Physico-chemical and biological properties of dental calcium silicate cements - literature review

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Abstract

Dental cement materials have been developed with the aim to replace hard dental tissues. The first material used for pulp capping, root canal obturation, bifurcation perforation and apexification is calcium hydroxide (in 1920). A half century later, glass-ionomer cements began to suppress it as dentine substitutes. Finally, in the 1990s, calcium silicate (CS) material appeared in the dental research community as the most promising dentine substitute capable to adequately meet all clinical requirements. The aim of this paper is to present an overview of literature related to studies about CS materials taking into account their physical, chemical and biological properties and clinical applications. This review aims to discuss beneficial and adverse characteristics of CSs concerning interactions to the hard dentine and soft pulp/periodontal tissues. This review article deals with the literature data about currently commercially available CS concerning laboratory and clinical findings. 109 scientific articles were analyzed of which 62 references reported *in vitro* and 26 *in vivo* investigations while 21 references comprised reports, reviews and books dealing with both, *in vitro* and in vivo investigations. Although further data collection is necessary, CSs are promising materials that represent a gold standard for numerous dental clinical procedures.

Keywords: Bioactive material; dentine substituent; Portland cement; mineral trioxide aggregate; Biodentine^{TR}

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Bone and dental cements are based on general principles of binding systems. Usually, they have a heterogeneous composition that contains one or more dispersed active solid phases and a liquid as a binder. Hardening of such compositions, as a rule, occurs because of the formation of new chemical compounds and processes of polymerization, polycondensation and adhesion. The extent of these processes is determined by chemical properties of the solid component, its activity with respect to the binder, dispersion level, composition and process conditions. Difficulty in handling of existing materials is to make the required form to fill a defect, while ensuring that the implant fits snugly to the tissue [1]. Use of cement materials, which have to be formable with the ability to completely fill defects *in situ* at a given setting speed and hardening and providing required mechanical properties can provide realization of many tasks arising in dentistry. Cement materials in dentistry have been developed in order to imitate the lost dentine tissue, to mimic biological features as much as possible and to display bioactive characteristics. Those tasks are difficult to achieve because of dentine specificity, namely, its close contact to the pulp and periodontal tissues. In that sense, local bioactivity of these cement materials is important in order to induce mineralization within the adjacent dentine

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substrate. One additional prerequisite for dental cement materials is induction of the local ion-rich alkaline environment to allow mineral reparation [2].

The first attempt of exposed pulp capping by inert gold foils was described by Pfaff in 1756 [3]. The first successful capping of a pulp with gross dentine loss was achieved by using alkaline calcium hydroxide (CH) introduced by Codman in 1851 and described in literature by Herman in 1920 [3]. Schröder provided a detailed scenario of the effects of CH-containing pulp-capping agents on pulp cell migration, proliferation and differentiation [4]. The initial effect of CH applied to exposed pulp is development of a superficial necrosis. Namely, a chemical injury is provoked by hydroxyl ions leading to formation of a zone of firm necrosis over the vital tissue. The necrosis causes slight irritation and stimulates the pulp to regenerate. Thereafter, the repair process occurs, including migration and proliferation of mesenchymal and endothelial pulp cells as well as collagen formation. Odontoblasts are being differentiated creating tertiary dentine and the pulp function is normalized by deposition of minerals in the newly formed collagen. The presence of Ca ions stimulates precipitation of $CaCO_3$ contributing to the mineralization initiation [5].

Shortcomings of CH based materials include: poor mechanical characteristics, inability to preserve high pH values at the site of administration for a certain period of time, possibility of primary tooth resorption, dissolution after one year and degradation during acid etching or tooth flexure, poor marginal seal with composite/amalgam restoration and weakening of the root during apexogenesis in a long-term therapy [6]. Indeed, long-term use of CH capping may cause progressive calcification of the root canal space.

In order to overcome disadvantages of CH novel generations of cement materials are fabricated. Chronologically speaking, the next cement formulation was glass ionomer cement (GIC), the improved version of Zn-polycarboxilate cement. GIC is produced in the reaction of silicate glass powder (calcium-alumino-fluorosilicate glass) and polyacrylic acid resulting in the cement that bonds to dentine in the presence of body fluids. GIC can be used for post-resection root-end filling, root canal obturation, bifurcation perforation repair and similar procedures. The main drawback of GICs is their poor biocompatibility.

Having in mind afore mentioned drawbacks of materials for dentine replacement a significant improvement in this field occurred in 1993 when Torabinejad introduced a novel material mineral trioxide aggregate (MTA) that is based on calcium silicate (CS) particles. The main advantage of CS in comparison to CH is its superior mechanical and bioactive behavior. The term bioactivity was introduced in dentistry by authors who investigated and compared properties of GIC and CS [7]. They defined bioactivity as the ability of a material to elicit a specific biological response at the interface between the material and adjacent tissues, which results in formation of a bond. Terms bioactivity and bioactive cement have become very common in the dental literature, especially after 2009 when Septodont (Saint Maur, France) launched new CS dental formulation - Biodentine^{TR}[8].

The aim of this work is to present an overview of literature data about dental CS materials regarding their physical, chemical and biological properties and clinical applications.

2. METHODS

The authors searched hard copy literature and PubMed databases, using following keywords: calcium silicate, endodontic sealers, mineral trioxide aggregate, Biodentine^{TR}, pulp capping, root end filling, apexification and apexogenesis and root perforation. The initial search led to 310 articles until January 2019, of which 201 were excluded due to the inappropriate topic while the remaining 108 reached the desired criteria and were processed herein. Out of these references, 61 reported *in vitro* studies, 26 investigated CS cements *in vivo* while 21 references were reports, reviews and books dealing with both, *in vitro* and *in vivo* investigations. Three researchers independently reviewed the data regarding: composition, physico-chemical properties, biological properties and clinical findings upon application of the cement.

