ISSN Print: 2394-7489
ISSN Online: 2394-7497
IJADS 2021; 7(1): 345-351

www.oraljournal.com
Received: 16-11-2020
Accepted: 20-12-2020

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Bio active materials in pediatric dentistry: A review

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DOI: https://doi.org/10.22271/oral.2021.v7.i1e.1153

Abstract
Remineralization, a natural repair process of carious tooth, is widely followed treatment strategy and requires action of specific agents, which may further assist in preventing formation of newer lesions in the oral cavity. Materials which promote the remineralization are extensively researched and understanding the action of these materials and their dynamics is utmost important.
These bioactive and biomimetic materials have evolved over a period of four decades and have become specialized, easier to manipulate with better properties. A continuous research for further betterment of these materials to meet the increasing clinical and restorative needs should be promoted. The future of dentistry shifts towards use of these biomimetic materials and the aim is to provide the tooth with minerals rather than using chemicals to restore. This article focuses about various bio active materials and their applications in pediatric dentistry.

Keywords: Remineralization, bio active materials, pediatric dentistry

1. Introduction
Dentistry is an ever evolving branch with continuous stipulation for advancements in dental materials. From the dawn of history, dental practitioners have been in the quest of ideal restorative dental materials. Initially ideal restorative materials were thought to be biologically inert and biocompatible but in the last two decades bioactive materials seem to be alternative to these inert biocompatible materials [1]. The teeth undergo a constant cycle of demineralization and re-mineralization, but this natural re-mineralization process is inadequate to prevent progression of dental caries. Hence there is a need to supplement the tooth with a biomaterial which is bioactive in nature to re-mineralize, repair or regenerate the tissues of tooth [2]. The term 'Bioactivity' is defined as the ability of a material to elicit a response in a living tissue [3]. Bioactive Material is a material that has the effect on or eliciting a response from living tissue, organisms or cell such as inducing the formation of hydroxyapatite [4]. The ideal properties of bioactive materials are bactericidal and bacteriostatic, sterile, stimulate reparative dentine formation and maintain pulp vitality [5].
Restoratively we use these bio active materials to prevent pulpal death and initiate the formation of a dentinal bridge during direct or indirect pulp capping. Alkalinity is a critical factor that contributes to the effectiveness of bio active materials. The bio active material contributes to pulpal repair not only by stimulating two proteins i.e bone morphogenic protein [BMP] and transforming growth factor–beta [TBF BETA] from the surrounding dentin but also by forming an anti-bacterial seal over the pulp exposure [6].

1.1 Uses of bioactive materials in pediatric dentistry
- Promotes tooth re-mineralization
- As pulp capping material
- For permanent restorations
- In apexification procedure
- Act as scaffold and helps in regeneration of bone tissue.

These bio active materials play a very important role in pediatric dentistry and hence this article emphasize on various bioactive materials and their importance in pediatric dentistry.

1.2 Bio active materials in pediatric dentistry

Bio-active materials used in pediatric dentistry are calcium hydroxide, Mineral tri oxide aggregate (MTA), Bio dentine, Bio glass, Bio-ionomer, Calcium enriched mixture (CEM), Amorphous calcium phosphate (ACP), Bio aggregate, TheraCal LC, Endo sequence root repair material (ERRM).

2. Calcium hydroxide

HERMAN introduced calcium hydroxide to dentistry in 1990 [7]. Calcium hydroxide has been included in several materials and antimicrobial formulations that are used in various treatment modalities. When used as a pulp-capping agent and in apexification cases, a calcified barrier may be induced by calcium hydroxide [8].

2.1 Biological action

The hydroxyl group of $Ca(OH)_2$ provides an alkaline environment, which encourages repair and active calcification. The alkaline pH induced not only neutralizes lactic acid from osteoclasts, thus preventing dissolution of the mineral components of dentine, but could also activate alkaline phosphatases that play an important role in hard-tissue formation [9]. Alkaline phosphatase, a hydrolytic enzyme acts by liberation of inorganic phosphatase from the esters of phosphate, which then react with calcium ions from the bloodstream to form a precipitate, calcium phosphate, in the organic matrix. This precipitate is the molecular unit of hydroxyapatite, which is believed to be intimately related to the process of mineralization [10].

2.2 Applications in pediatric dentistry

- Pulp capping agent,
- Pulpotomy agent and
- In apexification procedure.

2.3 Limitations of calcium hydroxide [11]

- Length of time for induction of coronal or apical hard tissue barriers. This ranges from 2–3 months in the case of pulp capping and 6–18 months in the case of apexification.
- Incomplete coronal and apical hard tissue barriers because of vascular inclusions, which may allow bacterial invasion.
- Changes in the physical structure of dentin related to the loss of inorganic and organic components which frequently leads to cervical root fractures.
- Induction of initial zones of sterile pulp necrosis. These zones represent the contact area between calcium hydroxide and vital pulp tissue; they may become infected at a later time through microleakage under restorations, leading to pulpitis and subsequent pulp necrosis.

