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Recent advancement in Periodontal Regenerative Materials

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ABSTRACT: Periodontitis, a highly prevalent oral disease, breaks down the integrity of the tooth supporting system through a series of chronic inflammatory pathological processes and leads to damage of the periodontal structures, which may eventually lead to tooth loss. Therefore, the exploration of effective and safe periodontal therapies that can be translated into the clinic is an urgent health need worldwide. Modern day periodontics aims at maintaining the health of teeth and their supporting structures with the main goal of controlling the infection and regenerating the lost supporting structures by means of either mechanical re-contouring or by grafting techniques such as barrier membranes, bone replacement grafts, growth factors, tissue engineering or by various combination of these above materials. The aim of this literature is to know in detail about these current regenerative materials and their advancement for periodontal hard and soft tissue regeneration with conventional and advanced surgical techniques.

Key words: Regeneration, Stem Cells, Scaffold, Growth factors

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I. INTRODUCTION

Periodontitis, a highly prevalent oral disease, breaks down the integrity of the tooth supporting system through a series of chronic inflammatory pathological processes and leads to damage of the periodontal structures, which may eventually lead to tooth loss.[1] An epidemiological survey has suggested that more than half of all adults are affected by periodontal disease to varying degrees [2–4], and a remarkable surge (25.4% increase) in the prevalence rates of periodontal disease was observed from 2005 to 2015.[2] It has been observed that the total surface area of pocket epithelium in contact with the subgingival pathogens and their products in a patient with generalized periodontitis is approximately the size of the palm of an adult hand (**72 cm2**), with even larger areas of exposure in cases of more advanced periodontal destruction.[3] Modern day periodontics aims at maintaining the health of teeth and their supporting structures with the main goal of controlling the infection and regenerating the lost supporting structures by means of either mechanical recontouring or by grafting techniques such as barrier membranes, bone replacement grafts, growth factors, tissue engineering or by various combination of these above materials.[4] The basic dogma of tissue regeneration is to stimulate a cascade of healing events which, if coordinated, can result in the completion of integrated tissue formation and may prove to be a huge step-up in managing advanced periodontal disease and preventing tooth loss.[5] The aim of this literature is to know in detail about these current regenerative materials and their advancements for periodontal hard and soft tissue regeneration with conventional and advanced surgical techniques.

Definitions & different terminologies used in regeneration

- **Regeneration** refers to the reproduction or reconstitution of a lost or injured tissue.
- **Periodontal regeneration** is defined as the restoration of lost periodontium or supporting tissues and includes formation of new alveolar bone, new cementum, and new periodontal ligament.
- **Repair** describes healing of a wound by tissue that does not fully restore the architecture or the function of the part.
- **New attachment** is defined as the union of connective tissue or epithelium with a root surface that has been deprived of its original attachment apparatus. This new attachment may be epithelial adhesion or connective tissue adaptation or attachment and may include new cementum.
- **Re-attachment** describes the reunion of epithelial and connective tissue with a root surface.

II. OBJECTIVE OF GRAFT THERAPY

The objectives of graft therapy as stated by Schallhorn et al. in 1970[6] include:

1. Probing depth reduction

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2. Clinical attachment gain
3. Bone fill of the osseous defect
4. Regeneration of new bone, cementum, and periodontal ligament.

For better efficacy and result of bone graft therapy, the following additional objectives should also be considered –

1. Easy availability
2. Good handling properties
3. Easy storage
4. No/less adverse tissue reactions
5. Cost-effectiveness[5]

Different Regenerative materials used in the field of Periodontics- Here I have tried to assemble all the materials that were used and currently being used for regeneration in the field of Periodontology.

