Paradigm Shift in Biomaterials in Dentistry- From inert to active: A review

Abstract:

Biomaterials engineered to interact with biological system for either therapeutic (treat, augment, repair or replace a tissue function of the body) or a diagnostic purpose have underwent biological evolution over a period of time. This can be attributed to advent of new innovative technology combined with human curiosity for search of new materials that mimic biological tissues in terms of physical and chemical properties for orchestration of wound healing and tissue regeneration. The present review focus on the advancements biomaterials have undergone so far and new era of biomimetic dentistry.

Key-words: Biomimetics, Tissue Engineering, Biocompatible materials, Nature, Tissue scaffolds, Therapeutics, Osseointegration, Tissues, Biological Evolution,Therapeutics

Introduction:

Nature has long been a wonderful resource for creating extremely complex yet elegant and functional structures and life forms across a multitude of length scales. Evolution over billion of years have produced natural materials that are extremely efficient and are increasingly becoming source of inspiration for dental material scientists and tissue engineers leading to development of new era of biomaterials in dentistry.[1]

The most accepted definition of biomaterials is currently the one employed by the American National Institute of Health that describes biomaterial as "Any substance or combination of substances, other than drugs, synthetic or natural in origin, which can be used for any period of time, which augments or replaces partially or totally any tissue, organ or function of the body, in order to maintain or improve the quality of life of the individual"[2].

Biomaterials due to associated novel properties make them appropriate to be used while in immediate contact with the living tissue without eliciting any adverse immune rejection reactions[2].

In addition to natural sources biomaterials can be prepared in the laboratory using a variety of chemical approaches utilizing polymers, ceramics, composite materials or metallic components. Biomaterialsthat perform, augment or replace natural function by comprising whole or part of living structure are often used for medical applications[3].

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Based on interaction with environment dental biomaterials can be classified as bioinert, bioactive or biomimetic and are used in restorative procedures such as dental restorations, dental implants and surgical procedures, endodontic materials, in devices such as orthodontic materials etc.[2]

Dental biomaterials have evolved over years [2].Traditionally materials used in dentistry were bioinert such as metals (stainless steel and Co-Cr based alloys), Ceramics (Alumina, Zirconia)which were designed to be passive,inert and biocompatible and simply replace a damaged tissue and provide mechanical support, with minimal biological response of the patient and exhibiting little or no interaction with body tissues & fluids.[4]

But with advent of innovative new technologies[4] and better understanding of biomaterial tissue interaction at nano and microscale led to introduction of novel bioactive/biomimetic materials with enhanced properties in terms of color, morphology, strength to mimic natural teeth[5] and at same time exhibiting interaction with biological tissues.[1]6]

Bioactive material like Bioactive glasses and hydroxyapatite elicits a response from living tissue, organisms or cell by inducing the formation of hydroxyapatite6 owing to their osteoinductive ,osteoconductive[7] and biomineralising properties[8]. On the other side Biomimetic Material[9] which attempt to design system and synthesize materials through biomimicry are based on concept of taking ideas from nature and implementing them in other technology such as engineering design, computing etc owing to their biocompatible nature & excellent physico – chemical properties[10]. Both Bioactive and Biomimetic materials are considered as boon to dentistry and are widely used nowadays.[6]

Use of biomimetic therapeutic approaches improvise and also help dental professionals to work closer with natural biological structures and function. Term Biomimetic is applied for two important perspectives: a purist perspective which focuses on recreating biological tissues and a descriptive perspective which focuses on using materials that result in a mimicked biological effect. Although different, both share a common goal of mimicking biology in restoration.[10]

In field of dentistry, research for newer material that could mimic natural teeth in appearance, function, and strength[11] is never ending as with every discovery we are coming one step closer to therapeutic biomimetic approach which further endows human curiosity.**[**10] Adhesion, integration, and sealing of dentin using bioactive and biomimetic technologies are currently new area of focus.[6]

Overall advent of new biomaterials has led to a paradigm shift from conventional bioinert based dentistry to contemporary bioactive/biomimetic dentistry[4]. The present review describes the evolution of various materials over theperiod of time with primary focus on the materials intended to be used in the restorative dentistry and endodontics.

