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Noval hydrogel-based scaffold- The futuristic biomaterial for integrated periodontal regeneration

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Abstract

Periodontium is the structural and functional unit of tissues surrounding the tooth. Periodontal disease results in the destruction of supporting periodontal tissues resulting in the loss of teeth. Several types of research are being done to regenerate the lost periodontal tissues using various biomaterials. The best approach for regeneration requires three elements for restoring functions of affected or diseased tissues. It includes cells, bioactive molecules, and scaffolds. This triad is capable of modulating the processes to replace lost or damaged tissues and restore their function. Various scaffolds are available for integrated periodontal regeneration for the last few years. Recently, a new futuristic biomaterial- Hydrogel was discovered as a scaffold for integrated periodontal regeneration. The aim of the study is to know that hydrogel can be used as a scaffold in periodontal regeneration. Many animal studies and in-vitro studies have been done using hydrogel as a scaffold for periodontal regeneration. It is in the early phase of development which are leading pathways to randomized clinical studies for it to be used in clinical practice.

Keywords: Periodontal tissue, Periodontal regeneration, Scaffold, Biomaterials, hydrogel.

Introduction

The periodontium is the functional and structural unit of the tooth including the cementum, periodontal ligament, and alveolar bone. Periodontal tissues can be destroyed by periodontal disease eventually resulting in the loss of a tooth [(1-3)].

Periodontal management involves the elimination of the disease-causing factor, dental plaque. This removes only the inflammatory component not help in gaining the lost periodontal tissues. The ultimate goal of periodontal therapy is to regenerate the lost periodontal tissues which involve the formation of new cementum, new periodontal ligament, and new alveolar bone.

Regenerative therapy has gained importance in restoring the lost periodontal tissues. It needs three elements: cells, bioactive molecules, and scaffolds. They influence the behaviour of cells positively and help in regeneration. Conventional regenerative approaches promote the growth and differentiation of progenitor cells into cement oblast, fibroblast and osteoblast by preventing the down growth of epithelial cells into the periodontal defect. This is the gold standard approach termed guided tissue regeneration involving the concept of barrier membrane with or without the bioactive molecules such as recombinant growth factors and enamel matrix derivative.

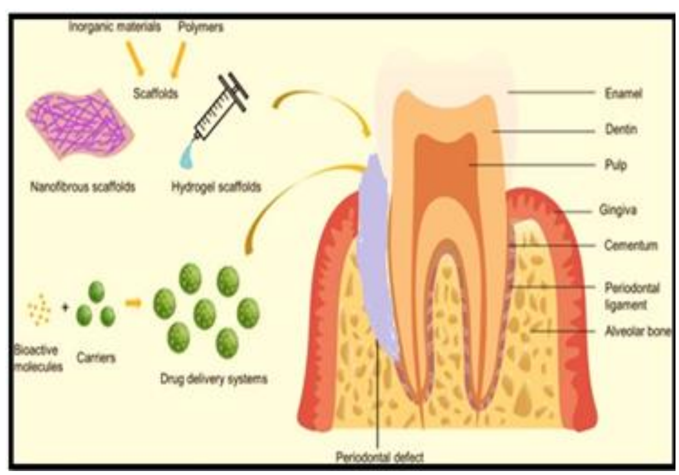
Other methods of using autogenous bone or allogenic bone substitutes, xenografts, and alloplastic materials can be used as a scaffold for cell growth and migration. Studies showed that these methods are unpredictable clinically also complete regeneration is not achieved [4-7]. Also, they carry the risk of disease transmission and autoimmune reactions. Bone substitute materials (scaffolds) when delivered to the periodontal defects stimulate the progenitor cells to grow and differentiate into mature osteoblast. This new approach to tissue engineering combines exogenous progenitor cells, biomaterial scaffolds, and bioactive molecules to regulate the growth and destination of the progenitor cells temporospatial [8-9].

It has led to the invention of bioinspired scaffolding biomaterial of cementum-periodontal ligament-alveolar bone complex regeneration and multi-drug delivery [10]. This review emphasizes the innovative approach to designing the scaffold from a new biomaterial “Hydrogel”. This emerging system of scaffold guides the integrated regeneration of periodontium. They deliver bioactive clues for periodontal regeneration which undergo degradation to be replaced by new tissues.

