Journal of Contemporary Dental Sciences

Review Article

Recent Advances of Tissue Engineering in Dental Applications. A Literature Review

Amir Assarian[1]*, Ban Almudarris[2], Ahmed Tarek[3], Farah Alqaderi[3], Manea Alahmari[4], Hossam Abdelmagyd[5,6]

[1]Dental Intern, College of Dentistry, City University Ajman, Ajman, UAE, [2]Department of Prosthodontics, College of Dentistry, City University Ajman, Ajman, UAE, [3]Clinical Instructor, Department of Preventive Dental Sciences, College of Dentistry, City University Ajman, Ajman, UAE, [4]Department of Periodontics and Community Dental Sciences, College of Dentistry, King Khalid University, Abha, Saudi Arabia, [5]Department of Periodontics, College of Dentistry, City University, Ajman, UAE, [6]Department of Oral medicine and Periodolontolgy, Faculty of Dentistry, Suez Canal University, Ismailia, Egypt

***Corresponding Author:**
Prof. Hossam Abdelmagyd
E-mail: h.abdelatty@cu.ac.ae

Access the journal online
Website: https://jcds.qu.edu.sa/index.php/JCDS
e-ISSN: 1658-8207 **PUBLISHER:** Qassim University

ABSTRACT

Introduction: The birth of tissue engineering as a new dentistry sphere opened up new horizons and created a platform for the introduction of innovative and effective methods of regenerating dental tissues and structures. The aim of this work is to summarize recent advances of tissue engineering in dental applications. **Methods:** The search was conducted through MEDLINE, Google Scholar, and PubMed as well, a sort of healthcare metadata that emphasizes health-focused content. **Results:** Recent advancements in tissue engineering have enhanced the potential for creating new biomaterials. **Conclusion:** Several strategies are under investigation including techniques such as stem cell use, growth factor application, and scaffold grafting.

Keywords: Biocompatible materials, dental implants, dental tissue engineering, regenerative dentistry

Introduction

The restoration of dentition is a significant challenge in the field of dentistry which makes it a necessary factor to create innovative approaches to address the consequences and limitations that are mainly associated with conventional treatment options of dental implantations, dentures, and bridges.[1] Even though there are drawbacks to using autologous grafts from living donors or even bodies these traditional standard techniques are still utilized in dentistry and other medical fields to replace missing or weakening tissue, such as the opportunity of infection and rejection after the transplantation process.[2]

Regenerative medicine offers an inventive substitute by fusing human self-healing capacity with tissue engineering to guarantee the regeneration, repair, or replacement of damaged tissues and the restoration of their compromised function.[3] Together with materials science, medicine, bioengineering, cell, genetics, molecular biology, and other multidisciplinary fields, the developing discipline of biotechnology is involved in the *in vitro* engineering of tissues and organs. Patients experience severe physiological and psychological effects when this happens in the craniofacial region. Affected patients consequently want the craniofacial area to be restored to its optimal degree of function and aesthetics. Loss of tissue as a result of illness, trauma, or congenital defects is a significant global health issue.[4]

Tissue engineering ensures the restoration and regeneration of dental tissues, a promising factor in the reformative field of medicine by offering these opportunities.[5] Including pulp, periodontal ligaments, dentin, and even enamel. Because stem cells are non-specialized and have the ability to differentiate into other types of cells as well as self-renew, they have found widespread application in regenerative medicine. Stem cells may be classified according to their nature, into embryonic or adult types.[6] Integrating bioengineering, stem cell biology, material science, regenerative medicine, and other multidisciplinary strategies will assist in revolutionizing the field of oral rehabilitation and provide patients with various solutions regarding their functional and aesthetic dental solutions.[7]

Regenerative medicine and tissue engineering aim to endorse tissue regeneration or replace failed or damaged organs, combining support or provision materials, appropriate cells, and bioactive molecules.[8] In contrast to other existing treatments, which have a number of drawbacks for patients, due to prosthetic alloplastic materials such as the loss of sensory and motor functions of craniofacial structures, a high risk of infection and inflammation, the need for lifelong immunosuppression, or unpredictable donor compatibility in the case of autologous grafts, tissue engineering offers the potential to regenerate tissue for specific defects.[9] Furthermore, immunosuppression is not necessary for the limitless bioengineered resources that are available.[10]

Dimensional porous scaffolds and hydrogel matrices for specific tissue engineering strategies, among the various materials, have been proposed for formal applications. Polymers of natural origin are one of the most interesting strategies, mainly due to their extracellular matrix (ECM), a wide range of chemical applications, and generally for good biological performance.[11] Tissue engineering and regenerative medicine aim to promote tissue regeneration or replace failed or damaged organs, combining scaffold or support materials, appropriate cells, and bioactive molecules.[3] Dimensional porous scaffolds and hydrogel matrices for specific tissue engineering strategies among the various materials have been proposed for formal applications, polymers of natural origin are one of the most interesting strategies, mainly due to their ECM, a wide range of chemical applications, and generally for good biological performance.[12]

Materials and Methods

The materials and methods of the systematic review are the process of a thorough search and the digest of the suitable data, which are related to the pre-determined issue. The process is made of multiple steps, including search criteria that help narrow the search, systematic searching from multiple databases using pre-defined terms, and reviewing and selection of studies that meet the pre-allocated criteria. The next step is to search and collect studies that relate to chosen data and then data extraction and synthesis methods will synthesize and summarize important information from the studies. Quality assessment tools are usually employed to address the methodological issues of those included studies. The systematic review is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines in place to guarantee the systematics and reproducibility in the process of the review (Figure 1).

