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Review Article

Stem Cells in Endodontics Regenerative: Review of Changing Paradigms and Innovative Concepts

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Abstract

Background: The new field is expected to guarantee the sensitiveness and functionality of the pulp-dentin complex due to the endogenous repairing and tissue engineering service. Regenerative therapies are designed to offer the healing and functional regeneration biological milieu instead of curing diseases, like in the clinical success of conventional endodontics.

Methods: The reviewed narrative is an integration and discussion of the recent developments in the field of regenerative endodontics, the advancements under the focus of stem cells, scaffold and signalling pathways and clinical procedures. Critical literature review on articles, which explored experimental models, new biomaterials, and clinical outcome studies, was conducted to establish the status of regenerative treatments and our capacities to enhance these treatments.

Findings: The regenerative endodontic (RE) is a process that has become more threatening with multiple advances in emerging technology. The scaffolds have been designed to resemble the extracellular matrix and offer the cell a scaffold upon which it can attach itself and organize the tissue. Further source of stem cells and more advanced methods of delivering growth factors to regulate cell proliferation, and differentiation provide more possibilities of cell-based therapy. The findings are encouraging and the research is faced with the heterogeneity of therapeutic responses, unstable treatment outcome and unstandardization of treatment regimen.

Conclusion: Regenerative endodontics is an effective, biologically-induced, restorative-reflective therapy of non-vital tooth. Even though the technical and biological heterogeneity process remains, studies in the field of genetic manipulation, scaffolding architecture and 3D bioprinting do leave a room of hope in the outlook of reproducibility and predictability of the outcome. The state of the art in these fronts is to conduct further research to remove the current limitations, and to render the regenerative endodontics as a non-drug option in the conventional endodontic procedure.

Key words: Endodontic Regeneration, Stem Like- Mesenchymal Cells, Biomimetic Scaffolds, Stem Cells From Apical Papilla

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Introduction

Regenerative endodontics is a somewhat novel field that is grounded on an endogenous pulp-complex healing regimen according to which non-vital teeth are regenerated. The history of endodontics has been continuously inclined towards the provision of a pulp sacrifice by destruction with a view of annihilating the pathology as far as possible to leave the structures undamaged to be able to restore even a functional tooth. Root canal operation and apexification may prove quite handy because a tooth will be preserved against infection, abscess and premature death though the tooth has been denied the natural biological activity. Consequently, such conventional methods hamper the pulp mediated functions such as sense and immune/ repair ability of teeth. The ways address the redress of such problems but the disadvantage of it is that alive enamel passes them on to lives. When they grow old the tumbler becomes too mushy and break. This has led to the identification of alternative types of therapy which though efficient in the hostage of controlling infections has not influenced the physiology of the denture tissues [1].

The regenerative endodontics has been oriented to a high-technology biological paradigm of repairing damaged or necrotic pulp substrate instead of preserving it. Although all the diversity of traditional methods aimed to render the canal area airtight with the assistance of an inert material, the regenerative endodontic procedures (REPs) are speculated to restore the functions of the dentin-pulp units and apical periodontitis lost in the case of the pulp necrosis and apical periodontitis (e.g., sensitivity, immune response and plasticity). This kind of treatment should be highly assisted in their treatment of pulp since the conventional methods might not be more competent in such a long-run view to guarantee the survival of the pulp, survival of the immature avital permanent teeth. It is required to change to biologically based restorations[2] as opposed to modern dentistry that is obsessed with restorations (biologically based restorations restorative endodontics) in order to restore lost form and functionality.

The unusual combination of the endodontics clinical requirements and the concept of tissue engineering, i.e. there is the engineering of biological substitutes, which replaces damaged tissue, is a special one. This group is a combination of three classes of components, which are elementary namely, the scaffolds, the signaling molecules and stem cells. All these are involved in the restoration of the dentinal and the pulpal tissue in the root canal separately. One can distinguish between these mesenchymal like cells of the stem cells to healthy, activating, pulpal assist cell and dentin producing odontoblast-like cell production. Regenerative endodontics is conceptualized on the basis of scaffold tissue engineering scientific discipline which is a combination of molecular biology, cell biology and biomaterials to create biologics replacement to simulate functioning of damaged tissue. As it was anticipated, the area is founded on tissue engineering. This triad contains three elements namely scaffolds, signalling molecules and stem cells. The parts have their individual contribution to the revitalization of the root canal. The embryonic cells are capable of growing to odontoblast - like cells and thus can be employed as a biological building block of tissues in which the pulp and dentin will be constructed[3].