Hydrogel

Hydrogel was discovered by Wichterle and Lim in 1960. It has a three-dimensional network of hydrophilic polymers crosslinking [11-12]. Hydrogel alone or combined can enhance remineralization or increase the thickness and mechanical properties of regenerated enamel and dentin. Slaughter et al have defined hydrogel as 3D insoluble polymer matrices created from crosslinked hydrophilic homopolymers, copolymers, or macromers. Hydrogels are formed from alginate, hyaluronan, chitosan, agarose, collagen, and fibrin (Lee and Mooney 2001, Malafaya et al 2007). Hydrogel has shown excellent mechanical, chemical, and biological activities (Moussa and Aparicio 2019). Hydrogels find their implications in the dental field and biomedical fields as a material of choice in tissue engineering (Fan and Wang 2017). The hydrogel can retain high water content which enhances the transportation of cell essential nutrients and unwanted products and is elastic and flexible mimicking the extracellular matrix (ECM) [13-20]. Hydrogel as a scaffold provides structural guidance for the formation of periodontal tissues by enabling high surface area and porosity to facilitate cell attachment, migration, and proliferation. Hydrogel when injected into the site it gets cross-linked in-situ making it desirable in irregular periodontal defects as shown in figure 1.

Figure 1: Schematic representation of injectable hydrogel into a periodontal defect.

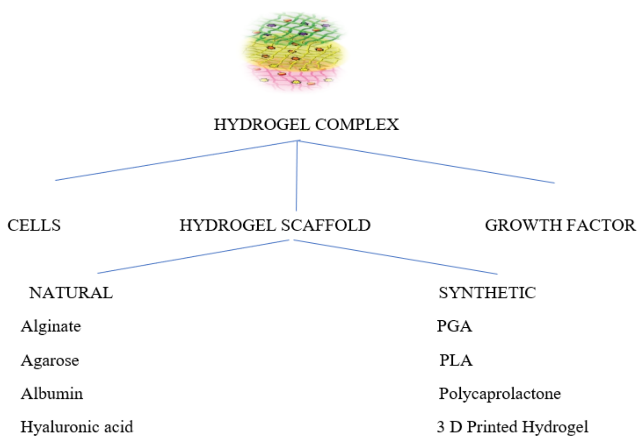


Hydrogels for periodontal regeneration

Hydrogels can be injected into irregular periodontal defects caused by periodontitis (Shi et al 2017, Xu et al

2019). Various biomaterials available as a scaffold for periodontal regeneration are naturally derived materials like ceramics, polymers, chitosan, collagen, hydroxy apatite, tricalcium phosphate, natural polymers like hyaluronic acid, alginate, agarose, albumin and synthetic are polyesters- PGA, PLA, and poly caprolactone as shown in figure 2. Co polymers of polyethylene oxide and polypropylene oxide are known as "Pluronic, polyphosphazene, and nano calcium sulfate.

Figure 2: Classification of Hydrogel complex in Periodontal regeneration.



The hydrogels used for periodontal regeneration are as follows

1. Transglutaminase Gelatin-Based Hydrogel (TG-Gels)
2. Chitosan Hydrogels
3. Chitin-Based Hydrogels
4. Synthetic Extracellular Matrix Hydrogels

Transglutaminase Gelatin-Based Hydrogel (TG-Gels)

Recently it is found that highly-rigid matrices-based materials such as TG-gels enhance periodontal regeneration by modulating MØ polarization and promoting endogenous stem cell recruitment. In this in-vivo experimental studies done by Xia-Tao He et al 2019, it was found that incorporation of IL-4 in high stiffness TG-gels coaxed macrophages to polarize into M2 phenotypes and stromal cell-derived factor (SDF)-1α could be applied to absolute autogenous cell honing concluding that hydrogels can be a simple and effective strategy that can support a high level of periodontal regeneration.

Chitosan Hydrogels

An In-vivo study done by Yan et al 2015, evaluated the biocompatibility and periodontal regeneration potential of enzymatically solidified chitosan hydrogels with or without incorporated periodontal ligament cells (PDLCs).

The result showed that chitosan hydrogel without cell loading can improve periodontal regeneration in terms of functional periodontal ligament length indicating its potential use in clinical practice.

Chitin-Based Hydrogel

Chitin-based hydrogel looks like the structure of extracellular matrix ECM enabling a conducive environment for periodontal healing and regeneration, Xie et al 2020.

Chitin HA hybrid HG generates a perfect scaffold material that can support osteoblast, gingival fibroblast, cement oblast, and periodontal ligament fibroblast cells.

