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Recent Advances in Biomimetic Materials Used in Restorative Dentistry: An Updated Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

The advances in biomimetic materials have seen a rapid rise in the last decade, with the introduction of several newer materials being launched into the market. These materials aim at preserving tooth structure, restoring the overall health of the tooth and making treatment outcomes more predictable. This review article aims at comprehensively describing biomimetic materials used in restorative dentistry.

Keywords: Dentistry; operative; tooth remineralization; biomimetic materials; dental materials.

1. INTRODUCTION

All human inventions and achievements that have advanced dentistry, are inspired by nature. In an attempt to restore the natural tissues of the body, various materials have been introduced into the market over the years. The term biomimetic is derived from two Latin words – "bios" meaning life and "mimetic" meaning imitating or inspired by.[1] The term was first coined by Otto Schmitt in 1969[2] and can be defined as –"*the study of formation, structure or function of biologically produced substances and materials and biological mechanisms and*

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processes, for the purpose of synthesizing similar products by artificial mechanisms that mimic natural structures".[3] In restorative dentistry, these materials primarily aim at replacing two tissue layers – enamel and dentin.[3,4] Each material aims at achieving either "dentin like" or "enamel like" properties but cannot replace both as these tissues differ significantly in their composition, mechanical properties, and characteristics.

Requirements of a biomimetic material are [3] –

1. It should be biocompatible
2. It should be synthetic in origin
3. It should mimic biology
4. It should bond with natural structure
5. It should not elicit any undesirable biological responses

Taking all the above factors into consideration, various biomimetic materials have been introduced into the market in an attempt to replace enamel and dentin.

Enamel Replacement

The enamel is the outer most layer of the tooth. The colour, textures and thickness protect the tooth, provide resistance to masticatory forces and impart aesthetics. Materials that aim at replacing enamel by attempting to replicate the tissue, should have the following properties, listed in Table 1.

Dentin Replacement

The replacement of dentin is fairly more challenging than enamel as it is a semi-vital tissue. The challenges faced are as follows –

- Dentin has 60-65% inorganic matter making the substrate for bonding significantly lesser as compared to that of enamel
- Dentinal fluid is dynamic and moves withing the tubules on stimulation through thermal, chemical or tactile signals. The intra tubular pressure exerts an external displacement force, making penetration of bonding agent into the tubules to form micro-tags for bonding to the dentin challenging
- The open dentinal tubules act as a gateway for the entry of bacterial toxins, chemical substances and leaching of ions into the pulp space through the process of micro leakage. This could result in a range of secondary outcomes – post-operative sensitivity to pulp inflammation and necrosis.

Table 1. Recommended material properties for enamel and dentin replacement

Physical property	Enamel replacement	Dentin replacement
Modulus of Elasticity	~95GPa	~18GPa
Thermal Conductivity	~0.9W/mK	~0.5W/mK
Refractive Index	~1.6	~1.5
Compressive Strength	~400MPa	~300MPa
Adhesive Properties	Ability to me mechanically retained in the cavity or bonded to the remaining enamel and dentin	Ability to be mechanically retained in the cavity or bonded to the remining dentin Ability to induce secondary dentin formation by stimulating the undifferentiated odontoblastic cells in the pulp

2. GLASS IONOMER CEMENT [3]

Glass Ionomer Cement (GIC) is a tooth-coloured material used extensively in restorative dentistry. It was first introduced by Wilson and Kent in 1972. The material is based on a reaction between silicate glass powder and polyacrylic acid which chemically bonds to the tooth substrate and releases fluoride over time. It is also known as *"man-made dentin"* or *"dentin replacement"* material.

Biomimetic Properties

- Modulus of elasticity is similar to that of dentin
- Fluoride release properties
- Fluoride recharge
- Aesthetics

Uses

1. Cavity base
2. Pit and fissure restorations
3. Class one restorations
4. Class 5 restorations
5. Root perforation materials
6. Core material

3. NANO-HYDROXYAPATITE/ YTTRIUM STABILIZED ZIRCONIA /"WHITE AMALGAM"[4]

Yttria-stabilized zirconia (YSZ) is a ceramic in which the cubic crystal structure of zirconium dioxide is made stable at room temperature by an addition of yttrium oxide. The incorporation of Nano Hydroxyapatite along with Yittrium Stabilized Zirconia in conventional GIC has shown to have superior properties.