Methodology – Ontology and epistemology

This evaluation technique provides procedures for the implementation of tissue engineering in cases of dental applications, authoring for the development of detailed guidelines. With it, you are fully guided from the problem state identification to the hypothesis testing, and so you are sure that the subject is well grasped. Despite the acknowledged utility of analysis in the area of tissue engineering in dentistry, the interpretive method is preferred because it allows for an account of what people feel and the meaning that they make out of their engagements. This way of work makes the field complex, but it provides critical assessments as well as the actual issues and progress in the field. The scientific subject of tissue engineering is super complex here, so researching logically and in context are of paramount importance when it comes to this domain of science, because they allow scientists to cover all aspects of the tissue engineering outcome, including biomaterial properties, biological responses, and clinical applications. Acknowledging the multi-layered essence of tissue engineering in odontology, scientists should make a scientific study design that accommodates the scientific foundation and vision, enabling a complete insight of new issues and difficulties in the field.

Theoretical frameworks

In considering the brand-new prospects in tissue engineering for dental applications in the background

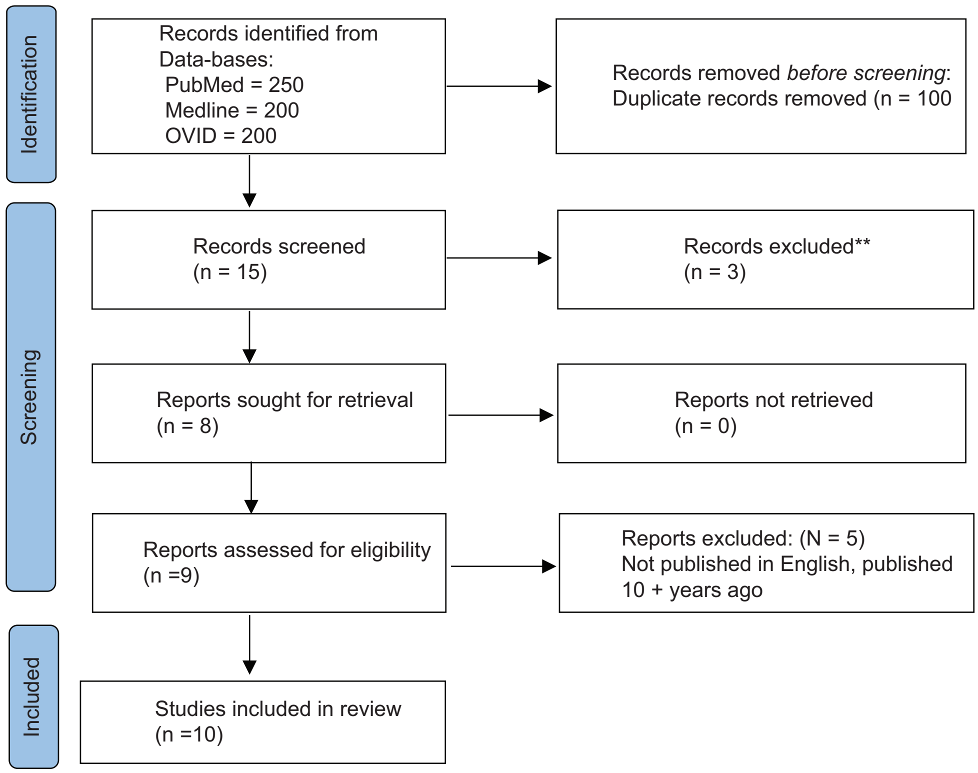

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart

of a couple of theoretical frameworks, they can help a lot in clarification of the complexities and application of this field. One instance of such design is the biomimicry idea, which nurtures the innate ability to acquire materials, construction, and functionalities that are just like nature. Biomimicry is one of the biggest factors that contribute to the development of necessary biomaterials by imitating the properties and function of the natural tissues, which facilitate better biocompatibility and tissue regeneration in the tissue engineering.

Research strategy and design

While relatively a small-scale research with slight, among other, limitations of second data analysis and the complex and sensitive topics considered, this study attempts to investigate recent novelty and innovation in contemporary tissue engineering in dental practice by using literature review as the research method and available data as the main sources. Relevant keywords were chosen, the databases were selected, and the required researchers were staffed. Initially, literature research was undertaken with different searching sites type being utilized for identifying relevant studies. First, an in-depth and systematic search was conducted through MEDLINE, Google Scholar, and PubMed as well, a sort of healthcare metadata that emphasize health-focused content. On the other hand, government websites, scholarly databases, and archives were employed which are directly linked to the tissue engineering and dentistry experimental research.

Methods - Data collection

The list of secondary sources for the study on the recent progress in tissue engineering related to dental applications was extensive: the comprehensive research strategy targeted the identification of relevant peer-reviewed research publications and academic journals that were related to the area of interest. Moreover, publications and reports of significant health departments, hospital networks, and dental union's information have also been researched. Besides the national surveys and the data acting as a source for tissue engineering and dentistry, the search was performed together with policies, guidelines, and documents related to the advising technologies of tissue engineering and dentistry. An analysis study was done finding out the context of the topic from different reputable research reports and qualitative surveys that are essential in providing such a concept. It was initially concentrated on the articles and works which were published between the periods 2000–2023.

Results

This review employs a quantitative technique that analyzes the secondary data in relation to the recent findings in tissue engineering in the dental field. Secondary data sources involve professional journals, papers, official publications, and databases specializing in the area of tissue engineering for treatment in dentistry. Thematic analysis and content analysis are the chosen research methods. They are actually the systematic coding and categorizing of information belonging to the analyzed group which then identifies the key themes.