Synthetic Extracellular Matrix Hydrogels

In this new generation, hydrogel modification is done by adding IL-1receptor antagonist IL-1ra. Periodontal regeneration employing gingival margin-derived stem cell/progenitor cells in conjunction with IL-1ra. In the animal study done by Karim M Fawzy EL-Syed 2015 using hydrogel synthetic extracellular matrix and autologous G-MSCs isolated from free gingival margin incorporated into IL-ra loaded and unloaded G-MSCs/ HA in ECM showed a higher/ significant periodontal regeneration potential.

GeIMA (Gelatin methacrylate hydrogel) enfold human PDL stem cells in a rat model, micro-CT showed significant alveolar regeneration, Jie Pan 2019.

Approaches for integrated periodontal regeneration

Periodontal regeneration is done on the following tissues- periodontal ligament, alveolar bone, and cementum. The grafts are placed into the periodontal defects independent from PDL cells employing tissue engineering and scaffold methods [21]. This integrated periodontal regeneration has been made possible based on the four principles: scaffolds, blood supply, cells, and signaling molecules along with periodontal management that comprises biofilm removal and reducing inflammation [22]. With the advancement of scaffold fabrication, cell seeding, and delivery strategies for signaling molecules, various approaches are considered to achieve integrated periodontal regeneration [23].

Multi-phasic Scaffolds

Single or multiple cells seeded directly into the multi-phasic scaffold are suitable for integrated periodontal regeneration. Cells that are most widely applied in integrated periodontal tissue regeneration are periodontal ligament stem cells (PDLSC) and bone marrow mesenchymal stem cells (BMMSC) as they are directly involved with target tissues.

Multi-phasic scaffolds can be of two groups: bi- and triphasic. Each layer is designed to guide a specific target tissue regeneration. In integrated periodontium regeneration, of which the target tissues are periodontal ligament, alveolar bone, cementum, bi-phasic or tri-phasic scaffolds are suitable for the purpose of true periodontium regeneration. Bi-phasic scaffolds have two different phases that can simultaneously target two different tissues: PDL-AB, AB-CM, or PDL-CM. Tri-phasic scaffolds have three phases that simultaneously target three different tissues: PDL-AM-CM.

When compared to conventional GTR materials or single phasic scaffolds, there are advantages of applying multiphasic scaffolds to periodontal tissue regeneration. Temporospatial cues along with multiple signaling molecules are accurately engineered to the target tissue regeneration and can allow direct and prolonged initiation of the regeneration pathway. Periodontal tissue regeneration requires three-dimensional spaces for new CM, PDL, and AB. Multi-phasic scaffolds can provide spatial niches where new cells and tissues can effectively harbour and communicate between the cells.

The signaling molecules are the main factor for integrated periodontal tissue regeneration. Bioactive cues such as growth factors can be locally delivered for the regeneration of target tissue. Host immune responses and inflammatory regulations are an integral part of the homeostasis and regenerative therapy of periodontium and involve various kinds of bioactive cues. Henceforth, delivering bioactive cues via scaffolds can create a niche for stem cells to be effectively differentiated and increase the chances of producing desired periodontal tissue regeneration. Futuristic advancement of the integrated periodontal tissue regeneration is the discovery of new innovative biological clues in the biomaterial used as a scaffold with a better understanding of the mechanism of function of new and existing ones as well. Most widely studied bioactive cues for periodontal tissue regeneration include Amelogenin, BMP-2, and PDGF-BB but also BMP-6, BMP-7, FGF-2, TGF-β1, and IGF-1. Delivery of these molecules has also advanced and diversified as the bioactive cues become critical in periodontal regeneration. The efficacy and effectiveness of various scaffolds with different bioactive cues need careful examination and evaluation. Zhang et al. showed the efficacy of in vivo delivery of mesoporous silk scaffolds loaded with adenovirus for PDFG-B and BMP-7 into periodontal defects of beagle dogs. The result in 8 weeks showed a higher degree of regeneration of CM, AB, and

PDL than PDGF-B or BMP-7 alone but mostly it was seen horizontal with little vertical regeneration.

Many animal studies and in-vitro/in-vivo studies are done using Hydrogel as a scaffold for periodontal regeneration, as shown in Table 1 and Table 2.

