Journal of Research in Medical and Dental Science
2022, Volume 10, Issue 10, Page No: 260-264

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

Recent Advances in Scaffolds for Periodontal Regeneration

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ABSTRACT

The periodontium is a coordinated, utilitarian unit of different tissues encompassing and supporting the tooth, including cementum, periodontal ligament encompassing the alveolar bone. Persistent periodontal infections can ruin the periodontal tissues, resulting in tooth loss. On the subject of periodontally diseased teeth therapy numerous biomaterials have been used beginning as a contact restraint layer in the directed tissue recovery that is the current best quality level in dental centre. This review examines current advancements in periodontal regeneration using tissue engineering and other regenerative techniques. Periodontal recovery requires the various levelled rearrangement of delicate and hard tissues. Three-dimensional micro porous frameworks offer underlying scaffolding and spatiotemporal direction for cell development and separation.

Key words: Periodontium, Scaffolds, Periodontal regeneration, Tissue engineering

HOW TO CITE THIS ARTICLE: Mariyam Sheikh, Prasad Dhadse, Recent Advances in Scaffolds for Periodontal Regeneration, J Res Med Dent Sci, 2022, 10 (10): 260-264.

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E-mail: mariyam81999@gmail.com
Received: 11-Aug-2022, Manuscript No. JRMDS-22-47889;
Editor assigned: 16-Aug-2022, PreQC No. JRMDS-22-47889 (PQ);
Reviewed: 30-Aug-2022, QC No. JRMDS-22-47889;
Revised: 13-Oct-2022, Manuscript No. JRMDS-22-47889 (R);
Published: 21-Oct-2022

INTRODUCTION

The periodontium including the cementum, periodontal ligament and alveolar bone forms the tooth supporting tissues. This integrated unit once lost by various factors such as bacterial proliferation, trauma, abnormalities and periodontal diseases can result in loosening of the tooth and in the final stage tooth loss [1-3]. There are various treatment method available *i.e.* scaling for plaque control, root planning and surgeries that prevents the disease progression but does not aim in regeneration of the affected periodontium. To overcome this barrier several methods were implemented *via* tissue engineering. Tissue engineering is a rapidly enhancing area which uses stem cells or progenitor cells, growth factors or signalling molecules and scaffolds for regenerating tissues [4]. Scaffolds are extracellular matrix which acts as base onto to which cells attach and proliferate leading to tissue formation. But the regenerated tissue formed differs in its quality and is variable in different individuals. Hence there is need for the alternative approach to rebuild the structure and function in the patients with chronic periodontitis. This review focuses on the various materials available for regeneration their adequacy and mostly accepted material, recent advancements of scaffolds and future prospective [5].

LITERATURE REVIEW

Role of scaffolds in tissue engineering

A scaffold is a biological/synthetic substance that gives a climate which permits embedded cells to multiply, separate, and structure the expected tissue or organ. As a general rule, they are isolated in three broad gatherings; natural polymers, manufactured polymers *i.e.* synthetic and Bioceramics. Its roles include:

- Promoting adherent cells attachment to the biomaterial surface and extracellular matrixes' position; and
- Permitting supplements, gases, and factors to be moved all together for a cell to endure, multiply, and separate.
- Have an option to biodegrade at a regulated rate while allowing tissue to regenerate
- Should not induce inflammation in the surrounding tissue when placed.

Natural polymer scaffolds improve cell performance in the biological environment because of their bioactive qualities, which allow for improved interaction. Proteins, polysaccharides, and nucleic acids (DNA and RNA) are the three types of natural scaffolds. Proteins like collagen, gelatine, fibrin, and silk, just as polysaccharides like chitosan, hyaluronic acid, alginate, and agarose are some of the natural scaffolds which are now being utilized in dental tissue recovery [6]. The biocompatibility of these scaffolds for cell attachment is usually excellent. Hence, this natural biomaterial is widely used in dentistry for periodontal tissue regeneration.

Synthetic polymers have reproducible physical and chemical properties. Their mechanical and physiochemical properties are comparable to that of the biological tissues. The advantage of this material is that it can be produced on a large scale of uniform size and design because it can be manufactured under required condition. Synthetic scaffolds are nothing but organic polymers which include polylactic acid *i.e.* PLA, Poly Glycolic Acid (PGA), Poly Lactide-Co-Glycolic Acid (PLGA), and Poly Capro Lactone (PCL). PGLA is the most commonly used synthetic polymer for periodontal regeneration [1,6].

