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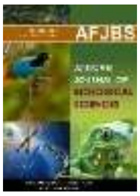

TITLE : Stem Cells For A Smile Reborn : Regenerative Strategies In Dentistry

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ABSTRACT :

In the modern era, dentistry goes beyond simple prosthesis replacement; it's forging ahead into the future with the goal of tissue augmentation through regeneration. Regenerative dentistry encompasses a wide array of techniques and procedures aimed at restoring and enhancing oral function, aesthetics, and overall quality of life. It's a cutting-edge realm where science meets artistry, with recent breakthroughs that harness regenerative techniques to enhance oral health and function, wherein dental implants lead the charge. From bone grafting to tissue engineering marvels, these innovations have paved the way for successful implant placement, periodontal rejuvenation, ridge augmentation, soft tissue augmentation, denture stabilization to maxillofacial reconstruction and craniofacial prosthetics, regenerative dentistry offers hope to enhance treatment planning and execution. With the integration of bioactive materials and digital technologies, precision and customization have reached new heights. In the domain of regenerative advancements, we transcend mere restoration; we pioneer the evolution of possibility, where new beginnings flourish and old limitations fade into insignificance. This review article focuses exclusively on the evolution and potential of regenerative dentistry, shedding light on its role in reshaping the future of dental care.

KEYWORD : Regenerative Dentistry , Prosthetic regeneration, Dental tissue engineering, Regenerative implantology, Tissue engineering in dentistry, Oral tissue regeneration, Stem cell therapy in prosthodontics, Digital technologies in regenerativedentistry

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INTRODUCTION AND BACKGROUND :

In recent years, the field of prosthodontics has witnessed remarkable advancements, particularly in the realm of regenerative techniques aimed at enhancing oral health and function. Dental implants have emerged as a cornerstone in this progress, utilizing regenerative methodologies such as bone grafting and guided bone regeneration to augment bone volume and density, thereby facilitating successful implant placement [1]. Concurrently, the principles of tissue engineering have been harnessed to develop and apply biomaterials and scaffolds for the regeneration of lost or damaged oral tissues, including gums (gingiva) and periodontal ligaments [2]. Moreover, innovative techniques for periodontal regeneration have been devised, focusing on the restoration of periodontal tissues, encompassing bone and attachment apparatus, to address periodontal disease and promote periodontal health. Additionally, procedures such as ridge augmentation have been refined to rebuild and reshape the alveolar ridge, optimizing conditions for implant placement and support. Soft tissue augmentation techniques further contribute to improved aesthetics and function by restoring and enhancing soft tissue contours and volume through approaches like gum grafting and mucogingival surgery. Furthermore, denture stabilization methodologies, incorporating implants and regenerative strategies, enhance the stability, retention, and comfort of removable dentures [3].

The scope of regenerative Dentistry extends beyond these fundamental techniques to encompass maxillofacial reconstruction, where advanced prosthetic techniques and materials restore form and function following trauma, surgery, or congenital defects affecting the maxillofacial region. Similarly, craniofacial prosthetics play a pivotal role in designing and fabricating custom prostheses to replace missing or damaged facial structures, such as ears, noses, and eyes[4-5]. The integration of bioactive materials, including growth factors and scaffolds, promotes tissue regeneration and integration with dental implants and other prosthetic devices, further augmenting the efficacy of regenerative interventions [6]. Moreover, the advent of digital technologies, including digital imaging, CAD/CAM, and 3D printing, revolutionizes precision, customization, and efficiency in regenerative prosthodontic procedures [7]. Collectively, regenerative prosthodontics embodies a dynamic and rapidly evolving discipline, synthesizing principles of prosthodontics, tissue engineering, and

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regenerative medicine to offer innovative solutions for restoring and rejuvenating the oral cavity and facial structures, ultimately enhancing patients' quality of life [8-9].

