



Smart Biomaterials For Periodontal Regeneration: Self-Healing And Bioactive Approaches

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ABSTRACT:

Periodontitis is a chronic inflammatory disease which affects both the soft and hard tissues of the oral cavity. The periodontium is a complex structure which is complicated as it does not functionally restore itself after disease. Considering this complexity, tissue engineering accomplished to make it possible. Tissue engineering approaches can provide a new perspective to the affected or damaged tissues and help to reconstruct it. Severe and chronic periodontitis involves massive destruction of tissues and generally the process is irreversible. In these cases, bone grafts, delivery of growth hormones, guided tissue regeneration have been used but these approaches do not result in good treatment outcome. As a result, smart biomaterials were introduced to improve the clinical performance. Periodontitis is a multifactorial disease. It can cause damage to both soft and hard tissues of the periodontium. Regular periodontal treatment comprises of surgical and non-surgical procedures. An ideal goal of periodontal treatment is to achieve sufficient regeneration of damaged tissues. periodontal tissue engineering has emerged as a promising approach. Biomaterials provide a good added value to drug delivery, antibacterial properties and helps in tissue regeneration to treat several periodontal diseases. Smart biomaterials can be divided into 0-dimensional, 1-dimensional, 2-dimensional and 3-dimensional biomaterials. Hydrogel provide attachment of cells and growth of periodontal cells and help in tissue regeneration. The technology uses biomaterial scaffold which mimics the extracellular matrix of native

periodontal tissues. The smart biomaterials have evolved to provide good clinical performance in periodontal tissue engineering.

KEYWORDS: ‘Periodontitis’, ‘Biomaterials’, ‘Tissue engineering’, ‘Periodontal regeneration’, ‘Scaffolds’.

INTRODUCTION:

Periodontitis is a chronic, destructive inflammation caused by microbial infection leading to loss of alveolar bone resulting in loss of teeth [1]. Among global population 20-50% suffer from periodontal diseases. Approximately 10% suffer periodontitis [2]. Systemic diseases such as diabetes, cardiovascular disease, Alzheimer’s disease play an important role in causing periodontal disease [3]. periodontal tissue regeneration contributes to the regeneration of periodontal ligament, alveolar bone and cementum [4]. The main role of periodontal treatment is to achieve ideal regeneration of damaged tissues. There are several periodontal therapies such as mechanical debridement and flap surgery. Their main concern is removal of plaque and granulation tissue to prevent inflammation [5]. The clinical approaches in periodontal tissue regeneration are mainly guided tissue regeneration and bone grafts [6]. Periodontal tissue engineering is an ideal technology that helps to identify periodontal diseases. This technique uses stem cells, biological scaffold material to help in tissue regeneration in periodontal diseases [7]. Smart biomaterial is defined as ‘the designed materials that have one or more properties that can be significantly changed in a controlled fashion by external stimuli such as stress, temperature, moisture, Ph and electric or magnetic fields [8]. These smart biomaterials provide good drug delivery, antibacterial properties and have the tendency to play a role in tissue regeneration to treat several periodontal diseases. Smart biomaterials can be categorized into 0-D, 1D, 2D, 3Dimensional. 0 dimensional biomaterials, all dimensions are targeted to nanoscale and seen as particles, spheres or dots. They are effective for drug delivery. In 1 dimensional biomaterial, one dimension appears outside the nanoscale and seen as tubes, fibres or wires. They are used as scaffolds. 2 dimensional biomaterials, 2 dimensions are outside the nanoscale seen as sheets, films or coating. It is used for guided tissue regeneration. 3 dimensional biomaterials, three dimensions are outside the nanoscale forming structures like gels, scaffolds and implants. They are used for cell adhesion, proliferation and differentiation [8]. Hydrogels are three dimensional biomaterials which is water-swollen polymeric materials with properties like biocompatibility, mechanical strength and accessibility which is purposeful for cell culture [9], drug delivery [10 and tissue engineering [11]. Generally scaffolds should be porous and 3-dimensional which makes it suitable for cell attachment, proliferation and differentiation [12]. Hydrogels are widely used as scaffolds and have greater impact in periodontal tissue regeneration.