Bio-ceramics have limited clinical use because of its insufficient biodegradability and biocompatibility but with recent advances researchers have managed to overcome this issue by combining natural and synthetic polymer and thereby enhancing its properties. This material so formed is known as composite with improved toughness, compressive strength and degradation rate.

Properties of scaffolds

Natural scaffold when used for regeneration can be derived from allogeneic sources or xenogenic sources which can lead to immunogenic reaction in the host due to its antigenicity. Xenograft scaffold when used for reconstruction of the craniofacial defect stimulates immunogenicity leading to the transmission of diseases. Hence, the most important property that the scaffold should exhibit is to avoid immune responses. The concept of immune inert scaffolds has been implemented recently that is successful in regulating the immune system by decreasing the natural killer cell activity.

DISCUSSION

As discussed previously that the scaffold should be biodegradable this property is desired as it remains in the body for some time and hence, should not produce toxic material in the body after the degradation process. The time when the scaffold biodegrade should match with the matrix production of the developing tissues. It should provide space for new tissue generation *via* controllable absorption [7].

Proper void volume should be offered by the scaffolds for angiogenesis which is the key in survival of the developing new tissues. Porosity should be good enough for adequate nutrient and metabolite exchange with its surroundings. A porous scaffold provides stability as it interlocks mechanically with its surrounding as well as guides and promotes the formation of new tissues. The usefulness of the scaffold during deployment directly depends on its pore size or pore diameter a larger pore size of 100-200 μm is generally preferred for mineralized bone regeneration after implantation. This large pore size allows the macrophages to infiltrate preventing bacterial accumulation and inducing colonization and migration of cells. Whereas a smaller pore size of less than 100 μm is considered to promote the formation of fibrous tissue. A size of more than 500 μm is not preferred as it might not retain during *in vivo* application.

Scaffolds should have consistent mechanical properties as the tooth is subjected to various forces in the oral cavity so it must have sufficient strength to resist the applied forces. In addition, it is significant that the framework material matches the properties of the individual local tissue hence, before selection of the scaffold it is necessary to consider the anticipated tissue's properties.

Foundation for periodontal regeneration

The reason for the periodontal therapy is to recover the periodontium where in the periodontal ligament; cementum and the alveolar bone are formed in their correct position in patients with periodontitis. As it is an inflammatory disease because of the bacterial accumulation there is infiltration of macrophages and neutrophils. The disease starts with gingivitis and further leads to progressive periodontitis. Dental plaque and calculus on the teeth contribute to the disease progression by raising the bacterial burden. The current practice focuses on the anchoring of the functional epithelium to the surface of the root by hemi desmosomes but its capability to safeguard the periodontium is less than the sharpeys fibres. It's likely that the disease may recur if the patient is not able to maintain its oral hygiene or the host defence mechanism is repressed. Thus, regenerative periodontal therapy emerged which involved bone grafts earlier but doesn't forestall the downward growth of the functional epithelium. Hence, GTR that is guided tissue regeneration is being used where the mucogingival flap of the affected tooth is raised with scaling and planning the root surfaces and then placement of the barrier membrane underneath the gingiva. This technique works by preventing the growth of the epithelium on the denuded surface with the help of the barrier membrane. This allows enough space for the osteoblasts and PDL cells for formation of alveolar bone and periodontal ligament. Following the treatment there is significant reduction of periodontal pocket depth and increased clinical attachment level. For it to be affective the barrier membrane should fulfil the basic properties enlisted earlier (Biocompatibility, space maintenance and tissue integration) [8]. GTR barrier membranes are absorbable and non-absorbable types. The space maintenance property of non-absorbable membrane is greater in comparison to absorbable membranes. The first GTR membrane formed of PTFE *i.e.* polytetrafluroethylene with high mechanical properties. In spite of the positive outcomes there are limitations to this treatment, the regenerative ability differs for individual and other factors such as systemic disease like diabetes may hamper the regeneration process. The results are also affected by smoking and poor oral hygiene which makes this difficult to succeed in the clinical trial. Moreover it can lead to ankylosis and root resorption.

Researchers came up with tissue engineering approaches *i.e.* various biomaterial scaffolds which can be applied in association with GTR. More improved scaffold technologies have recently been designed to guide

integrated periodontal regeneration. These are required to offer bioactive signs for periodontal recovery and can degrade so that new tissues can take their place.