3. Results and discussion

3. 1. Calcium silicate cements - general considerations

Generally, CSs exhibit superior characteristics in comparison to previous formulations of cements used for pulp capping, apical obturation, perforation healing, apexogenesis/apexification and other endodontic procedures. Main

advantages of CS cements include their high compressive strength and longer Ca ions release. On the other hand, problematic issues so far include discoloration, poor handling properties and long setting times.

3. 2. Composition of CS cements

Experimental MTA, the first CS formulation introduced by Torabinejad, is composed of tricalcium silicate ($3CaO{\cdot}SiO_2$, C_3S), dicalcium silicate ($2CaO{\cdot}SiO_2$, C_2S), tricalcium aluminate, tetracalciumaluminoferrite, calcium sulfate and bismuth oxide (Bi_2O_3) [9]. MTA formulations sometimes include impurities of harmful metals: Cr, As and Pb [10]. Composition of white MTA (WMTA) is like the gray one but without tetracalciumaluminoferrite [11] and with lower amounts of aluminates resulting in a more desirable white shade [12,13].

MTA Angelus (Angelus science and technology, Londrina, Brazil) and MTA-Fillapex-Angelus (Angelus science and technology, Londrina, Brazil) consist of Portland cement (PC), Bi_2O_3, salicylate resin, nanoparticulate silica and pigments [14-16]. ProRoot MTA (Dentsply, Tulsa, Oklahoma, USA) is prepared by mixing following powders: C_3S, C_2S, calcium sulphate, Bi_2O_3 and a small amount of tricalcium aluminate with a viscous aqueous solution of a water-soluble polymer [14]. MTA Flow (Ultradent, Utah, USA) is a system consisting of C_2S and C_3S as an extremely fine, radiopaque powder that sets with a water-based gel [16].

PC clinker is a hydraulic material, which mostly consists of CSs (C_2S and C_3S), which comprise by mass at least two-thirds. The rest include Al- and Fe-containing clinker phases and other compounds. The ratio of CaO to SiO_2 is not less than 2:1 where MgO does not exceed 5.0 wt% [15].

Biodentine^{TR} is composed of a highly purified C_3S powder prepared synthetically from a mixture of powder constituents: SiO_2-16.9 %, CaO-62.9 % and ZrO_2-5 %. C_2S and C_3S particles form 70 wt% of the above mixture's dehydrated powder. Biodentine does not contain $CaSO_4$, aluminate or aluminaferrite. Liquid component is distilled water with the addition of $CaCl_2$ [8,14,17].

Bioaggregate (Innovative BioCeramix, Burnaby, Canada) cement differs from MTA mainly by the presence of amorphous silicon dioxide, calcium phosphate monobasic, Ta_2O_5 radiopacifiers and trace elements (Cr, As and Pb) while aluminum is omitted [14,16].

Theracal LC^{R} (Bisco Dental, Illionois, USA) consists of: PC, Ba_2SO_4, AeroSil® 200 Bis-GMA and additives associated with a light curing 4-N,N-dimethyl amino benzoic acid ethylester (DMABEE) and camphorquinone that were detected in amounts of 4.11×10^{-2} kg m^{-2} and 19.95×10^{-2} kg m^{-2}, respectively [18].

iRoot (IBCeramix, Vancouver, Canada) has been introduced in three forms: iRootSp, iRoot BP and iRoot BP Plus. iRootSp is composed of CS, $Ca_3(PO_4)_2$, ZrO_2, CH, a filler and thickening agents. iRoot BP and iRoot BP Plus injectable root repair filling materials contain the same compounds except for the filler and thickening agents [16,19].

Endo CPM (Egeo, Buenos Aires, Argentina) is composed of CS, $CaCO_3$, Bi_2O_3, $BaSO_4$, propylene glycol alginate, Na-citrate, $CaCl_2$ and active ingredients [16].

Calcium enriched mixture cement (CEM) (BioniqueDent, Tehran, Iran) is a relatively new multipurpose endodontic material introduced by Asgary [20] consisting of: SiO_2 (6.32 wt%), CaO (51.75 wt%), SO_3 (9.53 wt%), P_2O_5 (8.49 wt%) and minor components: Al_2O_3>Na_2O>MgO>Cl [23]. The important constituents of CEM are alkaline earth metal oxides and hydroxides (CaO, CH, Ca_3PO_4 and calcium silicate) [21].

AlboMPCA1 and AlboMPCA2 (Albodent d.o.o., Belgrade, Serbia) are experimental CS cements consisting of: CS, $CaCO_3$ and $BaSO_4$ or Bi_2O_3 [22].

3. 3. Physico-chemical properties of CS cements

MTA exhibits superior mechanical characteristics to GIC, especially regarding the higher compressive strength and lower wear [23]. Although the color is like the color of the human dentine it does not perfectly match the original tooth color [24]. Due to the lower marginal leakage (264 s for MTA Angelus + GuttaFlow apical plug *vs*. 178 s for Acroseal sealer by the argon porosity method), MTA is considered the gold standard for apical resected teeth [25-27]. MTA flow during setting forms a layer of hydroxyapatite, which induces a healing reaction. The combination of MTA's powder and gel allows numerous advantages during clinical work due to its non-gritty consistency and adequate handling properties [28,29].