Scaffolds It is the supportive agents that allow the cells to be attached and grow and orient themselves in the space of three dimensions that signals moieties regulate the quality of cells during via differentiation, tissue regeneration, vasculogenesis, Stampings, and all these, it forms a biologically favorable niche within the root canal which is conducive to regeneration of the pulpal tissue in answering the definition of a functional and persistent tooth[4]. Nevertheless, it is only in 2000 that the researchers have come up with actual advances in the teeth generation aspect when the concept of tooth tissue regeneration had been evolving over the decades. First, in vitro (in vivo) regenerative potency of different forms of stem cells such as: dental pulp stem cells (DPSCs), stem cells of apical papilla (SCAPs), and dental follicle progenitor cells (DFPCs) and apical papilla stem cells, was also found to be great and given the proper conditions, they can be transformed into odontoblast-like cells. These epochal findings led to a colossal study on regeneration perspective of dental stem cells to be used with dentin-pulp complex regeneration[5].

Pulp-dentin complex re-formation may be achieved by using DPSCs, SCAPs and DFPCs which are significant biological factors. On these results, regenerative therapies have been designed to be built with the goal of the restoration of a natural and viable pulpal tissue, which will presumably fulfill the duration-of-stability and functionality of teeth. Presently the regenerative endodontics therapy is usually applied to the treatment of vitalization of the pulp necrosis of immature permanent teeth in a situation where the conventional endodontic treatment (i.e. apexification or pulpectomy) is not possible, only the infection can be suppressed, but hardly further root development can be stimulated and leaves the tooth vulnerable. In its turn, regenerative endodontic procedures (REPs) imply the application of biological events to stimulate the development of roots and dentin formation, and support the tooth[6,7]. Enhanced lengthening and seal apex, which are the thickness of the dentin walls, have been demonstrated to be better in other minor clinical trials and cases. Most of the studies in the general context suggest that the modern process of endodontics regeneration at an immature age with necrotic pulp is more suitable than the traditional one to rescue such a tooth. Regenerative endodontics too has enjoyed much harvest but there is still a lot to be had before it can become a mainstream clinical gamification. The cause of why the outcomes were not non-homogeneous following the REPs was the non-homogeneity of treatment regimens[8]. Such factors as the type of scaffold, its viability and preservation of the stem property, and purity of the canal determine the further success. The extreme, on the other end which is the use of cytotoxic antimicrobial agent, has proven to be able to paralyze the stem cells, thus preventing the regeneration of the tissue[9] although the ultimate solution must be capable of not only counterbalancing the risk of re-infecting but also affording some degree of clinical acceptability of need. Also in the biological-level, with the pulp-dentin regeneration process, the heterogeneity of this process, that is, the variation in response to varying factors, e.g., but not limited to, age, biological individuality and immune condition, makes it quite difficult to predict the best-case scenario result[10].

Additionally, the room of improvement of the materials employed in regenerative endodontics is also considerable and the same the scope of the restriction of the methodology. These comprise biomaterials and scaffold to form microenvironment to provide cells with cell adhesion and numerous other manifestations of differentiation and ordered tissue forming technologies which will, naturally, be part of the principle tools required to provide bioengineered organ systems. As an alternative to boost cellular orientation and differentiation, alternative methods (such as 3D bioprinting) are suggested to create custom-made scaffold material that is even more reminiscent of the in-vivo ECM environment of the dental pulp[11]. New therapies, including also gene therapy or more advanced controlled release vectors of growth factors are quite welcome, since they not only can enable the specific control of cellular functions, but equally can induce tissue repair pathway and predictable results with regenerative endodontic therapies[12].