MATERIALS AND METHODS:

Databases searched for literature review includes Scopus, Web of Science and PubMed. The search was accomplished using the keywords 'periodontitis', 'biomaterials', 'tissue engineering', 'periodontal regeneration', 'scaffolds'.

SEARCH STRATEGY:

A literature search was conducted in Scopus, Web of Science and PubMed to identify articles that investigates the smart biomaterials used in periodontal treatment. The following search lines were used for each database: (periodontitis) or (biomaterials) or (tissue engineering) OR (periodontal regeneration) OR (scaffolds).

CONCEPT OF SMART BIOMATERIALS:

Smart biomaterials are defined as 'the designed materials that have one or more properties that can be significantly changed in a controlled fashion by external stimuli such as stress, temperature, moisture, pH and electric or magnetic field. They play a major role in drug delivery. In the context of periodontitis, the desirable features are controlled delivery of antimicrobials, growth factors, response to periodontal-specific stimuli, biocompatibility and biodegradability, ability to enhance regeneration of tissues, helps to mimic the periodontal complex [13. Smart biomaterials provide precision therapy and guide tissue regeneration, and enhancing treatment outcomes and reducing side effects in periodontitis management.

MECHANISMS OF ACTION IN PERIODONTAL REGENERATION:

A dental papilla forms two main structures such as odontoblasts and dental pulp during the process of tooth formation. During which the dental follicle develops into cementum, periodontal ligament and alveolar bone [14. Dental follicles originate from periodontal tissues which is derived from neural crest and develop along the roots. Periodontium consists of tissues such as gingiva, root-lining cementum, periodontal ligament and alveolar bone that aids support of the tooth.

Tissue engineering strategies have been implemented to restore damaged/lost periodontium. Tissue engineering is a complex process. It is necessary to control infection and suppress inflammation and helps to maintain healthy environment. Two main factors should be taken into account when considering tissue engineering are (a) a scaffold (b) drug delivery, growth factors [15. Loss of tissues caused by periodontitis, the injectable biomaterials flow freely in the complex structures enabling complete and effective eradication of infection completely [16. The injectable biomaterials is a method used to inhibit the growth of *Enterococcus faecalis* [17. They can be readily administered through a needle, it is simple and less invasive and minimizes damage. During injection, the biomaterials are in fluidic state fill the irregularly shaped pockets.

In recent times, to manage inflammation and aid healthy bone growth, bioprinted osteoblasts-laden alginate-based hydrogels were used. The printed system improves scaffolds properties and increases biocompatibility. Macrophages reduce the inflammatory cytokines and establish a favourable microenvironment [18]. Biomaterial scaffolds are designed to support proliferation and cell differentiation for tissue regeneration [19]. The optimal scaffold would be extracellular matrix (ECM) of the native tissue. There are many types of ECM found in several human tissues. Biomaterial scaffold is porous in structure which enables the transportation of essentials and vascularization and development of new tissues, hence enhancing the attachment of cells. Scaffolds serve as good drug delivery system. Biomaterials may be monophasic or multiphasic scaffolds. Monophasic scaffolds are easy to fabricate, enhances cell attachment and are potential delivery vehicles. Multiphasic scaffolds have many layers with several characteristics such as composition of the material, architecture and function that possess to target different tissue at once [20]. Main drawback is that it should be prefabricated and then implanted surgically and complicates the fabrication process. Tri-layered scaffolds resemble the periodontium with successive layers. Each individual part provides adequate mechanical cues for tissue regeneration.

