Bioactive and Biomimetic Restorative Materials: A Comprehensive Review. Part I

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ABSTRACT

The objective of this two-part review article is to compare and contrast the composition, properties, and performance of the calcium silicate- and calcium aluminate-based, bioactive dental materials, with an emphasis on the restorative applications of this evolving class of materials. Part I examines the development and application of the calcium silicate-based materials ranging from dental materials derived from Portland cement to more recent materials based on further modifications of calcium silicate cement chemistry. Part II will consider the development, composition, properties, and application of the bioactive calcium aluminate-based materials that have recently been developed for several indications in restorative dentistry.

CLINICAL SIGNIFICANCE

Bioactive materials have evolved over the past three decades from relatively specialized, highly biocompatible, but low-strength dental materials to now emerge in product compositions for expanded clinical uses in restorative dentistry. Further developments to meet additional restorative clinical needs are anticipated in this newly emerging category of dental materials.

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INTRODUCTION

The objectives for this review are:

1. Understand the relative position of bioactive materials in the context of past and present dental materials;
2. Discuss and understand the various compositional and material elements of certain biomimetic and bioactive dental materials utilized in endodontics and now increasing being applied in restorative dentistry;
3. Review the history and evolution of these materials in dentistry;
4. Review our current knowledge regarding selected physical property attributes of these materials;
5. Explain the definition of "bioactivity" in the context of these materials, review research regarding understanding the property of "bioactivity," and consider how it may relate to restorative dentistry;
6. Review current documented clinical findings and evidenced-base literature information regarding these materials as it relates to their properties and use in dentistry; and
7. Future directions and conclusions.

This review will examine this subject in a context more closely related to restorative dentistry but with the clear acknowledgement that much of the information has been developed in the context of the standards and relevance of other specialty disciplines in dentistry. As such, this review will attempt to provide a better understanding of the relative position of bioactive materials in the context of past and present dental materials.

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The general concept of bioactive restorative dental materials is not a totally new idea. If we consider the general concepts of adhesion to tooth structure and the release of fluoride as an adjunct to the prevention of secondary or recurrent decay, dentistry has had the availability of "bioactive" restorative materials now for several decades in the form of fluoride-releasing materials. For the purpose of this review and discussion, bioactivity in this review will be defined as follows: A bioactive material is one that forms a surface layer of an apatite-like material in the presence of an inorganic phosphate solution.[1]

Although this review will consider the two specific categories, the calcium silicate- and calcium aluminate-based cements, within the broad group of bioactive materials, a wide range of calcium-based or calcium-containing materials have demonstrated bioactivity. These materials include, but may not be limited to crystalline calcium phosphate materials including various apatites and hydroapatites, various glasses under the generic terms "bioactive glasses" or "bioglasses," various glass ceramics such as apatite-wollantonite materials, calcium silicate-based cements, and calcium aluminate-based cements. We will focus on the later two material categories, the calcium silicates and calcium aluminates, in this review as these two materials have had the greatest impact in the area of restorative and endodontic dental materials. In the field of bioactive glass and its variants, a recent excellent review by Jones[2] considers the main developments covering the evolution and properties of this class of bioactive materials ranging from Hench's Bioglass 45S5 to new hybrid materials that have tailorable mechanical properties and degradation rates.

With respect to the two basic types of material compositions covered by this review, the topics considered will include the history and evolution of these materials in dentistry, examining our current knowledge regarding selected physical property attributes of these materials, and how the "bioactivity" of these materials has been examined and studied. Bioactivity will also be considered in the context of the broad and now well-established category of fluoride-releasing dental materials. Also examined will be how this phenomenon of bioactivity may be of significance in the performance of these materials in restorative dentistry, as well as a review of current documented evidence-based literature regarding these materials as it relates to their properties and use in dentistry.

