**Journal of Research in Medical and Dental Science**
**2022, Volume 10, Issue 11, Page No: 110-114**

Available Online at: www.jrmds.in
eISSN No.2347-2367: pISSN No.2347-2545

# Use of Biopolymers in Teeth Regeneration

**Kasturi Wankhede, Pavan Bajaj, Madhumita Choudhari***

*Department of Periodontics, Sharad Pawar Dental College and Hospital, Datta Meghe Institute of Medical Sciences (Deemed to be University) Sawangi (Meghe) Wardha, Maharashtra, India*

## ABSTRACT

*Tissue engineering is a promising way of regenerating lost or damaged tissue structures. Arranging an environment that is suitable to carry out regeneration is done through, scaffolds, stem cells, biopolymers, growth factors, scaffold free method, and signalling pathways. Taking into consideration the regeneration of dental tissues, nanostructured biopolymers, such as nanofibre, hydrogels, scaffolds, dendrimers, hydrogels, films, and nanobioceramic, such as hydroxyapatite, bio glass/ bioactive glass ceramic, etc., in the form of nanocrystals, rods and particles, paste; spheroids and cells sheets and so on, are being used to regenerate both soft as well as hard tissues of the human body at the same time. These materials have a striking resemblance with tooth tissues that are enamel, dentin, cementum and pulp. In general this article focuses on the biomaterials that can be utilized to regenerate a tooth outlining their features as well as future strategies that will be required.*

**Key words:** Nanobioceramic, Signalling pathways, Scaffold, Hydrogels, Bio-glass/bioactive

**HOW TO CITE THIS ARTICLE:** Kasturi Wankhede, Pavan Bajaj, Madhumita Choudhari, Use of Biopolymers in Teeth Regeneration, J Res Med Dent Sci, 2022, 10 (11): 110-114.

**Corresponding author:** Madhumita Choudhari
**E-mail**: madhumita.a.choudhari@gmail.com
**Received:** 02-Sep-2022, Manuscript No. JRMDS-22-49427;
**Editor assigned:** 06-Sep-2022, PreQC No. JRMDS-22-49427 (PQ);
**Reviewed:** 21-Sep-2022, QC No. JRMDS-22-49427;
**Revised:** 03-Nov-2022, Manuscript No. JRMDS-22-49427 (R);
**Published:** 10-Nov-2022

## INTRODUCTION

In the oral cavity, teeth perform the primary function of masticating ingested food: Chewing and grinding food to allow the tongue and oropharynx to mould it into a bolus that can be swallowed. Other than mastication, they also play a key role in phonation [1]. If the teeth are lost by any extreme wear, destruction, caries or fracture, the person might suffer from over close jaws, accentuated nasolabial folds, inability to make fricative sounds, loss of support by soft tissues and difficulty in chewing as well as swallowing. By keeping in mind the importance of healthy functional teeth, it is necessary to focus on ways for regenerating these lost tissues [2]. Tissue Engineering, a multidisciplinary field focusing on the regeneration and replacement of various tissues and organs of the human body, is a huge breakthrough in medical and dental sciences [3]. A felt need for tissue engineering was observed when treatments involving auto grafts, allografts, and transplants, although ground breaking, came up with severe flaws. They were expensive, painful and often came with the risk of patients rejecting to the graft with introduction of infections or diseases from the donor to the recipient. Tissue engineering, on the other hand, tries to repair or replace damaged tissues, by finding biological alternatives rather than replacing them that help tissue function be restored, maintained, or improved [4]. This technique uses a combination of cells, and signalling molecules and pathways along with 3D biomaterials to restore impaired and ailing tissues [5]. The interaction of cells whether it is autologous or allogeneic with foam or sponge porous scaffolds, serves as a tissue forming template and, produces 3D tissue architectures. At predetermined rates, they develop, disintegrate, or are resorbed [6]. In scaffold cell seeding, the first step is to spread or circulate isolated cells within the scaffold developing a 3D culture, and it could be critical in influencing how tissue formation progresses [7]. Due to this interaction the 3D culture should be able to form new tissue in an organized and differentiated manner. These scaffolds should be biocompatible, meaning they shouldn't trigger an immune or other adverse reaction when they come into contact with the host tissues; highly porous, with a high surface area to volume ratio, letting cells to affix, multiply, and in grow to fill the voids with newly generated tissue; and biodegradable, which excludes the need of surgical removal [8,9]. And as Oral health is integral to general health, the felt need to recover dental tissues is recognized for the sake of well-being of a patient [10].

