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Bioactive Tri/dicalcium Silicate Cements for Treatment of Pulpal and Periapical Tissues

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Abstract

Over 2500 articles and 200 reviews have been published on the bioactive tri/dicalcium silicate dental materials. The indications have expanded since their introduction in the 1990s from endodontic restorative and pulpal treatments to endodontic sealing and obturation. Bioactive ceramics, based on tri/dicalcium silicate cements, are now an indispensable part of the contemporary dental armamentarium for specialists including endodontists, pediatric dentists, oral surgeons andfor general dentists. This review emphasizes research on how these materials have conformed to international standards for dental materials ranging from biocompatibility (ISO 7405) to conformance as root canal sealers (ISO 6876). Potential future developments of alternative hydraulic materials were included. This review provides accurate materials science information on these important materials.

Graphical Abstract

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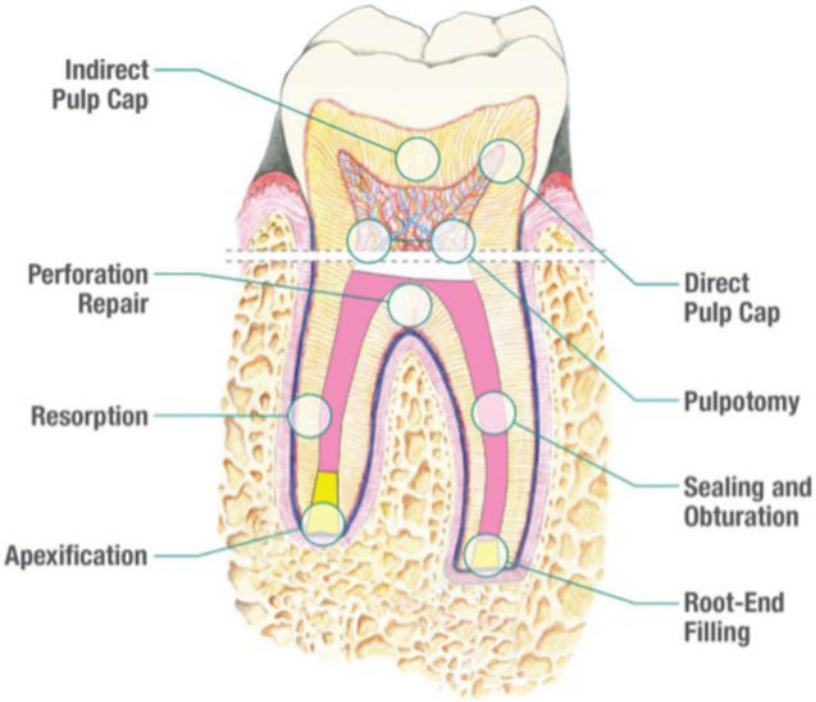

Keywords

bioactive; bioceramic; biosilicate; dicalcium silicate; hydraulic ceramic cement mineral trioxide aggregate; tricalcium silicate

1. Introduction

Bioactive materials are used in pulpal and other endodontic procedures for enhancing healing outcomes, particularly reducing the likelihood of extraction. Tooth loss is negatively associated with health, psychological well-being, and freedom from disability, and is prevalent on a worldwide basis. The current products for the various indications contain primarily two ceramic compounds, tricalcium silicate and dicalcium silicate [1]. These ceramic powders are the same phases as in commercial Portland cement used for construction, but are modified for medical grades and use in dentistry, as discussed herein. This situation is analogous to the industrial uses of poly(methyl) methacrylate for lightbulb covers, car, ship or aircraft windows, and nail products, in parallel with the use of medical grades of poly(methyl) methacrylate in dental materials containing other fillers and pigments.

These unique ceramic compounds are capable of room temperature reaction with water, a hydraulic setting reaction, to form a solid mass; that is, these powders are hydraulic. Being moisture tolerant (hydrophilic, hygroscopic) is a great advantage in dentistry where moist tissues can interfere with materials' placement and setting. This review only discusses the hydraulic tri/dicalcium silicates, which are most common, although other ceramic powders, e.g. calcium aluminate cement, are also hydraulic.

The first reference to the use of Portland cement in dentistry came from Dr. Witte, a 19th century dentist [2, 3]. He mixed Portland cement with water, carbolic acid or creosote for placement under a gold filling. A century later, Portland cement was revisited for dental use by Dr. Torabinejad and Mr. White who patented the use of Portland cement in endodontics (US Patents 5,415,547 and 5,769,638). The first 20th century article on such hydraulic ceramics for dentistry introduced the experimental material as "MT aggregate" [4]. The material was later dubbed MTA, a non-chemical descriptive name. The MTA material was described as a hydrophilic powder composed of "tricalcium silicate, tricalcium aluminate, tricalcium oxide, silicate oxide and a few other mineral oxides". Tricalcium oxide is a fictitious ceramic compound; unfortunately, many other publications have repeated this compound as a component [5–7]. A better description was given in the first patent: "a Portland cement ceramic powder composed of these phases: tricalcium silicate ($3CaO.SiO_2$), dicalcium silicate ($2CaO.SiO_2$), tricalcium aluminate ($3CaO.Al_2O_3$) and tetracalcium aluminoferrite ($4CaO.Al_2O_3.Fe_2O_3$)". Other oxides were mentioned in the first claim: "bismuth oxide with minor amounts of magnesia (MgO), potassia (K_2O) soda (Na_2O) and sulfates (e.g., $CaSO_4$ and its hydrates)".

Early literature reiterated the name mineral trioxide aggregate or MTA so often that "MTA" has become a generic name for these hydraulic tricalcium/dicalcium (tri/dicalcium) silicate-based products, although often misunderstood. "Mineral" is suitable for the name because naturally occurring minerals are used to create tri/dicalcium silicates, which do not occur in nature. Presumably, the trioxides in the name MTA refer to the oxides commonly used in describing Portland cement: calcia, silica and alumina. These three oxides are used by ceramic engineers in phase diagrams to show the range of compositions that create Portland cement [8]. The aluminum oxide (alumina) is common in construction-grade Portland cement because of alumina's concurrence with calcium and silicate minerals, although alumina is not an essential component to create a hydraulic tri/dicalcium silicate powder. The designation "trioxide" is a misnomer since other oxides were present in the original experimental material in quantities greater than 1%, including iron oxide and bismuth oxide. Some researchers have used the term "tetrasilicate cements" to describe their Portland cement-based materials that contain bismuth oxide and phyllosilicate [9, 10]. "Aggregate" may denote the addition of the radiopaque component, originally bismuth oxide, to the hydraulic powder, analogous to addition of sand or gravel to make concrete. Alternatively, aggregate may refer to the aggregation of the dicalcium silicate, tricalcium silicate, and tricalcium aluminate crystals in grains (particles) of the powdered cement. Other papers use the terms and abbreviations of hydraulic calcium silicate cements (hCSCs) [1] or tricalcium silicate (TCS) [11] for the same MTA-type materials. The term bi-phasic has been used to indicate the addition of a calcium phosphate phase [12] to the tri/dicalcium silicates, which is misleading since more than two ceramic phases are present in all such products. Although imperfect, the names "MTA-type materials", "tricalcium silicate" and "tri/dicalcium silicate-based" materials are used interchangeably in this paper to denote this category of hydraulic materials that principally set, and are bioactive, because of the inclusion of tri/dicalcium silicate powder.

Nomenclature has been further confused for the materials based on tri/dicalcium silicate by the use of other non-specific terminology [13], such as bioceramic and biosilicate. These are

either general [14], similar to MTA, or marketing terms. Bioceramics are a subset of ceramic materials and encompass a broad group of ceramic materials used *in vivo*, not specific to tri/dicalcium silicate cement. Dental bioceramics include ceramics for fixed prosthodontics (porcelain, alumina, zirconia, lithium disilicate), ceramic implants (zirconia). A broad range of glass (biosilicate) compositions are used in dental composites and glass ionomer cements. Biosilicates encompass all glasses used in vivo. For dentistry biosilicates include dental porcelain, bioactive glasses", and radiopaque glasses included as fillers in a variety of cements and restorative dental materials. Needless distinctions have been made between "MTA" and "bioceramics" that confuse the dental community, although the evolution of commercial tri/dicalcium silicate products is clear [15]. Many papers refer to these hydraulic cements as calcium silicate. In the ceramic realm, calcium silicate is wollastonite ($CaSiO_3$), which is not an appreciably hydraulic phase [16]; that is, it does not set when water is added. The scientific terminology for the MTA-type cements is preferably tricalcium silicate-based, tri/dicalcium silicate-based, "calcium silicates", or calcium silicate-based.

Dentists commonly use type classification for materials, but no type designations have been adopted in dental standards for these hydraulic materials. "Type I" and "Type III" Portland cement has been used to describe some MTA-type dental products [18–20], based on classification used in ASTM C150 (Standard Specification for Portland Cement). ASTM C150 specifies a minimum surface area (>260 m^2/kg) for Type I cement and a maximum for Type II cement as (430 m^2/kg); however, this surface area is low, compared to the 1st patented MTA cement (450 – 460 m^2/kg), or that of, for instance, OrthoMTA product (961 m^2/kg http://www.biomta.com/shop/eng/technology_1.php; accessed 2/8/19) and low compared to ZnO powders used in dentistry and medicine (~10,000 m^2/kg) [18]. Low surface area is indicative of coarse particles.

Various dental articles have described the manufacture of tri/dicalcium silicate for tri/dicalcium silicate cement for dentistry [21, 22]. However, these authors have no intimate knowledge of the various manufacturers' methods, which are closely guarded trade secrets. Likewise, literature that reports on the major and trace raw materials, methods of mixing, firing and grinding of tri/dicalcium silicate cements cannot be relied upon [23, 24]. Studies have compared Portland cements from around the world to the tri/dicalcium silicate (MTA-type) cements used in dentistry. The specialized particle size, purity and radiopaque compositions used for these dental materials are generally recognized and accepted [25].

2. Hydraulic, bioactive tri/dicalcium silicate products

Only one experimental MTA-type material was available until 1998, personally available through the inventor. Articles published in the 1990s on this material demonstrated the benefits of the experimental MTA over amalgam and zinc-oxide eugenol in cytotoxicity [25] and bone implantation [27]. Microleakage studies confirmed the performance of the material using fluid filtration [18, 28], dye leakage, bacterial and endotoxin tests [4, 29–31]. Animal tests showed efficacy in root-end fillings in monkeys [32] or dogs [33]. The experimental MTA cement was advocated for endodontic restoration indications such as apexification [34], root-end filling [31] perforation repair [4] and vital pulp procedures such as pulp-capping [35].

From one experimental material in the 1990s, the marketplace now has grown to include over twenty commercial hydraulic tri/dicalcium silicate dental products sold world-wide. Table I lists the tri/dicalcium silicate materials indicated for endodontic restorative procedures such as root-end filling, perforation repair, apexification or pulp-capping. Many products were cleared by the US Food and Drug Administration under the 510(k) process from eleven manufacturers; others are available in select international markets. The tri/dicalcium silicate product indications include internal [36] or external root resorption [37], obturation [36] for horizontally fractured teeth [38], regenerative endodontics [39], and for replantation [40] or external cervical resorption treatment [41]. These indications fall under contact with pulpal or periapical tissue. Figure 1 has an example of each in extracted teeth.

