



GRADUATION PROJECT

Degree in Dentistry

Stem Cell Applications in the Treatment of Dental Pulp and Periodontal Diseases

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ABSTRACT

Introduction: In dentistry, pulp and periodontal disease are the 2 most frequent outcomes of a dental pathogenic process. For decades now, conventional treatment like root canal therapy and periodontal surgery have been efficient in containing the infection but fall short in recovering the lost tissue. Consequently, the dental field has been obliged to turn itself into regenerative procedures capable of promising such recovery of what once has been lost.

Objective: This study aimed to evaluate the effectiveness and long-term benefits of stem cell-based therapies in treating pulp and periodontal diseases compared to traditional methods, while assessing associated risks and clinical outcomes. **Methods:** A systematic review was conducted using PubMed, ResearchGate, and the Journal of Endodontics. Articles were filtered using a 10-year publication range (2014–2024), with inclusion criteria based on study type and relevance to stem cell applications in dentistry. **Results:** From 330 initial records, 11 articles met the inclusion criteria. In periodontics, stem cells particularly PDLSCs and mesenchymal stem cells showed improvements in key factor indicators like depth fill percentage, probing depth and attachment gain. In endodontics, the use of DPSCs and BM-MSCs restored pulp vitality, apical closure, and dentin formation in previously non-vital teeth. **Discussion:** Stem cell therapies demonstrated clear regenerative results. While some studies showed no significant difference compared to conventional approaches, others highlighted superior integration, healing speed, and long-term stability. **Conclusion:** Stem cell-based regenerative therapies show significant promise in the treatment of pulp and periodontal diseases.

KEYWORDS

Dentistry, Stem cells, Periodontics, Endodontics, Regeneration.

ABSTRACTO

Introducción: En odontología, las enfermedades pulpaes y periodontales son las dos consecuencias más frecuentes de un proceso patógeno dental. Durante décadas, tratamientos convencionales como la terapia de conductos y la cirugía periodontal han sido eficaces para contener la infección, pero no logran recuperar el tejido perdido. En consecuencia, el campo odontológico se ha visto obligado a enfocarse en procedimientos regenerativos capaces de prometer la recuperación de lo que alguna vez se perdió. **Objetivo:** Este estudio tuvo como objetivo evaluar la eficacia y los beneficios a largo plazo de las terapias basadas en células madre para tratar enfermedades pulpaes y periodontales en comparación con los métodos tradicionales, además de analizar los riesgos asociados y los resultados clínicos. **Métodos:** Se realizó una revisión sistemática utilizando bases de datos como PubMed, ResearchGate y el *Journal of Endodontics*. Los artículos se filtraron aplicando un rango de publicación de 10 años (2014–2024) y criterios de inclusión basados en el tipo de estudio y su relevancia en aplicaciones de células madre en odontología. **Resultados:** De 330 registros iniciales, 11 artículos cumplieron los criterios. En periodoncia, las células madre especialmente PDLSCs y MSCs mostraron mejoras en indicadores clave. En endodoncia, el uso de DPSCs y BM-MSCs restauró la vitalidad pulpar, el cierre apical y la formación de dentina. **Conclusión:** Las terapias regenerativas con células madre muestran un potencial significativo en el tratamiento de enfermedades pulpaes y periodontales.

PALABRAS CLAVES

Odontología, Células madre, Periodoncia, Endodoncia, Regeneración.

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1. INTRODUCTION

1.1. Regenerative procedures

The term regeneration comes from the Latin term “Regenerare” which means “Create again”; In fact, this biomedical field is related to tissue engineering and research on self-healing. Tissue engineering is “a field that applies the principles of engineering and life sciences towards the development of biological substitutes that restore, maintain or improve the tissue function or a whole organ.”. The objective of regenerative science is to use the autonomy of body systems sometimes with the help of foreign biological material to “create again” and reconstitute tissues and organs. Regenerative science is a multidisciplinary field using the foundations of traditional transplantation and replacing therapies(1). The human body when it reaches adult age is set with a certain number of organs and tissues which some of them can regenerate. Nevertheless, some other parts of the human flesh don’t regenerate, they usually remodel with the amount of tissue left. Regenerative science history debuted by the organ transplantation procedures and more specifically in 1954 by Dr. Joseph Murray when he performed the first organ transplantation (kidney) from one twin to another(1). The procedure, successful as it was raised a good number of questions and set limitations, one of which being the lack of organ availability and the increasing amount of patient needing the procedure (aging population)(1). At the time the incidence of chronic diseases and tissue degradation was on the rise. All of these factors back then created a certain urgency for the rise of regenerative science field(1).

By the time and with the technology available; only 6 years later the researchers from Boston attempted to regenerate skin and cartilage tissue and by the year 2006 the first engineered tissue is implanted (1). Today regenerative procedures are not an isolated field and are the main questions of the medicine of tomorrow.

In dentistry as well, the term regeneration stands for the re-creation of a lost tissue through active processes using body systems to recreate a certain part of the organ which is lost. The most common pathologies in oral mouth are the caries (before 40 years old) and periodontitis (after 40 years old). This process, once active, leads to the irreversible loss of dental tissue which cannot be grown back. Up to the 20th century biomimicking those tissues was the norm, but in the late 50s, the question about regenerating them is still a main subject. Indeed, the technologies evolved and today with the graft of connective tissue or bone from a donor area we might be able to regenerate certain lost tissues, but we still did not find a solution to the lack of organ availability and the increasing amount of demand.

The first regenerative procedures in dentistry started in the 17th century when we were already talking about Vital pulp therapies but it's really by the 20th century and specifically in early 1960s where we acknowledged the work of Dr. Otsby. He investigated the regeneration of necrotic teeth by over-instrumenting them beyond the apex. This procedure is today the premises of "revascularization"(2).

In periodontics, the first treatments for guided tissue regeneration (GTR) were defined by Hurley et al. in the 1950s where they isolated soft tissues from the active regions with a membrane barrier to prove the potential for osteogenesis. By the 1980s was recognized as a proven treatment of periodontal damages(3).

1.1.1. Stem Cells and their origin

Stem cells are cells in the human body defined by the unique ability to self-renew and differentiate into one or more lineage. By such definition they need to be classified and one of the classification methods is based on their differentiation capacity. They spread on from Totipotent where they can give rise to any cell of the body all the way to Unipotent giving rise to only one cell lineage. The classification of stem cells revolves around their capacity to differentiate into one or more lineage, thus being able to regenerate highly differentiated cells. It's upon this basic principle we know today four classes of stem cells, totipotent, pluripotent, multipotent and unipotent. The totipotent stem cells are defined by their capacity to generate embryonic and extra-embryonic (placenta), giving the possibility of creating a whole human body from one cell(4). The multipotent has the same capacity as the totipotent excluding the capacity to generate extra-embryonic cells, marking their incapacity to successfully generate a whole human body(5). The pluripotent stem cells are distinguished from the unipotent by their capacity to generate into all type of cells within one lineage. The Unipotent Cells are only capable to give rise to only one type of cell of a specific lineage, they are the least interesting cells in terms of differentiation potency.