Biodentine^{TR} was first used as a coronal restoration due to the short setting time (12 min) enabling easy restoration in comparison to MTA Angelus (Angelus science and technology, Londrina, Brazil) (final setting time of 3–4 h). Biodentine^{TR} leads to mineralization of decayed dentine that remains in the cavity after the tooth preparation [30]. Although many materials (amalgam, ZOE, GIC) were used as root-end fillings, Biodentine^{TR} provides some advantages for root-end filling after apicotomy due to improved tissue-simulative effects, better consistency, superior handling properties and faster setting time [31-33]. Biodentine^{TR} has shown increased adhesion and lower porosity (0.01 ± 0.005 %) than Dycal® calcium hydroxide cavity lining material (0.106 ± 0.007 %) and MTA (0.094 ± 0.006 %) [34]. There is a sharp increase in the compressive strength reaching more than 100 MPa after 1h and more than 200 MPa after 24h, which is higher than values found for previous CS formulations (and more than most GICs provide) [8,35]. Biodentine^{TR} has a capacity to reach compressive strengths of even 300 MPa after a month becoming quite stable and similar to natural dentine [35]. Septodont (France) reported deposition of apatite like calcium phosphate crystals on the surface of Biodentine^{TR} (Figure 1), which improved the interface with the adjacent phosphate-rich hard tissue substance by increasing resistance to acid erosion as well as possibility of releasing Ca and OH ions (95±13 ppm), higher than those found for MTA Angelus (48 ± 8 ppm)or Dycal® (26 ± 7 ppm) (Dentsply, Tulsa, Oklahoma, USA) [34-37]. Acid-etching treatment reduced Biodentine^{TR} microhardness (0.4 GPa) while its immersion in simulated body fluid (SBF) resulted in greater microhardness (1.6 GPa) compared to the control group (non–treated Biodentine^{TR}) (1.5 GPa) [38]. A study that compared the quality of 3D obturation of retrograde root canal filling with Biodentine^{TR}, MTA Angelus and GIC revealed that Biodentine^{TR} demonstrated superior ability to hermetically seal root canals [39].

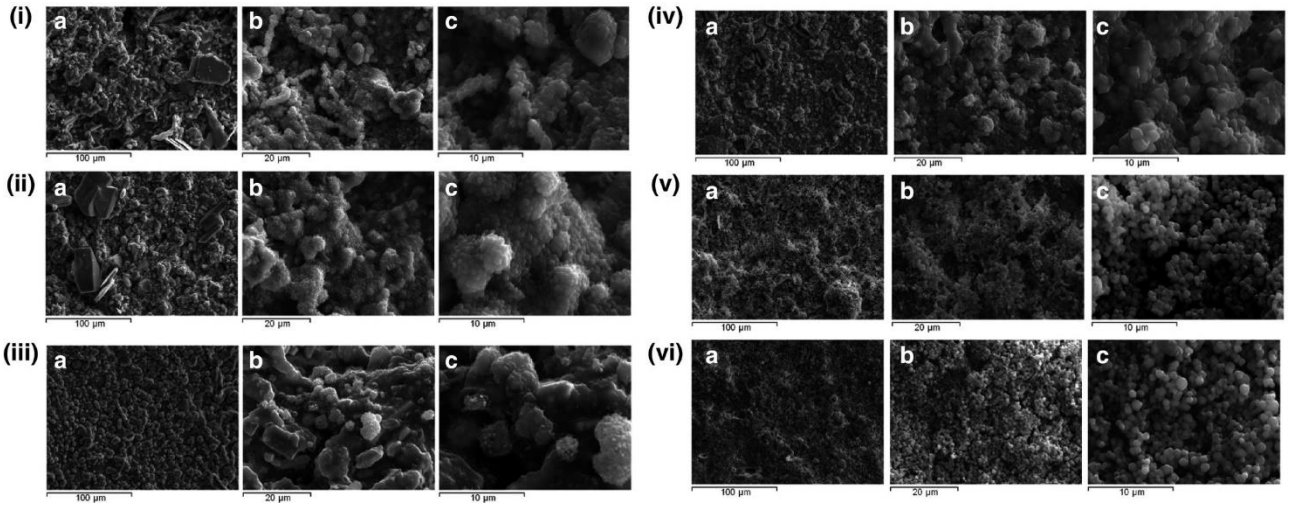

Figure 1. Scanning electron microscopy images of MTA surface after 1 day. (I) MTA+ (Cerkamed Medical Company, Stalowa, Poland) stored at 95% relative humidity, (II) ProRoot MTA stored at 95% relative humidity, (III) MTA+ immersed in saline, (IV) ProRoot MTA immersed in saline for 1 day, (V) MTA+ immersed in HBSS for 1 day, (VI) ProRoot MTA immersed in Hank's balanced salt solution for 1 day. Magnifications: (a) ×500, (b) ×2000, (c) ×5000.(Kindly Reproduced from John Wiley and Sons reference number: 4706421080300 [40]).