Biomimetic Properties

- Superior hardness
- Chemical inertness
- Increased modulus of elasticity
- Decreased dissolution of cement

Uses

1. Core build up material
2. Class 1 cavities

4. FIBER REINFORCED GIC/PRIMM [4]

A continuous network / scaffold of alumina and Sio_2 ceramic fibers is referred to as the PRIMM CONCEPT (*Polymeric rigid inorganic matrix material*). Glass particles are liquified to form molten glass which is forced through a die to form thin strands of glass fibers. These glass fibers are then crushed into small fragments and then reheated to a sufficient temperature to cause superficial fusion of glass Fibers at selected sites This forms a continuous network of small cavities These spaces are then infiltrated with an optimized resin (BIS- GMA/ UDMA).

Biomimetic Properties

- Higher level of cross linking
- Increased strength to withstand masticatory forces
- Decreases the total amount of composite to be used and hence decreased polymerization shrinkage stresses

Uses

1. Compound and extensive restorations – Class 1, Class 2 and mesio-occlusal-distal (MOD) restorations
2. Core build up material

5. CERAMICS [4]

These are glass based non-metallic materials made from firing at high temperatures. Their application in dentistry is extensive and can be attributed to their biomimetic properties especially as an enamel replacement.

Biomimetic Properties

- Highly aesthetic and long term colour stability
- High wear resistant
- High biocompatibility
- Impervious to oral fluids

Uses

1. Full coverage crowns – PFM, all ceramic, Richmond crowns
2. Partial coverage restorations – inlays, onlays, overlays, endocrowns, vonlays, digiposts and veneers

6. POLYMERS [4]

These are restorative resins used extensively in dentistry and range from bonding agents to adhesive composite resins.

Biomimetic Properties

- Biocompatible
- Possesses good mechanical properties
- Esthetics, increased hardness, wear resistance and longevity

Uses

1. Temporary crowns – lab fabricated or chairside
2. Restorative materials for both anterior and posterior direct restorations
3. Indirect restorations – inlays, onlays, veneers, etc
4. Luting cements

7. BIOGLASS®/BIOACTIVE GLASS [5]

These are silicate based materials that have similar composition to hydroxyapatite. The form strong bonds with the hard tissues containing HA such as enamel, dentin, cementum and bone.

Bioactive Properties

- Similar composition to bone causes complex bonds with mineralized tissue
- Has to ability to Induce tissue mineralization at the glass tissue interface

Uses

1. Treatment of deep carious lesions
2. Dentinal hypersensitivity
3. Root apex sealer
4. Endodontic surgeries – bony defects, periapical lesions, palatogingival groove repair
5. Management of bony defects in periapical and periodontal surgeries

8. NANO HYDROXYAPATITE [5]

Nano hydroxyapatite coatings are used to made biomaterials more biocompatible. Due to their nano size, they have two main properties – osteoconduction and enhancing biocompatibility.

Bioactive Properties

- Bridge formation by Osteoconductive property
- Bioactive properties due to its non-toxic and non-inflammatory nature

Uses

1. Pulp capping agent
2. Modified GIC- restorative treatments
3. Desensitizing agent post bleaching
4. Remineralization agent in toothpastes
5. Early carious lesion treatment

9. CALCIUM HYDROXIDE [5]

Calcium hydroxide cements are used for lining specific areas of deep cavities or for direct pulp capping. The antibacterial action of calcium hydroxide makes these cements useful in indirect pulp-capping procedures involving carious dentin.

Bioactive Properties

- Dissociates into calcium & Hydroxyl ions
- Ca ion →↓ capillary permeability
- Hydroxyl ions → neutralize acid produced by osteoclasts
- *Antimicrobial activity*: damage to bacterial cytoplasmic membrane, protein denaturation and damage to DNA
- *Mineralization activity*: formation of the calcified barrier results in a superficial layer of necrosis. This layer induces an inflammatory response 2mm below the necrotic layer and stimulates the “dentin bridge formation”

Uses

1. Direct or indirect pulp capping
2. Interappointment medication
3. Root canal sealer
4. Apexification
5. Pulpotomy

10. MINERAL TRIOXIDE AGGREGATE/ MTA [5]

This revolutionary cement was first introduced my Mahmoud Torabinajad in the year 1993. This is an aggregate of mineral oxides added to “trioxides” of tricalcium silicate, tricalcium aluminate, and tricalcium oxide silicate oxide.

