SVOA Dentistry

ISSN:2753-9172

ScienceVolks Open Access

Review Article

Bioactive Materials in Restorative Dentistry: A Literature Review

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***Received:** February 25, 2021* ***Published:** March 10, 2021*

Abstract:

Bioactive materials have had a great impact on restorative dentistry, favoring the longevity of restorations, cell stimulation for dentin repair, increasing adhesive resistance, and reducing the recurrence of cavities and bacterial microfiltration. Treatment with bioactive materials has covered various fields in restorative dentistry, generating direct interactions are the substrate and remineralization by initiating precipitation and ion exchange that allow the development of a hydroxyapatite layer favoring the dental remineralization process. Its antimicrobial action has an impact on the protection of recurrent cavities and bacterial microfiltration. Besides, interdigitation with the collagen mesh and apatite crystallization in the dentinal tubules favors the treatment of tooth sensitivity. This article provides a review of the characteristics of bioactive materials used in restorative dentistry.

Keywords: *Dental Materials, Bioceramics, Bioactive Materials, Remineralization*

Introduction

Currently, there is a change in the behavior of dental materials, going from being passive biomaterials without having a positive or negative reaction in the body to having constant bioactivity with a positive and expected reaction, causing cellular stimulation or antimicrobial activity[1]. With the advances established in the late 1960s in the second generation of biomaterials and the research of Dr. Hench in bone regeneration and the introduction of bioactive glasses, various compounds that generate bioactivity have been implemented in various areas of dentistry[2]. Bioactivity in dentistry depends on its clinical applicability, they can be defined as “a material that forms a surface layer of a material similar to apatite in the presence of an inorganic phosphate solution” [3]. They can also be defined as those materials capable of inducing a desired tissue response of the host [4]. Bioactive materials have evolved in their composition and have been used in various fields of medicine and dentistry (in bone regeneration, coating of implants, bactericidal and bacteriostatic in caries processes, cavity bases, dental sensitivity, remineralization of enamel and dentin, dental adhesives, endodontic perforation repair, pulp capping, root canal disinfection, endodontic sealants) [5].

1. Evolution of Bioactive Materials

The purpose of tissue bioengineering is to accelerate the regeneration and repair of affected tissues, in this way science produces and increases new therapies and/or develops new biomaterials that restore, improve, or prevent the deterioration of the function of compromised tissues[6].

Dental materials have a passive or active interaction with the surrounding tissues[7]. Bioactive materials have recently appeared, which are all those that promote a biological response at the interface of the material and the tissue, generating a union between them[8]. In general, bioactive materials have been shown to promote the release of calcium, sodium, silica, and phosphate ions, which produce an effect such as angiogenesis and antimicrobial activity[6].

Osteogenic properties in bone defects have been reported since the 1920s with the use of calcium phosphate or "tricalcium phosphate", being one of the first biominerals used in the field of medicine; in the same decade, calcium hydroxide was used as a bioactive agent as a promoter in the formation of a dentinal bridge on the exposed pulp tissue, since then it has been the "gold standard" of pulp capping[9].

In 1950 the word biomimetic was cited by the biomedical and biophysical engineer Otto Schmitt referring to the study of multidisciplinary and biological mechanisms of products that imitate nature; the word biomimetic derives from the Latin "Bio" which means life and "mimetic" which is related to the imitation of the biomechanical process inspired by nature. Understanding the biomimetic approach involves the concept of multiple ideas from biochemistry, materials science, and bioengineering. In clinical dentistry, the term refers to the repair of the affected dentition by imitating the characteristics of a natural tooth in terms of appearance, biomechanics, and function[10].

The first generation of biomaterials had the characteristic of being bio-inert, they did not generate any or little response to the tissue where they are used, they were limited to simulating the mechanical characteristics of the surrounding tissue[11].