Bioaggregate was introduced as a material for apical canal filling, perforation repair and pulp capping [38,41]. It showed significantly lower resistance to displacement (4.7 ± 1.3 MPa) as compared to MTA (8.5 ± 1.8 MPa) during exposure to phosphate buffered saline (PBS). However, when the specimens were exposed to an acidic environment for 4 days, the push-out bond strength of Bioaggregate had not been influenced (4.7 ± 1.3 *vs*. 4.7 ± 0.9 MPa) whereas this parameter decreased significantly for MTA (8.5 ± 1.8 *vs*. 5.0 ± 1.0 MPa). Specimens of MTA showed significantly higher push-out bond strength compared to that of Bioaggregate when kept in PBS for 30 days (10 ± 3 *vs*. 6.7 ± 1.4 MPa) [38]. Resistance to fracture in teeth with immature roots filled with Bioaggregate was significantly higher than in those obturated with CH, evaluated 1 year after filling. In addition, there was not significant differences among teeth filled with MTA Angelus (14 ± 2 MPa), ProRoot MTA (19 ± 5 MPa) and Bioaggregate (20 ± 3 MPa) after 1 year [42].

iRoot cement was introduced in dentistry as a material for root filling, root repair or root canal sealer. It is similar to WMTA and very reliable to inject into root canals [19]. It shows a significantly higher bond to dentine as compared to

MTA-Fillapex and Epiphany (Resilon Research LLC, Madison, Conecticat, USA) [19,41] due to the smaller particle size, lower viscosity and minimal shrinkage during setting. The smaller particle size and low viscosity increase its flow. Placement of CH inside the root canal prior to iRoot injection improves its bond strength to dentine [42]. In an *in vitro* study it was found that using iRoot with gutta-percha improved resistance to fracture (1.5 ± 0.5 MPa) [43].

CEM is a material similar to ProRoot MTA regarding the working time (4.5 *vs*. 5 min) and dimensional changes (0.07 *vs*. 0.08 mm) [20] while it differs in the setting time, flow and film thickness [21]. CEM radiopacity is reported to be 2.23 mmAl, lower than the ISO standard requirement and lower than that reported for ProRoot MTA (5.01 mm Al) and MTA (5.59 mm Al) [20]. The percentage of the particle size between 0.5 and 2.5 μm diameter in CEM is significantly higher than those in ProRoot MTA and WPC [44].

ProRoot MTA and CEM significantly decreased the flexural strength of bovine root dentine after 30 days compared to the control (CH) [45]. Shear bond strengths of both CEM and ProRoot MTA to a composite resin were not improved after acid etching leading to a recommendation to use CEM or MTA for vital pulp therapy with resin modified GIC before restoring by the composite resin [46].

Obturating simulated open apex teeth with either MTA or CEM significantly increased teeth resistance to fracture after 6 months as compared to control specimens (composite resin). The push-out bond strength of CEM was comparable to that of ProRoot MTA (7 ± 3 *vs*. 7 ± 4 MPa). Both materials showed higher resistance to displacement when the root-end preparation was performed by ultrasound [47,48].

A study on setting time and solubility of two commercially available MTA cements (WMTA Angelus and MTA Bio (Angelus, Londrina, Brazil) and experimental cements (light-cured MTA, PC with 20 % Bi_2O_3 and 5 % $CaSO_4$ and epoxyresin-based cement) revealed that WMTA Angelus and MTA Bio had the shortest final setting time and the highest solubility (23 s and 3.5 %, respectively, for both materials). The epoxy resin-based cement and light-cured MTA showed lower solubility than the other cements [49]. Improved interface between Biodentine^{TR} and phosphate-rich hard tissue enabled lower micro-leakage than that found in MTA, Dycal® and GIC [34]. Biodentine^{TR} showed respectable compressive strength as a repair material even after being exposed to various endodontic irrigation solutions (NaOCl, chlorhexidine and saline (~7±3 MPa for all solutions)) [50].

Addition of 5 wt% CH to MTA-Fillapex is an alternative to reduce high flow of the sealant alone without influencing its alkalinity [35,51]. WMTA Angelus and MTA-Bio induced higher pH (9±1 and 10±1, respectively) and Ca-ion release ($(2.6\pm1.3)\times10^{-2}$ kg m^{-2} and $(8.8\pm1.6)\times10^{-2}$ kg m^{-2} respectively) than the epoxy resin-based cement ($(9.3 \pm 0.3)\times10^{-2}$ kg m^{-2} and $(1.5\pm0.8)\times10^{-2}$ kg m^{-2} for pH and Ca-ion release, respectively) and light-cured MTA ($(8.3\pm0.1)\times10^{-2}$ kg m^{-2} and $(2.3\pm1.5)\times10^{-2}$ kg m^{-2} for pH and Ca-ion release respectively). In contrast, the epoxy resin-based cement and light-cured MTA showed lower solubility values [49].

Biodentine^{TR} and ProRoot MTA showed significantly higher bond strengths than Bioaggregate in coronal and apical root dentine, respectively. Bond failure was predominantly adhesive in Biodentine^{TR} and ProRoot MTA, while Bioaggregate showed mixture of adhesive and cohesive failure [52,53].

iRoot-BP is an injectable ready-to-use white paste for root repair and root filling. The manufacturer claims that the products iRoot-BP and iRoot-BP Plus are insoluble, radiopaque, need moisture to set and do not shrink during setting. However, recent results showed iRoot-SP as very soluble that does not fulfill the ANSI/ADA Specification 57/2000 [54].

A study on interactions and underlying chemistry of CS cements and GIC with tooth tissues focusing on the dentin-restoration interface revealed local bioactivity of these materials manifested as a mineralization process and creation of an underlining dentine substrate [55]. The important chemistry during CS cement bonding to dentine comprises extrafibrillar remineralization of dentine's collagen matrix without mineralization of collagen's intrafibrillar particles [56]. A relatively new idea of application of protein matrix analogues as nucleation sites might be a challenge for scientists and practitioners and a step forward for clinical usage [57].

TheraCal LC^{R} with its unique apatite stimulating ability is an ideal material for direct/indirect pulp capping and as a protective base/liner. The success rates of Theracal LC^{R} in indirect pulp capping were reported to be 88 %, similarly to those found for ProRoot MTA and Dycal® that is 94 % and 85 %, respectively [58]. Also, it displayed higher Ca-releasing ability and lower solubility than either ProRoot MTA or Dycal® [59].

