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Biomaterials in endodontics: a review

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Abstract

Biomaterials have evolved over the past three decades and are relatively specialized, highly biocompatible, but low-strength dental materials. Bioactive materials can interact with living tissues or systems. The newly emerging bioactive category of dental materials has expanded clinical uses in restorative dentistry and endodontics. Examples of bioactive materials are Calcium Silicate containing Mineral Trioxide Aggregate (Portland cement); Calcium Silicate cements lacking aluminium and containing phosphate: Bioagrregate, iRoot SP and iRoot BP (Endosequence), Calcium Silicate cements containing predominantly Tricalcium Silicate: Bio-active Glass, Calcium Phosphate based materials: Tricalcium Phosphate, Hydroxyapatite, Calcium Phosphate cements and Calcium Aluminate based materials: GIC based luting cements; Bioactive Glass. Other biomimetic materials include Emdogain, Platelet Rich Plasma, Platelet Rich Fibrin, Bone grafts and barrier membranes. Thus, the objective of this review was to compare and review the composition, and properties of these bioactive materials in endodontics.

Keywords: Bioactive materials, Biomimetic materials, Endodontics, MTA, Biodentine.

1. Introduction

The evolution of dentistry is closely associated with the advancements in dental materials. From the dawn of history, there has been a quest for ideal restorative dental materials. Research on bioactive materials and molecules is one of the thrust areas of development in material science, which have widespread applications in dentistry and the biomedical field [1].

Biomaterials are native or synthetic polymers that perform as scaffolds for tissue regeneration and hold wide importance in root canal therapy, tooth repair, pulp therapy and dental surgery. The versatility of sol-gel technology for making bioactive materials allows for manipulating the materials' characteristics required for a particular application [2]. The interaction between restorative dental materials and tooth tissue encompasses multiple aspects of dental anatomy and materials science [1].

Biomaterials have evolved over the past three decades and are relatively specialized, highly biocompatible, but low-strength dental materials. The newly emerging bioactive category of dental materials has expanded clinical uses in restorative dentistry and endodontics [3]. This review was aimed to compare and review the composition and properties of these bioactive restorative materials in dentistry.

2. Classification

2.1 Based on bioactivity [4]

Based on reactivity, Hench (1994) defined two classes of bioactivity

Class A: Osteoproductive Material

Bioactivity occurs when a material elicits both an intracellular and an extracellular response brought by the colonization of osteogenic stem cells at its interface, resulting in osteoproductive and osteoconductive properties.

E.g.: 45S5 Bioglass.

CLASS B: Osteoconductive Materials

Osteoconductive bioactivity occurs when a material elicits only an extracellular response at its interface by providing a biocompatible interface along which bone migrates.

E.g.: Synthetic hydroxyapatite.

2.2 Based on biomineralization [4]

Based on biomineralization, biomaterials are classified as remineralization of enamel, remineralization of dentin, and repair of bone and it was detailed in figure 1.

Biomaterial science: Biomaterial science is the physical and biological study of materials and their interaction with the biological environment.

Biomaterial: Biomaterial is any substance or combination of substances, other than drugs, synthetic or natural in origin, which can be used for any period, which augments or replaces partially any tissue, organ or function of the body, to maintain or improve the quality of life of the individual.

Bioinert material: Bioinert refers to any material that, if

once placed in the human body, has minimal interaction with its surrounding tissues, e.g., stainless steel, titanium, alumina, partially stabilized zirconia (PSZ), and ultra-high molecular weight polyethylene.

Bioactive materials: Bioactive refers to a material which, upon being placed within the human body, interacts with the surrounding bone and in some cases even with soft tissues.

Bioresorbable biomaterials: Bioresorbable refers to a material that, upon placement within the human body, starts to dissolve (resorb) by cellular activity (phagocytosis) and is slowly replaced by advancing tissue (such as bone).

Biomimetic materials: Biomimetics is defined as the study of the formation, structure, or function of biologically produced substances and materials. These biological mechanisms are processed specially to synthesize similar products by artificial mechanisms which mimic natural ones.

