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# Mineral Trioxide Aggregate Material Use in Endodontic Treatment: A Review of the Literature

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## Abstract

### Objective

The purpose of this paper was to review the composition, properties, biocompatibility, and the clinical results involving the use of mineral trioxide aggregate (MTA) materials in endodontic treatment.

## Methods

Electronic search of scientific papers from January 1990 to August 2006 was accomplished using PubMed and Scopus search engines (search terms: MTA, GMTA, WMTA, mineral AND trioxide AND aggregate).

## Results

Selected exclusion criteria resulted in 156 citations from the scientific, peer-reviewed dental literature. MTA materials are derived from a Portland cement parent compound and have been demonstrated to be biocompatible endodontic repair materials, with its biocompatible nature strongly suggested by its ability to form hydroxyappatite when exposed to physiologic solutions. With some exceptions, MTA materials provide better microleakage protection than traditional endodontic repair materials using dye, fluid filtration, and bacterial penetration leakage models. In both animal and human studies, MTA materials have been shown to have excellent potential as pulp-capping and pulpotomy medicaments but studies with long-term follow-up are limited. Preliminary studies suggested a favorable MTA material use as apical and furcation restorative materials as well as medicaments for apexogenesis and apexification treatments; however, long-term clinical studies are needed in these areas.

## Conclusion

MTA materials have been shown to have a biocompatible nature and have excellent potential in endodontic use. MTA materials are a refined Portland cement material and the substitution of Portland cement for MTA products is presently discouraged. Existing human studies involving MTA materials are very promising, however, insufficient randomized, double-blind clinical studies of sufficient duration exist involving MTA for all of its clinical indications. Further clinical studies are needed in these areas.

## Keywords

Hydroxyapatite; Portland cement; Biocompatibility; Pulp-capping; Apexification; Root-end filling; Pulpotomy; Endodontics; GMTA; WMTA; MTA; Mineral trioxide aggregate

# 1. Introduction

It is estimated that over 24 million endodontic procedures are performed on an annual basis, with up to 5.5% of those procedures involving endodontic apical surgery, perforation repair, and apexification treatment.[1] Endodontic surgery is performed to resolve inflammatory processes that cannot be successfully treated by conventional techniques, which may be due to complex canal and/or apical anatomy and external inflammatory processes.[2] Surgical procedures may also be indicated for the resolution of procedural misadventures, to include root perforation that may occur either during canal instrumentation or post-space preparation.[2,3] Surgical treatment usually involves the placement of a material designed to seal the root canal contents from the peri-radicular tissues and repair root defects.[2] Understandably, this material should demonstrate the ability to form a seal with dental tissues while also exhibiting biocompatible behavior with the periodontal tissues.[3]

An ideal endodontic repair material ideally would adhere to tooth structure, maintain a sufficient seal, be insoluble in tissue fluids, dimensionally stable, non-resorbable, radiopaque, and exhibit biocompatibility if not bioactivity.[2,4,5] A number of materials have historically been used for retrograde fillings and perforation repair, such as amalgam, zinc-oxide-eugenol cements, composite resin, and

glass-ionomer cements.[4,6] Unfortunately, none of these materials have been able to satisfy the total requirements of an ideal material.[4,5]

Mineral trioxide aggregate (MTA) is a biomaterial that has been investigated for endodontic applications since the early 1990s. MTA was first described in the dental scientific literature in 1993[7] and was given approval for endodontic use by the U.S. Food and Drug Administration in 1998.[8] As it will soon follow, MTA materials are derived from a Portland cement parent compound: it is interesting that no information has been published regarding to any investigations that led to the precise delineation of the present MTA materials. The aim of this article is to present a systematic review of the physical properties, biocompatibility testing, and pertinent clinical studies involving MTA materials.

A structured literature review was performed for articles published between January 1990 and August 2006. The Internet database PubMed (www.ncbi.nlm.nih.gov/entrez) and Scopus (www.scopus.com) was used to search for the keywords *MTA*, *GMTA*, *WMTA*, and *mineral* AND *trioxide* AND *aggregate*. For further refinement, the following exclusion criteria were defined: Publications were limited to those of English language and from the scientific, peer-reviewed literature. Furthermore, publications possessing a questionable peer-review process (e.g., manufacturer-supported) were excluded for consideration. Although clinical case reports were included, only clinical studies involving appropriate number, sufficient controls and analysis were given serious consideration.[9] Using the search keywords limited to dental publications produced a total of 245 results, of which application of inclusion criteria produced the 156 citations that forms the basis for this review (Fig. 1).

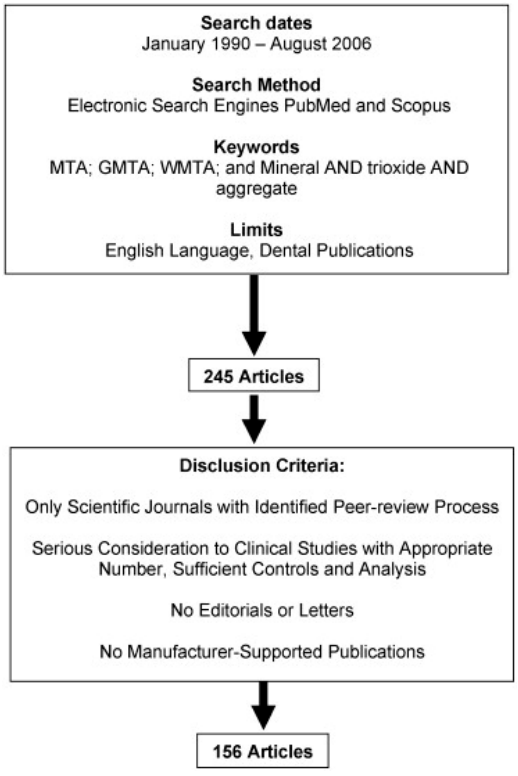


*Fig. 1. Literature search criteria.*

## 2. Chemical, physical, and mechanical properties

MTA materials are a mixture of a refined Portland cement and bismuth oxide, and are reported to contain trace amounts of $SiO_2$, CaO, MgO, $K_2SO_4$, and $Na_2SO_4$.[10,11,12] The major component, Portland cement, is a mixture of dicalcium silicate, tricalcium silicate, tricalcium aluminate, gypsum, and tetracalcium aluminoferrite.[10,11,12] Gypsum is an important determinant of setting time, as is tetracalcium aluminoferrate, although to a lesser extent.[12] MTA products may contain approximately half the gypsum content of Portland cement, as well as smaller amounts of aluminum species, which provides a longer working time than Portland cement. Although it may be inferred that Portland cement could serve as a MTA substitute, it is important to emphasize Portland cement and MTA are not identical materials. MTA products have been reported to have a smaller mean particle size, contain fewer toxic heavy metals, has a longer working time, and appears to have undergone additional processing/purification than regular Portland cements.[13,14]