MTA-Fillapex obturation sealer is less soluble than the CH-based canal sealer Sealapex (Sybron-Kerr, Romulus, Michigan, USA) both in organic solvents and after ultrasonic agitation [60,61]. Another study on solubility revealed that TheraCal LC^R releases higher amounts of Ca ions and shows lower solubility than ProRoot-MTA and Dycal® [35]. By the capability of TheraCal LC^R to be cured to a depth of 1.7 mm the risk of premature dissolution may be avoided, which could be a great advantage in direct pulp-capping procedures [59,62].

A study about addition of fluoride-containing radiopacifiers to cement mixtures (CS+$CaCO_3$, CS+nanoHAP and PC) showed significant improvements of the materials: addition of 30 wt% of YbF_3 improved the radiopacity from 1.6 ± 0.05 to 5.45 ± 0.05 mm Al and the setting time from 20 ± 2 to 6 ± 2 min. Greatest Yb and F releases occurred in the PC+YbF_3 group. The CS+nanoHAP+YbF_3 mixture presented micromechanical indentation strength and porosity similar to those of the PC-based formulation [63]. The study revealed significant difference in microhardness and indentation values between pure CS cements, which demonstrated better features and radio pacified cements. Micromechanical properties were not affected by using different liquid components [64]. When adding different radiopacifiers to CS cements, engineers should be careful having in mind that some radiopaque agents ($BaSO_4$ and CHI_3) result in different radiopacities of the final mixture on dental film and digital sensor [65]. The variations in the radiopacity of tested cements on film and CCD-based digital sensor arise from the different sensitivity of the detector used. Silver on x-ray film is most sensitive to 26 keV, while iodine in a CCD-based digital x-ray sensor is most sensitive to 37 keV photons. Therefore, elements that selectively filter out high energy photons (when compared to aluminum alloy 1100) appear more radiopaque on CCD sensor while elements that mostly filter out photons with energies less than 35 keV (compared to aluminum alloy 1100) appear more radiopaque on film [65]. In addition, various radiopacifying agents were proved to affect the compressive strength, setting time and porosity of CS [66].

Guimarães and coworkers analyzed pH values and HAP-forming ability in SBF of CS based dental materials. MTA Flow-Ultradent and MTA Angelus showed similar alkalizing activities. A solubility test resulted in very low, but similar values for both cements (1.3 ± 0.8 % for both). The investigated materials showed a significant alkalinity after 3 hours of soaking (pH 9.9 ± 0.9 for both materials), having the both materials preserving the high alkalinity of the solution even after 168 hours of soaking (8.6 ± 0.9 for both materials) [29].

From the chemical point of view, propylene glycol added in the liquid component is one of the most commonly used chemicals in CS fabrication employed to induce higher and extended Ca ion release from the CH mixture. One study compared Ca ion release from a CH powder mixed with different chemicals and different types of MTA. Propylene glycol mixed with the CH powder produced higher and extended release of Ca ions ($(1.14 \pm 0.02)\times10^{-2}$ kg m^{-2}) than the mixture with distilled water ($(0.23 \pm 0.02)\times10^{-2}$ kg m^{-2}) [55].

One review provided evaluation of published *in vitro* studies about influences of various CS cements to the tooth discoloration (390 articles analyzed). Significant tooth staining was reported to be induced by GMTA-ProRoot and WMTA Angelus, gray and white ProRoot MTA and Ortho MTA (BioMTA, Korea). The study also reported the lowest discoloration levels for: Biodentine^{TR}, Retro MTA (BioMTA, Seoul, Korea), PC, Endosequence Root Repair Material (Brasseler, Savannah, Georgia, USA), Odontocem (ADM, Kenmore Hills, Australia), MM-MTA (Micro Mega, Besancon, France) and MTA Ledermix (Riemser Pharma Gmbh, Greiswald-InselRiems, Germany) [67].

3. 4. Biological properties of CS cements

Biomaterials can be classified regarding the reaction of surrounding tissues as: bioinert - when they do not interact with adjacent biological systems, bioactive - when they can undergo interfacial interactions with surrounding tissues and are biodegradable - when they are changed in volume during time in contactwith anatomical tissue structures or when incorporated into surrounding tissues [68,69]. In previous times, a preference was given to biologically inert materials that are non-toxic and resistant to biochemical effects of the organism and the environment. However, such materials have found only limited applications in reconstructive surgery and dentistry in particular, due to the inevitable reactions of rejection, negative impact on the surrounding tissues and aesthetic discrepancies. Significant progress in the dental materials market has been achieved with the use of biologically active materials. The term biological activity means the ability of a synthetic material to actively interact with surrounding tissues forming a direct connection with

them, showing osteoconductiveness and/or osteoinductiveness [70]. The term osteoconductiveness is commonly understood as the ability of a material to bind osteogenic cells that adhere to material surfaces, conduct biological fluxes, maintain the processes of proliferation and differentiation of cells from the surrounding tissue with the formation of a direct connection (Figure 2) [70]. On the other hand, osteoinductiveness is the ability of a material to induce differentiation of cells into osteogenic cell lineages. It is also possible to combine these two properties, and in this sense, CS cements are considered as bioactive materials.