Bioactive cements fall under a well-known and long-standing group of dental and medical materials: the chemically bonded ceramic (CBC) cements. These cements are water-based and hence also often termed "hydraulic" cements. This group of dental materials is very familiar to clinicians in restorative dentistry. Therefore, it is useful to consider those long-standing and well-established cements that set by an acid-base reaction that are the basis of CBC cements in dentistry. These cements include:

- Zinc phosphate cements
- Silicate cements
- Polycarboxylate cements
- Glass ionomer (GI) cements

Each of these materials have represented two general trends: First, the evolution of traditional CBC materials (zinc phosphate → polycarboxylate → GI) demonstrates a major evolving trend away from more inert compositions to materials with more interactive or dynamic functions with respect to their interaction with tooth structure. This trend is further defined by three significant functional aspects: (1) adhesion to tooth structure, (2) continuous release of measurable levels of fluoride, and (3) an increasing trend toward the development, use, or incorporation resin methacrylate chemistry in dental restorative materials and cements. Materials incorporating these new functionalities fall within the following general categories:

1. Cements that set by a radical polymerization reaction:
   - Resin cements
2. Cements that set by a radical polymerization reaction + an acid-base reaction:
   - Resin-modified GI (RMGI) cements
   - Phosphate monomer-based self-etch adhesive

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Let us now consider the potential rationales for the use and incorporation of bioactive materials in restorative dentistry.

IS THERE A NEED FOR BIOACTIVE MATERIALS IN RESTORATIVE DENTISTRY?

Clearly, the quest for "interactive" or "bioactive" dental restorative materials is not a totally new endeavor and does not necessarily start with the materials that are the focus of this review: calcium silicate- or calcium aluminate-based dental materials. For example, as a general concept, GIs have been ascribed bioactive properties because of their dynamic release of fluoride, as well as their unique mineral-based poly-salt matrix composition that has been claimed to also contribute to the ability to remineralize calcium-depleted tooth structure. The continuous release of fluoride by GI and RMGIs has also been positioned as a potential mechanism to delay or inhibit secondary caries at the margins of these restorations (GI and RMGI).[3] Yet despite the release of fluoride ions, in some studies, secondary caries has been found to be a reason for clinical failure of glass ionomer cement restorations.[4] GIs are excellent materials in particular restorative situations and clinical indications, but their ability to prevent recurrent caries may be somewhat variable. The literature suggests that this mode of protection by GIs still remains equivocal.[5]

Likewise, the potential benefits of the use of adhesive monomers both in free-standing dentin-enamel adhesives and now in the self-adhesive cement formulations are still somewhat areas of debate. Current restorative resin/dentin adhesive systems have demonstrated outstanding long-term clinical performance in prospective clinical studies.[6] Nevertheless, consider the paradoxical and somewhat contradictory data concerning the performance of posterior composite resins and dentin-enamel adhesives. Many prospective university-based clinical studies conducted in the 1980s, 1990s, and early 2000s executed with protocol-directed procedures and experienced clinical researchers demonstrated quite acceptable performance of enamel-dentin adhesives used in combination with posterior composite resins.[7–10] In contrast, more recent randomized, controlled, clinical studies conducted with multiple sites and multiple operators suggest less favorable results.[11–13] In a similar time frame, advanced analytical techniques to examine the adhesive resin-dentin interfacial region have revealed a number of potentially deleterious phenomena that could interfere with successful dentin bonding.[14–16] These mechanisms include adverse effects from delayed hydrolysis within the resin-dentin collagen hybrid zone because of "water-tree" formation[17–20] and enzymatic degradation of the collagen component within and immediately adjacent to resin-collagen hybrid zone because of reactivation of metalloproteinase enzymes exposed by acidic demineralization of the dentin.[21,22] Although continual improvement in both adhesives and posterior composites may well address these issues, the potential may exist for radically different material chemistries and alternative mechanisms to secure a stable interface between tooth structure and the restoration. For example, it may be possible to secure integration to tooth structure without the use of adhesive monomers. So it appears that although the course of dental materials development has produced a number of new technologies to improve dental restoration performance, challenges and issues still remain that encourage the consideration of new chemistries and compositions in restorative dentistry.

