BIOACTIVITY AND BIOCOMPATIBILITY OF BIOCERAMIC CEMENTS IN ENDODONTICS: AN INTEGRATIVE REVIEW.

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ABSTRACT

Introduction: Bioceramic sealers have been gaining prominence in endodontics, meaning a great advance for endodontic therapy, mainly due to their biocompatibility and bioactivity. Objectives: research and discuss the literature about the bioactivity and biocompatibility of bioceramic sealants. **Materials and methods:** An integrative review was performed. The systematic plan consisted of four steps. In the first stage, a bibliographic survey was carried out in the Capes Periódicos Portal database. The search criteria were articles published between 2017 and 2022, found in the "advanced search" mode, using cross-references with the following keywords: bioceramics sealers AND endodontology AND root canals AND endodontic sealer AND bioactivity AND biocompatibility. Only documents found and published in full were evaluated. In the second stage, the titles and abstracts of the articles were read. In the third stage, a selection was made of those containing 3 to 5 keywords and a wording equal to or close to the proposed keywords. The fourth step consisted of reading the texts in full, followed by checking for duplicity and building a table with the collected information.
Results: In view of the research carried out, 23 articles were obtained in the first stage. After reading the titles and abstracts, 21 articles were obtained. After selecting those containing 3 to 5 keywords, 10 articles met the criteria. One article was deleted due to duplicates. 9 articles met the exclusion and inclusion criteria and were selected to be part of the integrative review.
Discussion: The selected studies in this literature review showed that bioceramic endodontic sealants perform well in endodontic therapy. Conclusion: To advance in its clinical application, more in vivo and in vitro studies with precise methods are needed to obtain more reliable data about its properties.
KEYWORDS: Bioceramic sealants. Endodontics. Root canals. Endodontic cement. Bioactivity. Biocompatibility.

INTRODUCTION

Bioceramic materials have recently been introduced in endodontics, mainly as restorative cements and as endodontic obturator sealants [1]. From the need for better results, new techniques emerge, which, by the way, are developed as problem solutions, having tissue regenerative capacity controlled and to the periodontium, in addition to being totally biocompatible [2].

An ideal endodontic sealer should be able to fill the entire root canal system, have a stable size, be biocompatible, bacteriostatic, non-absorbable, not irritate the periapical tissues, be easy to handle, have

adequate radiopacity and be sterile [1]. It is not desirable that it promotes changes in the color of the tooth structure, that it does not promote heat conduction, that it is not immunogenic or carcinogenic [3,4].

Currently, there are several endodontic sealers available on the market [5]. These materials have different physicochemical properties and compositions, such as the antimicrobial activity observed in cements based on zinc oxide and eugenol cements and those based on calcium hydroxide, and adhesion, of cements based on glass ionomer cements and resin [6].

More recently, bioceramic sealers based on calcium silicate 6,7. The Mineral Trioxide Aggregate (MTA) was the first cement that demonstrated excellent results in filling retrograde cavities and in direct pulp capping 8.

To meet such ideal needs, bioceramics were administered. Signifying a great advance for endodontic therapy, given by its biocompatibility and excellent physical-chemical properties [9]. The new bioceramic endodontic sealants presented for use in endodontics are natural sealers, mainly, by calcium silicates, zirconium oxide, tantalum oxide and monobasic calcium phosphate [3,10].

In the same way, these materials can act as repairing cements, obturator endodontic sealants and applied to vital pulp therapy [6,11]. In tested pulp therapies, they can be used in cases of pulp exposure due to trauma, caries, as direct pulp capping and revascularization therapies [12].

When used as root canal filling endodontic sealants, bioceramics have certain advantages such as: their biocompatibility, containing calcium phosphate, which increases their hardening properties and their chemical composition, like tooth structures [13].

Applied as repairing cements, these are often used in situations where the prognosis is often complex [6]. Clinical situations such as closure of root perforations and for filling internal resorptions and sealing external resorptions [14].

Bioceramic sealers are biocompatible, non-toxic, do not exhibit volumetric contraction and are chemically stable in the biological environment [15]. In addition, the main differential is their bioactivity, due to their ability to form hydroxyapatite, promoting the formation of dentin bridges that result in higher micromechanical retention. Thus, it exerts influence on the connection between dentin and filling material [9]. Based on new analyzes, they were categorized as bioinert, bioactive and biodegradable [16].

The introduction of bioceramics as endodontic sealants makes it possible to exploit all the advantages associated with this material [10]. Bioceramic cements use the moisture present in the dentinal tubules to initiate the hardening reaction. After hydration of the calcium silicate, hydrated calcium silicate and calcium hydroxide gel is formed [13]. This newly formed calcium hydroxide reacts with phosphate ions and precipitates to form hydroxyapatite and water [17].

Many studies have shown that bioceramic cement has excellent biocompatibility [18]. Authors report that bioceramic cement has low biocompatibility, like MTA on this point [19,20].