Recent advances in regenerative dentistry and tissue engineering in dental applications

Stem cells and fibers tissue engineering

Every odontoblast that produces dentin behind that is lodged a single dentinal tubule leaves a cellular process. Dentin and odontoblasts have a close relationship that makes them essential tissues because of their same developmental history.[13] The cementum, a different type of mineralized tissue, covers the root dentin. Tendon-like fibers penetrate the surrounding alveolar tissue as well as the cementum. While it is still difficult to replace entire teeth, it may be more feasible in the near term to regenerate tooth elements, such as dentin or enamel that are often lost due to illness. A significant advancement in regenerative dentistry has been made from the recent isolation of postpartum stem cells in a range of oral tissues.[14] These cells provide a perfect tool for future therapeutic options. On the other hand, bioactive matrices, in tissue engineering frameworks which enable the integration of biomolecules and consequently can induce the desired cellular response, replace the passive cell delivery technologies.[13]

Innovative scaffolding materials and dental stem cells in regenerative dentistry

The possibility of achieving the stated objective may be possible thanks to the engineering of oral tissues with innovative scaffolding materials and the combination of dental stem cells. New biologically based regenerative medicines may soon render obsolete the use of non-functional biomaterials to replace lost jaw teeth. Regenerative dentistry will be built around three key pillars in dentistry: molecular principles of tooth wear, the repair and growth, and tissue engineering of biomaterials in new technologies.[14]

Necessary components for successful tissue engineering

Convinced that a matrix scaffold, cells, vasculature, and space each with a unique and substantial molecular basis are necessary components for successful tissue engineering. Our method makes use of these components. With the potential due to trauma to reinstate tissues lost, cancer surgery, or organ failure, tissue engineering is a multidisciplinary arena. Numerous molecular connections both outside and inside the cell are required for the effective creation, addition, and conservation of any tissue-engineered product.[15] Models, which were first created in the mouse, with cells and ECM such as endogenous fibrin or Matrigel. In a polycarbonate housing, there is an arteriovenous loop (venous supply) embedded.

Innovative applications of tissue engineering in periodontics and dentin pulp restoration

This technique has been adapted for the mouse to generate islet cells and adipose tissue for rabbits and pigs and has also been extended. Using numerous sorts of stem cells, the area of regenerative dentistry which encompasses periodontics growth factors (GFs), scaffolds, endodontics, and maxillofacial management of lost oral tissues surgery aims to smear the principles of tissue engineering to the according.[16] In the field of periodontics to restore the injured periodontal organ tissue engineering techniques have previously been utilized, with promising outcomes documented in clinical practice. In addition, procedures for tissue engineering are being used to rebuild the dentin pulp.

Responsible factors in tissue engineering

Most cells and tissue structures are surrounded by an elastic network called the ECM, which is made up of a variety of proteins including collagen, proteoglycans, and laminins. Depending on the type of tissue and stage of development, the ECM has varied distribution, organization, and composition. Examples of proteins and glycoproteins that make up the ECM are collagen, laminin, fibronectin, proteoglycans, polysaccharides, and hyaluronic acid.[17]

Advantages and drawbacks of naturally generated materials in tissue engineering

Narrated that receptor-GF interactions are introduced in embryonic morphogenesis and important functions are played. When compared to synthetic scaffolds, naturally generated materials, such as Matrigel and collagen have certain advantages. These substances have established cell binding sites and are recyclable. The degree of immunogenicity and the rate of degradation, for particular qualities, are some possible drawbacks, such as the alleged inability to customize the native matrix. It is used extensively in basic science to study the interactions between cells and matrices, and it is being used more and more in tissue engineering, especially in areas, such as nerve, skeletal muscle, and adipose tissue.[17]

Applications of collagen scaffolds in tissue engineering and tooth regeneration

Examined osteogenesis, after 4 weeks usage of a collagen sponge scaffold. Tissue engineering also has promise in essential pulp remedies for tooth regeneration in particular.[18] I Moreover, a collagen sponge impregnated with periodontitis cells was located to flawlessly restore the entire authentic cementum of bone defects in dog teeth consistent with,[19] using bioresorbable collagen and bovine-derived xenografts in patients with periodontal pathology confirmed sizeable development; One 12 months after remedy, the intensity of probing and treatment inclusion reduced. To promote mobile migration and differentiation, a brand new matrix can be needed if the damaged section of the matrix has restrained its potential to regenerate. By the usage of artificial scaffolds, dentin manufacturing has been completed, such as alginate hydrogels.

Biological responses to mechanical forces in tissue engineering

Mechanical forces have recently attracted renewed attention to understanding the complexity of biological organizers of living tissue. Despite numerous *in vitro* studies many cellular processes important for developmental control have shown that they are affected by the physiological deformation of cells through their known ECM. Although the exact process or mechanisms of a biological reaction are unknown by which mechanical stress is converted, through their connections to the actin cytoskeleton and other signal transduction proteins there is evidence that integrins play a significant role. The notion that adhering cells to understanding how changes in ECM tension can regulate the cellular structure and function under a state of isometric tension is crucial.[20]

Researchers must ascertain the effects that[21] with surrounding native tissues these physical forces will have on the composition, long-term integration, and be subjected to mechanical forces *in vivo* the function of the cells within tissue-engineered constructs, as these constructs will continue. Ultimately, for tissue regeneration, the goal is to better understand how mechanical variables contribute so that physical factors can be used to promote tissue regeneration both *in vivo* and *in vitro*. Physical variables have been shown to enhance or hasten tissue regeneration and repair *in vitro*. An *in vitro* model for mechanically driven cell growth that does not directly involve soluble GFs is predicted to be developed shortly.