Bioactive Properties

- Initial pH of 10.2 which increases to 12.5 after three hours- antibacterial effect and encourages differentiation of undifferentiated odontoblasts in the pulp tissue

- Induces cytologic & functional changes within pulpal cells resulting in the formation of fibrodentin and reparative dentin
- Causes proliferation, migration and differentiation of odontoblast like cells that produce collagen matrix which mineralizes after deposition of hydroxyapatite crystals
- Induces “dentin bridge formation” without the production of superficial layer of necrosis
- Hydrophilic in nature – easy to adapt to tooth substrate

Uses

1. Vital pulp therapy
2. Pulp capping agent
3. Apexification
4. Retrograde filling
5. Apicectomy
6. Perforation repair
7. Regenerative endodontic therapies

11. BIODENTINE [7]

Biodentine is a calcium-silicate based material that has drawn attention in recent years and has been advocated to be used in various clinical applications, such as root perforations, apexification, resorptions, retrograde fillings, pulp capping procedures, and dentine replacement. As compared to MTA, it has a shorted setting time and better handling characteristics.

Bioactive Properties

- It has a positive effect on vital pulp cells and stimulates tertiary dentin formation.
- In direct contact with vital pulp tissue it also promotes the formation of reparative dentin.

Uses

1. Vital pulp therapy
2. Pulp capping agent
3. Apexification
4. Retrograde filling
5. Apicectomy
6. Perforation repair
7. Regenerative endodontic therapies

12. ENDOSEQUENCE [7]

Endosequence is a calcium silicate based endodontic sealer by Brassler®. Due to its availability as a uniform putty, it is also an ideal material for direct pulp capping procedures.

Bioactive Properties

- Setting occurs in the presence of moisture present in the dentinal tubules
- Survival and proliferation of dental pulp cells is similar to that with MTA
- Hydration reaction containing monocalcium phosphate resulting in formation of hydroxyapatite

Uses

1. Pulp capping
2. Perforation repair
3. Apical surgeries

13. BIOAGGREGATE [8]

This is a bioceramic material composed of calcium silicate, aluminium free, ceramic nano particles, produced as an alternative to MTA.

Bioactive Properties

- Induce mineralization & odontoblastic differentiation associated gene expression in human dental pulp cells

Uses

1. Vital pulp therapy
2. Pulp capping agent
3. Apexification
4. Retrograde filling
5. Apicectomy
6. Perforation repair
7. Regenerative endodontic therapies

14. CEM (CALCIUM ENRICHED MIXTURE)/NEC (NOVEL ENDODONTIC CEMENT) [8]

Calcium-enriched mixture cement is composed of different calcium compounds, that is, calcium phosphate, CH, calcium sulfate, calcium silicate, calcium chloride, calcium carbonate and calcium oxide. CEM cement is a white powder consisting of hydrophilic particles that sets in the presence of the water base solution.

Bioactive Properties

- Releases both calcium and phosphorous ions leading to hydroxyapatite formation

Uses

1. Vital pulp therapy

2. Pulp capping
3. Apexogenesis
4. Obturating material
5. Perforation repair
6. Root end filling material

15. CALCIUM PHOSPHATE [7] AND TETRA CALCIUM PHOSPHATE (TTCP) [8]

Applications are calcium phosphates, because their chemical composition is very similar to that of the mineral phase in human teeth, especially of natural enamel.

Bioactive Properties

- Osteoconductive -induces bridge formation
- Remineralization of early carious lesions

Uses

1. Remineralization of early carious lesions
2. Pulp capping agent
3. Regenerative endodontic therapies

16. THERACAL [9]

This is a light cured resin modified calcium silicate (containing calcium hydroxide). It is extensively used as a pulp capping agent.

Bioactive Properties

- Dissociates into calcium & Hydroxyl ions
- Ca ion →↓ capillary permeability
- Hydroxyl ions → neutralize acid produced by osteoclasts

Uses

1. Direct and indirect pulp capping
2. Protective base/liner under composites, amalgam, cements & other base materials

17. CASTOR OIL BEAN CEMENT [10]

This is the triglyceride of ricinolein acid (derived from *Ricinus communis*).

Bioactive Properties

- Promotes tissue regeneration – concentration of growth factors like IL-6, TNF- β

Uses

1. Pulp capping agent

18. MTYA1-CA [11]

This is a newly developed resinous direct pulp capping agent containing calcium hydroxide. The powder of MTY1-Ca is composed of 89.0% microfiller, 10.0% calcium hydroxide and 1.0% benzoyl peroxide and was mixed with liquid (67.5% triethyleneglycol dimethacrylate, 30.0% glyceryl methacrylate, 1.0% o-methacryloyl tyrosine amide, 1.0% dimethylaminoethylmethacrylate, and 0.5% camphorquinone).

