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Bioceramics in Dentistry

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1.1 Introduction

Biomaterials as described by the American National Institute of Health are natural or synthetic substance(s) other than drugs that can be used for therapeutic or diagnostic medical purposes to maintain or improve the quality of life[1]. Along with biocompatibility, biological sustainability is also a very important property of any biomaterials that are intended to be used to reconstruct body function for an unspecified duration. However, materials are also required for temporary support of functions. Therefore, depending on the tissues to be replaced and function required, different types of materials are used as a biomaterial, e.g. metal, ceramic, polymer, hydrogel, or composite.

Ceramics are inorganic, non-metallic materials that are hard, brittle, heat-resistant, and corrosion-resistant. In addition to their biocompatibility, ceramics can be obtained with biostable, bioactive, or bioresorbable properties making them eligible to be used as biomaterials. Ceramic base biomaterials that are specially developed for biological applications (both medical and dental)

are categorized as Bioceramics. Porous bioceramics (BC) can facilitate neo-angiogenesis and neo-osteogenesis inside their porous structure. Additionally, resorbable bioceramics get replaced by the newly formed desired tissues.

Josette Camilleri described bioceramics in endodontics as the materials that are composed of tricalcium silicate-based cement synthesized from lab-grade chemicals and that do not include aluminum in their composition [2].

1.2 History and Evolution of Bioceramics

- Portland cement that was obtained from the limestones coming from Portland got patented in 1824 [3, 4].
- According to Peltier, the use of plaster of Paris, a resorbable ceramic, was first described by Dressman in 1892 to fill the bone cavities which were later found to be filled with solid bone [5].
- In the early 1920s, the use of calcium phosphates as a stimulus to osteogenesis for bone defect repair started [6].
- Use of ceramic hydroxyapatite (HA) granules for bone defect repair was first reported in the early 1950s [7].
- In 1963, Smith worked on a ceramic bone substitute, Cerosium [8].
- In 1969, researchers found a new material called bioglass that could be easily integrated into human bone [9].
- In the 1980s, the first hydroxyapatite coated implants were marketed.
- LeGeros et al. in 1982 used calcium phosphate in restorative dental cement as a bioceramics material [10].
- In 1984, the use of bioceramics started as a root canal sealer [11].
- The first self-hardening calcium phosphate cements (CPCs) were developed in 1986 [12].
- MTA was developed in the Loma Linda University, California, and was first documented in 1993 [13, 14] as a retrograde filling and perforations repair material.
- Chevalier et al. in 1997 found that the friction between zirconia and alumina is very low.
- In 1998, “TH-Zirconia” implants were introduced.
- The United States witnessed the first commercial MTA product, ProRoot MTA (Dentsply Tulsa Dental Specialties, Johnson City, TN) in 1999.
- In 2009, Septodont, France, marketed the calcium silicate-based product “Biodentine” as a permanent bulk dentin substitute.
- Angelus was the first company to launch a paste/paste bioceramic root canal sealer (MTA-Fillapex) in 2010.
- In 2019, Bio-C® Temp, a ready-to-use bioceramic paste for intracanal dressing was developed by Angelus, Brazil.

Earlier in the 1950s, bioceramics were used in dentistry because of their inertness and good biocompatibility that had no reaction with living tissues, e.g. zirconia, alumina, and carbon. They were primarily used for the fabrication of dental implants and prosthesis. Later on, the development of bioactive ceramics, e.g. bioglass (45S5) by Hench [9], extended the scope of these bioceramic materials as they offered in vivo benefits by inducing biomineralization (i.e. formation of apatite crystal layer). Bioglass (45S5) is composed of 45% SiO_2, 24.5% CaO, and 24.5% NaO_2. The addition of 6% P_2O_5 by weight enhanced the bioactivity of the glass [15]. However, this glass material was very weak and brittle. In the 1980s, the trend changed toward using implant ceramics that react with the environment and produce newly formed bone.

This bioglass was later modified to create variants by adding magnesium, borates, etc., for improving mechanical and setting properties of bioceramics [3].

Acknowledging the bioactivity property of bioceramics and their application into dentistry as mineralizing and regenerative materials has brought enormous productive changes [16].

Bioactive materials such as sintered hydroxyapatite (HA) [17] and β-wollastonite ($CaO–SiO_2$) in an $MgO–CaO–SiO_2$ glass-based matrix [18, 19] have been developed for over the last four decades [20].

Ternary $CaO–MgO–SiO_2$ system-based glass ceramics possessed better mechanical and chemical properties and thus are suitable materials for wear resistance, biomedical, and ceramic coating applications [21–23]. The addition of fluorides of Ca and Mg to substitute Na_2O in the conventional composition ($SiO_2–CaO–Na_2O–P_2O_5$) led to the development of antibacterials and bioceramics with higher flexure strength and hardness [20]. Ion substitutions (Ca^{2+}, Mg^{2+}, and B^{3+}) decreased the coefficient of thermal expansion of the bioactive glass ceramics [19]. In addition to bioglass, calcium silicate and aluminate based bioceramics also showed the property of biomineralization.

Although the shift from older to newer formulations is quite slow, many bioceramic materials have been developed that overcome the previous drawbacks.

1.3 Classification of Bioceramics

Bioceramics are classified on the basis of their generations, interaction with tissues, structure, composition, resorbability, and uses.

1.3.1 Based on Generations

Bioceramics are divided into three generations:

1) First generation: The first generation bioceramics are inert, thus do not initiate any reaction with living tissues, e.g. zirconia and alumina. Although they are biocompatible, for the body tissue they are like a foreign body,

leading to the formation of an acellular collagen capsule which isolates them from the body tissues.

2) Second generation: In the 1980s, the trend changed toward the development of bioceramics with improved bioactivity and the second generation bioactive bioceramics were developed, e.g. calcium phosphates, glasses and ceramic glasses, and calcium silicate. These bioceramics can react with the physiological fluids forming biological-type apatite as a byproduct of said reaction; in the presence of living cells, this apatite can form new bone.
3) Third generation: The third generation bioactive, porous bioceramics were developed because of biological requirements. Only porous ceramics can fulfil physiological requirements in their use as scaffolds for cells and inducting molecules and being able to drive self-regeneration of tissues. Example: nanometric apatites, shaped in the form of pieces with interconnected and hierarchical porosity, within the micron range so that cells can perform their bone formation and regeneration tasks.

1.3.2 Based on Tissue Interaction

The fact that the reactivity of solids begins on their surface is of particular importance in the field of bioceramics because on application they remain in contact with an aqueous medium and in the presence of cells and proteins [24]. Based on different types of interactions [25, 26] shown by bioceramics, it is classified as:

1) Bioinert: These materials have a high chemical stability in vivo; thus, they do not interact and show no chemical changes when they are in contact with living tissues. They also possess high mechanical strength, e.g. alumina, zirconia, and carbon.
2) Bioactive: Bioactive bioceramics have the character of osteoconduction and the capability of chemical bonding with living bone tissue. These materials bond directly with living tissues by undergoing interfacial interactions, e.g. bioactive glasses, HA, calcium silicates, and calcium aluminates.
3) Biodegradable: These materials when in contact with living tissues either become soluble or resorb and eventually get replaced or incorporated into tissue, e.g. tricalcium phosphate, calcium phosphate, aluminum–calcium–phosphates, and calcium aluminates.

1.3.3 Based on Structure

Depending on the structure type, bioceramics are classified into:

1) Dense: Bioceramics that are available as solid bulk structures like bars, rods, or to any shape through injection molding fall in this category. Because of their nonporous nature, these bioceramics show poor vascularization and osteoinduction ability, e.g. zirconia.

2) Porous: Porous bioceramics have attracted tremendous attention with their excellent biological function and osteoinduction ability. They provide scaffolds for cells to adhere, proliferate, differentiate, and regenerate tissues. The mean size and surface area of porosity plays an important role in the growth and migration of a tissue into the bioceramic scaffolds, e.g. CaP scaffold.