Regenerative Dentistry has evolved significantly over the past decades, driven by key milestones and innovations in dental science and technology[10]. Originating in the 1950s and 1960s, seminal research laid the foundation for understanding tissue regeneration in the oral cavity, leading to advancements in bone grafting techniques and biomaterial utilization[11]. The introduction of dental implants in the 1960s marked a pivotal moment, facilitating the application of regenerative techniques and spurring progress in implant materials and surgical methodologies [12]. The subsequent decades witnessed rapid developments in bone grafting and guided bone regeneration, enhancing support for implant placement[13]. The late 20th century saw tissue engineering emerge as a promising avenue, exploring growth factors, scaffolds, and stem cells for tissue regeneration[14]. The 21st century brought digital technologies like CAD/CAM and 3D printing, revolutionizing regenerative procedures with precise planning and customization[15,16]. Ongoing research focuses on the use of novel biomaterials, such as bioactive glasses, biodegradable polymers, and tissue-engineered scaffolds, for regenerative prosthodontics. These materials hold promise for improving biocompatibility, functionality, and longevity for enhanced tissue regeneration and patient outcomes [17].

REVIEW :

This review comprehensively analyzed published articles exploring the application of regenerative dentistry and stem cells in dentistry. To capture all relevant research, we conducted a thorough search across various databases, including PubMed and Google Scholar. Our search strategy employed a combination of keywords such as "regenerative dentistry," "regenerative therapy," "stem cells," and "dentistry." This approach ensured we retrieved all pertinent publications in these fields. Following the initial search, 54 articles demonstrating significant relevance were chosen for in-depth review. By analyzing these articles, this review aimed to illustrate the development and potential of regenerative prosthodontics, highlighting its capacity to revolutionize the future of dental care.

Regenerative Dentistry is an interdisciplinary field that combines the principles of tissue engineering, stem cell biology, and biomaterials science to regenerate damaged or lost dental and oral tissues. Stem cells are undifferentiated cells that have the capacity to differentiate into various types of cells in the body, including extraembryonic cells such as those found in the placenta, as well as specialized cells like fibroblasts, odontoblasts, and adipocytes. These cells can be classified as either embryonic or adult stem cells. Adult stem cells are particularly interesting because of their ability to differentiate into multiple types of cells, making them multipotent, or in some cases, pluripotent (derivation of somatic cells) [18].

Dental stem cells are a specific type of adult stem cell that are derived from the cranial neural crest and are mesenchymal in nature. These stem cells are responsible for the formation of several important structures in the mouth, including the dental papilla and dental follicle, which ultimately lead to the development of teeth [19].

Dental pulp stem cells (DPSCs) can differentiate and are used in various types of tissue regeneration, including mandibular bone defect regeneration, muscle regeneration, craniofacial skeletal regeneration, and angiogenesis. Other dental stem cells include periodontal ligament stem cells (PDLSCs) and stem cells from apical papilla (SCAP), which are used in bone regeneration, neurogenic defects, and angiogenesis [20]. Tissue engineering is a process used for the regeneration of damaged tissue using stem cells, scaffolds, and signaling molecules. It eliminates common complications associated with prosthetic alloplasts, such as infections, inflammation, immunosuppression requirements, and compatibility with host tissues. Tissue engineering strategies include cell injection therapy, cell induction therapy, and cell seeded scaffolds. Biomaterial scaffolds act as a guiding platform for stem cells and help in differentiation and tissue regeneration. Scaffolds can be made of metals, ceramics, natural polymers, or synthetic polymers. The mechanical properties of scaffolds, such as fiber, porosity, and stiffness, affect biomaterial cell adherence and potential differentiation ability [21]. Growth factors used in regenerative therapy can be classified as inflammatory growth factors and cytokines, angiogenic growth factors, and osteogenic growth factors. Extracellular vesicles (EVs) are lipid bilayer-bound vesicles produced by cells and are used in intercellular communication and can have paracrine or autocrine biological effects in tissue metabolism [22].