3. Mineral trioxide aggregate

Mineral Trioxide Aggregate (MTA) is a bio active material, which was introduced by Mahmoud Torabinejad at Loma Linda University, California, USA. MTA was first described in the dental scientific literature in 1993 [12]. Studies on MTA reveal that it not only exhibits good sealing ability, excellent long term prognosis, has relative ease of manipulation and good biocompatibility but favors tissue regeneration as well[12]. MTA was developed and recommended for endodontic procedures because of it is nontoxic, non-carcinogenic, non-genotoxic, biocompatible, insoluble in tissue fluids and dimensionally stable nature [13].

3.1 Biological Action of MTA

The mechanism of action of MTA is very similar to the effect of Calcium Hydroxide [14].

According to Parirokh and Torabinejad *et al*. when MTA is placed in direct contact with human tissues, material does the following [13]:

1. Forms Calcium hydroxide that releases calcium ions for cell attachment and proliferation
2. Creates an antibacterial environment by its alkaline pH
3. Modulates cytokine production.
4. Encourages differentiation and migration of hard tissue-producing cells
5. Forms Hydroxyapatite on the MTA surface and provides a biologic seal

3.2 Applications in Pediatric Dentistry

- Pulp capping agent,
- Pulpotomy agent,
- Apexification procedure and
- Obturation of retained primary tooth where the succedaneous permanent tooth is absent.

3.3 Limitations

The drawbacks of MTA include its discoloration potential, presence of toxic elements in the material composition, difficult handling characteristics, long setting time, high material cost, an absence of a known solvent for this material, and the difficulty of its removal after curing [15].

4. Biodentine

Biodentine is a calcium silicate-based material introduced in 2010 by Gilles and Olivier. It is in effect a dentin substitute that can be used as a coronal restoration material (for indirect pulp capping), but can also be placed in contact with the pulp. Its faster setting time allows either immediate crown restoration or to make it directly intraorally "functional" without fear of the material deteriorating [16].

4.1 Biological Action

Biodentine induces formation of osteodentine by expressing markers of odontoblasts & increases TGF-Beta1 secretion from pulpal cells enabling early mineralization. During the setting of the cement, calcium hydroxide is formed. Due to its high pH, Calcium hydroxide causes irritation at the area of exposure. This zone of coagulation necrosis has been suggested to cause division and migration of precursor cells to substrate surface, addition and cytodifferentiation into odontoblast like cells. Thereby Biodentine induces apposition of reactionary dentine by odontoblast stimulation and reparative dentin by cell differentiation. Because of its high alkalinity it has inhibitory effects on microorganisms [17].

4.2 Applications in Pediatric Dentistry

- Dentine substitute under a composite restoration:
- Pulp capping
- Pulpotomy
- Apexification

5. Amorphous calcium phosphate

Amorphous calcium phosphate (ACP) is the initial solid phase that precipitates from a highly supersaturated calcium phosphate solution, and can convert readily to stable crystalline phases such as octacalcium phosphate or apatitic products.

5.1 Biological Action

ACP can increase alkaline phosphatase activity of mesoblasts, enhance cell proliferation and promote cell adhesion. The unique role of ACP during the formation of mineralized tissues makes it a promising material for tissue repair and regeneration. ACP may also be a potential remineralizing agent in dental applications [18].

5.2 Clinical Applications in Pediatric Dentistry

5.2.1 ACP in Bio-Mineralization

It has been stated that ACP likely plays a special role as a precursor to bio apatite and as a transient phase in bio-mineralization. One bio-mineralization strategy that has received significant attention in recent years is mineralization via transient precursor phases. The transient ACP phase may conceivably be deposited directly inside the gap regions of collagen fibrils, but it may also be delivered as extra fibrillar particles. A variety of proteins and ions have been proposed to be involved in the bio-mineralization of ACP to Hydroxyapatite. Dentin matrix protein 1 (DMP1) is one of such bio mineralization proteins [19].

5.2.2 ACP-Filled Polymeric Composites

ACP has been evaluated as a filler phase in bioactive polymeric composites. Skrtic has developed unique biologically active restorative materials containing ACP as filler encapsulated in a polymer binder, which may stimulate the repair of tooth structure because of releasing significant amounts of calcium and phosphate ions in a sustained manner. In addition to excellent biocompatibility, the ACP-containing composites release calcium and phosphate ions into saliva milieus, especially in the oral environment caused by bacterial plaque or acidic foods. Then these ions can be deposited into tooth structures as apatitite mineral, which is similar to the hydroxyapatite found naturally in teeth and bone [20-21].

5.2.3 CPP-ACP

Casein phospho peptide (CPP) has a remarkable ability to stabilize clusters of ACP into CPP-ACP complexes, preventing their growth to the critical size required for nucleation, phase transformation and precipitation [22].