The first MTA material was described as a fine hydrophilic powder composed predominantly of calcium and phosphorus ions, with added bismuth oxide to provide radiopacity greater than dentin.[15] However, later investigations.[10,11,16] found phosphorus levels in MTA products to be very low, near electron probe microanalysis detection limit, which correlates with the manufacturer's material safety data sheet.[17] Since it is unlikely that a significant compositional change in MTA materials occurred from the time of the first report and given that Portland cement is primarily composed of silicate and aluminate materials[10,13,18,19] earlier reports[15] of MTA product phosphorus content are most likely in error.[16]

The MTA product powder is mixed with supplied sterile water in a 3:1 powder/liquid ratio and it is recommended that a moist cotton pellet be temporarily placed in direct contact with the material and left until a follow-up appointment. Upon hydration, MTA materials form a colloidal gel that solidifies to a hard structure in approximately 3–4 h,[12,15] with moisture from the surrounding tissues purportedly assisting the setting reaction.[7] Hydrated MTA products have an initial pH of 10.2, which rises to 12.5 three hours after mixing.[11,15] The setting process is described as a hydration reaction of tricalcium silicate ($3CaO{\cdot}SiO_2$) and dicalcium silicate ($2CaO{\cdot}SiO_2$), which the latter is said to be responsible for the development of material strength.[12] Although weaker than other materials used for similar purposes, MTA compressive strength has been reported to increase in the presence of moisture for up to 21 days,[15] while MTA product microhardness and hydration behavior has been reported to be adversely affected with exposure to the pH range of inflammatory environments (pH 5) as compared to physiologic conditions (pH 7).[3]

MTA materials have been reported to solidify similar to other mineral cements, in which the anhydrous material dissolves, followed by the crystallization of hydrates in an interlocking mass.[3] The basic framework of the hydrated mass is formed by the interlocking of cubic and needle-like crystals in which the needle-like crystals form in sharply delineated thick bundles that fill the inter-grain space between the cubic crystals.[3] The effect of mixing MTA powder with different liquids and additives has shown that the choice of preparation liquid can have an effect on setting time and compressive strength.[20] Three and five percent calcium chloride solutions, a water-based lubricant, and sodium hypochlorite gels decreased setting time; however final compressive strength was significantly lower than that obtained prepared with sterile water. Preparation with saline and 2% lidocaine anesthetic solution increased setting time; but compressive strength was not significantly affected. Interestingly, a MTA product prepared with chlorhexidine gluconate gel did not set.[20] It seems to reason that the setting reaction of

MTA products, like its Portland cement parent compound, is a hydration reaction; sufficient water in potential preparation liquids must be present for reaction.[21] Furthermore, it should also be intuitive that the chosen preparation liquid must also possess water with the necessary diffusion ability to be available for the hydration reaction. Clinicians may consider different solutions instead of sterile water in the preparation of MTA materials; however, clinicians should consider the potential therapeutic gain versus the loss of MTA material physical properties in these situations.

Up to 2002, only one MTA material consisting of gray-colored powder was available, and in that year white mineral trioxide aggregate (WMTA) was introduced as ProRoot MTA (Dentsply Endodontics, Tulsa, OK, USA) to address esthetic concerns.[12] After that time, two forms of MTA materials were categorized: the traditional gray MTA (GMTA) and WMTA. Scanning electron microscopy (SEM) and electron probe microanalysis characterized the differences between GMTA and WMTA and found that the major difference between GMTA and WMTA is in the concentrations of $Al_2O_3$, MgO, and FeO[12,16] (Table 1). WMTA was found to have 54.9% less $Al_2O_3$, 56.5% less MgO, and 90.8% less FeO, which leads to the conclusion that the FeO reduction is most likely the cause for the color change.[16] WMTA was also reported to possess an overall smaller particle size than GMTA[22] while it was also suggested the reduction in magnesium could also contribute to the lighter color of WMTA.[12] A reported elemental analysis comparing a commercial form of WMTA, a Portland cement, and the stated MTA patent can be observed in Table 2.

*Table 1. Chemical compositions of GMTA and WMTA (wt%)*

| Chemical | WMTA | GMTA |
|---|---|---|
| CaO | 44.23 | 40.45 |
| $SiO_2$ | 21.20 | 17.00 |
| $Bi_2O_3$ | 16.13 | 15.90 |
| $Al_2O_3$ | 1.92 | 4.26 |
| MgO | 1.35 | 3.10 |
| $SO_3$ | 0.53 | 0.51 |
| Cl | 0.43 | 0.43 |
| FeO | 0.40 | 4.39 |
| $P_2O_5$ | 0.21 | 0.18 |
| $TiO_2$ | 0.11 | 0.06 |
| $H_2O + CO_2$ | 14.49 | 13.72 |

*Adapted from Asgary et al.[16]*

*Table 2. Elemental analysis comparison portland cement and ProRoot WMTA (wt%)*

| Element | Portland cement | WMTA | Patent |
|---|---|---|---|
| O | 48.1 | 38.0 | 30.5 |
| Ca | 40.3 | 37.1 | 37.2 |
| Si | 6.7 | 6.5 | 7.9 |
| Al | 2.1 | 0.6 | 1.7 |
| S | 1.5 | 0.9 | 0.8 |
| K | 0.9 | 0.0 | 0.3 |
| Mg | 0.3 | 0.0 | 1.0 |
| Fe | 1.0 | 0.0 | 2.8 |
| Bi | 0 | 16.9 | 17.9 |

*Adapted from Dammaschke et al.[12]*

The setting mechanism of WMTA has been examined using X-ray photoelectron spectroscopy (XPS) that reported surface sulfur and potassium species increase 3-fold during the setting reaction. This suggested that MTA material setting time could be prolonged by the formation of a passivating trisulfate species layer, which may serve to prevent further hydration and reaction.[12] This trisulfate species may serve a protective function, as it was reported that that WMTA flexural strength was significantly reduced when 2-mm thick layers were exposed to sterile saline moisture for more than 24 h.[23] Calcium release from MTA materials diminishes slightly with time[22] while MTA materials were reported to form a porous matrix characterized by internal capillaries and water channels in which increased liquid/powder ratio produced more porosity and increased solubility.[24] GMTA solubility levels have been reported to be stable over time, but the usually-reported pH of between 11 or 12 may slightly decrease.[25] The high pH level of MTA materials has led some to theorize that the biologic activity is due to the formation of calcium hydroxide.[22,23,24,25] WMTA solubility, hardness, and radiopacity has been compared to two Portland cements reporting that WMTA was significantly less soluble, exhibited greater Vickers hardness, and was more radiopaque.[26]