## LITERATURE REVIEW

### Strategies for regeneration of enamel

Mineralization of a tissue, in our body is found the most in enamel. It is the strongest tissue in human body, and is

primarily an assembly of hydroxyapatite crystals. It is formed by the process of Amelogenesis by the Ameloblast cells [11]. Enamel is made up of a lot of enamel rods that are the basic building blocks of it. Every rod is constructed up of closely packed nano HAP crystals ranging in size from 25 to 100 nm, which are then coated with enamel in. All these features add up to the enhanced properties of enamel [12]. But when the tooth experiences any kind of wear, trauma or microbial infection, the tooth structure is lost, especially enamel, and this hard tissue is unable to repair itself because of loss of Ameloblasts, following tooth development. Thus it is essential to regenerate this tissue. Under recent advances, it was observed that enamel cell rests of molasses could be cultured to form new Ameloblasts, which will eventually form sound enamel. For this culture to work, biomaterial substance is used. This substance must show the same properties as the nanofibrillar structure of the enamel. Peptide Amphiphile (PA) molecules are used to make favourable nanofibrillar biomaterial structures for depositing enamel mineral [13]. Cells from various sources for enamel regeneration were bone marrow stromal cells; human embryonic stem cell derived epithelial cells, oral keratinocytes and skin epithelial cells [14]. Studies also showed that nanoHAp has the potential for regenerating enamel especially because of its cell adhesive and proliferative activity. It also undergoes osteointegration and shows Alkaline Phosphatase (ALP) activity [15]. Nano HAP also has a high surface area to volume ratio. Its ultrafine structure and ratio mirror biological structures [16]. As a result, it becomes crucial in hard tissue engineering [17]. Another capability for enamel regeneration was seen in structures called dendrimers. Dendrimers are a type of synthetic polymer with a distinct dendritic architecture defined by the regular emission of cascade-branched repeating units from a central point: Radially symmetrical and a huge surface end groups [18]. Dendrimers have a molecular weight that is typically uniform, with no distinct molecular weight dispersion. PAMAM dendrimers, for example, which are now widely in use where the first of their kind to be developed [19]. These dendrimers have the capability of mimicking amelogenin nanospheres just like the ones found in enamel. Amelogenin are hydrophobic in nature and thus can organise themselves into nanospheres, because of which they can perform formation, orientation, and mineralization of hydroxyapatite crystals found in enamel, similar to the nano HAp crystals [20].

**Strategies for regeneration of dentin**

The dentin is the most densely packed component of the human tooth. Pulp, the soft tissue of the tooth is protected from harmful stimuli by dentin. It also gives enamel crucial support, allowing heavily mineralized and consequently brittle enamel to resist occlusal as well as masticatory forces and stresses without cracking. Dentin is the first vital tissue to be irritated by an external stimulus, and rather than acting as a passive mechanical barrier, it can play a role in dentin pulp complex defensive mechanisms [21]. The dentin is mineralized and contains collagenous and non-collagenous proteins. Like enamel it also contains apatite crystals encased in ECM. These contents all together perform various processes in dentinogenesis. These processes involve stimulation, control, regulation, and mineralization in formation in dentin [22]. Dentin is composed of dentinal tubules that run away from the pulp towards the enamel. These tubules are filled with dentinal fluid [23]. Dentin cannot undergo remodelling unlike bone, but shows response to injury or trauma by formation of reparative and sclerotic dentin. Thus it becomes evident to regenerate dentin on loss of this tooth structure [24]. Polymers that are biodegradable in nature such as poly L lactic acid have attracted a lot of attention as scaffold matter used in regeneration of tissue because they are compatible and degradable biologically [25]. This scaffold material was successful in resembling the natural type 1 collagen on scanning electron microscopy. DPSCs have also been proven in earlier research to exhibit clonogenic capacities, high proliferation rates, and diverse differentiation potentials, making them an ideal cell source for dental tissue engineering [26-28]. Dentin contains closely aligned tubular pores which gives its porous nature. Materials like Nano hybrid matrix scaffolds made of poly (Ethyl Methacrylate co-hydroxyethyl acrylate), pure along with a sol gel derived interpenetrated silica nano phase, were able to closely resemble and show this dentin behaviour [29,30]. Murine cells with phenotypic differences from those seen in dermal connective tissue colonised these biomaterials, demonstrating structural differences. A neo dentinal pattern was observed with colonisation and viability [31]. Another potent tissue engineering material that provided natural tissue elasticity, relative biocompatibility and had high water content was hydrogels [32]. In the presence of osteogenic supplements, it was observed that the PA Nano fibre hydrogel scaffolds when cultured with DPSC showed differentiation of hard tissues thus showing signs of dentin regeneration [33].