Table 1: Animal studies using Hydrogel as a scaffold for periodontal regeneration

Hydrogel	**Method**	**Inference**	**Reference**
Thermosensitive Chitosan	Injectable chitosan-based thermosensitive hydrogel (CS/CSn-GP) injected into the muscle pouches of rats	Enhanced new bone formation in rat calvarial defects	Hui Li et al. 2016
Collagen	Collagen HG mingled with FGF2 implanted into Class-II furcation defects in dogs Assessed at 10 days and 4 weeks.	On day 10-Promotion of considerable cell and tissue ingrowth. In 4 weeks- Reconstruction of alveolar bone seen. Furthermore, periodontal attachment was repaired.	Takehito Momose et al. 2016
Si-HPMC/BCP	Injectable composite silanized hydroxy propyl methyl cellulose/biphasic calcium phosphate Canine fenestrations and premolar furcation in dogs.	Bone formation around BCP particles was observed. Enhanced intergranular cohesion by Si-HPMC Hydrogel acts as an exclusion barrier	Xavier Struillou et al. 2011
Trilayered nanocomposire HG	Composed of chitin-PLGA/nBGC/platelet-rich plasma implanted into rabbit maxillary periodontal defects and compared at month 1 and 3 months postoperatively.	It demonstrated complete defect closure and healing with new cancellous-like tissue formation	S Sowmya et al. 2017
Polyethylene glycol (PEG)	PEG with growth factors platelet-derived growth factor-BB (PDGF-BB). 4 Mandibular alveolar ridge defects were created in eight hound dogs. After 8 weeks, titanium dental implants were placed into augmented sites. After 8 weeks of allowed time for osseointegration, the animals were sacrificed to and ridge width histomorphometric analysis.	Promotes cell proliferation, angiogenesis and chemotaxis in osteogenic processes.	Matthew Vierra et al. 2016.
Polyethylene glycol with BMP-2	48 dental implants embedded in mandibles of 12 mini-pigs with shoulder of implant located 3mm above bone crest.	New supracrestal mineralized tissue volume formation.	Bo Wen et al. 2017.

	At 9 weeks, soft tissue healing was assessed and the extent of new vertical bone was evaluated with micro - CT and histo morphometry.	Increase in height and volume of bone along the implant.	

Table 2: In-vitro studies done using Hydrogel as a scaffold in periodontal regeneration.

Hydrogel	**Method**	**Inference**	**Reference**
Bioceramic reinforced HG	Chitosan-pectin HG is reinforced by biphasic calcium phosphate particles.	Promote high osteoblast proliferation.	Giorgio Iviglia et al. 2016
Trilayered nanocomposire HG	Composed of chitin-PLGA/nBGC/platelet-rich plasma	Favoured cement genic, fibro genic, osteogenic differentiation of human dental follicle stem cells.	S Sowmya et al. 2017
Alginate/Hyaluronic acid	Alginate/hyaluronic acid (HA) loaded with TGF-β1 ligand, encapsulating PDLSCs; and investigated the chondrogenic differentiation of encapsulated cells in alginate/HA hydrogel microspheres in vitro.	PDLSCs exhibited high levels of gene expression of Col II, Aggrecan and Sox-9 related to chondrogenesis.	Sahar Ansari et al. 2017.
Fibrin	PEGylated fibrin hydrogel was combined with DPSCs	All cell types proliferated in PEGylated fibrin. Histological analysis revealed fibrin degradation and production of a collagen matrix.	Kerstin M Galler et al. 2011.
Gelatin methacrylate	Gelatin methacrylate encapsulated human periodontal ligament stem cells (hPDLSCs)	Proliferation, migration, and osteogenic differentiation are critical for alveolar bone regeneration.	Jie Pan et al. 2019
Hyaluronic acid with BMP-7	HA hydrogels containing human OB ± BMP-7.	Mineralized collagen formation after 6 weeks. Increased osteogenic impression.	Stephen M Hamlet et al. 2017

Peptide Hydrogel	Octapeptide of phenylalanine, glutamic acid, and lysine.	Sustained viability and proliferation and differentiation of human mesenchymal stem cells into osteoblasts	Luis A Castillo Diaz et al. 2016

Conclusion

More modern techniques are below improved withinside the area of regenerative medication for the cause of regeneration of misplaced tissues. Periodontal regeneration with complete healing of the periodontal tissues and formation of alveolar bone, new connective attachment via collagen fibers functionally orientated at the newly created cementum. This can be achieved through periodontal regeneration facilitated through biometric scaffolds. Many biocompatible biometric scaffolds are available for use in scientific practice. For any biomaterial, it's miles crucial for it to be biocompatible and powerful whilst located clinically. Hydrogels are compacted scaffolds mimicking our body's extracellular matrix (ECM) that degrade fast and provide bone regeneration efficiently which is proven in in-vitro and in-vivo research. This article reviews the capability of the hydrogel as a scaffold providing a 3D environment in regenerating the lost periodontal tissues Though hydrogels as a scaffold for included periodontal regeneration are below the experimental process, it paves a pathway for extra-scientific and randomized scientific research due to their excellent results.

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