There are some evidence that MTA materials possess a prolonged maturation process that continues past the stated setting time of 3–4 h, as GMTA retention strength for furcation repairs has been reported to resist significantly more dislodgement at 72 h as compared to 24 h.[27] This was corroborated by one study that reported increase push-out strength up to 7 days[28] with an additional study reporting maximum GMTA push-out strength observed at 21 days.[27] Interestingly, GMTA that has not reached full maturity has been suggested to possess an ability to re-establish dislodgement resistance after partial displacement; but the re-established resistance strength decreased as dislodgement time increased after placement.[27]

Different intracanal irrigant/oxidizing agents have been found to affect the push-out strength of GMTA as it was susceptible to sodium hypochlorite, sodium perborate mixed with saline, 30% hydrogen

peroxide, sodium perborate mixed with 30% hydrogen peroxide, and saline at 7 days.[29] GMTA push-out strength was also reported to be similar to Super-EBA and IRM when exposed to saline or sodium hypochlorite, but GMTA was more susceptible to oxidizing agents,[29] which was reinforced by a report that a hydrogen peroxide-based canal preparatory agent significantly reduced the push-out strength of GMTA to dentin, whereas 2% chlorhexidine and 5.25% sodium hypochlorite did not.[30] Another report found that perforation retention strength was not affected by preparing GMTA with either saline, sterile water, or lidocaine, but the bond strength to blood-contaminated root dentin was significantly less than that observed to uncontaminated dentin.[28] Any adhesion that may be formed between GMTA and dentin may be stronger than the cohesive strength of the GMTA material, as it was reported that GMTA–dentin bond failures was usually cohesive within the MTA material.[28] Furthermore, total GMTA–dentin bond strength is also heightened by increased surface area, as one report states that 4 mm of GMTA has been reported to afford more resistance to displacement than 1-mm thick applications, and was not affected by previous calcium hydroxide placement.[31]

Placement of GMTA using hand condensation techniques has been suggested to provide less porosity than ultrasonic-assisted techniques in simulated straight canals.[32] However, different results were found that suggested a denser MTA fill was obtained in both straight and curved canals with a combination hand and ultrasonic placement over a solely manual condensation technique.[33] GMTA root-end marginal adaptation and stability was reported to be significantly better than a ZOE preparation after being submitted to a computer controlled, simulated masticating apparatus that produced an estimated 5 year equivalence of chewing cycles.[34] Prefabricated posts luted with GMTA were reported to provide significantly less retentive strength than a glass-ionomer and zinc phosphate luting agents.[35] WMTA has been reported to strengthen the cervical fracture resistance of immature sheep incisors as compared to the use of calcium hydroxide.[36] Although this result is considered promising, it should be noted that within the groups sample number were low (<10) and the sample dimensions were also varied in dimension.

WMTA and a ZOE preparation was found to have similar antibacterial properties against *Staphylococcus aureus*, *Enterococcus faecalis*, and *Pseudomonas aeruginosa* in a direct contact test[37] while substituting 0.12% chlorhexidine gluconate provided more antibacterial activity against *Actinomyces odontolyticus*, *Fusobacterium nucleatum*, *Streptococcus sanguis*, *E. faecalis*, *Escherichia coli*, *S. aureus*, *P. aeruginosa*, and *Candida albicans* than WMTA prepared with sterile water alone.[38] This finding should be tempered with knowledge that MTA materials may not set when mixed with some chlorhexidine preparations.[20] Both freshly mixed and set GMTA was reported to be inhibitory to *C. albicans* using an antifungal tube-dilution method[39] while another study reported differences in that GMTA and WMTA at different powder/liquid mixtures were not equally effective at preventing the growth of *C. albicans.*[40] Both WMTA and GMTA in concentrations of 50 and 25 mg/ml were equally inhibitive against *C. albicans* for up to 7 days; however, at lower concentrations only GMTA was effective.[40] This is evidence of not only the importance of proper powder/liquid ratios but also raises possible questions concerning that the two MTA preparations may not be equally effective in some clinical applications.

In conclusion, MTA materials are derived from Portland cement, and although it could be inferred that Portland cement could serve as a suitable substitute, it is important to emphasize that MTA products and Portland cement are not identical materials. 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/purification than the Portland cement parent compound. WMTA has been marketed since 2002 due to 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 3–4 h but whose maturation and resistance to dislodgement increases with time. 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 pH.

## 3. Microleakage studies

The success of an endodontic material may largely depend on its sealing ability, as most post-treatment endodontic disease is thought to occur due to tissue and other materials in uncleaned and/or unobturated areas of the root canal system that egress into the surrounding tissues.[41]

### 3.1. *In vitro* dye/fluid filtration method leakage studies

The microleakage of MTA materials compared to other traditional endodontic materials via *in vitro* dye and fluid filtration methods have been the subject of many studies.[42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64] GMTA has been reported to have less microleakage than amalgam,[42,43,44,45,47,48,51,52] zinc-oxide-eugenol (ZOE) preparations,[42,43,44] and a conventional glass-ionomer material[59] when used as a root-end restoration following apical resection. However, other studies reported no difference in leakage between MTA materials and zinc-oxide-eugenol preparations,[45,51,52,59] and conventional glass-ionomer restorative materials.[48] The minimal thickness for MTA to effectively seal the apical area has been investigated with one study reporting a placement thickness of at least 3 mm[49] with another report stating a minimal of 4 mm is required for significant microleakage prevention.[50] The addition of calcium chloride has been reported to enhance the sealing ability of both GMTA and WMTA, probably by the effect of calcium chloride's enhancement of MTA material setting time.[57] WMTA and GMTA have been compared for the sealing of simulated canals with open apices using thicknesses of 2 and 5 mm followed by gutta percha obturation either immediately after MTA material placement or 24 h later.[53] Results found that GMTA had less microleakage than WMTA in samples obturated 24 h after MTA placement; in all groups 5 mm of MTA material allowed less leakage. Based on the results, the authors recommended a 5-mm GMTA apical barrier placed for treatment of open apices with gutta percha obturation followed 24 h later.[53] Visual topography evaluations of root-end restorations restored with GMTA, ZOE materials, and amalgam have reported that root-end restoration finishing method had no effect on marginal adaptation of GMTA and ZOE material[63] while another report stated that GMTA appeared to have better root-end marginal adaptation than amalgam.[64]

For repair of furcation perforations, a ZOE preparation was reported to provide a better seal than GMTA at 24 h, after which no difference in leakage was observed.[60] However, in another report, GMTA was found to allow more microleakage in furcation repairs when compared to a ZOE preparation and a self-etch, one step bonding agent.[58] The furcation perforation repair microleakage of GMTA and WMTA was compared from both an orthograde and retrograde direction.[56] The results found no difference in leakage between the two MTA materials; but the more interesting findings were that significantly more leakage was found from a microleakage challenge from an orthograde direction.[56] This suggests an impelling need for an adequate coronal barrier material over MTA furcation repairs to adequately protect against coronal microleakage.

