

Biomimetic Materials in Dentistry

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ABSTRACT

With the arrival of technology, during the last two decades, numerous changes have been made in the field of restorative dentistry. This article reviews the various biomimetic materials and its biological properties in the field of restorative dentistry and endodontics. Biomimetic materials, with their biocompatible nature and excellent physico-chemical properties are widely used nowadays. They can function as long lasting esthetic and restorative materials, cements, root repair materials, root canal sealers and filling materials, which have the advantages of enhanced biocompatibility, high strength, sealing ability and antibacterial properties. New biomimetic materials have demonstrated the ability to overcome some of the significant limitations of earlier generation materials. Although in vitro studies, the uses of biomimetic materials in restorative dentistry endodontic have given encouraging results, randomized and double-blind clinical studies of sufficient length with these materials are needed to confirm long-term success following their use.

INTRODUCTION

MTA due to its excellent physico-chemical and biological properties has been considered as gold standard since its introduction in dentistry. The application of biomimetic technology has demonstrated promising results in the field of dentistry ^[1]. These materials have gained increased acceptance due to their biological and physico-chemical properties, potential biocompatibility with the living tissues, acting synergistically with body tissues, thus depicting their repair role in eliminating body defects like bone loss etc.

This review article will have the prime focus in updating the previous literature by presenting a comprehensive list of literature from 1970's to till 2016, summarizing their properties, role and estimating future perspectives in dentistry.

Biomimetics, term was coined by Otto Schmitt in the 1950s ^[2]. Biomimetic is defined as the study of the structure and function of biological systems as models for the design and engineering of materials and machines ^[3].

BENEFITS OF BIOMIMETIC DENTISTRY

Biomimetically restored tooth flexes in a similar manner as natural dentin. Such restorations are more cost-effective, aesthetic and long lasting with minimum to non-existent post-operative sensitivity than traditional restorations ^[3].

SCOPE

Biomimesis copies the principle of synthesizing materials under ambient conditions which reproduces mechanism found in nature and thus addresses more than one issue ^[3].

BIOMIMETIC MATERIALS

Glass Ionomer Cement (GIC)

Glass ionomer cement (GIC) which was invented in 1969 is composed of fluoroaluminosilicate glass powder and water soluble polymer (acids). When powder and liquid is blended, it undergoes hardening reaction that involves neutralization of the acidic group together with significant release of fluorides ^[4].

Bioactive formulation (such as 45S5, S53P4) has bioactive glass and hydroxyapatite. The mechanical properties of GIC have been improved with incorporation of metals such as stainless steel and bio inert ceramics like zirconia [5].

KT-308 (GC Corporation Company, Tokyo, Japan) a GIC sealers, provides more resistance to coronal ingress of bacteria into the root canal system better zinc oxide-eugenol-based sealer [6].

ZUT (University of Toronto, Ontario, Canada) a combination of GIC and an antimicrobial silver-containing zeolite is effective against E fecalis and hence can be more effective in treating teeth of persistent apical periodontitis [7].

Active Gutta-Percha (GP) (Brasseler USA, Savannah, GA, USA) has GI impregnated Gutta-Percha (GP) cones that are bondable to GIC based sealer and claims to offer adhesive bonding of the active GP to intraradicular dentine [8,9].

Resin Based Composite

Introduced by Bowen in 1962, offers wear resistance, color stability, improved physical properties and radiopacity (Table 1) [10].

Table 1. Developments in Nanocomposites.

Modifications	Materials used
Reinforced Fillers	<ul style="list-style-type: none"> Electro spun nylon Nano fibers containing highly aligned silicate single crystals Nano fibers and e-glass fibers with baal SiO₂ in semi-interpenetrating polymer network (IPN) matrix TiO₂ Nano composites modified with Allytriethoxysilane (ATES)
Caries prevention fillers	<ul style="list-style-type: none"> Nano-DCPA whiskers TTCP-whiskers Caf2 nanoparticles with reinforcing whisker fillers Polymer-kaolinite Nano composite
Resins	<ul style="list-style-type: none"> Epoxy-polyol matrix Epoxy functionalized cyclic siloxane Bioactive poly i.e. methyl methacrylate/SiO₂-CaO Nano composite Epoxy resin ERL-4221 (3,4-Epoxy cyclohexylmethyl-(3,4-epoxy) cyclohexane carboxylate) Silsesquioxane (SSQ)
Nanoparticles surface modification with different silanes	<ul style="list-style-type: none"> 3-methacryloxypropyltrimethoxysilane (MPTS) n-octyltrimethoxysilane (OTMS) Dual salinization with MPTS and OTMS Equal masses of MPTS and MPTS γ glycidoxypropyl trimethoxysilane (GPS) Allytriethoxysilane (ATES)

Smart Dentin Replacement (SDR)

SDR is a first flowable composite material, characterized by low polymerization stress, low polymerization shrinkage, high depth of cure and bulk-fill material in increments of up to 4mm in class i and ii cavities [11-13].