In the 1960s, Wilson and Kent, seeking to improve the properties of zinc polyalkeonate cement, introduced glass ionomer (GI), with anticariogenic properties because of the release of fluoride, direct bonding to the tooth structure, low coefficient of thermal expansion, similar to the tooth structure and low cytotoxicity, with "active" and biomimetic characteristics [7,10]. Since then, several modifications have been introduced in order to improve its mechanical properties. The introduction of resin-modified glass ionomers (RMGI) with superior mechanical strength, were used for posterior restorations. Besides, the new generations of glass ionomers maintain the desirable characteristics of conventional ones such as fluoride release, ion exchange, adhesion enamel, and dentin, and low filtration[12].

Larry L. Hench in 1969 developed a material that precipitates hydroxyapatite in aqueous solutions with the ability to bind to hard and soft tissues that, unlike bio-inert materials, was not encapsulated in fibrous tissue10. Thus, he introduced the term bioactive glass composed of silicate glasses which he called "Bioglass 45S5" acting on the surrounding tissues without generating a response such as foreign body, toxicity, or inflammation[13].

The second generation of bioactive materials sought to provoke a specific and controlled action in a biological environment[11].

The third generation started in the 1990s, it focused on the processes of tissue regeneration including cell adhesion, proliferation, differentiation through the activation of specific genes. At the University of Melbourne in Australia, a compound was developed that mixes casein phosphopeptides in 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 release ions under acidic conditions[6].

In the late 1990s, the Mineral Trioxide Aggregate (MTA) developed by Lee in association with Loma Linda University 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® [14].

This is how in recent years biomimetic approaches have been generated to develop dental materials with nanoparticles that have remineralizing, regenerative, and antimicrobial capacities such as mouth rinses, toothpaste, composites, bioceramics, bonding materials (adhesives), dentin substitute materials, and dental cement [15].

2. Mechanisms of action of bioactive materials.

Hench classifies bioactive materials into two groups: a) in which bioactivity leads to induction and production as a consequence of the rapid surface reaction of the material; Furthermore, it induces an intracellular and extracellular response, generating the binding of the material to hard tissue and soft tissue b) in which only conduction occurs due to a slower surface reaction that only induces extracellular response[16].

The oral cavity has a dynamic and complex environment in which restorative materials and dental tissues are exposed to a wide range of variations in terms of pH, temperature, microorganisms, and nutrients; dental tissues are in constant ionic exchange of fluorine, calcium, phosphate, generating a balance thanks to the regulatory role of saliva[17].

3. Classification

We can then classify the action of bioactive materials in dentistry depending on their intervention with the tissues.

Restorative

The incorporation of bioactive agents induces the mineralization of the collagen mesh and the fossilization of metalloproteinases, playing a protective therapeutic role from dental restorations[18].

The hydrolysis of the adhesive interface between dental tissue and the bonding agent of the restorative material is a predominant factor in longevity in restorative dentistry; with the exposure of the collagen mesh during demineralization, interdigitation is favored and the bond strength between the dental substrate and the restorative material increases, but captesin k proteases are activated, which are matrix metalloproteinases (MMPs) that degrade the adhesive interface[19]. The remineralization process can induce a reduction in the enzymatic degradation given by proteases. To do this, bioactive glasses have the potential to release silicon and fluorine that generate a structural change by having a chelating action with Ca2 + and Zn2 +, capable of inhibiting the action of metalloproteinases (MMPs) cathepsin K, preserving the integrity of the mesh collagen within the hybrid layer[20].

The incorporation of bioactive fillers in the restorative materials induces the formation of apatite crystals, thus generating a bond by interdigitation directly proportional to the exposure time between the bioactive glasses and the collagen mesh of demineralized dentin, and saliva plays an important role in the release of phosphate, calcium and silica ions showing a direct correlation between the ability to form apatite induced by bioactive glass and adhesion to dentin, penetrating deep into the dentinal tubules, generating an entanglement that increases adhesive strength [10,16]. The interfacial layer of apatite, due to the deposition and formation within the dentin tubules that are at a depth of 270 μm, allows the presence of bioactive glass to be beneficial in the interfaces of adhesive restorations, improving the interface between dentin and the restorative substrate, reducing the microgaps[21].