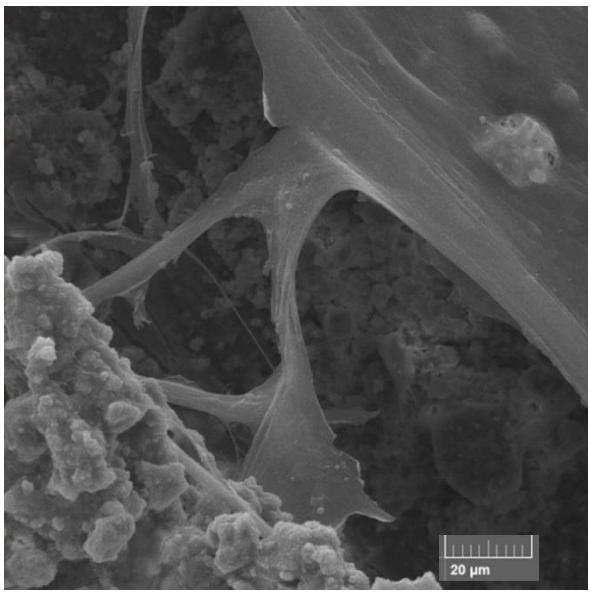

Figure 2. Attachment of osteoblasts on the surface of an experimental calcium silicate cement. Note the cytoplasmatic extensions intimately adhering on the cement surface (scale bar = 20 µm) (from the authors' collection)

In a study of cell viability by using the MTT assay, MTA provided slightly better results than PC and PC+Bi_2O_3 without significant differences in tissue reactions induced by the three investigated cements [71-73].

Septodont (France) claims numerous beneficial biological features of Biodentine^{TR} such as: inducing tissue mineralization upon application, while the mineralization occurs in the form of osteodentine (form of a reparative dentine), Ca ion release as a key factor for successful pulp capping due to positive influences on differentiation and proliferation without mineralization of osteoblasts, cementoblasts, and odontoblasts [8,35]. Laureant and coworkers found that Ca and OH ions released from Biodentine^{TR} enhanced the activity of osteopontin, alkaline phosphatase, pyrophosphatase and bone morphogenetic protein 2 (BMP-2). Consequently, it helps the maintenance of dentine mineralization and dentine bridge formation [74].

Bioaggregate exhibited low and similar cytotoxicity effects to the human mesenchymal stem cells as the MTA cement [75]. Bioaggregate and ProRoot MTA neutralized very resistant bacteria *Enterococcus faecalis* at the same level while faster effects were achieved by the set materials as compared with the fresh mixtures. In addition, dentine powder added to Bioaggregate increased its antibacterial activity [76]. Zhenglin and coworkers reported low toxicity and an inductive action of Bioaggregate to periodontal ligament cells as well as increased expression of collagen type I, osteocalcin and osteopontin [76].

iRoot cement as a root canal sealer is a bioactive alkaline material of high toxicity and with certain antibacterial properties. It was shown to be capable of neutralizing *E. faecalis* in bacterial growth medium [77]. Also, this material induced higher toxicity of human osteoblasts and L929 cells as compared to the effects of white ProRoot-MTA [77,78].

Rootdent (TehnoDent, Ahmedabad, India) and Biodentine^{TR} showed antibacterial activity against *Escherichia coli, Staphylococcus aureus, Candida albicans* and *Streptococcus Faecalis* both being advised for treatment of deep caries lesions [79]. Subcutaneous implantation of new CS formulations containing CS and nanoHAP in rats has shown good tolerance of the surrounding tissue even 60 days after implantation [80]. Also, an experimental CS-HAP cement implanted subcutaneously in rats has induced a low inflammatory reaction of the tissue over the same period of time, which was lower than that of ProRoot MTA [81]. In addition, a nanostructured CS mixture did not show any negative effect on liver in rats after thirty days of oral administration [82]. Pulp capping in this animal model revealed statistically significantly lower

inflammatory reaction of CS samples, in comparison to the Super-EBA (Keystone Ind., Muerstown, Pensilvania, USA) and ProRoot MTA. Tissue reaction to MTA implantation, as indicated by response of inflammatory cells, was similar to that observed for Super-EBA implanted in guinea pig mandibles [83]. Similar beneficial histological results were obtained for pulp capping in dog animal model when using CS-HAP formulation [84,85]. In general, CS and CS-HAP elutes induced lower cytotoxicity than MTA elutes. CS and especially CS-HAP induced significantly lower cytotoxicity in comparison with MTA, which could be associated with slower ion elution and steady pH values. In addition, nanostructured calcium silicate cements show increased osteoblast adhesion, proliferation and differentiation, since bone itself is nanostructured, and the crystal size and geometry can modify response of the surrounding tissue. Therefore, it is to assume that CS with the addition of nanostructured HAP presents numerous advantages in comparison to MTA Angelus and may be considered for further clinical trials [81].

Biocompatibility of PC is not changed significantly by addition of 20 % Bi_2O_3 [71]. AlboMPCA1 and AlboMPCA2 (Albodent d.o.o., Belgrade, Serbia) did not have statistically significant differences in the intensity of inflammatory response in comparison to MTA after 60 days [86,87].

Altogether, CS cements release Ca ions, create alkaline medium, modulate production of cytokines, encourage differentiation and migration of hard-tissue producing cells, form HAP on the cements' surfaces and consequently improve tooth healing.

3. 5. Clinical findings in applications of calcium silicate cements

CSs are widely used in restorative, endodontic and surgical clinical procedures for the following clinical applications: pulp capping, pulpotomy, orthrograde/retrograde root canal filling, root canal perforation repair, apexification and apexogenesis [88].

A clinical success of MTA Angelus, Biodentine^{TR} and formocresol in the treatment of primary molars' pulpotomy (children of 5-9 years old) is reported to be 100 % for both CS cements when clinical symptoms were assessed. Radiographic success was around 87 and 100 % for MTA Angelus and Biodentine^{TR}, respectively, which was significantly better than in the pulpotomy treatment with formocresol [89].