Ceramic

Ceramics are being examined for bone tissue engineering and also have dental applications. Hydroxyapatite (HA), a major inorganic component of bone is a calcium phosphate based ceramic.²

In Novel ceramic bone replacement material Ceraball, new bone formation first takes place on the scaffold surface. Ceraballs may act as a carrier for pluripotent mesenchymal stem cells, stromal cells and bone marrow [14].

Calcium Hydroxide

In 1928, Calcium Hydroxide was introduced by Hermann in dentistry. Calcium hydroxide has been widely used as a mineralizing agent and antimicrobial agent. Depending on whether existing odontoblasts perish or survive the insult, two types of dentin can be laid down. Reactionary dentinogenesis where tertiary dentine matrix is secreted by focally up regulated pre-existing odontoblasts, and Reparative dentinogenesis, where secretion of tertiary dentine matrix is by an outright new generation of secreting cells after the death of primary odontoblasts [15].

Calcium hydroxide causes release of extracellular matrix molecules (like dentine phosphoproteins, dentine sialoproteins), raises expression of biomolecules (like BMP, FGP etc.), has antimicrobial and anti-inflammatory action [15].

Formation of tunnel defects and decrease in dentine strength following its long term use as intracanal medicament are its limitations [15,16].

To improve its biological performance, Controlled-release Calcium hydroxide loaded microcapsules based on polylactic acid (PLA) and ethyl cellulose (EC) have been developed. These formulations prolonged ion release [17].

Calcium Sulfate

Calcium sulfate (CS) has been shown to be completely bio absorbable, osteoconductive, allow fibroblast migration, do not cause an inflammatory response and also do not elevate serum calcium levels. Recently, it has been shown that CS can be manufactured into a granular composite of CS and poly-L-lactic acid to decrease the degradation rate [18].

Calcium Phosphate

Calcium phosphates plays important role in biological and pathological mineralization. Most commonly used in the form of paste, cement, ceramics and scaffold. The following are calcium phosphate materials (**Table 2**) [19].

Table 2. Calcium phosphate materials.

Calcium phosphate materials	Examples
Calcium phosphate ceramics	Calcium hydroxyapatite [calcitek (calcitek, Inc.)] Beta-tricalcium phosphate [synthograp, augment (miter, Inc.)] Biphasic calcium phosphates [triosit (Zimmer)]
Calcium phosphate materials from natural products	Coralline ha [interpore 200 (interpore)] Bio-oss (from sintered bovine bone)
Glass ceramics	Bio glass (American biomaterials corporation)

Calcium Enriched Mixture (CEM)

It contains calcium oxide, sulfur trioxide, phosphorous pentoxide, and silicon dioxide. It might promote differentiation of stem cells and cementogenesis [20].

Bio ceramic based material/tricalcium silicate (calcium silicate based materials)

Mineral Trioxide Aggregate (MTA)

MTA which was developed by Mahmood Torabinejad at Loma Linda University, consists of 50-75 % (wt.) calcium oxide and 15-25 % silicon dioxide. It has high pH (12.5), causes regeneration of the periodontal ligament (PDL), dentinal bridge formation, biomineralisation and stimulation of cell differentiation and has antimicrobial activity. However, difficulty in manipulation and longer setting time are its limitations [1].

i). MTA angelus (Aangelus, Londrina, PR, Brazil) is composed of 80% Portland cement and 20% bismuth oxide and has setting time of 14 minutes [21,22].

ii). MTA fillapex (angelus solutions odontological, Londrina, PR, Brazil) is a calcium silicate-based bio ceramic sealer, created with an attempt to incorporate physical and chemical properties of a resin-based root canal sealer and the biological properties of MTA [23,24].

iii). MTA plus (Avalon biomed Inc., Bradenton, FL, USA) is a fine powder root canal sealer with composition similar to ProRoot MTA [25].

iv). Pozzolan cement (Endocem) (Maruchi, Wonju, Korea) is a fast setting MTA derived material which does not contain any chemical accelerator [26].