5.2.4 Incorporation of CPP-ACP into Glass Ionomer Restorative Material

Mqazzaoui *et al*. (2003) determined the effect of incorporation of CPP-ACP into glass ionomer cement Fuji IX and demonstrated significant increase in micro tensile bond strength (33%) and compressive strength (23%) and significantly enhanced the release of calcium, phosphate and fluoride ions at neutral and acidic pH. This Fuji IX GIC containing CPP-ACP enhanced protection of the enamel and dentin adjacent to the restoration compared with Fuji IX GIC alone [23].

5.2.5 Mouth Rinses

CPP-ACP in mouth rinses significantly increases the level of calcium and phosphate ions in supragingival plaque. The results of a study by Rose (2000) showed CPP-ACP would compete with calcium for plaque Calcium binding sites. As a result, this will reduce the amount of calcium bridging between the pellicle and adhering bacterial cells and between bacterial cells themselves. This is likely to restrict mineral loss during a cariogenic episode and provide a potential source of calcium for the inhibition of demineralization and assist in subsequent re-mineralization after the mouthwash for a three-day period [24].

5.2.6 Food Products

CPP-ACP, with no adverse effect on taste, can be a selected for the treatment of demineralization. Recent studies have shown that application of CPP-ACP in drinks, sweets and milk products can prevent their cariogenic properties [24].

5.2.7 Tooth Pastes

CPP-ACP and Fluoride (F) have significant effects on decreasing caries [25]. The additive anti-cariogenic effect of CPP-ACP and F may be attributable to the localization of Amorphous Calcium Fluoride Phosphate (ACFP) at the tooth surface by the CPP which in effect would co-localize Calcium, Phosphate and Fluoride. These results suggest that CPP may be an excellent delivery vehicle to co-localize calcium, phosphate and fluoride at the tooth surface in a slow release amorphous form with superior clinical efficacy [26].

GC Tooth Mousse: This product is in the form of a soft, sugar-free, water-based topical crème and is used for remineralization of dentin and enamel for prevention of caries. In-vivo and in-vitro studies published in 2013 have stated that CPP-ACP was more effective than sodium fluoride mouthwash and fluoridated toothpaste for remineralization of enamel caries [27-28].

6. Bio-Ionomers

In recent years, the ability of glass ionomers to release ions apart from fluoride, notably calcium and aluminum, has been studied, and there is evidence to show that they promote re-mineralization of the tooth [29]. This seems to be related to their ability to buffer lactic acid [30], an effect that was originally thought to be negative, because of its association with loss of cement by erosion [31]. However, very recently, it has been found that lactic acid at the pH of active caries (4.5) can be buffered to the pH of arrested caries (5.5) within less than 30 seconds, and with negligible erosion [32]. This effect is likely to be beneficial, and would inhibit the development of secondary caries around a glass ionomer restoration.

Bio active glass (BAG) contains silicon, sodium, calcium and phosphorus oxides with specific weight percentages, which was introduced by Larry Hench in 1969 as 45S5 Bioglass. In some recent studies [33-37], BAG has been added to GI structure to improve its bioactivity and tooth regeneration capacity.

7. Calcium enriched mixture

Novel endodontic cement named calcium-enriched mixture (CEM) cement was introduced to dentistry in 2006 as an endodontic filling material [38]. The physical properties of this biomaterial, such as flow, film thickness, and primary setting time are favorable [39].

7.1 Biological Action

It has the ability to promote hydroxyapatite (HAP) formation in saline solution and might promote the process of differentiation in stem cells and induce hard tissue

Formation [40-42]. It also possesses the ability to set in aqueous environments with shorter setting time than MTA and sealing ability comparable to MTA [39-43].

7.2 Clinical Application in Pediatric Dentistry

7.2.1 Root End Filling Material

The micro-leakage of CEM cement, which is comparable with

MTA and Portland cement, indicates its good apical sealing. Due to the other beneficial properties of this material such as biocompatibility, flow ability, good clinical handling, antibacterial and low cytotoxic effect, CEM cement is suggested as an appropriate root-end filling material [44].

7.2.2 Regenerative Endodontic Treatment with CEM Cement

Revascularization is a valuable treatment in immature necrotic teeth that allows the continuation of root development. Successful revascularization in necrotic immature molars by using CEM cement as new endodontic biomaterial with a modified approach have been reported by Nosrat *et al.* (2011) [42].

7.2.3 Pulpotomy

Studies of complete pulpotomy treatment in permanent teeth using CEM, MTA, and Calcium Hydroxide have shown that compared to Calcium Hydroxide, samples in the CEM group exhibited lower inflammation, improved quality or thickness of calcified bridge, superior pulp vitality status, and morphology of odontoblast cells [45]. A randomized clinical trial study on the success rates of MTA and CEM in pulpotomy of deciduous molars with a two-year follow-up period was conducted and concluded that pulpotomy treatment of deciduous molars using CEM is a successful treatment modality [46].