This approach offers several advantages over traditional prosthodontic methods, which often rely on the use of artificial materials to replace missing tissues. One of the key benefits of regenerative prosthodontics is its ability to promote the growth of new, healthy tissue, rather than simply replacing damaged tissue with artificial materials. This can lead to improved function and aesthetics, as well as a reduced risk of complications such as infection or implant failure.

Moreover, regenerative dentistry holds particular promise for the treatment of complex cases, such as those involving extensive tissue damage or the loss of multiple teeth. In these situations, traditional prosthodontic methods may be insufficient to fully restore oral function and aesthetics. Regenerative dentistry , on the other hand, offers the potential to completely regenerate lost tissues, providing a more comprehensive and effective solution.

CASE STUDY :

A number of studies have demonstrated the potential of regenerative dentistry in clinical settings. For example, a study by Duan et al. (2019) found that the use of autologous stem cells and biodegradable scaffolds resulted in the successful regeneration of alveolar bone in patients with periodontitis [23]. Similarly, a study by Yang et al. (2018) found that the use of a tissue-engineered construct composed of mesenchymal stem cells and a biodegradable scaffold resulted in the regeneration of dental pulp tissue in patients with pulp necrosis [24].

Despite these promising results, regenerative prosthodontics is still a relatively new field, and further research is needed to fully understand its potential and limitations. Nevertheless, the early evidence suggests that this approach has the potential to revolutionize the field of oral rehabilitation, offering new hope to patients with complex dental and oral conditions.

Smart Biomaterial-tissue Interface

The ability to control cellular response through the development of a smart biomaterial-tissue interface may allow for regulated cell delivery and regeneration in biomedical implants.. Biomedical metal implants cannot sustain the cell's growth for an extended period of time, in contrast to tissue-engineered scaffolds, where the cell-seeded matrix can regenerate a bone matrix.Stimulussensitive hydrogels can stop metal implants from corroding and inflaming the body. To speed up the healing process, mesenchymal stem cells (MSCs) are being injected into the damaged area. This strategy might lessen the risk of osteolysis and enhance patients' quality of life.[25,26]

Tissue-engineered Cell Sheet

A bio-implant covered in multilayered cell sheets was created by Le et al. [27]. Human cementifying fibroma cells and immortalised human cementoblasts were co-cultured. Furthermore, human umbilical vein endothelial cells and epithelial cells that had been tagged with GFP (Green Fluorescent Protein) were used to create multilayered cell sheets. The study's findings unequivocally showed how each type of cell is involved in an implant fixture when there is newly formed calcified tissue on the fixture's surface. Moreover, on the bi- and tri-layered cell sheets that resembled periodontal tissue, oxytalan fibres could be seen. This work gives us convincing proof that regenerative medicine techniques are used in biomedical implantation.

Dental Pulp Stem Cells on Implant Surface

DPSCs' osteogenic capacity, accessibility, and cryopreservation resistance make them ideal for studying bone differentiation. They hold promise for bone tissue engineering, integrating with 3D scaffolds for advanced analysis.Di Carlo et al. [28] analysis of graphene oxide was centred on a titanium modified surface. The authors assessed the cytotoxicity, osteogenic differentiation, and viability of dental pulp stem cells on titanium surfaces coated with graphene oxide.

Laino et al. [29] evaluated dental implant surfaces (Myth, Maipek Manufacturer Industrial Care, Naples, Italy) for their cytotoxicity, cell adhesion, and influence on key factors for successful implant osseointegration, such as osteoinduction and vasculogenesis. Their study employed various techniques including 3D cell culture (histology), immunofluorescence FIGURE 1, proliferation assays, scanning electron microscopy, and PCR analysis. These methods revealed promising results, suggesting the Myth implant surface promotes increased mineralization of tissues when interacting with DPSCs..