In order to conduct a comprehensive, in situational analysis of the existing literature available, which is currently found within the sphere of regenerative endodontics, to be more precise, regarding the theoretical background and the feasibility of the viability of the proposed innovative guidelines. We shall point out the progress achieved over the recent few years of creating molecular cues that can be conjugated to any of the three key components that have been engineered as constitutions of the engineering tissue canon of scaffolds, which are signaling molecules and are stem cells. Nevertheless, the particular clinical uses of protocols and disinfectants with the help of REPs are protocol specific and disinfectant specific that will be also presented during the conference presentation. It is against this backdrop that body of work will be presented and also, relevant articles that were published within the past 5 years and were indexed in PubMed will be reviewed. Another goal of the research paper is also to conduct a literature review and indicate the areas that are up-to-date regarding the development of the research in the future concerning the translational research, gene therapy and 3D bioprinting. endodontics Regeneration is also a new alternative to treat non-vital teeth through spontaneous healing of the injured or necrotic pulp tissue[13].

Literature Sears Methodology.

A literature search has been conducted to retrieve the literature that described the existing practices in the area of endodontics revitalization. The search strategy involved the following research plan; Regenerative Endodontics " Endodontic Tissue Engineering " Dental Pulp Stem Cells Endodontic Scaffolds Biomaterials in pulp regeneration Clinical Endodontic Regeneration had been searched in various online databases (PubMed, Scopus and Consensus) till the date October 2025. The literature of the studies has been narrowed down with the help of time filters depending on practice and discourse that is being pursued today in the field of clinical practice and the use of helpful discovery and trips such as landmark trial and newer advancements.

Exclusion and Inclusion Criteria.

Inclusion and exclusion criteria (presented in Table (1)) were formulated in such a way that they assisted them to incorporate and exclude reviews in studies.

Table [1]: Exclusion and Inclusion criteria

Scope of study	Research on endodontic regeneration methods, such as stem cell, scaffolding materials, approaches and cleaning procedures	Researches that have no effect on regeneration of dentin -pulp endodontics
Type of research	laboratory and clinical researches, such as clinical trials, in vitro and in vivo experiments, exhaustive novel and rigorous analysis research."	Publications that are not empirical, such as editorials and opinion pieces, unless they offer significant insights into potential avenues for evolving research
Quality of publication	publications in journals with peer-reviewed	Unreview works, such as preprints and unofficial publications, unless they are pertinent to recently developed topics
Relevance to objectives	Researches revealing light on the limitations, effectiveness and future prospects regenerative endodontics	only research on traditional endodontic procedures that don't use regenerative techniques.
Publication date	Studies published between 2021 and 2025 will be given priority in order to capture modern methods, while older foundational studies will also be taken into account.	previous studies only if it is irrelevant to current developments or if newer findings have replaced it.
Outcome focus	clinical outcome reports like improved dentin thickness, pulp vitality restoration, root maturation, and apical closure	Studies that only focus on microbiology or unrelated pathologies, for example, lack outcome data pertinent to regeneration.

Data Mining and Data Derivation.

To help standardize the measurement of the methods of regenerative endodontic procedures in accordance with the information of the domains of data gathering and data analysis, the spheres of design areas were identified in accordance with the data about the clinical procedures, scaffold biomaterials, applications, and measurements of the stem cell (Table (2)).

Table [2]: The key areas of Analyzing and Extracting Data

Key area	Description	Focus of extraction
Stem cell types and applications	Details regarding the different kinds of stem cells, where they come from, and how they help to regenerate the dentin –pulp complex	Type, origin, and application in pulp-dentin complex regeneration
Scaffold materials and design	Information about scaffold materials and design technologies that promote distinction, development, and structural organization of cells	Material type (e.g., collagen, hydrogels), structural properties, design innovations
Signaling molecules	Different forms of signaling molecules, including cytokines and growth factors, and how they influence tissue development	types of Molecules, method of administration, function in tissue formation
Clinical protocols and disinfection methods	Different types of signaling molecules, including cytokines and growth factors, and how they influence tissue development	Disinfection agents, methods, stem cell viability support
Outcome measurements	Clinical results include increased dentin thickness, pulp vitality recovery, apical closure, and ongoing root development.	Primary patient outcomes linked to healing effectiveness and tissue repair enhancements

Essential area Description Extraction focus.