The first commercial material, ProRoot MTA (Dentsply Sirona, York, PA, USA) has a composition that followed the patents (US Patents 5,415,547 and 5,769,638) and contains bismuth oxide as radiopacifier. MTA Angelus (Angelus Indústria de Produtos Odontológicos S/A, Londrina, PR, Brazil) followed with a similar composition, and is also distributed by other companies. Recently, the Angelus company has introduced a tri/dicalcium silicate with calcium tungstate for radiopacity. Bioaggregate (Innovative Bioceramic, Inc., Vancouver, British Columbia, Canada) was another early product that contains tri/dicalcium silicate and tantalum oxide, the latter instead of bismuth oxide for radiopacity. This material does not contain tricalcium aluminate. These three product kits contain water to mix with the powder. Biodentine (Septodont, Saint-Maur-des-Fossés, France) was the first tri/dicalcium silicate product to contain zirconia as radiopacifier; however, its radiopacity is lower than the aforementioned products. The powder in Biodentine also contains calcium carbonate, perhaps to speed setting of the tri/dicalcium silicate cement [42]. Biodentine kits include a water-based solution containing calcium chloride and carboxylate in the liquid for triturating with the powder. The calcium carbonate, the modified water solution and trituration may have reduced the setting time [43], which has been reported to be 12 minutes [44]. Other companies have manufactured or distributed tri/dicalcium silicate products with various attributes such as bulk powder and gel for convenience and economy, faster setting and discoloration resistance with dual-use as a putty and endodontic sealer (NuSmile, Houston, TX, USA). Smaller unit doses (0.1 to 0.3 gm) are also available for hand mixed materials (BioMTA, Seoul, Korea; Endoseal MTA, Maruchi, Wonju, Korea) or trituration (S&C Polymers, Elmshorn, Germany). Other products are less well known, but have their own attributes such as price and availability in a specific country.

Table I includes one light-curable tri/dicalcium silicate material, indicated only for direct and indirect pulp-capping. The TheraCal (Bisco, Inc., Schaumburg, IL, USA) material contains mostly resin, with 45% of “hydraulic cement” [45], which may include the barium zirconate component, although the $BaZrO_3$ is not hydraulic. Light-curing is fast [46] and contributes to low solubility [20]. Some have reported higher calcium ion release [18] than the other tri/dicalcium silicates without resin; however, the calcium ion release from TheraCal has been disputed [47]. The radiopacity is low (only 1 mm of equivalent aluminum) [19], which is similar to dentin [48].

Maruchi and BioMTA companies introduced hydraulic tri/dicalcium silicate materials described as pozzolans or pozzolanic cement. Pozzolan cement is the term used for cements

that rely on the reaction of silica and calcium oxide with water [16, 49]. Pozzolanic cement preceded the development of Portland cement and dates to ancient Roman “cement”. Nowadays, when silica is added to Portland cement, the term pozzolanic Portland cement may be used. The silica added to Portland cement may react with the calcium hydroxide (aka. Portlandite phase, Ca(OH)2) during setting to increase strength. Endocem (Maruchi, Gangwon-do, South Korea) is described as an “MTA-derived pozzolan containing small particle pozzolan cement” [50, 51], and its safety data sheet states that “Natural Pure Cement” is present. Although not explicit, this indicates that very fine silica particles are present [52] with a tri/dicalcium silicate powder. RetroMTA (BioMTA, Seoul, Korea) is a fast setting (< 5 minutes) so-called pozzolan cement; it contains calcium carbonate (60%–80%), silicon dioxide (5–15%), aluminum oxide (5–10 %), and “calcium zirconia complex” (20–30%) [53]. RetroMTA is also marketed by Sprig for pediatric dentistry. These pozzolanic cements are included in this review.

The aforementioned materials are indicated for endodontic restoratives (subgingival, that is, not in contact with saliva and entirely encased within the tooth) or intracoronal procedures (pulp-capping or pulpotomies). For conventional endodontic sealing with gutta-percha, root canal sealers must be in a tacky paste form [54]. Calcium hydroxide-containing root canal sealers have been advocated for use in endodontic treatment [55]. Therefore, tri/dicalcium silicate materials would be considered for root canal therapy because these materials form calcium hydroxide during setting [56]. The bioactivity (discussed below) of such sealers [57] may improve the barrier between the oral cavity and the alveolar bone. Hydraulic tri/dicalcium silicate endodontic sealers have been developed for use with gutta-percha [58] (Table I). The tri/dicalcium silicate-containing sealers available are offered with as powder with water-based liquid (BioRoot RCS, Septodont; NeoMTA Plus, NuSmile), as a two-paste resin system (MTA Fillapex, Angelus), or as a single paste with organic liquid such as a glycol liquid (iRoot, Innovative BioCeramix Inc., Burnaby, British Columbia, Canada). The iRoot sealer is also available under other tradenames: Endosequence BC sealer, (Brasseler USA, Savannah, GA, USA), EdgeEndo Bioceramic Sealer, (EdgeEndo, Albuquerque, NM, USA) and TotalFill (La Chaux-de-Fonds, Switzerland). Gutta-percha points containing “bioceramic” are marketed by Brasseler USA for use with their single paste sealer. No publications are available about the use of the two components and their joint benefits.

Brazilian Seal Plus BC (MK Life, Porto Alegre, RS, Brazil) and Maruchi EndoSeal are also single paste sealers. For the single paste sealers, the organic liquid must be displaced *in vivo* by body fluids for the cement to set.

The MTA Fillapex sealer (formerly known as MTA Obtura) is primarily disalicylate resin with only 13% added MTA-type particles [58]. Other products are formatted for powder/water-based liquid mixing [59]. These products include Endo CPM (EGEO SRL, Buenos Aires, Argentina, not on the US market), and ProRoot Endo Sealer (Dentsply-Sirona, York, PA USA), which is no longer on the market. Tri/dicalcium silicate-containing root canal sealers have been erroneously separately categorized as MTA sealers or Bioceramic sealers, when the compositions are both based on tri/dicalcium silicate. Furthermore, some manufacturers stated that hydroxyapatite is co-precipitated during setting. The precipitation

of hydroxyapatite occurs on the cement surface upon reaction with body fluids, but is not precipitated within the cement.

The literature is replete with articles and reviews on all aspects of these products in the 25 years since the first contemporary paper [4] was published on MTA-type materials. The many tri/dicalcium silicate products, excluding the resin-based products, have common features: hydraulic setting (reaction with water), creating alkaline pH (>7), calcium ion release, bioactive, relatively slower setting compared to many dental materials, and gradual strengthening by hydration over about 4 weeks. The radiopaque components and radiopacity vary among the many products. Formats of the products are wide-ranging, and the indications also are broad. Yet the versatile hydraulic tri/dicalcium silicate ceramic material is now recognized as the gold standard for many endodontic procedures [60, 61], and is likely to replace formocresol as the gold standard for pediatric pulpotomies [62].

3. International Standards

International and US regulatory organizations rely on International Organization for Standardization (ISO) requirements for dental materials. The hierarchy for evaluating materials and products begins with knowing the physical/chemical properties, progressing to *ex vivo* (extracted tooth) and cellular testing, animal tests, and finally to clinical testing in animals and humans [63]. This review describes the compliance of the tri/dicalcium silicate hydraulic materials with ISO dental requirements from physical to biocompatibility requirements, including clinical performance. Table II has a list of the ISO documents pertinent to the tri/dicalcium silicates. The American Dental Association's standards are often identical to the ISO documents although some exceptions for particular properties are noted in this review.

Using the definitions in ISO 10993–1 for medical device biocompatibility, the indications for endodontic uses discussed above make tri/dicalcium silicates (permanent) implant medical devices for contacting tissue or bone; that is, long-term exposure. These materials are not used supragingivally because of their acid solubility. The risk-focused ISO 10993–1 (2018 edition) requires that the first step is to assess the chemical and physical properties for a medical device, such as a dental material. Thereafter, nine biological tests are listed in ISO 10993–1 for biological evaluation and risk assessment of such implanted materials. Relevant implantation sites should be used where possible. According to the document, comprehensive implantation assessments may supplant acute systemic toxicity, subacute toxicity, subchronic toxicity and/or chronic toxicity, if sufficient animals and time-points are included, such that separate studies for acute, subacute, subchronic, and chronic toxicity are not always necessary.

Bioactivity is defined in ISO 22317, Implants for surgery — In vitro evaluation for apatite-forming ability of implant materials. Bioactive materials implanted in a living body form a thin layer rich in Ca and P on its surface. ISO 23317 describes *in vitro* tests for materials that stimulate the formation of apatite, calcium phosphate, in synthetic body fluids. When precipitation of hydroxyapatite occurs on the surface of a material in simulated body fluid, the same bioactivity can be expected *in vivo*. The implanted material then connects to the

living tissue through the apatite layer without a distinct boundary. Herein, apatite is used to refer to hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$, the calcium-phosphate of bone mineral and the inorganic constituent of bones and teeth. To detect bioactivity hydroxyapatite may be detected, for instance, by x-ray diffraction of the precipitant on the surface of the material, or by microscopic examination of its characteristic crystal growth.

The ISO 7405 is a biocompatibility standard related to ISO 10993–1, specifically for dental materials. The classification is slightly different for the tri/dicalcium silicate-type materials as a “permanent implant contacting the pulpodentinal system”. The ISO 7405 tests for consideration are similar to ISO 10993–1. ISO 7405 also defines dental bioactive endodontic materials as capable of stimulating apical hard tissue formation, used for either orthograde or retrograde indications. For such materials, an endodontic usage test should be considered, which evaluates the biocompatibility of endodontic materials with the remaining apical pulp tissues (stumps) and the periapical tissues using clinical procedures. A pulp-capping test for bioactive materials is also useful for tri/dicalcium silicate materials indicated for vital pulp treatment.

Two tests from ISO 9917–1 for water-based dental cements have been used to test tri/dicalcium dental materials: compressive strength and acid-soluble arsenic and lead [64]. The hydraulic tri/dicalcium cements do not fit the classifications of ISO 9917–1 because they are not zinc phosphate, polycarboxylate or glass polyalkenoate cements, nor are they used as luting or restorative cements. However, tri/dicalcium silicate cements may be used as base or liner, which is within the field of ISO 9917–1. The other tests in this standard are not relevant to these indications for tri/dicalcium silicates cements.

