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Scaffolds in Restorative and Regenerative Dentistry

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Abstract

Restorative or regenerative dentistry involve the association of 1-stem cells, 2- an appropriate scaffold, and 3- molecules implicated as growth or transcription factors. Each of the three groups contributes to indirect or direct pulp capping. Naturally-derived polymeric scaffolds include fibrin, alginate, hyaluronic acid, chitosan, cellulose, and collagen combined with glycosaminoglycans. Synthetic scaffolds involve composite resins, glass ionomers, hydroxyapatite precursors, bioceramics, bioactive glasses, and silicate-based cements. The most common synthetic polymers in tissue engineering are poly-(l-lactic acid) (PLLA), poly-(glycolic acid) (PGA), and the copolymer poly-(lactic-co-glycolic acid) (PLGA). These scaffolds are biodegradable and biocompatible factors. The association of these components allows cell growth and differentiation, making them highly suitable for tissue engineering applications.

Keywords: Naturally-derived Polymeric Scaffolds, Synthetic Scaffolds, Biodegradable, Biocompatible, Stem cells, Tissue Engineering.

I-Introduction

Dental and pulp tissues restorative and/or regenerative dentistry involve the association of three components: 1- stem cells, 2- scaffolds, 3- molecules implicated in growth and transcription factors. Altogether, these components contribute to enamel and dentin regeneration and/or tissue engineering. In dentin, interdigitations are occurring with the collagen mesh and apatite crystallization. The accumulation of intraluminal materials within the dentinal tubules favors the treatment of tooth sensitivity.

At the University of Melbourne in Australia, a compound was developed that mixes casein phosphopeptides to a solution of phosphate

and calcium salts (CPP-ACP) capable of forming an amorphous crystal of calcium phosphate, having anti-cariogenic properties by adhering to the biofilm and releasing ions under acidic conditions. Summarizing the evolution of the various carriers and scaffolds implicated in restoratrice dentistry, a series of biomaterials was deviced. In the late 1990s, the Mineral Trioxide Aggregate (MTA) became commercially available. Septodont in 2008, developed a material based on the purification of calcium silicate (Biodentine®), with better setting time, mechanical properties, and handling. In 2010, the Bisco company launched the resin-modified calcium silicate known as (RMCS) or by its trade name TheraCal LC®. These bioactive preparations are either naturally-derived polymeric scaffolds or synthetic scaffolds. They contribute efficiently to restorative and regenerative dentistry.