1.3.4 Based on Composition

On the basis of their composition, bioceramics are classified into:

1) Calcium silicate-based: The calcium silicate-based bioceramics can be further categorized on the basis of their application:
   a) Cement: e.g. Biodentine (Septodont, France), mineral trioxide aggregate (MTA), Portland cement.
   b) Sealer: BioRoot RCS (Septodont, France), Endo-CPM-Sealer (EGO SRL, Buenos Aires, Argentina), MTA Fillapex (Angelus, Brazil), TECHBiosealer (Profident, Kielce, Poland).
2) Calcium phosphate-based bioceramics: These materials are obtainable as bone cements, paste, scaffolds, and coatings. The tricalcium phosphate has shown the property of osteogenesis during bony defect treatment, e.g. tricalcium phosphate and HA. Bioglass, a glass ceramic containing calcium and phosphate, showed bonding with the living bone with a calcium phosphate-rich layer [27].
3) Mixture of calcium silicates and calcium phosphates: EndoSequence BC Sealer (Brasseler, Savannah, GA, USA)/Total Fill, BioAggregate (Innovative Bioceramix Inc., Vancouver, Canada), Tech Biosealer, Ceramicrete (developed at Argonne National Lab, IL, USA), iRoot BP, iRoot BP plus, iRoot SP (Innovative Bioceramix Inc., Vancouver, Canada)
4) Calcium aluminate-based: These materials can set, harden, and maintain their physical and mechanical properties over time in an oral environment. They have the ability to create apatite on their surface and provide tight seal between the tooth and itself. The cements can also contribute to the healing of the dental pulp or in the tissue surrounding the root of a tooth by eluting ions to stimulate cytokines, e.g. EndoBinder, Generex, Capasio, and Quick-set.

1.3.5 Based on Resorbability

1) Nonresorbable: Alumina, zirconia, carbon, HA, and calcium phosphate cement.
2) Resorbable: β tricalcium phosphate and calcium sulfate

1.3.6 Based on Their Location-Specific Use in Endodontology

They are classified as [28]:

1) Intracoronal
   - Pulp capping materials
   - Regenerative endodontic cements
2) Intraradicular root canal sealers
   - Apical plug cements
   - Perforation repair cements
3) Extraradicular
   - Root-end filling materials
   - Perforation repair cements

1.4 Forms of Bioceramics

Bioceramics are available in different forms and phases:

- Powder or microspheres
- As a thin coating on a metal or polymer
- Porous 3D structure
- Composites with a polymer component
- Solid dense structure.

1.4.1 Alumina

Aluminum oxide **(**Al_2O_3) is commonly known as alumina. It is highly inert and resistant to corrosion even in a highly dynamic oral environment. Additionally, it has high wear resistance and surface finish. As an implant material, it was first used in the 1970s. It does not integrate with bone or soft tissues. Because of its hardness being higher than the other metal alloys, alumina found its main application as biomaterials in the articular surfaces of joint replacements [29].

1.4.2 Zirconia

Zirconium dioxide is commonly known as zirconia. As zirconium is a very strong metal, it is also known as “ceramic steel.” The inherent properties of zirconia such as inertness, high toughness, strength, wear resistance, fatigue resistance, and biocompatibility make it suitable to be used as dental bioceramics.

Zirconia established itself as implant material in the 1960s. Compared to zirconia, partially stabilized zirconia showed superior flexural strength, fracture toughness, lower stiffness, and a superior surface [30].

1.4.3 Hydroxyapatite (HA)

HA ($Ca_{10}(PO_4)_6(OH)_2$) is a major component of human bones and teeth. It belongs to the calcium phosphate family with a calcium to phosphorus ratio of 1.67. Since most of the inorganic portion of the human bone tissue is HA, it can be effective in reconstructing human bone tissue. It is capable of integrating and supporting bone growth, without breaking down or dissolving. It has higher stability in aqueous media than other calcium phosphate ceramics within a pH range of 4.2–8.0 [31]. In the 1970s, resorbed residual ridge repair started with HA and in 1988 in North America it was declared as a successful implant material.

To fill the bone defects or spaces, HA may be used in the form of either powder, blocks, or beads. The bone filler acts as a scaffold to facilitate the formation of natural bone.

HA is also used to alter the surface properties of metals by the application of coating on its surface. Because of the poor mechanical properties, HA cannot be used for load-bearing applications.

1.4.4 Calcium Phosphate

Examples of calcium phosphate-based bioceramics used in dentistry are CPC, tricalcium phosphate, HA, and bioglass that are used as bone substitutes and also an adjunct with the dental cements [25]. CPC offers the potential for in situ molding and injectability.

Tricalcium phosphate is a biodegradable bioceramic. Tricalcium phosphate has four polymorphs; the most common ones are the α and β forms. It dissolves in physiological media and can be replaced with bone during implantation.

When the ratio of Ca/P in calcium phosphate compounds is less than 1, it becomes highly soluble and is thus unsuitable for biological implantation. It is used as a coating on metallic implants, as fillers in polymer matrices, as self-setting bone cements, as granules or as larger shaped structures.

1.4.5 Mineral Trioxide Aggregate

Dr. Torabinajed introduced MTA in 1993. MTA powder comprises 75% mixture of tricalcium silicate $(CaO)_3SiO_2$, dicalcium silicate $(CaO)_2SiO_2$, and tricalcium aluminate $(CaO)_3\ Al_2O_3$ 20% bismuth oxide; and 5% gypsum. This combination

possesses osteoconductive, osteoinductive, and biocompatible properties. When mineral trioxide powder is mixed with water, initially calcium hydroxide and calcium silicate hydrate are formed [32]. MTA is an active biomaterial with the potential to interact with the fluids in the tissues. The pH value is 10.2 after mixing and it rises to 12.5 at three hours resulting in an alkaline environment [32].

1.4.6 Biodentine

Biodentine, a tricalcium silicate-based hydraulic cement, was developed by Septodont research group (Septodont, Saint-Maur-des-Fosses, France) as a bioactive dentin substitute material. Tricalcium silicate is the main component and the additives include calcium carbonate in the powder; calcium chloride, water-soluble polymer, and water make the liquid. Calcium chloride controls the setting time. Biodentine exhibits a higher initial rate of calcium ion release compared to other similar material types [33, 34]. This is due to the interaction of the calcium carbonate that enhances the reaction rate [35].

Hydrated calcium silicate gel and calcium hydroxide are produced because of the hydration of tricalcium silicate. The hydrated calcium silicate gel and calcium hydroxide gradually fill in the spaces between the tricalcium grains by precipitating at the surface of the particles. Biodentine continues to improve in terms of internal structure toward a denser material, with a decrease in porosity after the initial setting.

1.5 Physicochemical Properties of Bioceramics

The physiochemical properties of bioceramics govern the application and outcome of the use of bioceramic materials. The therapeutic effect of these biomaterials in aiding healing and restoring function is dependent on the chemical reactions that affect their setting, hardening in the presence of oral tissues and fluids. The biological response of the tissues is mediated through a dynamic interaction between these materials, depending on their composition, biocompatibility, and specific properties such as surface microhardness, flow, pH, flexural strength, etc. related to them. The following discussion is focused on the physiochemical properties of commercially used bioceramics commonly used in endodontics.

1.5.1 Portland Cement

Portland cement (PC) offers antibacterial activity, biocompatibility, bio-inductivity, and acceptable physical and chemical properties when used for varied

applications in dentistry, particularly endodontics. The physical and chemical properties of Portland cement resemble more closely to MTA.