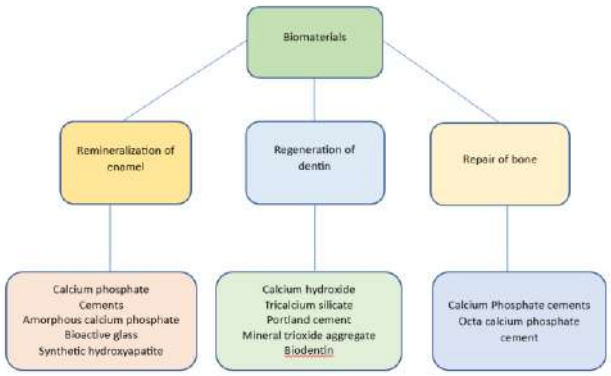


Figure 1. Biomaterials Based on Biomineralization.

3. Calcium hydroxide

Calcium hydroxide was introduced to dentistry as a direct pulp-capping agent by Hermann in 1920. It is a white, odourless powder with the chemical formula $Ca(OH)_2$ and a molecular weight of 74.08 [5]. The calcium oxide (CaO) known as "quicklime "contacts water, and the following reaction occurs:

$$CaO + H_2O \rightarrow Ca(OH)_2$$

3.1 Mechanism of antimicrobial activity

The antimicrobial activity of $Ca(OH)_2$ depends on the release of hydroxyl ions in an aqueous environment. Hydroxyl ions are highly oxidant free radicals with extreme reactivity with several biomolecules. This reactivity is indiscriminate; thus, this free radical rarely diffuses away from sites of generation. The lethal effects of hydroxyl ions on bacterial cells are probably due to damage to the bacterial cytoplasmic membrane, denaturation of proteins, or damage to the DNA [5,6].

3.2 Applications

The applications of $Ca(OH)_2$ include, pulp capping or pulpotomy agent, in apexification, as a medicament in root canals, in horizontal root fractures, in perforations, in root resorption, as apical plug and a root canal sealer.

3.3 Advantages

The $Ca(OH)_2$ exhibits bactericidal characteristics initially, then bacteriostatic character, neutralizes acidity, posessess high pH, which helps in stimulating fibroblasts, stops internal resorption, inexpensive and easy to use [5].

3.4 Disadvantages

The $Ca(OH)_2$ does not exclusively stimulate dentinogenesis, and exclusively stimulate reparative dentin. Associated with primary tooth resorption, may dissolve after one year with cavosurface dissolution, degrade during acid etching, degrades upon tooth flexure, possible marginal failure with amalgam condensation and does not adhere to dentin or resin restoration [5].

In a systematic review and meta-analysis, Ahmad MZ (2022) compared the effectiveness of $Ca(OH)_2$ as an intracanal medicament with no dressing and/or other intracanal medicaments to control postoperative pain in patients with apical periodontitis requiring primary root canal therapy. He concluded that $Ca(OH)_2$ may be an effective intracanal medicament for controlling interappointment pain. Combination therapies appear to be more effective than using $Ca(OH)_2$ alone [7]. In a retrospective study, Ricucci D *et al.* (2023) evaluated the long-term outcome of direct pulp capping in mature teeth using specific case selection and treatment procedures. A very high success rate of direct pulp capping with calcium hydroxide was observed, especially in the first ten years following treatment. The main variable influencing the outcome was the quality of the coronal restoration [8].

4. Mineral Trioxide Aggregate (MTA)

In the 1990s, Professor Mahmoud Torabinejad developed Mineral Trioxide aggregate (MTA), a novel retro-filling material.[9] MTA has been determined as a bioactive material that is hard tissue conductive, hard tissue inductive, and biocompatible [10]. Two forms of MTA materials were categorized: the traditional grey MTA (GMTA), and white MTA (WMTA). The chemical compositions of WMTA and GMTA are detailed in Table 1.

4.1 Mechanism of action of MTA [11]

Stage 1: hydrolysis and ion exchange.
Stage 2: formation of calcium silicate hydrate.
Stage 3: binding of calcium silicate hydrate with calcium ions.
Stage 4: precipitation of amorphous calcium phosphate.
Stage 5: nucleation and transformation of amorphous calcium phosphate into carbonated apatite.