COMPOSITIONAL AND MATERIAL ELEMENTS OF BIOMIMETIC/BIOACTIVE DENTAL MATERIALS

This review will consider exclusively the calcium silicate- and calcium aluminate-based dental materials. Although the basic compositional aspect of both materials will be explored, it should be noted at the outset that continual adjustments and variations are occurring in these materials as new products and compositions are made available to the clinician. The relative compositions of the calcium aluminate and calcium silicate cements are composed of three basic constituents comprising various proportions of calcium oxide (CaO)/silicon dioxide (SiO_2)/calcium aluminate

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(Al_2O_3). Most of these cements used in dentistry are fairly heterogeneous in their composition, and as such contain both silicate and aluminate components in varying proportions. Nevertheless, these materials can be considered in one of two groups: those containing predominantly silicate components versus those who contain predominantly aluminate components. It is within this basic chemical compositional framework that we will discuss later the history and evolution of these materials and their basic compositions in dentistry. Table 1 provides a partial list of materials and products currently available for use in dentistry that contain either calcium silicate or calcium aluminate components and will be discussed in this review.

The setting reaction of both the calcium silicate and calcium aluminate cements follows a similar sequence of chemical events in their setting reactions that includes the following events when water or an aqueous solution is added to the cement power:

1. Dissolution of cement grains
2. Growing ionic concentration in aqueous solution
3. Formation of ionic compounds in solution
4. After reaching a saturation concentration, compounds precipitate out as solids (hydration products)
5. In later stages, products form on or very near the surface of the anhydrous cement

Calcium silicate materials derived from the basic building material Portland cement were the first of these types of bioactive materials to appear for use in dentistry and most specifically in the field of endodontic therapy.

CALCIUM SILICATE MATERIALS BASED ON MINERAL TRIOXIDE AGGREGATE (PORTLAND CEMENT)

The calcium silicate-based cements were the first to appear in dentistry and were focused primarily for use in endodontic therapy as a general root replacement material. The first of these calcium silicate materials to appear and develop into a viable material for clinical use was mineral trioxide aggregate (MTA).[23–27]

Abedi and Ingle, Torabinejad et al., and Torabinejad and White first introduced MTA to dentistry and this material was ultimately demonstrated to be the first of the bioactive cements to be adopted for use in endodontics and restorative dentistry.[23–25] The MTA formulation is closely related to the long-standing and ubiquitous construction material, Portland cement.[24,28,29]Portland cements are categorized as hydraulic cements containing primarily calcium silicates derivatives (tricalcium and dicalcium silicates) with a complex composition and setting reaction.[28–30] The major constituents of Portland Cement are tricalcium and dicalcium silicate, with decreasing proportions of tricalcium aluminate and tetracalcium aluminoferrite. The initial interest in the use of Portland cement as a dental material, particularly for use as a root-end filling material, was its hydraulic nature. Root-end filling materials have to set and develop their properties in a wet environment. A mixture of Portland cement and bismuth oxide was marketed as MTA. Bismuth oxide is added as a radiopacifier, thus making the cement visible on radiographs.[25] Root-end filling materials need to be radiopaque as they have to be identified after placement for medicolegal reasons.[27] MTA exhibited desirable physical and mechanical properties,[24,28,31–33] and has been shown to be bioactive when in contact with tissue fluids.[34–36] MTA is currently being used for a variety of applications in endodontics and restorative dentistry.[26,37]

In view of MTA's very close compositional relationship to Portland cement, some basic chemical facts regarding MTA are in order:[38]

- MTA is a derivative of a type I ordinary Portland cement (a hydraulic cement) with 4 : 1 proportions of bismuth oxide added for radiopacity. Portland cement is the active ingredient in white MTA (WMTA).
- White Portland cements components are: (1) dicalcium and tricalcium silicate ($2CaO.SiO_2$ belite and $3CaO.SiO_2$ alite), (2) tricalcium aluminate 3CaO.Al2O3, and (3) gypsum $CaSO_4{\cdot}2H_2O$ hydrophilic powders.