7.2.4 Apexogenesis

A randomized clinical study of permanent molars with open apices showed extensive caries and signs of reversible/irreversible pulpitis. A 1-year follow-up randomized clinical trial concluded that complete pulpotomy of the teeth using MTA and CEM were beneficially successful [47-48].

7.2.5 Direct Pulp Capping

Zarrabi MH *et al.* concluded in his study that under immunohistochemical examinations, thickness of dentinal bridge beneath CEM was higher than MTA at various time intervals; pulp inflammation was also lower in the CEM groups [49]. In addition, expressions of fibronectin/tenascin in the CEM groups were higher than the MTA groups during both time intervals; however, the above differences were not statistically significant [50].

There is controversy amongst pediatric dentists regarding DPC treatment of human deciduous molars with calcium hydroxide. A recent randomized clinical trial study has shown that CEM and MTA exhibit similar and acceptable outcomes in DPC treatment of human deciduous molars [51].

7.2.6 Indirect Pulp Capping with CEM Cement

An interesting case report of IPC treatment with CEM of a mature symptomatic first mandibular molar with irreversible pulpitis associated with apical periodontitis demonstrated favorable clinical and radiographic outcomes, such as complete resolution of symptoms and healing of the apical lesion within a 15 month follow-up period [52].

8. Bio active glass

Bioactive glass is made of synthetic mineral containing sodium, calcium, phosphorous and silica (sodium calcium phospho silicate) which are naturally found in the body. When these particles come in contact with saliva or water, they rapidly release sodium, calcium and phosphorous ions into the saliva which are available for re-mineralization of the tooth surface. Unlike other calcium phosphate technologies, the ions that bioactive glass release form hydroxycarbonate apatite (HCA) directly, without the intermediate amorphous calcium phosphate phase [53]. These particles also attach to the tooth surface and continue to release ions and re-mineralize the tooth surface after the initial application. These particles have been shown, in in-vitro studies, to release ions and transform into HCA for up to two weeks [54]. Ultimately these particles will completely transform into HCA which is the mineral of our teeth. In a clinical trial on tooth hypersensitivity a bioactive glass containing toothpaste was shown to decrease sensitivity significantly greater than strontium chloride toothpaste. They have also been shown to have significant anti microbial properties and can kill up to 99.99% of oral pathogens associated with periodontal disease and caries [53-54].

9. Bio aggregate

Bio Aggregate, new generation of bio ceramic material is developed as a result of utilizing the advanced science of nano-technology to produce ceramic particles that, upon reaction with water produce biocompatible and aluminum-free ceramic biomaterials. Bio Aggregate has excellent handling characteristics which aids in a repair process of the affected tooth. Bio Aggregate's radiopacity properties, convenient setting and hardening time and easy workability and handling properties make it an ideal root canal filling material. The working time of BioAggregate is around 5 minutes. Upon mixing a thick paste-like mixture is formed. If additional working time is required, simply cover the mixture with a moist gauze sponge [55].

9.1 Clinical Applications

Bio Aggregate promotes cementogenesis and forms a hermetic seal inside the root canal. It is effective in clinically blocking the bacterial infection, its ease of manipulation and superior quality makes Bio Aggregate the most innovative and unique root canal repair material. According to manufacturer, the Bio Aggregate is indicated for repair of root perforation, repair of root resorption, root end filling, apexification, and pulp capping [55].

10. Theracal LC

TheraCal LC is a light-curable resin-modified tricalcium silicate classified as a 4th generation calcium silicate material. It is a single paste calcium silicate-based material promoted by the manufacturer for use as a pulp capping agent and as a protective liner for use with restorative materials, cement, or other base materials [56]. TheraCal LC is claimed to be a hydraulic silicate material that sets by hydration. Hydration is the chemical reaction that leads to the setting of hydrophilic cement. The setting starts with the contact of the material and water. TheraCal LC does not include water for material hydration. It depends on the water taken up from the environment and its diffusion within the material. Hence, the manufacturer instructions implement placing the material on moist dentin [57].

10.1 Biological Action

TheraCal LC has displayed calcium release properties. The bioavailability of calcium ions plays a key role in the material-induced proliferation and differentiation of human dental pulp cells and the new formation of mineralized hard tissues. The amount of calcium ions released from TheraCal

LC was in the concentration range with potential stimulatory activity for dental pulp and odontoblasts [57-58]. On the other hand, the release of hydroxyl ions raises the pH of the surrounding environment and causes irritation of the pulp tissue. This develops superficial necrosis on exposed pulp, provoking mineralization directly against the necrotic zone [59]. TheraCal LC is reported to have an apatite forming ability. The resultant "apatite coating" plays a key role in dentine repair and mineralization [60]. Its ability to induce the formation of hydroxyapatite-like crystals could contribute to the chemical bond to dentine and provides a biological seal [61].