The microleakage of MTA materials used for root canal obturation has been reported by two studies.[54,61] The first study suggested that GMTA displayed more microleakage than laterally-condensed as well as thermoplasticized gutta percha[54] but this was contrasted by the other study which reported that both

WMTA and GMTA allowed less apical microleakage than warm, vertically condensed gutta percha.[61] The second study also reported no significant difference in leakage between GMTA and WMTA, but importantly noted that root canal obturation with MTA materials would severely limit retreatment options and should be considered in only select cases.[61] Another report reported that root resection of canals obturated with GMTA did not affect its sealing ability.[62]

## 3.2. *In vitro* bacterial leakage studies

The microleakage of MTA materials has also been evaluated, to a lesser extent, using bacterial penetration methods.[31,41,65,66,67,68,69,70,71,72,73,74,75] GMTA has been evaluated for resistance against apical bacterial leakage when utilized as a root-end filling compared with amalgam and ZOE materials within endodontically prepared but unobturated root canals inoculated with *Staphylococcus epidermis*[41] and *Serratia marcescens*.[65] GMTA was found to have significantly more resistance to *S. epidermis* penetration than amalgam and ZOE preparations with no leakage evident after 90 days, with the other materials exhibiting bacterial penetration ranging from 6 to 57 days.[41] The second study found that GMTA resisted *S. macescens* penetration for up to 49 days after inoculation while the amalgam and ZOE materials displayed trends for more bacterial penetration.[65] WMTA and a bonded polymer-based material were found to exhibit similar root-end bacterial leakage resistance using a *Streptococcus salivarius* model with both materials having significantly less bacterial leakage than a ZOE preparation.[71] GMTA was also reported to allow significantly less *E. coli* endotoxin penetration using a modified Limulus Amebocyte Lysate test than amalgam and two ZOE preparations over a 12-week evaluation [69].

In contrast, GMTA was found to have the same bacterial penetration resistance as a ZOE preparation, amalgam, a bonded resin composite, as well as a bonded amalgam during a 12-week evaluation using *Streptococcus salivarius*.[68] Similar results were reported during a 47-day study with GMTA compared against a polyacid-modified resin composite and a ZOE preparation using *Prevotella nigrescens*.[70] Furthermore, WMTA root-end fillings contaminated with either blood, saline, or saliva during placement were found to display varying resistance to *Staphylococcus epidermidis* with saliva contamination causing significantly more leakage.[72]

When used as perforation repair materials, GMTA did not demonstrate any bacterial leakage during a 45-day evaluation while approximately half of the amalgam-repaired furcations allowed penetration and transmission of *F. nucleatum*.[68] Furthermore, no significant difference was found between GMTA and WMTA in the resistance to *F. nucleatum* penetration when used for furcation repair.[67] When used in the treatment of immature apices, GMTA has been reported to provide resistance to bacterial penetration by *E. faecalis* and *S. epidermis* but not *Enterobacter aerogenes*.[31] A similar report reinforced GMTA resistance to *E. faecalis* penetration with no leakage identified by *E. faecalis* 16S rDNA polymerase chain reaction assay after 10 days.[73] GMTA was also evaluated against *Actinomyces viscosus* microleakage for up to 70 days in simulated immature apices that had received either a 2- or 5-mm apical GMTA restoration, or a series of 2-mm GMTA apical retrograde fillings. Results reported that only the 5-mm thick restoration resisted microleakage for the entire evaluation, and exhibited significantly less leakage compared to the positive control and other GMTA groups.[74] When evaluated as a coronal barrier, no difference against human saliva bacterial penetration was found between GMTA, WMTA, or a resin-modified glass-ionomer restorative material.[75] One study attempted to evaluate the *in vivo* coronal sealing ability of WMTA in canine endodontically prepared and obturated root canals, but no conclusive results were found.[76]

In conclusion, MTA materials have been investigated using dye, fluid filtration and bacterial infiltration leakage methods. The majority of the dye and fluid filtration studies suggest that MTA materials overall allow less microleakage than traditional materials when used as an apical restoration while providing equivalent protection as a ZOE preparation when used to repair furcation perforations. GMTA and WMTA were shown to provide equivocal results compared against gutta percha when used as a root canal obturation material in the limited number of microleakage studies. MTA materials have been suggested to afford less microleakage than traditional materials in a majority of bacteria-based microleakage studies when used as an apical restoration, furcation repair, and in the treatment of immature apices. In both fluid filtration and bacterial leakage models, 3 mm of MTA material is suggested as the minimal amount for protection against microleakage while 5 mm is suggested in the treatment of immature apices.

## 3.3. Biocompatibility studies

### 3.3.1. *In vitro* studies

*In vitro* biocompatibility evaluations of MTA materials have been richly reported in the literature.[77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103] The mutagenicity of GMTA, ZOE-based, root-end filling materials, as well as positive and negative controls were evaluated using an Ames mutagenicity assay in which the materials were incubated with *Salmonella Typhimurium* LT-2 strains with reverting bacteria colony counts measured.[77] None of the root-end filling materials, including GMTA, produced statistically significant higher Ames test reversion rates, which indicates that none of the root-end filling materials would be considered mutagens.[77] Other evaluations have reported no genotoxic effects of WMTA or Portland cements by single cell gel (comet) assay on peripheral human lymphocytes,[78] mouse lymphoma cells,[79] as well as Chinese hamster ovary cells.[80] Taken as a whole, none of the studies have shown genotoxic effects of MTA. Although specific carcinogenicity testing for MTA materials was not found in the literature, it is thought that all carcinogens are mutagens. Therefore, based on the existing literature, it is unlikely that MTA is a carcinogenic substance since it is not a mutagenic substance.

The cytotoxicity of GMTA, amalgam, ZOE, as well as positive and negative controls was measured using a cell viability assay for mitochondrial dehydrogenase activity in human periodontal ligament fibroblasts after 24-h exposure to extracts of varying concentrations of the test materials, in both freshly mixed and 24-h set states.[82] In the freshly mixed state, the sequence of toxicity was amalgam > Super-EBA > MTA. In the 24-h set state, the sequence of toxicity at a low extract concentration was Super-EBA > MTA, amalgam; while at higher extract concentrations was Super-EBA > amalgam > MTA.[82] Similarly, another report reinforced that GMTA did not negatively affect human periodontal ligament fibroblast mitochondrial dehydrogenase activity.[86] SEM analysis of periodontal ligament fibroblasts was found to have a normal morphology and exhibit growth and attachment to 24-h set MTA surfaces.[83] However, in the freshly mixed GMTA samples, the cells were round, less in density, exhibited surface defects, and lacked attachment to MTA.[83] If the quality and quantity of cell attachment to the root-end filling materials can be used as a criterion to evaluate material's toxicity, then set GMTA appears to be less cytotoxic than fresh GMTA.[83] In a comparable study involving resected root surfaces, PDL cell attachment was observed on GMTA but was absent on gutta percha.[87] Similarly, PDL fibroblasts have been reported to display enhanced proliferation on WMTA in a study that analyzed cellular metabolic activity.[88] These analyses indicated that WMTA induced a general osteogenic phenotype in PDL

fibroblasts, with induction of alkaline phosphatase activity, as well as production of osteonidogen, osteonectin, and osteopontin.[88]