**Strategies for regeneration of cementum**

The periodontium, which surrounds and anchors the teeth, is made up of fibrous and efficiently mineralized tissues [34]. The mineralized or hard tissues are alveolar bone and cementum, and the fibrous or soft tissues are the PDL and gingiva and they all make up the periodontium. Cementum is an avascular structure that is not only a component of periodontium but also a part of tooth root. Along with principle fibres it plays a role in supporting the tooth. Cementum adjoins the alveolar bone with the help of periodontal ligament. It mainly anchors the tooth. In the alveolar bone, the tooth root is embedded in bony socket to hold them in position firmly. The tooth is surrounded by gingiva in a collar like fashion; it forms a barrier to avoid infection to enter the underlying bone [35,36]. Cementum forms a thin layer of hard tissue that protects the teeth's anatomic roots. Cementoblasts originate from undifferentiated mesenchymal cells in the connective tissue of the dental follicle to generate this structure. The texture of

cementum is softer than dentin, and it is made up of 45 to 50% inorganic material which is again hydroxyapatite and 50 to 55% organic matter and water by mass. Collagen and protein polysaccharides make up the majority of the organic part [37,38]. Some biological substances, including Enamel Matrix Derivative (EMD), Transforming Growth Factor (TGF), and Insulin like Growth Factor (IGF), have been discovered to enhance cemental tissue reformation [39]. In cementogenesis, using 3D scaffolds attempts were made to create formation of interfacial tissue between the pulp fibrous tissue and dentin [40]. Cementoblastic cells and similarly cementogenesis promoting biologics, such as platelet derived growth factor BB, were carried *via* PLGA scaffolds for cell activation and cementogenesis in *in vivo* contexts [41]. However, rather than architectural regulations for cementum formation, most research findings in this field have focused on the development of bio polymeric carriers for conveying bioactive molecules, as well as various physiological and pathological adaptations and cementogenic differentiations of dental stem cells in micro niches [42-44]. A setback occurred when difficulty was observed in regeneration of cementum in context to regulation of thin micron scaled mineral deposition on the tooth root surfaces. This was resolved with the introduction of biological activation of transplanted stem cells or biologically activated host tissues to the picture [45]. Despite the necessity to incorporate current techniques like as, cell sheet engineering, 3D printing, or cell spheroid approaches, these unique techniques will be the foremost dominating tactics for the new paradigm of periodontal regenerative approaches, with improved tediousness and controllability.