- PC like MTA is available as gray and white.
- **Discoloration** – Ordinary PC (gray) shows lesser discoloration compared to gray MTA. However, there is an equal lack of discoloration seen by white MTA and white PC [36].
- **Solubility** – Greater solubility is seen with MTA when compared to white PC. It also shows better washout resistance compared to MTA in different solutions [36].
- **Bioactivity** – Maturation of MTA after hydration is more structured than PC, hence the former displays better bioactivity. Calcium ion release and formation of HA crystals is seen with both gray and white PC [36].
- **Particle size** – The particle size of white ProRoot MTA is significantly smaller than white PC both before and after hydration [36].
- **Antibacterial properties** – PC shows antibacterial and antifungal properties similar to MTA against *Enterococcus faecalis*, *Micrococcus luteus*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, and *Candida albicans* [[36]].
- **Sealing ability** – White and gray MTA had similar sealing abilities as a root-end filling material when checked by means of dye penetration as compared to white and gray PC. However, when checked as a perforation repair material by means of protein leakage, white PC showed better sealing ability compared to white and gray MTA [36].
- **Biocompatibility** – Cell culture studies have shown variable result per the cell type. Essentially, there has been no genotoxicity or cytotoxicity seen associated with PC similar to MTA with respect to fibroblasts. However, with respect to human bone marrow derived mesenchymal stem cells, MTA displayed greater proliferation and migration compared to PC. Biomineralization is greater with MTA compared to PC when observed at 30 and 60 days. Pulpotomy performed with PC and MTA is successful both clinically and radiographically, but the root canals showed greater obliteration with PC [36].

1.5.2 ProRoot MTA

ProRoot MTA is made of fine hydrophilic particles that set in the presence of water. It seals off pathways between the root canal system and surrounding tissues, significantly reducing bacterial migration. Its excellent compatibility with the dentinal wall allows for a predictable clinical healing response. The physical and chemical properties of ProRoot MTA are:

- **pH value**: The pH value of MTA is 10.2 after mixing and rises to 12.5 after three hours. White MTA (WMTA) displays a significantly higher pH value 60 minutes after mixing compared to Gray MTA (GMTA) [37].
- **Compressive strength**: The compressive strength of ProRoot MTA is 40 MPa at 24 hours and ~67 MPa at 21 days [36].
- **Setting time**: The recommended powder liquid ratio for MTA is 3 : 1. The setting time of gray ProRoot MTA has been reported by Torabinejad et al. as 2 hours and 45 minutes (±5 minutes). The mean setting time of MTA has been reported to be approximately 165 minutes, which is longer than the amalgams, Super EBA and IRM. GMTA has significantly higher initial and final setting times than WMTA. Islam et al. reported final setting times of 140 minutes (2 hours and 20 minutes) for WMTA and 175 minutes (2 hours and 55 minutes) for GMTA. The presence of gypsum is reported to be the reason for the extended setting time. pH-hydrated MTA products have an initial pH of 10.2, which rises to 12.5 three hours after mixing.
- **Pushout bond strength**: The retentive strength of MTA is significantly less than that of glass ionomer or zinc phosphate cement and, thus, it is not considered to be a suitable luting agent. Studies have shown that a 4-mm thickness of MTA (apical barrier) offered more resistance to displacement than a 1-mm thickness. One of the study found the push-out bond strength of MTA after 24 hours to be ~5.2 ± 0.4 MPa. The strength significantly increased to 9.0 ± 0.9 MPa after the samples were allowed to set for seven days [36].
- **Flexural strength**: Raghavendra et al. in their review reported that placement of moist cotton pellets over the setting MTA for 24 hours showed significant increase in flexural strength, i.e. ~14.27 ± 1.96 MPa [36].
- **Porosity**: The amount of porosity in mixed cement is related to the amount of water added to make a paste, entrapment of air bubbles during the mixing procedure, or the environmental acidic pH value [36].
- **Microhardness**: Less humidity, low pH values, the presence of a chelating agent, and more condensation pressure might adversely affect MTA microhardness [36].
- **Sealing ability**: The majority of the dye and fluid filtration studies suggest that MTA materials overall allow less microleakage than traditional materials when used as an apical restoration while providing equivalent protection as a zinc oxide eugenol (ZOE) preparation when used to repair furcation perforations. GMTA and WMTA are shown to provide equivocal results compared against gutta-percha when used as a root canal obturation material in microleakage studies. No significant leakage is observed when at least 3 mm of MTA remains after root-end resection. However, significantly more leakage is seen when 2 mm or less thickness of MTA remains after root-end resection [36].

- **Particle size**: The physical properties of cement might be influenced by crystal size. Smaller sized particles increase surface contact with the liquid and lead to greater early strength and ease of handling [36].

1.5.3 MTA Angelus

MTA Angelus exhibits a reduced setting time, is sold in containers that permit more controlled dispensing, and possesses the same desirable properties as traditional MTA.

- **Setting time**: The setting time of MTA Angelus is approximately 14 minutes, which is considerably less than WMTA and GMTA [38].
- **pH value**: The results on the pH and calcium ion release of MTA Angelus are conflicting. While one of the studies suggests that MTA Angelus produced a higher pH value and calcium ion release than GMTA within 168 hours after mixing while other reported that pH and calcium release is lower in MTA Angelus than in MTA. Yet another study concluded that the pH and calcium ion release between MTA and MTA Angelus is not significantly different [38].
- **Microhardness**: The microhardness of MTA Angelus has been reported to be increasing with incubation time and influenced by the technique of mixing [38].
- **Sealing ability:** Several dye leakage studies have compared the quality of the seal by MTA Angelus, zinc-free amalgam, Vitremer (a resin-modified glass ionomer cement), and Super EBA, with conflicting reports. Wang in a review reported that MTA Angelus gave the best seal against root dentin among all the tested materials. In contrast, another study found more leakage with MTA Angelus and Vitremer compared to Super EBA in apical sections. However, no significant difference could be found between MTA Angelus and Super EBA in other tooth sections. Controversy also exists between MTA Angelus and MTA. One study showed no significant difference in dye penetration between them, whereas GMTA showed less dye leakage when used as a perforation repair material in another investigation. When an internal matrix was used for MTA Angelus, it demonstrated a better seal [38].
- **Radiopacity:** MTA Angelus has also shown to have a lower radiopacity than WMTA and GMTA [38].

1.5.4 Biodentine

”Biodentine” is a calcium silicate-based product that became commercially available in 2009. The material is formulated using the MTA-based cement technology and possesses better physical and biological properties compared to other tricalcium silicate cements such as mineral trioxide aggregate (MTA) and BioAggregate.

- **Setting time:** The setting time of Biodentine according to manufacturer's instructions is 9–12 minutes. The presence of setting accelerator in Biodentine results in faster setting, thereby improving its strength and handling characteristics [36]. Grech et al. compared the setting times of Biodentine, zirconium replaced tricalcium silicate cement, and BioAggregate and concluded that Biodentine had the shortest setting time among tricalcium silicate cements (ProRoot MTA, MTA Angelus, etc.).
- **Density and porosity:** A study done by De Souza et al. compared Biodentine to other silicate-based cements, IRoot BP Plus, Ceramicrete, and ProRoot MTA using micro-CT characterization. No significant difference in porosity has been found between IRoot BP Plus, Ceramicrete, and Biodentine [39].
- **Compressive strength:** During the setting of Biodentine, the compressive strength of Biodentine increases up to 100 MPa in the first hour and 200 MPa at the 24th hour. It continues to improve with time over several days reaching 300 MPa after one month, which is comparable to the compressive strength of natural dentin, i.e. 297 MPa [36]. Biodentine had the highest compressive strength in the study when compared to other tested materials because of the low water/cement ratio used [40].
- **Flexural strength:** Flexural strength of Biodentine recorded after two hours has been found to be 34 MPa [36].
- **Microhardness:** In the study done by Grech et al. Biodentine showed superior value of microhardness when compared to BioAggregate and IRM. Goldberg et al. found the microhardness of Biodentine to be 51 Vickers Hardness Number (VHN) at two hours and 69 VHN after one month [40].
- **Radiopacity:** ISO 6876:2001 has established that 3 mm Al is the minimum radiopacity value for endodontic cements. Grech et al. studied the radiopacity of tricalcium silicate cement, BioAggregate, and Biodentine and concluded that all the materials had radiopacity values greater than 3 mm Al [40].
- **Microleakage:** Biodentine is found to be associated with high pH 12 and releases calcium and silicon ions that stimulate mineralization. This creates a mineral infiltration zone along the dentin-cement interface that imparts a better seal [40].
- **Marginal adaptation and sealing ability:** Micromechanical adhesion of Biodentine allowed excellent adaptability of Biodentine crystals to the underlying dentin. According to a study, MTA and IRM were significantly superior to Biodentine in terms of marginal adaptation when used as a root-end filling material [40].
- **Bond strength:** Hashem et al. concluded that Biodentine has low strength during the initial stages of setting, hence the application of a final overlying resin composite restoration (laminated or layered) should be delayed for more than two weeks to achieve adequate bond strength of matured Biodentine to withstand contraction forces caused by polymerization shrinkage of resin composite [40].