Calcium Aluminate Cement (Binderware, São Carlos, SP, Brazil), was developed by the Federal University of São Carlos. It is composed of oxides of aluminium (Al_2O_3), calcium, (CaO), silicon (SiO_2), magnesium(MgO) and iron (Fe_2O_3) [27,28]. It also allows the control of impurities such as Fe_2O_3 (which promotes tooth darkening) and is free of MgO and CaO which restricts the undesirable expansion of the material upon moisture contact [29,30].

Biodentine™ (Septodont, Saint-Maur-des-Fossés, France), introduced in 2011 is composed of calcium carbonate, tricalcium silicate and zirconium oxide and a water based liquid containing calcium chloride as the setting accelerator [20,31]. When biodentine comes in contact with dentine it results into formation of the tag-like structures next to an interfacial layer and is called “Mineral Infiltration Zone,” which may contribute to adhesive properties [32]. It has improved physical properties, reduced setting time (12 min) and induces odontoblast-like cell differentiation and mineralization [20].

Bioaggregate (BA) (Innovative Bioceramix Inc., Vancouver, BC, Canada) introduced in 2006, is delivered as powder form of nanoparticles containing tricalcium silicate, dicalcium silicate, calcium phosphate monobasic, amorphous silicon dioxide, tantalum pentoxide (radio pacifier) while it's liquid form contains deionized water. It is aluminum free formulation, thus it stimulates proliferation of human PDL fibroblasts and aids in periodontal regeneration [31-35].

Endosequence Root Repair Material (ERRM) putty, ERRM paste RRM putty fast set (FS) and iroot FS

Endosequence root repair material (ERRM) (Brasseler USA, Savannah, GA) delivered as a premixed mouldable putty (iRoot BP Plus) or as a preloaded paste in a syringe with delivery tips for intracanal placement. It contains calcium phosphate monobasic, calcium silicates, zirconium oxide and tantalum oxide [20,36,37]. Inside dentinal tubules, ERRM forms tag-like structures [20]. The RRM allows gingival fibroblasts to grow on their surface [38,39]. RRM is premixed, single component material which is ready to use from the syringe or a tiny screw-cap box and does not require mixing, thus differentiating it from MTA, bioaggregate and biodentin [31]. RRM putty fast set (FS) has the initial setting time of 20 min [31].

iRoot FS (Brasseler USA, Savannah, GA) is iRoot series material with improved handling properties and shorter setting time [20].

Bioceramic Sealers

Endosequence BC sealer (Brasseler USA, Savannah, GA) or iRoot SP root canal sealer (Innovative Bioceramics Inc., Vancouver, BC, Canada) is premixed bioceramic endodontic sealer containing tricalcium silicate, zirconium oxide, dicalcium silicate, calcium phosphate monobasic, colloidal silica, calcium silicates and calcium hydroxide [40]. The iRoot SP possesses high pH, hydrophilicity, and active calcium hydroxide release [41].

Bioceramic Gutta-Percha

These are Gutta-Percha cones impregnated and coated with bioceramic nanoparticles and are verified with laser for tip and taper accuracy. Such cones with BC sealers allow “three-dimensional” bonded obturation [20].

Bioactive Glass (BAG)

Calcium sodium phosphosilicate is used in cariology, restorative dentistry and periodontology, air polishing procedures, desensitizing toothpastes, and as a bonding and bone regeneration material [42,44]. Mohn et al mixed BAG particles with 50% bismuth oxide and used it as root canal filling material. BAG has directly and indirectly pH related antibacterial effect [45].

Remineralizing Agents

Casein phosphopeptide amorphous calcium phosphate (CPP-ACP): Subsurface carious lesion can be remineralized through diffusion of calcium and phosphate ions into tooth structure. Casein is the predominant phosphoprotein in bovine milk and has organoleptic properties. CPP stabilizes calcium and phosphate in solution state and thus acts as calcium and phosphate reservoir [46].

