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Mineral trioxide aggregate and areas of its use in dentistry: A literature review

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Abstract
Mineral trioxide aggregate is a biocompatible dental material consisting of thyroxide powder and hydrophilic particles. In addition to their dentinogenic and osteogenic potentials, it also exhibits good sealing properties. It has a wide range of areas of use in endodontic and restorative dentistry. In clinical practice, it is a material of choice in many applications such as repair of perforations, root-end fillings, apexhivation and regenerative endodontic treatment procedures, vital pulp treatments.

Keywords: Mineral trioxide, biocompatible dental, thyroxide powder and hydrophilic particles

Introduction
Mineral trioxide aggregate (MTA) is a biomaterial that has been studied for endodontic applications since the early 1990s. MTA was first described in the dental literature in 1993 and was approved for endodontic use by the U.S. Food and Drug Administration in 1998 [1, 2].
MTA is a hydrophilic and biocompatible endodontic material that promotes the growth of cement and bone formation thanks to both its dentinogenic and osteogenic potentials [3]. In studies evaluating the microleakage level of MTA using dye penetration, liquid filtration and bacterial leakage models, it was observed that it provided better sealing compared to conventional endodontic materials [4]. MTA has a wide range of areas of use in both endodontic and restorative dentistry. MTA, which is becoming more widespread in clinical practice, has become the center of attraction for many researchers. Its physicochemical structure, setting reaction, characteristics of biocompatibility are areas requiring further studies. MTA has undergone many changes since its introduction for dental purposes, its physical and chemical properties have been improved, and it seems these properties will be improved further. This review aims to conduct an up-to-date research on the components, properties, clinical applications, and advantages/disadvantages of MTA.

Content and Chemical, Physical, and Mechanical Properties
MTA consists of fine trioxide powder (tricalcium oxide, silicon oxide, bismuth oxide) which sets in the presence of moisture and hydrophilic particles (tricalcium silicate, tricalcium aluminum) [5].
MTA material was first described as hydrophilic fine powder, mainly consisting of calcium and phosphorus ion and bismuth oxide was added into it to provide a higher radio-opacity than dentine [6]. Torabinejad reported that the mean radio-opacity of MTA was sufficient for radiographic visibility and equivalent to aluminum thickness of 7.17 mm [6]. Portland cement (75%), which constitutes a considerable amount of MTA content, is a mixture of tricalcium silicate $(CaO)_3SiO_2$, di-calcium silicate $(CaO)_2SiO_2$, tricalcium aluminate $(CaO)_3Al_2O_3$ and tetra-calcium aluminoferrite $(CaO)_4Al_2O_3Fe_2O_3$. Bismuth oxide (20%) and gypsum (5%) are other components of MTA [7]. Gypsum stone is an important factor in adjusting the setting time, although it is less effective than tetra-calcium aluminoferrite [8].
Until 2002, there was only one MTA material consisting of gray powder, and in the same year, white mineral trioxide aggregate (WMTA) as ProRoot MTA (Dentsply Endodontics, Tulsa, OK, USA) was introduced to address aesthetic concerns [9]. MTA material was then categorized into two types: conventional gray MTA (GMTA) and white MTA (WMTA).

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The results of the studies performed using scanning electron microscopy (SEM) and electron probe microanalysis showed that the biggest difference between GMTA and WMTA was in Al_2O_3, MgO and FeO concentrations. WMTA contains less Al_2O_3, MgO, and FeO than GMTA at a rate of 54.9%, 56.5%, and 92.8%, respectively [10]. It was also reported that WMTA had a smaller particle size than GMTA and that the decrease in the amount of magnesium oxide and iron oxide could contribute to the changing color of WMTA from gray to white [11-13].

During the preparation of MTA, the powder is mixed with sterile water in a powder/liquid ratio of 3:1 and obtaining the consistency of wet sand is the objective. Mixing can be performed using a metal or plastic putty knife on a glass or paper pad. When MTA is first mixed, it forms a colloidal gel structure, which sets in about 3-4 hours [14, 15]. Moisture from surrounding tissues or a wet cotton pellet helps with the setting reaction [16]. Paper cones, pluggers, special carriers of syringe type can be used to move the MTA mixture prepared to the desired area [17, 18]. The mixing time of MTA is very important. The recommended mixing time is less than four minutes. It is also preferable to implement it immediately after mixing to prevent dehydration of the mixture and drying out as a sandy mixture [19].

After mixing MTA, the initial pH level is 10.2, and pH level increases to 12.5 after three hours [6, 20]. The setting process is defined as a hydration reaction of tri-calcium silicate ($3CaO \cdot SiO_2$) and di-calcilic silicate ($2CaO \cdot SiO_2$) [21]. Hydration has been reported to be adversely affected by exposure to the inflammatory pH (pH 5.0) range compared to physiological conditions (pH 7.0) [22].