Physical pressures to improve tissue regeneration have also been applied *in vivo* in a variety of tissues, urogenital viscera, bone, skin, and skeletal muscle including nerve, colon, and lung. The documented clinical practice of skin expansion and distraction osteogenesis is based on the application of tissue stretch, local hypoxia, a recognized angiogenesis stimulator, that occurs in tissue engineering constructions and scaffold areas devoid of an underlying capillary network. In hypoxia-precipitated transcription elements (HIF-1a, HIF-2a) hypoxia ends in a growth, which in flip triggers the expression of angiogenic elements, which includes vascular endothelial growth component, erythropoietin, angiotensin-2, hepatocyte increase component, a placental growth element. The information on vascular growth is used by tissue engineering techniques to choose appropriate matrix materials and include boom factors that can be bonded to the scaffold or covered in composite beads for constant and well-timed launch.[22]

Angiogenesis in tissue engineering: Implications for dental applications

Angiogenesis is exemplified in the adult body by the development of new blood vessels during cancer growth, inflammation, and wound healing. It will be quite helpful to recapitulate this in the context of dentistry when using any new construct. In engineered tissue, the endothelium that is created anew may result from the attraction of circulating endothelial progenitor cells or from the migration and co-optation of the pre-existing endothelium. Peripheral blood contains endothelial progenitor cells, as was first noted in 1997.[23]

The adult organism lacks hemangioblasts, the pre-cursor cells that give rise to endothelial cells and red blood cells in the embryo. They express the AC133 antigen, on endothelial progenitor cells which is expressed exclusively, as well as CD34, VE-cadherin, and vascular endothelial GF-R2. Given that CD34+ FLK-1+ cells have been demonstrated to be able to differentiate into both endothelial and hematopoietic cells, it has been proposed that these cells bear similarities to the post-natal hemangioblasts population.[24] Numerous *in vivo* studies have reported the role of endothelial progenitor cells in adult neovascularization. However, the exact amount of their contribution varies greatly according to the model employed.[25] The tissue of the periodontium is likewise much vascularized. The periodontium perforations of the anastomoses and alveolar sockets with blood vessels are supplied from the periodontal ligaments by the interseptal artery, forming a polyhedral network around the tooth that resembles a stocking. Numerous different GF investigations have been carried out to stimulate angiogenic activity and the proliferation of periodontal ligament cells.

Application of fibroblast-2

A study showed that the application of fibroblast-2 in periodontal ligament cells increased laminin, which was suggested to affect angiogenesis Hepatocyte GF can promote tubulogenic and proliferation in these endothelial cells *in vitro*, protein effect on periodontal endothelial cells and tissue repair of the according to a separate study on the topic, major nerves such as the sublingual and mental facial nerves are major blood vessels of the nasopharynx the final branches of the peripheral nerves.[26] A unique class of biomaterials known as bioceramics is used to replace, supplement, cure, or repair the body's diseased or injured hard tissues.[27] Ceramics are used not just in the medical profession but also in the electronic, optical, and energy fields. The first bioceramic material to be used for crown treatment in the eighteenth century was porcelain. Later, in the 19th century, plaster of Paris[28] was used to treat dental diseases. Due to technological advances in the 20th century, bioceramics have increased in biomedical applications. These materials are mainly used for their high mechanical strength, moderate degradation, and biocompatibility. In addition, clays have properties such as high melting temperature, low temperature, and high plastic shrinkage. These properties make bioceramics body-friendly. Specific techniques and guidelines are needed to produce a high-quality porous scaffold. These materials can be composite (such as polyethylene hydroxyapatite [HA]) or polycrystalline (such as alumina or HA), and bioactive glass or glass ceramic (A/W) (13 bio-glasses, zirconium oxide (ZrO_2), calcium phosphate due to its excellent mechanical properties. Materials, such as (CaO), and aluminum oxide (Al_2O_3) are widely used in the biomedical field, especially in hard tissue engineering The functionality and biocompatibility of these ceramic materials are important for their success (Table 1).[29]

Discussion

The field of tissue engineering holds great promise for revolutionizing dental care by offering innovative solutions for regenerating damaged or lost dental tissues.[30] The articles reviewed provide valuable insights into various aspects of tissue engineering in dentistry, including the use of stem cells, biomaterials, and advanced techniques for tooth regeneration.[31]

One of the key findings highlighted in the literature is the significant role of stem cells in dental tissue regeneration. Stem cell-based approaches offer a promising avenue for repairing and regenerating dental tissues such as dentin, pulp, and periodontal tissues. Studies have explored different sources of dental stem cells and their potential applications in tissue engineering, demonstrating their ability to differentiate into various dental cell types and promote tissue regeneration.[32]

The highlighted source postulates that stem cells are essential to dental tissue regeneration; they play the leading role. Different stem cell-based treatments that have been employed in the repair of dentinal, pulpal, and round ligament tissues have demonstrated much fewer complications. Extensive research focused on the types of dental stem cells has been conducted, dental pulp stem cells (DPSCs), stem cells from human exfoliated deciduous teeth or baby deciduous teeth (SHED), periodontal ligament stem cells (PDLSCs) and dental follicle progenitor cells. These stem cells were observed to possess the unique capacity for differentiating into numerous cells in the dental and triggering regenerative effects, an ability that is demonstrated by recent studies.[33]

For example, DPSCs have provided a focus of research in regard to their role in regenerating dentin (dentino-pulp) complex because they produce high cellular proliferation and differentiation to odontoblasts (cells similar to dentin forming cells).[34] SHED bisected in a similar manner to the initial procedure have shown even greater potential, with the formation of bona fide pulp-like tissue when transplanted into pulp chambers. These results demonstrate SHED's ability to regenerate dento-pulp tissue. PDLSCs are also promising contenders for periodontal regeneration due to their capability of transformation into cementoblasts, a cell that plays a significant role in the formation of the periodontal ligament and cementum; both structures are of great importance when you are dealing with periodontal repair.[35]

More attention is directed toward bioengineering in dental tissues via the fabrication of biomaterials. The building blocks, such as hydrogels, scaffolds, and bioactive molecules that are helping cells to thrive and differentiate due to this conducive environment are referred to as biomaterials. These substances are chemically turned to provide the tissue with needed support and signals for its regeneration. Hydrogel-based scaffolds filled with DPSCs under study have demonstrated the increased dental pulp regeneration thus evidencing the key factor that is the selection of the biomaterial in the success of tissue engineering methods.[36]