The cytotoxicity of amalgam, ZOE preparations, and GMTA was reported via an ATC L-929 mouse fibroblast agar overlay and radiochromium method.[81] Results of the agar overlay found that set amalgam was significantly less toxic compared to the other materials, while the set GMTA was significantly less toxic than the ZOE preparations. Contrasting, the radiochromium method suggested that GMTA was significantly less toxic than amalgam. Although it was suggested that the increased agar cytotoxicity of the ZOE preparations was due to the leaching of eugenol, the report concluded that GMTA was no more cytotoxic than other root-end filling materials currently in use.[81] These findings were reinforced by another study using human gingival fibroblasts and a L-929 cell line.[85] GMTA and a CP titanium alloy was found to have similar affect on gingival fibroblast cellular activity, causing no negative affect on cell viability, Prostaglandin $E_2$ assays, protein and lactate synthesis, and cell proliferation. Overall results indicated that gingival fibroblast growth was similar for both GMTA and titanium, as either material did not initiate $PGE_2$ release or cause alteration of gingival fibroblast cellular metabolism.[84]

The high pH value of freshly mixed GMTA was found to induce cell lysis in L-929 mouse fibroblasts and macrophage cell lines in direct contact with the material; however, set GMTA demonstrated favorable biocompatibility with no observed effect on cell morphology as well as limited impact on cell growth at 72 h.[89] WMTA, as well as calcium hydroxide and a ZOE sealer, was shown not to affect the cell viability or the Prostaglandin $E_2$ synthesis of murine macrophages and fibroblasts.[91] In a different study, murine fibroblast and macrophage cells displayed significantly greater cytotoxicity using flow cytometry with WMTA prepared with 0.12% chlorhexidine gluconate than to WMTA prepared with sterile water.[90]

MG-63 cultured human osteoblasts were exposed to GMTA with cellular response evaluated via alkaline phosphatase activity as well as inflammatory cytokine and osteocalcin production.[92] The MG-63 cells were found to adhere closely to the GMTA surface while cytokines for osteoclast recruitment (M-CSF) and activation (IL-1α, IL-1β, IL-6) were found to be produced, along with observed osteocalcin production and alkaline phosphatase activity.[92] This led to speculation that GMTA causes osteoblast adhesion with release of cytokines from the attached osteoblasts resulting in osteoclast activation via coupled resorption. Therefore, MTA might be considered a suitable substitute for PMMA when used for an orthopedic bone cement.[92] This was corroborated by another study that found that MG-63 osteoblast-like and Saos-2 human osteosarcoma cells exposed to GMTA exhibited viability, attachment, proliferation, and collagen production after 24 h.[96]

ELISA assays have been used to assess the osteocompatibility of GMTA by monitoring the expression of Interleukin (IL)-1α, IL-6, IL-8, IL-11 and macrophage colony stimulating factor (M-CSF).[93] Although osteoblast cell growth was reported, production of IL-1α and IL-11 were not detected from the cells exposed to the GMTA materials. However, osteoblastic IL-6 and IL-8 were detected as well as M-CSF.[93] Osteoblasts in another study were found to demonstrate good adhesion and spreading on GMTA surface, but did not demonstrate the same ultrastructural characteristics when exposed to a ZOE preparation and amalgam.[94] GMTA osteocompatibility was reported after U2OS human osteosarcoma cell lines were incubated with GMTA and evaluated using Western blot assay.[95] In this study, GMTA had a positive effect on the mitogen-activated protein kinase (MAPK) pathways. The authors also reported that a dose-dependent influence was present on the extracellular signal-regulated kinase MAPK

pathway, which is a known pathway leading to osteoblastic activation and overgrowth.[95] This was reinforced by another study that reported both 1- and 28-day cured GMTA and WMTA displayed biocompatibility when exposed to a Saos-2 human osteosarcoma cell line,[97] while an additional another study reported both cell attachment and IL-4 and IL-10 cytokine production.[98]

Freshly mixed or set GMTA has been reported to display little to no neurotoxicity. Neurotoxicity effects were quantitatively assessed by exposing fetal mice cortical neuronal and glial cells and measuring lactate dehydrogenase activity, an assay for cell death.[99] In this study, an amalgam, ZOE preparation, and a resin endodontic sealer exhibited neurotoxicity that affected approximately 50–100% of the neuronal and glial cells, while GMTA exhibited little to no neurotoxicity.[99] GMTA has also been reported to be biocompatible with a murine cementoblast model, with the cementoblasts displaying ultrastructural attachment to GMTA surface with normal reverse transcriptase polymerase chain reaction analysis (RT-PCR) indicating osteocalcin production.[100] Another study suggested that WMTA was more biocompatible than GMTA in supporting human cementoblast and keratinocyte growth.[103]

WMTA effect on dental pulp cell viability and proliferation has been evaluated using mouse MDPC-23 odontoblast-like cells and OD-21 undifferentiated pulp cells. After 24-h exposure to WMTA, apoptosis was not induced in either cell line, and WMTA was reported to cause DNA synthesis increase, suggesting a positive effect on cellular proliferation.[101] This was reinforced by another report that suggested that WMTA had more of a stimulating effect on human dental pulp cells than a commercial calcium hydroxide preparation.[102]

### 3.3.2. *In vivo* studies

GMTA was reported to induce little or no inflammation compared to a ZOE preparation when implanted into guinea pig mandibles, with one GMTA sample demonstrating bone formation on its surface.[104] Similar tissue reactions with both GMTA and Portland cement that demonstrate direct bone deposition on the materials' surfaces have been reported.[105] Another study found no inflammation difference in rat connective tissue exposed to both WMTA and a Portland cement mixture.[106] An additional study reported a more favorable tissue reaction to GMTA compared to amalgam and two ZOE preparations that were implanted in guinea pig tibias and mandibles with direct bone apposition observed on some GMTA samples.[107] However, a different study found no difference in rat bone tissue reaction between WMTA, GMTA, amalgam, and an epoxy-based, calcium hydroxide root canal sealer.[108] In a rat connective tissue model, GMTA was observed to induce calcification which served as a nidus for ossification,[109] whereas in a similar model amalgam, WMTA, and GMTA were reported to have similar Cox inflammatory cell grading at 3 weeks, although the amalgam samples exhibited more severe inflammation at the study onset than the MTA samples.[110] GMTA and a calcium hydroxide-containing root canal sealer was reported to be well tolerated when implanted into rabbit ear chamber connective tissue, although the root canal sealer induced connective tissue dissolution with precipitate barrier formation.[111]