Evolution of Biomaterials:

Generation of Biomaterials

1950 1960 1970 1980 1990 2000 2010 2020 2030

1st Generation Biomaterials	*2nd Generation Biomaterials*	*3rd Generation Biomaterials*	*4th Generation Biomaterials*
Bio-inert biomaterials	**Bioactive or bioresorbable biomaterials**	**Bioactive and bioresorbable biomaterials**	**Biomimetic biomaterials**
Metals and Alloys (Stainless steel, titanium alloys, etc)	Bioceramics and Polymers (HA, BG, PCL, PLGA, PLA, Collagen, etc)	Nano/Composites and O/I hybrids (HA/PLA, BG/PLGA, etc)	Tissue-engineered scaffolds (nanoHA/collagen/cellular/biological molecules, etc)

First generation: Traditionally materials used in dentistry to replace missing part of oral tissues were designed to be passive , inert and biocompatible[12]and selection of these was mainly based on there mechanical properties. This generation included bioinert materials.

Bioinert Material: Any material that once placed in the human body has minimal interaction with its surrounding tissue. These materials evolved between *1960 – 1970* were later categorized as the 1st generation of biomaterials.[13]

METALS-Metals owing to there **inertness**(minimal /no interaction with surrounding tissues),biocompatibility(do not elicit adverse reaction when placed), high corrosion resistance, osseointegration, appropriate mechanical properties,great strength, excellent thermal and electrical conductivity[13]

Main advantage of metal is cost benefit ratio with versatile properties. Mechanical properties that help to decide type of metallic material to be used are hardness, tensile strength, Young's Modulus and elongation[2]

Ni-Ti Rotary Protaper Files:

Cobalt-based alloys are one of the only alloys with its good corrosion resistance and good mechanical strength in chloride environments, which is due to alloying additions and the formation of the chromium oxide Cobalt-based alloys are one of the only alloys with its good corrosion resistance and good mechanical strength in chloride environments, which is due to alloying additions and the formation of the chromium oxid

The most important applications of metallic biomaterials in dentistry include:

- Endodontic instruments(files and reamers)
- Direct restorations (amalgam and gold fillings)
- Indirect restorations (inlay and onlay)
- Post and core
- Crown (all metal and porcelain fused to metal (PFM)[14]

Ceramics- Bioinert ceramics maintain there physical and mechanical properties while in host**.** Ceramics are refractory, polycrystalline compounds usually inorganic, non-metallic materials[15] made by heating raw minerals at high temperature . There relative inertness to body fluids, high compressive strength and esthetically pleasing appearance led to use of ceramics in dentistry as dental crown[2]. Eg: Aluminia, Zirconia.[15] They are attractive because of biocompatibility,wear resistance, long term color stability, and ability to be formed in precise shapes,bond micromechanically to tooth structure.[2]

Applications in Dentistry:

Fabrication of endo posts,inlay , onlay and single crown.[15]

Second generation:

Advances in knowledge combined with the research on biological mechanisms and understanding of biological interactions with biomaterial surfaces switched gears from "passive" materials to bioactive materials (eg: ceramics to bioceramics , metals to bioactive metals)that could actively interact and integrate with the biological environment and led to the development of second generation biomedical materials which were bioactive.[13]

These materials evolved between 1970-1990[13]

Bioactive materials: Bioactive refers to a material, which when placed within the human body release ions thereby interacting withthe surrounding tissues to elicit a specific biological response ultimately resulting in formation of apatite like bond at interface of material and tissue.[13]

They can be either osteoinductive(induce osteogenesis by stimulating nearby stem cells)eg: Bioglass or can be be osteoconductive where it simply act as scaffold over which bone is formed eg: Synthetic hydroxyapatite (HA)[16] or both (osteoinductive and osteoconductive) eg:MTA,Biodentin[7]

Bioceramics :

Concept introduced in 1969[15]. CaP bioceramics are known for bioactivity and commonly used for fabricating synthetic bone grafts . Among these are amorphous CaP (ACP), β-tricalcium phosphate (TCP), calcium-deficient hydroxyapatite, dicalcium phosphate dihydrate hydroxyapatite (HA, $Ca_{10}(PO_4)_6(OH)_2$), dicalcium phosphate anhydrous hydroxyapatite, monocalcium phosphate monohydrate, monocalcium phosphate anhydrous, tricalcium phosphate (TCP, $Ca_3(PO4)_2$) and octacalcium phosphate . These bioceramics have been widely used in the regeneration of hard tissues[5]and coating metal prosthesis[15] due to their distinctive features such as biocompatibility, good bioactivity, osteoinductivity, and osteoconductivity. Recently, a bone defect due to ameloblastoma has been filled successfully with a nanocrystalline, ceramic HA enriched with magnesium .[5]