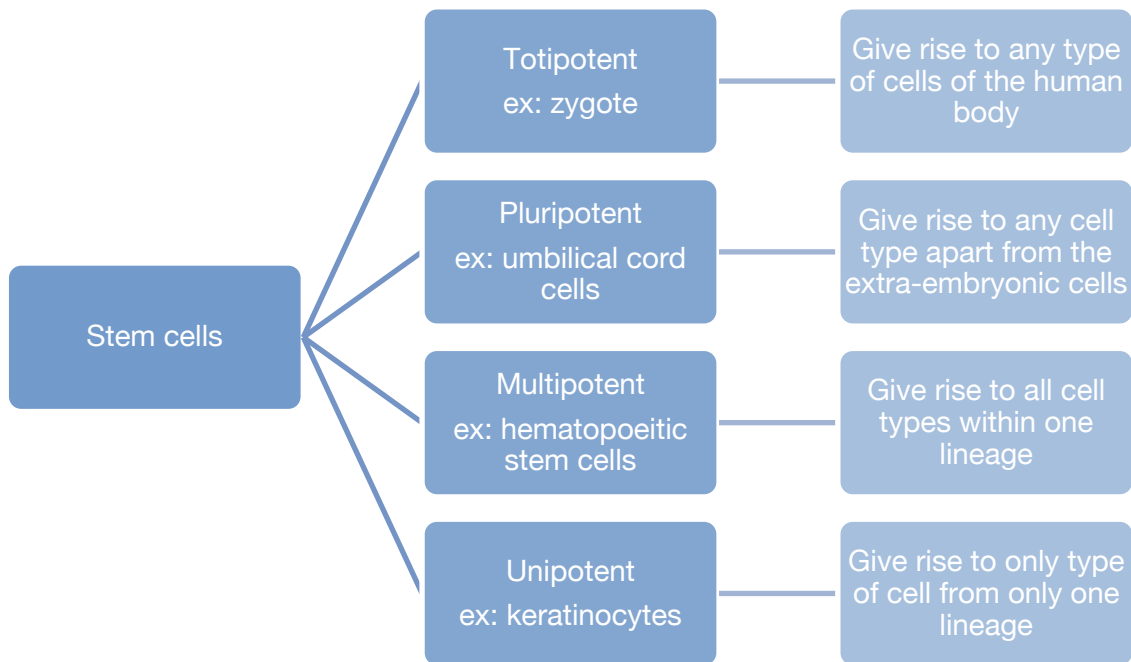


FIGURE 1. The differentiation of Stem Cell Lineage according to their differentiation potential

In Figure 1, the classification of stem cells based on their differentiation potential can be expanded as follows:

1. **Totipotent Stem Cells:** These are the most versatile stem cells, capable of differentiating into any cell type in an organism, including both embryonic and extra-embryonic tissues (e.g., placenta). The zygote and the first few embryonic cells up to the 16-cell morula stage are totipotent.
2. **Pluripotent Stem Cells:** These stem cells can give rise to all cell types within the three germ layers (ectoderm, mesoderm, and endoderm) but lack the ability to develop into extra-embryonic tissues. Examples include embryonic stem cells (ESCs) derived from the inner cell mass of the blastocyst and induced pluripotent stem cells (iPSCs) reprogrammed from somatic cells.
3. **Multipotent Stem Cells:** These cells can differentiate into multiple cell types within a specific lineage. For instance, hematopoietic stem cells (HSCs) can generate all blood cells, while mesenchymal stem cells (MSCs) can differentiate into bone, cartilage, and fat cells.
4. **Oligopotent Stem Cells:** More restricted than multipotent cells, these stem cells can only differentiate into a few closely related cell types. Examples include myeloid and lymphoid progenitor cells, which give rise to specific blood cell lineages.

5. **Unipotent Stem Cells:** *These are the least versatile, as they can only generate one specific cell type but retain self-renewal properties. Examples include muscle stem cells (satellite cells) and epidermal stem cells.*

The first research around the mystery of stem cell was in the mid-1800s by Rudolf Virchow, Rudolf Remak and Theodor Schwann when they discovered cell multiplication and birth through the process of cell division (theory of cell development)(6). The first discoveries on their potential was in the 1950s with a bone marrow transplantation (1956). The International society for Stem cell Research has been created back in 2002 to regulate the ethical research on stem cells and by 2006 the “Guidelines for the conduct of human embryonic Stem cell research” was published(6). Today, Stem cell therapies are trending as they have been indicated for a whole range of treatments going from basic treatments to treat genetic diseases. In fact, they have been announced to be capable of curing certain disease like Parkinson or Alzheimer diseases. One of the other key discoveries of stem cells are their availability and their which finally answers the previous limitations were set back in the 50s. They can be found in the bone marrow (hematopoietic stem cells), amniotic epithelial cells, in the adipose tissue, the umbilical cord or the placental tissues.(7)

1.1.2. Stem Cells and their use in Biomedical field

The whole idea of Stem cells refers to the art of biomimetics which is conventionally recognized as the science of imitating nature. The idea of biomimicking isn't new, as the first relics of dental replacement of lost teeth were fabricated 3500 years ago by the Egyptians(8). The principle stayed the same throughout the centuries with the same idea of recovering the loss of aesthetics and function, but the materials were evolving(8). From human teeth (of cadavers) reimplanted on human livings, animal teeth carved into human teeth shape and size, ivory, gold, and finally porcelain, materials never ceased to try and copy to the perfection the permanent dentition which once was there. Throughout the advancement of technology and science, series of materials and prosthesis have seen rise in the field of dentistry, one of them famously known as implants. Implants are known to be one of the best solutions to remediate the loss of a tooth, biomimicking the root of the tooth through a pillar and the crown by prosthetics arrangements. The term biomimetics though was first used back in 1950s by Otto Herbert Schmitt and referred to the capacity to recopy not just the esthetic of a tooth but also its primary function(9).

The application of stem cell in dentistry is much more recent than in medicine, the theory being introduced by the stomatologist G.L. Feldman (1932) showing the regenerative capacity of dental pulp under certain circumstances(10). The real introduction of Stem cell was in the year 2000 by Gronthos et al. successfully isolating dental pulp regenerating cells in permanent teeth. In dentistry we recognize different types of regeneration-capable cells as Dental Pulp Stem Cells, Stem cells from human exfoliated deciduous teeth (SHED), the Stem cells from Apical papilla (SCAP), bone marrow mesenchymal stem/stromal cells and Periodontal ligament Stem Cells (PDLSCs)(10). All these different types of cells can differentiate themselves into multiple lineages of cells, thus making them the ideal regenerative support system. In the case of SHED cells, Dr Songtao discovered them in 2003 and their capacity to give rise to a variety of cell types like osteoblast-like, odontoblast-like, adipocyte and neural cells(10). Their potential according to Dr Songtao was even greater than the one of Dental Pulp of stem cells (of permanent teeth). According to Dr Sonoyama et al, SCAP cells are capable of producing dentin in vivo (main source of production of root dentin), support apexogenesis and even generate primary odontoblast (10). PDLSCs have the capacity of generating a cementum or periodontal ligament-like structure contributing to the periodontium repair.