## DISCUSSION

### Strategies for regeneration of pulp

The pulp is that tissue of the tooth which is highly vascularized with blood connective tissues and is also innervated with nerves. This structure lies inside the pulp chamber. An ECM made up of collagen fibres and ground substance is also present [46]. Simply put, the pulp's four primary roles are dentin production and nourishment, as well as tooth innervation and defence. Dentin development is one of the pulp's most important functions, and the odontoblasts are responsible for it. The pulp also provides moisture and nutrients to the dentin in the form of albumin, transferrin, tenascin, and other proteoglycans. The pulp's protective function is carried out by the formation of neo dentin, which can act as a barrier between irritants and inhibit the progression of caries [47]. The pulp gets its blood supply from arterioles that enter from the apical foramen, crossing the periodontium and the radicular pulp. They reside under the odontoblastic layer. One to two arterioles along with a large venule is present in each pulp chamber [48]. The pulp is innervated by two main types of nerves: autonomic and afferent nerve fibres [49]. Diseases like reversible and irreversible pulpitis and periodontitis harm the pulp, which can be detrimental to the whole tooth [50]. Among the various approaches to save the dental pulp, scaffolding turns out to be a great way to regenerate the pulp tissues, but it fails to mimic the natural ECM. Creating an appropriate microenvironment that replicates natural pulp's Extracellular Matrix (ECM) and ensuring a sufficient supply of blood for cell transplant survival are important challenges in pulp regeneration. In this work, scaffold free micro tissue spheroids of Dental Pulp Stem Cells (DPSCs) pre vascularized by Human Umbilical Vein Endothelial Cells (HUVECs) were used to test a unique strategy to pulp regeneration [51]. The pulp regeneration of scaffold less 3 dimensional tissues generated from human DPCs was tested in this work. DSP expression revealed that a pulp like tissue was reformed in a human tooth root which was able to generate dentin/bone resembling tissue comprising of odontoblast cells towards the dentinal surface which was vascular in nature [52].

## CONCLUSION

In the case of enamel, all these investigations are successful only in *in vitro*. The challenge to create a three dimensional structure of hydroxyapatite crystals from nano scale to micro scale with other components of enamel still persists. To acquire the same strength and hardness as enamel will be the major goal of future investigations. In the case of dentin, PLLA nanofibrous scaffolds turned out to be successful in regenerating dentin like tissue by odontogenic dental pulp stem cells differentiation *in vitro* as well as *in vivo*. Other investigations like PA Nano fibre hydrogel scaffolds and their ability to regenerate is still limited to *in vitro*. The true potential of these materials is yet to be discovered. The studies for cementum regeneration are also limited to *in vitro* stages. PLGA scaffolds and stimulating different ways of cementogenesis will be the aims to focus in the future. Pulp, the soul of a tooth; is supposed to be preserved for a tooth to be saved. Scaffold free techniques are being used in the regeneration of pulp and are fortunate to be able to do it to some extent. The combination of nano medicine and tissue rehabilitation and engineering has resulted in significant advancements in the field of dental tissue regeneration. The loss of parent cell after tooth eruption is the major limitation for dental tissue engineering. More clinical trials are supposed to be run in order to perfectly demonstrate the potential futuristic clinical benefits of these materials.

## REFERENCES

1. Zimmerman B, Shumway KR, Jenzer AC. Physiology, Tooth. In: StatPearls. Treasure Island (FL): StatPearls. 2022.
2. Otsu K, Kumakami Sakano M, Fujiwara N, et al. Stem cell sources for tooth regeneration: Current status and future prospects. Front Physiol 2014; 5:36.
3. Sowmya S, Bumgardener JD, Chennazhi KP, et al. Role of nanostructured biopolymers and bio ceramics in enamel, dentin and periodontal tissue regeneration. Prog Polym Sci 2013; 38:1748–1772.