Quality and bias All the used studies were analyzed to guarantee reliability. Separation of experimentally conducted studies was done in regards to reproducibility variable, methodological consistency and sample size. We also evaluated the possible source of bias in clinical research and trials, particularly, in the selection of patient, blinding and reporting of the results. The study had been rated on a modified version of Cochrane Risk of Bias assessment as high, moderate or low risks of bias. It created a deep trace of evidence in that it was only the one that passed the test conducted.

Synthesis of Data

Besides the clinical manifestations, the data summarization occurred in the three thematic categories in relation to three elements of the tissue-engineering paradigm (signaling molecules, scaffolds and allogeneic stem-cells). The latest of 2021-2025 will also be placed first among those added to the list to rule out any chance of being incomplete of the newer tendencies of the methodological approaches but none of the older studies of the foundations will be left out. The creation of this summary will help in making a more generalized account of the pertinent developments and challenges in the field that will be implemented in the recommendations and directions of future studies.

Results:

Root Endodontics -based on Stem Cell: New developments.

The immense magnitude of the differentiation capacity of the particular type of the cellular type required in regenerative endodontics gives a significant part of the possibilities of the regeneration of mesenchymal stem cells. Cells that have been utilized in dental pulp revitalization are of many kinds; dental pulp stem cell (DPSCs), apical papilla stem cell (SCAPs), periodontal ligament stem cell (PDLSC) and oral follicular precursor cell (DFPC) have been used 2. The advantage of both sources of tissues lies in the fact that e.g., the odontogenic dental pulp stem cells (DPSCs) have a critical potential that can be best applied in dentinal restorative 6. Similarly, further differentiation of the SCAPs of the developing tooth in the apical papilla could result in the production of dentin of the roots in the necrotic pulp of the immature tooth to continue their root-forming process [1]. Moreover, DPFPCs, DPSCs, SCAPs and periodontal ligament stem cells (PDLSCs) also were underway of being considered as players of pulp dentin regeneration 3. PDLSCs are end potent, that is, able to cover both sides of the regenerative spectrum that restores periodontal ligament and pulp [6], instead, dental-derived tissues generate pulpal stem cells (DPSCs) that can be regenerated in biobanks and used to treat the patient in a customized way [8]. Even, DPSCs and SCAPs are already implanted into root canal of an animal pre-clinical study model which has demonstrated re-formation of pulp-dentin like structures with some of the key components 5. instrument gGOL, however successful results were obtained, is not however a limitation to clinical translation. Ainden. There is also a thorough look into pathways where the targets gain in the cell survival and regenerative capacity of the target genre activation of the gene-modulated stem cells [7]. But the lack of guidelines concerning the use of the stem cells in Endodontics indicates that further findings are needed to present the rules of thumb and make the right selection of the type of cell and applications in the endodontics regeneration[3]. a summary of the properties and treatment applications of the various types of stem cells utilized in endodontics regeneration would be provided in table [3].

Table (3): Characteristics and applications of stem cell types in regenerative endodontics

Stem cell type	Source	Application in endodontics	Advantages	Challenges
Dental pulp stem cells (DPSCs)	Dental pulp tissue	Dentin regeneration and pulp tissue	formation High odontogenic potential	Limited available in mature teeth
Stem cells from apical papilla (SCAPs)	Apical papilla	Root dentin formation, root lengthening in immature teeth	Vitality in immature teeth	Limited to immature teeth only
Periodontal ligament stem cells (PDLSCs) Less	Periodontal ligament	Periodontal regeneration and pulp repair	Supports periodontal ligament repair	studied in endodontic applications
Dental follicle progenitor cells (DFPCs)	Dental follicle	Pulp-dentin complex regeneration	High proliferative potential	Limited availability and research focus

Polymers Regenerative Dentistry.