Applications- Bioactive Sealers (Endosequence BC Sealer, iRoot SP),Bioactive Luting Agents(Ceramir), Tissue scaffolds for bone tissue engineering, control hypersensitivity by blocking tubules , repair of tooth roots.[17]

Calcium phosphate Cements:

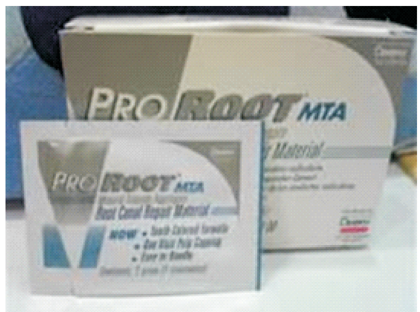
Concept first introduced in 1982.[18-19] Hydroxyapatite most documented calcium phosphate materials are similar to bone in composition and in having bioactive and osteoconductive properties. It has properties such as good biocompatibility, superior compressive strength, and undergoes transformation into hydroxyapatite and calcium hydroxide [9]over time. It induces bridge formation with no superficial tissue necrosis and significant absence of pulpal inflammation[2]. Applications in dentistry include Pulp capping,Apexification,root canal sealer, furcation perforation repair.[18-19]

Calcium Silicates :

Bioactive material mainly comprised of calcium and silicates. Hydration of powder results in calcium silicate hydrogel and calcium hydroxide [17] which accounts for its bioactivity. Example include: MTA and Biodentin. Compared to traditional calcium hydroxide beside being bioactive and antimicrobial these materials possess additional osteoinductive and osteoconductive property which induce hard tissue formation.[15] along with superior compressive strength[19]

Though the concept of bioactive materials dates back to late20th century these materials were introduced commercially in market in early 21th century where they have again evolved to compensate associated drawbacks and gradually replaced the usage of metallic restorations.Some of these have been discussed below:

MTA- MTA was introduced in 1993by Torabinejad and Parirokh and later marketed as Pro root MTA by 2002 to overcome disadvantages associated with $Ca(OH)_2$ by reducing multiple appointments of $Ca(OH)_2$ with single visit appointment,[20] by uniform and thicker dentin bridge formation(free of tunnel defects) leading to superior marginal adaptation.[21] Besides this faster healing time, low cytotoxicity, minimal or no leakage are some other advantages . This is a material of choice for vital pulp therapy, apexification, apexogenesis,[22] repair of accidental perforations[2], root canal sealer [23] as well as for root-end filling material in apicoectomy procedures.[22]



Modified MTA and MTA like materials overcoming drawbacks of original MTA were marketed after 2006 to overcome drawbacks associated with MTA of prolonged setting time, handling properties and tooth discoloration . They were primarily aimed to shorten setting time by modifying composition or particle size of powder[24-25] and were aluminium free so as to avoid tooth discoloration associated with MTA[20]

Biodentin:

Introduced by Gilles and Olivier in (Septodont, Saint Maur des Fosses, France).Biodentin with similar efficacy to MTA but with relatively shorter period of setting time (6.5-45 min) compared to 4h of MTA was introduced. Other advantages associated with Biodentin include superior compressive strength that is equivalent to dentin and superior marginal adaptation. Biodentine has been advocated to be used in various clinical applications, such as root perforations, apexification, resorptions, retrograde fillings, pulp capping procedures, and dentine replacement[26].

Endo Sequence Root Repair Material:

Introduced in 2009 by Brassler USA.The particle size was 0.35 micrometer compared to 1-30 micrometer of MTA which overall improvised the handling characterstics of these materials. They are available as premixed products to provide clinician with homogenous consistent materials. Alanezi et alcompared ERRM with MTA (gray and white) using fibroblast cell culture from mice and evaluated cytotoxicity of these materials .The results of their study showed that ERRM had similar cytotoxicity[2]. It is hydrophilic , radiopaque with easy handeling properties[27] has been recommended for perforation repair, apical surgery, and pulp capping[2]

Third generation biomaterials :

- These biomaterials evolved between 1990-2010 . This time period marked introduction new biomaterials that combined properties of both bioactive and bioresorbable materials and were able to activate genes that stimulate regeneration of living tissues[13]

Biodegradable and Bioresorbable ,materials:

They were introduced so as to overcome major stumbling block in development of tissue engineering scaffolds. Since natural bone matrix is a composite of biological ceramic (hydroxyapatite) and polymer (collagen)it is not surprising that several synthetic and natural biomaterials based on natural/synthetic polymers, bioceramics and their composites, and hybrids have been used to prepare scaffolds for bone tissue engineering application.