4. O'Brien FJ. Biomaterials and scaffolds for tissue engineering. Mater Today 2011; 14:88–95.
5. Sheehy EJ, Cunniffe GM, O'Brien FJ. Collagen based biomaterials for tissue regeneration and repair. In peptides and proteins as biomaterials for tissue regeneration and repair. Elsevier 2018; 127–150.
6. Martin I, Wendt D, Heberer M. The role of bioreactors in tissue engineering. Trends Biotechnol 2004; 22:80–86.
7. Vunjak-Novakovic G, Obradovic B, Martin I, et al. Dynamic cell seeding of polymer scaffolds for cartilage tissue engineering. Biotechnol Prog 1998; 14:193–202.
8. Rezwan K, Chen QZ, Blaker JJ, et al. Biodegradable and bioactive porous polymer/inorganic composite scaffolds for bone tissue engineering. Biomaterials 2006; 27:3413–3431.
9. Chandak PG, Ghanshyamdasj M, Chandak C, et al. Nanoparticles in Endodontics a Review. J Evol Med Dent Sci 2021; 10:976–982.
10. National Institute of Dental and Craniofacial Research. 2000 Surgeon general's report on oral health in America. U.S. Department of Health and Human Services. 2000.
11. Margolis HC, Beniash E, Fowler CE. Role of macromolecular assembly of enamel matrix proteins in enamel formation. J Dent Res 2006; 85:775–793.
12. Bechtle S, Ang SF, Schneider GA. On the mechanical properties of hierarchically structured biological materials. Biomaterials 2010; 31:6378–6385.
13. Zhao B, Tian W, Feng H, et al. Effects of RGD peptide grafting to titanium dental implants on the adhesion of human gingival fibroblasts and epithelial cells. Curr Appl Phys 2005; 5:407–410.
14. Jayasudha, Baswaraj, Navin HK, et al. Enamel regeneration current progress and challenges. J Clin Diagn Res 2014; 8:ZE06–ZE09.
15. Pushpakanth S, Srinivasan B, Sreedhar B, et al. An *in situ* approach to prepare nanorods of titania hydroxyapatite ($TiO_2$-HAP) nanocomposite by microwave hydrothermal technique. Mater Chem Phys 2008; 107:492–498.
16. Patel RM, Dahane TM, Godbole S, et al. Applications of Nanotechnology in Prosthodontics. J Evol Med Dent Sci 2020; 9:3566–3571.
17. Wei G, Ma PX. Structure and properties of nano hydroxyapatite/polymer composite scaffolds for bone tissue engineering. Biomaterials 2004; 25:4749–4757.
18. Lyu Z, Ding L, Huang AYT, et al. Poly (Amidoamine) dendrimers: covalent and supra molecular synthesis. Mater Today Chem 2019; 13:34–48.
19. Jang WD, Kamruzzaman Selim KM, Lee CH, et al. Bio inspired application of dendrimers: From bio mimicry to biomedical applications. Prog Polym Sci 2009; 34:1–23.
20. Wang L, Guan X, Du C, et al. Amelogenin promotes the formation of elongated apatite microstructures in a controlled crystallization system. J Phys Chem 2007; 111:6398–6404.
21. Tjaderhane L, Carrilho MR, Breschi L, et al. Dentin basic structure and composition an overview. Endod Top 2009; 20:3–29.
22. Orsini G, Ruggeri A, Mazzoni A, et al. A review of the nature, role, and function of dentin non-collagenous proteins. Part 1: Proteoglycans and glycoproteins: Non collagenous proteins of dentin. Endod Top 2009; 21:1–18.
23. Kumar A. Nanofibers. Books on Demand (BoD), 2010; 454.
24. Nakashima M, Akamine A. The application of tissue engineering to regeneration of pulp and dentin in endodontics. J Endod 2005; 31:711–718.
25. Chen Y, Li J, Tuan RS, et al. A One step method to fabricate plla scaffolds with deposition of bioactive hydroxyapatite and collagen using ice-based microporogens. Acta Biomater 2010; 6:2013-2019.
26. Wang J, Liu X, Jin X, et al. The odontogenic differentiation of human dental pulp stem cells on nanofibrous poly (l-lactic acid) scaffolds *in vitro* and *in vivo*. Acta Biomater 2010; 6:3856-3863.
27. Panchbhai A. 11-Nanocomposites: Past, present, and future of dentistry. In: Asiri AM, Inamuddin, Mohammad A, editors. Applications of Nanocomposite Materials in Dentistry. 1st Edition, App Nanocomposite Mater Dent 2018.
28. Panchbhai A. 12-Nanotechnology in dentistry. In: Asiri AM, Inamuddin, Mohammad A, editors. Applications of Nanocomposite Materials in Dentistry. Woodhead Publishing, 2019; 191–203.
29. Motwani NM, Ikhar A, Nikhade P, et al. Dentinal Pre-Treatment in Restorative Dentistry. J Evol Med Dent Sci 2020; 9:804–809.
30. Shah KB, Mankar NP, Bajaj PS, et al. Comparative evaluation of micro leakage in cavities restored with nanohybrid and micro filled composites using oblique incremental technique an *in vitro* study. J Evol Med Dent Sci 2020; 9:1087–1090.
31. Valles-Lluch A, Novella-Maestre E, Sancho-Tello M, et al. Mimicking natural dentin using bioactive nanohybrid scaffolds for dentinal tissue engineering. Tissue Eng Part A 2010; 16:2783–2793.
32. Nuttelman CR, Henry SM, Anseth KS. Synthesis and characterization of photo cross linkable, degradable poly (vinyl alcohol)-based tissue engineering scaffolds. Biomaterials 2002; 23:3617–3626.
33. Galler KM, Cavender A, Yuwono V, et al. Self-assembling peptide Amphiphile Nanofibers as a scaffold for dental stem cells. Tissue Engineering Part A 2008; 14.
34. Lindhe J. The anatomy of the periodontium. Toxtbook Clin Periodontol 1989; 19–65.