Dental Pulp stem cells are mesenchymal cells inside the pulp showcasing osteogenic and chondrogenic capacities, them among other regenerative cells have many advantages : easy surgical access to collection site and low morbidity after dental extraction, the capacity of generation within a determined time period, the ability to be preserved (cryopreservation) and their immunological and anti-inflammatory capabilities for allotransplantation(10). Periodontal ligament stem cells are a multipotent lineage of cells with the capacity to regenerate cementum and periodontal ligament-like structure(10).



Figure 2. Dental Stem Cell Location (1 is the Stem cell from human exfoliated tooth in case of a deciduous tooth or Dental Pulp stem cell in case of a permanent tooth; 2 is the Stem Cells from the apical Papilla; 3 is the Periodontal Ligament stem cells)

The main research of regenerative dentistry is aimed at the recovery of damaged dentin, pulp, resorbed root, periodontal lesions. The idea of regenerating a whole tooth to replace the implants is also in development. The use of stem cells have been recently identified as capable of osteogenic capabilities and is thoroughly investigated(10).

1.2. Pulp disease and periodontal defects

1.2.1. Pulp disease: causes, pathophysiology and available treatments

Causes

Pulp diseases are defined as the degeneration of the inner chamber of the tooth following an inflammation process. The sensitivity of the pulp is triggered by external factors such as caries and/or mechanical or chemical irritation. The factors inducing inflammation in the inner chamber of the tooth are various: invasion of microorganisms by the means of caries, a crack or mechanical trauma affecting the dentin, chemical irritation from restorative procedures, trauma from occlusion or orthodontic movement in the teeth(11). These factors could initiate an inflammatory reaction of the pulp leading to pulp pathogeny.

Pathophysiology

Caries is characterized by the gradual wearing of the teeth by infectious pathogens, the most famous being *Streptococcus Mutans*. It has been scientifically proved that *Streptococcus Mutans* is part of the microbial flora but it's excess can lead to decay(12). The prevalence of this pathology is based on its multifactorial nature where "the host immune system, the genetic susceptibility, diet, the tooth structure, biofilm, pH, oral hygiene and social status" all influence the incidence of a caries(12). Decay is the leading pathology in the oral medium in population aged under 40 years old. If the pathogen succeeds in their attempt to wear down the tooth, they will eventually get into the inner chamber, the pulp. Pulpitis typically is the inflammation of the pulp, which could be acute or chronic, symptomatic, or asymptomatic, with the capacity of being reverted or not. The reversibility of pulp disease is based upon the final diagnostics provided by a battery of test and final categorization of the pathology.

To this day, we recognize 3 types of pulp pathology, reversible pulpitis, irreversible pulpitis and necrosis.

The reversible pulpitis is characterized by the capacity of the pulp to recover from any harm if the subsequent factors are eliminated. The irreversible pulpitis is determined when the pulp is not capable of healing itself regardless of the capacity of the physician to heal it. Finally, the pulpal necrosis happens when the inner chamber is no longer "alive", the blood supply has been

severed, and the necrosis happened over time. These two last pathologies lead to irreversible lesions leading to radical treatments of the name of endodontics.

Available treatment

The indicated treatment to follow in this case would be the root canal treatment which consist in the opening of the pulp chamber, its cleaning and its definitive sealing leaving the tooth in a state of “healthy death” in the oral mucosa. This therapy has evolved over time and became very effective and today over 81% of the teeth which have undergone endodontics survive over 10 years in the dentated arch(13). The idea of endodontics suggests the sacrifice of the tooth life to keep it the mouth but does not comply with the main definition of regenerative medicine based upon tissue engineering and self-healing. Indeed, endodontic is an effective way to keep the tooth sound in the oral mucosa but the final objective is to obtain a patient with a pulp pathology capable after regenerative treatments to get back a “living pulp”.

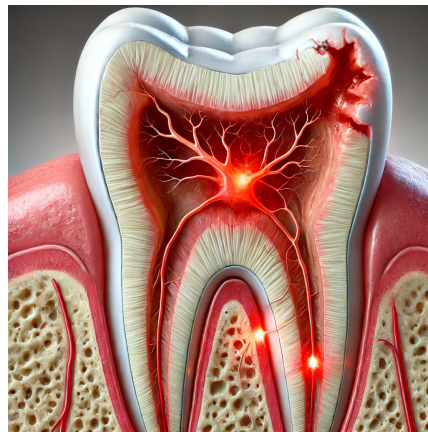


Figure 3. The visual interpretation of pulp disease (*the red dots stand for the stinging pain feeling like an electric shock*)

1.2.2.Periodontitis: causes, pathophysiology and available treatment

Periodontitis is a “common disorder affecting more than 40% of Adults” and is the most prevalent dental pathology upon population over 40 years old(14). It is characterized by the loss of the periodontium or so-defined tissues surrounding the tooth, leading ultimately to the loss of the periodontal ligament and bony levels.

Cause and pathophysiology

Periodontitis is a multifactorial disease implicating the dental biofilm of the oral biofilm but also the response of the host and the environmental factors or risk factors(14). The loss of periodontium by the host is characterized by an “irreversible destruction” of the bone and the

gums. Periodontal disease exists and goes as far back as 5000 BC where clear evidence of periodontitis is listed. Throughout the centuries, it has been characterized as a destructive gum disease with unknown causes. It is only in May 1914 when two female dentists by the name of Gillette Hayden and Grace Rogers Spalding established the first national organization “the American Academy of Oral Prophylaxis” that the world started to realize the prevalence of the leading oral pathology. The healthcare of the time evolved to the treatments indicated now to control the periodontal destruction. Education on oral medium health has been acknowledged as the best way to prevent the occurrence of the disease(14). Unfortunately, as mentioned above, periodontitis is a multifactorial disease, hence the fact that education alone cannot prevent it from happening.