1.5.5 BioAggregate

BioAggregate™ is a novel material introduced for use as a root-end filling material. It is tricalcium silicate-based, free of aluminum, and uses tantalum oxide as radiopacifier. BioAggregate contains additives to enhance the material performance.

- Properties of BioAggregate

Tuna et al. assessed the long-term fracture resistance of human immature permanent teeth filled with BioAggregate, MTA, and calcium hydroxide. They suggested that BioAggregate-filled immature teeth demonstrate higher fracture resistance than the other groups at one year. Considering the long-term risk of cervical root fracture associated with immature teeth, the use of BioAggregate as a root canal filling material appears to be the most advantageous of the materials tested [41].

Saghiri et al. investigated the compressive strength of MTA, a nanomodification of white MTA and BioAggregate after its exposure to a range of environmental pH conditions during hydration. The authors concluded that the force needed for the displacement of the nanomodification of white MTA was significantly higher than for Angelus White MTA and BioAggregate. They stated that the more acidic the environmental pH, the lower is the compressive strength [42].

Hashem and Amin compared the effect of acidic environment on the dislodgement resistance of MTA and BioAggregate when used as perforation repair materials. They concluded that MTA is more influenced by acidic pH than BioAggregate [43].

- Sealing Ability and Success

El Sayed and Saeed evaluated and compared the sealing ability of BioAggregate versus amalgam, IRM, and MTA. They reported that BioAggregate has a high sealing ability. The authors considered utilizing BioAggregate as an alternative to MTA [44].

1.5.6 Ceramicrete

Ceramicrete-D is a self-setting material composed of HA powder, phosphosilicate ceramic, and cerium oxide radiopaque filler, although it may also contain bismuth oxide as a radiopacifier. The pH of the material is reported differently in two separate studies. Porter et al. in their review mentioned different pH values of Ceramicrete reported by different authors range from alkaline to acidic pH [45].

The radiopacity of Ceramicrete-D is similar to that of root dentin and fulfills the requirement of ISO 6876/2001, although it is lower than that of white ProRoot MTA [46].

The material's handling and washout resistance properties are superior to those of white ProRoot MTA. Its setting time is 150 minutes. Ceramicrete-D's compressive strength is significantly lower than that of white ProRoot MTA [46].

It has been claimed that the material has the potential for bioactivity in the presence of phosphate-containing fluids. It also has significantly better sealing ability compared to white ProRoot MTA [46].

1.5.7 Calcium-Enriched Mixture Cement

Calcium-enriched mixture (CEM) cement is a powder/liquid material.

Raghavendra et al. in their review reported the introduction of a new endodontic material by Asgary et al in 2008 to combine the superior biocompatibility of MTA with appropriate setting time (less than one hour), handling characteristics, chemical properties, and reasonable price. This newly formulated biomaterial, calcium-enriched mixture (CEM) cement, has been made using different calcium compounds [36].

1.5.7.1 Physical Properties

pH: CEM cement and white ProRoot MTA have no significant difference in pH (10.61 versus 10.71), working times (4.5 minutes versus 5 minutes), or dimensional changes (0.075 versus 0.085 mm). However, there have been significant differences between the materials' setting times, film thickness, and flow [46].

CEM cement produces an alkaline pH and releases calcium in a similar manner to white ProRoot MTA. In addition, CEM cement releases significantly higher levels of phosphate compared to PC and white ProRoot MTA during the first hour after mixing.

Radioopacity: CEM cement radiopacity is reported to be 2.227 mm Al, which is lower than that of ProRoot MTA (5.009 mm Al) and MTA – A (4.72 mm Al). CEM cement's radiopacity did not fulfill the requirement of ANSI/ADA specification numbers 57/2000 and ISO 6876/2001 each for endodontic sealing materials (3 mm Al) [46].

Particle size: The particle size of CEM cement is between 0.5 and 30 μm. The percentage of the particle size between 0.5 and 2.5 μm diameter in CEM cement is significantly higher than that in white ProRoot MTA and white PC [46].

The effect of using CH, ProRoot MTA, and CEM cement on flexural strength of bovine root dentin after 30 days showed that all tested materials significantly decreased flexural strength compared to the control [46].

Push-out bond strength of CEM cement as root-end filling material is comparable with white ProRoot MTA. Both materials showed higher resistance to displacement when the root-end preparation has been performed with ultrasonic technique rather than Er, Cr: YSGG laser [46].

1.5.7.2 Antibacterial Activity

Two separate antibacterial investigations evaluated the activity of CEM cement, gray and white ProRoot MTA, PC, and CH on *E. faecalis*, *P. aeruginosa, Escherichia coli*, and *S. aureus*. Results showed that both CH and CEM cement had significantly higher antibacterial activity against the microorganisms used in these studies compared to white and gray ProRoot MTA. Both white ProRoot MTA and CEM cement showed similar fungicidal activity after 24 and 48 hours of incubation with *C. albicans* [46].

1.5.7.3 Sealing Ability

When used as a root-end filling material, CEM cement showed no significant difference to white ProRoot MTA and MTA. However, all materials showed significantly lower dye leakage compared to IRM. A fluid filtration study that stored CEM cement as a root-end filling material in different media reported that when the teeth were kept in phosphate buffered saline (PBS), the samples showed significantly less leakage compared to the ones that had been stored in distilled water. There was no significant difference in microleakage when ProRoot MTA and CEM cement were compared as root end restorations in the presence of blood as a contaminant although CEM cement showed a lesser degree of microleakage in the presence of saliva [46].

1.5.8 EndoSequence Root Repair Material

EndoSequence root repair material (ERRM) has been developed as ready-to-use. These premixed bioceramic materials are recommended for perforation repair, apical surgery, apical plug, and pulp capping. The manufacturer stated that the moisture present in the dentinal tubules is adequate to allow the material to set. The physical and chemical properties are:

1.5.8.1 Setting and Working Time

The material has a working time of more than 30 minutes and approximately a four-hour setting time. The presence of moisture is required for the material to harden [38].

1.5.8.2 pH Value

The pH value of ERRM has been reported to be as high as 12.4, which is probably responsible for its antibacterial properties during the setting reaction. Hansen et al. compared the pH changes in simulated root resorption defects filled with MTA and ERRM, and concluded that intracanal placement of MTA resulted in a higher pH than with ERRM. The pH value of both ERRM and MTA

treated canals declined to the levels of the negative control after a four-week incubation in saline [47].

1.5.8.3 Microhardness

A recent study showed that the microhardness values of ERRM putty and ERRM paste can be reduced in an acidic environment, and resulted in these materials having more porous and less crystalline microstructures [38].

1.5.8.4 Bioactivity

This material is bioactive because of its ability to form a HA or apatite-like layer on its surface when it comes in contact with phosphate-containing fluids. Hansen et al. compared the diffusion of hydroxyl ions for ERRM and WMTA through root dentin. They found that although both materials showed diffusion of ions through dentin, the effect is less pronounced and of shorter duration for EndoSequence than for WMTA [47].

1.5.8.5 Sealing Ability

Hirschberg et al. compared the sealing ability of MTA to the sealing ability of ERRM using a bacterial leakage model. They concluded that samples in the ERRM group leaked significantly more than samples in the MTA group. Although there are no studies so far showing the bonding strength of ERRM, the adhesion of ERRM to dentin forms tag-like structures inside the dentinal tubules that act as a micromechanical anchor to dentin [48].