When used as a root-end restoration in a canine model, GMTA was reported to be associated with significantly less periapical inflammation than amalgam at both 5 and 18 weeks after placement, with almost all of the GMTA specimens exhibited new cementum tissue growth on the GMTA surface.[112] In another study, GMTA and an epoxy-based, root canal cement both exhibited excellent canine peri-radicular tissue response at 60 days with no statistically significant difference between the materials for new cementum, bone, or periodontal ligament formation.[113] These results were corroborated by a

report that evaluated the canine peri-radicular response to GMTA and a ZOE preparation which found the presence of periodontal ligament formation and hard tissue ingrowth on the GMTA surface.[114]

For periapical surgery on obturated canals associated with induced periapical lesions in a canine model, GMTA was reported to induce a favorable periapical tissue healing response compared to amalgam and a ZOE preparation.[115] Blinded histologic evaluation 42 days after periapical surgery reported that tissues adjacent to GMTA displayed a minor degree of inflammation, while tissues adjacent to the ZOE preparation moderate inflammation. Tissues adjacent to amalgam exhibited marked inflammation. Only the GMTA groups exhibited cementum growth over the root-end filling material which led to speculation that the new cementum may have originated from both the periodontal ligament and alveolar bone.[115] Using a canine model, neither freshly prepared nor fully-set GMTA was found to make a difference in periapical healing, with new cementum deposition and bone healing observed in both groups.[116] A subsequent study evaluated the healing of canine periapical tissues after calcium sulfate and GMTA placement following peri-radicular surgery. Histologic analysis 4 months post-surgery revealed that simultaneous use of calcium sulfate and GMTA does not significantly affect peri-radicular healing.[117]

Periapical tissue response to GMTA and zinc-free amalgam root-end filling materials using a mammalian Cynomolgus monkey model found that at 5 months after surgery, peri-radicular tissues adjacent to the amalgam restorations displayed moderate to severe inflammation with fibrous capsule formation, while only one tissue specimen adjacent to the GMTA material displayed inflammation.[118] For both groups, cementum was observed to have re-formed associated with the resected root surface, but no cementum was observed on the amalgam surface. However, cementoblast activity associated with thick cementum was observed on the GMTA surface with five of six specimens, with some specimens exhibiting new periodontal fiber insertion.[118]

For furcation repair, GMTA and amalgam were compared using a canine model using both an immediate- and delayed-repair scenario.[119] Endodontically treated teeth with standardized furcation perforations were repaired with both materials either immediately or after 6 weeks of salivary contamination. For the immediate-repair situation at 4 months, the amalgam samples were all associated with inflammation and no repair site cementum formation. The GMTA-repaired specimens were characterized by lack of inflammation with cementum formation noted in five of six specimens. For the delayed-repair group, half of the GMTA-repaired specimens were free from inflammation with cementum formation. The delayed-repair group with amalgam-restored specimens exhibited either moderate or severe inflammation. Although this study did not use statistical analysis, the authors concluded that GMTA had potential when used for furcation repairs.[119]

GMTA was compared to a resin-based, calcium hydroxide root canal sealer repairing lateral root perforations at the junction of the middle and coronal thirds using a canine model.[120] At 30 days, GMTA-treated samples displayed either cementum deposition and/or small areas of ankylosis adjacent to the perforation site. Furthermore, all areas were reported to exhibit little inflammation except for areas with GMTA overfill. However, the root canal sealer largely induced chronic inflammation and ankylosis, with localized periodontal ligament necrosis associated with overfilled areas.[120] At 180 days, GMTA-repaired specimens exhibited no ankylosis with most specimens exhibiting healing characterized by cellular cementum formation with PDL formation between the cementum and alveolar bone. In contrast, sealer-repaired specimens exhibited some cementum formation but was associated with a

chronic inflammatory response consisting of foreign body giant cells and macrophages. Although the authors reported that this study supported the use of GMTA for perforation repair, there was no statistical analysis of the data.[120] The histologic response of canine periapical tissues was reported comparing GMTA and a glass-ionomer material used as obturation materials. Six months after obturation, all root canals obturated with GMTA exhibited apical closure with new cementum formation, whereas only partial cementum closure was observed in a minority of the glass-ionomer materials. Although both materials were reported to exhibit good biocompatibility, the authors suggested that GMTA exhibited better biologic properties.[121]

In conclusion, regarding the biocompatibility of MTA materials, studies in general tend to support the biocompatibility of both GMTA and WMTA, although cytotoxicity studies are inclined to suggest less response to the set material as compared to the freshly prepared material. Nevertheless, the published literature tends to support the biocompatibility of both the set material and freshly prepared material, especially in relation to other dental materials.

### 3.4. Characterization of MTA biocompatibility

Numerous studies have been devoted to evaluate the biocompatibility of GMTA and WMTA. Interestingly, only a few studies have attempted to identify the specific quality of MTA materials that provides their biocompatible nature. Some reports speculated that MTA material biocompatibility was derived from calcium hydroxide formation,[11,22,24,90,120] and one report did observe the formation of a white interfacial material between GMTA and tooth structure when exposed to a phosphate-buffered physiologic solution.[48]

Sarkar et al.[10] reported the first investigation aimed solely at investigating the biocompatible nature of MTA materials and reported the formation of white precipitates within 1–2 h on the GMTA surface along with suspended precipitates within the physiologic phosphate-buffered saline solution. 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, while X-ray diffraction (XRD) analysis suggested the presence of hydroxyapatite, although it should be noted that the calcium-to-phosphorus ratios reported differed from that reported of hydroxyapatite.[10] In spite of this disparity, this report was reinforced by Bozeman et al.[122] who also used XRD and SEM analysis of both WMTA and GMTA crystal precipitates under the same conditions. This report reinforced that the crystal precipitates on both MTA materials were chemically and structurally similar to hydroxyapatite. Interestingly, 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.[122]

## 4. Clinical applications of mineral trioxide aggregate materials

### 4.1. Pulp-capping

#### 4.1.1. Animal models

GMTA has been compared with calcium hydroxide as a pulp-capping medicament using a cynomolgus monkey model in which GMTA was found associated with little tissue inflammation and a thick and continuous dentin bridge at 5 months. In contrast, only one-third of the calcium hydroxide-treated specimens exhibited dentin bridge formation with all displaying severe tissue inflammation.[123] A canine model study reported similar results with GMTA exhibiting good tissue response and dentinal bridge

formation while one-third of the calcium hydroxide specimens exhibited dentin bridge formation with 75% of the specimens displaying bacteria and chronic pulp tissue inflammation.[124] Another canine model study reported that GMTA when used as a pulp-capping medicament induced an osteodentin matrix at 3 weeks that was typically observed with reparative dentin,[125] while WMTA in a different study was reported to exhibit neodentinal bridge formation at 2 weeks with an ultrastructural intimate relationship observed between the pulpal tissues and the WMTA crystals.[126] WMTA and GMTA used as pulp-capping agents were both reported to form calcified bridge formation in which all WMTA and a majority of the GMTA specimens exhibited complete calcified bridge formation with mild inflammatory reactions at 2 weeks.[127] In a rodent pulp-capping model, GMTA was reported to induce complete hard tissue bridge formation at 2 weeks that stained positive for dentin sialoprotein.[128]