In regenerative dentistry, injectable biomaterials are preferable when compared to implantable types for the application in the oral cavity. They are viscous in nature and can be administered in flowable state, either liquid or gel-like. This type of biomaterials includes but is not limited to hydrogels [21], cryogels [22], supramolecular hydrogels [23], microspheres [24], cement [25] and so on. Resorbable membrane are fabricated from collagen which has high biocompatibility and promotes wound healing. Bio-Gide, BioMend, OssGuide and Genoss have various collagen types. This type of biomaterials includes but is not limited to cell membranes enhance osteoblastic cell migration and new bone formation [26]. Collagen is a natural biomaterial have low mechanical strength and high biodegradation rate [27]. To increase the mechanical properties and decrease the degradation rate, several cross-linking methods are developed. The tested natural resorbable biomaterials include gelatin, chitosan and silk fibroin [28]. Gelatin is derived from collagen and have good biocompatibility to enhance osteoblasts adhesive and growth. Chitosan and silk fibroin have good biocompatibility, antimicrobial activity and wound healing. Compared to collagen, these natural biomaterials are used as barrier membranes are at the preclinical stage. There are several synthetic biodegradable polymers have been synthesized for resorbable GTR/GBR membranes. These polymers include poly(lactic acid), poly(glycolic acid), poly(ethylene glycol) membrane, poly(ϵ -caprolactone) (PCL), poly(lactico-glycolic acid) (PLGA), and their copolymers.

HYDROGEL IN PERIODONTAL TISSUE REGENERATION:

Hydrogel are three-dimensional water-swollen polymeric materials which exhibit characteristics such as biocompatibility, mechanical strength and accessibility. It is widely used for cell culture, drug delivery and tissue engineering. Hydrogels can mimic the microenvironment of extracellular matrix that is suitable for cell attachment, proliferation and differentiation. Hydrogels provide antibacterial, anti-inflammatory, osteogenetic and osteoimmunology capabilities to improve tissue regeneration.

Hydrogels have brittle properties and poor mechanical strength and low solubility which limits its application.

The fundamental components of hydrogels in periodontal tissue regeneration are natural polymers and synthetic polymers [29]. Natural polymer comprises of chitosan, sodium alginate, hyaluronic acid, collagen and several other particles. Chitosan is a natural polysaccharide with a chemical and biological structure similar to the extracellular matrix. It exhibits good biocompatibility [30], haemostatic properties [31], higher adhesiveness [32] and anti-microbial activity. Hydrogels are brittle and poor mechanical strength and show low solubility at a physiological pH of 7.4, which limits its application [33]. Sodium alginate is a natural, high productivity polysaccharide derived from brown seaweed and bacteria [34]. It is extensively used in wound healing [35], drug delivery [36] and cell transplantation [37]. Hyaluronic acid is a natural linear glycosaminoglycan with its highest concentration in eyes and joints [38]. It has good effect on periodontal inflammation by promoting the migration in gingival fibroblasts cells. It shows greater potential in periodontal therapy [39]. Collagen is an essential component of the extracellular matrix. It can enhance cell adhesion, growth, proliferation associated with periodontal regeneration [40]. It is suitable for guided tissue regeneration. There are several other natural polymers such as gelatin [41], chondroitin sulfate [42] and silk proteins [43] used in tissue engineering. They also exhibit excellent biocompatibility, degradability and cytocompatibility. Synthetic polymers are prepared through chemical reactions. Common synthetic compounds such as polyethylene glycol (PEG), PVA, and poly(lactic-co-glycolic acid) (PLGA) are generally accessible and trained to achieve excellent mechanical properties. However, the biocompatibility and degradability of synthetic polymer-based hydrogels are not as good as those of natural polymer-based hydrogels.

There are two main methods of hydrogel preparation are chemical crosslinking and physical crosslinking. Physical crosslinking refers to connections through ionic interactions, electrostatic interactions, hydrophobic interactions, crystallization and hydrogen bonding [44]. Chemical crosslinking reactions prescribes Michael's addition reaction, Schiff's base reaction, the Diels-Alder cycloaddition reaction, and free radical polymerization [45]. The key factors used to maintain the control of cell behaviour by the biomaterials are the chemical composition, mechanical properties, hydrophilicity and morphology of biomaterials [46]. There are three types of hydrogel and they are biomimetic hydrogel, intelligent hydrogel and self-healing hydrogel.