1. **Guided tissue regeneration**
1. Membranes
1.1. Collagen barriers
1.2. Cargile membranes
1.3. Polylactic, polyglycolic and polyglactin copolymer acid barriers
1.4. Oxidized cellulose mesh barriers
1.5. Autogenous periosteal barrier membranes
1.6. Laminar bone allograft membranes

2. **Bone replacement grafts**
2.1. Autografts
2.2. Allografts
2.3. Xenografts
2.4. Alloplastic grafts

3. **Active biomaterials**
3.1. Stem cells
3.2. Conductive scaffolds
3.3. Signalling molecules/growth factors
3.3.1. Platelet-rich plasma
3.3.2. Bone morphogenetic proteins
3.3.3. Cell-binding peptide
3.3.4. Fibroblast growth factor
3.3.5. Enamel matrix derivatives (EMD)
3.3.6. Platelet derived growth factors (PDGF)
3.3.7. Growth/differentiation factor-5
4. Laser assisted new regeneration procedure
5. Local Drug delivery system

III. RECENTLY ADVANCED REGENERATIVE MATERIALS USED IN PERIODONTICS

Active biomaterials

A relatively new discipline, the tissue engineering in periodontal therapy has been developed in part due to a growing body of evidence regarding the biologic functions of the human body. The biological basis for this innovation was based on the concept that certain factors were able to regulate both, the differentiation and function of progenitor cells within the healing wound area (periodontal tissues) which would lead to a more favourable outcome of new bone, cementum and PDL formation.

Three basic elements have been investigated in order to manipulate the sequence of events that may lead to complete periodontal healing:
(1) stem/progenitor cells,
(2) conductive scaffolds and
(3) signalling molecules/ growth factors (Chen and Jin, 2010).[7]

Fig 1- Role of different molecules for Periodontal Regeneration

3.1. Stem cells

The term ‘‘stem cells” refers to undifferentiated cells that are capable of self-renewal and multi-lineage differentiation depending on their intrinsic signals that can be regulated by extrinsic factors (Lin et al., 2008).[8]

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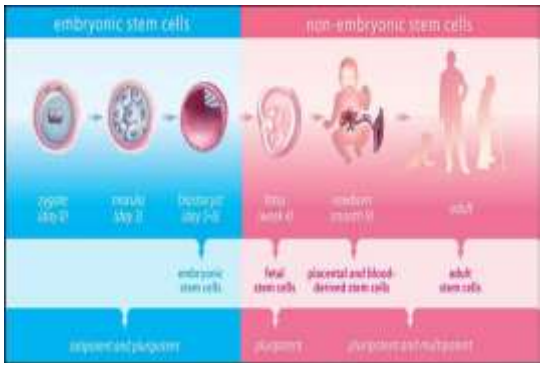

Fig 2- Types of Stem Cells

Hematopoietic stem cells from bone marrow have been identified first and were already in use for therapeutic purposes. Bone marrow stromal cells (BMSSCs) or mesenchymal stem cells (MSCs) are a different population of stem cells that has been identified in the adult body. It appears that all the tissues with tendency for renewal contain at least a small number of stem cells (Lin et al., 2008).[8]As a novel alternative to conventional cell delivery methods, such as cell suspension injection, grafting and scaffolds, cell sheet technology (CST) has recently been developed as a scaffold free strategy, referred to as '**Cell Sheet Engineering**'.

CST has been widely applied in tissue and organ reconstruction, including kidney, myocardial tissues, cornea, hepatocytes, cartilage, esophageal mucosa, trachea, urothelium, bone, dentin-pulp complex, skin etc.The first two studies to adopt cell sheets in periodontal therapy were published in 2005[9] and since then cell sheets derived from various cell types have been fabricated for periodontal regeneration and tested both in vitro and in vivo. (Flores MG et al, 2008)[10]

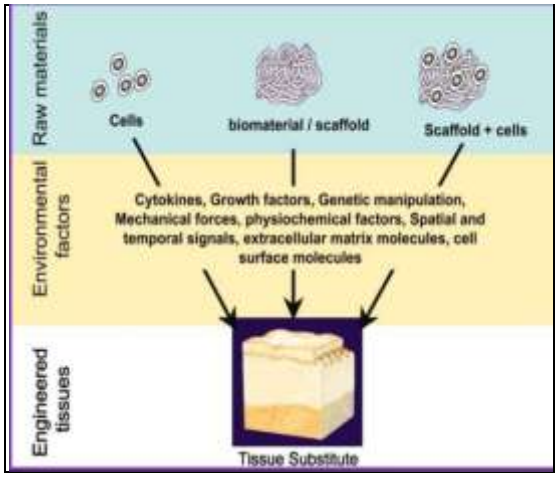

Fig 3- Steps of forming a tissue substitute by CST

Types of Cell Sheets

According to Chen et al[11], in their review of CST for bone regeneration, cell sheets can be classified as follows:

1. **Monolayered Cell Sheet (MCS)**
2. **Multilayered Cell Sheet (MLS)**
3. **Cell Sheet Fragment (CSF) and Cell Sheet Pellet (CSP)**

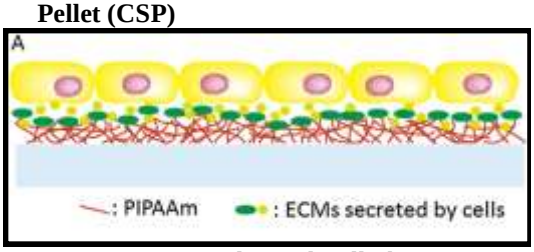

Fig 4- Monolayered Cell Sheet

STEM CELLS FOR PERIODONTAL BIOENGINEERING

Sources-

1.Intra Oral Mesenchymal Stem Cells (Intra oral MSCs)

2.Extra Oral Mesenchymal Stem Cells (Extra oral MSCs)

1. Intraoral MSCs

Several cell populations with stem cell properties have now been harvested from different tissues in and around a tooth and subjected to enrichment and expansion techniques. These populations generally include dental pulp stem cells (DPSCs), stem cells from exfoliated deciduous teeth (SHED), PDL stem cells (PDLSCs), stem cells from apical papilla (SCAP), dental follicle stem cells (DFSCs) and MSCs from gingival tissues and alveolar bone.

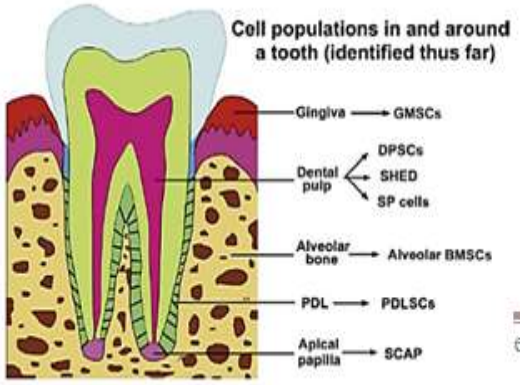

Fig 5- Different source of Intra-Oral MSCs

These stem cell populations have an advantage over other stem cells, such as bone marrow derived MSCs (BMMSCs), because they

can be obtained from patients in the dental clinic rather than requiring an invasive bone marrow aspiration procedure at a secondary clinic. Because of their particular characteristics of proliferation, differentiation and plasticity, dental stem cells have also enabled significant progress towards clinical orthopaedics and oral maxillofacial bone reconstruction. (Yamada Y et al, 2011)[12]Thus, while not largely exploited, it can be seen that the humble tooth has an important role to play in the development of future regenerative therapies.

1.1. Periodontal tissue-derived stem cells (PDLSC)

When considering application to periodontal regeneration, stem cells derived from the tissues surrounding the teeth, i.e., the Periodontium should be considered the first choice. (Chen FM et al, 2012)[13]Early observations indicated that the PDL has a regenerative capacity and that a population of multipotent progenitor cells exist within this tissue.(Shimono M et al, 2003)[14]PDLSCs were first isolated in 2004 and have been shown to give rise to adherent clonogenic clusters resembling fibroblasts. (Seo BM et al, 2004)[15]They are capable of developing into adipocytes, osteoblast-like cells and cementoblast-like cells in vitro as well as producing cementum-like and PDL-like tissues in vivo.(Kawanabe N et al, 2010)[16]Meanwhile, PDLSCs have also shown the capacity to differentiate into vascular cells, forming blood vessel-like structures.(Okubo N et al, 2010)[17]These findings suggest that the PDL constitutes an important stem cell source for the regeneration of periodontal tissues.