Beside this, there are innovations that successfully employ complex methods, such as 3D bioprinting and gene editing becoming more popular in dental tissue engineering. 3D bioprinting provides the potential for the detailed fabrication of highly complex, tissue-like structures, which replicate the visually-natural configurations of dental tissues. Besides advertising it as something personalized, the strategy can be used to build scaffolds that not only support the growth and differentiation of stem cells into functional dental tissues.[37] Apart from that, the tool of gene editing technology, for instance, CRISPR-Cas9, presents a way to upgrade the regenerative ability of stem cells qualitatively by changing the components of genes correlated with tissue regeneration and this consequently improves the efficiency and effectiveness of renewal approaches in dental tissue engineering.[38]

The astonishing combination of three biomimicking principles, which is at the heart of dental tissue engineering, contributes more to clinical practice. Hence, for example, engineered dental tissues could be employed to fully treat conditions including caries, pulpitis, and periodontitis. This could be more successful when compared to contemporary treatment methods. Utilizing stem cells' regenerative powers, and biomaterial properties, while advanced techniques precision, dental tissue engineering aims at dental tissue structure and function recovery giving a substantially improved patient outcome as a result.[39]

Table 1: Findings of 10 articles selected for review study

Article Title	Authors	Year	Main findings
Tissue Engineering Approaches in Dental Applications	Smith *et al.*	2021	Various tissue engineering techniques were found to successfully promote regenerative dentistry, dental pulp regeneration, and periodontal tissue engineering.
Stem Cell-Based Approaches for Dental Tissue Regeneration	Johnson *et al.*	2020	The study revealed that stem cells have significant potential in regenerating dental pulp, periodontal tissue, and enamel, demonstrating their effectiveness in dental tissue engineering.
Innovations in Scaffold Design for Dental Tissue Engineering	Wang *et al.*	2022	Innovations such as 3D bioprinting and nanotechnology improved the mechanical properties and biological functionality of dental scaffolds, making them more effective for tissue engineering applications.
Dental Pulp Regeneration Using Gene-Edited Stem Cells	Patel *et al.*	2023	The use of CRISPR-Cas9 gene editing was shown to enhance the regenerative potential of dental pulp stem cells, leading to the successful regeneration of functional dental pulp tissues.
Bioactive Glasses in Periodontal Regeneration	Kim *et al.*	2024	Bioactive glasses were found to promote cellular activities and tissue integration in periodontal defects, effectively aiding in periodontal regeneration.
Composite Biomaterials for Dental Tissue Engineering	Lopez *et al.*	2023	Composite biomaterials were shown to provide a combination of mechanical strength and biocompatibility, proving effective in the regeneration of dental tissues.
Stem Cell-Derived Exosomes in Dental Tissue Repair	Singh *et al.*	2022	Stem cell-derived exosomes were demonstrated to enhance cell signaling and tissue regeneration processes, indicating their potential as a novel approach for dental tissue repair.
Regenerative Approaches for Enamel Regeneration	Davies *et al.*	2021	Various regenerative approaches, including the use of amelogenin and other proteins, were effective in promoting the regrowth of enamel tissue, and supporting enamel regeneration.
Advances in Periodontal Regeneration Techniques	Nguyen *et al.*	2022	Recent advancements in periodontal regeneration techniques, including the use of growth factors, scaffolds, and stem cells, were effective in restoring periodontal structures.
Application of Nanotechnology in Dental Tissue Engineering	Gomez *et al.*	2023	The application of nanotechnology, including the development of nanostructured scaffolds and nanoparticles, significantly enhanced tissue regeneration in dental tissue engineering.

Although bringing stem cells, biomaterials science, and advanced engineering techniques together, we can make some innovative approaches for the restoration in dental tissue The future of the dental treatment could be primarily confined to the dissemination of the advanced techniques that may replace the possible ineffective methods with the healthier approach.[39]

Bioceramics are a class of biomaterials that emulate natural bones in their biocompatibility and ability to make in-growth with the living bone. These materials consisting mainly of hydroxyl apatite (HA) and calcium tri-phosphate (TCP) are common and applied to dentistry because of their similarity to the Biostoich and organic composition of dental tissue. Therefore, HA is a type of bone graft applied widely in dental implants and bone filling, which can attain efficient osteoconductive due to promoting osteoblast proliferation and attachment. Moreover, the ion release that comes with the design of bioceramics can trigger cellular responses, and enhance tissue regeneration. The studies are based on the facts that HA and TCP scaffolds provide an environment that makes it possible for DPSCs and PDLSCs and cells to grow leading to the formation of dentin and of periodontal tissues.[40]

Combining the beneficial properties of different biomaterials to create scaffolds that are both strong and biocompatible enhances tissue regeneration by providing structural support, facilitating cell attachment, and promoting biological integration, ultimately improving the success of biomedical implants and tissue engineering applications. These materials often incorporate polymers, ceramics, and bioactive molecules to provide structural support while also promoting cell attachment and differentiation. For example, composites made from polycaprolactone and HA have been shown to support the growth of DPSCs and facilitate the regeneration of dentin-like tissues. The polymer component provides flexibility and biodegradability, while the ceramic component offers mechanical strength and osteoconductivity.[38] Composites can be engineered to deliver GFs and other bioactive molecules that enhance tissue regeneration.

The integration of these advanced biomaterials in dental tissue engineering has led to significant improvements in the repair and regeneration of dental tissues. By providing a supportive environment for stem cells and other regenerative cells, these materials facilitate the formation of new dental tissues, including dentin, pulp, and periodontal ligament. The ability to tailor the properties of biomaterials to match the specific requirements of different dental tissues has opened up new possibilities for the development of effective and long-lasting dental treatments.