GMTA was reported to foster the same tissue reaction as two sterilized Portland cement preparations when used as a pulpotomy medicament in a canine model, with all four materials associated with a dentin bridge with normal pulpal tissue at 120 days.[129] WMTA was reported to produce both incomplete and complete barrier formation with mild tissue inflammation when used as an apexification medicament in a canine model. Specimens that were treated solely with WMTA were found to produce barriers within the root confines whereas specimens treated first with calcium hydroxide had mostly incomplete barrier formation that were predominately extracanal, beyond the previous apical area.[130]

## 4.2. Human studies

### 4.2.1. Pulp-capping

A prospective study compared calcium hydroxide and GMTA as permanent dentition pulp-capping medicaments using third molars with mature apices in a split-mouth design.[131] Mechanical pulp exposures in 11 pairs of maxillary third molars were analyzed at 1 week, and at 2, 3, 4, and 6 months after treatment. The calcium hydroxide specimens were hallmarked by tissue inflammation with a 0.15-mm thick dentinal bridge with adjacent pulp tissue necrosis noted at 6 months. These findings were contrasted with GMTA specimens displaying mild tissue reactions with a 0.28-mm dentin bridge noted at 2 months, with 6-month specimens displaying 0.43-mm dentin bridge formation, no pulp tissue inflammation, all associated with a near-regular odontoblastic layer.[131] However, the authors did acknowledge a small sample size and the need for further studies. A second prospective study compared WMTA and a calcium hydroxide preparation as direct pulp cap medicaments in 48 third molars in a single-blinded, randomized, controlled clinical study.[132] At 30-days post-treatment, the WMTA group had 20 teeth with clinically normal pulpal status while three were diagnosed with reversible pulpal disease. The calcium hydroxide group had 17 teeth with normal pulpal signs, 6 exhibited signs of reversible pulpal disease, and 1 was diagnosed with irreversible pulpal disease. At the 136-day recall, all 23 teeth present for the WMTA group were clinically diagnosed as successful as well as 22 teeth of the calcium hydroxide group. At both evaluation periods, no significant difference was found between the groups in regards to the clinical presentation as well as the histologic status.[132] Two case studies involving GMTA used as a deciduous pulp-capping agent and in treatment of dens evaginatus reported good follow-up results with minimal clinical or radiographic pathology.[133,134]

For use of MTA materials as direct pulp cap medicaments, the two clinical prospective studies suggest that both GMTA and WMTA may perform equally as well as traditional calcium hydroxide in non-carious mechanical pulp exposures in teeth with normal pulp tissue. Although the initial results are positive,

further clinical studies are needed, especially in the more clinically relevant situations involving carious pulp exposures before MTA materials can be unequivocally indicated for a direct pulp-capping agents.

### 4.2.2. Pulpotomy dressing

There are seven prospective studies involving the use of MTA materials as pulpotomy dressings for primary teeth[135,136,137,138,139,140,141] while two studies investigated a similar role in permanent teeth.[142,143]

GMTA and formocresol were compared as pulpotomy dressings in primary molars with carious pulp exposures, with only one reported failure (internal resorption in a formocresol-treated specimen) in the 32 teeth available for evaluation ranging 6–30 months.[135] Pulp canal obliteration was noted at a higher frequency in GMTA-treated specimens (7/17) than that seen with formocresol (2/15).[135] Another study compared GMTA, WMTA, and formocresol as pulpotomy dressings in primary teeth demonstrating radiographic caries pulpal involvement with recalls at 1, 3, 6, and 12 months.[136] All teeth were judged as clinical and radiographic successes at 1 month, while at 3 months one WMTA-treated tooth failed due to abscess formation; all remaining teeth were rated successful at 6 months. At 12 months all GMTA specimens were judged to be successful, but three WMTA-treated teeth were found to be clinical and radiographic failures, along with two formocresol-treated teeth. GMTA as found to provide a significantly better outcome than WMTA, with no difference found between WMTA and formocresol.[136] These results were contrasted by a different randomized, prospective study that compared formocresol and WMTA as pulpotomy medicaments in primary molars. At 24 months none of the WMTA-treated teeth exhibited clinical or radiographic pathology while the formocresol-treated teeth demonstrated approximately 13% radiographic and 2% clinical failure.[139] Another longer (range 4–74, mean 38 months) prospective, randomized study found both formocresol and a MTA material (authors did not delineate MTA material type) equally successful statistically when used as pulpotomy dressings in primary molars with carious pulp exposures.[140] Similar results were reported in a 12-month study in which WMTA was compared with calcium hydroxide for pulpotomy treatment in 90 cariously exposed primary molars.[141] In this study, treatment was curiously provided in two sessions, in which WMTA and/or the calcium hydroxide paste was applied after an interim dressing of a corticosteroid/antibiotic solution. At the end of the evaluation period six failures had occurred with the calcium hydroxide treatments and two failures had occurred with the WMTA treatments.[141]

GMTA and WMTA were evaluated as pulpotomy dressings for primary molars in two different short-term studies[137,138] by the same group of researchers. The first reported that GMTA exhibited clinical success at 6 months with radiographic dentin bridges observed in 50% of the specimens.[137] The second study found similar results with WMTA but radiographic analysis was limited only to the mandibular teeth. Within this limitation, results were that 69% of the pulp canals demonstrated signs of stenosis, 11.5% of the pulp canals exhibited dentin bridges, and one canal exhibited possible early signs of internal resorption adjacent to the WMTA dressing.[138] In these two studies no statistical difference was found in the rate of pulp canal stenosis between GMTA and WMTA whereas GMTA was found to produce significantly more dentin bridges.[137,138]

One prospective clinical study reported GMTA as a pulpotomy medicament in 31 vital, cariously exposed, first molar permanent teeth.[142] At 24 months, 79% of the 28 teeth available for evaluation maintained a positive response to vitality testing with the remainder free of clinical or radiographic pathology. Sixty-four percent of the specimens had pulpal radiographic hard tissue bridge formation, while seven teeth that initially presented with immature apices displayed radiographic signs of

continued root development.[142] Although this study is favorable, it should be noted that the teeth were restored immediately with the manufacturer recommendation of interim placement of the MTA dressing with a moist cotton pellet not observed. However, this did not appear to affect the results and could identify the importance of an early coronal seal provided by a definitive restoration, especially in the pediatric population. Furthermore, it would have been of interest if this study had been able to compare other treatment groups using traditional pulpotomy dressing materials. It is hoped that the authors will report the continued follow-up results of this work.