The scaffold is the most important material of the regenerative endodontics owing to the fact that it will serve as a structural support on which the property of cell division, proliferation and orientation will be supported. Ideally a scaffold would be preferable to be alike with the extracellular matrix of the original pulp tissue and should be biocompatible and biodegradable. Hydro gels, Collagen and chitosan are natural polymers, polycaprolactone and polylastic acid are synthetic polymers are common scaffolds used. Among them, they like collagen-based scaffolds due to the highest biocompatibility and bioreactivity to recap the pulp tissue structure that promotes cell migration and adhesion[11]. Hydrogels and a high water content of these gels also possess the same properties that make them create a humid environment that is conducive to the survival of the cells and delivers the nutrients, which is highly beneficial to regenerative endodontics and its most significant requirement, which is the continuous development of hydrogel [15]. The hydrogen gels are more similar to natural in cellular activity based on its high water content that provides it with an environment of exchange of nutrients and the elimination of wastes[13]. Moreover, growth factors can also be delivered to tissue growth through scaffolded hydrogels, and are able to be localized in time to control cell differentiation[2]. Besides offering the viability of these stem cells, polycaprolactone and other artificial polymers studies have found out that the rate of degradation of these polymers can be programmed to suit the regeneration requirement. Although these were made, however, the scaffold design had issues, that is, it had to be aligned in the pore diameter, mechanical properties and degradation profiles, and the de novo tissue formation process had to be reconciled 10. Moreover, one can also recommend the usage of biologically active scaffolds to enhance the pulp-dentin complex regeneration processes to activate the movement and attachment of the embryonic cells into the odontoblast-like cells 9. A summary of the properties and application of the scaffold materials in regenerative dentistry is represented in Table [4].

Table [4]: The characteristics and uses of scaffold materials in regenerative endodontics

Scaffold material	Type	Properties	Advantages	Challenges
Collagen	Natural polymer	Biocompatible	encourages migration and cell adhesion Endodontics uses a lot of natural extracellular matrix mimicking.	Limited structural strength
Chitosan	Natural polymer	Antimicrobial properties, biocompatible	Supports cell growth and differentiation	Variable degradation rate
Polycaprolactone	Synthetic polymer	Biodegradable, tunable mechanical properties	Supports stem cell	viability Slow degradation in the body
Hydrogels High	Synthetic/natural	water content, can encapsulate growth factors	Promotes nutrient diffusion, customizable	Weakness in structure and difficult handling

Ray out of Endodontics Regeneration.

The regeneration process in the endodontics requires the presence of signalling molecules that trigger stem cell differentiation since they facilitate growth of tissues. Cooperation; this requires the growth factor -b (TGF-B), vascular endothelial growth factor (VEGF) and Bone morphogenetic proteins (BMPs) to work together in this process. VEGF induces angiogenesis and enhances sufficient vascularization that provides a favourable environment to the pulp provided that BMPs are the dominant ones to promote odontogenic differentiation and dentin formation [6]. They are to a large extent utilized in scaffolds or controlled-release systems to retain these bioactive compounds in the root canal[3]. It is an original design of scaffolds having the ability to present the signalling molecules in a spatio-temporal manner which can be characterized by environmental effects that can potentially lead to the achievement of a localized and controlled activation of the cells. However, timing, dosage and control cannot be controlled and abnormality may lead to infection or unsustainable tissue formation[2]. The alternative method, which will be applied, is the gene therapy, meaning the idea of inserting the genes that express the growth factors in target cells, that will allow the formation of the necessary signaling molecules on the long-term and controlled level[5]. Despite the fact that at this time, the approach is still in the experimentation phase, it is also capable of endowing biomolecules with long and regulated bioactivity to save time to achieve adequate regeneration[8]. The (Table 5) that incorporated the production of the key biochemical cues that could be adopted in the regeneration and cell differentiation of the tissue in the course of the endodontics.

Table [5]: Functions and delivery approaches important signaling molecules in endodontic regeneration.

Signaling molecule	Function	Delivery method	Advantages	Challenges
Bone morphogenetic proteins (BMPs)	Promotes odontogenic differentiation	Scaffold-based release	Supports dentin formation	Requires precise dosing
Vascular endothelial growth factor (VEGF)	Stimulates blood vessel formation	Controlled-release hydrogels	Enhances tissue vascularization	Potential for over stimulation
Transforming growth factor beta (TGF-β)	Cell proliferation and differentiation	Gene therapy, microspheres	Broad role in cell growth and immune modulation	Inflammatory response in high doses
Fibroblast growth factor (FGF)	Cell growth and proliferation	Injectable systems	Promotes cellular proliferation and differentiation	Short half-life, challenging delivery

Disinfection, Principles, Clinical Methods and Approaches.