1.2. Stem cells from apical papilla (SCAP)

The apical papilla tissue is only present during root development before the tooth erupts into the oral cavity. (Huang GT et al, 2008)[18]A unique population of dental stem cells known as SCAP is located at the tips of growing tooth roots. These cells are capable of differentiating into adipocytes and osteoblasts in vitro. (Huang GT et al, 2008)[18]

1.3. Dental follicle stem cells

The dental follicle is a loose mesenchymal tissue surrounding the developing tooth germ which participates in the formation of periodontal progenitor cells. It is believed that this tissue contains stem cells or precursor cells for cementoblasts, PDL cells and osteoblasts. (Luan X et al, 2008)[19]

1.4. Stem cells from dental pulp (DPSC) or exfoliated deciduous teeth (SHED)

DPSCs were found to be highly proliferative cells capable of differentiating into odontoblast-like cells and forming dentin/pulp-like complex. Furthermore, compared with DPSCs, SHED grows and proliferates more rapidly. (Miura M et al, 2003)[20]The clinical trial of alveolar bone reconstruction using DPSCs was successfully carried out, and the data suggest that a DPSC can completely restore mandible bone defects. (d'Aquino R et al, 2009)[21]

2. Extraoral MSCs

Extraoral MSCs, i.e., non-dental stem cells, such as bone marrow derived mesenchymal stem cell (BMMSC) and adipose-derived stem cells (ASCs), have also been investigated as alternative cell sources for periodontal regeneration and bio-engineering. (Kawaguchi H et al, 2004)[22]

2.1. Bone marrow-derived MSCs (BMMSCs)

BMMSCs are the most widely investigated MSCs because they are easily accessible, their isolation is straightforward, they can be bio-preserved with minimal loss of potency, and they have shown no adverse reactions.These cells are clonogenic and have demonstrated the ability to form bone and cartilage. (Malgieri A et al, 2010)[23]BMMSCs can efficiently regenerate not only bone tissue, but also periodontal tissue . (Lin NH et al, 2009)[24]

2.2. Adipose-derived stem cells (ASC)

Adipose tissue is an abundant source of MSCs. ASCs can be readily harvested in large quantities and can be obtained with relative ease with low donor site morbidity. ASCs have adipogenic, myogenic, osteogenic and chondrogenic potential, and they are very angiogenic in nature.

2. Conductive scaffolds

The wound healing process occurs within in a three dimensional environment, the extracellular matrix (ECM) that facilitates the molecule regulation of the cellular activity. It is therefore evident that, in regenerative procedures an artificial tissue-engineering scaffold is an essential prerequisite in order to facilitate bone formation. (Chen and Jin, 2010)[25]A matrix may assist the penetration, attachment, proliferation, differentiation and in-growth of cells that are necessary for regeneration and inhibit the infiltration of undesirable cells on the healing site. The biomaterial scaffold, like the natural biological

tissues should have an ‘‘ideal” porosity for cell in-growth, adequate surface area, adequate mechanical strength and favourable degradation (bio-degradable) properties (Ahmed et al., 2008)[26]Biomaterial scaffolds may be fabricated from either natural materials (i.e., collagen and fibrin) or from synthetic materials (i.e., polyglycolide and polylactide polymers and copolymers). These materials may also be designed with a microstructure that has the ability to release molecules to induce and accelerate the periodontal regeneration cascade events. (Chen and Jin, 2010)[25]

3. Signalling molecules/growth factors

3.1. Platelet-rich plasma (PRP)

PRP is an autogenous concentration of platelets in a small volume of plasma and is considered to be an extremely rich source of autogenous growth factors. (Marx RE, 2004)[27]PRP has been used alone or in combination with autografts, allografts or with bio-materials for the treatment of periodontal defects, extraction socket preservation, alveolar ridge augmentation, mandibular reconstruction, sinus floor elevation and maxillary cleft repair. (Plachokova AS et al, 2008)[28]Results have shown greater volume and denser bone compared to autografts used alone for bone regeneration. (Marx RE, 1998)[29]The improvement in the bone healing potential is believed to be due to the growth factors present in PRP. (Plachokova AS et al, 2008)[28]