4.2 Applications [12]

The MTA is used as pulp capping agent, in pulpotomy, for apexogenesis, as calcific apical barrier formation in teeth with open apices, for repair of furcal & root perforations, and root canal filling material.

Different MTA-based root canal sealers are ProRoot Endo Sealer (Dentsply Tulsa Dental Specialties, Dentsply/Maillefer, Ballaigues, Switzerland), MTA Fillapex (Angelus), CPM Sealer (EGEO SRL, MTM Argentina SA, Buenos Aires, Argentina), MTA Obtura (Angelus, Angelus Odontologica, Londrina, PR, Brazil), MTAS experimental sealer MTAS (association between 80% of white Portlandcement and 20% of bismuth oxide) with and

addition of water soluble polymers, and F-doped MTA cements.

4.3 Advantages [10,13]

MTA is a highly biocompatible and stimulate mineralization, also they are bioactive, stimulating hard tissue formation. Antimicrobial activity through their alkaline pH. MTA modulates cytokinin production. Form hydroxyapatite on the MTA surface and provide a biological seal. Higher adhesiveness to dentin and sealing ability similar to epoxy resin-based cements. It releases of calcium ions help in cell attachment and proliferation. MTA is a nonmutagenic and non-neurotoxic. No side effects on microcirculation, even though it can influence vessel contraction. MTA effectively seal with dentin and cementum, promotes repair and regeneration of periodontal ligament.

4.4 Disadvantages [13,14]

However, MTA may cause discolouration due to the release of ferrous ions. It possesses longer setting time (2 hours 45 minutes) and shorter working time (less than 4 minutes). Improper handling properties. Compressive strength is inadequate. No known solvent for MTA, Bio-Pure MTAD partially dissolves MTA. when used It remains in contact with the material for 5 minutes; therefore, it is difficult to remove from a root canal.

Table 1. Chemical Composition of GMTA and WMTA

Chemical	WMTA	GMTA
CaO	44.23	40.45
SiO_2	21.20	17.00
$Bi_2 0_3$	16.13	15.90
Al_2O_3	1.92	4.26
Mgo	1.35	3.10
SO_3	0.53	0.51
Cl	0.43	0.43
FeO	0.40	4.39
P_2O5	0.21	0.18
TiO_2	0.11	0.06
H_2O+CO_2	14.49	13.72

In a systematic review, Salem Milani *et al.* (2023) reviewed the effect of different mixing methods on the physicochemical properties of MTA. They reported that the mechanical and ultrasonic mixing methods are superior to the manual mixing method in terms of improving the physicochemical properties of MTA [15]. In a retrospective study, Terauchi Y *et al.* (2023) examined treatment outcomes in three cohorts that compared overfilling, flush filling, and underfilling after orthograde retreatment using MTA. They concluded that MTA obturation is a viable retreatment option for teeth with nonhealing endodontic treatment. MTA overfills or flush fillings do not adversely affect healing outcomes. However, MTA underfilling increases the chances for nonhealing and surgical intervention [16].

5. Biodentine

Biodentine™ (Septodont Ltd., Saint Maur des Fausse's, France) is a new tricalcium silicate (Ca_3SiO_5) based inorganic restorative commercial cement and was introduced as 'bioactive dentine substitute' also known as "DENTIN IN A CAPSULE". The material is claimed to possess better biological and physical properties compared to other tricalcium silicate cements [17]. This Calcium silicate-based material has been recently developed to overcome some of the shortcomings or disadvantages of MTA, which are difficult handling, long setting time, and potential discolouration [18]. The composition of Biodentine is given in Table 2.