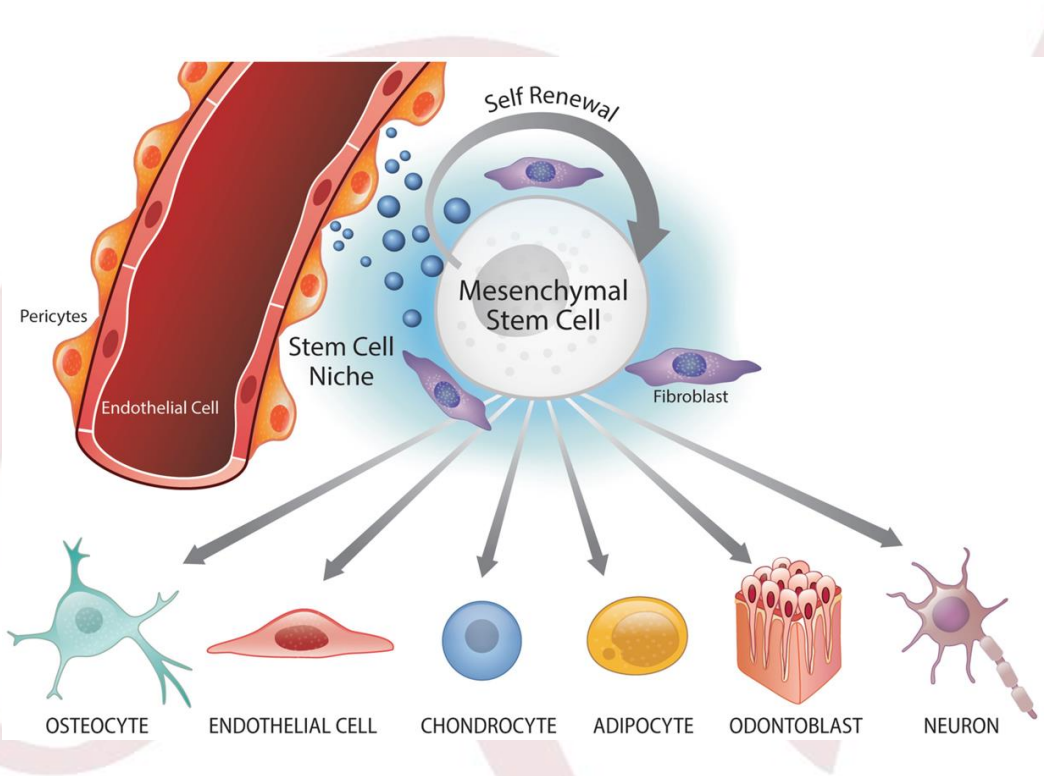

Figure 1: Oh & Nör, 2015

II- Naturally-derived Polymeric Scaffolds

Fibrin, alginate, hyaluronic acid and derivatives, chitosan derivative, cellulose, peptide-based scaffolds are naturally-derived polymeric scaffolds. Bioactive agents induce the mineralisation of collagen mesh. Captesin K proteases are activated as matrix metalloproteinases (MMPs) that degrade the adhesive interface. The remineralization process induces a reduction in the enzymatic degradation given by proteases. Bioactive glasses have the potential to release silicon and fluorine that generate structural changes by having a chelating action with Ca2+ and Zn2+. These scaffolds may inhibit the action of metalloproteinases (MMPs). In addition, cathepsin K preserves the integrity of the mesh collagen within the hybrid layer.

New bioactive glass compositions have been developed to promote and improve bioactivity. The addition of calcium oxide is essential in the first step of the formation of hydroxyapatite due to an exchange of hydrogen ions, and bioactive glass compositions created with calcium and silica oxide. They improve mechanical resistance, better mineralization ability and lower surface roughness. The addition of fluorine to bioactive glass maintains the polymerization of the silicate network, the connectivity of the structure, and the bioactivity of the bioactive glass, resulting in the formation of fluoroapatite (FAP). Its importance is due to the resistance of the substrate in acidic media, lower solubility compared to hydroxyapatite, and it chemical stability rather than hydroxyapatite or carbonated hydroxyapatites, favoring enamel remineralization during the initial steps of carious lesions.

The components of these materials have the ability to generate an alkaline medium, with a pH between 8 and 9 that favors bacterial inhibition, reducing the formation of secondary caries thanks to the Zn ions that bind to the proteins of the microorganisms generating structural changes in the membrane inducing cell lysis. They become a long-lasting immobilized agent in contact against oral bacteria. It has antibacterial activity against S. Mutans, Lactobacillus Casei, and Actinomyces Naeslundi. It is capable of eradicating residual bacteria located in the lumen of dentinal tubules.

In addition to naturally-derived polymeric scaffolds, attempts were also initiated to produce scaffolds including polystyrene, poly-l-lactic acid (PLLA), polyglycolic acid (PGA) and poly-dl-lactic-co-glycolic acid (PLGA) resulting from numerous synthetic polymers. While these materials can be fabricated with a tailored architecture, and their degradation characteristics controlled by varying the composition of the individual polymer, polymeric scaffolds have drawbacks including the risk of rejection due to a reduced bioactivity. In addition, concerns exist about the degradation process of PLLA and PGA as they degrade by hydrolysis.of naturally-derived biological materials such as collagen, various proteoglycans, alginate-based substrates and chitosan.

Unlike synthetic polymer-based scaffolds, natural polymers are biologically active and promote excellent cell adhesion and growth. They allow the host cells to produce their own extracellular matrix and replace the degraded scaffold. In addition to biomechanical signals, cellular behavior is strongly influenced by biological and biochemical signals from the extracellular matrix. Therefore, the use of scaffolds as delivery systems for growth factors, adhesion peptides and cytokines has received considerable attention (O'Brien 2011, Ma 2004).

II-1- Naturally-derived polymeric scaffolds

Collagen (Type I) combined with glycosaminoglycans is the most important extracellular matrix component of dental pulp. Present in the pulp and sharing this distribution with type III collagen as well as within dentin, other non-collagenous matrix proteins are implicated in the formation of the tooth ECM. The molecules are implicated in the proliferation of pulp stem cells (SC) located in human exfolliated teeth (SHED) and with a potential of differentiation into odontoblasts. Collagen represents the most abundant structural protein, accounting for approximately 30% of total body proteins in mammals. Twenty eight different types of collagens have been identified. Prolyl 4-hydroxyproline (P4H) is a hetero-tetramer molecule and is essential for the folding of the synthesized collagen polypeptide chains into triple helical chains. The recombinant collagen polypeptide remains as non-triple helical and non-functional protein. The chains can only form unstable triple helices even at low temperature into the recombinant system to enable proline hydroxylation and the stability of the product. By electrospinning, collagen type I produced fibers are exhibiting the banding pattern, which is characteristic of native collagen. Collagens display collagen cross-linking agents with high efficiency and negligible toxicity.