2.3.2. Bone morphogenetic proteins (BMPs)

Through their chemotactic, mitogenic and differentiating mechanisms, BMPs play a crucial role in bone remodelling. (Sykaras N et al, 2003)[30] BMP use has shown promising results for intraoral applications such as sinus augmentation and alveolar ridge preservation. The most commonly used and investigated BMPs for bone regeneration applications are **BMP-2 & 7**. (Rao SM et al, 2013)[31]

2.3.3. Cell-binding peptide

This is a synthetic clone of a specific amino acid sequence of Type I collagen, which has been reported to be involved in the binding of cells, e.g., osteoblasts and fibroblasts (Yukna et al., 2000).[32]PepGen P-15 is a product that has been tested in conjunction and compared to an organic bovine-derived hydroxyapatite bone matrix and demonstrated positive effects on periodontal regeneration (Yukna et al., 2000)[32]

2.3.4. Fibroblast growth factor (FGF)

Fibroblast growth factor-2 (FGF-2) is a member of the heparin binding growth factor family and has been demonstrated to promote the proliferation and attachment of endothelial and PDL cells in wound healing.

2.3.5. Enamel matrix derivatives (EMD)

These are the purified fraction from the enamel layer of developing porcine teeth. It was assumed that those proteins, mostly made of **amelogenins**, might stimulate cementum deposition and periodontal regeneration. (Miron RJ et al, 2016)[33]Studies reported that EMD with/ without the addition of a synthetic bone graft lead to clinical improvement in advanced intrabony defects. (Hoffmann T et al, 2016)[34]

2.3.6. Platelet derived growth factors (PDGF)

It acts as a serum GF for fibroblasts, has five isoforms (AA, AB, BB, CC and DD); of these, **PDGF-BB** was found to be more potent than the other isoforms in promoting mitogenesis of PDL cells. (Boyan LA et al, 1994)[35]At concentrations of 10-20 ng/ml, in vitro studies suggested that PDGF-BB stimulated the proliferation of fibroblasts and osteoblasts, whereas a higher concentration (>50 ng/ml) is required for the adhesion of PDL fibroblasts to roots. (Strayhorn CL et al, 1999)[36]

2.3.7. Growth/differentiation factor-5 (GDF-5)

Growth/differentiation factor (GDF)-5 is a member of the TGF-b superfamily, which shows a close structural relationship to BMPs and plays critical roles in skeletal, tendon and ligament morphogenesis. (Francis-West PH et al, 1999)[37]In vitro studies have shown that recombinant human GDF-5 at concentrations of 10-1000 ng/ml has mitogenic activity in human PDL cells. (Nakamura T et al, 2003)[38]

Laser assisted new regeneration/ attachment procedure (LANAP)

More than 30 years ago, Gregg and McCarthy published research on the use of a specific free-running pulsed neodymium-doped:yttrium–aluminum–garnet (Nd:YAG) laser for the treatment of periodontal disease. First conceived and developed in the 1990s, they later proposed its use for achieving bone regeneration. (Gregg RH et al, 2001)[39]They developed a specific protocol, laser-assisted new attachment procedure (LANAP), with research-proven operating parameters. LANAP received Food and Drug Administration clearance in 2004. An Nd:YAG laser was developed that

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operates at a wavelength of 1,064 nm to deliver the therapeutic LANAP.

The potential for **regeneration** is facilitated by:

1) Delivering intense, precise, and selective energy to the affected area (periodontal pocket), without damage to adjacent tissues;

2) Being bactericidal to pigmented periodontal pathogens;

3) Sealing the pocket orifice with a "thermal fibrin clot";

4) Creating a physical barrier preventing downgrowth of epithelium;

5) Promoting healing from the **bottom up** rather than the top down by stimulating the release of pluripotential cells from the PDL and alveolar bone.