Lesions

Periodontal diseases are classified according to the form of lesions they produce. The very first step of periodontal pathogenic process starts with gingivitis affecting up to 90% of the general population. Gingivitis is characterized by the reaction of the periodontium to the oral biofilm which can be reversed by the improvement of oral hygiene. According to the literature, the term “periodontitis” is used when bacteria (*Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis*) reached deeper levels of the periodontium producing a long term and irreversible inflammatory disease. Since 2017, the American Academy of Periodontology classify periodontitis into 3 categories (Necrotizing periodontitis, Periodontitis, and Periodontitis as result of systemic diseases) and added a new classification for peri-implant disease. The histopathology of periodontal lesions is divided into 4 different stages: The initial lesions, early lesions, established lesions, and advanced lesions. The initial lesion phase is defined by the accumulation in plaque resulting in vascular changes, increasing levels of gingival crevicular fluids. The early lesions produce the arrival of immunological cells, Polymorphonuclear Neutrophils, into the lesions area. Later the established lesions are characterized by the increased amount of immune system cells (leukocytes and B cells) changing the junctional and sulcular epithelium. Finally, the advanced lesions are the final stage of periodontitis where the biofilm migrated to the pocket. Attachment loss can be appreciated clinically and is at this stage irreversible. The Staging Guidelines of Periodontal Disease has also divided staging and grading of periodontitis. Staging is based on “the severity and the extent” while grading relates to the speed of progression of the disease based on evident factors such as harmful habits or systemic diseases. (15) The different grading and staging are shown in the following chart:

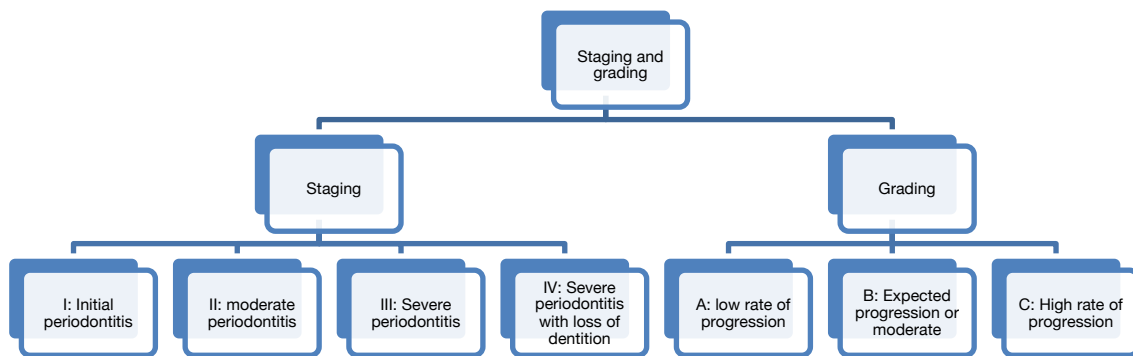


Figure 4. Staging and grading of Periodontitis

Available treatment

Basic treatment as Scaling and root planning on periodontal sites (probing depth of 5mm or greater) has been indicated to remove the active subgingival plaque(14). The patient is then reviewed some months later to compare the initial probing depths to the current ones. Those which persist pathological would have to undergo periodontal surgical therapy as for resective periodontal surgery where the gum would be moved apically to seal the subgingival aspect of the tooth and therefore reduce the probing depth(14). In the eventuality the periodontium was to be safe regenerative and mucogingival periodontal surgery is indicated to recover the loss of attachment and the aesthetics that once were, but again the materials existing on the market could only do so much, not answering the limitation set previously (the lack of organ availability and the increasing demand)(14). Some techniques and materials rose to the light using the human body facilities as plasma rich platelets or emdogain to regenerate bone loss(14).

The race to regenerative medicine has never been this accentuated and the discovery of stem cells and their capacity to self-heal open the doors leading to the hope in the near future to be able to completely remit from two of the most prevalent pathologies for the human species.

1.2.3. Combined Lesions

While some lesions are categorically endodontically related or focused only on periodontal lesions, some of them can be more complex. The difficulty resides in the correct diagnosis because the tooth presents the symptoms of both lesions. The etiology is agreed to be the bacterial infection, leading to the confusion of which pathogenic process is responsible for

triggering the other. (16) An endodontic pathogenic process leading to periodontal loss or the opposite, literature suggests a close relation between endodontic and periodontal diseases. This complexity can challenge the practitioner in the diagnosis of the cause, the management of the pathogen, the prognosis of the tooth and the treatment choice. The endodontic-periodontal lesions have been classified into the following list:

- Primary pulp infection triggering a chronic periodontitis once reaching the apex
- Primary periodontal lesions lead to the migration of the alveolar crest bone to the apex
- Both primary pulpal and primary periodontal lesions happen at the same time showcasing both symptoms of these infections.
- Primary pulpal and primary periodontal infection occur in a matrix called pure “endo-periodontal lesions”(17)

1.3. Relevance and Justification

Pulp and periodontal diseases are common dental conditions that, if left untreated, can lead to tooth loss and significant deterioration of oral health. The traditional treatments for these conditions, such as root canal therapy and periodontal surgery, have shown success in the partial recovery of the tooth function. However, they often fail to promote complete tissue regeneration or restore the natural function of the affected areas. Recent advances in regenerative medicine, particularly the use of stem cell-based therapies, offer promising alternatives. Stem cells have the potential to stimulate tissue regeneration, reduce inflammation, and promote healing at a molecular level, which could transform the management of pulp and periodontal diseases.

The relevance of this work lies in its potential to contribute valuable insights into the ongoing exploration of stem cell therapies in dentistry and its current applications. By comparing stem cell-based treatments with conventional methods, this study aims to provide a deeper understanding of the clinical outcomes, long-term benefits, and associated risks. The findings could not only improve treatment protocols but also help bridge the gap in the current literature regarding the practical application of stem cell therapies in dental practice. Furthermore, this research could guide future clinical decisions, offering a pathway to more effective and regenerative treatments for pulp and periodontal diseases, with potential long-term benefits for patient care.

2. OBJECTIVE

2.1 Primary objective

- The primary objective of this scientific review is to evaluate the effectiveness of stem cell-based therapies in the treatment of pulp and periodontal diseases, in comparison to conventional treatment methods.

2.2 Secondary objective

- The secondary objective of this scientific review is to assess the long-term benefits of stem cell-based therapies in the treatment of pulp and periodontal diseases, relative to conventional treatment approaches. We will try to justify the use of stem cells by examining the potential risks and complications associated with stem cell therapies, in comparison to conventional treatment methods.

3. MATERIAL AND METHODS

To ensure a comprehensive and systematic review of the literature, we used web-based research on reliable literature bibliotheca as PubMed, ResearchGate and Journal of endodontics filtering the relevant article from the duplicates. These Clones were identified and removed using a reference management tool to ensure the uniqueness of the included records to limit our search to the latest advances we also filtered our research to a timeline of published articles of 10 years, specifically between 2014-2024.

Keywords have been used to narrow the articles using the PubMed Advanced Search Builder and their query box to only keep the relevant articles. Initially we searched the term "Stem Cells" and crossed it with the articles published in the last 10 years narrowing the scope to 243,486 articles. Further filtering the type of articles matters in the research and its relevance to give us a solid review; thus, we only used the article which corresponded to Case Reports, Controlled Clinical Trials, Meta analysis, Randomized Controlled Trial and Systematic Reviews. This new filter constrained the results in approximately 6,226 articles.