Table 2. Composition of Biodentine

Powder	Role
Tri-calcium silicate (C_3S)	Main core material
Di-calcium silicate (C_2S)	Second core material
Calcium carbonate and	Filler
oxide	Shade
Iron oxide	Radio-opacifier
Zirconium oxide	
Liquid	
Calcium chloride	Setting accelerator
Hydrosoluble polymer	Water reducing agent

5.1 Setting reaction

Hydrating the tricalcium silicate leads to forming a hydrated calcium silicate gel (CSH gel) and calcium hydroxide.

$$2(3CaO.SiO_2) + 6H_2O \rightarrow 3CaO.2SiO_2.3H_2O + 3Ca(OH)_2$$

(calcium silicate) (hydrated calcium silicate gel)

5.2 Mechanism of action [19]

Biodentine induces mineralization after its application in osteodentine by expressing markers of odontoblasts and increases TGF-Beta1 secretion from pulpal cells helping in early mineralization. During setting, Calcium hydroxide is formed. Due to its high pH, Calcium hydroxide irritates the areas of contact. This zone of coagulation necrosis causes division and migration of precursor cells to the substrate surface, addition, and cytodifferentiation into odontoblast-like cells. Biodentine induces the apposition of reactionary dentine by odontoblast stimulation and reparative dentin by cell differentiation. Because of its high alkalinity, it exhibits inhibitory effects on microorganisms.

Clinical applications of Biodentine are given in Table 3 [18,19].

The Biodentine has got wide range of advantages of this dentin substitute, the ones with clinical significance are reduced setting time, better handling & manipulation, improved mechanical properties and bioactivity of material [17,20]. However, Biodentine is expensive, has got long

setting time than Calcium hydroxide, and insufficient radiopacity [20].

The differences between MTA and Biodentine are given in Table 4 [20].

Table 3. Clinical applications of Biodentine are given [18,19]

S. No	Clinical applications	Endodontics	Restorative dentistry	Dental traumatology	Pediatric dentistry
1	*Deep Cavities*	✗	✓	✗	✓
2	*Apexification*	✓	✗	✓	✓
3	*Apexogenesis*	✓	✗	✓	✓
4	*Pulp chamber floor perforation*	✓	✗	✗	✓
5	*Lateral root perforation*	✓	✗	✗	✗
6	*Root-end filling*	✓	✗	✗	✗
7	*Direct pulp capping*	✓	✗	✓	✓
8	*Indirect pulp capping*	✓	✗	✓	✓
9	*Partial pulpotomy*	✓	✗	✓	✓
10	*Pulpotomy*	✓	✗	✓	✓
11	*Apical external root resorption*	✓	✗	✓	✗
12	*Cervical external root resorption*	✗	✓	✓	✗

Table 4. Differences between MTA and Biodentine [20]

MTA	BIODENTINE
Manufactured naturally with raw materials	Manufactured synthetically
Contains gypsum acts as a retarded	It does not contain gypsum
It does not contain calcium chloride	Contains calcium chloride
Slow setting	Fast setting
Bismuth oxide	Zirconium oxide
Push-out bond strength is lower	Higher
Porous	Denser

Al-Nazhan S *et al.* (2022) reported, in a systematic review, that repair of furcal perforation with Biodentine yielded a better outcome than MTA [21]. Eshghi A *et al.* (2022) compared the clinical and radiographic success between MTA and Biodentine in pulpotomy of primary mandibular second molars with irreversible pulpitis. The results of this study showed that Biodentine properties are similar to MTA, and both materials showed high clinical and radiographic success rates in long-term follow-up [22].

6. BioAggregate

BioAggregate, root canal repair material, a product of Innovative Bioceramic (IBC), is a biocompatible pure white powder composed of ceramic nanoparticles [23]. This material is available as a powder and liquid. The powder is majorly composed of tricalcium silicate (41%), dicalcium silicate (24%), tantalum pentoxide (25%), calcium phosphate monobasic (6%), and Amorphous silicon oxide (4%). These are contained in a crystalline mass, not separable into individual components. The liquid is the deionized water.

This material is used for repair of root perforation, root-end filling material, apexification, as pulp capping agent, and for also for repair of root resorption.

The advantages of BioAggregate over other biomimetic materials, including aluminum-free composition, highly biocompatible and pure white teeth-coloured powder [23].

7. iRoot SP, BioAggregate-based sealer

A new obturation sealer, iRoot SP root canal sealer (Innovative BioCreamix Inc, Vancouver, Canada), has recently been introduced. It is composed of zirconium oxide, calcium phosphate, calcium hydroxide, fillers and thickening agents.