A substantial part of the advancement of regenerative endodontics is the finding of how to deliver the supply of means of treatment that is not a total disinfection and the provision of such a milieu as instead activates the healing and the regeneration of tissue[6]. They form the most used disinfectants in the endodontic therapy because of the high bactericidal effect of sodium hypochlorite(NaOCl), EDTA, and Chlorhexidine in addition, they may precondition the canal to allow easier accessibility of the cell to the canal wall[12]. This is unnecessary to say that sodium hypochlorite is a potent anti-bacterial solution and high-percentage sodium hypochlorite is lethal and can cause the possibility of loss of viability of the stem cells[2]. To circumvent such problems, though, new ones that have been proposed to enhance the efficacy of cleaning without necessarily using strong chemical agents include laser-assisted irrigation as well as light-activated disinfection, among others[13]. Another solution would be use of triple antibiotic paste- metronidazole, ciprofloxacin and minocycline. It has been demonstrated to reduce the survival of stem cells and its bactericidal effect very extensive[7]. That is why the specified study focuses on the aqueous solution to reduce the number of processes available to provide the balance between the biocompatibility and the antimicrobial activity. Success in the regeneration process has been inextricably linked to the survival and quantification of the stem cells, therefore, the reason behind the justification of new methodology that would reduce the risk of cytotoxicity including the rinsing with EDTA following a minimal level of mild sodium hypochlorite. The different procedures and techniques of multiple regenerative disinfection of the endodontics are listing in (Table 6).

Table (6): Disinfection methods and protocols in regenerative endodontics

Type	concertation	Duration (min)	Advantages	Disadvantages
NaOCl	2.5%	5	Most widely used irritant in REPs, A lower concentration preferably is recommended	At higher concentration has toxic effect to stem cells
NaOCl,	5.25%	1	Promotes stem cell attachment	Toxic effect to stem cells at higher concentration
NaOCl	6%	1	Promotes stem cell attachment	Toxic to stem cells with higher concentration
EDTA	17%	5	Excellent smear layer removal and antibiofilm property, promote odontoblast proliferation by inducing a growth factor into the matrix of dentin, Promotes stem cell attachment	Diminishes stem cell attachment
CHX gel,	2%	5	Effectively eliminates bacteria from infected dentin, nontoxic to stem cells	cytotoxic to stem cells, Diminishes stem cell attachment
CHX gel, NaOCl	2%+2.5%	5	Promotes proliferation of stem cells	toxic to stem cell survival

Several New Solutions and Direction.

The last few years have boded well regarding the improvement in the area of regenerative endodontics based on the usage of cell-free technology, the novel architecture of scaffolds, and gene therapy among others. One of the possible methods that could be used to regulate the controlled expression of releasing growth factors through the pulp-dentin complex is to regulate the gene therapy[12]. Genetic alteration of the cells may lead to generation of signaling molecules that are vital towards the path of differentiation as well as tissue regeneration. Such a method can, however, only be practically used in clinical endodontics[15]. With the recent findings on 3D bioprinting, now one can produce patient-specific scaffolds, which can regenerate the natural pulp tissue structure. The pulp ambience yet might be beneficial to the outcome of pulp-dentin regeneration in terms of cellular structure and neovascularisation[16]. Actually, the liberation of the bioactive compounds inherent in the 3D printed scaffolds and whose liberation is controlled leads to the increase in the better and stronger incorporation of the structure which is manifested in enhanced healing[16]. Lastly, one can mention cell-free regeneration strategy which is the substitute of invasive stem cell transplantation based on the delivery of growth factors devices and/or bioactive scaffolds. The therapies have been found capable of averting the probability of immunological rejection, offer an equivalent degree of outcome to the cell-based therapies, and remove the ethical concerns that are involved in the utilization of the stem cells[18]. The approaches can streamline the regenerative process, increases the regenerative process, makes it less expensive, and improves its clinical application[19]. Other than this, further solidified attempts are found to be directed towards the creation of the standardized protocols of regenerative endodontics which can be implemented in the clinical set up. The overall aims of these guidelines are the reduction of disparity in treatment effects, the most appropriate practices in disinfection protocol, the choice of scaffold and the use of signaling molecules. This will require such practices to be put in place to take the regenerative endodontics beyond the animal laboratory and into the clinical practice [20]. Table 7 gives an understanding of the latest approaches and opportunities of the study in the regenerative endodontics field.