ISO 6876 and American Dental Association (ADA) 57 documents were written for endodontic sealers used in conjunction with gutta-percha, but they are relevant to the tri/dicalcium silicate hydraulic cements, within limits. The ISO 6876 and ADA 57 standards are similar, but ADA 57 includes an additional requirement for dimensional stability, which is noted in Table II. ADA 57 requires larger sample sizes for the determination of working time and setting time. The larger samples are suitable for manufacturers to use, but difficult for researchers who have less access to materials that are sometimes costly. The ISO 6876 and ADA 57 standards have limited applicability to the tri/dicalcium silicate materials. These two standards have not considered endodontic restorative materials used in dentinal walls, such as for sealing perforations, treating root resorption or root-end filling. For these uses, materials need not have a low film thickness or high flow as do endodontic sealing materials used with gutta-percha. Zinc oxide and amalgam have been appropriated for these endodontic restorative indications, so no standard has yet been created for such uses.

4. Chemical and physical properties

As described in the Introduction, the ceramic phases (compounds) present in the MTA-type materials were initially not well understood or described. A convenient analysis method for materials analysis is energy dispersive x-ray analysis (EDX) with a scanning electron microscope. The EDX detector senses x-ray emission of elements stimulated by the microscope electron beam. EDX software can convert the elemental data into oxides which

has been reported [65]; however, EDX cannot determine what phases are present. That is, EDX cannot distinguish between calcium and aluminum and the compound tricalcium aluminate. As a result, when the constituents of the MTA-type materials were reported as individual oxides using the SEM-EDX technique, the ceramic compounds were not identified. The compounds are crucial to know because these phases determine the setting reactions. For example, Torabinejad and co-workers [66] reported that the prototype gray MTA contained calcium silicates and calcium aluminates. Later in the reference, the material was described as containing calcium and phosphorous atoms, even though phosphorous oxide was not a constituent listed. Other authors followed further confused the compositional understanding of the MTA-type materials by reporting the individual oxides using energy dispersive x-ray fluorescence [67]. Metals are also analyzed with XRF, the results of which are also converted with software to oxides. The XRF technique is more precise than EDX. For MTA-type materials, the metal oxides are predominantly silica (SiO_2, silicon dioxide) and calcia (CaO, calcium oxide) and less than 5% of iron oxide, alumina, magnesia (Al_2O_3, MgO), calcium sulfates (anhydrate, hemihydrate or dihydrate of $CaSO_4$) and alkali oxide (Na_2O, K_2O). Minor amounts of oxides such as titania or phosphorous pentoxide may be present. Scanning electron microscopy-EDX was used to compare five dental materials and four white Portland cements after mixing with water and setting. Four of the dental materials contained bismuth oxide and other oxides present in the white Portland cement. The New Experimental Cement (NEC) prototype material did not contain any radiopaque additive, but did include higher amounts of (calcium) phosphate and sulfate [69] than the ProRoot MTA product using electron microprobe microanalysis.

Although the atomic composition is informative to compare similar materials, the behavior will not be that of the phases (compounds). For example, Portland cement is not an admixture of the oxides of calcium, silicon, and aluminum. X-ray diffraction is the best technique to determine the phases that are present [47, 66]. The dental MTA-type materials contain several ceramic compounds: tricalcium silicate (alite), dicalcium silicate (belite), commonly with lesser amounts of tricalcium aluminate, tetracalcium aluminoferrite, and calcium sulfate [$(CaO)_3{\cdot}SiO_2$, $(CaO)_2{\cdot}SiO_2$, $(CaO)_3Al_2O_3$, $(CaO)_4Al_2O_3Fe_2O_3$, and $CaSO_4$, respectively]. The tricalcium silicate is usually the most prevalent of the hydraulic phases, followed by dicalcium silicate [16]. If present, calcium sulfate may be partially or fully hydrated as gypsum. Calcium sulfate is commonly added to the tri/dicalcium silicate cements to avoid flash setting, just it is used in commercial Portland cement, or in alginate. Notably, calcium silicate ($CaSiO_3$) is not a phase of Portland cement. This silicate compound is not hydraulic (does not set with water); however, it is being used in some prototype medical devices [70, 71].

The setting reaction of these hydraulic materials is valuable. The hydration of tri/dicalcium silicate cement is complicated [72] and continues over about 4 weeks, although hydration may continue at a glacial pace for years [16]. Additives and manufacturing processes have been investigated to accelerate or retard the hydration studied for constructions and well-bore uses of cement [73]. In brief, when water is added to tricalcium silicate cement, the particles start to dissolve (equation 1). As hydration and dissolution progress, calcium hydroxide precipitates, giving an overall reaction of forming an amorphous calcium silicate hydrate with embedded calcium hydroxide (equation 2).

$$Ca_3SiO_5 + 3H_2O \rightarrow 3Ca^{2+} + 4OH^- + H_2SiO_2^{-4} \text{(dissolution phase)} \quad (1)$$

$$2Ca_3SiO_5 + 7H_2O \rightarrow 3CaO{\cdot}SiO_2{\cdot}4H_2O + 3Ca(OH)_2 \text{(overall reaction)} \quad (2)$$

A similar reaction occurs for dicalcium silicate powder. The minor phases also hydrate, including tricalcium aluminate, calcium sulfate and tetracalcium aluminoferrite phase occur, but at different rates. Each MTA-type product on the market has singular proportions of these phases, which may account for the variations in setting and strength. Major and minor phases present in currently available commercial products powder-type tri/dicalcium silicate materials are summarized in Table III, based on the manufacturers' safety data sheets. During cement setting, calcium sulfate reacts with the tricalcium aluminate to form ettringite, a hexacalcium aluminate trisulfate hydrate [$(CaO)_3(Al_2O_3)(CaSO_3)_3{\cdot}32H_2O$] [74] Micro-Raman and environmental scanning electron microscopes and attenuated total reflectance-Fourier transform infrared (ATRFTIR) are useful for such analyses. This reaction has been studied [22, 75], but is less important than the tri/dicalcium silicate reactions. Calcium sulfate and ettringite are naturally occurring minerals, unlike the tri- and dicalcium silicates. Some compositional variations have been applied in dentistry, such as adding calcium chloride or reducing calcium sulfate to accelerate initial setting. Other variations are discussed later.

5. Test results according to ISO standards

Bioactivity was evident in the favorable healing responses of the early histological studies using tri/dicalcium silicates [31], but bioactivity according to ISO 22317 was first identified by Sarkar [75]. The tri/dicalcium silicate cements react with water and form a hydrated matrix, with residual cement particles and an embedded calcium hydroxide solution [47], as described above. During and after setting, calcium hydroxide may be released from the surface, creating a high pH, especially near the surface. The calcium ions react with the phosphate ions in blood and interstitial fluids [76] and the high pH causes the calcium and phosphate to react and precipitate on the surface of the tri/dicalcium silicate cement forming what has been identified as hydroxyapatite (carbonated apatite) or a pseudo-apatite [75, 77, 78, 80]. The reaction begins within hours [79], forming amorphous calcium phosphate apatite precursors on the surface of the tri/dicalcium silicates [81]. The bioactivity, superficial formation of calcium phosphate, effectively cloaks the foreign body (the cement) from the tissues within hours, and allows the four phases of wound healing to begin [81]. Wound healing is critical for maintaining pulp vitality in procedures such as pulp capping and pulpotomy with the concomitant formation of a reparative dentinal barrier [83]. The precipitation of an apatite surficial layer may allow the stimulation of osteopontin to induce osteogenesis [50]. Tri/dicalcium silicate materials upregulate the differentiation of osteoblasts, fibroblasts, cementoblasts, odontoblasts, pulp cells and many stem cells [1]. Healing reactions of periapical tissue have been observed with MTA treatment [84] including reformation of cementum [33], periodontal ligament and reattachment of

Sharpey's fibers [32]. ProRoot MTA, Biodentine and other similar materials have been documented to be bioactive [44, 85, 86]. The bioactivity of tri/dicalcium silicate materials is well accepted. Bioactivity is not observed with other types of materials such as zinc oxide-eugenol cements or glass ionomer cement; hence the distinct value of tri/dicalcium silicates as dental materials. MTA Fillapex, a salicylate resin-based sealer, developed a surficial apatite layer after 28 days in synthetic body fluid [87]. MTA Fillapex demonstrated bioactivity and elevated pH, but lower release of calcium ions, despite the lower amount of tri/dicalcium silicate.

The late Dr. Larry Hench, of bioactive glass fame, used a slightly different definition for bioactivity: a material that elicits a specific biological response which results in bonding of the tissues and material [88]. Bonding is important for bone fracture healing, a main concern of Hench [89]. Unlike bone, eliciting the formation of apatite on an implanted material has been sufficient to initiate the healing of dental tissues such as pulp or the periodontal ligament. Bonding tests are discussed later.

Researchers have measured trace metals present the MTA-type materials as in ISO 9917–1, particularly arsenic and lead [64], but also cadmium, chromium and assorted metal oxides (Table IV). ISO 9917–1 requires low Pb and As contents (<100 and < 2 ppm, respectively), using an acid-leaching test. Construction-grade Portland cements are known to vary in their purity [90] and include arsenic oxide as a trace constituent. The first MTA-patent and experimental material cited commercial Portland cement as the main constituent; hence the origin of the concern and research. The values and testing techniques for the MTA-materials have varied widely [67, 91]. Only Camilleri and co-workers [67] reported significant (violative) amounts of As (up to 53 ppm), Pb (up to 15 ppm) or Cr (<14 ppm) from dental tri/dicalcium silicate cement leached in acid. When repeated using Hank's balanced salt solution, the amounts of Cr, As, and Pb were less than 3, 2 and 1 ppm, respectively, significantly less than in acid, even after an extended period (28 days) of elution. Tri/dicalcium silicate cement is known to be more soluble in acid, which may account for differences in the acid leaching and saline extraction results. Schembri *et al.* noted the greatly diminished release of Cr, As and Pb when materials were exposed to water or synthetic body fluid for as long as 30 days; all values were <2 ppm for the two prominent cements tested [64]. Gray and white ProRoot MTA were tested using the acid extraction method [90] and the values for arsenic were less than 0.01 ppm or 0.001 ppm, for materials extracted in phosphate buffer, for gray or white ProRoot MTA. The ISO 9917–1 acid solubility test is designed for cements that would be exposed to the oral environment, which is acidic from dietary ingestion. The use of the MTA-type hydraulic materials is subgingival or intracoronal where the likelihood of exposure to acid is less. The conflicting values for arsenic and lead do not indicate a severe health hazard, but testing variation is clear.

Compressive strength measurements have been reported according to the ISO 9917–1 method [66]. The ISO 9917–1 test requires testing after 24 hours. Extended times have been used for the tri/dicalcium silicate materials because of their gradual strength occurring especially the first week and continuing for about twenty-eight days [93]. The first report of compressive strength [66] was 40 to 67 MPa after 1 and 28 days. Another measurement of the compressive strength was only 25 to 40 MPa [94]. Other values range from 45 to 194

MPa [95], for four tri/dicalcium silicates after seven days, but irrigant solutions reduced the strengths to 18 to 94 MPa. Etching with 37% phosphoric acid reduced the compressive strength of two tri/dicalcium silicates: Angelus MTA and Biodentine. Biodentine was remarkably strong after 3 days (13 vs. 50 MPa) in these tests. These values are lower than resin composites which can be as high as 360 MPa [96]. Some variation in the sample sizes has been used because the ISO 9917–1 compressive strength samples used for concrete should have a higher length to diameter ratio per ASTM C470 than ISO 9917–1.