This material is indicated for the obturation of the root canals, it is also suitable for lateral, single cone and vertical condensation. iRoot SP has a setting time of 4 hours. This material does not require mixing and heating. iRoot SP exhibits excellent bonding with root canal dentine. iRoot SP can be used directly for filling root canals with or without Gutta Percha Points. This material can be applied immediately and introduced directly into the root canal. iRoot SP's outstanding viscosity and tiny particle size allows it to conform to the surface of the gutta-percha and flow readily into the dentinal tubules, lateral canals and webs. The result is a seamless, gap-free interface between the cone, sealer and dentine. Thus, it has an outstanding sealing property.

The setting time of iRoot SP is dependent upon the presence of moisture in the root canal. The amount of moisture required for the setting reaction to reach the root canal through the dentinal tubules. Therefore, adding moisture to the root canals is not required to perform the obturation [24].

8. Endosequence root repair material (ERRM) [25]

ERRM, a new bioceramic aluminium-free material, was introduced in 2009 by Brasseler, USA, as a modified version of MTA to improve its handling properties and clinical outcome. ERRM is an excellent alternative for MTA because of its superior antimicrobial efficacy, biocompatibility, and improved physical properties. The ERRM is composed of calcium silicates, monobasic calcium phosphate, zirconium oxide, tantalum oxide, proprietary fillers, and thickening agents.

ERRM is used as a pulp capping agent, root-endo filling (Retrograde fills) materials, repair of root perforation and root resorption, and for apexification.

The advantages of ERRM, including they are available in premixed-syringable forms, shorter setting time (20 mins), highly resistant to washout, highly biocompatible, osteogenic, acts as an antibacterial (+12 pH) agent, and causes no staining [25,26].

Research reported that both Bio-dentine and Endo-sequence root repair material has comparable effects on the pulpal tissues. Hence, they can be used as suitable pulp capping agents [27].

9. EndoSequence BC sealer

Unlike conventional base/catalyst sealers, BC Sealer utilizes the moisture content naturally present in the dentinal tubules to initiate its setting reaction. This highly radiopaque and hydrophilic sealer forms hydroxyapatite upon setting and chemical bonds to dentin and our bioceramic points (EndoSequence® BC Points™). BC Sealer is antibacterial during setting due to its highly alkaline pH, and unlike traditional sealers, BC Sealer exhibits absolutely zero shrinkage [28].

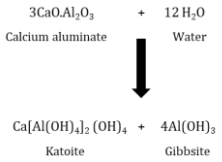
These sealers are biocompatible and osteogenic, chemically bond to Dentin as well as filling materials, considerably Less Expensive than carriers, highly antibacterial (+12 pH upon setting) & Radiopaque, Hydrophilic in nature, produce hydroxyapatite, possess ideal working and setting times, user-friendly (premixed syringable sealer), exhibits zero Shrinkage of Sealer and filling Material, and a 3-D bonded obturation at room temperature.

However, changes in environmental water content adversely affect the setting time and microhardness of EndoSequence BC Sealer. Conventional retreatment techniques are not able to entirely remove Bioceramic sealer.

In a systematic review and meta-analysis, Rekha R *et al.* (2022) reported that the Bioceramic sealers and epoxy resin-based sealers exhibited comparable sealing ability [29].

10. Calcium Aluminate cements

Calcium aluminate cement (CAC) is derived from the class of cement called "hydraulic" or natural cement. Typical CAC contains pre-reacted constituents: Al2O3 = 43%; CaO = 19%; H_2O = 15%; ZrO_2 = 19% (silicon, iron, magnesium, titanium, and alkali oxides less than 10%). The chemical reaction forming the CAC is depicted as follows [30]:



A new calcium aluminate–based endodontic cement (patent number PI0704502-6, 2007), called ENDOBINDER (Binderware, Sao Carlos, SP, Brazil), has been developed to preserve the properties and clinical applications of MTA without its negative characteristics.