It was shown that mixing MTA powder with different liquids and additives could have an effect on the setting time and compressive strength [23]. Different solutions may be considered instead of sterile water in the preparation of MTA material, but it should be noted that the physical properties of the material may be lost. Sodium hypochlorite gels shorten the setting time of 3% and 5% calcium chloride solution; however, the compressive strength is significantly lower than those prepared using sterile water. The preparation with saline and 2% lidocaine anesthetic solution prolonged the setting time, but the compressive strength was not affected significantly. A MTA material prepared using chlorhexidine gluconate gel was not set [23]. Moreover, $CaCl_2$, Ca $(HCO2)_2$ and Na_2HPO_4 may be used as accelerators, but the strength of MTA substantially reduces, while the setting time is shortened [23, 24].

The compressive strength of MTA is around 40 MPa in 24 hours and is reported as 67.3 MPa after 21 days. In the literature, it was reported that GMTA exhibited greater compressive strength than WMTA [25]. In a study, it was found that irrigation/oxidizing agents sodium perborate mixed with sodium hypochlorite, saline, and sodium hypochlorite mixed with 30% hydrogen peroxide affected the compressive strength of MTA [26]. There is some evidence that MTA material has a long maturation process which continues following the specified setting period of 3-4 hours. A study showing that MTA used to repair furcation perforations had greater compressive strength in 72 hours compared to 24 hours supports this evidence [27].

Any adhesion between MTA and dentine may be stronger than the cohesive strength of MTA material, as it was reported that MTA-dentine separations were usually occur cohesive separations occurring in MTA material [19].

MTA exhibits excellent sealing as it expands during the setting reaction. Therefore, it is recommended to make MTA contact a moistened cotton pellet before placing permanent restoration to provide better sealing. MTA material of 4 mm thickness was identified to be sufficient for sealing [28]. It was also reported that MTA must have a thickness of at least 3mm to seamlessly seal the apical area [29].

In a study reporting that MTA showed antibacterial activity against enterococcus faecalis and streptococcus sanguis, there was no significant antimicrobial effect against anaerobes [30]. In a different study, it was identified that WMTA and a ZOE preparation had similar antibacterial properties against to Staphylococcus aureus, Enterococcus faecalis, and Pseudomonas aeruginosa in direct contact test [31]. The effect of freshly mixed and set GMTA on C.albicans was investigated using the antifungal tube dilution method and it was reported that GMTA inhibited C. albicans [32].

Biocompatibility properties of MTA material were evaluated in many *in vitro* studies in the literature. In different studies, the mutagenicity of MTA and its genotoxic effect on peripheral human lymphocytes were evaluated. There is no study showing mutagenic and genotoxic properties of MTA [33, 34]. It can also be suggested that MTA with no mutagenic properties is not carcinogenic, considering that all carcinogenic substances are mutagens. Many studies showed that MTA did not adversely affect the activity of periodontal ligament (PDL) fibroblasts. It was identified in SEM analysis that PDL fibroblasts had normal morphology and exhibited growth and bonding to 24-hour MTA surfaces [35, 36]. Moreover, it was reported in a study that PDL fibroblasts showed improved proliferation on MTA [37]. MTA activates osteoclasts by increasing the production of interleukin, promotes the formation of new blood vessels and induces bone resorption, resulting in bone matrix production. Therefore, MTA is a material that has the potential to induce periodontal ligament and bone regeneration [38].

Areas of Clinical Use
Repair of perforations
Materials widely used to repair perforations include amalgam, Super EBA (Bosworth, Skokie, IL), composites, and recently MTA (Pro-Root MTA, Dentsply, York, PA and MTA Angelus, Londrina, PR, Brazil), Biodentine (Septodont, Saint Maur des Fosses, France) and EndoSequence (Brasseler USA, Savannah, GA) [39].

When MTA was introduced to the market, it became more clear which repair material to use to repair perforations [40, 41]. MTA has many advantages over previous restorative materials when used for the repair of perforations. Its biocompatibility is quite high and has a very low level of probability to create any reaction in periradicular tissues. After the material is placed in the perforation area, a cement-like tissue is shown to expand directly over the material [42, 43]. Moreover, MTA, which is used as a perforation repair material, has been reported to have a positive clinical prognosis in the long term [40, 41].

In a study which included MTA as a perforation repair material, it was shown that MTA did lead to any bacterial leakage based on a 45-day evaluation [44]. On the other hand, when used for furcation repair, there was no significant difference between GMTA and WMTA in resistance to penetration of F. nucleatum [45]. In a different study, microleakage of GMTA and WMTA used in furcation perforation repair was compared in both orthograde and retrograde directions. The results showed that there was no difference in the leakage between the two MTA materials.