Table [7]: Future ways and Innovative Approaches in regenerative endodontics

Technique	Description	Potential advantages	Challenges
Gene therapy	introduces growth factor genes into cells through genetic alteration to promote regeneration.	Accurate regulation of cellular activity and targeted tissue repair	Experimental; risk of off-target effects, immune responses
3D bioprinting	using personalized, biomimetic scaffolds that mimic pulp tissue using bioprinting technology.	Enhanced structural integration, supports cell alignment and nutrient diffusion	Equipment complexity; high cost, accessibility limitations
Cell-free regeneration	depends on growth factors and bioactive scaffolds rather than direct stem cell implantation.	Reduced immune rejection risk, simplified protocol	Sometimes less successful than cell-based techniques
Standardized protocols	creates universal clinical standards for regenerative medicine.	Consistent outcomes, easier mainstream clinical adoption	Reaching an agreement; varying patient reactions

Developments in Biomaterials of Regenerative Dentistry

The discovery of biomaterial science has resulted in inventions of new materials that would aid in pulp-dentin repair through last couple of years. Bioactivity can be included in other bioactive substitutes (e.g., bioactive Glass) and mechanical characteristic in order to support cell adhesion and proliferation like injectable hydrogels, nanofibrous scaffolds and calcium silicate-based cements 12. Calcium silicate-based compounds such as MTA and Biodentine have been used effectively through the formation of a thick layer, which enables the formation of a hard tissue to develop the dentin-pulpal complex 22. Since the biomaterial has a vast surface and structural similarity to the extracellular matrix, that occurs in nature, nanofibrous scaffolds commonly consisting of polylactic-co-glycolic acid (PLGA) would likely increase the surface of interfaces resulting in enhanced stem cell growth and differentiation 23. It has been found that these scaffolds have the capacity to induce the cell activity and biomineralization which ultimately increases the regenerative process[24]. On this basis, injectable hydrogels, including bioactive peptides or nanoparticles, are increasingly becoming popular, due to their simplicity, fine controlled delivery of growth factors and controlled growth of tissue regeneration[25].

Endodontics regeneration in Immunomodulation

The occupation of endodontics regeneration has grown and instead of being a procedure that was previously inspected to focus on revascularization, it has transformed into an immunomodulation (purposeful modulation of immune response) operation. Pulp healing has been known to be mediated by the immune system but excessive amount of immune response or lack of control of the immune system will lead to adverse effects on the process of regeneration 26. Among them, the macrophages take the leading role because of its capacity to develop into the pro- (M1) or anti-inflammatory (M2)-related states that considerably affect the success of regenerative therapies[27]. Thus, they believe that the inflammation of the root canal must be reduced, which is a prerequisite to a successful regeneration[28]. Immune-modulating biomaterials and anti-inflammatory agents (corticosteroids and cytokine inhibitors) have been found to be promising as they increase regenerative fate by maintaining a microenvironment in which the stem cell survival and development is possible[29].

Endodontic Regeneration Procedure Success Rates and Long Term Clinical Outcomes

The long-term effectiveness of them might allow providing the data on the clinical performance of the regenerative endodontic treatment (RETs) and whether this treatment option can be considered one of the standard treatment. The previous researches have found out that REPs could lead to the formation of apex of the root closure, root formation and thickening of the dentin wall of the growing tooth[30]. The outcomes however vary depending on the age of the patient, the stem cells and procedures used[31]. The example of young patients and of imature roots has already recorded favorable reports of subsequent research of permanent but the majority of the well-growth teeth or instances with a tough anatomy of the root still lie ahead to lead to a normal regenerative success[32].