Nevertheless, despite the good results obtained for EB, it is valid to emphasize that studies related to other biological properties of this new cement, such as reparative capacity, must be conducted before its validation as an endodontic treatment option [31].

11. Calcium phosphate-based materials

Calcium phosphate materials have received much research attention due to their chemical similarity to bones and teeth. They are attractive biomedical materials owing to their excellent biocompatibility and the non-toxicity of their chemical components [32]. Depending on composition, three varities of materials are there. They include, calcium hydroxyapatite (HA), Ca10(P04)6(OH)2; Beta-tricalcium phosphate (β- TCP), Ca3(P04)2; and Biphasic calcium phosphates (BCP), a mixture of HA and P-TCP. The HA ceramics may be further subdivided into HA from synthetic or HA from natural products [33].

One essential application of calcium phosphate is its use for caries prevention. Calcium phosphate products claim to enhance the availability of calcium and phosphate ions; this aids in improved remineralization. Calcium phosphate-based technologies currently available are amorphous calcium phosphate, casein phosphopeptide amorphous calcium phosphate, calcium sodium phosphosilicate, and tricalcium phosphate [34]. Different calcium phosphate-based sealers are presented in Table 5.

Table 5. Calcium phosphate-based sealers

Name (Manufacturer)	Composition
Apatite Root Sealer Type I (Sankin Kogyo, Tokyo, Japan)	α-Tricalcium phosphate Hydroxyapatite Polyacrylic acid Water
Apatite Root Sealer Type III (Sankin Kogyo, Tokyo, Japan)	α -Tricalcium phosphate Hydroxyapatite Iodoform Bismuth Polyacrylic acid Water
CAPSEAL I	Calcium phosphate Gray Portland cement Tetracalcium phosphate Dicalcium phosphate dihydrate Sodium phosphate solution
CAPSEAL II	Calcium phosphate White Portland cement Tetracalcium phosphate Dicalcium phosphate dihydrate Sodium phosphate solution
Pulp Canal Sealer EWT (Kerr, Detroit, MI)	Zinc oxide eugenol

11.1 Advantages [32]

- CAPSEAL I and II show less cytotoxicity and inflammatory mediators than other sealers and can promote bone regeneration as root canal sealers.
- CAPSEAL I and II facilitate the periapical dentoalveolar and alveolar healing by controlling cellular mediators from PDL cells and osteoblast differentiation of precursor cells.
- CAPSEAL I and II sealers were well-adapted to the canal wall and diffused into the dentinal tubules.

11.2 Disadvantages

- Retreatment is not easy.
- CPS-1 sealer is not biocompatible.

12. Bioactive glass

Bioactive glass (BG) is a biomaterial introduced by Prof. Larry Hench in 1969 (Hench, 2006) to develop a biocompatible material that forms an intimate bond with the bone. The first glass discovered is 45S5 (Bioglass), with a glass composition of 46.1 mol.% SiO2, 24.4 mol.% Na2O, 26.9 mol.% CaO, and 2.6 mol.% P_2O_5 [35]. BG can interact with the body tissues to form a resilient bond, and its controlled degradation over time is useful in releasing therapeutic ions, which can help bone regeneration. The composition of different bioactive glasses is presented in Table 6 [36].

Table 6. Composition of different bioactive glasses.

	Na_2O	K_2O	MgO	CaO	SiO_2	P_2O_5	B_2O_3
45s5	24.5	0	0	24.5	45.0	6.0	0
13-93	6.0	12.0	5.0	20.0	53.0	4.0	0
6P53B	10.3	2.8	10.2	18.0	52.7	6.0	0
58S	0	0	0	32.6	58.2	9.2	0
70S30C	0	0	0	28.6	71.4	0	0
13-93B1	5.8	11.7	4.9	19.5	34.4	3.8	19.9
13-93B1	5.5	11.1	4.6	18.5	0	3.7	56.6
P50C35N15	9.3	0	0	19.7	0	71.0	0