The incorporation of the CPP-ACP nanoparticles into the cross-linked matrix of the GIC aids to increase compressive strength, microtensile bond strength and enhances release of calcium, phosphate and fluoride ions [47]. Tooth Mousse™ (Europe and Australasia) or MI Paste™ (USA and Japan) contains 10% w/w CPP-ACP nanocomplexes [46].

Deminerallized dentin (dDM): The dentin matrix which are used for implant biomaterial has osteogenic and chemotactic potential. Demineralized bone matrix when comes in contact with mesenchymal cells it induces chondrogenesis and osteogenesis [48]. Incorporation of *Galla chinensis* extract into dentin matrix may improve biochemical and biomechanical properties [49].

Enamel matrix derivative (EMD): Enamel matrix derivative is derived from pig enamel matrix (Emdogain; Straumann AG, Basel, Switzerland) has been employed in patients with severe attachment loss through recruitment of cementoblasts on to the root-surface to restore functional periodontal ligament, cementum and Alveolar bone [50].

Growth Factors

Growth factors are considered as engines that drive wound healing. Platelet derived growth factor (PDGF) plays key role in chemotaxis of neutrophils that acts with other growth factors to produce collagen. Keratinocyte growth factor (KGF) through keratinocyte differentiation, plays vital role in wound re-epithelialization. Transforming growth factor (TGF) induces extracellular matrix deposition and collagen formation. Fibroblast growth factor (FGF) plays role in fibroblast proliferation, angiogenesis, and matrix deposition. Vascular endothelial growth factor (VEGF) increases vascular permeability at the capillary level. Epidermal growth factors (EGF) acts in an autocrine fashion [51]. Kevivance (KGF-2) is used in preventing oral mucositis. Juvista, a recombinant TGF-β3 may be used as a growth factor enhancer for all surgically created wounds [51].

Bone Morphogenic Proteins (BMP)

BMP plays a key role in dental bone grafting and implant placement, fracture healing and spinal fusion. It increases alkaline phosphatase activity, stimulates proteoglycan synthesis in chondroblasts, collagen synthesis in osteoblasts, differentiation of neural cells and chemo taxis of monocytes. In patients with known risk factors, BMP-2 and BMP-7 are superior to autologous bone grafting [52].

Platelet Concentrates

It was first described by Whitman et al ^[53]. Platelet rich plasma (PRP) is generated by differential centrifugation and serves as reservoir of critical growth factors such as platelet-derived growth factor (PDGF), transforming growth factor-b (TGF-B) and insulin-like growth factor-1 (IGF-1) and thus regulates wound-healing. PRP requires biochemical blood handling with addition of anticoagulants while platelet rich fibrin (PRF) does not ^[54]. A second generation platelet concentrate, Leucocyte and platelet rich fibrin (L-PRF) was developed by Choukroun et al in France does not contain any anticoagulant or gelifying agents ^[55,56].

Polyhedral Oligomeric Silsesquioxanes (POSS)

Biomaterials such as polyhedral oligomeric silsesquioxanes (POSS) and polyhedral oligomeric silicates (POS) may be fabricated by the incorporation of POSS molecules to provide a nanoscopic topology which favors cellular modulation, bioavailability and differentiation. Advent of POSS has led to formulation of dental adhesives and composites with improved mechanical and physical properties ^[57].

Metallic Biomaterials

Metallic biomaterials are mainly used for fabrication of medical devices for hard tissue replacement such as artificial hip joints, bone plates and dental implants ^[58].

Stainless steel (**SUS 316L SS** an austenitic stainless steel), cobalt alloys, pure Ti and Ti-6Al-4V are mainly used for biomedical applications ^[59].

Implant Biomaterials/Biomimetic Coatings on Implants

It includes metals and metallic alloys, ceramics, natural materials and synthetic polymers.

Metals and metallic alloys include titanium, tantalum and alloy of Ti-Al-Va, Co-Cr-Mb, Fe-Cr-Ni. Devices made from zirconium, hafnium and tungsten have been evaluated recently.⁶⁰ Hydroxyapatite-coated metal's coating is done using robotic techniques ^[60]. Hydroxyapatite-tricalcium phosphate bioceramics must not be confused with tricalcium phosphate (TCP) as it is chemically similar to Hydroxyapatite but it is not a natural bone material. Arg-Gly-Asp tripeptide, protein kinase a bone morphogenic protein-2 (BMP2) and phospholipase A2 are some bioactive agents ^[60]. Carbon and carbon silicon compounds are usually classified as ceramics because of their chemical inertness and absence of ductility ^[60].