In addition to not being considered cytotoxic and being biocompatible, it was observed that the bioceramic cement has antibacterial activity, unlike the AH Plus® cement (Dentsply DeTrey, Konstanz, Germany) [7]. This resin cement is considered the gold standard in studies [8].

Studies report that bioceramic cements exhibit high cytotoxicity in the first 24 hours after their use or application, which gradually decreases over 6 weeks, but "that" remains moderately cytotoxic [7]. Authors differ in their opinions regarding the cytotoxicity of bioceramic cements in relation to MTA in the first 24 hours after setting, although they present similar cytotoxicity levels after the initial 24 hours [21].

The bioactivity of bioceramics can also be identified by their ability to stimulate the formation of apatite precipitates and thereby form dentin bridges [5,10,18,20]. Indicating that these materials are biologically active [22].

Furthermore, dental pulp cells have the best levels of concentration and mineralization on their surfaces using bioceramics [23]. The release of Ca $(OH)^2$ ions has been reported, having a greater inductive potential for hard tissue deposition [6].

The integrative review is a study carried out through the literature survey, being a method that allows an analysis of the synthesis of knowledge and the applicability of its results in practice [24].

It is widely used in the field of health, as it allows synthesizing available research on a given topic and directing it to practice, based on scientific evidence. It can delimit more precise methodological steps to provide a better use of evidence elucidated in previous studies [25]. It also allows the inclusion of experimental and non-experimental studies, by combining data from both theoretical and empirical literature [26].

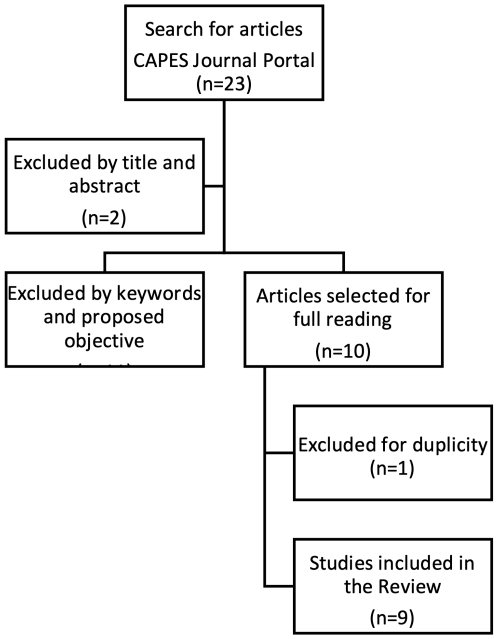
Thus, the aim of this integrative review is to discuss the bioactivity and biocompatibility of bioceramic sealants.

MATERIALS AND METHODS

The systematic plan for carrying out this integrative review consisted of four steps. In the first stage, a survey of the literature was carried out in the Portal de Periódicos Capes database. Documents published

between 2017 and 2022 were used as search criteria and were found in the "advanced search" mode, using intersections with the following keywords: bioceramics sealers AND endodontology AND root canals AND endodontic sealer AND bioactivity and biocompatibility. Among the documents found, only those that were published in full were evaluated in the next stage of the review. The second stage consisted of reading the titles and abstracts of the articles. In the third stage, among the collected abstracts, a selection was made of those that included 3 to 5 keywords and formulation equal to or close to the keywords proposed in the search carried out for this study; in addition, the content presented in the objective should be related to the proposed objective. The fourth step consisted of reading the texts in full, followed by checking for duplicity and building a table with the information collected in this process. If, after reading it in full, the author had doubts regarding the inclusion of the article, a second author would also make the evaluation. Inclusion criteria were full texts published in Portuguese or English between 2017 and 2022.

Figure 1. Flowchart with the results of article selection



RESULTS

In view of the research carried out, 23 articles were obtained in the first stage. After reading the titles and abstracts, a total of 21 articles were obtained after applying the inclusion and exclusion criteria. After selecting studies that included 3 to 5 keywords, and with similar content, their validation was verified. Ten articles met the inclusion criteria, and the full texts were read. One study was excluded due to duplication. Nine studies were then selected to be part of this integrative review, as shown in **Figure 1**.

The articles included in this study were all in English and presented in specific journals in the area of dentistry or of greater scope, such as multidisciplinary ones. The methodological design of the articles included in this review were 4 *in vitro* studies, 1 *ex vivo* study and 4 literature reviews (**Table 1**).

DISCUSSION

Several studies carried out with different cell culture lines have shown that bioceramic materials induce cell proliferation and differentiation, as well as mineralization.

Although there is a wide range of quality endodontic material options, there is still no cement that meets all ideal properties [5,10]. Due to this need, it is necessary to discuss the bioactivity and biocompatibility of bioceramic endodontic sealants.

The biocompatibility of bioceramics, excellent sealing capacity, induction and conduction of hard tissue and high success rate make them ideal materials for endodontic therapy [6]. The excellent processing properties and bioactivity of bioceramics make them suitable materials for endodontic treatment mainly in live [17].

These materials are biocompatible, antibacterial and biologically active. Although the composition of bioceramics can be considered similar to MTA, their osteoinductive and regenerative capacities do not surpass it [3,16].