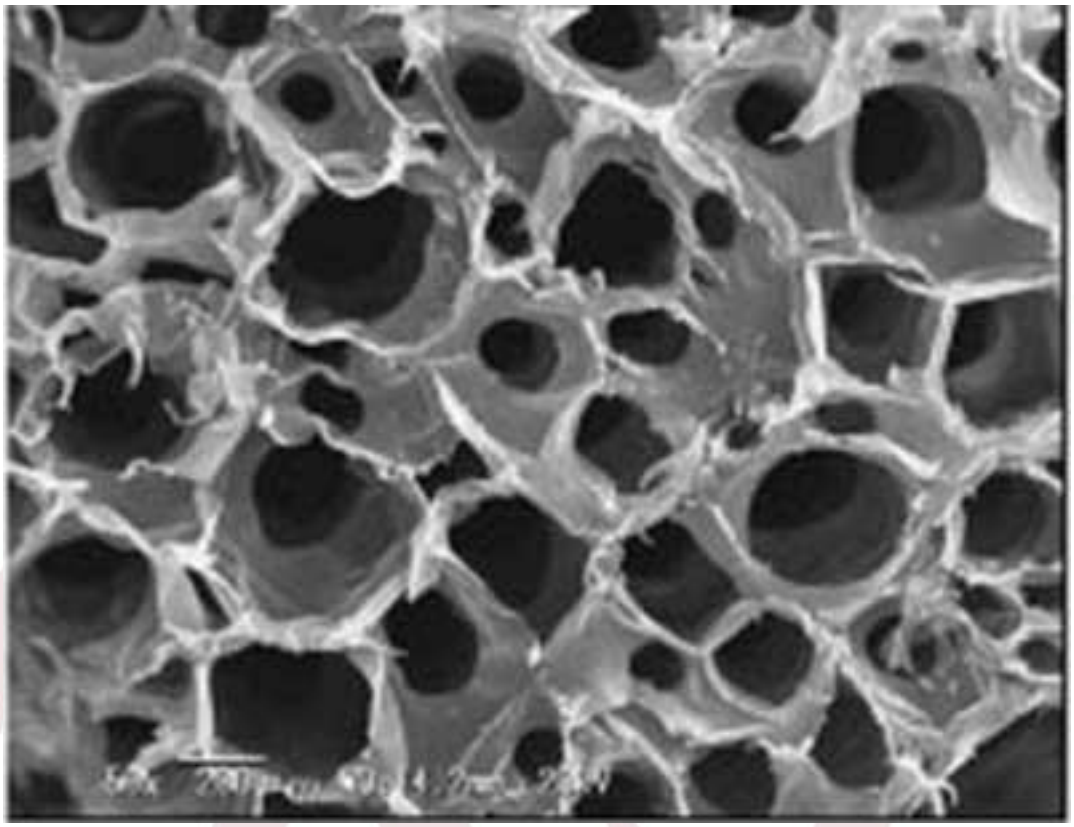

Figure 2: Type I collagen

Scaffolds composed of collagen and synthetic polymers, such as poly (ε-caprolactone) (PCL), polylactic acid (PLA), poly (ethylene glycol) (PEG), polyglycolide (PGA), poly (lactate-co-glycoside) (PLGA) and polyvinyl alcohol (PVA) have been widely used for tissue engineering. Collagen could be defined into four major classes based on their compositional and structural characteristics. Collagen is a trimeric molecule consisting of three polypeptide α chains.

(1) Collagen with classically compact banded film structures, including types I, II and III collagens,
(2) Collagen with open fiber structures, like type IV and basement membrane collagen,
(3) Type V collagen and molecules containing the E and F chains,
(4) Collagen with a discontinuous triple helix.

Collagen is a trimeric molecule consisting of three polypeptides-α chains collagen. Type I produced fibers exhibiting the 67-nm D-repeat banding pattern, which is a characteristic of native collagen.