The last segregation of articles has been using MESH terms allowing us the precisely study the "Stem Cells" in the dentistry field using "dentistry" [MeSH Terms] refining the research into only 86 articles.

Concerning the second part of the subject regarding pulp diseases and the periodontal defects, the same sorting was used to only extract articles and journals. The terms "Pulp Disease" and "Periodontal diseases" have been used with the advanced search bar of PubMed allowing to specifically target all the articles of the 10 last years which were "full texts" with the Boolean operator "OR" and the previous filters (Case Reports, Controlled Clinical Trials, Meta analysis, Randomized Controlled Trial and Systematic Reviews). The MeSH terms "regenerative dentistry"

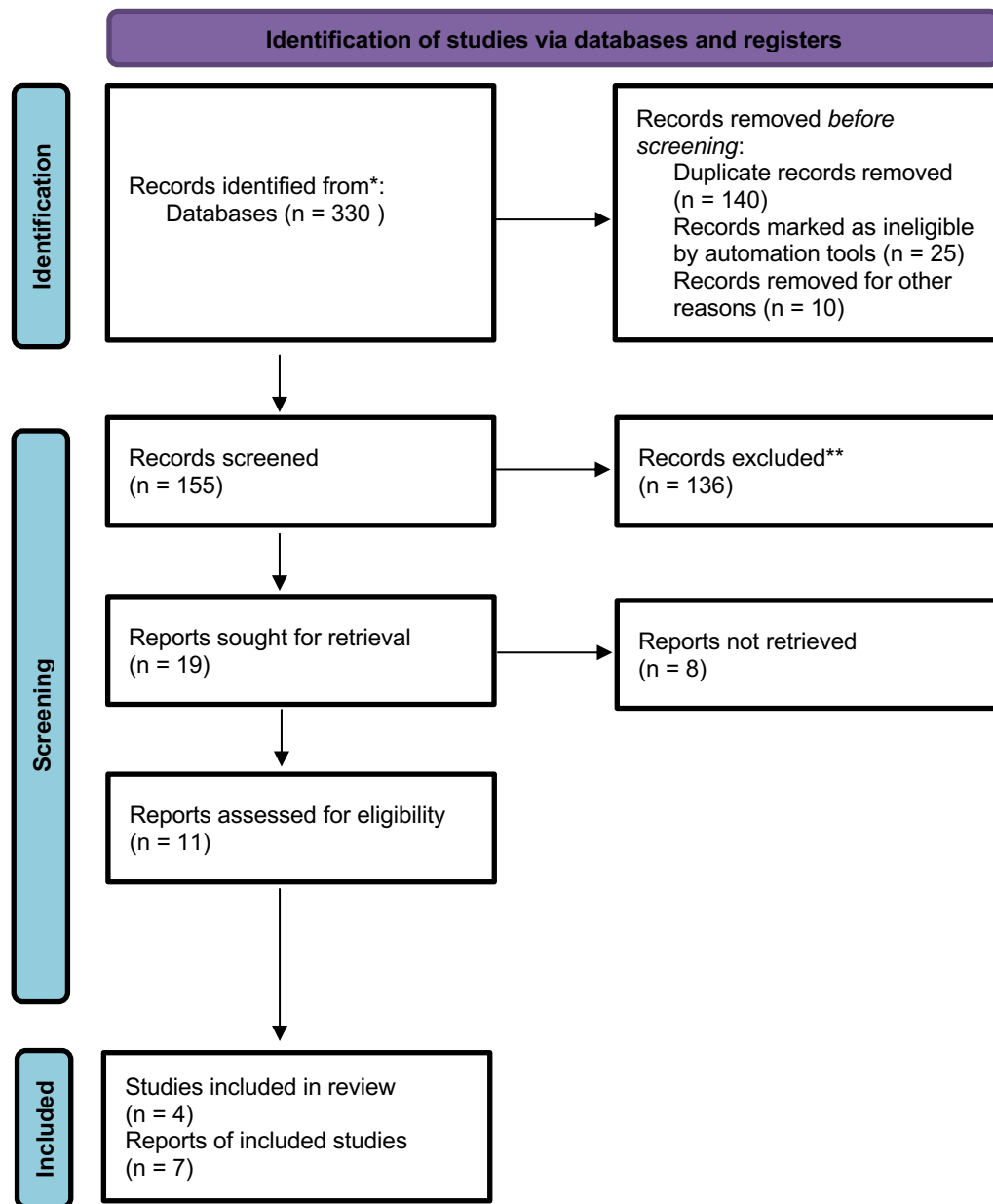
also was used to only qualify articles talking about pulp and periodontal diseases in regenerative procedures. Focusing on these key terms gave us a refined lot of articles (330 articles). We will also now use the PRISMA method to critically identify the articles we will record in this documentary review according to their eligibility and their relevance.

Articles were excluded if they did not meet the defined inclusion criteria, lacked the full text availability, or exhibited significant methodological limitations. This structured approach ensured the inclusion of high quality and relevant studies.

4. RESULTS

1. Review of the PRISMA Model

After the articles were searched in PubMed and ResearchGate, 330 articles were yielded during the preliminary searching. After using the PRISMA method to filter the type of evidence used to expose the results of the review, 155 articles were left. Out of the 155 articles, only 19 of them focused on periodontal/endodontic regeneration using Stem Cells as the primary technique. 11 articles were retained for the results when we finished assessing the full text, focusing on the cell therapy for periodontal and endodontic regeneration.



2. Stem Cell use in Periodontics vs Conventional Periodontics Procedure

The success of periodontic regenerative procedure is based on the comparison between the ante-surgery parameters and the post-surgery parameters. While diagnosing a periodontal

patient clinical sign as bleeding on probing (BP), the probing depth (PD) and gingival recession (GR) and the radiographical bone loss should be assessed prior to any therapy(18). These same parameters are used to assess the result of the therapy, in this case the use of stem cell on the regeneration of the periodontium.