Remineralize

Remineralization is defined as the gain of calcified material in the dental structure that replaces that previously lost by demineralization and that is generated by acids and a decrease in the pH of bacterial metabolism that generate the exit of ions from the dental tissue[22].

Bioactive materials play a fundamental role in remineralization processes thanks to ionic exchange, generating supersaturation of the fluids that lead to ionic precipitation in demineralized tissues and the formation of amorphous calcium phosphate with the growth of hydroxyapatite crystals, not only of the extra fibrillar collagen mesh but also improves the mechanical properties of the intra fibrillar network, besides, emulating the histomorphology of the dental substrate[13].

Khoroushi et al. compared the flexural strength of demineralized and non-demineralized dentin bars in interaction with resin-modified glass ionomer and with resin-modified glass ionomer with a composition of 20% bioactive glass, immersed in a saliva solution artificial, demonstrating that demineralization and immersion conditions have an effect on the biomechanical behavior of demineralized dentin. In this same condition, it was also observed that the flexural resistance values were higher for ionomers modified with resin with bioactive glasses compared to ionomers without the addition of bioactive components[7]. The high concentration of calcium ions close to the interface of the material favors the precipitation and nucleation of calcium phosphate, improving the remineralizing capacity of the ionomers, but affecting the microhardness of the material by acting as fillers that united to the ionomer matrix[23].

There is a similar behavior with the addition of bioactive to composites; Although it does not affect the degree of polymeric conversion, a reduction in mechanical properties has been observed with increasing content by volume; presenting a lack of cohesion between the composite conglomerate and the bioactive filler[24].

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, bioactive glass compositions created with calcium and silica oxide were shown to improve mechanical resistance and better mineralization ability and lower surface roughness[1]. The addition of fluorine to the 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 fluorapatite (FAP), important due to the resistance of the substrate in acidic media, lower solubility compared to hydroxyapatite, and it is more chemically stable than hydroxyapatite or carbonated hydroxyapatite, favoring enamel remineralization in initial caries lesions; It increases the mechanical properties, the mineral content, the recovery of mineral volume, It presents a covering with a layer of crystals and produces ultra-structural changes[20,25]. At the dentin level, the formation of an apatite layer achieves a decrease in the degree of decalcification during the mineralization process, promoting an increase in the mineral matrix and the appearance of a new interface indicating a chemical interaction, significantly decreasing the values of the roughness of the tissue, the deposition in the tubules with obliteration by the apatite precipitation increasing the percentage of tubular occlusion, reducing the permeability of the dentin and generating a barrier against bacterial microfiltration and, therefore, preventing pulpal inflammation[1,25].

Desensitizing

Bioactive glasses have been accepted as mineralizing agents as well as desensitizing agents in the treatment of dental hypersensitivity caused by the opening of the dentinal tubules8. Bioactive glass reacts with artificial saliva to form apatite hydroxycarbonate crystals within collagen fibers that are equivalent to the mineral phase of human hard tissues[14].

These deposits occlude the dentinal tubules, due to its physical-chemical behavior, which makes it a candidate material for dental remineralization and desensitization processes, causing an increase in calcium and phosphate on the surface of dental enamel; The term "remineralization" should be used when the mineral components come from the exterior of the enamel, that is, from the calcium and phosphate contained in saliva[7,8].

The remineralization process induced by bioactive glasses is probably due to a simultaneous bioactive phenomenon characterized by the release of silica and a subsequent polycondensation reaction induced by the precipitation of calcium and phosphate on the organic matrix creating a base for the formation of calcium phosphate[26].

A study by Ubaldini et al. devalued the effects of bioglass45S5 and biosilicate in the remineralization process after a dental whitening process, found an increase in the mineral content of the samples, and additionally the adhesion strength was increased after treatment with bioglass[27].