1.5.8.6 Antibacterial Activity

Lovato and Sedgley investigated the antibacterial activity of ERRM against *E. faecalis*. They found that ERRM and white ProRoot MTA demonstrated similar antibacterial efficacy against clinical strains of *E. faecalis*. This research again validated earlier studies that found ERRM displayed similar in vitro biocompatibility to MTA. Additionally, another study found that the ERRM had cell viability like gray and white MTA in both set and fresh conditions [49].

1.5.9 iROOT

iRoot has been introduced in three forms:

1) iRoot SP
2) iRoot BP
3) iRoot BP Plus

These forms have been introduced for use in root filling, root repair (iRoot BP and iRoot BP plus), and root canal sealer (iRoot SP) materials. iRoot SP is an injectable, ready-to-use, insoluble, radiopaque white paste that needs moisture to initiate and complete its setting.

1.5.9.1 Physical Properties

iRoot SP shows a significantly higher bond to dentin compared with MTA Fillapex and Epiphany. The higher bond strength has been attributed to the smaller particle size, level of viscosity, and minimal shrinkage during the setting period. The smaller particle size and high level of viscosity increase the flow of the material into the dentinal tubules and other anatomic structures of the root canal space when gutta-percha is used as the root canal filling material [46].

iRoot SP provides the highest bond strength when adapted to moist root dentin wall. Placement of CH inside the root canal before using iRoot SP as a root canal sealer improves its bond strength to dentin. The results of another study have shown that using iRoot SP with gutta-percha improves resistance to fractures in simulated open apex teeth. iRoot SP showed an alkaline pH up to seven days after setting and can kill *E. faecalis* in an antibacterial investigation [46].

1.5.10 Endo-CPM

Endo-CPM sealer is an MTA-based root canal sealer that has been developed in Argentina in 2004.

1.5.10.1 Physical Properties

The addition of calcium carbonate to the material was for decreasing the pH after setting. The release of calcium ion from Endo-CPM was detected during two in vitro investigations. The sealer has an alkaline pH value and significantly higher bond strength to dentin compared with MTA Fillapex and AH Plus [46].

Another study compared the dislodgement resistance of calcium silicate-based sealers (TotalFill BC Sealer, Endo-CPM-Sealer, and BioRoot RCS) with an epoxy resin-based sealer (AH Plus) and concluded that the push-out bond strength of the investigated calcium silicate-based sealers has been lower than that of AH Plus [46].

Endo-CPM showed antibacterial activity similar to that of white ProRoot MTA and white MTA. Endo-CPM sealer has no antibacterial activity against *E. faecalis*. No significant difference was observed in the marginal adaptation of these two materials and MTA when used as apical plugs in teeth with open apices [46] (Table 1.1).

Table 1.1 Physicochemical and biological properties of bioceramic materials used in endodontics.

	Biodentine	MTA	MTA Angelus	ERRM	iRoot SP BC Sealer	MTA Fillapex	MTA Plus	Total Fill BC Sealer	EndoSequence BC Sealer
pH	11.7–12.4	9.0–12.5	7.3–9.6	7.3–8.9	10.3–11.1	9.7–10.5	8.3–11.7	11.4–12	11–12
Calcium release (mg/l)	14.7–34	9.7–24	0.8–122.3	179.6	2.5–11.3	144.4	7.7–43.4	—	—
Flow rate (mm)	—	—	—	—	26.9	31.0	—	24.83	—
Porosity (%)	6.8	30.3–38.4	28.0	—	—	—	40.3	—	—
Solubility (%)	<0.0	1.7–2.8	1.2–6.4	—	20.6	14.8–16.1	18.5	7.44	—
Radiopacity (mm AL)	3.3–4.1	7.1	5.3–6.9	—	3.8	7.0	—	6.15	3.84
Setting time (h)	0.1–0.7	6.9	0.2–5.3	>24.0	72.0–240.0	>12.0	0.9	9.6	37.15
Microhardness (VHN or KHN)	48.4–130 VHN	53.2–60.0 VHN	36.3–84.3 VHN	—	>15.0 KHN	—	—	—	—
Compressive strength (MPa)	67.1–316	60.0–101.7	53.4–81.3	41.0–43.0	—	—	32.0–47.0	—	—
Push-out bond strength (MPa)	6.47–7.64	3.0–9.4	—	—	0.8–3.4	0.2–3.0	0.98–2.3	—	3.0
Flexural strength (MPa)	34.0	10.7–14.2	—	—	—	—	—	—	—
Cell viability (%)	60.0–100.0	55.0–110.0	88.9–105.4	40.0–110.0	>90.0–100.0	35.0–95.0	>80.0	—	95.0–100.0

Source: Adapted from Wang [38].

1.6 Physicochemical Properties of Some Bioinert Bioceramics

Bioinert ceramics are biologically inert in nature when implanted into biological system and do not instigate an immediate interaction with the adjacent biological tissues.

1.6.1 Alumina (High Purity Dense Alumina/Al_2O_3)

Physical properties: Alumina as a bioceramics insert and implant offers excellent properties, such as good corrosion resistance, low wear and friction, excellent strength, and chemical inertness, which make them especially useful in the field of hard tissue engineering [50]. A few other properties of alumina include:

1) Minimum density: $3.94 \pm 0.01\,g/cm^3$
2) Median grain size: 4.5 μm or less
3) High flexural strength: 300 MPa
4) High Young's modulus: 380 GPa
5) Pore volume: $0.1–1.4\,cm^3/g$
6) Average pore size: 2–177 nm.

Chemical properties: They have inherently low levels of reactivity compared with other materials such as polymers and metals as well as surface reactive or resorbable ceramics. In a human body, they are expected to be non-toxic, non-allergenic, and non-carcinogenic for a lifetime.

1.6.2 Zirconia

Yttria tetragonal zirconia polycrystal (Y-TZP) is the most common type of zirconia used in dentistry with its fracture toughness being twice that of alumina-based bioceramics. Y-TZP is available as presintered, partially sintered, or those that require sintering after milling and offer the following properties:

1) Density: greater than $6\,g/m^3$
2) Porosity: less than 0.1%
3) Grain size:0.2 μm
4) Young's Modulus: 150–200 MPa
5) Compressive strength: >2000 MPa
6) Bending strength: 900–1200 MPa
7) Hardness: 1200 VHN
8) Thermal conductivity: 2 Wm/K
9) Thermal expansion: $11 \times 10^{-6}/K$

The overall high toughness strength, small particle size and porosity volume, resistance to heat, low thermal conductivity, and chemical inertness make this a material of choice for dental implants and prostheses [50].

1.7 Biological Properties of Bioceramics

As human bodies are known to be a complex biological system, there is every chance that some sort of response would occur when foreign materials are placed in them.

The understanding of the active interface between biomaterials and biological systems led to several important basic ideas about biocompatibility. First, the interactions at the material–tissue interface occur for both; the material elicits a response from the body and the body elicits a response from the material. The second idea is that the material–tissue interface is dynamic. Thus, the interface is changing over its lifetime. Furthermore, because the human oral conditions are always changing, any equilibrium established at a material–tissue interface is subject to change. The third idea is that reactions at the material–tissue interface are a function of the tissue where the interface is created. The fourth idea about biological–tissue interfaces is that the biomaterials are foreign bodies and biological responses to these materials are characterized by foreign body responses. Finally, the most recent idea about biocompatibility is that it is possible to customize interactions at the material–tissue interface [1].

Biological properties of bioceramics have been evaluated using criteria such as cell expression and growth, subcutaneous and intraosseous implantation, and direct contact with dental tissues in vivo.

1.7.1 Cytological Investigation of Biocompatibility

A lot of literature is available on the biocompatibility of bioceramic materials. A study evaluating the biocompatibility of alumina ceramic material histopathalogically had shown no signs of cytotoxic reaction. After a period of four weeks of implantation, fibroblast proliferation and vascular invasion were noted [51]. Also, cytotoxicity of alumina ceramics was studied in L cell line culture, which showed that they have no cytotoxicity and if implanted in bone marrow they would not be toxic to circumferential tissue [51]. Powders and particles of zirconia when tested in vitro on different cell lines of lymphocytes, monocytes, and macrophages did not induce cytotoxicity or inflammation [52]. A majority of the published in vitro studies conducted on osteoblasts, fibroblasts, lymphocytes, monocytes, and macrophages to test the biocompatibility of zirconia observed that it had no cytotoxic effect on osteoblasts [53, 54] and did not induce a pseudo-teratogenic effect, which makes it biocompatible [54].