DPSC combined with human endothelial cells exhibited vascularized pulp-like tissue. Cell-cell interactions and migration contribute to successful dental pulp regeneration (Dissanayaka et al., 2015).

Silk fibroin is a natural macromolecular protein polymer with excellent biocompatibility, remarkable mechanical properties and biodegradability. It is concerned as a promising biomaterial for scaffold fabrication.

Polyglycolic acid (PGA) should be oriented to form 13 • m diameter fibers (Freed et al., 1994). Six properties of the scaffold are listed here:

1) The surface should permit cell adhesion and growth

2) Neither the polymer or its degradation products should provoke toxicity when implanted in vivo,

3) 3D structures should be processable,

4) The porosity should be at least 90% to provide a template for the regenerative tissue ,

5) The scaffold degradation should match to the tissue regeneration (Li et al., 2005).

Utilizing poly (lactic-co-glycolic acid) and multistage vector composite microspheres (PLGA-MSV), it was shown that:

(1) BMP/ PLGA-MSV microspheres had the ability to release small but effective doses of BMP-2 for 40 days in a controlled, linear fashion;

(2) The release profile of the BMP/ PLGA-MSV microspheres was dependent on the PLGA coating;

(3) The PLGA-MSV system did not impact cell metabolic activity;

(4) BMP-2 released from PLGA-MSV microspheres was capable of osteoinduction of BM-MSCs.

This biocompatible, biodegradable, and osteogenic PLGA-MSV microsphere system holds promise as a candidate for the delivery of effective doses of bioactive proteins for pharmaceutical induction of osteoregeneration. (Minardi et al.,2020).

Biologically-active growth factors are trapped in the matrix during dentinogenesis, namely transforming growth factor-beta 1 (TGF- • 1) and bone morphogenetic protein 2 (BMP-2), which are keys in driving the odontogenic differentiation of SCAP, as well as VEGF, PDGF and other angiogenic factors. In addition, IGF (insulin-like growth factor) and EGF (epidermal growth factor) were used for vascularization and regeneration (Demarco et al., 2011).

Different type of naturally devoided polymeric scaffolds

The most common polysaccharides used are alginate, hyaluronic acid, chitosan, and starch, but agarose, glucans, and dextran find also their application. The unmodified polymer is used for hydrogel or capsule formation (Witzler et al., 2019).

Early stages of mesenchymal stem cells (MSCs) differentiation towards osteoblasts are characterized by RUNX2 expression, which induces the expression of bone matrix protein genes such as alpha-1 type I collagen (COL1A1), alkaline phosphatase (ALP), bone sialoprotein (BSP) and osteocalcin (OCN) in the differentiating cells through the Wnt and BMPs signaling. Mature osteoblasts express osterix and actively secrete bone matrix proteins such as OCN, BSP I/ II, and COL1A1.

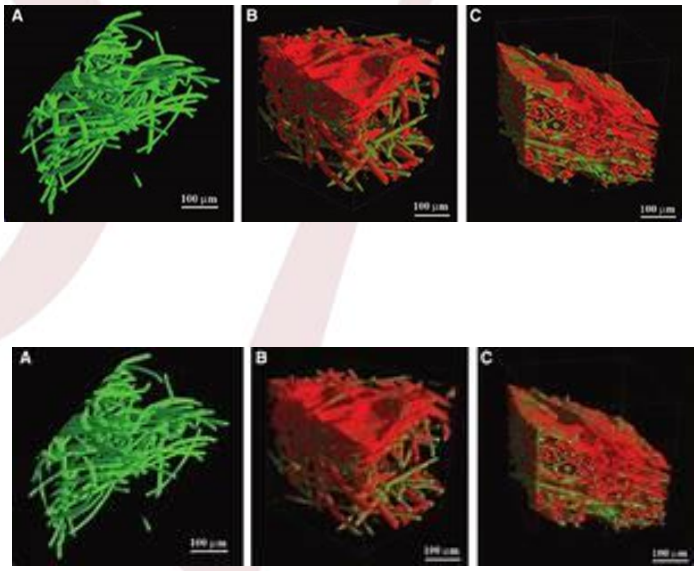

Figure 3: Polyglycolic ACI

Fibrin: Fibrin-based scaffolds have been used for soft tissue engineering and the revascularization of dental pulp as a result of odontoblastic differentiation. Fibrinogen and thrombin are combined to form a fibrin hydrogel. Fibrin can be prepared as a glue or as engineered microbeads. Fibrin is a versatile biopolymer, showing a great potential in tissue regeneration and wound healing (Ahmed et al., 2008). It is a blood component responsible for homeostasis. Fibrin is available either as glue or engineered microbeads. This versatile biopolymer is used in tissue regeneration and wound healing.