Antibacterial

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[18].

The incorporation of Methacryloxydodecylpyridinium (MDPB) monomers creates a long-lasting antibacterial effect and does not compromise mechanical properties such as strength and biocompatibility; These monomers depend on quaternary ammonium to show antibacterial activities and have a bactericidal effect on a wide range of microorganisms produced by the breakdown of the bilipid layer and subsequent death of these microorganisms.[28]

The MDPB monomer can be copolymerized and covalently bound in the resin matrix, becoming a long-lasting immobilized agent and in contact against oral bacteria, it has antibacterial activity against *S. Mutans*, *Lactobacillus Casei*, and *Actinomyces Naeslundi*, it is capable of eradicating residual bacteria from the interior of dentinal tubules of prepared dental cavities[29].

4. Bioactive materials in restorative dentistry.

A bioactive material must be biocompatible, sterile, not soluble or resorbable, Bactericidal, bacteriostatic, maintain pulp vitality, stimulate reparative dentin, with adhesive properties, radiopaque, resistant to compression and traction, interact with a moist environment, and easy to handle[14]. Ideally, restorative materials should mimic the tissues, facilitate the distribution of forces during the masticatory function, emulate the hardness of the tissues, not generate allergic or cytotoxic reactions, and generate a positive response in the surrounding tissues10. Bioactive materials cover a great variety within preventive and restorative dentistry[30,31].

Composite Resin

Composite resins can generate bioactivity by modifying their organic phase by adhering antibacterial monomers or by adding bioactive fillers, generating an antibacterial and remineralizing mechanism. The incorporation of bioactive glasses in the inorganic matrix of the resin generates a significant bacterial reduction (*E. Coli, S. Aureus, S. Mutans*), without altering the mechanical properties; This reaction can be explained due to the alkalinization of the medium promoting the precipitation of ions, Silicate, Calcium, Sodium and phosphate, generating tissue damage and inhibition of bacterial enzymes and finally lysis[32].

To avoid degradation of the adhesive interface, quaternary ammonium methacrylates (QAM) composite resins such as 12-methacryloxydodecypyridiumbromide (MDPB) with protease inhibitory and antibacterial activities have been integrated, reducing bacterial microfiltration and the prevalence of secondary caries[33].

The addition of bioactive glasses generates more mineral precipitation between the collagen fibers and with the presence of zinc ions, cell proliferation and differentiation are stimulated; zinc intervenes in the mineralization mechanism and interferes in the collagen degradation process mediated by metal proteinases34. The incorporation of amorphous calcium phosphate ACP fillers generates Hydroxyapatite (HA) precursors, favoring the remineralization process through a process of dissolution of calcium and phosphate ions, generating a supersaturation of the medium and subsequently ionic precipitation for the crystallization of HA favoring biomimetic mineralization and in turn decreasing the micro gap of the adhesive interface[35].

Glass ionomer

The glass ionomer was one of the first so-called "smart" materials, given the characteristics that allow it to release fluoride ions, favoring dentinal repair; the release of fluorine increases acids, carrying out a buffer effect in the medium where it is found, due to the presence of aluminum fluoride and hydrogen fluoride ions that are concentrated in their dissolution and gelation stage, but they decrease in their hardening and maturation[36].

The incorporation of bioactive agents such as Bioglass in glass ionomers decreases the mechanical properties by increasing their percentage by weight of filler but increases the bioactive properties[37].

The bioactive glasses together with the ionomers favor the formation of hydroxyapatite in the collagen mesh exposed in an acidic environment, improving the mechanical properties of the dentin in its remineralization process; This ionic precipitation occludes the dentinal tubules, decreasing the hydrodynamic flow, playing an important role as a desensitizer[38].