10.2 Applications in pediatric dentistry

10.2.1 Direct Pulp Capping

Cannon *et al.* compared the effectiveness of TheraCal LC, pure Portland cement, resin-based calcium hydroxide and glass ionomer in the healing of bacterially contaminated primate pulps. They found no statistical difference between the groups in regard to pulpal inflammation. However, they reported that the light-cured TheraCal LC groups had significantly more frequent hard tissue bridge formation, a greater thickness of the dentinal bridge and better dentinal bridge qualities than the Glass ionomer and VLC Dycal groups [62]. Gopika *et al*. compared and evaluated the response of the human pulp following direct pulp capping with TheraCal LC, Septocal LC, and Dycal. Their study found that TheraCal LC and Septocal LC (Calcium hydroxide with hydroxyapatite) cements were as effective as Dycal in inducing the formation of reparative dentin and evoking an inflammatory response [63].

10.2.2 Indirect Pulp Capping

One randomized clinical trial reported successful clinical (no pain and absence of sinus tract) and radiographic (no sign of external and internal resorption and presence of bridge) outcomes following the use of MTA and TheraCal LC when used for indirect pulp capping in primary teeth [64]. A. T. Gurcan, F. Seymen *et al.* conduted a study on ProRoot MTA, TheraCal LC, and Dycal as IPC material on primary and permanent teeth and concluded that there were no statistically significant differences between the materials and success rates of ProRoot MTA, TheraCal LC, and Dycal were 94.4%, 87.8%, and 84.6% in both primary and permanent teeth according to the modified USPHS criteria ($p>0.05$) [65].

10.2.3 Pulpotomy

Mariem O. Wassel, Dina H. Amin and Amira S. Badran conduted a study on TheraCal as pulpotomy agent in primary teeth and concluded that TheraCal LC is a relatively biocompatible material with comparable clinical and radiographic success rates over 6 months to Formocresol[66]. Hengameh *Bakhtiar-et al.* conducted a study on human pulp responses to partial pulpotomy treatment with TheraCal as compared with Biodentine and ProRoot MTA and concluded that Biodentine and MTA performed better than TheraCal when used as partial pulpotomy agent and presented the best clinical outcomes [67].

10.2.4 Revascularization

Eduardo A. Bortoluzzi *et al.* conducted a study on Cytotoxicity and Osteogenic Potential of Silicate Calcium Cements as Potential Protective Materials for Pulpal Revascularization and concluded that the cytotoxic effects of Biodentine and TheraCal LC on human dental pulp stem cells (hDPSCs) were time and concentration-dependent. Osteogenic differentiation of hDPSCs was enhanced after exposure to Biodentine that was depleted of its cytotoxic components. This effect was less readily observed in hDPSCs exposed to TheraCal LC, although both cements supported extracelluar mineralization better than the positive control (zinc oxide-eugenol–based cement). Further investigations with the use of *in vivo* animal models are required to validate the potential adverse biological effects of TheraCal LC on hDPSCs [68].

11. Endosequence root repair material

Endo sequence root repair material (ERRM) is composed of tricalcium silicate, zirconium oxide, tantalum pentoxide, dicalcium silicate, calcium sulfate, calcium phosphate monobasic, and filler agent. Setting time is a minimum of 2hours, which requires the existence of water to set and harden. Setting may prolong if the application site on the tooth is arid. The moisture needed for setting depends on the moisture present within the dentin, which reaches the root canal through dentinal tubules, therefore eliminating the need to add moisture before placing the material. ERRM is biocompatible, insoluble, produce caustic calcium hydroxide when coming into contact with water, and do not shrink during setting. The pH is more than 12; have an antimicrobial effect, radiopaque, have an excellent sealing ability when used as root-end fillings, and known to be aluminum free [69].
In human studies, one study concluded that there was no difference between ERRM and MTA in the appearance of the dentinal bridge and pulp inflammation, and there was less sensitivity to cold in patients treated with MTA [70]. Anujalkhur *et al*. performed direct pulp capping using ERRM and MTA found that the dentinal bridge formed with ERRM showed chronic mild inflammation cells in two sample specimens of five [71]. Sultana N *et al*. performed vital pulp therapies with ERRM, MTA, and Biodentine in 41 participants with a follow-up period of 730 average days. The results showed that the failure of patients who get ERRM was double the odds of failure when compared to patients who get MTA [72]. However more clinical studies need to be done to evaluate the prognosis and outcomes for long-term follow-up to assess the material as pulp-capping agent in both primary and permanent teeth.

12. Conclusion

In the present era of regeneration, re-mineralization of de-mineralized dental hard tissue is a pre eminent requisite. With advances in technology, a ceaseless quest for bio mimetic materials which protects and maintains the health of hard and soft tissue persists. It becomes necessary to understand the properties of the current bioactive materials available to thoroughly avail their beneficial actions. Further there is a call for increased research in the field to develop more materials based on current concepts available and create bio active materials which can mimic and replace the natural hard and soft tooth structure and also the surrounding bone. Newer concepts for adhesion and incorporation of these materials are to be sought after which may change the approach towards treating tooth and also the future of dentistry.