However, in the orthograde direction, the microleakage was significantly more. This result suggests that an adequate coronal restoration is required on MTA to prevent coronal microleakage [46].

The material provides good sealing even if the perforation area is contaminated with blood [47]. Although this may seem as an advantage, another study showed that the bond strength to the blood-contaminated root dentine was significantly less than that to the uncontaminated dentine [48].

MTA can also be used for the treatment of perforations occurring as a result of resorption [49, 50]. The main disadvantage of MTA in such cases is the long setting time. The material will remain in contact with oral fluids during the long setting period and move away from the related area. This makes MTA inappropriate for transgingival defects associated with cervical resorption. Therefore, a faster-setting resin ionomer such as Geristore (Den-Mat, Santa Maria, CA) is recommended for lesions going beyond the border of the gums [51-53]. Moreover, both types of MTA cause a discoloration of teeth. Although this is an effect observed in all bioceramics, it is observed much less with new materials such as Biodentine and EndoSequence [54].

Root-end filling material

Cement accumulation is essential for the regeneration of periodontal tissue following apical surgical procedures [55]. Increasing the new cement along the root end and restoration of the root end are necessary for the ideal recovery of the periodontium. This layer also creates a biological barrier that increases the integrity of the apical barrier, making it more resistant to the penetration of microorganisms [56]. The importance of the presence of cement-like tissue adjacent to MTA cannot be underestimated. This situation is mostly observed in sections where MTA is used as a filling material. MTA seems to be able to induce cementoblastic cells to create hard tissue. The results of an analysis (SEM) in a study suggested that cementoblasts could connect to MTA and grow [57]. Furthermore, MTA can increase the production of both proinflammatory and anti-inflammatory cytokines from osteoblasts. The effect of MTA on periradicular tissues is probably due to these reactions.

It is necessary to apply MTA with a thickness of at least three mm to seal the apical area [29]. Although there are studies with different results in the literature, it was reported that MTA led to less microleakage compared to amalgam, ZOE, and conventional glass ionomer when used as a root-en filler following an apical resection [1, 33, 47, 58] (65 to be added). There are also studies reporting that the setting of MTA and the ability to prevent microleakage are not affected by the presence of blood [47]. When used as a root-end filling, MTA is less cytotoxic than amalgam, Super EBA, and IRM [59]. In studies on endodontic surgery including dogs and monkeys, it was reported that less periradicular inflammation occurred around the root-end filling material [42, 60-63]. Holland *et al.* theorized that calcium hydroxide, resulting from the reaction of tricalcium oxide in MTA with tissue fluids, supported hard tissue formation [61, 64]. In a clinical study using MTA as a root-end filler following microsurgical applications, it was reported that a clinical success rate of 89% was achieved after a follow-up period ranging from four to 72 months [65].

Canal filling material

Root canal sealers, in which tricalcium silicate and dicalcium silicate content stands out, form the latest bioactive group of the root canal filling materials [66]. These sealers emerged as a result of the popularity of MTA material based on tricalcium silicate and dicalcium silicate, which bursts hydraulic powder [67-69]. Reports on their bioactivity have made these canal sealers even more attractive [70]. It was reported that MTA Fillapex had decreased cytotoxicity following the setting and the sealer offered appropriate bioactivity to stimulate hydroxyapatite nucleation [71, 72].

Radioopacity is a very important property for root canal filling materials. MTA is indistinguishable in radiography, unless a radio-opaque substance is added. It is a significant disadvantage that bismuth oxide providing radioopacity of MTA dyes dentin at the crown in changing colors from brown in the presence of NaOCl, gray in the presence of chlorhexidine, and to black in the presence of glutaraldehyde. This led researchers to search new materials for radioopacity and components such as zirconia dioxide or tantalum oxide were used in different commercial formulations [73].

Sealers including tricalcium and dicalcium silicate sets by reacting with water. The result of this reaction is a mixture of alkaline structure (pH; 12) consisting of calcium silicate hydrates and the matrix $Ca(OH)_2$ [74, 75]. These resulting hydrates are on the surface of the original calcium silicate particles, and hydration gradually penetrates inwards. When tricalcium silicate cement sets, it expands dimensionally at a rate of less than 0.1%. This property helps create a barrier and is a very important for uses of endodontic purposes. Although the long setting time of tricalcium silicate cement is a disadvantage for their use in different treatments, they do not have a negative effect on their use as canal sealers. The first MTA introduced to the market was affected by moisture and this prevented its use as a canal sealer. Moreover, the first MTA materials intended for surgical use were not considered suitable for use as canal sealer due to their large particle size and very high film thickness. Negative properties were eliminated in the subsequent studies and many tricalcium and dicalcium silicate-based canal sealers were introduced. Todayi there are many canal sealers under different trademarks [66, 76-80]

Apexification and Regenerative Endodontic Treatment Procedures

In the treatment of immature teeth with pulp necrosis, conventional approaches using calcium hydroxide for apexification and apical barrier techniques using MTA are preferred.