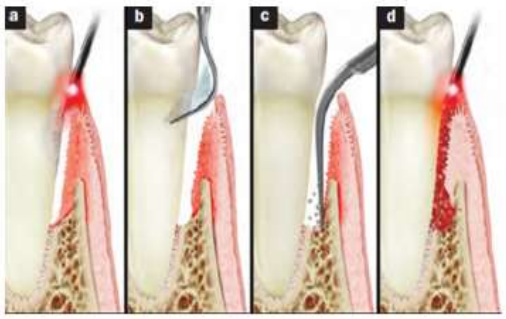

Fig 6- Steps of LANAP (Robert H. Gregg II, Dawn M. Gregg, 2003)

The benefits have been described as less invasive and less traumatic, minimal postoperative discomfort, minimal recession and thermal sensitivity, quicker healing, and equally successful results treating dental implants and natural teeth. (Gregg RH et al, 2001)[39]

In one of the largest human histology studies, Yukna et al., 2007[40] were the first to publish and prove incontrovertibly the positive results of LANAP therapy when compared to conventional periodontal treatment. The results showed unequivocally that 100% of the teeth treated with LANAP formed new attachment as opposed to 0% of the control teeth. More recently, in 2012[41], Nevins et al. reported another landmark human block study demonstrating highly successful outcomes of patients treated with LANAP in cases of extreme periodontitis.

2.5 Local Drug delivery system

Data support the efficacy of locally delivered, controlled-release antimicrobials, supporting the conclusion that SRP plus adjunctive therapy could be considered a new standard for nonsurgical periodontal therapy.

Classification of local delivery devices

1. Sustained release devices (drug delivery for less than 24 hrs)
2. Controlled delivery devices (drug release exceeding 1 day)

Drug	Concentration	Device composition of delivery device	Type	Duration of reservoir
Tetracycline fibres	25%	Ethylene-vinyl acetate monolytic fiber	Controlled - delivery device	>240 hr
Metronidazole	25%	Glyceryl monooleate + sesame oil gel	Sustained-release device	<12 hr
Minocycline gel	2%	LS-007 gel	Sustained-release device	–
Doxycyline	8.5%	Polymer	Controlled - delivery device	>7 days
Chlorhexidine	34%	Cross linked gelatin	Controlled - delivery device	>200 hr

Chart 1- Some important local delivery drugs

Available Products

1. Tetracycline fibers- Actisite, Periodontal Plus
2. Metronidazole- Elyzol, Metrogene
3. Minocycline ointment- Arestin, Periocline
4. Chlorhexidene chip- Periochip
5. Doxycycline polymers-Atridox

Reference	T- fiber	T- fiber + scaling	Scaling	Duration of study
Goodson et al	0.57	0.93	0.54	1 year
Heiji et al	1.98	2.15	1.78	62 days
Killoy et al	2.16	No treatment	0.93	1 year
Newman et al	No treatment	1.81	1.08	6 months

Chart 2- Probing depth reduction with tetracycline fibers

Another study showed maintained superior results for 1 year following Tetracycline therapy & low incidence of recurrence. (Michalowicz,1995)[42] A European study used a split mouth design with SRP + Periochipvs SRP alone. Greater decrease in probing depth & increase in CAL in case group. (Soskolne et al, 1997)[43]A study was carried out comparing Tetracycline + SRP, Minocycline + SRP & Metronidazole + SRP. (Radvar et al, 1996)[44] Tetracycline results were superior especially in sites with Suppuration.All 3 systems offer advantage over SRP alone but

Tetracycline gave greatest advantage in treatment of persistent lesions.

IV. CONCLUSION

With the emerging trends in the fields of periodontology, periodontal regeneration is gaining a faster pace. Most of the clinical studies focuses on the regeneration of the periodontium in one way or other. This is because once we regenerate the periodontium, we can save the tooth/teeth to maximum and ultimately help the patient to enjoy the dentition for life. The future of periodontal repair/ regeneration seems promising with doors wide open for researchers to use new and emerging technologies in transforming predictable full periodontal regeneration from a being a dream into becoming a clinical reality.

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