Discussion

Regenerative endodontics not only rebuilt teeth, but also rebuilt their biology, their functionality and this is a game changer of the conventional treatment procedures. Not only in this transition, the stem cells are also capable of regenerating the damaged pulp-dentin complex in addition to offering a vascularity and innervation and immunity defense of the root canal system. The new concepts analysis indicates that the application of stem cells is not a test option but it is gradually finding its way in preclinical and mini clinical practice.

Some of the interesting questions would concern the discovery and characterization of the various sources of a stem cell such as dental pulp stem cells (DPSCs), stem cells in the apical papilla (SCAP), periodontal ligament stem cells

(PDLSCs) 2. The regenerative capacity of different types of cell varies and due to the high proliferation and differentiation capacity of SCAP, it appears to be a desirable choice that can be made to be used in immature teeth with necrotic pulps. The scientists confront the historical paradigm of the application of the inert root canal filling materials through the proposing of other biological methods that allow the root to grow and restore functions[31].

In addition, the scaffolds and signatory molecules of the stem cells increase the pace at which the paradigm shift occurs. The biomimetic scaffolds provide the three dimensional microenvironment where the survival and differentiation of the stem cells, BMPs, VEGF, TGF-b, and other growth factors can stimulate the desirable tissue architecture and maturation. All these will lead to a biological triplication of the proposed regenerative endodontic goal with biological orientation in contrast to the mere mechanical goal of the traditional endodontic treatment. However, the fact that the findings across the different studies are variable also suggests that there is a need to accomplish further standardisation as regards structure of scaffold is addressed, delivery of cell and delivery of signalling molecules are addressed[28].

Obstacles, however, left with good promises are few and far between. On the top of all these merits, harvesting, expanding and storing of stem cells have many ethical and logistical concerns involved, which makes it impossible to scale up and transfer them into clinical therapy. There are also long term safety issues like the existent of abnormal cell growth and the likelihood of immune response. The lack of knowledge regarding how the regeneration should be translated to the field of medicine, and the uncertainty over the success rates which are not always determinable, can be considered the challenges to regeneration. This dilemma is one of the sureties that although the regenerative model can be radical in its concept, the practical implementation is only a few years old[21]. The new technologies including gene editing, exosome-target therapy, and bioprinting are positive measures made to address the existing drawbacks. The directed differentiation of the extracellular vesicles, and the directed differentiation of the gene-modified stem cells, in cell-free substitutes which, in turn, is likely to address the ethical issues which often surround the regenerative cell therapy. Bio printing in its turn allows engaging spatial-designed patient-specific pulp-dentin complex. It is the one that can capture the multifactorial and multidisciplinary character of the concept of regenerative endodontics; the combination of the knowledge of the stem cell biology, material science, and bioengineering [26]. The second notable finding is that the use of the stem cell in the regenerative endodontics can introduce a paradigm shift of what the profession can potentially have a future of dental care. Luckily enough, the traditional treatments are geared towards the control of the disease and the structural integrity, whereas the regenerative ones are geared towards the restoration of the vitality and the functionality.

Conclusions

The Endodontics of Regeneration will be novel, and it will be employed in the final future of the dentistry practice, and the bio-logical pulp-dentin complex restoration shall substitute the biological prescriptive dentistry and restoration, which is examined within the boundaries of preservation theories. The reciprocal association between the stem cell technology, the scaffold formation, and the signaling molecules has developed the new opportunities of non- vital teeth restoration and provided the new aspects of the restoration of the form and functions. However, these problems do not prevent the fact that, despite these challenges, the absence of research results, the inadequacy of the current practice, the new biomaterials, genetic engineering, and bioprinting provide numerous opportunities in overcoming these obstacles, and make it possible to expect predictable treatment. As the regenerative endodontics lab research business is converted to the clinic practice, the paradigm of clinical care can be altered within the dentistry sector whereby the traditional, non-biological based dental care is changed to the biologically based one where a practice-based care is encouraged in the context of the long-term sustainability and the operation of the teeth.

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