It was reported that MTA could create both incomplete and complete barrier with mild tissue inflammation when used in apexification. In a study comparing calcium hydroxide and MTA, barrier formation was only observed within the root boundaries of the teeth to which MTA was applied. On the other hand, the formation of an incomplete barrier was observed mostly outside the canal, beyond the previous apical area, in the teeth to which calcium hydroxide was applied [81].

Regenerative endodontic procedures were compared with the apical barrier techniques in which conventional calcium hydroxide apexification and MTA were used and similar results were obtained [82, 83]. In a study comparing conventional and regenerative treatment protocols, it was reported that revascularization led to a significant increase in the length and thickness of the root and had a better prognosis compared to the apical barrier techniques including calcium hydroxide apexification and MTA [84]. Although MTA is the most commonly used material in regenerative endodontics, the discoloration of the front teeth poses a serious aesthetic problem. Therefore, other materials such as Biodentin may be preferred in the front teeth [85].

Vital pulp treatments

MTA is a material showing physicochemical properties that stimulate restorative dentinogenesis through the collection and activation of cells forming hard tissue material and contribute to matrix formation and mineralization [86]. It stimulates restorative hard tissue formation by separating growth factors in the extracellular matrix that mediate wound repair of the dentine-pulp complex and soluble cytokines embedded in the surrounding dentine [87-90] MTA activates the migration of progenitor cells (fibroblasts) from the central pulp to the site of wound. It promotes the proliferation of progenitor cells without induction of cell apoptosis and the differentiation into odontoblast-like cells. MTA also stimulates the production of *in vitro* mRNA, increases the protein expression of mineralized matrix genes, which are very important for mineralization, and cellular markers [86].

In a study conducted using MTA, it was suggested that the tissue formed as a result of pulp capping procedure was not dentine or dentine-like tissue and that it might be dystrophic intrapulpal mineralization in response to pulp capping procedure [91]. The researchers also noted that this tissue had the same properties as the tissue observed following a direct pulp capping with calcium hydroxide.

The biocompatibility of MTA that is set regulates the expression of gene products such as dentin sialoprotein, osteocalsin and alkaline phosphatase, along with transcription and angiogenesis factors [92]. Odontoblast signal proteins are very important in the differentiation of progenitor cells into the cells responsible for the repair and accumulation of hard tissues [92, 93]. Sialoprotein and osteopontin were observed in the mineralized hard tissue matrix in the relevant area following the pulp capping with MTA, [94].

MTA shows superior marginal adaptation to dentine compared to other calcium hydroxide-based materials. The bond strength to dentine is quite high and it shows a bond similar to glass ionomer cement penetrating dentinal tubules thanks to its mineral components [95]. Moreover, another important property of the material is that it creates a sticky interface layer during mineral nucleation on the surface of dentine [86, 96, 97].

In a study, when MTA and calcium hydroxide were used in direct pulp capping, there was very low inflammatory response in the pulp treated with MTA, a thick and continuous dentine bridge appeared and, on the other hand, the dentine bridge was observed only in 1/3 of the samples treated with calcium hydroxide [98]. In another study, MTA used in direct pulp capping induced the matrix of osteodentine which is typically observed in reparative dentine in three weeks [99]. The formation of neodentinal bridges was observed between pulpal tissues and MTA crystals in 2 weeks [100]. MTA materials used as pulp capping agents were reported to form calcified bridges in 2 weeks, exhibiting fully calcified bridge formation with mild inflammatory reactions [101].

MTA stimulates the release of dentine matrix components necessary for hard tissue repair and regeneration in healthy and partially inflamed pulps which are mechanically exposed [98, 102]. Data obtained from the studies in the literature generally suggest that MTA is a material promoting biocompatible, non-cytotoxic, antibacterial environment and surface morphology that is favorable for the formation of restorative calcific bridges.

When used in pulpotomy, MTA was reported to lead to less pulpal inflammation compared to the histological pulpal response caused by calcium hydroxide [100]. In a study conducted using MTA in the pulpotomy of 23 permanent teeth with clinical findings of irreversible pulpitis, positive results were obtained regarding prognosis [103].

Conclusion

MTA has a wide range of areas of use in clinical practice. In addition to its biocompatibility, it is a material that has promising properties such as sealing property, antibacterial property, and compressive strength. Although it was reported to show positive biological performance in the studies, there is a further need for a greater number of clinical research including long-term follow-up results.

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