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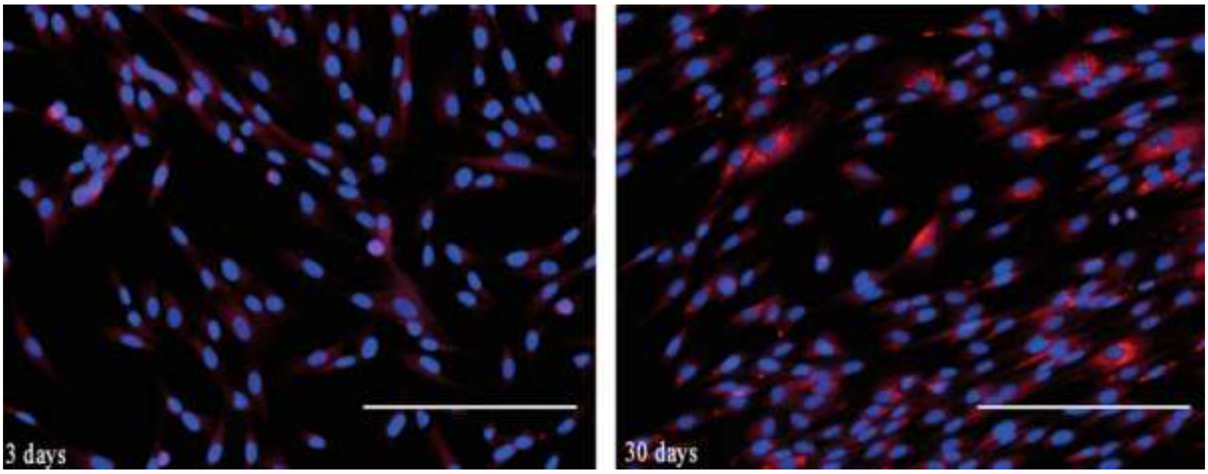

Immunofluorescence by Hoechst and OSTC on device DPSCs/Myth (Maipek Manufacturer Industrial Care, Naples, Italy) at 3 and 30 days of culture.[29]
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Stem cells from human exfoliated deciduous teeth (SHEDs)

Stem cells derived from shed baby teeth (SHEDs) offer several advantages for bone regeneration therapy. Compared to other mesenchymal stem cells (MSCs), SHEDs exhibit a faster proliferation rate and a stronger ability to stimulate bone formation in living organisms (in vivo) [30-33]. Additionally, obtaining SHEDs is simpler than acquiring other types of MSCs. Xu Cao et al. [34] investigated the effects of SHEDs on early bone formation around implants in an in vivo experiment.They discovered that loading the implant with SHEDs before implantation enhanced the beagle dogs' initial osseointegration , boosted bone formation in the thread and surrounding the implant, and produced thicker, denser trabecular bone. According to these findings, SHEDs may encourage early osteogenesis surrounding implants and offer a potential avenue for stem cell therapy in upcoming implant-related clinical trials.

Mesenchymal stem cells (MSCs) in sinus lift augmentation (SLA)

Studies suggest that using bone marrow-derived mesenchymal stem cells (BM-MSCs) during maxillary sinus floor elevation can improve bone formation. Q. Zhou et al. [35] observed a significant increase in BM-MSC differentiation into bone-forming cells (osteoblasts) and enhanced new bone formation after implantation. Similarly, D. Kaigler et al. [36] found that patients receiving stem cell enriched with a specific marker (CD90+) experienced higher bone density and safe application in maxillary sinus reconstruction. Additionally, D. Rickert et al. [37] reported successful osseointegration in all patients receiving implants with BM-MSCs in a clinical trial. These findings suggest potential benefits of BM-MSCs for promoting bone regeneration and successful dental implant placement.

Human umbilical cord mesenchymal stem cells(hUCMSCs)

According to Kuntjoro M. et al., the in vivo injection of hUCMSCs successfully increased osteoblasts, BIC value, and Runx2, while also decreasing Osterix expression, suggesting a faster rate of bone maturation.The findings demonstrated that in diabetic rat models, hUCMSCs could improve and speed up implant osseointegration[38].