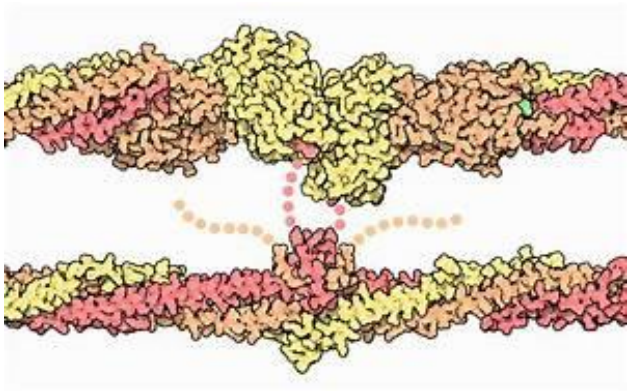

Figure 4: Fibrin

Alginate scaffolds in tissue engineering have intrinsic properties attributed to its biocompatibility, favorable immunogenicity, low cost, and mild gelation requirements. Alginate is one of the most commonly used polysaccharide, as it is easily cross-linked with multivalent cations such as Ca2+. Alginate seems to be an ideal material with confer specific cellular interactive properties, potentially allowing for the control of long-term gene expression of cells within these matrices.

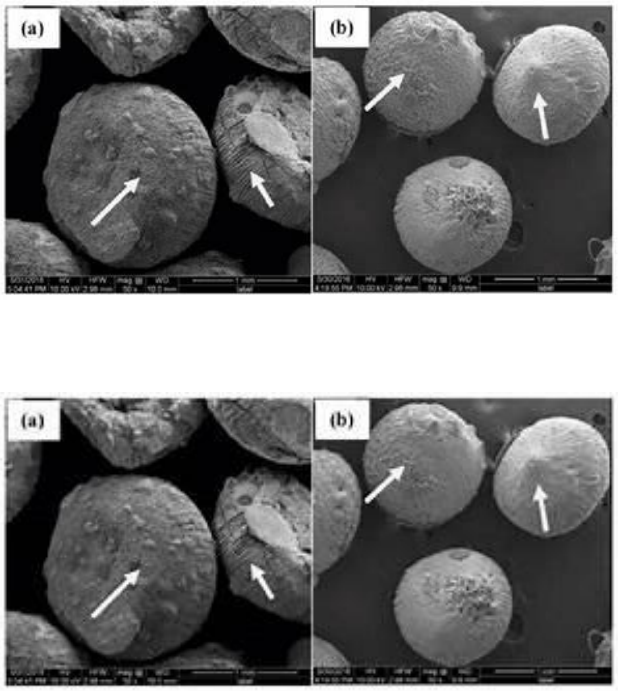

Figure 5: Alginate

Hyaluronic acid and derivatives, is a linear glycosaminoglycan (comprised of d -glucuronic acid and N -acetyl-d -glucosamine). Present in most embryonic tissues, it is the only GAG to be non-sulfated. With its biocompatibility, enzymatic degradability in vivo, and mechanical properties, it is a good candidate for the use in regenerative medicine. HA based scaffolds combined with stem cells have shown to have a synergistic effect in the regeneration capacity (Agarwal et al. 2020). Hydrogels made by cross-linking maleimide-functionalized hyaluronic acid with a cell-adhesive and a degradable peptide showed a release of these growth factors correlated with the degradation of the scaffold.

Chitosan derivatives are biocompatibile, biodegradable, displaying low cytotoxicity, and immunogenicity. It has a broad-spectrum of antibacterial properties, One of the most frequent composant is a chitosan. It is a glucosamine obtained through deacetylation of chitin. It can act as a polycation due to its deacetylated amino groups and supporting cell attachment, differentiation, and migration, as well as osteoconduction and the promotion of osteoblast growing. Chitosan as antimicrobial agent shows antibacterial efficacy of chitosan that is dependent on the degree of deacetylation, molecular weight, pH of environment, solubility, hydrophilicity. Other chitosan-based dental plaque-control agents including mouthwashes, varnishes and nanogels have been developed. New generation of anti-cariogenic formulations including metallic nanoparticles such as copper or silver incorporated in chitosan have been recently investigated. It is also an anti-fungal agent.