The histologic pulpal response comparing WMTA to calcium hydroxide as pulpotomy dressings was investigated in premolar teeth extracted for orthodontic purposes, reporting that WMTA induced a more homogenous and continuous dentin bridge with less pulpal inflammation than calcium hydroxide at both 4 and 8 weeks after treatment.[126] A favorable outcome was also reported in a private endodontic practice assessment using WMTA as a pulpotomy dressing in 23 permanent teeth that exhibited clinical signs of irreversible pulpal disease.[143] Of the 19 teeth available for recall (range 6–53 months) one tooth presented signs of persistent pulpal disease; this case did not receive a permanent restoration and presented with recurrent caries upon recall. Based on these limited results, the authors reported a Kaplan–Meier survival probability of 0.95.[143]

### 4.2.3. Other MTA material use

Compared to other clinical usage of MTA materials, very few clinical studies exist that report the outcome of clinical use of MTA materials as root-end filling materials and root repair, as in the clinical cases noted in Fig. 2, Fig. 3. A prospective 24-month clinical study compared GMTA to a ZOE preparation as root-end filling materials in 122 adult patients referred for endodontic surgery.[144] At both 12- and 24-month recalls, acceptable results were noted with both materials; while the authors implied a higher success rate with GMTA treatment, no statistical difference was noted between the two materials.[144] It is hoped that this 24-month report will continue to be followed. A retrospective study concerning GMTA use for root perforation repair in 16 cases within an endodontic residency caseload has been reported.[145] This report involved five lateral root perforations, five strip perforations, three furcation perforations, and three apical perforations that were treated with a follow-up range of 12–45 months. Results were that all treatments demonstrated clinical and radiographic signs of healing with return of normal radiographic architecture to the repair sites.[145] Although these initial results are promising, this study represents a limited number of clinical cases and no comparison group was included. Clinical case reports in which GMTA has been used to repair horizontal root fractures, root resorption, internal resorption, and furcation perforations with both clinical and radiographic success have also been reported.[146,147,148,149,150,151,152]

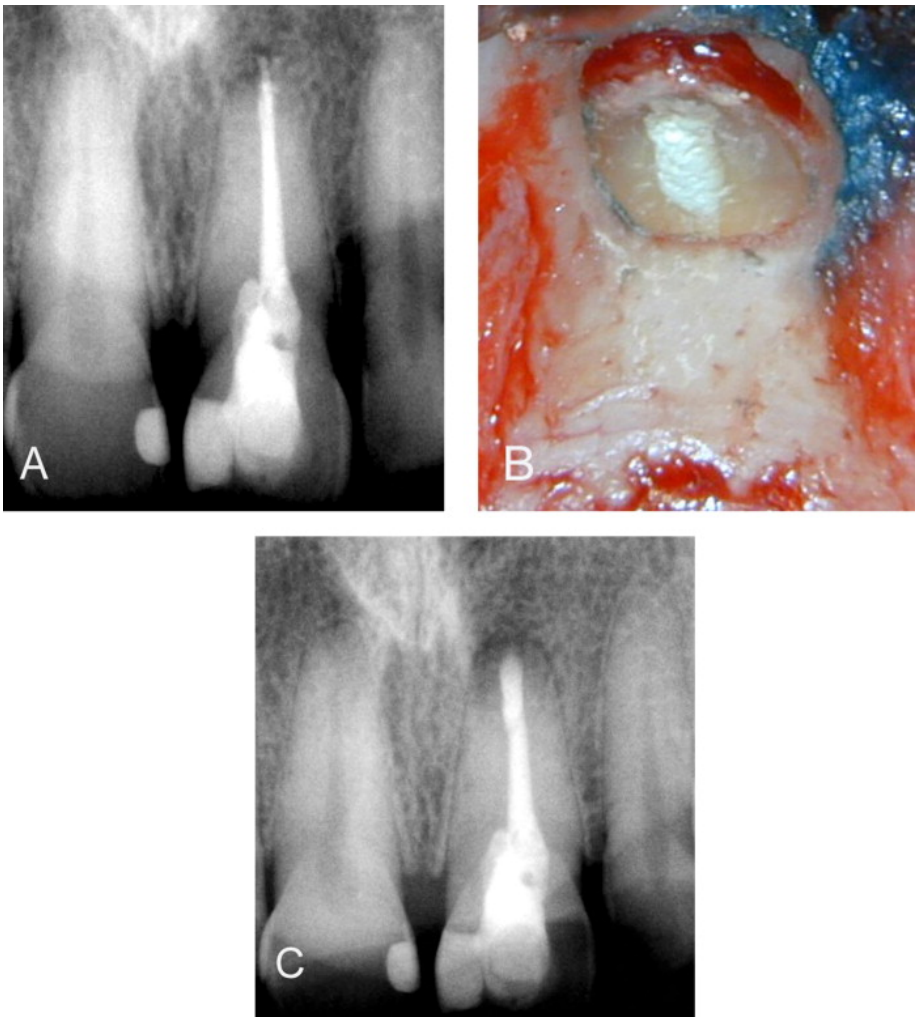


*Fig. 2. (A) Preoperative radiograph of maxillary central incisor. (B) Reveals apical surgical procedure accomplished with WMTA apical restoration placed. (C) Post-operative radiograph. Images courtesy of Dr. Brian Min.*


*Fig. 3. (A) Preoperative radiograph of mandibular second molar with furcal perforation. (B) Shows WMTA placement. (C) Post-operative radiograph. Images courtesy of Dr. Brian Min.*

At the time of this review, no prospective studies using MTA materials for apexification and/or apexogenesis procedures have been reported. However, successful individual case reports of using GMTA and/or WMTA for apexification/apexogenesis treatments do exist.[147,148,153,154,155,156]

## 5. Conclusion

The physical properties, sealing ability, biocompatibility, and clinical performance of MTA materials have been discussed. MTA materials appear not only to demonstrate acceptable biocompatible behavior but also exhibits acceptable *in vivo* biologic performance when used for root-end fillings, perforation repairs, pulp-capping and pulpotomy, and apexification treatment. However, it should be noted that the

supporting data have been overwhelmingly from either *in vitro* or animal studies. Reports have strongly suggested that the favorable biologic performance exhibited by MTA materials is due to hydroxyapatite formation when these materials are exposed to physiologic solutions. Although some studies suggest that the less-expensive Portland cement parent compound could possibly be used in the place of MTA, characterization studies have shown that MTA materials are compositionally different than Portland cement and it is not recommended at this time that Portland cement can serve as a suitable MTA substitute. GMTA has been investigated more than the more-esthetic WMTA, and while some reports suggest that GMTA may invoke a more desirable biologic response than WMTA, existing reports as a whole are equivocal and more studies are encouraged. Although the overall results in human studies involving MTA materials are very positive, further longitudinal studies are encouraged, as at present insufficient well-designed and controlled clinical studies exists that allow systematic and meta-analysis review of MTA materials in all of its suggested clinical indications.

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