Most of the cell studies showed good cell growth over MTA with the formation of a cell monolayer over the material [32, 55, 56]. However, Haglund et al. [57] showed that MTA was cytotoxic to both macrophages and fibroblasts. Cell studies test the cytotoxicity in vitro but cannot examine the complex interactions between materials and host. As MTA is a calcium silicate cement, its biocompatibility may be questioned. The observed biocompatibility of MTA could arise from reaction by-products. Good cell growth was demonstrated on material extracts [58–60]. MTA induced expression of inflammatory cytokines from bone cells and exhibited good cell attachment [61]. In contrast, no cytokine production was observed in one study. The lack of cytokines was accompanied by cell lysis and protein denaturing around the MTA [57]. There has been some conflicting data on the biocompatibility of gray and white MTA. Perez et al. [62] showed that white MTA was not as biocompatible as the gray version and postulated that the difference might be because of surface morphology of the materials. On the contrary, Camilleri et al. [63] showed no difference between the two variants; however, both materials exhibited reduced cell growth when allowed to set for 28 days. The biocompatibility of Portland cement was tested using a cell culture study and the material allowed complete cell confluence [64].

The available data regarding the biocompatibility of Biodentine generally is in favor of the material in terms of its lack of cytotoxicity and tissue acceptability [65]. Laurent et al. [66] were the first to show the promising biological properties of Biodentine on human fibroblast cultures. In addition, studies have demonstrated the absence of toxicity of Biodentine in human MG63 human osteoblast cells with properties comparable to that of MTA [67]. In a study performed by Zhou et al. [68], where Biodentine was compared with white MTA and glass ionomer cement using human fibroblasts, both white MTA and Biodentine were found to be less toxic compared to glass ionomer during the one- and seven-day observation period. The authors commented that despite the uneven and crystalline surface topography of both Biodentine and MTA compared to the smooth surface texture of the glass ionomer, cell adhesion and growth were determined to be more favorable in the aforementioned materials compared to glass ionomer.

Calcium phosphate bioceramics, depending on their chemical composition and physical features, may favor either stem cell proliferation or differentiation. Blocks of bioceramics presenting rough surfaces and a higher number of micro- and macro-porosity favor cell viability, proliferation, and differentiation over biomaterials with smooth surfaces and less porosity, even if their chemical composition is considered less favorable for osteogenesis [69]. Thus, it can be said that bioceramic materials in general are less cytotoxic and more biocompatible.

1.7.2 Subcutaneous and Intraosseous Implantation

Histological evaluation of tissue reaction has been evaluated by subcutaneous and intraosseous implantation of the materials in test animals.

When the histologic reaction was examined after surgical insertion of alumina ceramic in the knee joints of Japanese white rabbits, it was observed that alumina ceramic induced weak tissue reaction. When the osteointegration of zirconia was investigated in rats by means of histomorphometry, it was seen that zirconia was biocompatible in vitro [51]. In addition, Styles et al. [70] in their study concluded that when zirconia was tested in different physical forms, it did not induce cytotoxicity in soft tissues. Also, it appeared that the various forms of zirconia tested in hard tissues did not induce any adverse reaction or local toxic effects.

Subcutaneous implantation in rats showed that MTA initially elicited severe reactions with coagulation necrosis and dystrophic calcification. The reactions, however, subsided with time [71, 72]. Reactions to intraosseous implants of MTA were less intense than with subcutaneous implantation. Osteogenesis occurred in association with these implants [71]. With intraosseous implantation, the tissue reactions to the material subsided with time over a period of 12 weeks [73]. In another study, MTA was shown to be biocompatible and did not produce any adverse effect on microcirculation of the connective tissue [74]. Implantation of Portland cement in rat mandibles of guinea pigs showed that it was biocompatible [75]. Therefore, most studies have shown that the initial reaction seen after implantation of bioceramic materials subsided with time.

1.7.3 Periradicular Tissue Reactions

When MTA was used for root-end filling in vivo, less periradicular inflammation was reported compared with amalgam [76]. The presence of cementum on the surface of MTA was a frequent finding [77]. MTA induced apical hard tissue formation with significantly greater consistency, but not quantity [78]. Also, MTA supported almost complete regeneration of the periradicular periodontium when used as a root-end filling material on non-infected teeth [79]. The most characteristic tissue reaction to MTA was the presence of organizing connective tissue with occasional signs of inflammation after the first postoperative week [80]. Early tissue healing events after MTA root-end filling were characterized by hard tissue formation on the peripheral root walls along the MTA–soft tissue interface [80]. It has been seen that when either fresh or set MTA was used after apical surgery there was cementum deposition [81]. In addition, MTA showed the most favorable periapical tissue response of the three materials tested, with formation of cemental coverage over MTA [82]. Hence, most studies in vivo have shown a favorable tissue response to MTA.

It has been observed that a tricalcium phosphate compound used in a bony defect promoted osteogenesis or new bone formation. Hench [27] in 1971 developed a calcium phosphate-containing glass ceramic known as bioglass. He showed that it chemically bonded with the host bone through a calcium phosphate rich layer. Biphasic calcium phosphate (BCP) bioceramics have been considered optimum bone graft substitutes because of their proven safety, osteoconductivity, and bioactivity [69]. CaP bioceramics are considered bioactive materials because they partially dissolve in vivo by either cellular or extracellular activity or both [83]. Cellular resorption usually occurs by macrophages and osteoclasts; this active cellular process is equivalent to bone remodeling [84]. The core mechanism of bioactivity is the partial dissolution and release of ionic products in vivo, elevating the local concentrations of calcium and phosphate ions and precipitating a biological apatite on the surface of the ceramics [84].

1.7.4 Pulpal Reactions

MTA used for pulp capping or partial pulpotomy stimulates reparative dentin formation. MTA-capped pulps showed complete bridge formation with no signs of inflammation [85, 86]. Similar results were obtained when MTA was placed over pulp stumps following pulpotomy [87]. This hard tissue bridge formed over the pulp was documented after using ProRoot MTA and MTA Angelus and both gray and white Portland cement. Histological evaluation showed that both types of material were equally effective as pulp protection materials [88].

The biocompatibility of Biodentine was investigated through its direct application to human pulp cells simulating the direct pulp condition and indirectly through a dentin slice to simulate its indirect pulp capping. Under both conditions, Biodentine was not found to affect target cell viability under in vivo application conditions [66]. Additionally, when Biodentine was applied onto human pulp cells to investigate its effects on their specific functions by studying the expression of odontoblast specific functions such as expression of nestin (a human odontoblast specific marker) and dentin sialoprotein, Biodentine was found not to inhibit the expression of these proteins but rather induce their expression and the cells' mineralization capacity [66, 89, 90].

Additionally, when Biodentine was used for vital pulp therapy in vivo, investigations carried out on different animal models showed that this material induced tertiary dentin synthesis when applied as direct or indirect pulp capping material in rat teeth [91, 92]. In case of direct pulp capping, the dentin bridge formation observed after four weeks in rat teeth was tubular and its porosity was similar to that of MTA [92]. Similar results were demonstrated in miniature swine teeth. After pulp capping with Biodentine, no pulp inflammation was observed while a thick dentin bridge was formed after three and eight8 weeks [93]. This mineralization seems to be due to the release of a growth factor, namely transforming

factor beta 1 (TGF-b1) from pulp cells. This factor has been shown to be involved in odontoblastic differentiation and recent investigations revealed that this factor is involved in the recruitment of pulp stem cells to TGF-b1 production site [94]. In a study by Laurent et al. [89] Biodentine was found to significantly increase TGF-b1 secretion from pulp cells. TGF is a growth factor that plays a role in angiogenesis, recruitment of progenitor cells, cell differentiation, and mineralization. Interestingly, increase in TGF-b1 was significant whatever the ratio between the Biodentine surface area and cell culture volume [89]. This is an important clinical information because it indicates that this cement can be applied onto the pulp whatever be the surface area of the injured pulp. Additionally, investigation on the application of Biodentine in pulpotomy in primary pig teeth and comparison with formacresol and white MTA suggested that Biodentine showed no inflammation and a thick dentin bridge formed in 90% of the cases, which was comparable to the results obtained with WMTA [95]. This result gives an indication about the biocompatibility of these materials and their suitability for pulp capping and pulpotomy.