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TABLE 1. Summary data for calcium silicate and calcium aluminate cements included in this review of bioactive dental materials

Generic Description	Commercial Trade Name	Manufacturer	Product Format	Indications for Use
Calcium silicate—PC-like Contains iron	Gray ProRoot Mineral Trioxide Aggregate (GMTA)	Dentsply/Tulsa, Dentsply International, York, PA,USA	Powder-Liquid	Pulp cap, pulpotomy, root ending filling, repair of root resorption, repair of root perforations, apexification
Calcium silicate—PC-like Iron-free or reduced	White ProRoot Mineral Trioxide Aggregate (WMTA)	Dentsply/Tulsa Dentsply International	Powder-Liquid	Pulp cap, pulpotomy, root ending filling, repair of root resorption, repair of root perforations, apexification
Calcium silicate—PC-like	MTA—Angelus	Angelus Indistria de Produtos Odontologicos S/A, Rua Waldir Landgraf, 10 1, Londrina—PR—86031-218, Brazil	Powder-Liquid	Pulp cap, pulpotomy, root ending filling, repair of root resorption, repair of root perforations, apexification
Calcium silicate (aluminum absent)	Bioaggregate	Innovative BioCeramix, Inc., 3650 Wesbrook Mall, Vancouver, BC V6S 2L2, Canada	Powder-Liquid	Repair of root perforations, repair of root resorption, root end filling, apexification, pulp capping
Calcium silicate (aluminum absent)	Endosequence Root Repair Material	Brasseler USA, One Brasseler Boulevard, Savannah, GA 31419, USA	Single component—paste or putty	Repair of root perforations, repair of root resorption, root end filling, apexification, pulp capping
Calcium silicate (aluminum absent)	iRoot BP	Innovative BioCeramix, Inc.	Single component—paste or putty	Injectable root repair material
Calcium silicate (aluminum absent)	iRoot SP	Innovative BioCeramix, Inc.	Single component—paste or putty	Root canal sealer
Tricalcium silicate	Biodentine	Septodont, 205 Granite Run Drive, Suite 150, Lancaster, PA 17601, USA	Powder-liquid/capsule/trituration	Pulp cap, pulpotomy, root ending filling, repair of root resorption, repair of root perforations, apexification, liner/base, temporary restorative
Calcium aluminate	DoxaDent	Doxa Certex AB, Uppsala, Sweden	Powder-liquid/capsule/trituration	Permanent posterior restorative
Calcium aluminate/glass ionomer	Ceramir Crown & Bridge	Doxa Dental AB, Doxa AB, Axel Johanssons Gata 4-6, SE-754 50 Uppsala, Sweden	Powder-liquid/capsule/trituration	Permanent luting cement

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- When hydrated, the silicate phases of Portland cements (and MTA) undergo a series of physicochemical reactions resulting in the formation of a nanoporous matrix/gel of calcium silicate hydrates("C-S-H phases") and of a soluble fraction of calcium hydroxide Ca(OH)2 or portlandite.

Although ProRoot MTA and Portland cement have been shown to have similar constituents,[39–42] it is important to emphasize that MTA products produced by ethical device manufacturers and approved for marketing under applicable regulatory bodies have some significant differences from ordinary Portland cement. MTA materials have been reported to have a smaller mean particle size, contain less heavy metals, have a longer working time, and appears to have undergone additional processing and purification than the Portland cement parent compound.[43] Further analysis with respect to major differences between MTA and Portland cement have indicated a presence of bismuth oxide in MTA,[25] the fineness of MTA powder, and the lower levels of calcium aluminate and calcium sulfate in MTA when compared with Portland cement.[44]