To ease the interpretation of the results, a structured table has been created to summarize important information regarding the selected study. This table provides an overview of the article, including its **authors, study type, sample size, intervention to be done, the control group, and the measuring instruments.**

Authors/Year	Type	Sample	Intervention	Control group	Measurement	Outcome
Darnell Kaigler and cols (2015)(19)	Randomized clinical trial	30 patients with craniofacial osseous defects or deficiencies between 50 to 80%	Receive CD90+ stem cells and CD14+ monocyte delivered onto a β -tricalcium phosphate scaffold	15 patients only received a scaffold as a regeneration without stem cells	4 months and 1 year follow up	Bone volume: No difference Bone density & quality: Higher in stem cell group
Fa-Ming Chen and cols (2016)(20)	Randomized clinical trial	30 periodontal patients aged between 18 and 65 years old. A total of 48 teeth were included in the trial	Receive autologous PDLSCs in combination with bovine derived bone mineral materials	20 teeth were treated in the control group receiving only guided tissue regeneration and Bio-oss without stem cells	12 month follow up	Bone regeneration: Increased in both groups, no significant difference
R Sreeparvarthy and cols (2024)(21)	Randomized clinical	17 patients aged between 30 and 55 years old	Receive peripheral blood mesenchymal stem cells and platelet rich fibrin matrix	The split between the test group and the control group has been made in a split mouth design where the control group only received platelet rich fibrin matrix and open flap debridement	1 week, 3 and 6 months follow up	6-month checkpoint: Greater defect depth reduction & fill in experimental group Probing depth & attachment level: Significant improvement in

						experimental group
Beatriz Hernandez-Monjaraz et al. (2018)(22)	Case Report	1 Patient of 61 years old (lower left premolar)	DPSCs from a 7 years old donor tooth cultured and mixed with a dry scaffold of collagen-polyvinylpyrrolidone sponge	NO	3 month and 6 months	Tooth mobility, pocket depth & defect area: Decreased at recipient site Bone density: Increased at graft site
Arah Khojasteh and cols (2019)(23)	Case report	2 cases; first case being a 19 years old patient with large bone defects following extraction. The second patient is a 22-year-old patient with large bone defect post extractions.	Application of adipose derived stem cell from buccal fat pad	No	6, 10 and 48 months	10 & 48 months: Complete osseointegration observed

TABLE 1. Characteristics of the included studies

The characteristics of the included studies are presented in Table 1. The articles range from 2015 to 2024. 80 patients were enrolled in these studies. Autologous Stem cells from dental tissues, blood mesenchymal stem cells and adipose derived stem cells were used to restore a periodontium like tissue. The follow-up period ranged from 1 week to 48 months. All the outcomes were available as the studies were concluded.

Stem cell therapy has been assessed in the field of periodontal regeneration using a variety of research approaches, from case reports to randomized clinical trials. Probing depth (PD), clinical attachment level (CAL), radiographic defect fill, and overall bone quality were the main objectives.

Kaigler et al. (2015) investigated the utilization of CD90+ stem cells and CD14+ monocytes embedded in a β -tricalcium phosphate scaffold to cure severe craniofacial osseous abnormalities (50–80%) in a randomized clinical trial. A crucial difference was seen in the quality and density of the regenerated bone, which was noticeably higher in the stem cell group even though the experimental and control groups produced similar amounts of regenerated bone. This effect was more noticeable in individuals with larger starting abnormalities, indicating that stem cells may be useful in treating more complicated situations.

However, when autologous periodontal ligament stem cells (PDLSCs) were added to standard regenerative methods such guided tissue regeneration (GTR) with Bio-Oss, Chen et al. (2016) did not show a statistically significant difference in the results. This study suggests that stem cell efficacy might be influenced by case severity, scaffold integration, or follow-up period, even if both groups showed an overall improvement.

The randomized clinical trial by Sreeparvathy et al. (2024) compared open flap debridement (OFD) with platelet-rich fibrin matrix (PRFM) with and without peripheral blood mesenchymal stem cells (PBMSCs) using a split-mouth design, and the results were more encouraging. The group that received PBMSCs demonstrated improvements in gingival and CAL indices, as well as a significant decrease in probing depth and an increase in defect fill at six months. These results support the therapeutic combination between biological matrices like PRFM and stem cells.

The possibility of stem cell therapy in periodontology is further validated by supporting data from clinical situations. For example, mesenchymal stem cells from dental pulp were used to successfully treat a lower premolar with periodontal impairment, according to Hernandez-Monjaraz et al. (2018). Up to six months after treatment, there were no negative side effects from the technique, which reduced tooth movement, lowered pocket depth, and increased bone density at the graft site. Like this, Khojasteh et al. (2019) treated significant post-extraction

alveolar bone deficiencies using adipose-derived stem cells from the buccal fat pad. Complete osseointegration of the implants and long-term bone stability were confirmed by the follow-up over a period of 10 to 48 months, indicating that adipose-derived stem cells may provide long-lasting restorative benefits in implantology.

All these studies point to the potential of stem cells to promote periodontal regeneration, especially in patients who have experienced significant bone loss or when combined with biological scaffolds.

3. Stem Cell use in Endodontics vs Conventional Endodontics Procedure

The success of endodontic procedure is traditionally based on clinical and radiographical criteria as the absence of pain, the regression of the apical periodontitis and the long-term functionality and survival of the treated tooth(24). The goal of conventional root canal treatments is multiple, including sealing definitively the tooth with a sealing material and keeping a “necrotic” tooth while regenerative endodontic procedure intends to biologically regenerate a pulp-like tissue. The following criteria are the ones we will use to compare the results between Conventional and Regenerative endodontics:

Criteria	Conventional Endodontics	Regenerative Endodontics
Absence of pain	Required	Required
Regression of Apical Periodontitis	Required	Required
Root Canal Treatment	Restored with obturation material	Restored with potential pulp vitality
Root Canal Filling	Necessary (1 mm from apex)	Not necessary
Coronal and Apical seal	Required	Required
Vitality Response	NO	YES/ NO
Radiographic healing	Evidence of bone healing	Possible dentin regeneration and bone healing
Long term prognosis	Comparable	Comparable

TABLE 2. Primary and secondary criteria to the success of endodontic procedures

Authors	Study type	Sample size	Intervention	Control	Measurement	Outcome
Gaston Meza and col. (2019)(25)	Case report	1 tooth (n° 28), irreversible pulpitis	Use of DPSCs and L-PRF And cervical seal with Biodentine	None	6 months and 3 years follow up	Follow-up (6 months & 3 years): Positive delayed cold response & positive electric pulp test
Masako Nakashima et al. (2022)(26)	Case report	2 cases	Autologous DPSCs and sealing with Biodentine and composite resin	None	4 weeks, 24 weeks and 48 weeks follow up	48-week follow-up: No adverse events or systemic toxicity 4 weeks: Positive response to electric pulp test 24 weeks: Pulp tissue imaging comparable to normal adjacent teeth
Claudia Brizuela Cordero and col (2020)(27)	Case Report	1 tooth (N°7)	MSC encapsulated within platelet poor plasma implanted into root canal. Sealed with Biodentine and composite resin	None	6 months and 1 year follow up	1-year follow-up: Normal response to percussion & palpation; positive electric & vitality tests

Jose Francisco Gomez Sosa et al. (2022)(28)	Case Report	1 tooth (N°8)	Bone marrow MSC encapsulated in Platelet rich plasma implanted into the root canal, sealing with bioceramic cement and composite	None	14 month follow up	14-month follow-up: Sensitivity to cold, positive electric pulp test Radiographic findings: Healed periapical lesion, increased bone density, apical remodeling
Mohammad A. Sabeti et al. (2024)(29)	In vivo Investigation	32 dog teeth divided into 4 groups. Group 1: Positive control Group 2: Negative control Group 3: Class V cavities inducing inflammation Group 4: Class V cavities treated with 1ml of cord blood stem	Blood stem cells with a hydrogel scaffold and sealed with RMGI and composite.	Group 1, 2 and 3 served as control groups	3 month follow up	3-month results (Group 4): Apical closure, organized pulp-like tissue, no inflammation

		cells with hydrogel scaffold				
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TABLE 3. Characteristics of the included studies

The Characteristics of the 5 eligible articles are presented in Table 2. These studies were published from 2019 to 2024. 37 patients (human and animals) were enrolled in these studies. Autologous Stem cells from dental tissues and bone marrow were used to restore a pulp-dentine like tissue. The follow up period ranged from 4 weeks to 48 weeks. All the outcomes were available as the studies were concluded.