- **Biomimetic hydrogel:**

The biomimetic materials are used to mimic the composition or structure of the natural tissues. The extracellular matrix (ECM) is a 3D meshwork consists of macromolecular substances secreted by cells. Cues from the ECM can regulate certain cellular functions such as proliferation, apoptosis, migration and differentiation and eventually affect biosynthesis. By mimicking the structural composition of ECM providing good stimulation of cells and shows a favourable advantage of hydrogel in periodontal regeneration [47].

• **Intelligent hydrogels:**

Intelligent hydrogels are also called as stimulation-responsive hydrogels that can be responsive towards mild alterations to specific external stimuli. Depending on the specific stimulus received, smart hydrogels can be divided into thermosensitive hydrogels, pH-sensitive hydrogels, photosensitive hydrogels and other stimulation-responsive hydrogels. thermosensitive hydrogels are one such type which react according to external temperature alterations and play a vital role in drug delivery, cell encapsulation and tissue engineering. pHsensitive hydrogels have ionizable groups such as carboxylic acid groups and basic primary amines. Photosensitive hydrogels induce solvation-gelation changes by exposure to long-range photo light. GelMA is an important type of photosensitive, engineered gelatin-based material that is suitable for encapsulating PDLCs and has good biocompatibility and physical properties [48].

• **Self-healing hydrogels:**

Self-healing hydrogels are a group of hydrogels that has an ability to quickly repair their structure and function which is damaged. The gelation mechanisms of self-healing hydrogels include dynamic covalent bonds, supramolecular bonds, and multi-mechanism cross-links. These types of hydrogels are widely used in wound healing and tissue engineering due to their excellent self-healing properties. Injectable self-healing hydrogels have good drug delivery ability and could recover from tissue destruction in periodontitis [49].

RECENT ADVANCES AND EMERGING TECHNOLOGY:

Conventional treatments such as scaling and root planning, and guided tissue regeneration remain the gold standard in the clinical setting. Application of nanotechnology with a particle size of less than 100nm, replicates the native structure of the tissues leading to significant tissue regeneration. Newer fabrication techniques of bioprinting have enabled biomaterials to mimic different kinds of tissue regeneration.

Egg-shell-derived nanohydroxyapatite in which the egg shells contain 90% calcium that can be used to extract hydroxyapatite for bone regeneration [50]. It is inexpensive with limited drawbacks. In recent studies, the egg-shell-derived nanohydroxyapatite have been successful in animal models. In clinical studies, this is used in treating apicectomies, mandibular third molar defects and socket preservation providing promising results in remodelling and regeneration of bone [51].

Electrospinning is a technique which is used to produce ultrafine fibers from polymer solution with the use of electric field. It is currently used in creating biomaterials to replicate the natural extracellular matrix (ECM). It uses high-voltage electric field is applied to the polymer solution. The solution is then dispensed through a syringe. The electrostatic repulsion overcomes surface tension forming a fine jet. As the solvent evaporates, the solid nanofibers are deposited on the collector [52]. The electrospun

zein/gelatin/nanohydroxyapatite membranes shows increased cell adhesion, proliferation and osteogenic differentiation of human periodontal ligament stem cells [53].

Advancements in scaffold fabrication technologies such as 3D printing, multiphase scaffold, smart biomaterials have been developed to achieve optimal tissue regeneration. In several studies, the biomaterials with nanohydroxyapatite, immunomodulatory biomaterial, gingival fibroblasts, growth factors have shown beneficial results. However, clinical trials are required to assess the safety and efficacy of these biomaterials for periodontal tissue regeneration.