A WMTA version of the original gray MTA (GMTA) has been marketed since 2002 because of esthetic considerations and contains less iron, aluminum, and magnesium oxides than its GMTA counterpart. Both materials undergo a hydration setting reaction that is said to reach an initial set in 3 to 4 hours but whose maturation and resistance to dislodgement increases with time. The presence of iron (ferrite ion) in sufficient quantities tends to give the cement a gray color.[43] The physical properties and setting time of MTA materials can be affected by different preparation liquids, and both WMTA and GMTA have been shown to possess antibacterial and antifungal activity, which is presumably due to its alkaline pH.[43]

The setting time for Portland or calcium silicate cements is much longer than typically encountered with typical dental cements such as zinc phosphate, GI, polycarboxylate, or phenolate-based cements such as calcium hydroxide.[24,28] In addition to the slow setting properties of MTA- and Portland cement-derived materials (3–4 hours to full set), these materials also have limited physical strength properties, with compressive strengths on the order of 20 to 60 megapascals (MPa), a value sufficient for their initial clinical uses as pulp capping and root replacement materials.[28,31–33] The comparative strength properties of these various bioactive materials will be discussed further later in this review.

With respect to clinical uses in dentistry, MTA was originally developed as a root-end filling material following apicectomy and to repair root perforations.[45] The material has been used successfully in this regard, and indeed, its uses have expanded over the past few decades into other indications in the area of operative dentistry and pedodontics. For example, MTA has been reported to be suitable for use as a pulp capping agent,[46–50] as a dressing over pulpotomies of permanent,[51–54] and primary teeth replacing the formocresol pulpotomy procedure[55–57] for obturation of retained primary and permanent teeth,[58,59] and for single visit apexification procedures for immature teeth with necrotic pulps,[60,61] thereby acting as an apical barrier material[62] and as a root canal sealer cement.[51,63]

Numerous studies have evaluated the biocompatibility of GMTA and WMTA,[41] as well as its unique bioactive property. Interestingly, a few studies have attempted to identify the specific quality of MTA materials that provides their biocompatible nature. Some reports speculated that MTA's biocompatibility was derived from calcium hydroxide formation.[64,65] One report did observe the formation of a white interfacial material between GMTA and tooth structure when exposed to a phosphate-buffered physiological solution.[65] Sarkar *et al*.[66] reported the first investigation aimed solely at investigating the biocompatible nature of MTA materials and reported the formation of white precipitates within 1 to 2 hours on the GMTA surface along with suspended precipitates within the physiological phosphate-buffered saline solution. Scanning electron microscopy (SEM) analysis of these precipitates revealed a globular morphology with chemical composition of oxygen, calcium, and phosphorus, along with trace amounts of bismuth, silicon, and aluminum, whereas X-ray diffraction (XRD) analysis suggested the presence of hydroxyapatite,

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although it should be noted that the calcium-to-phosphorus ratios reported differed from that reported for hydroxyapatite.[66] This report, suggesting surface deposits similar to hydroxyapatite, was further reinforced by Bozeman *et al*.[67] who also used XRD and SEM analysis of both WMTA and GMTA crystal precipitates under the same conditions, and also demonstrated that the crystal precipitates on both MTA materials were chemically and structurally similar to hydroxyapatite. It is interesting to note that GMTA was found to produce twice as much hydroxyapatite crystals as WMTA, which leads to some speculation that GMTA and WMTA may not possess the same level of bioactivity.[67]

It should be noted that a number of manufacturers now provides calcium silicate cements closely related to the MTA/Portland cement formulation. These products are listed in Table 1 and will now also be described as follows.