Hydroxyapatite Precursors

Amorphous Calcium Phosphate (ACP) is stable calcium and fluorine ion precipitator, which promotes the formation of Hydroxyapatite. Due to its high solubility in aqueous media and its rapid conversion into HA, it has been stabilized with casein phosphopeptide (CPP) forming an amorphous calcium casein phosphate complex (CPP-ACP) favoring the saturation of fluorine and phosphate ions in saliva and bacterial plaque, generating anti-cariogenic and remineralizing benefits[15]. In initial caries lesions, it increases the surface hardness values in tissues demineralized by the acidic environment generated by the bacterial attack, significantly reducing the roughness of the enamel, decreasing the surface energy, and disfavoring the adhesion of biofilm[5,39].

Bioceramics

Bioceramics are bio-inert or bioactive compounds, with a crystalline phase embedded in a residual amorphous matrix with a wide variety of indications due to their biocompatibility, dimensional stability, and biomineralization ability, in which we can find silicates, aluminates, hydroxyapatite, zirconia, phosphates calcium, and bioactive glasses [4]. They can be synthesized by different methods: Fusion, vapor deposition, sol-gel synthesis, changing the physico-mechanical properties, and favoring biometry with the surrounding tissues[40]. The bioactivity of bioceramics is given by their adhesive properties to tissues and ionic precipitation that favors biomineralization and alkalinization of the medium that provides antimicrobial activity, [41].

Bioactive Glass

Although its first application given by Dr. Hench was in bone regeneration, bioactive glasses have had great applicability in different clinical settings. The principle of bioactivity is given by the formation of an apatite layer on the surface of the tissues that are capable of emulating their characteristics, although it retains less mechanical properties[1,17]. The incorporation of bioactive glasses to restorative materials facilitates the degradation of proteases, favoring the bond strength, and decreases the hydrolytic degradation of the adhesive interface[20]. The use of monomers with mixtures of bioactive glasses and monomers derived from quaternary ammonium generate antibacterial environments that decrease microfiltration and recurrent caries[42,43]. In addition, the interdigitation of the bioactive glass with the collagen mesh allows greater adhesive strength and facilitates the growth of apatite crystals, which consequently will lead to the continuous reduction of the micro gap between the restorative material and the dental tissue[44].

Silicate-based cements

They are hydrophilic compounds with a basic composition of calcium oxide (CaO), silicon dioxide (SiO_2), and calcium aluminate derived from Portland cement. One of the first materials to be evaluated was the Mineral Trioxide Aggregate (MTA), which has antimicrobial properties thanks to its alkaline pH and favors the formation of dentin bridges in pulp repair[3,45]. Biodentine is a tricalcium silicate-based cement with greater compressive and flexural strength, shorter setting time, and lower solubility. Its pH exerts a bacterial lethal effect, due to protein denaturation and damage to DNA and cell cytoplasm46. In 2018, Mahmoud et al. In their systematic review confirmed the bacteriostatic properties of Biodentine® and MTA, the induction of enamel bridges, promoting odontoblastic proliferation, reparative dentin, and preservation of pulp vitality[47]. Theracal® is a cement-based on calcium silicate modified with a hydrophilic resin that allows it to interact in humid environments and have sustained precipitation of calcium and hydroxide over time48. The interaction with the resinous compounds implies an inflammatory response in the pulp cells, being the one that offers the lowest therapeutic response compared to other cement based on calcium silicate[49].

Conclusion

Bioactive materials have evolved rapidly in recent years, their application includes different areas of dentistry. Particularly in restorative dentistry, bioactive materials are used mainly as pulp capping, and liner, thanks to the fact that they release products that help integration with tissues. Additionally, they are used to dentin adhesion systems are used for core building. There is a lack of literature on long-term follow-up on some of the materials, so their effectiveness should be interpreted with caution.

Conflict of Interest

The authors declare no conflict of interest.

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Citation: Luis Gabriel Ladino, Alejandra Bernal, Daniel Calderón and Diego Cortés. "Bioactive Materials in Restorative Dentistry: A Literature Review". SVOA Dentistry 2:2 (2021) pages 74-81.