DISCUSSION:

Periodontitis is a chronic, inflammatory disease caused by microbial infection leading to loss of tooth. There are many periodontal therapies such as mechanical debridement and flap surgery. An ideal goal of these therapies is to attain good tissue regeneration. Periodontal tissue engineering is a technology to identify periodontal diseases and cure them. This technology uses stem cells, scaffolds materials or biomaterials to help in tissue regeneration. Tissue engineering strategies have been implanted to restore the damaged tissues. Two main factors such as scaffold, drug delivery and growth factors should be considered while using tissue engineering.

Smart biomaterials are defined as ‘the designed materials that have one or more properties that can be significantly changed in a controlled fashion by external stimuli such as stress, temperature, pH and electric or magnetic field’. These biomaterials are categorized into 0-D, 1-D, 2-D and 3-Dimensional. Biomaterial scaffolds are proposed to support proliferation and cell differentiation for tissue regeneration. Scaffolds serve as a good drug delivery system. Biomaterials may be monophasic or multiphasic scaffolds. Injectable biomaterials are administered through needle to stop the growth of *Enterococcus faecalis* and its less invasive procedure.

Biomaterials may be monophasic or multiphasic scaffolds. Monophasic scaffolds are easier to fabricate and promote cell attachment and are good drug delivery vehicles. Multiphasic scaffolds have many layers and possess several characteristics such as composition of material, architecture and function of that aims to target different tissues at once. Injectable biomaterials are preferable when compared to implantable ones in the oral cavity. Resorbable biomaterials are extracted from the collagen that has high biocompatibility and promotes wound healing. The natural resorbable biomaterials include gelatin, chitosan and silk fibroin. Gelatin is derived from collagen and possesses good biocompatibility and promotes growth. Chitosan and silk fibroin also possess good biocompatibility along with antibacterial activity and wound healing [54].

Hydrogels are three-dimensional biomaterials that are used for cell culture, drug delivery and tissue engineering. The fundamental components of biomaterials are of two types such as natural polymers and synthetic polymers. Natural polymers consist of chitosan, sodium alginate, hyaluronic acid, collagen and several other particles. Common synthetic polymers are polyethylene glycol (PEG), PVA and poly(lactic-co-glycolic acid) (PLGA). There are two main methods for the preparation of hydrogels such

as chemical crosslinking and physical crosslinking. The key factors used to maintain the control of cell behaviour by the biomaterials is the chemical composition, mechanical properties, hydrophilicity and morphology of biomaterials. Biomimetic hydrogels, intelligent hydrogels and self-healing hydrogels are the three types of hydrogels. biomimetic hydrogels are used to mimic the composition or structure of the natural tissues [55]. Intelligent hydrogels are responsive towards mild alterations to specific external stimuli and they are subdivided into thermosensitive hydrogels, pH-sensitive hydrogels, photosensitive hydrogels and other stimulation-responsive hydrogels [56]. Selfhealing hydrogels have the ability to rapidly repair their structure and functions that is damaged.

Scaling and root planning, guided tissue regeneration remains the gold standard for the treatment of periodontitis. There are many new fabricated biomaterials have been introduced. Egg-shell derived hydroxyapatite in which the egg shells contain 90% calcium that is used for bone regeneration and this procedure is inexpensive. It is used in treating apicectomies, mandibular third molar defects and socket preservation. Electrospinning is a technique which uses electric field and used to replicate the natural extracellular matrix (ECM) [57]. Advancements in scaffold fabrication technologies such as 3D printing, multiphase scaffold, smart biomaterials are developed to achieve ideal bone regeneration.