The ISO 6876 properties were reported by several researchers for the original experimental [97] and subsequent MTA-type products including setting time, solubility and radiopacity. A sampling of properties for MTA-type restorative materials is included in Table V and those indicated as endodontic sealers are included in Table VI. The long setting time (2:45 hr) [66] of the first MTA material was a surprise to the dental community that thrives on quick setting at room temperature or 37 °C. Later measurements of setting time have confirmed equally long setting time for ProRoot MTA (see Table V). Importantly, the humidity and powder-to-liquid ratio have strong effects on the results for setting and working time results among researchers for these hydraulic materials. Using ISO 6876 method for testing the hydraulic materials has been confusing to researchers as these materials were not considered in test methods. Using humidified plaster molds, adding 1% water, and creating humid conditions cause interlaboratory variations.

Shorter setting times are now available in the newer products. To reduce the setting time, various approaches have been proffered, such as calcium chloride solution [98] or phytic acid [99], which have been identified in cement literature to reduce setting time of tri/dicalcium silicate cement. Various other liquids have been suggested for mixing to reduce setting time or improve handling, including propylene glycol [100], lidocaine [101], epoxy resin [87], solutions of 1% methylcellulose and 2% calcium chloride [102], citric acid, calcium lactate gluconate solution [93, 103], sodium hypochlorite, latex polymers [10], solutions of calcium chloride, calcium nitrite/nitrate, or calcium formate [103], polycarboxylate [43], chlorhexidine (CHX) [104–108], KY jelly [109], sodium fluoride [18] and a combination of propylene glycol alginate, propylene glycol, sodium citrate and calcium chloride [110]. However, not all additives had a setting time effect [107]. Powders have been modified to shorten setting time or improve handling with finer particle sizes which increase the surface area for faster hydration (setting). Other additions have improved the handling of the tri/dicalcium silicates and reduce setting time, including phyllosilicate [10], calcium carbonate [43], calcium sulfate and calcium aluminate cement [111, 112].

Under ISO 6876, a 1-mm thick sample of a root canal sealer must have a radiopacity of 3 mm or more of equivalent aluminum thickness. Tri/dicalcium silicate cement does not meet this requirement, so radiopaque additives are necessary [113]. Commercial tri/dicalcium silicate products, such as ProRoot MTA contain a radiopacifier such as bismuth oxide in addition to the Portland cement phases [114]. Many other radiopaque additives have been tested with the tri/dicalcium silicates, including those ceramic oxides listed in Table I. Generally, the higher the atomic number and the smaller the particle size will lead to higher radiopacity; therefore, zirconia-containing products tend to have the lowest radiopacity. Zirconium’s atomic number is 40 and bismuth’s atomic number is 83. Experimentally,

niobium oxide (micro and nano-size particles) has also been tested [86], but niobium's atomic number is only 41. Although added as an inert component, the original radiopaque component, bismuth oxide, lengthened the setting time [113]. Notably, the setting time of the Portland cement without bismuth oxide was still clinically irrelevant (> 2:10 hr) in this research.

The first MTA material had a high film thickness (>450 μm) and low flow (10 mm). Therefore, it did not meet the ISO 6876 requirements (<50 μm film thickness and >17 mm flow) for a root canal sealer, nor did the comparative New Experimental Cement material [68]. However, the indications for these materials, and many other tri/dicalcium silicates are for endodontic restorative use and not for use with gutta-percha for orthograde endodontic therapy. The ideal handling of the endodontic restorative materials is putty-like, unlike the syrupy (tacky) consistency desired for sealers used with gutta-percha [54]. The bioactivity of endodontic restorative materials sparked innovation for developing endodontic sealers. For example, the experimental addition of a polycarboxylic ether polymer dramatically reduced the film thickness and increased the flow of ProRoot MTA [115]; the powder-to-liquid ratio also had a strong effect on these properties. No studies have correlated particle size with film thickness, the original MTA products had particles as large as 80 μm which inhibits creating a uniform film thickness value of less than 50 μm [171].

Dimensional stability is a required test for ADA 57 for root canal sealers with the requirement of less than 1% shrinkage and less than 0.1% expansion. Limited data is available for the tri/dicalcium silicates such as experimental materials (<0.4% shrinkage) [28] or < 0.75% for the original or tooth-colored ProRoot MTA [116]. Conspicuously, using the tri/dicalcium silicate cement will accrue the same benefits that make construction Portland cement useful: dimensional stability required for the Portland Cement in ASTM C150.

Tri/dicalcium silicate-based products have been developed for endodontic sealing with guttapercha which meets the ISO 6876 requirements [117]. The working times was reported as much longer than the setting time, contrary to the usual view of materials reaction and setting. However, the moist conditions used for setting tests with a Gilmore needle at 37 °C differ from the ambient conditions for working time tests. Other reports show that endodontic sealer material (powder/liquid BioRoot RCS) are significantly closer to meeting the standards [118], compared with the original tri/dicalcium silicate endodontic restoratives. Another study of BioRoot RCS and MTA Fillapex verified the low solubility in water or phosphate-buffered saline,(<1.2%) and adequate radiopacity (~7 mm equivalent Al) [119]. Another research group compared 4 sealers including BioRoot RCS and MTA Fillapex and measured properties confirming the high pH, adequate radiopacity and bioactivity. Another brand of tri/dicalcium silicate (MTA Plus) is indicated for endodontic restorative and sealing indications [120], where a higher gel to powder ratio is used for sealing. None of the tri/dicalcium silicate materials have radiopacity as high as AH Plus root canal sealer (Dentsply Sirona), an epoxy resin-based root canal sealer [86]. MTA Fillapex sealer had 6.5 mm of equivalent Al radiopacity compared to 9.5 mm for AH Plus in one set of tests [121]. Proportions up to 50% by weight for radiopacifier have been used with cement, without matching the radiopacity of resin-containing sealers. One resin sealer containing salicylate

and other resins, only contains 20 to 25% MTA, but has been repeatedly referred to as "calcium silicate based" (MTA Fillapex). When tested according to ISO 6876:2001 methods, the flow and solubility met the requirements. The working and setting times were shorter than AH Plus [122] but adequate; there was no water sorption associated with the MTA Fillapex sealer. The bioactivity and clinical performance of this sealer have not been compared to the 100% tri/dicalcium silicate sealers. The properties of the iRoot premixed tri/dicalcium silicate sealer (AKA Endosequence BC sealer) was compared and contrasted to a conventional endodontic sealer [123]. From the literature the properties were summarized [123] versus the ISO 6876 requirements as having adequate radiopacity (but varied among studies) elevated pH, slight expansion, adequate flow, calcium ion release, antibacterial properties, non-cytotoxic, push-out bond strength like other sealers. Solubility (<3% is required) was disputed in some studies reviewed, undoubtedly because of the technique not being appropriate for the hydraulic ceramics.

6. Physical properties testing – non-ISO standards

Materials evaluations of the tri/dicalcium silicates have included using experimental methods other that tests specified in the ISO 6876, 9917–1 and 23317 standards. Such testing includes pH and Ca ion release, microleakage, push-out strength, porosity, discoloration, particle size analyses and antimicrobial tests.

The tri/dicalcium silicates inherently create an alkaline pH when they set because they form calcium hydroxide as a reaction product. Some of the pH values from the literature are listed in Table V and Table VI [96]; all are above 8. Many reports confirm the alkalinity of the tri/dicalcium silicate sealers, although the pH varies from 8 to 12 [66, 68]. Of course, pH values depend on the surface area of sample compared to the volume of liquid in which the set cement is placed; larger volumes reduce the alkalinity. High pH creates the same benefits as calcium hydroxide dressings have provided in the past [124]. Extracellular alkaline pH is known to promote the proliferation and mineralization of human cementoblasts *in vitro* [83]. Concomitant with the pH elevation is calcium ion release [85] by the tri/dicalcium silicates.

Preventing microleakage is the key to the success of endodontic materials; however, the variability of test results and test methods has led to this research method falling out of favor by journals [125, 126]. Microleakage and push-out bond testing are not codified in any ISO or ADA dental standard. However, many publications have reported results for these two properties, presumably as indicators for *in vivo* performance [127]. For example, experimental MTA was superior in bacterial leakage tests [30] compared with amalgam, Super EBA and Intermediate Restorative Material (IRM). Among the tri/dicalcium silicate materials, no significant differences were found among commercial hydraulic materials, in leakage tests such as glucose testing [128] or dye leakage [129]. Leakage reports have shown the superiority of the tri/dicalcium silicate over other materials [130, 131], as an endodontic restorative or as an endodontic sealer, with any of the previously described methods. A phosphate-containing medium is important to be included in such sealing evaluations, as noted in a bacterial sealing study using MTA-type material against *Enterococcus faecalis* [132]. The dimensional stability of the tri/dicalcium silicate cements

is superior to resin materials, which contributes to sealing ability. The formation of the surficial calcium phosphate will also help with sealing.

Push-out bond test methods have been used, not all of them acceptable for the tri/dicalcium silicate materials [133]. Although this test is popular, no case reports have been published for tri/dicalcium materials being pushed out. Hence, the clinical importance of this test is questionable. Higher powder-to-liquid ratios, longer time, and soaking in phosphate-buffered saline increased the push-out strength [134–137]. Dentin conditioning liquids (irrigants) were noted to alter push-out bond strength [120], the largest increase was with 6% sodium hypochlorite and 18% etidronic acid, among five protocols and three materials. The bond strengths of the tri/dicalcium silicates to dentin are usually low, less than 10 MPa in tests of 1-mm thick slices of tooth after less than seven days, with wide scatter [120, 138–142]. Higher push-out strengths (25 to 100 MPa) were recorded for 2-mm thick slices [136, 143]. Values as high as 66 MPa have been reported for Biodentine's tri/dicalcium silicate [144], but the test configuration was not slices of tooth. The bioactive effect of apatite formation at the interface with teeth improves bond strengths by mechanical friction for push-out tests. Clinically, the extrusion of unset MTA-type material may, but is not always [145], a patient problem, including apexification procedures [146–148].

Porosity has been studied for the MTA-type materials using Archimedes method, mercury intrusion equipment and micro-computed tomography (μCT) techniques. The results vary widely and are large for the Archimedes technique [44]. Using μCT, about 5% porosity was reported for BioRoot RCS and MTA Fillapex [149]; the values were similar for these tri/dicalcium silicate and resin-based materials. About 1% micro-porosity was detected with μCT (Biodentine & MTA) but 25 to 46% nano-porosity was detected using Hg intrusion techniques [150]. The values obtained from μCT scanning depend on the resolution. Porosity values have been reported as high as 40% for the endodontic restorative materials via the Archimedes method, considerably higher than the resin-based calcium hydroxide Dycal product (~9%) [151]. Using Hg porosimetry, values of 20 to 25% were reported 28 days after setting [152]. These high values for porosity, indicating high interconnected porosity through the material, are confusing given the sealing ability and clinical performance of the materials.