13. References

1. Geeta Asthana, Shaveta Bhargava *et al.* Bioactive Materials: A Comprehensive Review. Sch. J. App. Med. Sci 2014;2(6E):3231-3237.
2. Neeta Shetty, Kundabala M, *et al.* Biominerals in

restorative dentistry. Journal of Interdisciplinary Dentistry 2013;3(2):64-70.
3. Deeksha Grotra, Subbarao CV *et al*. Bio active materials used in endodontics. Recent Research in Science and Technology 2012;4(6):25-27.
4. Anusavice KJ, Shen C, Rawls HR. Emerging trends. In: Phillip's Science of Dental materials. 12th ed., Ch. 21. ST. Louis, Missouri: Elsevier Saunders 2013, 519.
5. Snehal Sonarkar, Rucheet Purba *et al*. Bioactive materials in conservative dentistry. International Journal of Contemporary Dental and Medical Reviews 2015.
6. Lee Ann Brady *et al*. Bio active materials. Dental materials 2013.
7. Mohammed Mustafa, Saujanya KP. Role of Calcium Hydroxide in Endodontics: A Review. GJMEDPH 2012;1(1):66-70.
8. Eda S. Histochemical analysis on the mechanism of dentin formation in dog's pulp. Bull Tokyo Dent Coll 1961;2:59-88.
9. Estrela C, Sydney GB, Bammann LL, Felippe O Jr. Mechanism of action of calcium and hydroxyl ions of calcium hydroxide on tissue and bacteria. Brazilian Dental Journal 1995;6:85-90.
10. Seltzer S, Bender IB. The dental pulp, 2nd edn. Philadelphia, PA: JB Lippincott 1975, 260.
11. Mohammadi Z, Dummer PMH, *et al*. Properties and applications of calcium hydroxide in endodontics and dental traumatology. International Endodontic Journal 2011;44(8):697-730.
12. Lee SJ, Monsef M, Torabinejad M. Sealing ability of a mineral trioxide aggregate for repair of lateral root perforations. J Endod 1993;19:541-544.
13. Reyes-Carmona JF, Felippe MS, Felippe WT. Biomineralization Ability and Interaction of Mineral Trioxide Aggregate and White Portland Cement With Dentin in a Phosphate-containing Fluid. J Endod 2009;35(5):731-6.
14. Butler WT. Dentin Matrix Proteins and Dentinogenesis. Connect Tissue Res 1995;33(1-3):59-65.
15. Glickman GN, Koch KA. 21st-century endodontics. J Am Dent Assoc 2000;131:39S-46.
16. Dr. Vipin Arora *et al*. Bioactive dentin replacement. Journal of Dental and Medical Sciences 2013;12(4):51-57.
17. Priyalakshmi S, Manish Ranjan, *et al*. Review on Biodentine-A Bioactive Dentin Substitute. IOSR Journal of Dental and Medical Sciences 2014;13(1):13-17.
18. Jie Zhao, Yu Liu, *et al*. Amorphous calcium phosphate and its application in dentistry. Chem Cent J 2011;5:40.
19. Mahamid J, Sharir A, Addadi L, Weiner S. Amorphous calcium phosphate is a major component of the forming fin bones of zebrafish: Indications for an amorphous precursor phase. Proc Natl Acad Sci 2008;105:12748-12753.
20. Olszta MJ, Cheng X, Jee XX. Bone structure and formation: A new perspective. Mat Sci Eng 2007;58:77-116.
21. Llena C, Forner L, Baca P. Anticariogenicity of casein phosphopeptide amorphous calcium phosphate: A review of the literature. J Contemp Dent Pract 2009;10:1-9.
22. Rose RK. Binding characteristics of Streptococcus mutans for calcium and casein phosphopeptide. Caries Res 2000;34:427-431.
23. Mqazzaoui *et al*. Incorporation of CPP-ACP into GIC. J Dent Res 2003;82(11):914-8.