CALCIUM SILICATE CEMENTS LACKING ALUMINUM AND CONTAINING PHOSPHATE

Bioaggregate (BA; Innovative BioCeramix, Vancouver, Canada), a calcium silicate-based material, is a modified type of MTA.[68–70]As noted in Table 1, BA is composed of calcium silicate oxides and calcium silicate. Also present are hydroxyapatite, calcium phosphate silicate, calcite, and tantalum oxide as a radiopacifier. In contrast with Portland cement, MTA, and related products, BA is reported to be free of calcium aluminate[68,69,71](see Table 1). Furthermore, BA is also reported to contain the addition of higher levels of phosphate in contrast with the minimal phosphate levels found in Portland cement and MTA.[68,69]

Therefore, most of the constituents of BA are the same as that in WMTA except that BA is aluminum-free, uses a different metallic oxide as an opacifier, and has added phosphate constituents such as hydroxyapatite. With respect to other points of comparison between BA and MTA, Zhang *et al*.[72] demonstrate that MTA and BA have similar antibacterial properties. BA and MTA also have similar ability to prevent leakage[73] and comparable cell toxicity.[71] However, the material push-out strength in furcal perforations repaired with WMTA was superior than those for BA in acidic condition, yet both cements are adversely affected by acidic pH.[74] Recently, a report has appeared concerning a comparison of physical strength properties of BA versus WMTA.[69] When incubated in a phosphate-containing synthetic tissue fluid (STF) buffered at a neutral pH of 7.4 for 3 days, WMTA recorded a mean compressive strength (mean + standard deviation) of approximately 86.2 + 11.8 MPa, whereas BAs mean value was 25.4 + 4.7 MPa. An experimental "nano-MTA" material was also evaluated in this study and recorded a mean compressive strength value of 126.8 + 9.8 MPa at pH 7.4. When the STF was buffered at an alkaline pH of 10.4, all three materials tested experience significant increases in mean compressive strength; however, when buffered at an acid pH of 4.4, the mean compressive strength values for both WMTA and BA decreased significantly.

IRoot SP and iRoot BP (Innovative BioCeramix) are calcium silicate-based root canal sealers and root canal repair/root replacement materials, respectively. According to the manufacturer, their composition is similar to BA. However, unlike BA that is a two-component, powder/liquid system requiring mixing, iRoot SP and iRoot BP are unique in that they are both single-component materials that use water-soluble polymer additives as a carrier and then set slowly once placed because of moisture either in the oral cavity or from interstitial tissue fluid.[75] Also, the manufacturer states that nanohydroxyapatite is utilized in the product, and the particle size of the calcium silicate fillers is reduced to permit ease of penetration of the sealer into the dentinal tubules.[76] The manufacturer also states on its website that iRoot SP also is available as Endosequence BC Sealer, which is a private label distributed by Brasseler USA, Savannah, GA, USA. The setting time of iRoot SP has been determined to be far longer than other MTA-like bioactive cements (on the order of 168 hours versus 3–4 hours) and exhibited higher cytotoxicity in in-vitro cell culture.[76] Another report, however, found the cytotoxicity of the related

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root repair material, iRoot BP (Endosequence Root Repair Material) to be acceptable.[77] The iRoot SP root canal sealer has also demonstrated antibacterial activity against *Enterococcus faecalis*.[78] MTA and iRoot SP induced human tooth germ stem cells differentiation into odontoblast-like cells, but MTA might provide more inductive potential and hard tissue deposition compared with iRoot SP.[79]

CALCIUM SILICATE CEMENTS CONTAINING PREDOMINANTLY TRICALCIUM SILICATE

As discussed earlier in this review, the Portland-type cements designed for medicine and dentistry, also termed hydraulic silicate cements,[80] mainly contain tricalcium silicate ($3CaO\text{-}SiO_2$; C_3S), which is responsible for rapid setting, development of early strength, and exhibits higher reactivity than the other calcium silicates.[81] Unfortunately, as noted earlier, MTA has had more limited applications in other major indications in operative dentistry because of its long setting time and low compressive strength compared with other materials. Nevertheless, MTA and calcium silicate-based cements from which it is derived appear to have two key attributes that account for their use as root replacement materials, endodontic sealing materials, and in vital pulp therapy as a pulp capping agent: excellent biocompatibility and marginal sealing ability. In order to exploit these properties, a fast-setting, calcium silicate-based restorative material designed for expanded indications in restorative dentistry has been brought onto the market (Biodentine, Septodont, St Maure des Foss'es, France).