Gandolfi and her colleagues have measured the water sorption and solubility of several tri/dicalcium silicate dental materials. The water sorption and solubility values have been reported as 10 and 15% [44], and 40 and 18 % for tri/dicalcium silicate materials [85] for two materials (MTA Plus and NeoMTA Plus. Such solubility is above the ISO 6876 limit for root canal sealers. After 7 days, the solubility was less, but the porosity was still above 40%.

In studies of Portland cement, the porosity is higher, but less than 30% for materials mixed to a fluid (lower powder-to-liquid) ratio [153]. Another study of solubility noted that initial solubility is higher than when the tri/dicalcium silicate dental material is allowed to set [154]. These researchers noted that MTA Angelus was more soluble than neat (100%) Portland cement, which one would predict because the MTA product has less water reactive component to bind the dense bismuth oxide. High porosity and high solubility would almost certainly indicate weak materials that are dissolving, yet clinically, the opposite has been

observed. Using the dental methods for evaluation of polymer water sorption does not appear to be suitable for water-based materials that react with water.

Some endodontic materials are known to discolor teeth [155], including root canal sealers and triple antibiotic paste. The first MTA material was dark gray powder which could cause immediate discoloration if used coronally or where the gingiva was thin. In 2002 a white version of ProRoot MTA was introduced which lacked the black tetracalcium aluminoferrite phase in the tri/dicalcium silicate powder. Nevertheless, case reports of primary teeth with discoloration (darkening) continued with white (tooth colored) ProRoot MTA [156]. Tri/dicalcium silicate materials have been evaluated for their initial color and color change of these materials over time [11]. *In vitro* studies [157] have confirmed color change differences among the commercial products [158]. Irrigants have been shown to darken some tri/dicalcium silicate materials [159, 160]. The common source for discoloration has been attributed to the presence of the bismuth oxide radiopaque component [159, 160]. Some have speculated that the color change is reduction to bismuth metal or bismuth carbonate [161], but these reactions are thermodynamically impossible. Bismuth oxide is known to be photoactive [162] such that UV radiation can partially oxidize yellow bismuth oxide (Bi_2O_3,[Bi^{+3}]) to a brown color by forming superficial Bi_2O_4 (Bi^{+3} and Bi^{+5}) exposed to light. The partial oxidation of Bi^{+3} to Bi^{+5} has also been reported for chemical reactions [163]. Therefore, discoloration of the bismuth oxide-containing cements may be attributed to irrigant [161] or light-induced partial oxidation in a high pH environment. These two chemical pathways account for the occurrence of darkening in the coronal and the primary tooth placement of bismuth oxide containing tri/dicalcium silicate cements. One might conclude this problem of darkening over time is solved with newer products without bismuth oxide; however, a clinical report of partial pulpotomy stated that even Biodentine, which contains no bismuth oxide, created perceptible darkening over time, although less than the original ProRoot MTA bismuth oxide-containing tri/dicalcium silicate [164].

The experimental MTA the tooth-colored ProRoot MTA and MTA Bianco Angelus products had clinical problems of being coarse [19], having poorer handling [165] and washing out from root-end fillings [166] compared to zinc oxide-eugenol. The coarse particles (> 40 μm) of these tri/dicalcium silicates are apparent in particle size studies [167, 168] and in scanning electron microscopy images [68]. Coarse particles were more frequently found in opened foil packets, due to the hygroscopic nature of the tri/dicalcium silicate powder which causes partial hydration and agglomeration of the powder [169]. Fine particles are desired for dentinal tubule occlusion. Original and tooth-colored ProRoot MTA material occluded tubules as much as did calcium hydroxide powder [170]. The median particle size for two popular tri/dicalcium silicate products was measured as 2 and 13 μm [171]; the particles are micron-sized for the majority of tri/dicalcium silicate products. Washout resistance is higher for some products [51,172].

Dentinal tubule penetration has been compared for endodontic restorative materials and for endodontic sealers. iRoot SP root canal sealer, a tri/dicalcium silicate-based premixed sealer, had greater penetration area than three polymer-based sealers [168]. The depth of penetration was inferior for ProRoot MTA compared to experimental calcium alumino silicate hydraulic material [77]. Another study demonstrated dentinal tubule penetration, up

to 2 mm of Endosequence sealer, a tri/dicalcium silicate-based material [177]. For sealers, tubule penetration has always been less towards the apex. In a μCT study of a commercial and experimental tri/dicalcium silicate sealer, the porosity was lowest at the apex [154] in three dimensions. The bioactivity reduced the voids detected to less than 2% after 6 days in synthetic body fluid, which was less than AH Plus root canal sealer. The tri/dicalcium silicate materials dissolve and then precipitate as they set, which leads to some tubule penetration to obstruct bacteria.

Nanoparticulates have been claimed for iRoot BP. However, scanning electron microscopy data did not support the presence of all particles being finer than 100 nm (<0.1 μm) [173]. Faster setting does occur with finer cement particles [174]; however, the US FDA is cautionary on the benefits of nanoparticles: “nanoscale materials may behave differently, the ability of these tests to support decisions about biological effects or further testing requirements need to be evaluated” [175]. When the particle size of ProRoot MTA was reduced [178], no clinically significant differences were determined as a root-end filling in dogs. No benefits of nanoparticulates for iRoot BP have been explained or demonstrated in the literature. New products favor smaller median or average particle sizes, with elimination of coarser particles. These features should make for smooth mixing with liquids and faster setting.

Higher fracture strength has been reported *in vitro* for teeth obturated with three tricalcium silicate products, compared to calcium hydroxide, after one year in saline [179]. Strengthening should be expected comparing a tri/dicalcium silicate cement that forms a hard matrix in contrast to non-setting calcium hydroxide which transforms to calcium carbonate. Vertical fracture was also higher for roots obturated with MTA-type material versus gutta-percha and an epoxy resin-based sealer [180]. In a simulated immature root model, roots obturated with MTA Angelus product were compared to roots with an apical plug and obturated with another sealer and guttapercha in bovine teeth [181]; obturated teeth were stronger. Using the stiffer MTA-type cement in the root reduces flexure and adds a stronger material than gutta-percha & sealer, which may provide clinical benefits for potentially cracked teeth.

Antimicrobial properties have been reported for MTA-type/tri/dicalcium silicate materials. The antimicrobial effects of tooth-colored ProRoot MTA have been demonstrated against *E. faecalis*, *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Candida albicans* in agar diffusion tests [183]. Several tri/dicalcium silicate materials have been tested with *C. albicans* and shown to be antifungal [183–185], including seven strains of the fungus, for as long as one week [186]. The product format of powder and liquid or a premixed putty did not affect the results [187, 188] for biofilm formation or direct contact tests. Using a Portland cement mixture or ProRoot MTA was also effective against *Streptococcus mutans*. In contrast, Shin *et al*. [189] did not observe antimicrobial activity of ProRoot MTA or an experimental “Fast-Set” MTA against *S. mutans*, *E. faecalis*, *Fusobacterium nucleatum*, *Porphyromonas gingivalis* or *Prevotella. intermedia*, using the Kirby-Bauer method; although neither material was cytotoxic.

When endodontic sealers were compared for antibacterial activity of *E. faecalis*, the higher pH tri/dicalcium silicate-containing sealers were superior [190], including the resin-based MTA Fillapex. A contrary result was published of direct contact agar diffusion test results which showed no antibacterial activity of two tri/dicalcium silicate materials, despite their higher pH values [191]; however, diffusion and solubility may have clouded those results.

The endodontic restorative or sealer tri/dicalcium silicate products are now accepted as having high pH, reduced microleakage compared to predecessors, medium to low push-out bond strength, porosity and solubility that defies the sealing results, some are discoloration free, able to occlude dentinal tubules, fine but not nano-sized particles, ability to strengthen roots when used for complete obturation, and antimicrobial characteristic. Complaints were published about the high cost the first tri/dicalcium silicate product, ProRoot MTA [21]. The costs of the contemporary tri/dicalcium silicate materials have been calculated [192], and with the plethora of new products, prices are now lower, especially those containing resins. The colors of the materials range from dark gray to slightly yellow or pink to white.

7. Biocompatibility

Wataha described a hierarchy for predicting clinical responses for dental materials, starting with broad *in vitro* testing, progressing to animal studies and followed by clinical tests in humans; the objective is to minimize pain or suffering of animals and humans [63]. For the tri/dicalcium silicate cements, a customized interaction is desired at the material-tissue interface. Bioactivity testing *in vitro* can help establish this, as well as the tubule penetration tests, or in the past, sealing tests.

The most elementary biocompatibility test is cytotoxicity, and many methods of cytotoxicity testing may be performed. The agar overlay and L929 radiochromium methods showed that fresh and set samples of the first experimental MTA were less cytotoxic than Super EBA and IRM materials [26]. The agar overlay has been used to confirm the lack of cytotoxicity of other tri/dicalcium silicates [189]. Direct and indirect contact tests were used in another study of experimental hydraulic materials that included tri/dicalcium silicate and calcium aluminate, for which the cytotoxicity was acceptable [111]. Other studies with NeoMTA and experimental cements based on tricalcium silicate also showed lack of cytotoxicity [24]. No study has shown superiority or inferiority of any material based on tri/dicalcium cement, including various Portland cements from around the world.

Cytotoxicity tests with human cells have also been performed with the tri/dicalcium silicates. For example, Bioaggregate, Biodentine and ProRoot MTA were not significantly different among the materials or compared to the control when tested for cytotoxicity with human periodontal ligament (hPDL) fibroblasts [193]. Another study with hPDL fibroblasts demonstrated equal lack of cytotoxicity (MTT method) and genotoxicity (comet method) for ProRoot MTA, TheraCal LC and Biodentine. A cytotoxicity of OrthoMTA (BioMTA, Seoul, Korea) and ProRoot MTA using osteosarcoma cells indicated inferiority of the OrthoMTA material (although superior to zinc oxide-eugenol), despite the compositional similarity of OrthoMTA to ProRoot MTA [194]. Another cytotoxicity test compared OrthoMTA, Endocem (Maruchi), and ProRoot MTA products; again, OrthoMTA was inferior to the other

2 materials. A study using human dental pulp cells and rat histology after 4 weeks showed equality of Endocem and ProRoot MTA [195]. Endocem ZR had zirconia instead of bismuth oxide for radiopacity; although it was bioactive, the cement was considered less biocompatible than ProRoot MTA [65]. Three tri/dicalcium silicate cements NeoMTA Plus, MTA Angelus and MTA repair HP (Angelus) were evaluated using human dental pulp stem cells, which represented 3 radiopaque components and three liquid variations. All showed equivalent cell viability, attachment and migration. These cytotoxicity studies do not identify any tri/dicalcium silicate product as being cytotoxic, despite their elevated pH.