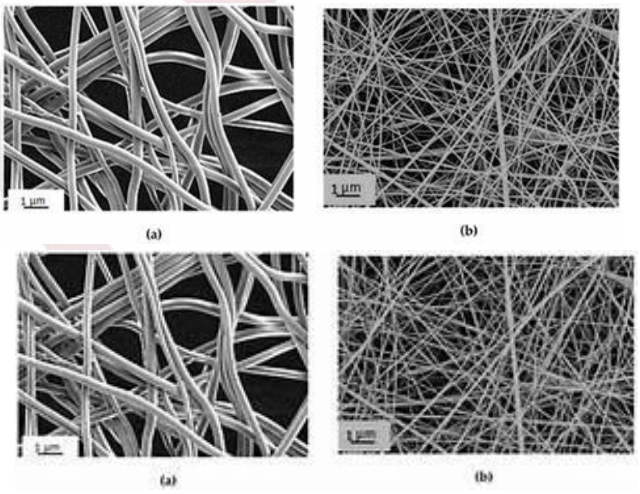

Figure 6: Chitosan

Films and/or gels: The key strategy in tissue engineering is to develop regenerated tissue on a bio-degradable scaffold as an interim substructure for attachment, proliferation and differentiation of cells. The scaffold alone acts as an essential

element in directing the differentiation lineage of stem cells. The other requisite properties of a biomaterial for being applied in tissue engineering are non-toxicity, biocompatibility and its structure must mimic the extracellular matrix (ECM) including glycosaminoglycans, glycoproteins and glycolipids in order to promote regeneration of the target tissue. Natural biomaterials are the first choice for providing scaffolds.

Nonetheless various synthetic polymers such as poly(ε-caprolactone), poly(vinyl alcohol) and polyethylene oxide have shown relative good degradation and cell affinity. Selection and application of biomaterials for fabrication of a favorable scaffold that provides a proper environment for cells require interdisciplinary knowledge. In addition to chemical composition, surface topography has a critical role in cellular fate by controlling cell behavior including migration, attachment and proliferation

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A carboxymethyl chitosan-based scaffold (CMCS) with TGF-・1-releasing chitosan nanoparticles (TGF-・1-CSnp) has been investigated. TGF-・1 induces the cytological and functional differentiation of odontoblasts which plays an important role in the secretion of the dentin matrix.

Chitosan-alginate is an hybrid biodegradable scaffold. It may serve as temporary skeleton to stimulate new tissue growth.. This scaffold provides a favorable environment with high porosity, mechanical and biological properties that can be used for clinical trials.

Chitosan in bone and dental engineering (Aguilar et coll1910)

Incorporating the bioactive molecules into these biocomposite scaffolds accelerates new bone regeneration and enhances neovascularization in vivo. It should not only be non-toxic, biocompatible, and biodegradable, but also be competent in promoting cell adhesion and retaining the metabolic functions of attached cells They are favorable, not only for pulp regeneration, but also for dentin formation because of their capacities to induce mineralization. Indeed, chitosan scaffolds containing β-tricalcium phosphate promoted a high expression of mineralization markers, such as osteopontin and alkaline phosphatase, and dentin formation by human periodontal ligament cells. As a positive-charged, low-cost natural polymer with good biodegradability and biocompatibility, as well as having non-toxic, muco-adhesive, hemostatic, and antimicrobial properties, chitosan is a good candidate for biomedical and biopharmaceutical research.

Dental pulp regeneration, dentin formation, revascularization and reinnervation are the different targets of this chitosan-based therapy. As a biopolymer with unique characteristics and wide range of applications in biomedicine, chitosan and its derivatives have been under multiple investigations, however, a number of issues are still open for further research. In order to extend the scope of applications and add new dimensions to the development of composite biomaterials in the future, various modifications have been made to the chitosan structure. In the field of dentistry, chitosan is widely serviceable in restorative dentistry, endodontics and particularly in different approaches for treatment of periodontitis including bone tissue engineering and drug delivery. It is important to highlight the crucial role of chitosan-based scaffolds in combination with natural biomolecules and drugs in bone and pulp regeneration. Nonetheless, the key issue is bringing the mentioned biomaterials in the clinical practice and evaluating them in bioenvironment.