24. Rose RK. Effects of an anticariogenic casein phosphopeptide on calcium diffusion in streptococcal model dental plaques. Arch Oral Biol 2000;45:569-575.
25. Nongonierma AB, FitzGerald RJ. Biofunctional Properties of Caseino phosphopeptides in the Oral Cavity. Caries Res 2012;46:234-267.
26. Shen Cai *et al*. Acid resistance of enamel subsurface lesions remineralized by a sugar-free chewing gum containing casein phosphopeptide-amorphous calcium phosphate. Caries Res 2004;38(6):551-6.
27. Krithikadatta J, Fredrick C, Abarajithan M, Kandaswamy D. Remineralization of occlusal white spot lesion with a combination of 10% CPP-ACP and 0.2% sodium fluoride evaluated using diagnodent: a pilot study. Oral Health Prev Dent 2013;11:191-196.
28. Somasundaram P, Vimala N, Mandke LG. Protective potential of casein phosphopeptide amorphous calcium phosphate containing paste on enamel surfaces. J Conserv Dent 2013;16:152-156.
29. Ngo H, Mount GJ, Peters MCRB. A study of glass ionomer cement and its interface with enamel and dentin using a low-temperature, high resolution scanning elctron microscopic technique. Quintessence Int 1997;28:63-69.
30. Nicholson JW, Czarnecka B, Limanowska-Shaw H. The long-term interaction of dental cements with lactic acid solutions. J Mater Sci Mater Med 1999;10:449-452.
31. Matsuya S, Matsuya Y, Yamamoto Y. Erosion process of glass ionomer cement in organic acids. Dent Mater J 1984;3:210-219.
32. Nicholson JW, Aggarwal A, Czarnecka B, Limanowska-Shaw H. The rate of change of pH of lactic acid exposed to glass ionomer dental cements. Biomaterials 2000;20:1989-1993.
33. Yli-Urpo H, Lassila LV, Närhi T, Vallittu PK. Compressive strength and surface characterization of glass ionomer cements modified by particles of bioactive glass. Dent Mater 2005;21:201-9.
34. Xie D, Brantley WA, Culbertson BM, Wang G. Mechanical properties and microstructures of glass-ionomer cements. Dent Mater 2000;16:129-38.
35. Yli-Urpo H, Närhi M, Närhi T. Compound changes and tooth mineralization effects of glass ionomer cements containing bioactive glass (S53P4), an *in vivo* study. Biomaterials 2005;26:5934-41.
36. Xie D, Zhao J, Weng Y, Park JG, Jiang H, Platt JA. Bioactive glass-ionomer cement with potential therapeutic function to dentin capping mineralization. Eur J Oral Sci 2008;116:479-87.
37. Ana ID, Matsuya S, Ohta M, Ishikawa K. Effects of added bioactive glass on the setting and mechanical properties of resin modified glass ionomer cement. Biomaterials 2003;24:3061-7.
38. Asgary S, Eghbal MJ, Parirokh M, Torabzadeh H. Sealing ability of three commercial mineral trioxide aggregate and an experimental root-end filling material. Iran Endod J 2006;1:101-105.
39. Asgary S, Shahabi S, Jafarzadeh T, Amini S, Kheirieh S. The properties of a new endodontic material. J Endod 2008;34:990-993.
40. Asgary S, Eghbal MJ, Parirokh M, Ghoddusi J. Effect of two storage solutions on surface topography of two root-end fillings. Aust Endod J 2009;35:147-152.
41. Asgary S, Eghbal MJ, Ehsani S. Periradicular regeneration after endodontic surgery with calcium-enriched mixture cement in dogs. J Endod 2010;36:837-