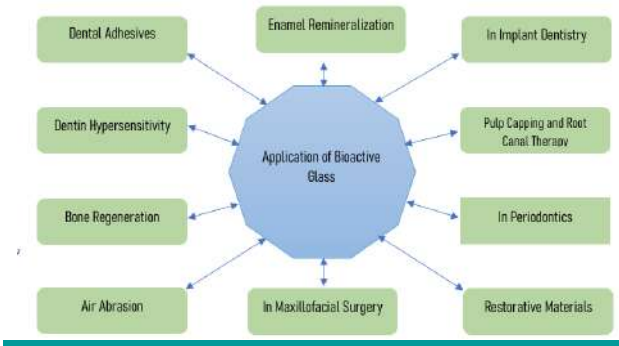


Figure 2. Clinical applications of bioactive glasses in dentistry.

12.1 Mechanism of action

These glasses' bioactivity depends on their mechanism and speed of action. Briefly, the reactions to form HAP involve the ion exchange of Ca and Na ions for H ions from the solution, a consequent increase in the pH of the solution, the formation of silanol (Si-OH) bonds on the surface of the glass, and the resulting formation of a silica-rich layer, degradation of silica (due to increased pH), and then then the development of a layer of amorphous CaOP2O5 on the silica-rich layer, which then crystallizes as HAP due to the absorption of hydroxyl and carbonate ions[37]. Clinical applications of bioactive glasses in dentistry are depicted in Figure 2 [36,37].

Behzadi S *et al.* (2022) [38] evaluated the occlusion effects of bioactive glasses and hydroxyapatite on dental tubules and demonstrated that bioactive glass and hydroxyapatite could effectively occlude the dentinal tubules. Thus, desensitizing agents containing bioactive glass and hydroxyapatite can be used to manage dentin hypersensitivity (DH).

13. Emdogain

Enamel Matrix Derivative (EMD) in the form of a purified acid extract of proteins from pig enamel matrix (Emdogain®; Straumann AG, Basel, Switzerland) has been successfully employed to restore functional periodontal ligament, cementum, and alveolar bone in patients with severe attachment loss.

Emdogain stimulates the release of bone morphogenetic protein, transforming growth factor beta and other growth factors like cytokines and platelet-derived growth factor. Also, it promotes the differentiation of mesenchymal cells into fibroblasts, cementoblasts, and osteoblasts and enhances the expression of tissue markers like alkaline phosphatase [39].

The principal constituent of EMD is amelogenins (>95%), a family of hydrophobic proteins derived from a single gene by alternative slicing and controlled post-secretory processing. The amelogenins are known to self-assemble into supramolecular aggregates that form an insoluble extracellular matrix with a high affinity for hydroxyl apatite and collagens when applied to denuded root surfaces; amelogenins, therefore, precipitate to form a stable, extracellular matrix with a hydrophobic surface with the potential for supporting interactions with cells in adjacent tissues.

Until now, Emdogain® is the only product on the market that has the potential for actually triggering clinically significant regenerative responses in periodontal ligament cells [40].

Tamzini M (2022) in his review stated that the EMD (Emdogain®) is the best choice to accelerate healing and minimise discomfort to the patients by providing less swelling, less pain and faster recovery after the surgical treatments. The EMD initiates and promotes the natural healing process of soft/hard tissues in the oral cavity leading to patient satisfaction [41].

14. Platelet derivatives

Platelet-derived growth factor (PDGF) is a potent moderator of soft tissue repair through induction of the inflammatory phase of repair and subsequent enhanced collagen deposition) In chemical terms, the platelet-derived growth factor is a dimeric glycoprotein incorporating 2 A (-

AA) or 2 B (-BB) chains or a combination of the two (-AB). DGF acts like a mitogen for cells of mesenchymal origin [42].

Functions of platelet-derived growth factor, including platelet-derived growth factor (PDGF), i) a potent chemoattractant and mitogen, is considered to be a key mediator in wound healing and tissue repair. In vitro studies indicate that PDGF stimulates the proliferation and activity of fetal and mature bone cells. It is chemotactic for neutrophils, monocytes, and fibroblasts, ii) moreover, PDGF, also known for its angiogenic effect, exerts an indirect angiogenic action by upregulating the expression of vascular endothelial growth factor (VEGF). Furthermore, PDGF stimulates the healing of skin incisions and excisions by increasing inflammatory cell infiltration, provisional matrix formation, collagen deposition, and neovascularization.