A recently published article focused on the influence of Biodentine from another perspective and assessed the proliferative, migratory, and adhesion effect of different concentrations of the material on human dental pulp stem cells (hDPSCs) obtained from impacted third molars. Results showed increased proliferation of stem cells at 0.2 and 2 mg/ml concentrations while the cellular activity decreased significantly at higher concentration of 20 mg/ml. Biodentine favorably affected healing when placed directly in contact with the pulp by enhancing the proliferation, migration, and adhesion of human dental pulp stem cells, confirming the bioactive and biocompatible characteristics of the material [96].

The dentinogenic effects of CaP materials and the formation of dentin bridge have been studied on pulp amputation and on pulp capping. Boyde and Jones [97] in 1983 had demonstrated the homogeneity of dentin formation at the surface of CaP. Energy dispersive Xray (EDX) microanalysis indicated that the newly formed mineralized tissue contained essentially Ca and P, with small amounts of Mg, as in normal dentin [98]. The principle of primary mineralization is different: the size of the particles is probably an important factor. The bridge obtained with microparticles of HA, TCP, and BCP was like a classical dentin bridge obtained with CH. Perhaps the microparticles are more easily absorbed by multinuclear giant cells or the macroparticles could promote the formation of a collagen fiber network. It is possible that microparticles are more irritative for pulpal tissue than the large particles and promote dystrophic mineralization. However, it was noticed that the microparticles formed a dense package in contact with the pulp. The bridge extended beyond the capping material with no necrotic layer using calcium phosphate materials. On the other hand, the macroparticles appeared to push in pulpal tissue, and the mineralization was formed around and in close contact with them [99].

1.7.5 Antibacterial Properties

A number of studies have investigated the antimicrobial effects of bioceramic materials. In a study that compared the inhibition of growth and adhesion of selected oral bacteria on titanium and zirconia implants, difference was found in the adhesion of some selected oral bacteria. But in an in vivo study, zirconia showed significantly lesser adhesion of bacteria than titanium [100].

Al-Hazaimi et al. [101] in 2006 stated that MTA has antibacterial effect especially against *E. faecalis* and *Streptococcus sanguis*. On the contrary, Torabinejad et al. [102] in 1995 showed that MTA had no antimicrobial action against any of the anaerobes. But it did show certain effect on facultative bacteria. In a study by Bhavana et al. [103] in 2015, Biodentine showed stronger inhibitory effect than MTA on *Streptococcus mutans*, *E. faecalis*, and *C. albicans*. Moreover, Asgary et al. [104] in 2007 found that antibacterial properties of calcium-enriched mixture (CEM) cement against *E. faecalis* were higher than those of MTA. According to Koruyucu et al. [105] in 2015, Biodentine and MTA showed similar antibacterial effects against *E. faecalis*. Also, the effect of CEM against gram-negative, gram-positive, and cocci/bacilli bacteria were compared with MTA and calcium hydroxide (CH) and the results showed comparable antibacterial effects with CH and significantly better results than MTA [58]. Recently, Esteki et al. [106] in 2021 concluded that MTA, Biodentine, and CEM had growth inhibitory effects on the microorganisms tested. However, compared with MTA, Biodentine showed greater inhibitory effects against *E. faecalis* and *C. albicans*, which are resistant microorganisms in endodontic treatment. Hence, Biodentine with its potent antimicrobial effect can be considered as an appropriate alternative to MTA and CEM cement in endodontic treatment. In another study, antibacterial activity of ERRM was compared with MTA, and the results demonstrated similar antimicrobial properties during their setting reaction against ten clinical strains of *E. faecalis* [49].

1.8 Application of Bioceramics in Dentistry

- Bioceramics have a wide array of applications in various fields of dentistry. In endodontics, bioactive BCs are frequently used in root canal obturation, perforation repair, retrograde root canal filling, apexification, and vital pulp therapy or regenerative endodontic procedures such as pulpotomies and revascularization. MTA and Biodentine have been most commonly used for the above-mentioned procedures and have produced positive treatment outcomes in both pediatric and adult patients [107]. Recently, BCs like Bio-C Temp have also been used as intracanal medicaments and have shown significant increase over time in the collagen content and in the immune expression of IL-10, a cytokine involved in the tissue repair.

- In restorative dentistry, BCs (glass ceramics) can be used as a temporary enamel substitute in Class II restorations and even as a permanent dentin substitute in large carious lesions especially in cases where the dentin is hypersensitive [108].
- Bioinert ceramics like zirconia and alumina are currently being used for improvement of aesthetics and for prosthetic rehabilitation by being included in all ceramic crowns [109], bridges and prosthesis, and prosthetic device implants or as implant coatings to improve osteointegration and biocompatibility [110]. Use of biphasic calcium phosphate BCs (composed of an intimate mixture of hydroxyapatite [HA] and β-tricalcium phosphate [β-TCP]) in the management of facial disharmony and facial deformities (caused by congenital malformations, trauma, infection, or tumors) has also shown to have good treatment outcomes [111].
- In orthodontics, bioglass particulates can be used in the form of pastes around orthodontic brackets that form a protective interaction layer on enamel surface and decrease the risk of enamel erosion by protecting against demineralization in acidic environment, and is especially useful in high caries-risk patients [112]. A combined paste of fluoride and bioactive glass pastes has been shown to further reduce the risk of eroding enamel in such cases [113].
- In periodontics, BCs can be used as periodontal regenerative material [114]. CPCs are used as bone defects filler and scaffold for bone formation that provides histocompatible healing of periodontal tissues [115]. These regenerative materials are also available as nano-hydroxyapatite (nHAP) that can be used as temporary osteoconductive grafts to aid the ingrowth of viable bone; however, these may not be intended to provide structural support. Such BCs can be used for clinical applications such as reconstructing bone defects caused by trauma, filling of periodontal defects, cystectomy filling, filling of alveolar bone defect, or during osteotomies, etc. [116]. Teeth exhibiting periodontal disease can be repaired using BCs where crushed bioglass particles (90–700 μm) are mixed with saline and placed around the tooth to stimulate bone growth 117].
- In oral and maxillofacial surgery, BCs have been used as an addition to or a substitute for autogenous bone [118] in filling surgical bone defects, joint replacements, alveolar bone augmentation, orbital floor fracture, sinus obliteration, and so on. [119, 120]. BCs in the form of porous HAP granules are very popular as bone defects fillers. HAP can be used to fill voids or defects in bones in the form of powders, porous blocks, or beads [121]. As an alternative to bone grafts, the bone filler acts as a scaffold and promotes the rapid filling of the gap by naturally forming bone [122].

  HAP is indicated for bone grafting in defects after the removal of bone cysts, augmentation of the atrophied alveolar ridge, sinus floor elevation, filling of alveolar defects following tooth extraction, filling of extraction defects to create an implant bed, defects after surgical removal of retained teeth or corrective osteotomies, and other multi-walled bone defects of the alveolar ridge [123].