Regenerative Treatments of Stem Cells in Dentistry

Tissue engineering uses a variety of methods, including scaffold-based cell cultures, biomolecular signalling, and stem cells, to achieve the goal of regeneration therapy, which is to restore damaged areas [39]. The first human PDL tissue-derived MSC populations were discovered in 2004[40]. Subsequently, a number of stem cell lineages with appropriate performance from diverse sources were found to be able to build the mineral structure resembling dentin and May be capable of restoring damaged structures [41]. For severely damaged dental pulp, endodontic treatments using mesenchymal stem cells (MSCs) aim to seal the root canal while maintaining its connection with the surrounding dentin. However, challenges exist. Caries and trauma can disrupt the pulp's cellular and molecular processes, triggering inflammation or regeneration attempts as the body's defense mechanisms [42, 43] .

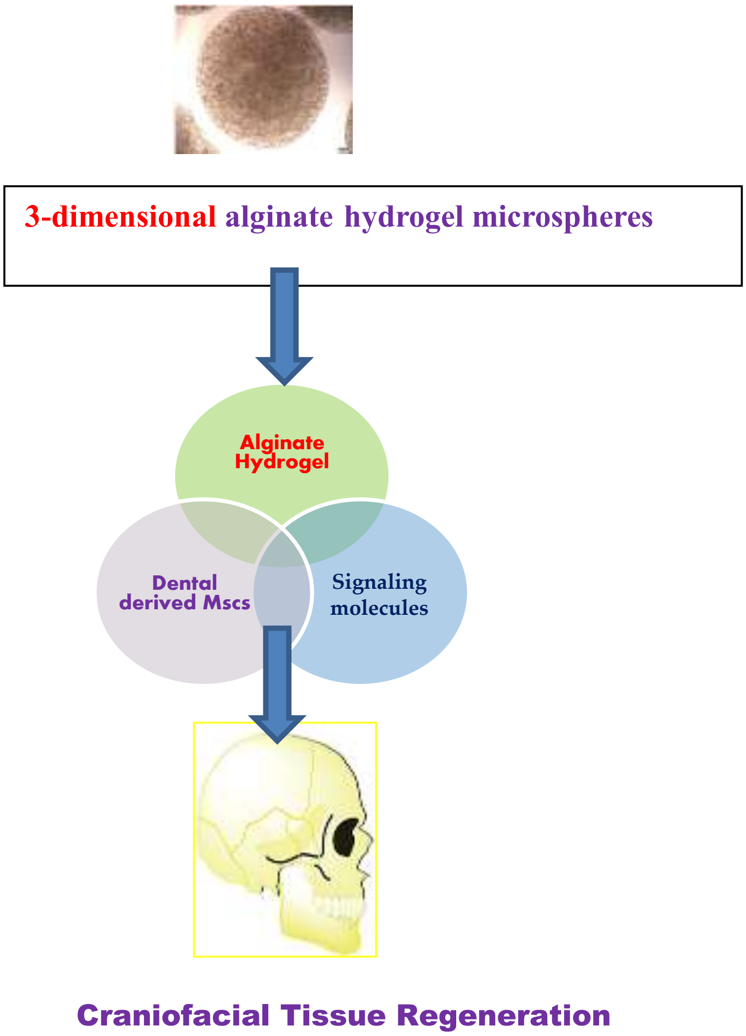
Regenerative Dentistry ” – Application & challenges

Oyanagi, T et al [44] suggests that Insulin-like Growth Factor 1 (IGF-1) plays a key role in growing larger bioengineered teeth. The study found that IGF-1 treatment increased the size of tooth germs, structures that develop into teeth. Interestingly, this growth factor not only increased the overall size of the bioengineered teeth but also the number of cusps on their surface. This is the first evidence that IGF-1 can be used to create larger and more complex bioengineered teeth.

Instead of patching tissues with stem cells, regenerative medicine might revolutionize healthcare by creating entirely new organs. This approach, called organ replacement regenerative therapy, utilizes 3D cell manipulation techniques in the lab to build functional replacements for failing organs[45,46].

