrabony periodontal defects were created and plaque was allowed to build-up to mimic characteristics of severe periodontitis. The cultured CDCs and PDLSCs were seeded into collagen scaffolds for implantation. It is important to note that the implanted cells were autologous, meaning they were implanted into the canine they were extracted from. The implantation effects were measured after 3 months. Clinical measurements of periodontal defects showed significant improvement in both stem cell treatments compared to the control group, reducing all parameters. The parameters being the distance between the alveolar bone crest and the cemento-enamel junction, the base of the intrabony defect, and the buccolingual width of the defect. In both trials involving CDCs and PDLSCs the distance between the alveolar bone crest and the parameter decreased. In this study, a decrease is a positive measurement meaning that the gap or defect was reduced indicating healing and regeneration. The trials' histological findings indicated that the stem cell therapy promoted new attachment of both cementum and new bone as well as connective tissue to root exposed in the manual defect procedure [14]. Findings of this pre-clinical research were overall positive and encouraging for the potential of stem-cell treatment specifically regarding CDCs and PDLSCs in clinical regeneration of periodontal disease.

Clinical research examined provided similar positive outcomes and promise for potential stem cell applications. A human clinical trial evaluated dental pulp micrografts in a collagen scaffold and assessed its potential for regeneration. The randomized trial involved 29 adult subjects suffering from chronic diagnosed periodontitis. The trial subjects had completed nonsurgical periodontal treatment and presented with at least one deep intrabony defect requiring tooth extraction. DPSCs were extracted from the dental pulp of the extracted tooth and seeded into collagen scaffolds to act as micrografts. 15 of the subjects underwent a procedure to fill the damaged periodontium with the DPSC seeded collagen scaffolds, and 14 underwent a procedure to fill the damaged periodontium with collagen scaffolds having no seeding. Parameters were measured after 6 and 12 months. In all parameters relevant to regeneration (clinical attachment level, probing depth, gingival recession, radiographic intrabony defect depth) except for gingival recession, the test distance was less than the control distance at 12 months post-procedure [15]. This indicates that regeneration had taken place. Although, it is important to note that the size difference between groups was not statistically significant for the gingival recession data. Despite the lack of significant data from a gingival recession standpoint, the clinical trial demonstrated strong regenerative capabilities from stem cells in bone, probing depth and attachment level capacities consistent with results seen in the pre-clinical trial.

An additional relevant clinical study performed using DPSCs measured bone density and oxidative stress in the oral cavity. The research trial subjects consisted of 22 adults diagnosed with chronic periodontitis and observed periodontal defects. The DPSCs used in this trial were extracted from three adolescent donors; they were not autologous cells. The intervention treatment here placed a DPSC seeded-collagen

scaffold into the periodontal defect upon exposure after scaling and root planing. Eleven subjects received the treatment, and eleven subjects received just the collagen scaffold without seeding. The results were analyzed 3 and 6 months after the procedure. In terms of clinical parameters, the DPSC treated subjects showed a greater improvement on bone mineral density and the depth of the periodontal defect than the control group. A greater number of DPSC treated subjects also decreased their dental mobility from Grade III to Grade II or I compared to control group subjects, indicating an increase in connective tissue presence. The radiographic and tomographic images reinforced the quantitative data regarding clinical parameters. The trial also investigated oral oxidative stress levels via markers in saliva. The results demonstrated an increase in superoxide dismutase (SOD) levels at a statistically significant level in the subjects treated with DPSCs. SOD protects tissues from harmful free radicals by neutralizing them, an increase in SOD levels means an increase in tissue protection and a potential decrease in tissue damage [13]. Overall, the results of this study are positive indicators for the use of stem cells in oral and periodontal regeneration.

These three clinical trials all demonstrated the regenerative abilities of mesenchymal stem cells, as well as a multitude of other pre-clinical and clinical studies. Despite the difference in type of mesenchymal stem cells between the pre-clinical trial and clinical studies, all three stem cell types (CDCs, PDLSCs, and DPSCs) showed greater regeneration capacity in the treatment than the control group, furthering the hypothesis that stem cells will have an impact on periodontal regeneration capacity. A key material difference between the studies was the use of autologous stem cells versus donor stem cells. In both cases, results indicated they were effective in regeneration and more so than the control group. Although, research needs to be done further on the most effective method of stem cell implantation. An important commonality and observation from clinical studies performed with stem cells is the improvement upon all clinical parameters observed. Meaning, stem cell treatments improved probing (pocket) depth, bone density, clinical attachment, and size of intrabony defects at a significantly greater rate than the control treatment. This is significant as the limitations of current stem cell therapies are their incomplete management of all symptoms. Stem cell therapies improve upon all parameters, whereas a bone graft will only affect bone density or structure. These results are promising for a future holistic approach to treating periodontitis using stem cells.