The iRoot (Innovative Bioceramix, Vancouver, Canada) tri/dicalcium silicate paste sealer has been compared to ProRoot MTA, which is not a root canal sealer for cytotoxicity. When exposed to human tooth germ stem cells, neither material was cytotoxic, unlike the calcium hydroxide-based Dycal product (Dentsply Sirona). Both of the tri/dicalcium silicates induced odontogenic differentiation [196]. The paste iRoot SP was dubbed less “efficient to stimulate mineralization” which may be attributed to the presence of the organic liquid with the ceramic powder, before water displaces the liquid and initiates setting. Similarities were also reported for the iRoot BP (putty format, not a sealer) compared to MTA Angelus [197]. Both iRoot BP Plus and ProRoot MTA had apatite-forming ability, promoted *in vitro* recruitment of dental pulp stem cells and facilitated dentin bridge formation in a pulp repair model *in vivo*. The premixed tri/dicalcium silicate containing organic liquid and another sealer mixed with a water-based liquid (Endosequence, Brasseler and ProRoot ES, Dentsply Sirona) were compared using murine osteoblast cells and dentin matrix protein-1 (DMP-1) expression [59]. Both MTA-type sealers were biocompatible, bioactive and less cytotoxic than other popular sealers (Roth sealer and AH Plus sealer).

Genotoxicity has been tested for some tri/dicalcium silicate products. Not surprisingly, the ceramic-based materials were not mutagenic [198–200]. Resin-based materials are more likely to be genotoxic [201], including MTA Fillapex sealer [202]. Modified MTA Angelus modified to contain disodium hydrogen phosphate or silver nanoparticles were non-mutagenic [203, 204].

Subcutaneous implantation of materials into muscle and less often into bone is often used to test biocompatibility, although the latter is more relevant to the bioactive bioceramics. Implants of the experimental MTA [27] into bones of guinea pigs showed low inflammation and excellent bone apposition. Implantation of three tri/dicalcium silicate-based materials in rabbit tibia for 30 days induced new bone formation, osteoblasts differentiation and angiogenesis (capillary formation close to the materials) [205]. The formation of bone without interposed connective tissue is part of the success of these bioactive materials for treatment of perforation, root resorption, and apicoectomy root-end filling. Some faster setting tri/dicalcium silicate materials, Biodentine and MTA Flow (Ultradent Products Inc., South Jordan, UT, USA), were dorsally implanted in rats [206], with the latter mixed at two consistencies (thin and thick). Inflammation and fibrous capsule decreased over 60 days for all three materials; however, the thick MTA Flow mixture had the fastest repair. Subcutaneous tests for up to 90 days demonstrated absence of necrosis and presence of calcification for the tri/dicalcium silicate-containing materials, but the results were not

superior to Sealapex (Kerr Endodontics, Orange, CA, USA), a polymer-calcium hydroxide root canal sealer [110].

Mineral Trioxide Aggregate-containing materials were implanted into alveolar sockets of rats for examining the level of aluminum in the blood and liver [27, 208]. These two studies used two resin-based tri/dicalcium silicate products (MTA Fillapex & Theracal) and one resin-free tri/dicalcium silicate (MTA Angelus). The authors' rationale was based on highly criticized research from 1973 implicating aluminum metal as a cause of Alzheimer's disease [209]. In the rat studies, the plasma aluminum levels rose for both the 100% MTA material as well as the resin-based sealer that contained only a minor amount of MTA powder. After 60 days, the Al content of the rat brains was not significantly different from the control. Notably, Al was present in the plasma, brain and liver samples from the control empty tubes. In a subcutaneous study of three tri/dicalcium silicate-based materials, no Al elevation was detected; the control rats had high Al content in the brain, liver and kidneys in eight out of nine assays [210]. Placing a human-sized dose in 400-gm rats (or less) and finding significant differences cannot be extrapolated to humans [209]. The aluminum compound present in the tri/dicalcium silicates is minor, if present and is a present as tricalcium aluminate, an oxide, not a metal. Furthermore, the suggestion that alumina-containing ceramics are similar to metals alloys [208] is speculative. Lidsky summarized the "Al hypothesis" stating that causation has not been established in humans, and that rats do not develop the human pathology of Alzheimer's disease [209]. If released from the MTA-like materials, the Al will be in the form of aluminum hydroxide, which has been available as an over-the-counter drug and adjuvant and used for decades [211] for the treatment of digestive disorders [212].

Pulp capping tests following ISO 7405 guidelines have shown calcific bridge formation after only 7 days in rats with ProRoot MTA or another tri/dicalcium silicate product (Bio-MA, M-Dent/SCG, Bangkok, Thailand) [97]. Inflammation was never completely absent with histological studies of these materials at seven or thirty days, but less than the control groups. No bacterium was reported to be present. Portland cement and TheraCal were both superior to Dycal (calcium hydroxide-containing) and to glass ionomer cement in treating primates with pulpal bacterial infections [213]. Pulp capping in dogs compared two tri/dicalcium silicate cements versus calcium hydroxide (Dycal) [214]. After 56 days, histological examination showed superiority of the two tri/dicalcium silicate materials over the calcium hydroxide. Despite the enhanced calcium and phosphate component of the New Experimental Cement tri/dicalcium silicate, no superiority was determined over ProRoot MTA for pulpotomies in dogs after 8 weeks [215], with superiority over calcium hydroxide.

Pulp capping and pulpotomies were performed in pig's primary teeth for comparison of two commercial tri/dicalcium silicates vs. calcium hydroxide and formocresol, respectively [216]. After only 7 days, calcified barriers were formed in the teeth capped with tri/dicalcium silicates, unlike formocresol. No differences were detected between a tri/dicalcium silicate material with bismuth oxide vs. a faster setting cement with zirconia, calcium carbonate, using a salt/polycarboxylate solution.

Pulpotomies were performed in dogs for comparison of calcium hydroxide powder, the original experimental MTA and the 1st commercialized MTA product. After 90 days the teeth were prepared for scanning electron microscopy [217]. The results were supportive of the superiority of the commercial product with regard to tubular dentin formation. The superiority of the experimental versus the commercial MTA may arise from the improved blending and fineness of the commercial formula over the laboratory made material. When Endocem Zr was compared to ProRoot MTA in dogs receiving pulpotomies, calcific barriers were formed in both materials, although considered inferior in Endocem ZR. The cause of the differences was not determined [65].

Endodontic usage tests with dogs have shown that two hydraulic materials (ProRoot MTA and CEM (experimental material, “calcium enriched”) were both effective in root-end filling after apicoectomies were performed to treat induced periodontal lesions [218]. Cementum formation and periodontal ligament fibers were observed 2 months after surgery. NeoMTA has also been tested in dogs for pulpotomy and root-end filling procedures with favorable histological healing at 90 days [219]. In a revascularization test using dogs with immature incisors and premolars and MTA coronal plugs, both the intentionally infected and non-infected teeth experienced apical closure, thickened canal walls and periapical healing [220]. Examples of the favorable healing responses in canine endodontic usage tests are shown in Figure 2. Root-end healing after an apicoectomy (Figure 2a) shows the re-formation of cementum and periodontal ligament. Figure 2b shows the formation of reparative/reactive dentin are after a pulpotomy or use as a cavity liner (indirect pulp capping).

8. Human studies

Human studies have been performed with the tri/dicalcium silicates for various indications from root-end filling to endodontic sealing. In a prospective study of apical microsurgery, the outcomes of root-end fillings performed with different materials were compared at 12-month recall; the extent of apical bone fill and absence of clinical signs/symptoms were equivalent for ethoxy-benzoic acid (Super EBA, Harry J Bosworth Co, Skokie, IL, USA) and ProRoot MTA [221].

Some researchers used ordinary Portland cement, and not surprisingly, had favorable biological responses for pulpotomies [222]. In adults, pulp-capping has been successfully treated using two tri/dicalcium silicate materials [223], but Theracal was less successful in partial pulpotomies. Biodentine and other materials with the name MTA were reviewed for human pulp-capping success and within the limitation of the review, no differences were found [224].

Pulp capping with the tri/dicalcium silicates versus calcium hydroxide dressing has been evaluated in sound teeth [225, 226]. Histology was been analyzed after 60 or 136 days, respectively. Faster dentinal bridging was observed for the tri/dicalcium silicate material [225]. Dentinal bridging with the tri/dicalcium silicate materials may be assisted by the sustained high pH that is achieved. Calcium hydroxide more quickly transforms to inert calcium carbonate (lower pH), compared to the calcium hydroxide embedded in the tri/dicalcium silicate matrix [228].

Indirect pulp-capping in deep lesions showed equal and effective performance for Dycal and MTA products for vitality and radiographically [227]. This study was a randomized clinical trial with 73 patients. Both products contain calcium hydroxide; however, Dycal is resin-based. In those procedures, reactionary dentin is formed by the proximity of the capping to the pulp and indirect communication [82]. When tri/dicalcium silicates set, a hydrated calcium silicate matrix is formed, in which calcium hydroxide solution is embedded; the calcium hydroxide creates a high pH (alkaline) environment near its surface. In one study, higher pH was produced by the tri/dicalcium silicate after 4 weeks, compared with UltraCal calcium hydroxide (Ultradent Products, Inc.) [228]. The setting of the ceramic hydrated matrix may have overcome problems associated with calcium hydroxide products such as dissolution in tissue fluids, degradation upon tooth flexure and poor quality of the proximal hard tissue barriers [229].

A case series was conducted wherein carious permanent human teeth were treated with a gray (tetracalcium aluminoferrite-containing) tri/dicalcium silicate; 93% success was reported after 3 years [230]. In this study, the teeth were temporized with a wet cotton pellet and a temporary material for one week. Re-entry was performed to ensure setting of an adequate layer of tri/dicalcium silicate prior to the placement of a final restoration. Faster setting materials are now available such that fears of washout and non-setting are alleviated [51] and one-visit treatment is possible.

RetroMTA and ProRoot MTA were compared at 8 weeks after partial pulpotomies were performed in young adults. Healing was observed for both materials; however, superior histological results were observed for the tri/dicalcium silicate cement (ProRoot MTA) over the pozzolanic RetroMTA [53].

Clinical tests have been performed on primary teeth, especially pulpotomies. For instance, pulpotomies were performed with white ProRoot MTA under resin composites and stainless steel crowns [231]. After 12 months, the clinical and radiographic results were successful and equivalent in radiographic findings; however, the color (grayish) and the margins were inferior for the resin composite restorations because of bismuth oxide discoloration. Clinical superiority has been demonstrated for tri/dicalcium silicate pulpotomy vs. formocresol pulpotomy in case series, although better results were reported for gray than tooth-colored ProRoot MTA [232]. In randomized clinical trials, tri/dicalcium silicates were at least equivalent to formocresol clinically and radiographically for pulpotomies after 24 months [233]. A retrospective review of primary molar pulpotomies consistently shows better performance for MTA products over formocresol for as long as 48 months postoperatively [234].