Oshima M et al reported[47]that transplanted bioengineered tooth units can successfully integrate into the jawbone, even in areas with significant bone loss. This integration appears to occur through recipient bone remodeling, a natural process where the body adjusts the bone structure. These findings hold promise for the future of tooth regeneration, not just for replacing single teeth but also for treating cases with severe bone loss alongside tooth loss.

Alginate hydrogel microspheres loaded with dental-derived mesenchymal stem cells (MSCs) offer a promising and minimally invasive approach for craniofacial tissue engineering. These microspheres can effectively fill irregular defects, reducing the need for extensive surgery[48] . **FIGURE 2**



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Previous research successfully showed that transplanting a natural tooth germ into a gap (diastema) in a mouse's jaw led to the tooth erupting functionally[49].

Transplanting a lab-grown tooth unit into the jawbone opposite the first upper molar resulted in successful integration within 40 days. The tooth unit formed its own periodontal ligament and fused with the jawbone[50].

Bio-hybrid dental implant

Safi IN et al[51] prepared β-TCP-coated(beta-tricalcium phosphate) Bio-hybrid dental implant using stem cells . Co-culture was key to reducing PDLSCs. Three-layered cell sheets were constructed, and mesenchymal-tissue-layered cell sheets were used to generate periodontal tissue. Temperature-responsive tissue culture dishes and collagen graft were used to surround the implant. Figure 3

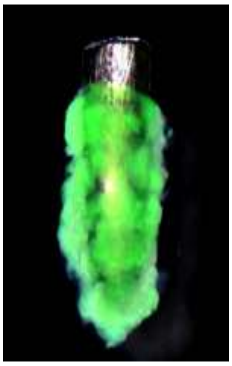

FIGURE3 **Bio-hybrid dental implant**

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In place of embryonic tissue, Lee, DJ et al [52] described the use of cell sheets made from immortalised human cells for implantation and the regeneration of a living periodontium. The cell sheet technique was created to get around the drawbacks of injecting single cells suspensions or biodegradable scaffolds for tissue reconstruction.

Regenerative therapy faces challenges in moving beyond nonbiological methodologies and relying on tissue-based therapies through better research, clinical translation, and knowledge dissemination.[46] Adult stem cells have limitations in cell differentiation post-transplantation, making it difficult to reproduce the whole human tooth with functional enamel intact.[49] Expanding epithelial cells is a strenuous process compared to mesenchymal cells, making alternative sources of dental epithelial cells urgently needed. The jaw's support for bioengineered tooth germs is also a concern, as the dental follicle is essential for tooth eruption.[50] Only a few successful reports of bioengineered root tooth formation with functional PDL tissues exist, and the immune response to bioengineered human teeth remains an uncharted territory[53] . Despite dentists managing periodontal diseases using stem cells and scaffolds, whole-tooth regeneration using regenerative therapy remains a challenge and requires further research[54].

Limitation & Future Direction

More extensive clinical trials are needed to validate the efficacy and safety of stem cell therapies in a broader patient population. Developing standardized protocols for stem cell isolation, manipulation, and delivery will ensure consistent and reliable treatment outcomes. Combining stem cell therapies with 3D printing technology could allow for the creation of customized biocompatible scaffolds to support tissue regeneration. Ethical considerations surrounding stem cell research, such as informed consent and source of stem cells, need to be carefully addressed. Long-term studies are crucial to evaluate the durability of treatment effects and identify any potential long-term side effects. By addressing these limitations and pursuing these future directions, regenerative prosthodontics has the potential to revolutionize oral healthcare, offering patients new possibilities for restoring lost or damaged teeth and tissues.

CONCLUSION :

In conclusion, regenerative prosthodontics represents a significant advancement in the field of oral rehabilitation. By promoting the growth of new, healthy tissue, this approach offers a more comprehensive and effective solution for the restoration of damaged or missing teeth and tissues. While further research is needed to fully understand the potential of this approach, the early evidence suggests that regenerative prosthodontics has the potential to transform the way dental professionals approach oral rehabilitation.

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