Advantages of scaffolds

Scaffolds when compared to GTR have a relatively fast healing process. GTR requires at least 4-6 weeks for the healing of the periodontal ligament. Persistence of periodontitis for this longer period of time can cause the failure of the GTR procedure by hindering the healing capacity of the cells in the PDL, reducing the immune response of the host and severely leading to denaturation of the cementum. Scaffolds helps in recovery by advancing the movement of cells into the impacted region. The migrations of cells are enhanced when scaffolds are given along with cytokines and growth factors. As indicated by Choe, et al. Cementum like tissue structure was shaped onto the outer layer of the dentin when brooded with human PDL stem/begetter cells cultivated in 3D printed poly ε-caprolactone PCL scaffolds spatially conveyed with Connective Tissue Development Factor (CTGF), bone morphogenic protein 2 and 7 (BMP-2 and BMP-7) [9]. Lee, et al. published a study in 2014 that used a 3D printed tri-phasic scaffold to recreate the periodontium complex. They used a single type of multi potent dental stem/progenitor cells to deliver amelogenin, connective tissue development factor, and BMP-2 for regeneration of CM, PDL, and AB, respectively [10]. Various scaffold methods have demonstrated considerable prospective for coordinated periodontal regeneration, as previously stated. The current technological advancement in micro-precise regional control in scaffold design has marked an essential step toward integrated multi-tissue periodontium regeneration. The numerous scaffolds and delivery systems used to regenerate integrated periodontium are addressed in greater detail below.

The shortcoming of GTR as we have seen is that it requires approximately 4-6 weeks for regeneration but any secondary infection should be avoided in this period which is difficult in long standing case of periodontitis causing its recurrence. Periodontitis is mainly caused by bacteria *P. gingivalis* and *T. denticola* [11]. Accumulation of plaque and calculus worsen the condition. Such re-infection leads to failure of the periodontal healing. About hundred GTR treatments at hundred sites, Schallhorn, et al. found retarded and unfavourable healing pattern being 8% and 3% related with re-infection by bacteria [12]. According to Sanctis, et al. microbial colonisation on e-PTFE membranes inhibited periodontal tissue regeneration by 50%. Hence, the scaffold is incorporated with anti-microbial properties to prevent re-infection and to achieve the periodontal regeneration to its fullest [13]. Chitin is a copolymer of glucosamine and N-acetyl glucosamine and is a deacetylated product of chitin. Chitosan is used not only because of its antimicrobial properties but also because it is biocompatible and biodegradable. Yeo, et al. demonstrated the regenerative impact of the chitosan films in one-wall intra bony defects in beagle dogs, the outcomes showed that chitosan layers incited more amount of new cementum and bone, and that cement oblasts and osteoblasts were densely arranged onto the new bone surface in the chitosan group. Other components used are silver nanoparticles; Mg doped HA nanoparticles, tetracycline and metronidazole. Various studies are now focusing on the use of PRP (Platelet Rich Plasma) for periodontal regeneration but yet more understanding is needed in this area for it to be used on clinical grounds successfully [14].

An inflammatory response is generated in periodontitis because of increased host response leading to its pathogenesis. Thus, use of pharmacological agents (e.g. NSAIDS) came into practice. Treatment aims at getting rid of the contributively factors like the plaque and calculus and inflammatory granulation tissue and placement of scaffold with sustained release (*i.e.* release their content steadily over the period of time) of meloxicam (NSAID) [15]. According to one of the study in a review, PCL scaffolds were conveyed with ibuprofen resulted in an anti-inflammatory effect [16]. A 3D PCL scaffold in combination with tannic acid, an anti-oxidant has a mitigating signal that suppressed inflammation induced by lipopolysaccharides.

Scaffold architecture

Many methodologies for scaffolds have been developed over the recent couple of years. The advancement has generally occurred in the tissue engineering field involving pre-made porous scaffold, injectable scaffold, decullularised extracellular matrix, cell sheets, cell encapsulated in self-assembly hydrogels and rapid prototyping.

The extracellular matrix has a permeable and amorphous structure that behaves as a scaffold in nature. It uses bioactive chemicals, spatial patterning, and mechanical stimulation to control the proliferation and differentiation of residing cells. Hence, Decellularized ECM is commonly used to recreate a 3D milieu for tissue repair and regeneration at implanted sites.