Determination of Micro-hardness:

The specimens were mounted on stage of Vickers micro-hardness tester (Matsuzawa – MMT 5421X, Japan). The mid-root portion is halfway from the outer surfaces was focused for testing. Indentations were made with Vickers diamond indenter using 100 gm load with a dwell time of 10 seconds. These indentations were measured and converted into Vickers hardness number (VHN) values by the monitor.

Determination of Surface Roughness:

The specimens were placed on the flat table surface of roughness tester (SURFCOM 130A) and the needle of the tester was on the mid root region of the tooth surface. The machine was then made to record the surface roughness values of root dentin by travelling on the Surface along the length. The values were displayed digitally on the screen of the roughness tester. These values were expressed as Ra (μm). The Ra parameter describes the overall roughness of the surface and is defined as the arithmetical average value of all absolute distances of the roughness profile from the centre line within the measuring length.

Peptide–based scaffolds bind growth factors and display a slow release profile for TGF2 and VEGF. SHED demonstrated to be a population of highly proliferative, clonogenic cells, differentiating into a diversity of cell type expressing STRO-1

and CD146, two MSC markers also present in DPSC. SHED exhibited higher proliferation rates than DPSC (Demarco et al., 2011).

As major components of the extracellular matrix, glycosaminoglycans (GAGs) like hyaluronic acid and chondroitin sulfate are a bioinspired class of scaffold materials providing biocompatibility and inherent bioactive properties that are beneficial for bone regeneration.

SCAP scaffolds require intracanal blood clot, platelet-rich plasma, alginate, hyaluronic acid, chitosan, PLLA NF-with BMP-2, PLGA-PEG nanoparticles, VitroGel 3D with SDF-1x and BMP-2 constitute scaffolds that can be used for pulp regeneration. Finally, polymeric scaffolds may be used efficiently for dental pulp tissue engineering (Jazayeri et al., 2020).

Naturally-derived biological materials such as collagen, various proteoglycans, alginate-based substrates and chitosan have been used in the production of scaffolds. Unlike synthetic polymer-based scaffolds, natural polymers are biologically active and promote excellent cell adhesion and growth. They allow the host cells to produce their own extracellular matrix and replace the degraded scaffold.

In addition to biomechanical signals, cellular behavior is strongly influenced by biological and biochemical signals from the extracellular matrix. Therefore, the use of scaffolds as delivery systems for growth factors, adhesion peptides and cytokines has received considerable attention (O'Brien 2011).

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In recent years, chitosan has been used as a carrier or stabilizing agent of calcium phosphates due to its excellent biological properties and further combined with biomimetic mineralization technology. The composite materials obtained in this way are widely applied in dental hard tissue restorations, especially in the biomimetic remineralization of enamel and dentin.

III- 2- Synthetic Scaffolds

Scaffolds made of synthetic polymers allow for the manipulation of their physicochemical properties such as degradation rate, pore size, and mechanical resistance.

The most common synthetic polymers in tissue engineering are likely poly-(l-lactic acid) (PLLA), poly-(glycolic acid) (PGA), and the copolymer poly-(lactic-co-glycolic acid) (PLGA). These scaffolds are biodegradable and biocompatible and allow for cell growth and differentiation, making them highly suitable for tissue engineering applications. The degradation rate can be controlled by the proportion of PLLA/PGA used in the manufacturing of these scaffolds. Notably, it is important for the rate of scaffold degradation to be compatible with the rate of tissue formation. In other words, the scaffold should be designed to provide structural integrity for the cells used in tissue engineering until the newly formed tissue becomes autosustainable. One of the first examples of successful replacement of scaffold by dental tissues was the

use of copolymers (PGA/PLLA and PLGA) that allowed the engineering of complex dental structures with characteristics similar to the crowns of natural teeth. The key strategy in tissue engineering is to develop regenerated tissue on a bio- degradable scaffold as an interim substructure for attachment, proliferation and differentiation of cells. Natural biomaterials are the first choice for providing scaffolds.

Nonetheless various synthetic polymers such as poly(ε-caprolactone), poly(vinyl alcohol) and polyethylene oxide have shown relative good degradation and cell affinity. Selection and application of biomaterials for fabrication of a favorable scaffold that provides a proper environment for cells require interdisciplinary knowledge. In addition to chemical composition, surface topography has a critical role in cellular fate by controlling cell behavior including migration, attachment and proliferation (Matson & Stupp, 2011; Oh & Nör 2015). Bioactive materials favor the longevity of restorations, cell repair, increasing adherence resistance, and reducing the recurrence of cavities and bacterial microinfiltration (Ladino et al., 2021). These properties allow the development of a hydroxyapatite layer favoring the dental remineralization process.