841.
42. Nosrat A, Seifi A, Asgary S. Regenerative endodontic treatment (revascularization) for necrotic immature permanent molars: a review and report of two cases with a new biomaterial. J Endod 2011;37:562-567.
43. Asgary S, Eghbal MJ, Parirokh M. Sealing ability of novel endodontic cement as a root-end filling material. J Biomed Mater Res A 2008;87:706-709.
44. Kazem M, Mahjour F, Dianat O, Fallahi S, Jahankhah M. Root-end filling with cement-based materials: An *in vitro* analysis of bacterial and dye microleakage. Dent Res J 2013;10:46-51.
45. Tabarsi B, Parirokh M, Eghbal MJ, Haghdoost AA, Torabzadeh H, Asgary S. A comparative study of dental pulp response to several pulpotomy agents. Int Endod J 2010;43:565-71.
46. Malekafzali B, Shekarchi F, Asgary S. Treatment outcomes of pulpotomy in primary molars using two endodontic biomaterials. A 2-year randomised clinical trial. Eur J Paediatr Dent 2011;12:189-93.
47. Asgary S, Eghbal MJ. The effect of pulpotomy using calcium-enriched mixture cement versus one-visit root canal therapy on postoperative pain relief in irreversible pulpitis: A randomized clinical trial. Odontology 2010;98:126-33.
48. Nosrat A, Seifi A, Asgary S. Pulpotomy in caries-exposed immature permanent molars using calcium-enriched mixture cement or mineral trioxide aggregate: A randomized clinical trial. Int J Paediatr Dent 2013;23:56-63.
49. Zarrabi MH, Javidi M, Jafarian AH, Joushan B. Histologic assessment of human pulp response to capping with mineral trioxide aggregate and novel endodontic cement. J Endod 2010;36:1778-81.
50. Zarrabi MH, Javidi M, Jafarian AH, Joushan B. Immunohistochemical expression of fibronectin and tenascin in human tooth pulp capped with mineral trioxide aggregate and a novel endodontic cement. J Endod 2011;37:1613-8.
51. Fallahinejad Ghajari M, Asgharian Jeddi T, Iri S, Asgary S. Direct pulp-capping with calcium enriched mixture in primary molar teeth: A randomized clinical trial. Iran Endod J 2010;1:1-4.
52. Torabzadeh H, Asgary S. Indirect pulp therapy in symptomatic mature molar using calcium enriched mixture cement. J Conserv Dent 2013;16:83-86.
53. Reynolds EC. Calcium phosphate-based remineralization systems: scientific evidence. Australian Dental Journal 2008;53:268-273.
54. Burwell AK, Litkowski L, Greenspan D. Calcium Sodium Phosphosilicate (Nova Min): Remineralization potential. Adv. Dent. Res 2009;21:83-86.
55. Ahmed Madfa A, Fadhel Al-Sanabani A, *et al*. Endodontic Repair Filling Materials: A Review Article. British Journal of Medicine & Medical Research 2014;4(16):3059-3079.
56. Dutta A, Saunders W. Calcium silicate materials in endodontics, Dental Updates 2014;41(8):708-722.
57. Naji Ziad Arandi, Tarek Rabi. TheraCal LC. From Biochemical and Bioactive Properties to Clinical Applications. International Journal of Dentistry, 2018.
58. Gandolfi MG, Siboni F, Prati C. Chemical-physical properties of TheraCal, a novel light-curable MTA-like material for pulp capping. International Endodontic Journal 2012;45(6):571-579.
59. Poggio C, Lombardini M, Colombo M, Beltrami R, Rindi S. Solubility and pH of direct pulp capping materials: a comparative study. Journal of Applied Biomaterials & Functional Materials 2015;13(2):73-193.
60. Yamamoto S, Han L, Noiri Y, Okiji T. Evaluation of the Ca ion release, pH and surface apatite formation of prototype tricalcium silicate cement. International Endodontic Journal 2017;50:1-10.
61. Gandolfi MG, Siboni F, Botero T, Bossu M, Riccitiello F, Prati C. Calcium silicate and calcium hydroxide materials for pulp capping: biointeractivity, porosity, solubility and bioactivity of current formulations. Journal of Applied Biomaterials and Fundamental Materials 2014;13(1):43-60.
62. Cannon M, Gerodias N, Viera A, Percinoto C, Jurado JR. Primate pulpal healing after exposure and TheraCal application. Journal of Clinical Pediatric Dentistry 2014;38(4):333-337.
63. Gopika GJ, Ramarao S, Usha C, *et al*. Histological evaluation of human pulp capped with light-cured calcium based cements: a randomized controlled clinical trial. International Journal of Scientific Reports 2017;3(5):120-127.
64. Menon NP, Varma BR, Janardhanan S, Kumaran P, Xavier AM, Govinda BS. Clinical and radiographic comparison of indirect pulp treatment using light-cured calcium silicate and mineral trioxide aggregate in primary molars: a randomized clinical trial. Contemporary Clinical Dentistry 2016;7(4):475-480.
65. Gurcan AT, Seymen F. Clinical and radiographic evaluation of indirect pulp capping with three different materials: a 2-year follow-up study. European Journal of paediatric dentistry 2019;20(2):105-110.
66. Mariem O, Wassel, Dina H, Amin, Amira Badran S. Clinical, Radiographic, and Histological Evaluation of TheraCal Pulpotomy in Human Primary Teeth. Egypt dental journal 2017;63(3):365-375.
67. Hengameh Bakhtiar, Mohammad Hossein Nekoofar, Pouyan Aminishakib. Human Pulp Responses to Partial Pulpotomy Treatment with TheraCal as Compared With Biodentine and ProRoot MTA: A Clinical Trial. J Endod 2017;43(11):1786-1791.
68. Eduardo Bortoluzzi A, Li-na Niu, Chithra Palani D, Ahmed El-Awady R, Barry Hammond D, Dan-dan Pei. Cytotoxicity and Osteogenic Potentia lof Silicate Calcium Cements as Potential Protective Materials for Pulpal Revascularization. Dent Mater 2015;31(12):1510-1522.
69. Mahgoub N, Alqadasi B, Aldhorae K, Assiry A, Altawili ZM, Tao Hong. Comparison between iRoot BP Plus (Endo Sequence Root Repair Material) and Mineral Trioxide Aggregate as Pulp-capping Agents: A Systematic Review. J Int Soc Prevent Communit Dent 2019;9:542-52.
70. Martínez-Cortés M, Tinajero-Morales C, Rosales C, UribeQuerol E. Cytotoxicity assessment of three endodontic sealing cements used in periapical surgery. *In vitro* study. Revista Odontol Mexicana 2017;21:40-8.
71. Anujalkhur. Comparative evaluation of response of human dental pulp on direct pulp capping with MTA. ERRM. IOSR-JDMS 2016;15(6):52-57.
72. Sultana N, Singh M, Nawal RR, Chaudhry S, Yadav S, Mohanty S *et al*. Evaluation of biocompatibility and osteogenic potential of tricalcium silicate–based cements using human bone marrow–derived mesenchymal stem cells. J Endodontics 2018;44:446-451.