Bioactive Properties

- Resin based direct pulp capping agent
- Dentine bridge formation without formation of a necrotic layer

Uses

1. Direct pulp capping agent

19. DOXADENTCAC (CALCIUM ALUMINATE CEMENT) [12]

This is an alternative to amalgam and resin composite introduced in an attempt to decrease the use of amalgam due to mercury toxicity to the environment. Mainly used in pediatric restorations – posterior restorations(class 1, 2) and class 5. Doxadent are available as tablets together with the liquid and the packing instrument.

Bioactive Properties

- Considered an alternative to amalgam
- Water dissolves calcium aluminate to release Ca^{2+}, $Al(OH)_4^-$, and $(OH)^-$ ions which is followed almost immediately by precipitation of new solid phases due to saturation of the solution. Crystalline growth takes place.
- Setting expansion of 0.05% -1% leads to elimination of possible gaps

Uses

1. Permanent restorative material – posterior teeth(class 1 and 2) and class 5

20. HX-BGC [13,14]

This is a new strontium doped bioactive glass that releases fluoride on demineralized enamel and dentin.

Bioactive Properties

- Property of occluding dentinal tubule

Uses

1. Treatment of dentinal hypersensitivity

21. RESIN IMPREGNATED WITH TITANIUM OXIDE [15]

Due to the long-term synergistic effects of acid-producing bacteria and fermentable carbohydrates in the oral environment, the antimicrobial activity of the composite resin is highly desirable in clinical applications. Due to the long-term synergistic effects of acid-producing bacteria and fermentable carbohydrates in the oral environment, the antimicrobial activity of the composite resin is highly desirable in clinical applications.

Bioactive Properties

- Titanium Dioxide impregnated in dental monomers and dentin result in hydroxyapatite formation

Uses

1. Treatment of caries

22. ENAMEL MATRIX DERIVATIVE-EMDOGAIN [16]

EMD is an extract of enamel matrix is an extract of porcine fetal tooth material used to biomimetically stimulate the soft and hard tissues surrounding teeth to regrow following tissue destruction. It contains amelogenins of various molecular weights. Amelogenins are involved in the formation of enamel and periodontal attachment formation during tooth development.

Bioactive Properties

- Promotes odontoblast differentiation and reparative dentin, cementum, attachment fibres formation
- Promotes the regrowth of hard and soft tissues lost during periodontal disease.

Uses

1. Direct pulp capping
2. Regeneration of intra-bony defects
3. Treatment of recession

23. KEPIVANCE - KGF-2 [17]

Keratinocyte growth factor is a proposed growth factor that can be used in dentistry in an array of treatments from oral sores to regenerative endodontics. It is still in the in-vitro stage of epreimental trial and has proved to successfully promote epithelial growth.

Bioactive Properties

- Acts by stimulating cell growth, proliferation, differentiation, and upregulation of cytoprotective mechanisms

Uses

1. Regenerative endodontics
2. Pulp capping agent
3. Management of oral sores and mucositis

24. JUVISTA: TGF-B3 [18]

This growth factor is available in the form of TGF-β3 containing alginate hydrogels.

Bioactive Properties

- Improves natural regenerative capacity of the pulp: induce odontoblast-like cell differentiation with subsequent secretion of regular tubular dentin matrix on cut pulpal surfaces

Uses

1. Pulp capping agent
2. Regenerative endodontics

25. BMPs [19]

Bone morphogenic proteins (BMPs) are a group of osteoinductive proteins obtained from nonmineralized bone matrix; they are capable of stimulating the differentiation of pluripotent mesenchymal cells to osteoprogenitor cells. rhBMP-2 is the most widely used in dentistry and is mainky used in oral surgery. Due to its regenerative properties, the

Bioactive Properties

- Bone formation - chemotaxis of progenitor cells;

- Proliferation of mesenchymal cells;
- Differentiation of cartilage;
- Vascular invasion;
- Differentiation, mineralization, and remodeling of bone due to its osteoconductive properties

Uses

1. Pulp capping agent
2. Repair of bony defects

26. CALCIUM SULPHATE [20]

Calcium sulfate has a long history of use in medicine and dentistry. It exists in two forms (alpha and beta), which differ greatly in physical properties. It has been used in bone regeneration as a graft material and graft binder/extender and as a barrier in guided tissue regeneration.