Ceramics

Ceramics are nonorganic, nonmetallic, non-polymeric materials manufactured by compacting and sintering at elevated temperatures. On the basis of tissue's response it can be classified as bioactive (bioglass/glass ceramic), bioresorbable (calcium phosphate) and bio inert (alumina, zirconia and carbon). The implant coating is intended for improving implant surface biocompatibility profiles and longevity ^[61].

Polymers

Polymers like polymethylmethacrylate (PMMA), polyethylene (PE), polyurethanes are used in dental surgery since decades. Polyglycolic acid (PGA), polylactide (PLA), polydioxanone (PDS) are mainly used as resorbable bone fixation devices or as suture materials ^[59]. For surgical wound repair fibrin glue is used as tissue adhesive ^[62]. Alginate can be used as growth factor delivery system ^[63].

Regenerative endodontics and tissue engineering

Dental regeneration is a process in humans by which specialized dental tissues are replaced by the recruitment, proliferation, migration, and differentiation of dental stem cells. Stem cells, scaffolds, and growth factors are 3 key elements for tissue regeneration ^[64].

Root Canal Revascularization via Blood Clot

In the Root canal revascularization via blood clot in apical region, the bioceramic material is placed as mid-root/coronal plug, thereby providing permanent and superior quality seal. Jung et al. reported that by activation of MAPK pathway biodentine, bioaggregate and MTA causes odontoblastic differentiation and mineralization ^[64].

Postnatal stem cell therapy, pulp implantation, scaffold implantation, injectable scaffold delivery, 3-D cell printing and gene therapy are some regenerative approaches ^[64].

Smart Materials

It is defined as the class of materials that are highly responsive and have the inherent capability to sense and react according to changes in the environment. They can be classified as active and passive smart materials. Passive smart materials responds to external change without any external control, while active smart materials utilizes a feedback loop to enable them to function like a cognitive response through an actuator circuit ^[65].

A) Smart pressure bandages - Upon exposure to blood, these bandages contracts thereby putting pressure on a wound.

B) Smart suture - It ties itself into the Perfect knot and possesses shape memory.

C) Hydrogel - It exhibit plastic contraction upon changes in temperature, pH, magnetic or electrical field.

D) Smart composites containing amorphous calcium phosphate (ACP)-

Inclusion of ACP into composite resin results into release of calcium and phosphorous for an extended period and are thus helpful in caries prevention.

E) Cercon - smart ceramics - It is a metal-free biocompatible life like restoration that has strength to resist crack formation. The drawbacks of porcelain fused to metal like unsightly dark margins and artificial grey shadows from the underlying metal are no longer a problem with Cercon.

Smart fibers for laser dentistry - Hollow-core photonic-crystal fibers (PCFS) are used for the delivery of high-fluency of laser radiation and are capable of ablating tooth enamel. The PCF is used to transmit emission from plasmas on to the tooth surface for detection and optical diagnostics ^[65].

Suture Materials

A suture is a strand or thread of material used to approximate tissues and also to ligate blood vessels. It helps the wound to withstand normal functional stresses and to resist wound reopening. They can be classified as absorbable (vicryl) and non-absorbable suture materials. The absorbable materials are often polymers or copolymers of lactic acid with glycolic acid (vicryl also called as polyglactin 910). Absorbable material can be broken down by natural metabolic processes while the Non absorbable material has to be removed later. Catgut an absorbable material of animal origin has not been used nowadays because of safety reason ^[66].

CONCLUSION

It is the designing of biomaterials that simulates physical and mechanical properties of the lost tissue, thus providing an opportunity to introduce and change treatment modalities for the disease. Biomimetic dentistry is an interdisciplinary approach and has potential for transforming everyday dental practice. It brings the power of modern biological, chemical, and physical science to solve real clinical problems.

Biomimetic materials functions as root canal sealer, filling materials, cements and root and crown repair material and possesses features as like strengthening the root following obturation, good sealing ability, enhanced biocompatibility and antibacterial properties. Contemporary biomaterials have shown ability to overcome the limitations of traditional materials. However, there exists limitations when considering criteria for categorizing them as ideal materials. Several invitro and invivo studies have demonstrated good results, however randomized and double blind studies of sufficient duration with biomimetic materials have been needed to confirm long term success.

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