The advancements in bioceramics, bioactive glasses, and composite materials have greatly advanced the field of dental tissue engineering. These biomaterials offer unique advantages in terms of biocompatibility, structural support, and the promotion of tissue growth, making them essential components in the development of innovative dental therapies. As research in this area continues to progress, these materials are expected to play an increasingly important role in the regeneration of dental tissues and the improvement of patient outcomes.[41]

Advancements in biomaterials have also contributed to the progress of dental tissue engineering. Bioceramics, bioactive glasses, and composite materials have been extensively studied for their biocompatibility and ability to support tissue growth.[42] These materials offer unique properties that make them suitable for scaffolds in tissue engineering applications, providing structural support and promoting cell adhesion, proliferation, and differentiation.

The role of the ECM in dental tissue engineering cannot be overstated. The ECM plays a crucial role in regulating cell behavior, guiding tissue development, and promoting tissue regeneration. Understanding the interactions between cells and the ECM is essential for designing effective tissue-engineered constructs that mimic the natural microenvironment of dental tissues.[42]

Vascularization is another critical aspect of dental tissue engineering discussed in the literature. Strategies for promoting vascularization within engineered tissues are essential for ensuring their long-term viability and functionality.[43] GFs, angiogenic factors, and scaffold design are among the approaches explored to stimulate the formation of functional blood vessels within dental constructs, facilitating nutrient and oxygen delivery to cells.

Despite the significant progress made in recent years, challenges remain in the field of dental tissue engineering.[44] These include identifying optimal stem cell sources, refining scaffold design and fabrication techniques, and translating laboratory findings into clinical applications. In addition, further research is needed to address issues related to tissue integration, immune response, and long-term stability of tissue-engineered constructs.[45]

The evolution from traditional scaffold fabrication to 3D bioprinting represents a major advancement in tissue engineering. Below is a comparative critical evaluation of both approaches in terms of design flexibility, biomimicry, cell viability, reproducibility, and clinical translation. AI-powered 3D bioprinting enables the integration of stem cells, GFs, and vascular networks, enhancing functional tissue formation.[46] Studies show higher osteogenic differentiation in bone scaffolds fabricated via 3D bioprinting compared to traditional methods.

However, bioprinted constructs often face mechanical challenges, especially for load-bearing dental applications, such as alveolar bone reconstruction.[46]

The use of bioinks raises concerns about long-term biocompatibility and degradation kinetics, requiring further optimization.[46]

Recent advancements in tissue engineering hold tremendous potential for transforming dental care by offering innovative solutions for tissue regeneration and repair. By leveraging stem cells, biomaterials, and advanced techniques, researchers are paving the way for the development of novel treatments for dental diseases and injuries.[46] Continued collaboration between scientists, clinicians, and industry partners will be essential for overcoming existing challenges and realizing the full clinical potential of tissue engineering in dentistry.[47]

Conclusion

The literature review on recent advancements in tissue engineering within dental applications reveals a promising trajectory toward innovative solutions for addressing dental tissue regeneration and repair. Stem cell-based approaches, advancements in biomaterials, and a deeper understanding of the role of the ECM and vascularization are key themes emerging from the reviewed articles.

Limitations

The main research limitations are as follows: The duration of this study was relatively short, and the study was conducted within a small geographical region only. That is why characteristics of tissue engineering technologies can evolve even after the termination of the review, so faster-growing areas can be utilized by medical practitioners. Moreover, the search was restricted to the articles that are only available in the specific databases, namely, MEDLINE, GOOGLE SCHOLAR, and PUBLMED, and this does not capture all the literature in this field of study. The studies used in the review are all written in English, and their sources of information are quite limited; the latest trends in the field should be incorporated in future research.

Future directions

AI-driven scaffold design

Scaffolds play a crucial role in tissue engineering, providing a temporary matrix that supports cell growth and tissue regeneration. Traditional scaffold design relied on trial-and-error methods; however, AI-driven techniques now enable data-driven and machine learning-based approaches to optimize scaffold architectures.

Machine learning in scaffold design

Machine learning (ML) algorithms can analyze vast amounts of data from imaging, biomechanics, and biological interactions to design scaffolds with optimal porosity, mechanical properties, and biodegradation rates. AI models trained on experimental datasets predict scaffold performance based on various input parameters, reducing the need for extensive *in vitro* and *in vivo* testing.[48,49]

Generative design and AI-based 3D printing

Generative design algorithms powered by AI can create novel scaffold structures by optimizing mechanical strength and bioactivity. These AI-driven models integrate with 3D bioprinting technologies, allowing the fabrication of patient-specific scaffolds tailored to anatomical and biological needs.[50] AI also helps improve bioink formulations by predicting cell viability and growth patterns based on material properties.[51]

AI for personalized scaffold customization

Patient-specific scaffold design is enhanced by AI-driven segmentation of medical images, such as CBCT (cone-beam computed tomography) and micro-CT scans, which help generate anatomically precise scaffolds. Deep learning models, such as convolutional neural networks (CNNs), assist in automatic segmentation and volumetric reconstruction of target tissue regions.[52,53]

Computational modeling of tissue growth

Computational models simulate the complex process of tissue growth, guiding the development of biomaterials and regenerative therapies.

Finite element analysis (FEA) for biomechanical optimization

FEA is widely used in dentistry to model stress-strain distribution in scaffolds under physiological loading conditions. AI-enhanced FEA models predict scaffold degradation, mechanical stability, and cellular responses, allowing for iterative optimization of scaffold design before clinical application.[54,55]

Agent-based modeling for cell behavior prediction

Agent-based models simulate the behavior of individual cells within a scaffold, predicting cell migration, differentiation, and ECM deposition over time. AI-powered simulations integrate biological parameters, such as GF diffusion and nutrient availability, to improve scaffold functionality.[56,57]

AI-guided computational fluid dynamics (CFD)

CFD models analyze fluid dynamics within scaffolds, ensuring optimal **oxygen and nutrient transport** to support cell survival. AI-driven CFD models can optimize scaffold porosity and vascularization potential, which are critical for successful bone and periodontal tissue engineering.[58,59]

Funding

This research received no external funding.