Bioactive Properties

Excellent biocompatibility with bone due to its similar chemical composition

Uses

Provides a resorbable scaffold for bone growth

1. As an apical barrier in open apices
2. Furcal perforation repair
3. Matrix for apexification procedure with MTA
4. As a delivery vehicle for pharmacologic agents adjunct to root resection
5. Root end filling material

27. CERAMIR [21]

Ceramir is a Calcium aluminate cement with GIC. The material consolidates through its reaction with water, first dissolving and then re-crystallizing as nanocrystalline hydrates. This reactions creates a unique type of bond between material and tooth (as well as the restoration material) built on surface energy and mechanical interlocking at the nano-level as well as providing an alkaline pH.

Bioactive Properties

- High alkaline pH after setting – antibacterial properties
- Production of excess calcium ions promotes regeneration
- Promotes the formation of hydroxyapatite as well as tertiary dentin

Uses

1. Direct and indirect pulp capping agent

28. ACTIVA BIOACTIVE – PULPDENT [22]

A composite resin which is ionic in nature (called embrace resin – patented technology) matrix (free of Bisphenols, Bis-GMA and BPA derivatives). Bioactive resin matrix - shock absorbing resin component and BAG fillers - similar properties of tooth

Bioactive Properties

- Release more fluoride than glass ionomer cement as well as calcium and phosphate
- Stimulates mineral apatite formation and natural remineralization
- “Smart” material - reacts to the continuous pH changes in the mouth to help fortify and recharge the ionic properties of saliva, teeth and the material itself

Uses

1. Class 1 dental caries
2. Class 2 dental caries
3. Core build up material
4. Class 5 dental caries
5. Bulk fill resin
6. Anterior restorations

29. SIMVASTATIN [23]

Simvastatins are a type of statins that aid in protein formation and regeneration. The use of statins in restorative dentistry is still a niche field and is still in the experimental stages but has shown positive results in secondary dentin formation.

Bioactive Properties

- Statin has multiple functions including anti-inflammation, induction of angiogenesis and improvement of the vascular endothelial cell function
- Have anabolic effects on bone metabolism by promoting mineralization in non-mineralizing osteoblasts through induction of BMP-2 and osteocalcin
- They promote osteoblastic differentiation in mouse osteoblastic cells

Uses

1. Direct pulp capping agent
2. Periodontal therapy

30. BIOENGINEERED TOOTH [24,25]

A bioengineered tooth is an embryonically generated tooth bud in which a patient's own germ cells are extracted and cultured in vitro to generate a tooth bud. This bud is implanted into the jaws. The tooth bud then follows the natural pathway of tooth development and erupts into the oral cavity. This has been successfully performed in animals such as pigs and rats. A bilayered hydrogel human tooth bud has been successfully generated as well. This is the future of single tooth replacement and may even overcome the shortcomings of dental implants.

Bioactive Properties

- Tooth is 100% biocompatible as it is derived from the patient's own stem cells
- Best replacement for a missing tooth
- Can be erupted into the jaws by implanting the follicle into the jaws

Uses

1. Replacement of a missing tooth

31. CONCLUSION

There has been a tremendous progress in the evolution of dental materials over the past 100 years. The epitome of these advances in the emergence of translational medicine which collectively is regenerative medicine, tissue engineering and biomimetic sciences. What first started as tooth substance loss replacements such as amalgam and cast metal then became dentin replacements such as GIC. The materials then progressed to materials that can control the bleeding of the pulp, produce a soothing effect on the pulp and disinfection of the tissue.

The science of biomimetic dentistry is an evolving one. Research and evidence-based dentistry have opened newer doorways to bring out the latest advances in materials. The currently available materials have proved to improve long term success of restorations by replacing lost tissue layers with dentin like and enamel like materials. The science of biomimetic innovation however has taken a new tangent in restorative dentistry with its focus changing from replacement to regeneration. The introduction of MTA by Mahmoud Torabinajed was the start of the regerative revolution in dentistry.

These materials are a boon to dentistry due to their regeneration potential. The stimulation of growth factor production, differentiation of progenitor pulp cells, anti-inflammatory properties and antibacterial properties are mechanisms through which these materials impart effect. Utilization of the regenerative capacity of the pulp to induce secondary dentin formation is the key to success. It is of utmost importance that one has a thorough knowledge of the materials, their indications and mechanism in which they impart biomimetic properties. Incorporation of these materials into routine practice as an adjunct to conventional treatment modalities will enhance favorable clinical outcomes of restorative treatments.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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