Despite the implications of stem cell use and results of a multitude of clinical trials and studies there are still significant limitations to stem cell therapies and the studies themselves. In human clinical trials, observation and radiographic evidence is the basis for conclusion. No histological data can be gathered due to ethical reasons, so certainty on regeneration potential is limited. The sample size of the clinical trial is imperative as well, the larger the sample size the greater the ability to generalize to a population. Most clinical studies regarding stem cell therapies have a relatively small sample size due to trial methods and cost limitations making it difficult to generalize the findings and results to a larger population. In addition to the population size limitation, trial length provides similar issues as the greatest study length was 12 months. We cannot generalize the results for long-term use or implications. Finally, and likely the greatest challenge in stem cell research are ethical concerns raised about mesenchymal stem cell use. In many cases to extract stem cells from the mouth, the dental pulp or periodontal ligament, a tooth needs to be extracted. Extracting a healthy tooth has raised ethical concerns. The potential for mesenchymal stem cells to differentiate into unwanted cell types poses a significant challenge and has raised various

additional concerns. Lastly, in the discussed clinical studies all participants were volunteers. This meaning that the patients were somewhat proactive and willing to adhere to hygiene recommendations and make habitual changes beneficial to periodontal regeneration. Dentistry is severely reliant on patient habits and effort. Results of the studies may vary depending on the patient and their motivation to improve their condition.

Current research has presented plenty of positive outcomes, although greater research is needed before stem cell therapies can be used regularly in patients. In the studies examined in this paper, the vessel of implantation for the stem cells was a collagen scaffold. Comparative evaluation of alternative implantation methods may provide valuable insight into the most effective approach. Further comparison of autologous versus donor stem cells could provide additional information regarding the most lucrative option. Similarly, a study comparing the effectiveness of DPSCs, PDLSCs and CDCs, rather than one type with a control group, will indicate the cell with the greatest potential for regeneration. Given the examined studies' limitations, studies observing a larger number of subjects and spanning a greater time are necessary for proper result generalization and regular implementation consideration. A key focus of future research should be on targeting the best approach to stem cell transplantation and therapy; optimizing its regeneration potential rather than further evaluation to determine if regeneration is possible.

Summary and Conclusion

Periodontal disease remains one of the largest public health concerns worldwide, and the leading cause of tooth loss in adults. Periodontitis, a severe form of periodontal disease, has plagued our population for centuries and is irreversible. The irreversible nature of this condition has drawn the attention of stem cell researchers and emerging stem cell research on the topic has shown significant promise. Current periodontitis treatments only partially manage the condition, treating one deficit at a time, rather than addressing periodontium loss. Emerging stem cell therapies provide an opportunity to regenerate deficits in all four components of the periodontium. The periodontium is formed by the alveolar bone, periodontal ligament, cementum and gingiva. These four components work in tandem to maintain oral homeostasis and health, damage to one element disrupts the periodontium. This concept reinforces the importance of the idea of holistic regenerative medicine in the periodontium.

Mesenchymal stem cells provide an opportunity to investigate holistic regeneration, specifically dental pulp stem cells and periodontal ligament derived stem cells in this case. MSCs are well-suited for regenerative medicine due to their highly variable and multipotent capacities. In the examined pre-clinical and clinical studies, the use of stem cell therapies provided a more lucrative regenerative capacity than the control methods. All three studies demonstrated the ability of CDCs, DPSCs and PDLSCs to regenerate multiple clinical parameters at a greater rate than the control collagen scaffold. While each study measured a different variety of clinical parameters, each indicated that stem cells have the potential to improve periodontitis treatments in a significant way. Each study showed an improvement in regeneration in all four components of the periodontium compared to the control group, demonstrating the potential for a holistic regeneration of the periodontium. Despite these positive results and a promising future, ethical concerns and necessary further research are hindering the use of stem cells in regular treatment

of periodontitis. Overall, if stem cell research continues its current trajectory, it is likely to provide a viable alternative to existing regenerative therapies and address the current limitations in periodontitis care and treatment.

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