~~With advances in biomaterial science in tissue engineering strategies, the future relays possibilities for complete rehabilitation and regeneration of the periodontium. The combination of bone grafts and biomaterials provide better outcome in terms of tissue and bone regeneration. Smart biomaterials are a breakthrough in the field of dentistry especially in treating periodontitis.~~

Type of Smart Biomaterial	Composition / Example	Stimuli or Key Property	Application in Periodontal Regeneration	Advantages	Limitations / Challenges
0-Dimensional (Nanoparticles)	Silver nanoparticles, Calcium phosphate, Hydroxyapatite nanoparticles	pH, ionic strength, magnetic/electric fields	Drug delivery (antimicrobials, growth factors), enhancement of bone mineralization	High surface area, easy modification, controlled release	Cytotoxicity risk at higher doses, aggregation tendency
1-Dimensional (Nanofibers, Nanotubes)	Electrospun collagen, chitosan, or PCL nanofibers	Mechanical/electrical responsiveness	Scaffold for periodontal ligament and cementum regeneration	Mimics ECM structure, promotes cell adhesion and proliferation	Limited mechanical strength, difficult scale-up
2-Dimensional (Films,	Collagen or PLGA membranes,	Surface charge, enzymatic degradation	Guided tissue regeneration (GTR)	Biocompatible, promotes	Rapid degradation, risk of

Type of Smart Biomaterial	Composition / Example	Stimuli or Key Property	Application in Periodontal Regeneration	Advantages	Limitations / Challenges
Membranes, Coatings)	Bio-Gide®, chitosan films		membranes, barrier function	selective cell migration	collapse in defects
3-Dimensional (Scaffolds, Gels, Implants)	PLGA, PCL, gelatin, hydroxyapatite composites	Mechanical stress, temperature	3D scaffolds for bone and PDL regeneration	Promotes vascularization and osteogenesis	Surgical placement needed, limited integration in deep defects
Hydrogels (Natural / Synthetic)	Chitosan, alginate, hyaluronic acid, PEG, PLGA	pH-, thermo-, or photo-responsive	Injectable scaffolds for drug/cell delivery and wound healing	Biocompatible, minimal invasiveness, conforms to irregular defects	Brittle, low mechanical strength, limited load-bearing ability
Self-Healing Hydrogels	Chitosan-polyurethane, oxidized alginate composites	Dynamic covalent/supramolecular bonds	Repairs microdamage, sustained release of drugs	Reversible bonding, long-term structural stability	Complex synthesis, variable healing efficiency
Biomimetic Hydrogels	ECM-mimicking GelMA, collagen-hyaluronic acid composites	Biochemical and mechanical cues mimic ECM	Enhances cell adhesion, migration, and differentiation	Closely replicates native tissue microenvironment	Costly synthesis, limited in vivo data
Intelligent (Stimuli-Responsive) Hydrogels	Thermosensitive PEG/PNIPAAm, pH-sensitive chitosan blends	Temperature, pH, or light	Targeted release of antimicrobials and growth factors	Controlled drug delivery, adaptable response	Requires precise tuning of responsiveness
Natural Polymers	Chitosan, gelatin, silk fibroin, alginate, collagen	Biodegradable and biocompatible	Barrier membranes, wound healing scaffolds	Low immunogenicity, supports osteogenesis	Variable degradation rates, weaker mechanics

Type of Smart Biomaterial	Composition / Example	Stimuli or Key Property	Application in Periodontal Regeneration	Advantages	Limitations / Challenges
Synthetic Polymers	PEG, PLGA, PVA, PCL	Chemically tunable	Long-term scaffolds and delivery systems	Tailorable degradation and strength	Lower biocompatibility vs natural polymers

CONCLUSION:

There are several difficulties stand in the way of periodontal tissue regeneration. It is necessary to mimic the structure of periodontal tissues to attain successful periodontal tissue regeneration. Although some positive feedback has been reported. The challenge lies in the complexity of the periodontium as it comprises of both hard and soft tissues. Biomaterials are evolved to accomplish the role of tissue regeneration. An important tenet for the success of periodontal therapy is regenerating all three types of tissues such as cementum, periodontal ligament and bone in the periodontal defect. With advances in biomaterial science in tissue engineering displays the future possibilities for complete rehabilitation and regeneration of the periodontium. However, clinical trials are required to attain effective regeneration of damaged tissues using smart biomaterials.

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