With respect to actual compositional elements particular to Biodentine, this material is generically classified as a tricalcium silicate-based material. Biodentine is present as a powder/liquid system comprising a powder consisting of tricalcium silicate, dicalcium silicate, calcium carbonate, CaO, and zirconium oxide as a radiopacifier (Biodentine Scientific file 2010[82]). The liquid used for mixing with the cement powder consists of calcium chloride and a hydrosoluble polymer. The tricalcium silicate component is the primary constituent that undergoes the setting reaction. Calcium carbonate is incorporated for both its ability to decrease the setting time, biocompatibility, and its calcium content. The hydrosoluble polymer is based on polycarboxylate and maintains a balance between low water content and consistency of the mixture. This hydrosoluble polymer (water-reducing agent) functions therefore to maintain acceptable flow properties with a low water/solid ratio.[82] The rate of the setting time is minimized with the use of calcium chloride and fine particle sizes.[83] Both parts, powder and liquid, are provided in separate single-dose units. The liquid is provided in a sealed ampule, which after opening is dispensed into a plastic trituration capsule containing the powder. Five drops of liquid are added to the powder in the plastic mixing capsule. The capsule is resealed and titurated for 30 seconds at 4,000 to 4,200 rpm in a conventional titurator. The mixing Biodentine paste is then applied to the tooth without requiring any prior surface treatment. The working time for the material is reported to be 6 minutes and the final setting time of approximately 10 to 12 minutes.[82] Thus, it appears that the setting time for Biodentine is significantly faster than either MTA or modified MTA materials such as BA and more in line with setting times displayed by conventional restorative cements such as zinc phosphate and GI.

Biodentine was developed as a multipurpose, dentin, and root replacement material. Nevertheless, some of its clinical indications go beyond those of MTA and related Portland cement/calcium silicate products. These new indications include restoration of deep and large coronal carious lesions, restoration of deep cervical and radicular lesions, as well as the well established MTA indications such as pulp capping and pulpotomy, repair of root perforations, furcation perforations, perforating internal resorptions, external resorption, apexification, and root-end filling in endodontic surgery.

Biodentine has been shown to be biocompatible.[84] It is also bioactive and demonstrates the deposition of hydroxyapatite on its cement surface in the presence of simulated body fluid.[85] Its radiopacity was greater than 3-mm aluminum thickness. Biodentine caused the

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uptake of calcium (Ca) and silicon (Si) in the adjacent root canal dentin in the presence of physiological solution.[86] Various physical properties of Biodentine, BA, and Intermediate Restorative Material (IRM) were evaluated by Grech *et al*.[87] Using the testing procedures described in the International Organization for Standardization, International Standard, ISO 9917-1; 2007,[88] these investigators found that Biodentine exhibited superior compressive strength values of these three materials tested, with mean compressive strength values, after 28 days immersion in Hanks balanced salt solution, for Biodentine of 67.18 MPa, for BA of 16.34 MPa, and for IRM of 20.38 MPa. Setting time, again using the testing procedure set out in ISO 9917-1; 2007, gave values for the materials as follows: Biodentine, 45 minutes; BA, 1,260 minutes, and IRM, 3 minutes.[87]

In-vitro microleakage behavior for the tricalcium silicate material, Biodentine has also been evaluated. Diffusion of glucose was utilized to compare microleakage of open sandwich composite resin/Biodentine restorations placed in Class II preparations in extracted human teeth and compared directly to corresponding open sandwich restorations utilizing instead an RMGI material (Ionolux; Voco, Cuxhaven, Germany) and the same composite resin (TetricEvo Ceram; Ivoclar Vivadent, Schaan, Principality of Liechtenstein).[89]Mean microleakage scores comparing Biodentine and the RMGI were equivalent. Raskin *et al*.[90] examined in-vitro microleakage of Biodentine as a dentin substitute compared with Fuji II LC in cervical lining, open sandwich restorations, and found here again no statistically significant difference in mean leakage values between the two base/lining materials.