14.1 Platelet-rich plasma: 1st generation platelet concentrate

Platelet-rich plasma is blood plasma enriched with platelets. It is a concentrated source of autologous platelets; PRP contains (releases through degranulation) different growth factors and cytokines that stimulate bone and soft tissue healing. Platelet-rich plasma (PRP) is an easily accessible source of growth factors to support bone and soft-tissue healing [44]. PRP is a simple strategy to concentrate platelets or enrich natural blood clots found in normal surgical wounds to initiate a more rapid and complete healing process. Natural blood clot contains 95% red blood cells, 5% platelets, less than 1% white blood cells, and numerous fibrin strands. PRP blood clot contains 4% red blood cells, 95% platelets, and 1 % white blood cells. Once injected or implanted, PRP is thought to release growth factors locally for several days, inducing accelerated tissue repair.

PRP, in the field of dentistry, has been used in different clinical procedures, including sinus floor elevation, alveolar ridge augmentation, mandibular reconstruction, maxillary cleft repair, treatment of periodontal defects, and treatment of extraction sockets where it has been applied alone or in addition to autogenous bone, an organic bone mineral, and organic bone substitutes [44].

14.2 Platelet-rich fibrin: 2nd generation platelet concentrate

Platelet-rich fibrin (PRF), developed in France by Choukroun *et al*. (2001), is a second-generation platelet concentrate that enhances soft and hard tissue healing. Platelet-rich fibrin (PRF) advances the platelet gel therapeutic concept with simplified processing minus artificial biochemical modification [45].

This material is most widely used for sinus lift procedure, ridge augmentation, socket preservation, bone augmentation, and pulp capping.

PRF has many advantages over PRP. The redundant process of adding anticoagulant and the need to neutralize it is eliminated. It also eliminates the addition of bovine-derived thrombin to promote the conversion of fibrinogen to fibrin in PRP. The elimination of these steps considerably reduces the biochemical handling of blood as well as the risks associated with the use of thrombin [46]. The conversion of fibrinogen into fibrin occurs at a slow pace, with small quantities of physiologically available thrombin present in the blood sample . Thus, physiologic architecture that is very favourable to the healing process is obtained due to this slow polymerization process [47].

PRF may present some disadvantages, including the final amount available is low because it is autologous blood. The success of the PRF protocol depends directly on the handling, mainly related to blood collection time and its transference for the centrifuge. There is a need to use a glass-coated tube to achieve clot polymerization [48].

Araújo LD *et al.* (2022) conducted an integrative review to identify whether alternative scaffolds used in regenerative endodontics contribute to better root development, in relation to the increase in root length and thickness of dentin walls, compared with blood clot (BC) scaffolds. They concluded that, In general, there was a significant increase in root length and dentin thickness promoted by PRF and PRP scaffolds, compared with Blood clots [49].

Comparative evaluation of clinical application properties of different biomaterials is presented in Table 7 [5,10,14,18,23].

Table 7. Comparative evaluation of clinical application properties of different biomaterials [5,10,14,18,23].

S/NO	PROPERTIES	MATERIAL			
		$Ca(OH)_2$	MTA	BIODENTINE	ENDOSEQUENCE
1	Strength	√	√√	√√√	√√
2	Solubility	√√√	√	√	√
3	Sealing ability	√	√√√	√√	√√
4	Setting time	2-5 Mins	175 mins	10.1 mins	4 Hrs
5	Handling	√	√√√	√√	√√
6	Discoloration	-	√	-	-
7	Radio opacity	-	√√	√	√√
8	Cost	Economical	x	xx	xxx

16. Conclusion

Bioactive materials can be considered a boon to dentistry because of their regeneration potential. Future dentistry would involve the use of bioactive materials which could successfully replace lost enamel, dentin, cementum, and even pulp tissue. Thus, shortly it can be envisioned that there will be better alternatives in the field of restorative dentistry in the form of bioactive and biomimetic materials.

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