Regenerating pulp-like tissue in non-vital or endodontically treated teeth is the main goal of stem cell therapy in endodontics. In addition to radiographic evidence of periapical healing and apical closure, case reports and in vivo studies have shown that dental pulp stem cells (DPSCs) and bone marrow-derived mesenchymal stem cells (BM-MSCs) can restore specific markers of pulp vitality, such as positive responses to electric pulp testing and cold stimulation.

Leukocyte platelet-rich fibrin (L-PRF) and autologous DPSCs were used by Gaston Meza et al. to cure an irreversible pulpitis case that was sealed with Biodentine. Clinical assessment at six months and three years showed that pulp vitality tests consistently produced positive results, suggesting that the regenerated tissue continued to function biologically. In the same way, two cases of DPSCs being extracted from third molars, cultivated, and then transplanted into root canals were reported by Nakashima et al. Both patients had positive electric pulp test results at 4 weeks, and imaging at 24 weeks showed pulp-like tissue that was similar to nearby healthy pulp. Additionally, there were no systemic toxicity or problems during the 48-week follow-up, indicating safety and long-term biocompatibility. (25,30)

Brizuela et al. used MSCs in platelet-poor plasma to treat a tooth that had undergone endodontic treatment and had a cervical perforation and apical periodontitis. A year's worth of clinical and radiographic follow-up showed apical healing and regained vitality, suggesting that stem cells can cure long-term problems in damaged teeth. Similarly, Gomez-Sosa et al. used cryopreserved allogeneic BM-MSCs with platelet-rich plasma to heal a tooth that had previously received a root canal. In addition to pulp vitality recovery, the 14-month follow-up showed distinct radiographic evidence of periapical healing and an increase in bone density at the root apex, indicating successful apical remodeling.(27,28)

Sabeti et al. (2024) investigated the regeneration potential of stem cells in a dog model in an in vivo investigation. In this experiment, pulp exposure was used to induce Class V cavities, which were then treated with cord blood stem cells placed in a hydrogel scaffold. Histological evidence of regeneration under controlled settings was provided by the experimental group's organized pulp-like tissue, apical closure, and lack of inflammation after three months.(29)

According to these cases and experimental findings, stem cell therapy may be able to restore the pulp-dentine complex's structural and functional elements, potentially outperforming traditional root canal therapy by restoring biological vitality.

5. DISCUSSION

The keen interest for stem cells in dentistry is highly justified; while promising matching capabilities as conventional treatment, they uplift most drawbacks the existing treatment proposes. Their regenerative capacities to restore the lost tissues and replace them with functional tissues is the most important advantage they showcase. Another edge they provide is the immunological benefits they provide, as the material used is autologous. They reduce inflammation scaffolding a favorable environment for tissues regeneration.(31)

In contrast to traditional treatments for pulp and periodontal diseases, the purpose of this review was to assess the efficacy and therapeutic significance of stem cell-based therapies. Our findings support the idea that stem cells have great restorative potential, especially when tissue breakdown has advanced. This promise must be weighed against methodological flaws, present clinical constraints, and the quite early stage of implementation into standard dental practice. We can evaluate the part stem cells are starting to play in changing dentistry by contrasting the chosen studies and connecting our results to the body of current scientific literature.

Numerous studies in periodontology have shown that stem cell-based therapies can improve clinical outcomes like attachment gain, defect fill, and probing depth reduction. When paired with platelet-rich fibrin, peripheral blood mesenchymal stem cells dramatically improved periodontal metrics in the randomized clinical trial by Sreeparvathy et al.(21) when compared to standard therapies. These findings are consistent with the regenerative hypothesis put forward by Salvi et al. (18), which holds that biological compatibility and the promotion of host tissue regeneration are frequently associated with long-term attachment stability.

In a comparable way, Kaigler et al.(19) found that using stem cells to treat significant craniofacial abnormalities increased bone density and structural quality. These results are not unique; rather, they corroborate the increasing amount of research indicating that cell-based therapy works especially well for healing extensive or complex abnormalities, where traditional regenerative methods would not be sufficient. The findings of Mirzaeei et al. (3), who highlighted the necessity of biological recipients to actively guide tissue regeneration, particularly when dealing with irregular or compromised bone regions, are consistent with the more favorable response in patients with more severe deficiencies seen in Kaigler's study.

It's interesting to note that not every randomized experiment found a substantial difference between conventional and cell-based therapy. Chen et al. (20) discovered no statistically significant difference in bone regeneration results between regular GTR with Bio-Oss and PDLSC-enhanced treatment. According to this, stem cells might offer qualitative benefits like better integration or quicker healing, which might become more noticeable in long-term research, even if they might not always outperform conventional therapies quantitatively. As noted by Bansal and Jain(10) , who emphasized that the regeneration ability of stem cells is frequently context-dependent, the disparity in results may also suggest that the clinical context and severity of the lesion significantly influence therapeutic success.

Stem cells have shown promise in endodontics by restoring pulp life in mature teeth, something that traditional root canal therapy is unable to accomplish. Both cold and electric pulp tests verified biological vitality months after treatment in several case reports, such as those by Gomez-Sosa et al., Nakashima et al., and Meza et al.(27,28,30) According to Sabeti et al. (29), the presence of apical closure and structured pulp-like tissue indicates not just reparative but also genuine regeneration maneuvers. These results cast doubt on the conventional wisdom that irreversible pulpitis must inevitably result in extraction or necrosis, and they lend validity to Lin and Kahler's (2) regenerative model, which holds that the endodontic gap is actively healed rather than merely passively filled.

According to the hypothesis, our findings give relevance to the idea that stem cell therapies in endodontics and periodontology seek to restore biological function rather than merely duplicate structural features, which may reinterpret treatment objectives in dental practice.

These results align with earlier research on regenerative medicine. For instance, Bansal and Jain (10) highlighted the multipotency of SHED and DPSCs, indicating their involvement in neurogenesis and osteogenesis in addition to dentinogenesis. As previously hypothesized by Poliwoda et al.(7), the immunological advantage of dental pulp stem cells is confirmed by the Hernandez-Monjaraz et al. (22) instance, in which these cell types contributed to both soft tissue and bone regeneration without immunological rejection.