Scaffold material should have sufficient mechanical strength to resist fractional and contractile forces by cells ,act as shield to intrusion of competiong cells and at same time being biodegradable to allow excretion of degradation by products and initial foreign material.

Typically, mechanically strong materials are bioinert , while bioactive and biodegradable materials tend to be mechanically weak. Most materials are not mechanically competent, bioactive and biodegradable all at the same time. To overcome this materials like nanocomposites and organic/Inorganic hybrid biomaterials which are based on combination of nanosized hydroxyapatite and bioactive glass fillers biodegradable polymers and bioactive inorganic material were introduced. Their nanosize accounts for increased bioactivity and superior mechanical properties compared to others. Due to their bioactivity, biodegradability and mechanical properties, bioactive and biodegradable scaffolds are becoming focus of recent trends in biomaterial development for bone regeneration.[28]

Fourth generation biomaterials :

This time period between 2010-2020 marked advent of biomimetic mateials.Ituses Tissue Engineering approaches relying on synthetic scaffolds that are generally resorbable.[13]

In dentistry since there is no one biomaterial that has the same, mechanical, physical and optical properties as tooth structure (i.e., dentin, enamel, and cementum) and possesses the physiological characteristics of intact teeth in function. To overcome this,[9] biomimetic mateials which uses natural system of synthesizing materials through biomimicry so as to return the tooth to its function, esthetics, and strength came into existence.[10]

Though there are two major perspectives to which the term "biomimetic" is applied: a purist perspective that focuses on recreating biological tissues and a descriptive perspective that focuses on using materials that result in a mimicked biological effect[10] but the prime area of focus of biomimetic field is tissue engineering.[29]

Biomimetic material in restorative Dentistry:

Natural teeth, through the superlative combination of enamel and dentin, make up the perfect and unmatched compromise between strength, rigidity and resilience (Magne and Belser, 2002). The goal of Biomimetics in restorative dentistry is to return all of the prepared dental tissues to full function by the creation of a hard tissue bond that allows functional stresses to pass through the tooth, making the entire crown into the final functional biologic and esthetic unit. The intact tooth in its ideal hues and shades, and more importantly in its intracoronal anatomy, location and mechanics in the arch, is the guide to reconstruction that determines success" (Magne, 2006). [30]

Table.1.Shows the similarity of these artificial materials to natural tooth substance: Physical Properties of Dental Hard Tissues and corresponding Biomaterials (Magne, 2006)

	Elastic Modulus (GPa)	Thermal Expansion Coefficient (x 10 -6/^{0}C)	Ultimate Tensile Strength (MPa)		Corresponding Material	Elastic Modulus (GPa)	Thermal expansion Coefficient (x10 -6/^{0}C)	Ultimate Tensile Strength (MPa)
Enamel	82	17	10	→	Feldspathic ceramics	60-70	13-16	25-40
Dentin	14	11	40-105	→	Hybrid Composites	10-20	20-40	40-60
				→	Glass-ionomer Cements	4-10	35	4-5

Composites ,GIC and Ceramics are biomimetic restorative materials since they mimic natural tissues eg:GIC[9] and composite are closest to mimic dentin and ceramics to enamel.[30]

Smart Composites:

Skrtic has developed unique biologically active restorative materials containing ACP as filler encapsulated in a polymer binder, which may stimulate the repair of tooth structure because of releasing significant amounts of calcium and phosphate ions in a sustained manner. In addition to excellent biocompatibility, the ACP containing composites release calcium and phosphate ions into saliva milieus, especially in the oral environment caused by bacterial plaque or acidic foods. Then these ions can be deposited into tooth structures as apatitic mineral, which is similar to the hydroxyapatite (HAP) found naturally in teeth and bone . ACP at neutral or high pH remains as ACP. When low pH values (at or below 5.8) occur during a carious attack, ACP converts into HAP and precipitates, thus replacing the HAP lost to the acid. So, when the pH level in the mouth drops below 5.8, these ions merge within seconds to form a gel. In less than 2 minutes, the gel becomes amorphous crystals, resulting in calcium and phosphate ions . This response of ACP containing composites to pH can be described as smart.[12]

GIC -Glass Ionomer Cement (GIC) Based:

Glass ionomer cement (GIC) 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

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 . [31]

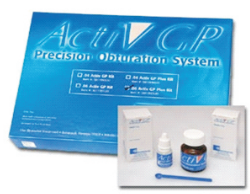
KT-308 (GC Corporation Company, Tokyo, Japan) :

It is a GIC sealers, provides more resistance to coronal ingress of bacteria into the root canal system better than zinc oxide-eugenol-based sealer [31].