35. Jayakumar R, Prabaharan M, Nair SV, et al. Novel Carboxymethyl derivatives of chitin and chitosan materials and their biomedical applications. Prog Mater Sci 2010; 55:675–709.
36. Bottino MC, Thomas V, Schmidt G, et al. Recent advances in the development of GTR/GBR membranes for periodontal regeneration a materials perspective. Dent Mater 2012; 28:703–721.
37. Boushell LW, Sturdevant JR. 1-Clinical Significance of Dental Anatomy, Histology, Physiology, and Occlusion. Sturdevant's Art and Science of Operative Dentistry 7th Edition. 2019; 1-39.
38. Nanci A, editor. Chapter 9 Periodontium. Ten Cate's Oral Histology 8th Edition, 2013; 205-232.
39. Wang J, Tian ZL, Liu YP, et al. Application of biological factor in cementum regeneration. Zhonghua Kou Qiang Yi Xue Za Zhi 2019; 54:568-572.
40. Lee CH, Hajibandeh J, Suzuki T, et al. Three dimensional printed multiphase scaffolds for regeneration of periodontium complex. Tissue Eng Part A 2014; 20:1342–1351.
41. Anusaksathien O, Jin Q, Zhao M, et al. Effect of sustained gene delivery of platelet derived growth factor or its antagonist (PDGF-1308) on tissue engineered cementum. J Periodontol 2004; 75:429–440.
42. Vaquette C, Fan W, Xiao Y, et al. A biphasic scaffold design combined with cell sheet technology for simultaneous regeneration of alveolar bone/ periodontal ligament complex. Biomaterials 2012; 33:5560–5573.
43. Lemaitre M, Monsarrat P, Blasco-Baque V, et al. Periodontal tissue regeneration using syngeneic adipose derived stromal cells in a mouse model. Stem Cells Transl Med 2017; 6:656-665.
44. Zhu W, Liang M. Periodontal ligament stem cells: current status, concerns, and future prospects. Stem Cells Int 2015; 2015:972313.
45. Park CH. Biomaterial based approaches for regeneration of periodontal ligament and cementum using 3D platforms. Int J Mol Sci. 2019; 20:4364.
46. Yu C, Abbott PV. An overview of the dental pulp: Its functions and responses to injury. Aust Dent J 2007; 52:S4-16.
47. Slavkin HC. The nature and nurture of epithelial mesenchymal interactions during tooth morphogenesis. J Biol Buccale 1978; 6:189–204.
48. Tønder KJ. Blood flow and vascular pressure in the dental pulp Summary. Acta Odontol Scand 1980; 38:135–144.
49. Byers MR, Narhi MV, Mecifi KB. Acute and chronic reactions of dental sensory nerve fibres to cavities and desiccation in rat molars. Anat Rec 1988; 221:872–883.
50. Madan K, Baliga S, Deulkar P, et al. A Comparative evaluation between Propolis and mineral Trioxide aggregate as pulpotomy medicaments in primary molars. J Evol Med Dent Sci 2020; 9:1256–1260.
51. Syed-Picard FN, Ray HL, Kumta PN, et al. Scaffold less tissue engineered dental pulp cell constructs for endodontic therapy. J Dent Res 2014; 93:250–255.
52. Dissanayaka WL, Zhu L, Hargreaves KM, et al. Scaffold free prevascularized micro tissue spheroids for pulp regeneration. J Dent Res 2014; 93:1296–1303.