A clinical trial compared apexification of immature permanent molars treated with either of two tri/dicalcium silicates [235]. In this trial, no sealer was used and the remainder of the root canal was only filled with gutta-percha over the apical plug prior to the placement of a restorative material. After 24 months, periapical healing was significant and equal for the materials. Bioactivity of the materials was evident by the formation of a calcific bridge over the MTA plug in the canal, facilitated by fluid from the dentinal tubules. Discoloration was observed, even though the bismuth oxide-containing tri/dicalcium silicates were placed

apically. Another clinical trial used tri/dicalcium silicates with bismuth oxide for coronal sealing in revascularization to successfully induce apical closure of immature roots [236]. Some discoloration occurred with either triple antibiotic pastes or chlorhexidine/calcium hydroxide, which was primarily attributed to the triple antibiotic paste.

Case reports have been made using MTA-type products for unusual dental abnormalities such as dens invaginatus [145, 237, 238] and apexification [238]. Tri/dicalcium silicates of the restorative type have been used clinically for complete obturation of instrumented root canals [34, 239] and treatment of root fractures [38, 238,240]. Molar-incisor-hypoplasia was treated with a light-curable tri/dicalcium silicate material [241].

9. Conclusions and future perspectives

The tri/dicalcium silicate materials were introduced relatively recently among dental materials-(1990s). With its commercialization, root and pulpal treatments have improved considerably in their outcome because of the superiority to historical materials (zinc oxide-eugenol cement and amalgam). The bioactive ceramic powders have induced the healing of periapical tissues (cementum and periodontal ligament) unlike any material used in the past. The bioactive materials are supplanting the use of the formaldehyde containing pulpal medicaments that have historically been used on primary teeth. Furthermore, these bioactive materials are integral to the future of endodontic regenerative procedures.

Many hydraulic bioactive bioceramic materials are now available world-wide, containing primarily tri/dicalcium silicate ceramic powder. These materials set with water, creating an alkaline pH and release calcium ions, which together, are responsible for their bioactivity via the formation of a superficial apatite layer. The minor phases with the tri/dicalcium silicates vary from tricalcium aluminate, calcium sulfate, calcium carbonate, calcium phosphate, and include a variety of radiopaque powders. The liquid vary from water, water-based, to organic liquids; the latter only setting in vivo with exchange of the organic liquid with body fluids. Setting times as brief as 3 minutes and as long as about 3 hours have been reported, although the conditions of measurement influence the setting time as well as the minor phases present. The radiopacity varies from 3 to 8 mm of equivalent aluminum with variations depending on the powder-to-liquid ratio for the materials that require mixing.

To date, the indications of using tri/dicalcium silicates broadly fit into three categories: vital pulp therapy, endodontic restoration and endodontic sealing. Sealing and obturation of teeth using tri/dicalcium silicates will continue to change vital pulp therapy and root canal treatment. Obturation of root canal systems may become more common, although the fear of retreating a canal filled with tri/dicalcium silicate material is problematic [242, 243]. However, retreatment of root canals that had been filled with gutta-percha and tri/dicalcium silicate sealers, removal of the sealer remnants was no worse than epoxy or resin-based sealers [244]. With MTA Fillapex, conventional solvents may be used to re-establish apical patency [245].

The bioactivity of the MTA-like materials leads one to prescind about bone cements and bone grafting. The combination of resorbable porous materials and tri/dicalcium silicate

materials may augment the potential uses of such materials. Remineralization of dentin or treatment of dentine hypersensitivity remains an elusive goal and tri/dicalcium silicate ceramics that elute calcium ions may be useful for such a purpose [246–249], for instance, in combination with hydrophilic resins that enable release of those ions from a polymerized resin matrix [250, 251]. Using tri/dicalcium silicates as a base under cavities may be a future trend to reduce invasive treatments in deeply decayed teeth [252], and perhaps delay or avoid immediate endodontic orthograde therapy.

No MTA-type product currently has FDA-cleared indications for coronal sealing in regenerative endodontics (*aka*. revascularization). However, these types of materials have been used as a coronal seal over the induced blood clot of the traumatized immature permanent teeth [253], or mixed with blood to induce hard tissue healing in teeth with root fracture [38]. Coronal placement of MTA for revascularization may be superior to an apical plug of the same material, by enabling continued deposition of bone-like hard tissues in devitalized anterior teeth with open apices and thin, immature dentinal walls [254]. Using the tri/dicalcium silicates for revascularization is comparable to apexification, except the plug is higher in the root. Stem cells, growth factors and tissue scaffolds will continue to be evaluated for their compatibility with tri/dicalcium silicate materials [39].

Other hydraulic ceramic cements are likely to be developed that have superior acid-resistance, faster setting or other properties. Alternative materials may be mono/di-calcium aluminates [255–257] or calcium aluminosilicates [258–264] which have both demonstrated good performance in biocompatibility and animal tests. Alternatively, tri/dicalcium silicates may be combined with magnesium phosphate cement [81] or calcium phosphate cements [265] for commercialization. Addition of hydroxyapatite has been suggested [198, 266], although the bioactivity may not be enhanced beyond what occurs with the tri/dicalcium silicates already. Nanoparticles may be used to enhance physical properties [171]. Creating ever smaller particles of the hydraulic cements may potentially improve their penetration into patent dentinal tubules. Nano-sized particles in the range of 100–150 nm are likely to be included in new materials [198]. Treating exposed dentine may be of benefit [267], if the acid solubility of the tri/dicalcium silicates can be reduced using modified materials such as calcium aluminosilicates [259, 268]. In the near future, formocresol and ferric sulfate will likely be supplanted by the tri/dicalcium silicate products for pulpotomies in primary teeth. Newly-trained dentists will adopt the use of bioactive materials for vital pulp therapy in their treatment plans, and costs per treatment will continue to decrease with new products.

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Statement of significance

The broadening indications and the proliferation of tri/dicalcium silicate-based products make this relatively new dental material important for all dentists and biomaterials scientists. Presenting the variations in compositions, properties, indications and clinical performance enable clinicians to choose the material most suitable for their cases. Researchers may expand their bioactive investigations to further validate and improve materials and outcomes.

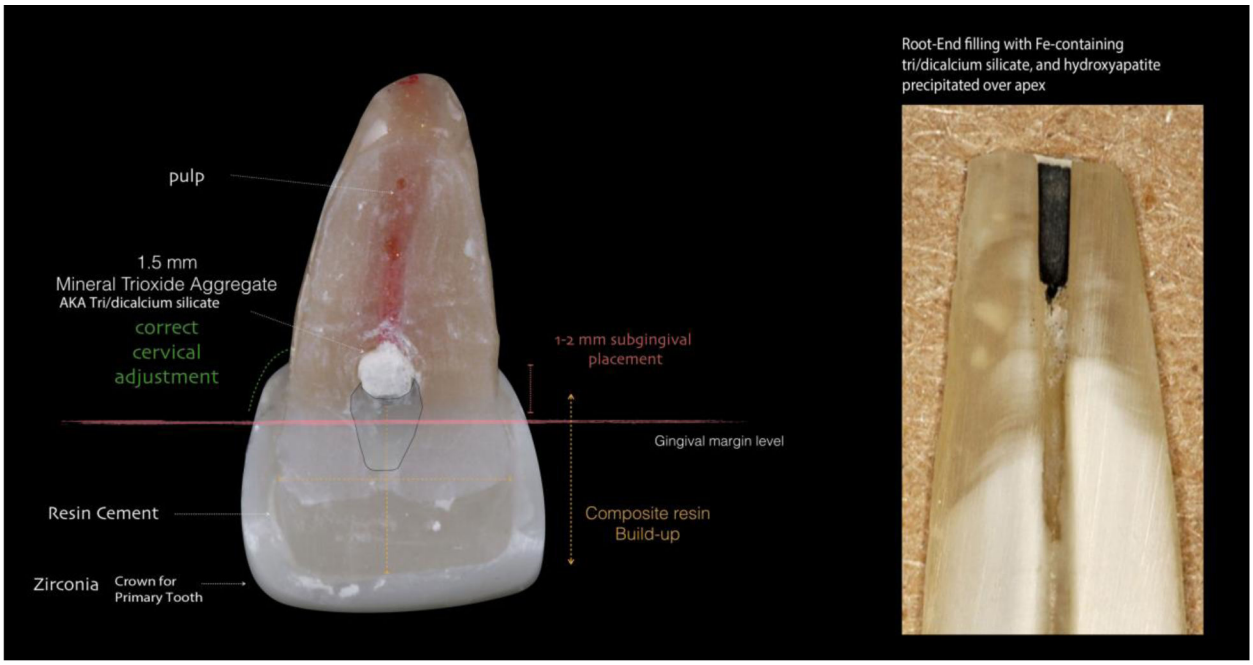

Figure 1.

Photos showing the location in teeth where tri/dicalcium silicate materials can be used for vital pulp therapy (left) or periapical tissue contact. Note the white layer of hydroxyapatite that was formed over the root tip after immersion in simulated body fluid. Photo on left reproduced with permissions from Dr. Jorge Casián Adem, DDS Odontología Pediátrica y Ortodoncia; on the right, courtesy of Dr. Franklin Tay, author.

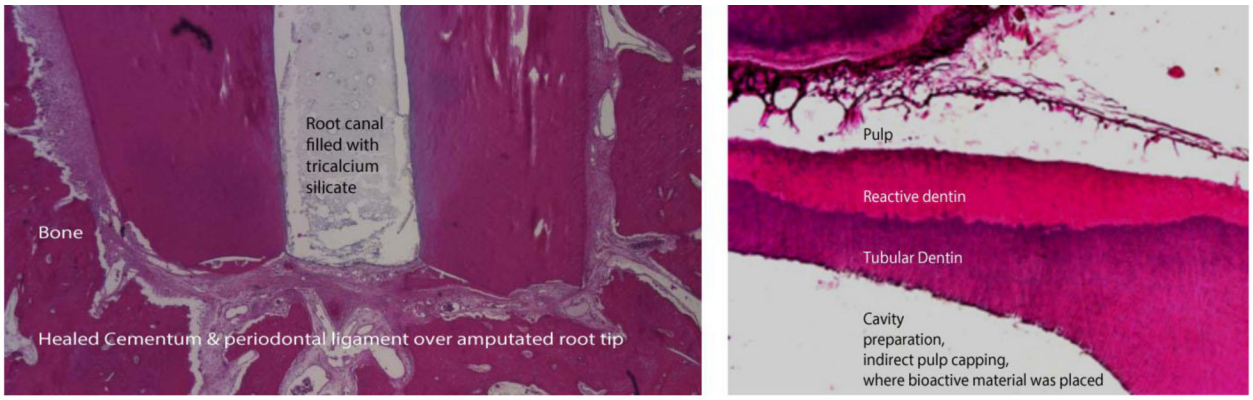

Figure 2.

Histological sections of canine subjects 60 days after obturation or cavity lining treatments with tri/dicalcium silicate materials. Both photos show the healing responses to the material. Photos reproduced with permission from Dr. James L. Gutmann, DDS, Cert Endo, PhD, FACD, FICD, FADI, FAAHD, FDSRCSEd, Dip ABE, Professor Emeritus, Texas A&M college of Dentistry.

Table I.