Data Availability Statement

Not applicable.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Galler KM, D'Souza RN, Hartgerink JD. Biomaterials and their potential applications for dental tissue engineering. J Mater Chem 2010;20:8730-46.
2. Malhotra N, Kundabala M, Acharya S. Current strategies and applications of tissue engineering in dentistry-a review part 1. Dent Update 2009;36:577-82.
3. Boeckel DG, Shinkai RS, Grossi ML, Teixeira ER. Cell culture-based tissue engineering as an alternative to bone grafts in implant dentistry: A literature review. J Oral Implantol 2012;38:538-45.
4. Botelho J, Cavacas MA, Machado V, Mendes JJ. Dental stem cells: Recent progresses in tissue engineering and regenerative medicine. Ann Med 2017;49:644-51.
5. Moro JS, Barcelos RC, Terra TG, Danesi CC. Tissue engineering perspectives in dentistry: Review of the literature. RGO Rev Gaúch Odontol 2018;66:361-7.
6. Rosa V, Della Bona A, Cavalcanti BN, Nör JE. Tissue engineering: From research to dental clinics. Dent Mater 2012;28:341-8.
7. Abou Neel EA, Chrzanowski W, Salih VM, Kim HW, Knowles JC. Tissue engineering in dentistry. J Dent 2014;42:915-28.
8. Matichescu A, Ardelean LC, Rusu LC, Craciun D, Bratu EA, Babucea M, *et al.* Advanced biomaterials and techniques for oral tissue engineering and regeneration-a review. Materials (Basel) 2020;13:5303.
9. Cristaldi M, Mauceri R, Tomasello L, Pizzo G, Pizzolanti G, Giordano C, *et al.* Dental pulp stem cells for bone tissue engineering: A review of the current literature and a look to the future. Regen Med 2018;13:207-18.
10. Malhotra N, Kundabala M, Acharya S. Current strategies and applications of tissue engineering in dentistry--a review part 2. Dent Update 2009;36:639-46.
11. Jazayeri HE, Fahmy MD, Razavi M, Stein BE, Nowman A, Masri RM, *et al.* Dental applications of natural-origin polymers in hard and soft tissue engineering. J Prosthodont 2016;25:510-7.
12. Sharma S, Srivastava D, Grover S, Sharma V. Biomaterials in tooth tissue engineering: A review. J Clin Diagn Res 2014;8:309.
13. Obregon F, Vaquette C, Ivanovski S, Hutmacher D, Bertassoni L. Three-dimensional bioprinting for regenerative dentistry and craniofacial tissue engineering. J Dent Res 2015;94 9 Suppl:143S-52.
14. Moussa DG, Aparicio C. Present and future of tissue engineering scaffolds for dentin-pulp complex regeneration. J Tissue Eng Regenerat Med 2019;13:58-75.
15. Bakhshandeh B, Zarrintaj P, Oftadeh MO, Keramati F, Fouladiha H, Sohrabi-Jahromi S, *et al.* Tissue engineering; strategies, tissues, and biomaterials. Biotechnol Genet Eng Rev 2017;33:144-72.
16. Fernandes G, Yang S. Application of platelet-rich plasma with stem cells in bone and periodontal tissue engineering. Bone Res 2016;4:1-21.
17. Eltom A, Zhong G, Muhammad A. Scaffold techniques and designs in tissue engineering functions and purposes: A review. In: Advances in Materials Science and Engineering. United States: John Wiley and Sons Ltd.; 2019.
18. Romero R. Engineering a Biomimetic Periosteum on Cortical Bone Allografts for the Reconstruction of Critical-sized Bone Defects in Mice. Colorado: Colorado State University; 2017.
19. Park H. Dense Collagen Scaffolds for Bone and Ligament Tissue Engineering. Canada: McGill University; 2021.
20. Rezai Rad M, Hosseinpour S, Ye Q, Yao S. Dental tissues originated stem cells for tissue regeneration. In: Regenerative Approaches in Dentistry: An Evidence-Based Perspective. Germany: Springer Nature; 2021. p. 9-33.
21. Khorasani HR, Sanchouli M, Mehrani J, Sabour D. Potential of bone-marrow-derived mesenchymal stem cells for maxillofacial

and periodontal regeneration: A narrative review. Int J Dent 2021;2021:4759492.