- Another BC, β-TCP, is receiving growing attention as a raw material for several injectable hydraulic bone cements and composites for bone repair filling, acetabulum reconstruction, and metaphyseal fractures. These grafts are indicated for filling of small bony defects, implantology (defect augmentation, elevation of sinus floor, etc.), and grafting after cyst removal [111].
- 3D printed BC(CSi-Mg10) scaffolds are being used as an efficient alternative for bone reconstruction in maxillofacial or craniofacial conditions. They are highly recommended because of their interconnected 3D porous structure, high mechanical strength, excellent bioactivity, and adequate biodegradation, and have a rapid fabrication time of 24 hours. These porous scaffolds stimulate bone regeneration without the aid of any osteogenic factor [124].
- Metallic implants are often associated with poor osseointegration, implant-associated infections, and poor biofunctionality. To overcome these issues, metal implants can be coated with bioresorbable and bioactive BCs (HAP coated or glass ceramic coated), which not only improve their biocompatibility but also function as resorbable lattices providing a temporary framework that is dissolved with time and replaced with body tissues, thus playing a vital role in uncemented implant fixation [3].
- In oral medicine, BCs can be used as drug carriers for antitumor drugs (low molecular weight drugs, high molecular weight biomolecules, or delivery of ions). CPC-based drug carriers work by encapsulating drugs and improving their biodistribution and pharmacokinetic properties. Improvement in the specificity and accuracy of treatment can be achieved by incorporating monoclonal antibodies and receptor-specific peptides that help in targeted delivery of these drugs leading to better accumulation at tumor sites [10].

1.9 Advantages of Bioceramics

- BCs are extremely biocompatible (nontoxic) ceramic materials that are chemically stable within the biological environment and have good antibacterial and antifungal activity [2, 125].
- BCs favor the regeneration of bone tissues because of their osteoinductive, osteoconductive, and bioresorbable properties [126, 127]. They can get rapidly integrated into the human body by forming a bond to bone leading to indistinguishable unions. The intrinsic osteoinductive capacity of BCs is supported by their ability to absorb osteoinductive substances and stimulate osteoblast cells. In addition, BCs also stimulate angiogenesis (enhances the expression of vascular endothelial growth factor (VEGF) leading to rapid vascular ingrowth during new bone formation, thus playing a vital role in regeneration. BCs can

also function as a regenerative scaffold of resorbable lattices that provide a framework that is eventually dissolved as the body rebuilds tissue.

- BCs can form a chemical bond with the dentin microstructure (because of the formation of hydroxyapatite during the setting process), thus leading to an excellent fluid tight seal with dentin. This property along with its antimicrobial nature has led to its ability to be used as a bonded restoration along with several other clinical applications.
- BCs do not shrink upon setting; rather, they actually expand slightly once the setting process is completed making them dimensionally stable. This property and the chemical bonding with dentin impart an excellent sealing ability to the material.
- BCs also possess good radiopacity, which is a prerequisite for dental materials to verify their proper placement in the intended clinical application.
- These are non-immunogenic and hence do not elicit an immune reaction on coming in contact with vital tissues like pulp.
- Furthermore, in cases of overfilling during the process of obturation or procedures like perforation repair, BCs will not result in a significant inflammatory response.
- BCs possess antibacterial properties because of the phenomenon of bacterial sequestration that occurs after the precipitation of materials in situ after setting. Bacterial adhesion is prevented by the formation of porous powders containing nanocrystals (1–3 nm diameter).
- Glass ceramic prosthetics such as those fabricated with zirconia and alumina offer several advantages including ease of fabrication, high strength with low processing shrinkage, reduced damage due to abrasion and chemicals, resistance to thermal shock, and excellent polishability. Additionally, the intrinsic property of translucency imparts lifelike aesthetics to restorations [128].

1.9.1 Regenerative Endodontic Therapy

Use of BCs in regenerative endodontic therapy (RET) enhances blood clot stabilization, provides for an antibacterial and anti-inflammatory action, and stimulates tissue repair, secretion and action of BMPs, and other growth factors. BCs have the ability not only to stimulate undifferentiated stem cells to form pulp-like tissue but also induce hard tissue formation and help in providing a tight seal [2].

1.9.2 Advantages of BCs When Used as a Sealer/Obturating Material

- Hydraulic cement pastes of BCs have been developed for obturation and sealing of root canals. These sealers offer several advantages such as increased pH during setting, high antimicrobial activity, biocompatibility, and bioactivity

when set with long-term dimensional stability. In addition, they are easy to manipulate and form a good bond at the cement–dentin interface, thus providing a good sealing ability [36, 128].

- Some BC sealers like CeraSeal are also highly resistant to initial washout because of the shorter setting time [109, 111].

1.10 Limitations

Older BC materials like Portland cements (PC) have many inherent drawbacks such as releasing high amounts of lead and arsenic, higher solubility, excessive setting expansion (jeopardizing the long-term seal of the material), lower compressive strength, and reduced long-term efficacy of the material [129].

Although newer BCs have come up with improved properties, some of the issues still remain unresolved. Mineral trioxide aggregate (MTA) has good biological properties but is expensive and has a long setting time and difficulty in handling with a potential for tooth discoloration when used for restorations and in endodontics. Also, the absence of a known solvent for this material poses difficulty in its removal after placement when used in root canals in endodontics [36].

Although BCs are excellent biomaterials, there are certain drawbacks that are inherent to it being a ceramic material. BCs in general have poor mechanical properties, i.e. they have a high Young modulus and low fracture toughness (brittle in nature), which is a reason for their inferior workability [130].

Brittleness is not a problem if BCs are used in stress-free positions but their use becomes limited in positions where high stress is loaded, which makes the usage of BC unreliable in bulk form for load-bearing applications [131].

The retrievability of BCs when used as sealers for obturation also remains a clinical problem, although it has been claimed that some sealers like Bio-C can be easily removed from the root canal with the conventional gutta-percha removal techniques [118, 131].

1.11 Future Trends

- To overcome the limited mechanical properties of BCs, utilizing bioengineering technology for substitution of strong metal ions in the glass network of BCs or fabrication of BCs with hard polymer composite can help to achieve better material for restoration. However, detailed analysis of such materials

would be imperative especially in terms of their structural properties, mechanical properties, and in vitro/in vivo compatibility before their actual clinical usage [132].

- The use of 3D-printed calcium silicate scaffolds and their modifications (like functionalization) can be utilized in the future as an effective method for regulating odontogenesis or regeneration of dentin or other hard tissues [124].
- Because of their low coefficient of friction for lubricating surfaces, they can find an important role in joint prosthesis (for replacement of temporomandibular joint [TMJ] joints).
- It has been seen that external and internal functionalization (coating of 3D-printed Ca-Si BC scaffolds with highly photothermal materials) renders desirable photothermal properties to BCs that enhances their antitumor potential (as seen in both in vitro and in vivo studies) [132]. This property can be utilized and explored further for antitumor therapy. In the future, development of such superior biomaterials having both antitumor properties and the potential for osteogenic repair would increase the prognosis of cancer patients, decrease their need and time for hospitalization and reduce the possibility of hospital-acquired infection [133].
- A promising use of BCs in the field of regeneration would be to combine the potential advantages of these nanostructured biomaterials with newly generated ameloblasts, odontoblasts, cementoblasts, osteoblasts, fibroblasts, or dental stem cells and growth factors to achieve the desired goal of enamel, dentin, and periodontal tissue regeneration [134].
- Development of new biofunctionalized CPCs (by incorporating biofunctional agents such as RGD (Arginine–Glycine–Aspartic), Fn (Biofunctional Peptide), FEPP (fibronectin-like engineered polymer protein), Geltrex, and platelets) have shown marked improvements in human umbilical cord-derived mesenchymal stem cells (hUCMSC) proliferation, actin stress fiber density, and osteogenic differentiation. Studies have shown that use of these biofunctionalized BCs shows marked elevation in alkaline phosphatase (ALA), Runx2, Osteocalcin (OC), and collagen I gene expressions and a threefold increase in synthesis of bone mineral matrix with similar mechanical properties as that of cancellous bone. Thus, these stem cell-seeded biofunctionalized BCs are promising to promote bone regeneration in a wide range of dental and craniofacial applications[135].

Collaboration from varied disciplines including basic ceramic research, biochemical research, clinical research, etc., would be required for further improvisation of BCs and making it more functional for its future dental applications [131].

1.12 Conclusion

The development of bioceramics and manufacturing techniques has evolved to become an integral part of the dental health care system. Variations in composition, microstructure, and molecular surface chemistry have broadened the diversity of its application in dentistry. Research is in progress for coupling these materials with tissue engineering ensuring a very bright future for bioceramics in dentistry.

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