Active Gutta-Percha (GP) (Brasseler USA, Savannah, GA, USA):

It has GIC 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 [31].

Activ GP patı (Brasseler, Savannah, GA, USA)



Biomimetic Approaches For Regeneration:

Stem Cell Therapy-The simplest method to administer cells of appropriate regenerative potential is to inject the postnatal stem cells into the disinfected root canal system. Among the eight different post natal dental stem cells Stem cells from human exfoliated deciduous teeth (SHED), Dental pulp stem cells (DPSCs) and Stem cells from the apical papilla (SCAP) were more commonly used in the field of regenerative endodontics [9] (Garcia and Murray, 2006).[12] It is hypothesized that DPSCs are likely the source of replacement odontoblast cells, whereas SCAP appear to be the source of primary odontoblast cells that are responsible for the formation of root dentin (Bakopoulou, 2011). These cells are able to survive even during the process of pulp necrosis, as these cells are present in apical papilla which has collateral circulation.[12]

Injectable scaffold delivery:

This procedure will allow tissue engineered pulp tissue to be administered in a soft three-dimensional scaffold matrix. Among the injectable biomaterials investigated so far, hydrogels are more attractive in the field of tissue engineering. Hydrogels are injectable scaffolds that can be delivered by syringe and are noninvasive and easy to deliver into root canal systems. In theory it is stated the hydrogel may promote pulp regeneration by providing a substrate for cell proliferation and differentiation into an organized tissue structure.[32] Earlier hydrogels had limited control over tissue formation and development, but recent advances in formulation have dramatically improved their ability to support cell survival (Desgrandchamps, 2000).[12]

Gene Therapy: Gene therapy is a method of delivering genes with the help of viral or non-viral vectors. The gene delivery in endodontics would be to deliver mineralizing genes into pulp tissue to promote tissue mineralization. Viral vectors are genetically altered to eliminate ability of causing disease, without losing infectious capacity to the cell. At present adenoviral, retroviral, adeno associated virus, herpes simplex virus, lentivirus are being developed. Nonviral delivery systems use plasmids, peptides, cationic liposomes, DNA- ligand complex, gene guns, electroporation, and sonoporation to address safety concerns such as immunogenicity and mutagenesis (Roemer and Friedmann, 1992).

Bioengineered tooth:

Research on whole tooth regeneration is also advancing using a strategy of transplanting artificial tooth germ and allowing it to develop in the adult oral environment. Ikeda *et al* reported a fully functioning tooth replacement achieved by transplantation of a bioengineered tooth germ into the alveolar bone of a lost tooth region in an adult mouse (Ikeda, 2009). Tooth regeneration is an important stepping stone in the establishment of engineered organ transplantation, which is one of the eventual goals of regenerative therapy.

Biomimetic mineralization:

A recently introduced technique of guided formation of an enamel-like fluorapatite layer on a mineral substrate has the potential to enable remineralization of superficial enamel defects and/or exposed dentin. The technique, BIMIN, utilizes the diffusion of calcium ions from solution into a glycerine enriched gelatin gel that contains phosphate and fluoride ions (Bush, 2004). When the conditioned gel is in direct contact with the exposed tooth surface, within 8 h, a firmly adhering mineral layer is formed on the tooth surface (Busch, 2004). [9]

Conclusion:

Traditionally dentistry relied on replacement of diseased or lost tooth structure with biocompatible materials associated with certain limitations and drawbacks but with biological evolution of materials a paradigm shift occurred in dentistry with advent of newer materials having bioactive and biomimetic properties whose primary focus is to regenerate lost tooth structure rather than replacement ensuring higher success rate and better prognosis The scope of biomimetic dentistry is enormous in the near future. Biomimetic dentistry would successfully replace lost dentin, enamel, cementum, and pulp and would open altogether a new era of dentistry.

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