Material biocompatibility was further investigated by Ames' testing and was determined to be nonmutagenic; the material did not interfere with lymphocyte cell function, exhibited a lack of cytotoxicity similar to MTA, and did not alter pulpal fibroblast function with respect to mineralization, as well as expression of collagen I, dentin sialoprotein, and Nestin.[91] Pulpal biocompatibility was also assessed in tissue culture and in animal models. In one tissue culture model, Biodentine was directly applied onto the dental pulp in an entire human tooth culture model.[92] After various culture periods, the interaction of the material with dental pulp tissue was analyzed on tissue sections. The effect of increasing surface area of this material on transforming growth factor beta1 (TGF-β1) secretion was investigated on pulp cell cultures and compared with that of MTA, calcium hydroxide, and Xeno III adhesive resin. After performing artificial injuries on pulp cell cultures, the materials' eluates were added for 24 hours and then TGF-β1 secretion was quantified by enzyme-linked immunosorbent assay. Controls were performed by incubating intact cells with the culture medium, whereas injured cells' TGF-β1 level was used as the baseline value. Biodentine induced mineralized foci formation early after its application. The mineralization appeared in the form of osteodentine and expressed markers of odontoblasts. Biodentine significantly increased TGF-β1 secretion from pulp cells ($p < 0.03$) independently of the contact surface increase. This increase was also observed with calcium hydroxide and MTA, but not with the resin-based self-etching adhesive Xeno III. The statistical analysis showed statistically significant differences between capping materials and the resinous Xeno III ($p < 0.001$). When Biodentine was applied directly onto the pulp cell cultures, it induced an early form of reparative dentine synthesis probably because of a modulation of pulp cell TGF-β1 secretion.[92]

Another study evaluated the biological effect of Biodentine on immortalized murine (OD-21) pulp cells.[93] The expression patterns of several genes confirmed the differentiation of OD-21 cells into odontoblasts during the period of cell culture. The results of this study demonstrated that Biodentine increased OD-21 cell proliferation and biomineralization in comparison with controls. The authors further speculated that due to this observed active in tissue culture, Biodentine can be considered as a suitable material for clinical indications of dentin-pulp complex regeneration, such as direct pulp capping.

Another research report documents an actual animal pulp study using Biodentine as a direct pulp capping

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agent.[94] For that purpose, cavities with mechanical pulp exposure were prepared on maxillary first molars of 27 6-week-old male rats, and damaged pulps were capped with either the new calcium-silicate-based restorative cement (Biodentine), MTA, or $Ca(OH)_2$. Cavities were sealed with GI cement, and the repair process was assessed at several time points. At day 7, the results of this study showed that both the evaluated cement (Biodentine) and MTA induced cell proliferation and formation of mineralization foci, which were strongly positive for osteopontin. At longer time points, the formation of a homogeneous dentin bridge was observed at the injury site secreted by cells displaying an odontoblastic phenotype. In contrast, the reparative tissue induced by $Ca(OH)_2$ showed porous organization, suggesting a reparative process different from those induced by calcium silicate cements. Analysis of these data suggests that the evaluated cement can be used for direct pulp-capping.

Biodentine has clinical indications for use that are similar to MTA but are also expanded to include certain intermediate stress restorative applications.[82] One report has described the use of Biodentine as a temporary restorative, and then when cut back, as a base/liner underneath a composite resin restorative material.[95] In this study, Biodentine was able to restore posterior teeth for up to 6 months as a temporary restorative, was then cut back to a standard cavity preparation form, and subsequently covered with a composite resin, Z100. Based on the results of this clinical study, the investigators concluded that Biodentine may be able to be a dentin substitute that can be used under a composite for posterior restorations.

Part II, which follows in this review series, will consider the development and application of dental restorative materials based on calcium aluminate cement chemistry.

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