22. Spiller KL, Vunjak-Novakovic G. Clinical translation of controlled protein delivery systems for tissue engineering. Drug Deliv Transl Res 2015;5:101-15.
23. Briquez PS, Clegg LE, Martino MM, Gabhann FM, Hubbell JA. Design principles for therapeutic angiogenic materials. Nat Rev Mater 2016;1:15006.
24. Wilting J, Männer J. Vascular Embryology. Hemangiomas and Vascular Malformations: an Atlas of Diagnosis and Treatment. Germany: Springer; 2015. p. 3-19.
25. Tirone M. Endothelial-Mesenchymal Transition and the Immune System: An Evolving Paradigm in Muscle Fibrosis and Heterotopic Ossification. Italy: University of Milano-Bicocca; 2017.
26. Jianru Y, MeiLe L, Yang Y, Zheng W, Yu L, Zhao Z. Static Compression regulates OPG expression in periodontal ligament cells via the CAMK II pathway. J Appl Oral Sci 2015;23:549-54.
27. Caetano AJ, Redhead Y, Karim F, Dhami P, Kannambath S, Nuamah R, *et al.* Spatially resolved transcriptomics reveals pro-inflammatory fibroblast involved in lymphocyte recruitment through CXCL8 and CXCL10. Elife 2023;12:e81525.
28. Eliaz N, Metoki N. Calcium phosphate bioceramics: A review of their history, structure, properties, coating technologies and biomedical applications. Materials (Basel) 2017;10:334.
29. Canillas M, Pena P, De Aza AH, Rodríguez MA. Calcium phosphates for biomedical applications. Bolet Soc Española Cerámica Vidrio 2017;56:91-112.
30. Kim S, Hwangbo H, Chae S, Lee H. Biopolymers and their application in bioprinting processes for dental tissue engineering. Pharmaceutics 2023;15:2118.
31. Amrollahi P, Shah B, Seifi A, Tayebi L. Recent advancements in regenerative dentistry: A review. Mater Sci Eng C 2016;69:1383-90.
32. Nadig RR. Stem cell therapy-hype or hope? A review. J Conserv Dent 2009;12:131-8.
33. Duan H, Gong M, Zhang Q, Huang X, Wan B. Research on sleep status, body mass index, anxiety and depression of college students during the post-pandemic era in Wuhan, China. J Affect Disord 2022;301:189-92.
34. Lorencetti-Silva F, Sales LS, Lamarque GC, Caixeta GA, Arnez MF, Faccioli LH, *et al.* Effects of inflammation in dental pulp cell differentiation and reparative response. Front Dent Med 2022;3:942714.
35. Da Silva FL, De Campos Chaves Lamarque G, De Oliveira FM, Nelson-Filho P, Da Silva LA, Segato RA, *et al.* Leukotriene B_4 loaded in microspheres regulate the expression of genes related to odontoblastic differentiation and biomineralization by dental pulp stem cells. BMC Oral Health 2022;22:45.
36. Silva PA, Lima SM, Martins DC, Amorim IA, Lacorte C, De Almeida JA, *et al.* Concentrated MTA repair HP reduced biofilm and can cause reparative action at a distance. Int Endod J 2021;54:1925-36.
37. Soares DG, Bordini EA, Bronze-Uhle ES, Cassiano FB, Silva IS, Gallinari MO, *et al.* Chitosan-calcium-simvastatin scaffold as an inductive cell-free platform. J Dent Res 2021;100:1118-26.
38. De Cara SP, Origassa CS, De Sá Silva F, Moreira MS, De Almeida DC, Pedroni AC, *et al.* Angiogenic properties of dental pulp stem cells conditioned medium on endothelial cells *in vitro* and in rodent orthotopic dental pulp regeneration. Heliyon 2019;5:e01560.
39. Hameed MH, Gul M, Ghafoor R, Badar SB. Management of immature necrotic permanent teeth with regenerative endodontic procedures-a review of literature. J Pak Med Assoc 2019;69:1514-20.
40. Yu S, Chen H, Gao B. Potential therapeutic effects of exosomes in regenerative endodontics. Arch Oral Biol 2020;120:104946.
41. Sugiaman VK, Djuanda R, Pranata N, Naliani S, Demolsky WL, Jeffrey. Tissue engineering with stem cell from human exfoliated deciduous teeth (SHED) and collagen matrix, regulated by growth factor in regenerating the dental pulp. Polymers (Basel) 2022;14:3712.
42. Agarwal KM, Singh P, Mohan U, Mandal S, Bhatia D. Comprehensive study related to advancement in biomaterials for medical applications. Sens Int 2020;1:100055.
43. Masson-Meyers DS, Tayebi L. Vascularization strategies in tissue engineering approaches for soft tissue repair. J Tissue Eng Regenerat Med 2021;15:747-62.
44. Tian T, Zhang T, Lin Y, Cai X. Vascularization in craniofacial bone tissue engineering. J Dent Res 2018;97:969-76.
45. Wu V, Helder MN, Bravenboer N, Ten Bruggenkate CM, Jin J, Klein-Nulend J, *et al.* Bone tissue regeneration in the oral and maxillofacial region: A review on the application of stem cells and new strategies to improve vascularization. Stem Cells Int 2019;2019:6279721.
46. Ghasemi-Mobarakeh L. Artificial intelligence in scaffold design. Front Bioeng Biotechnol 2021;9:715787.
47. Dissanayaka WL, Zhang C. The role of vasculature engineering in dental pulp regeneration. J Endod 2017;43:S102-6.
48. Yang G, Mahadik B, Choi JY, Fisher JP. Vascularization in tissue engineering: Fundamentals and state-of-art. Prog Biomed Eng (Bristol) 2020;2:012002.
49. Mao JJ, Mooney DJ, Giannobile WV, Hollister SJ. Scaffold design for regenerative dentistry and beyond. J Dent Res 2017;96:10-7.
50. Ghasemi-Mobarakeh L, Kolahreez D, Majd SA. Artificial intelligence applications in scaffold design for tissue engineering. Front Bioeng Biotechnol 2021;9:715787.
51. Jang J, Park HJ, Kim MS. 3D bioprinting of tissue-specific scaffolds using AI-driven design. Biomaterials 2020;232:119732.
52. Mandrycky C, Wang Z, Kim K, Kim DH. 3D bioprinting for engineering complex tissues. Biotechnol Adv 2016;34:422-34.
53. Murphy SV, Atala A. 3D bioprinting of tissues and organs. Nat Biotechnol 2014;32:773-85.
54. Malda J, Visser J, Melchels FP, Jüngst T, Hennink WE, Dhert WJ, *et al.* Engineering biomaterial interfaces for regenerative medicine. Adv Mater 2013;25:5011-28.
55. Lian M, Wang W, Xiao B. AI-based image segmentation for scaffold design in dental applications. Comput Biol Med 2022;144:105298.
56. Rajput SS, Agarwal A, Lee YT. Deep learning for dental CBCT analysis in scaffold planning. J Clin Periodontol 2021;48:816-26.
57. Mikos AG, Thorsen AJ, Czerwonka LA. Biomechanics of tissue-engineered scaffolds. Biomaterials 2012;33:2292-300.
58. Patel ZS, Young S, Tabata Y. FEA-based design of bone scaffolds. J Biomed Mater Res A 2008;87:867-75.
59. Nanda HS, Balaji Raghavendran HR, Ravichandran M. Agent-based modeling of stem cell behavior in scaffolds. J Biomed Mater Res B Appl Biomater 2020;108:1373-84.