Commercially available tri/dicalcium silicate-containing products

Tradenames	Manufacturer	Country/comment	Radiopacifier
For endodontic restoration and vital pulp procedures			
ProRoot MTA-original (gray) and tooth-colored	Dentsply Sirona	USA	Bi_2O_3
Bioaggregate, DiaRoot, IRoot FS, FM; Endosequence BC: root repair, fast set, & putty EdgeEndo root repair	Innovative BioCeramix Inc.	Canada	Ta_2O_5 ZrO_2, Ta_2O_5
MTA Angelus-gray and white, Channels MTA MTA HP, BIO-C Repair	Angelus Industria de Productos Odontologicos	Brazil	Bi_2O_3 $CaWO_4$
Biodentine	Septodont	France	ZrO_2
MTA Plus, Grey MTA Plus, NeoMTA Plus, NeoMTA, NeoMTA2.2	NuSmile Ltd.	USA	Bi_2O_3 Ta_2O_5
MTA Flow	Ultradent	USA	Bi_2O_3
Masterdent MTA	Dentonics	USA	Bi_2O_3
Medcem MTA Portland cement with radiopacifier	Medcem	Switzerland	ZrO_2
RetroMTA, OrthoMTA II	BioMTA	Korea	$CaZrO_3$
Ortho MTA	DO Co. Ltd	Korea	Bi_2O_3
ENDOCEM & ENDOCEM ZR	Maruchi	Korea	Bi_2O_3 ZrO_2
Well-Root ST	Vericom Co. Ltd.	Korea	ZrO_2
MTA-B, MTA-T, MTA-XR, and MTA-XR flow; [Harvard MTA, Zendo MTA, MTA Caps]	S&C Polymer First Scientific Dental	Germany	Bi_2O_3
MM MTA	Micro-Mega	France	Bi_2O_3
MTA Caps	Acteon S&C polymers	France	$CaWO_4$
SavDent MTA Root Canal Filling Materials	Chenselect Co. Ltd.	Taiwan	Bi_2O_3, ZnO
CEM, NEC	Bionique Dent	Iran	Unknown
TechBioSealer	Isasan	Italy	Bi_2O_3
Trioxident	VladMiVa	Russia	Bi_2CO_4
MTA +	Cerkamed	Poland	Bi2O3
Bio-MA	M-Dent/SCG	Thailand	Bi2O3
Theracal	Bisco Inc.	USA, [Only for pulp-capping]	BaZrO3
For endodontic sealing with gutta-percha			
NeoMTA Plus Neo Sealer	NuSmile Ltd.	USA Powder/liquid Single paste	Ta_2O_5 Ta_2O_5
BioRoot RCS	Septodont Inc.	France, Powder/liquid	ZrO_2
iRoot SP, Endosequence BC, TotalFill, EdgeEndo	Innovative BioCeramix Inc.	Canada, Single paste	ZrO_2, Ta_2O_5

Tradenames	Manufacturer	Country/comment	Radiopacifier
MTA Fillapex, Channels BIO-C	Angelus Industria de Productos Odontologicos	Brazil, Dual paste, Disalicylate resin-based, Single paste	Bi_2O_3 ZrO_2
Sealer Plus BC	MK Life	Brazil, Single paste	ZrO_2
EndoSeal	Maruchi	Korea, Single paste	ZrO_2, Bi_2O_3

Table II.

ISO & ADA documents pertinent to bioactive dental ceramics

ISO /ADA Document #	Title	Requirements
ISO 10993–1	Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process	**Evaluate:** Physical & chemical information Cytotoxicity Irritation or intracutaneous reactivity Pyrogenicity Acute systemic toxicity Subchronic toxicity Chronic toxicity Implantation effects Genotoxicity Carcinogenicity
ISO 7405	Dentistry — Evaluation of biocompatibility of medical devices used in dentistry	**Evaluate:** Cytotoxicity (2 methods are noted) Delayed-type hyper-sensitivity Irritation or intracutaneous reactivity Acute systemic toxicity Subchronic (subacute) toxicity Genotoxicity Chronic toxicity Implantation Pulp-capping Endodontic usage Endosseous implant usage
ISO 23317	Implants for surgery — In vitro evaluation for apatite-forming ability of implant materials	**Analyze:** Apatite formation on the surface after exposure to simulated body fluid
ISO 9917–1	Dentistry — Water-based cements Part 1: Powder/liquid acid-base cements	**Measure:** Compressive strength > 50 MPa Acid-soluble As < 2ppm Acid-soluble Pb < 100 ppm
ISO 6876	Dentistry — Root canal sealing materials	**Measure:** Flow > 17 mm Working time to be stated Setting time to be stated Film thickness<50 μm Solubility and disintegration < 3.0% Radiopacity > 3 mm aluminum
ADA 57	Endodontic sealing materials	Similar requirements as in ISO 6876 plus −0.1 %< Linear dimensional stability<+1.0 %

Table III.

Phases in tri/dicalcium silicate-containing powder materials from SDSs

	Endodontic Sealers									Endodontic Restoratives															
Material name → Phase or component	**NeoMTA**	**BioRoot RCS**	**iRoot SP**	**MTA Fillapex**	**Endoseal** ●	**Tooth colored ProRoot MTA**	**Bioaggregate**	**MTA Angelus**	**Biodentine** *	**NeoMTA**	**MTA Flow**	**Masterdent MTA**	**Medcem MTA with radiopacifier**	**RetroMTA, OrthoMTA II**	**Ortho MTA**	**ENDOCEM**	**ENDOCEM ZR**	**[MTA Caps]**	**MM MTA**	**MTA Caps**	**CEM, NEC**	**TechBioSealer**	**Trioxident**	**MTA +**	**Bio-MA**	**Theracal**
Tricalcium silicate	√		√	√	√	√	√	√	√	√	√	√	√	□	√	√	√	?	√	√	?	√	?	?	√	√
Dicalcium silicate	√		√	√	√	√	√	√	√	√	√	√	√	□	√	√	√	?	√	√	?	√	?	?	√	√
Tricalcium aluminate				√	√	√		√	□	□	□	□	√	□	√	√	√	?	√	√	?	□	?	?	√	√
Tetracalcium aluminoferrite					√			√	□	□	□	√	√	□	√	√	√	?	√	√	?	□	?	?	√	√
Calcium carbonate					□			□	√	□	□	□	√	√	□	□	□	□	√	√	√	√	□	□	□	□
Calcium oxide					□			√	√	□	□	□	√	√	□	□	□	□	□	□	√	□	□	√	√	√
Calcium hydroxide			√		□			□	□	□	□	□	√	□	□	□	□	□	□	□	√	□	□	□	□	□
Calcium sulfate	√				√	√		□	□	√	√	√	√	□	√	√	√	□	√	√	□	√	?	√	□	□
[Any] calcium phosphate					□		√	□	□	□	□	□	□	□	□	□	□	□	□	□	√	□	□	□	□	□
Hydroxyapatite					□			□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□
Silica (amorphous)	√			√	□		√	□	□	□	√	√	□	√	□	□	□	□	□	□	□	□	□	√	□	□
Zirconium dioxide			√		√			□	√	□	□	□	√	□	□	□	√	□	□	□	□	□	□	□	□	□
Bismuth oxide				√		√		√	□	□	√	√	□	□	√	?	□		√	√	?	√	□	√	?	□
Tantalum oxide	√						√	□	□		□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□
Calcium tungstate								□	□	□	□	□	□	□	□	□	◘	?	□	□	□	□	□	□	□	□
Calcium zirconate														√											√	
Barium zirconate														□											□	√
Alumina																									√	
Resins				√																						√
Citric acid					√																					
Calcium chloride					□				√																√	
Pigments				√																						

*Augmented by Jang [193];

●33.2 % unidentified “natural cement”; 1 radiopaque component not identified. ?= surmised but not confirmed from company literature or SDS. iRoot SP= Endosequence BC sealer, TotalFill & EdgeEndo sealers;

iRoot RRM= root repair material (Innovative Ceramix)= Endosequence & EdgeEndo repair/retrofill

SDS unavailable for Well-Root, Zendo MTA, SavDent, BIO-C or Sealer Plus.

Table IV.

Trace metal content measurements (ppm) in tri/dicalcium silicate materials

Trace metal element ppm)	Jang et al. [185] (in H_2O)	Kum et al. [256]	Camilleri et al. [64]	Schembri et al. [61]	De-Deus et al. [89]	Duarte et al. [255]
Arsenic (total leached)	<0.01	<2	31 to 53	30 to 36	<9	<0.0007
Lead, antimony & molybdenum	<0.002	ND	0.03–15 Pb	<1		
Chromium	<0.05	<6	4–23	85–87		
Nickel	<0.05					
Zinc	<0.1					
Cadmium	<0.001	<1				
Iron	<0.7	<1.4%				
Beryllium		<2				

ND: not detected

Table V.

Physical properties - endodontic restoratives

Property	Torabinejad et al. [66]	Chng et al. [129]*	Islam et al. [269]	Jang et al. [193]	Camilleri et al. [115]	Kumari et al. [96]	Zarra et al. [68] MTA Plus, ProRoot	Uyanik et al. [98] ProRoot, Bio-dentine	Gandolfi et al. [19]	Vargas et al. [266] BD,M†	Govin-daraju et al. [94]	Siboni et al. [85] NeoMTA, MTA Plus
Radiopacity (mm Al)	7	4–7	6.5–6.7		~7.5				4.3	3, 6.5		4, 9
Setting time (hnmm)	2:45	0:40–0:70°	0:40–0:70°	0:15–2:45•			4:20, 5:00	1:15, 0:15		0:22		2:05, 0:45
Solubility (%)	0.4*	1–2.2				<2	<1		18			
Flow (mm)					~8							
Film thickness (μm)					~850							
Compressive strength (MPa)	40, 67**		~47, ~90°°	22 to 65••						80, 20°	45, 68, 166, 194***	
pH	12.5	12–13 (@ 1hr)	12.8–13.0			8–9.5				9, 11		11, 12
Dimensional stability (linear %)		0.2–0.3	~9,30.3									

* solubility between days 1 and 21; 3 materials tested;

** 24 hours and 21 days

° final setting times of 2:20 to 2:35 hours

°° 3 and 28 days; at 28 days for Biodentine

• depending on material

•• 7 days, depending on material

† BD: Biodentine; M: MTA Angelus

*** MTA Angelus, Tooth-colored ProRoot MTA, NeoMTA Plus, Biodentine after 7 days

Table VI.

Physical properties - root canal sealers

Property	Zhou et al. [117] (Endosequence)	Zhou et. al. [117] (MTA Fillapex)	Vitti et al. [122] (MTA Fillapex)	Khalil [118] (BioRoot RCS)	Siboni [272] (BioRoot MTA RCS Fillapex)	
Radiopacity (mm Al)			4	8	5	7
Working time (hr:mm)	2:40	0:45	0:30			
Setting time (hr:mm)	>24:00	2:30	2:30	0:27	0:55	2:10
Solubility (%)	2.9	1.1	0.09		38	14
Flow (mm)	23	25	29	16		
Film thickness (μm)	22	24		52		
Dimensional stability (linear %)	<0.1	−0.7				
pH	11–12			12	12*	9.5*

*After 3 hr.