Furthermore, notably in three-dimensional bone defects, the osteogenic potential described by Khanlarkhani et al. (5) coincides with the capacity of adipose-derived stem cells to support stable osseointegration of the study of Khojasteh et al.(23). Their long-term clinical benefit is strongly supported by the fact that, even after 48 months, no indications of bone deterioration or implant failure were noted.

On the other hand, Kwon et al. (14) express concerns that stem cell therapies, despite their potential, frequently lack consistent delivery systems or patient selection criteria that could

maximize their effectiveness. This is in line with the disparity between experimental success and limited statistical differences in some trials (e.g., Chen et al., 2016). This emphasizes the value of standardization in stem cell procedures, a topic we'll touch on again in our suggestions.

When compared to conventional treatments, certain research (e.g., Chen et al., 2016) revealed relatively slight or non-significant differences, which is contrary to the supposed superiority of stem cell treatments across all parameters. The sample's low regeneration demand (moderate defects) or possibly inadequate stem cell dose or survival could be one factor. Furthermore, although employing stem cells is an attractive concept, their effectiveness is probably multifactorial and depends on several factors, including host immunological response, scaffold biocompatibility, and site preparation, in addition to cell type. These factors are not usually considered in current research.

It's interesting to note that in certain situations, the donor's age appears to affect results. Hernandez-Monjaraz et al.'s work involved the successful transplantation of stem cells from a 7-year-old donor into a 61-year-old recipient(22). This supports the clinical interest in obtaining cells from younger people and is consistent with data by Singh et al. (4) that indicate stem cell potency decreases with age.

These findings have significant clinical implications in addition to being pertinent from a scientific one. Stem cell-based treatments may someday take the role of traditional GTR in periodontics, especially in individuals with systemic restrictions whose ability to repair is impaired. The prospect of restoring actual pulp vitality in endodontics as opposed to conserving a "dead tooth" has the potential to completely alter treatment concepts, especially for young adults and children.

Furthermore, systemic inflammation or autoimmune-related oral disorders may be managed with the help of DPSCs and SHEDs' anti-inflammatory and immunoregulatory properties, an application that is still mainly unexplored.

Several constraints need to be noted. First, there was a great deal of variation in the methodology, sample size, stem cell source, distribution technology, and follow-up period among the included research, most of which were case reports or small-scale trials. This limits the capacity to perform meta-analytical synthesis and generalize findings. Second, although encouraging, most follow-up periods were brief, and stability over the long run is still unknown. Khojasteh et al. (23) were the only ones to provide follow-up data after two years.

Additionally, the diagnostic criteria, inclusion and exclusion criterias and outcome measures used in comparison research were not standardized. For example, rather than using quantitative

metrics like CT bone density scans, "bone quality" was frequently evaluated by subjective radiographic inspection. Comparisons between studies are jeopardized by this discrepancy.

The variety of stem cell origins, which included bone marrow, dental pulp, adipose tissue, and peripheral blood, each with a unique regeneration profile, was another drawback. Although there is promise in this diversity, it also makes it challenging to identify the best stem cell line for each therapeutic situation.

Future studies should try to:

- Use standardized procedures and higher sample sizes in multi-center randomized controlled trials.
- To verify the longevity of regenerated tissues, assess long-term results, preferably more than 24 months.
- Examine the best scaffold combinations and stem cell sources.

6. CONCLUSIONS

The main objective of this scientific review was to evaluate the effectiveness of stem cell-based therapies in the treatment of pulp and periodontal diseases in comparison to conventional treatment methods. After a thorough systematic literature reading based on the PRISMA model and filtered via reliable scientific databases (Pubmed, ResearchGate and Google Scholar), the investigation successfully identified and analyzed a body of evidence that sheds light on the clinical potential of stem cells in dentistry. The primary and secondary goals have both been attained. The review focused on the long-term advantages and possible drawbacks of stem cell therapies in comparison to conventional methods, in addition to displaying their capacity for regeneration.

According to the findings, regenerative dentistry, especially stem cell-based procedures, has the potential to restore tissue and function biologically rather than simply maintaining structure.

Studies in periodontics have demonstrated that autologous stem cells enhance important clinical indicators such as bone repair, attachment level, and probing depth. Regenerative techniques in endodontics were successful in giving previously necrotic or non-vital teeth their pulp-like tissue and biological vitality back. These results suggest that stem cell therapy may

eventually take over the role of traditional root canal therapy, as demonstrated by good pulp tests and radiographic healing responses.

Despite these encouraging results, the review process ran into several problems. First, the scarcity of many large-scale, high-quality randomized controlled trials (RCTs). The long-term stability and viability of regenerated tissues are also questionable because several trials had brief follow-up periods, very few went beyond 12 to 24 months. Another major challenge lies in the ethical and logistical aspects of stem cell collection, preservation, and transplantation.

The ethical and operational implications of stem cell harvesting, preservation, and transplantation present yet another significant obstacle.

One of the future considerations would be more rigorous multi-center RCTs with standardized protocols, bigger sample sizes, and long-term follow-up are required to overcome these obstacles in the future. The analysis should determine which combinations of scaffolds and stem cell types are best suited for therapeutic needs.

Innovations in delivery methods, ethical harvesting, and stem cell storing (such as cryopreservation banks) should be promoted. Furthermore, to guarantee the safe and efficient incorporation of these therapies into dentistry practice, clinical guidelines and regulatory protocols must change.

This review concludes by confirming the innovative promise of stem cell-based treatments in regenerative dentistry, but it also emphasizes the need for more thorough investigation and standardization to reach their full potential and make them available to a wider range of patients.

7. SUSTAINABILITY

Stem cell therapy investigation in dentistry supports a sustainable approach to future dental healthcare. From a social perspective, regenerative procedure promises different outcomes to conventional treatments by restoring what was once lost rather than simply containing structural integrity. The potential of stem cells could improve significantly the quality of life for patients by promoting oral health and reduce the rush to tooth extractions and/or prosthetic replacement. Economically, currently the cost of these therapies is more expensive than conventional treatments due to their complexity and their limited availability; but on the other hand, they propose fewer re-treatments, reduce long-term complications and greater durability associated with the cooperation of the patient. Thus, it suggests the potential for future cost-effective technology to reduce the financial burden of the patients. In terms of environmental sustainability, the development of regenerative procedure could lead to the diminution of

dental waste and the use of synthetic materials. In fact, regenerative procedures use biocompatible and biodegradable scaffolds, resulting in a lower environmental footprint. Ethically speaking, the sourcing of stem cells, whether autologous, allogeneic or derived from medical waste like extracted teeth, must follow strict regulatory guidelines to ensure the safety and consent of the patient. In conclusion, stem cell therapies not only present clinical innovation but also take part in a future where dentistry will be more sustainable while addressing social equity, economic efficiency for both the practitioner and the patient and ethical practice.

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9. ANNEXES