Nowadays, various synthetic composite materials are becoming more popular than human-derived biomaterials in the field of tissue engineering. Although biomaterials, such as decellularized ECM, have similar components and structure to natural ECM of organisms, they have some limits such as complicated preparation technique, possible immunogenicity and mechanical properties that are difficult to control. In contrast, the structure and mechanical properties of synthetic composite materials can be manipulated and controlled, and the presence of some components in synthetic materials can endow them with specific biological properties.

Glass Ionomer Cements

To compare the cytotoxicity of five RMGICs and metal-reinforced GIC, Stanislawski et al. (1999) carried out an in vitro pulp cell viability assay. The most toxic materials were the metal-reinforced GIC and RMGIC Vitremer (3M/ ESPE), while the least toxic were the RMGICs Compoglass (Ivoclar Vivadent Ltda., São Paulo, SP, Brasil) and Photac Fil (3M/ESPE). This toxicity was due to the presence of unpolymerized monomers, such as HEMA and TEGDMA, and polyacrilic acid, which were leached from resin modified materials and metal-reinforced GIC. The main elements responsible for the toxicity of the metal-reinforced GIC were Cu2+ and Ag+ present in toxic concentrations. It was further analyzed the possible cytotoxicity of some ions that are present in significant amounts in GICs, such as F-, Al3+, Zn2+ and Sr2+. The zinc was the only component that was found to be of a sufficiently high concentration to induce cytotoxicity. These elements were present in the metal- reinforced GIC and may have contributed to its cytotoxicity.

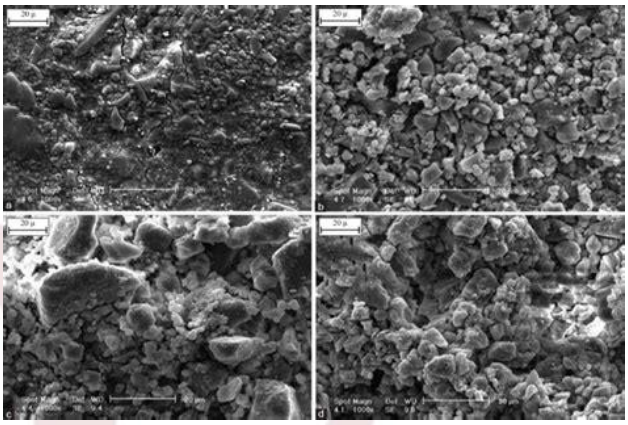

Figure 7: Glass Ionomer Cement

IV- Conclusions

Specific conclusion

Based on this literature review, it may be concluded that:

1. Calcium hydroxide products are the best choice for conservative treatment of the pulp due to their therapeutic and biological potential and the property of stimulating the formation of sclerotic and reparative dentin as well as protecting the pulp against thermal stimuli.

2. Monomers present in resin composites and adhesive systems (e.g.: BISGMA, UDMA, TEGDMA, HEMA) have been shown to have cytotoxic effects as a consequence of direct contact with fibroblasts and may be leached during the polymerization when the conversion degree is not fully reached.

3. In human pulps, direct pulp capping with adhesive systems produces different degrees of pulp inflammation, even without bacterial presence and absence of dentin bridge formation as well as pulp repair. Some studies support the idea that when hermetic seal of cavity is obtained, the dentin- pulp complex protective materials are unnecessary and they do not influence the pulp repair, although hermetic seal of the restoration is difficult to obtain.

4. RMGICs are more cytotoxic to the pulp cells than conventional GICs due to the presence of unpolymerized monomers, and should not be applied directly to the pulp tissue.

General conclusion: There are two possible scenarios:

(1) the pulp is reversibly inflamed and healthy root canal pulp tissue can remain after a pulpotomy,

(2) the pulp, irreversibly inflamed or necrotic, has to be completely removed, and following chemo-mechanical cleaning methods no vital tissue remains inside the root. SCAP may proliferate and recolonize the root.

In the first situation, the remnant tissue serves as a source of resident stem cells. The treatment aims to sustain pulp vitality.

Applying the cell homing approach may be appropriate to this less invasive situation as the cell-free scaffold delivers bioactive cues to recruit remaining resident stem cells and induce their differentiation (Modena et al., 2009).

However, the characteristics of stem cells might not be reliable to predict a successful outcome due to the patient-related variability.

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