The use of gray MTA ProRoot for clinical treatment of pulp necrosis of the incisors resulted in the absence of sensitivity to percussion or palpation tests. Radiographs revealed continued thickening of the dentinal walls, root lengthening, regression of the periapical lesion and apical closure. Incisors showed complete apical closure at the 10-month follow-up [90]. The survival rates of dental pulp in patients having Endoseal MTA (Maruchi, Guangwon do, South Korea) been used as an apical plug and regenerative endodontic material were around 97 and 98 %, respectively [85]. A high success rate was obtained by using white MTA ProRoot in traumatic and cariously exposed pulps operated by vital direct pulp capping [91]. Application of MTA (Bionique Dent, Iran) as a pulp capping material in adult patients resulted in complete healing, in contrast to the treatment with CH, which was associated with lack of a bond to dentine and poor marginal adaptation and gradual dissolution in a moist environment leaving a void beneath the restoration and tunnel defects in dentine bridges [92,93]. An investigation that compared CH mixed with distilled water to ProRoot MTA as direct pulp capping agents in carious teeth with exposed pulps did not reveal significant differences between the materials concerning the final outcome [94].

It was reported that the radiographic success rate of vital pulpotomy with using MTA was higher than with formocresol and Pulpotec (ProduitsDentaires, Vevey, Switzerland) [95]. In a study of wisdom teeth planned for extraction that underwent partial pulpotomy with Theracal LC^{R}, Biodentine^{TR} or ProRoot MTA clinical results showed absence of sensitivity to heat, cold or palpation for Biodentine^{TR} and ProRoot MTA. In the Theracal LC^{R} group 20 % of teeth exhibited significant pain in the first week of treatment. Periapical pathology was not recorded by radiographic examination as well as hypersensitivity by electro test. Inflammation was absent for all materials at 8 weeks check-up [96].

Direct pulp capping with CH, Biodentine^{TR} or MTA Angelus in 169 patients with one carious permanent tooth with pulp exposure exhibited clinically more suitable results for pulp capping with Biodentine^{TR} and MTA angelus than with CH, but without statistical significance [97].

Torabinejad and coworkers reported outcomes of the following CS cements: Bioaggregate, Biodentine^{TR}, BioRoot RCS, CEM cement, Endo-CPM (Egeo SRL, Buenos Aires, Argentina), Endocem, EndoSequence Root Repair Material, EndoBinder (Binderware, Sao Carlos SP, Brazil), EndoSeal MTA, iRoot, MicroMega MTA, MTA Bio, MTA Fillapex, MTA Plus (Avalon Biomed, Houston, Texas, USA) NeoMTAPlus (Avalon Biomed), Ortho MTA (Pearson, Sylmar, California, USA), Retro MTA (BioMTA, Daejeon, South Korea), Tech Biosealer (Isasan SRL, Rovelor, Italy) and Theracal LC^{R}. Namely, performances of these materials for vital pulp therapy, apical barrier in teeth with necrotic pulps and open apices, perforation repair, root canal and root-end filling during surgical endodontics were compared (Figure 3). As a summary, all investigated materials have been claimed to provide satisfactory results. Although some bioactive CS cements have shown promising results in clinical applications, the number of investigations is still limited, wherein the long-term efficacy of these cements is still unknown. The authors concluded that more investigations with high levels of evidence and rigorous methodologies are needed [91].

Two clinical studies reported successful clinical (absence of pain) and radiographic (absence of external and internal resorption) findings using ProRoot MTA and Theracal LC^{R} for indirect pulp capping in primary teeth. However, a short-term follow-up slightly discredits the results of this study [35,98]. Furthermore, randomized clinical trials and cohort investigations reported successful outcomes following the use of MTA Filapex, PC and Theracal LC^{R} as indirect pulp capping agents in permanent teeth [35,99].

Since its introduction in 2009, Biodentine^{TR} has been successfully applied for apical canal filling, perforation repair and pulp capping. Bioaggregate is reported as a clinical material for successful apical canal filling, perforation repair and pulp capping [41].

In human primary teeth direct pulp capping with ProRoot MTA, CEM and Bioactive GICs it was shown that all studied cements resulted in similar color stability and clinical radiographic outcomes [100,101].

Some investigations have emphasized that superior result of direct pulp capping in patients under 40 years old were obtained when using ProRoot MTA comparing to the results obtained by CH-based material (Dycal®) [97,102-104].

Several case reports demonstrated successful treatment outcomes of ProRoot MTA, MTA Angelus, Bioaggregate, Biodentine^{TR} and iRoot-BP cements application for pulpotomy treatment [104]. Complete pulpotomy of immature root apices in permanent humans' teeth with ProRoot MTA, Endocem, CEM and Biodentine^{TR} resulted in the successful healing rate [105-108]. Biological vital pulp therapy by combination of CEM cement and MTA (Dentsply) with a resin modified GIC before composite resin restoration is advised by Oskoee and coworkers [47].

The case report of 4 treated maxillary incisors with apical pathology and unfinished root growth treated using experimental nano-CS cement apical plug revealed a good success rate upon 6 months [109].