Pre-made porous scaffolds are broadly utilized in tissue engineering. For production of porous scaffolds, natural and synthetic scaffolds are used. In general, 3D scaffolds which are highly porous and that enables interconnectivity are preferred for rehabilitation of its structure and function as the architecture provides an appropriate milieu for proper contact between the cells and scaffold. The intrinsic physical and chemical properties can easily be tailored to match the natural ECM in the host tissue since this approach allows a relatively accurate design for tissue architecture and microstructure to tissue integration at the implanted location. A scaffold can be classified as pre-formed or injectable depending on how it is constructed [17]. The injectable scaffolds are better than the pre-formed scaffold on the fact that:

- It is performed in a highly efficient way, reducing the hazards of infection and enhancing convenience;
- It can fit in any randomly oriented defects;

- It resolves the challenges of cell attachment and its fixation,

As well as the transportation of bioactive molecules, by blending these elements with the solution containing materials before injecting in situ. An injectable scaffold is much enticing than a pre-formed one because of its size, shape, and intricate structure of dental and craniofacial tissues [18]. Furthermore, scaffolds can be monophasic and multiphasic depending on the overall consistency. Monophasic scaffolds are generally formed by the electro spinning technique that forms fine fibrous scaffolds that is said to be similar to existing collagen fibrous network; resulting structure is highly porous with different shapes and sizes. It is consistent in terms of its overall physical and chemical properties. Whereas multiphasic scaffolds is used when multiple materials are used each layer directing the regeneration of multiple tissues [19]. As different combination of cells can be used and there is no such perfect combination. Technology such as 3D printing has lately proposed as a viable strategy for producing multilevel constructions for tissue engineering as it overcomes the disadvantages of traditional making processes. The most significant benefit of 3D printing for scaffold production is its design freedom. Depending on the architecture of the 3D printed scaffolds, they can be monophasic or multiphasic. The interoperability of 3D printing with diagnostic testing devices as in cone beam computed tomography scan and an intraoral 3D scanner is another benefit.

PDL regeneration

Between the cementum and the alveolar bone lies the periodontal ligament. The orientations of the PDL primary fibres define the structure of the PDL. As a result, fibre alignment mimicking is crucial for PDL regeneration. To produce PDL fibre alignment electro spinning and channel containing scaffold, several approaches were devised [20]. The aligned fibres drove cell extension and collagen fibrils alignment on the matrices' surfaces, demonstrating that electro spinning is a simple way for fabricating orientated matrices. For partial alignment of fibres 3D printing micro-channel fibre-guiding scaffolds can be used but studied showed that the fibres are aligned parallel to dentin and not within the channel [21]. Because PDL fibre directions change between groups, a freeze-drying scaffold was created to imitate the fibre directions. However, there was no evidence of the scaffold's usefulness *in vitro* or *in vivo*. In a similar work, a 3D printing procedure was utilised to create microgroove structures that controlled cell orientations in parallel, oblique and perpendicular angles. Similarly, no *in vivo* data verified the 3D printing scaffold's guiding role. The most important factor after reconstruction is the functional regeneration. Various studies have indicated that when the PDL cells when fused with mechanical stress on the arranged scaffolds which was fibrous histologically presented more arranged PDL like tissue formation. Rapid innovations in nanomaterials and nanotechnology have given us a glimpse into the economic viability of nanomaterials in periodontal disease care. It is feasible to develop systems on a nano, micro, or even macro-scale utilising these concepts, resulting in distinctive nano-building elements with built-in nanocontrol and nanodelivery capabilities. As new nanotechnologies are extensively researched, this trajectory will improve much more in the future [22-29].

CONCLUSION

As previously stated, there has been significant progress in recent years in improving the clinical outcome of periodontal treatment. Tissue engineering is a burgeoning field in periodontics. When the potential for the treatment was first proposed, the majority of investigations on it exploded. This unique approach to periodontal regeneration is being propelled forward by advancements in material discovery, production techniques, and digital solutions. Several researches have presented archetypal scaffold designs that may be used to assist regeneration at the particular area. This approach is focused on the *ex vivo* fabrication of periodontal scaffolds using a variety of materials and functionalization techniques. High-resolution 3D printing technology currently enables for the quick manufacture of polymeric scaffolds in predetermined shapes. The approach appears to be well-suited to clinical settings, where CT scans and 3D intraoral scanners are ubiquitous. Despite the hopeful advancements, no scaffold technology has yet to produce a good clinical outcome in periodontal regeneration. The inadequate expertise of *in vivo* degradation of implanted materials has become one of the main impediments to the clinical application of scaffolding. But dynamic interdisciplinary coordinated efforts between biomaterial researcher, scientists, substance specialists and clinicians will fill in as a key impetus conceivably driving us toward practical recovery of periodontal tissues.

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