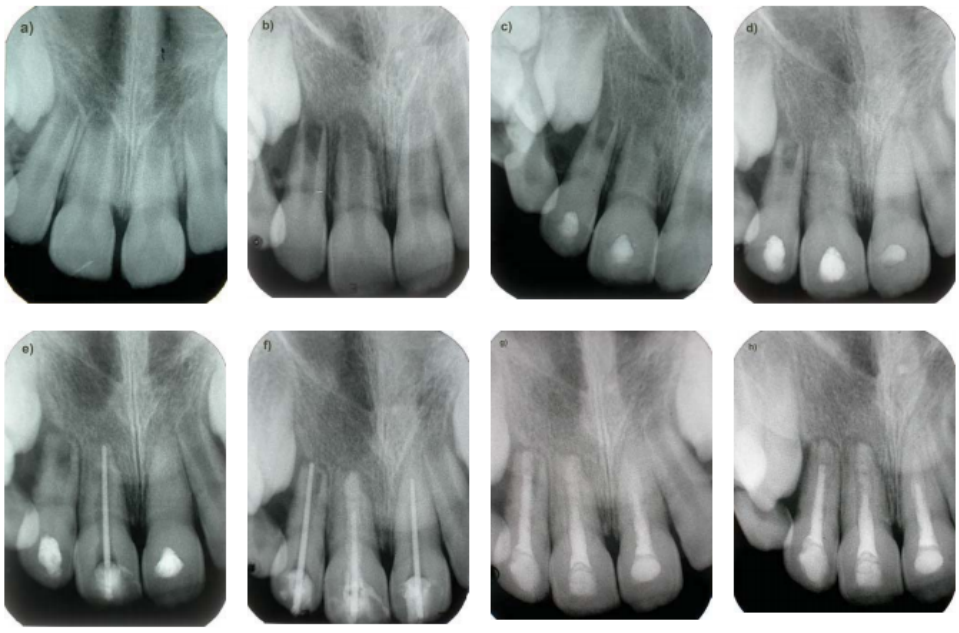

Figure 3. a) Radiographic view of the teeth immediately after trauma, b) Radiographic view after 2 months; c) Radiographic view after 4 months of calcium hydroxide dressing, d) Radiographic view after 6 months of calcium hydroxide dressing, e) Odontometry of the first upper right incisor, f) Odontometry of the first left upper incisor and second upper right incisor, g) Definitive obturation of the injured teeth with MTA Angelus, the application of root canal sealer and gutta-percha; h) Radigraphic follow-up after 6 months of MTA angelus treatment. (Reproduced from [109])

Altogether, it can be stated that CS cements dramatically increased the success rate of pulp diseases treatment (the success rate in CS is >95 % in comparison to ~30-50 % of the success rate in CH) and thus it bears a great potential to replace the CH that was used as a gold standard in pulp treatment for almost a century [91]. Thus, CS novel formulations should be developed and their application in clinical practice encouraged.

4. Conclusion

Calcium silicate cements are currently commercialized products widely used in dentistry. There are several products that differ in phase composition, setting time and mechanical properties. Such materials now represent the gold standard for the following dental restoration procedures: root / teeth resorption and perforation, apexification / apexogenesis, retrograde root canal filling, and pulp closure procedures. Superior performances of CS cements in comparison to the commonly used CH and GIC is grossly due to a) considerably improved compressive strength (significantly lower solubility) in comparison to CH and b) significantly higher bioactivity over both, CH and GIC, due to prolonged times of calcium ion release. Possibly, the following options can be considered as the most relevant areas for further research and development: formability of the cement paste, ease of dosing and manipulation during a specified time, improvement of mechanical properties and replacement of potentially toxic radiopacifiers such as Bi_2O_3 with more biocompatible ones. Finally, dental and engineering communities in future will have to consider shifting from bioactive to bioregenerative approaches in CS manufacturing with an ultimate goal to completely replace lost hard dental tissues. Everything noted above requires further in-depth research in not only the fields of chemistry, technology and biological behavior of materials, but also in the development of methods for diagnosis and material certification.

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SAŽETAK

Fizičko-hemijske i biološke karakteristike dentalnih kalcijum silikatnih cemenata – pregled literature

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(Pregledni rad)

Cementni materijali u stomatologiji su se usavršavali sa ciljem da zamene čvrsta zubna tkiva. U tom smislu je prvi primenjeni material bio kalcijum hidroksid (1920. godine), kao sredstvo za prekrivanje pulpe ili bifurkacije korena, punjenje kanala korena, kao i kod apeksifikacije i apeksogeneze. Pola veka kasnije glas-jonomer cementi kao dentinski zamenici počinju da potiskuju kalcijum hidroksid u mnogim kliničkim slučajevima. Devedesetih godina prošlog veka na stomatološkom tržištu se pojavio kalcijum silikatni cement (KS) i počeo uspešno da se primenjuje kao dentinski supstituent zadovoljavajući kliničke zahteve. Cilj ovog rada je da se prodiskutuju podaci iz literature u vezi istraživanja fizikohemijskih i bioloških osobina i kliničke primene KS cemenata. U tom smislu prodiskutovane su dobre i lose osobine ovih materijala u pogledu interakcija sa čvrstim dentinskim i mekim tkivima pulpe i periodoncijuma. Ovaj pregledni rad razmatra literaturne podatke o trenutno komercijalno dostupnim KS cementima sa aspekta laboratorijskih nalaza i kliničke primene. Analizirano je 109 naučnih članaka od kojih 62 prikazuje *in vitro* a 26 *in vivo* istraživanja, dok se 21 rad odnosio na pregledne članke i knjige koje su za predmet istraživanja imale i *in vitro* i *in vivo* studije. Iako su potrebna dalja istraživanja literaturnih podataka, već sada se može uočiti nesumnjiva prednost KS cemenata u odnosu na druge materijale pa mogu predstavljati materijal izbora u brojnim stomatološkim kliničkim intervencijama.

Ključne reči: bioaktivni materijal, dentinski zamenik, Portland cement, mineral trioksid agregat, Biodentine™