Bioceramic materials are widely used for vital pulp therapies, scaffold coverage during regenerative endodontic procedures, apical barrier in teeth with necrotic pulps and open apices, repair of perforation and root canal filling, retrograde filling and sealing of supraosseous external resorptions during surgical endodontics [27,28].

Among the three bioceramic sealers MTT®, MTA-HP® and iRoot-BP-Plus®, tested in vitro, the deposition of extracellular calcium and biological activity was significant, through the induction of dental pulp stem cells [27]. These materials also showed the ability to provide adequate binding surfaces [18,27,28]. Likewise, the TotalFill BC Sealer®

Table 1. Articles selected to be part of the integrative review

Title	Authors	Year	Studied intervention	Considerations
Evaluation of cytocompatibility of calcium silicate-based endodontic sealers and their effects on the biological responses of mesenchymal dental stem cells	Lozano *et al.*	2017	To investigate *in vitro* the cytocompatibility of endodontic cements containing calcium silicate MTA Fillapex and TotalFill BC Sealer on stem cells from the human periodontal ligament, testing their biological responses and comparing them with those observed when using an epoxy resin-based cement (AH Plus).	TotalFill BC Sealer showed greater cytocompatibility than AH Plus and MTA Fillapex. Additional investigations using *in vivo* animal models are needed to validate the potential biological responses of TotalFill BC Sealer on human periodontal ligament stem cells.
Mineral trioxide aggregate-A review of properties and testing methodologies.	William H, Timothy N, Bil K, Laurence W.	2017	PubMed search was performed regarding relevant tests within each ISO and "mineral trioxide aggregate".	The results of the ISO tests used to test MTA can be influenced by the method of curing the MTA. The MTA must be cured in a way that represents the clinical use of the material. This typically involves immediate placement and immediate testing of samples, rather than curing the cement outside of test conditions.
Mineral trioxide aggregate and other bioactive endodontic cements: an updated overview – part II: other clinical applications and complications.	Torabinejad M, Parirokh M, Dummer PMH.	2018	In this article, the clinical applications of MTA and other BECs were reviewed for apexification, regenerative endodontics, perforation sealing, root canal filling, restorative procedures, periodontal defects, and treatment of vertical and horizontal root fractures.	Compared to other bioceramics, MTA has been evaluated for the highest quality investigations for all clinical applications. Unfortunately, most investigations on MTA and other BECs have major deficiencies in their methodologies that make it difficult to assess them through systematic reviews and meta-analyses.
Cytocompatibility of Biodentine and iRoot FS with human periodontal ligament cells: an *in vitro* study.	Luo *et al.*	2018	To evaluate the cytocompatibility of Biodentine and iRoot FS with human periodontal ligament cells.	iRoot FS had a positive effect on adhesion, proliferation and biomineralization of human periodontal ligament cells compared to Biodentine.
Biocompatibility, induction of mineralization and antimicrobial activity of experimental intracanal pastes based on glass and glass-ceramic materials.	Lopes *et al.*	2020	To evaluate the biocompatibility, mineralization induction and antimicrobial activity of experimental bioceramic intracanal pastes based on two glass and glass-ceramic materials. Calcium hydroxide (Ca (OH)2) paste was used as a positive control.	Experimental pastes BS-2P and F18 were biocompatible, stimulated biomineralization and induced significant OPN immunostaining compared to Ca (OH)2. Only BS-2P paste demonstrated antimicrobial activity comparable to Ca (OH)2.
Oroactive dental biomaterials and their use in endodontic therapy.	Patel *et al.*	2020	This review delves into the biochemistry of materials to examine their deficiencies and where the opportunity lies to further enhance their effectiveness in endodontic practice.	Vital pulp therapies became largely successful with the introduction of MTA and bioceramics. Although these materials are not yet ideal, their modification may provide their appropriate use.
Bio-Inductive Materials in Direct and Indirect Pulp Capping- A Review Article.	Kunert M, Szymanska M.	2020	The article aims to analyze the available research and compare the properties of bio inductive materials in direct and indirect pulp capping procedures.	High biocompatibility and excellent bioactivity further favor this tooth replacement material, although more long-term clinical studies are needed for a definitive evaluation of Biodentine.
A laboratory study to test the responses of human dental pulp stem cells to extracts from three dental pulp capping biomaterials.	Abou *et al.*	2021	This laboratory study aimed to investigate the effects of three endodontic biomaterials.	In a laboratory environment, ACTIVA, MTA-HP and iRoot-BP-Plus promoted proliferation, mineralization and adhesion of stem cells from the human periodontal ligament, which may explain their success in situ as endodontic biomaterials.
Impact of Immersion Media on Physical Properties and Bioactivity of Epoxy Resin-Based and Bioceramic Endodontic Sealers.	Moraes *et al.*	2022	This study evaluated the effects of immersion medium distilled water, phosphate-buffered saline (pbs) and simulated body fluid (sbf) on the physical properties of fluid uptake/sorption/solubility and alkalization activity (pH) and bioactivity of a bioceramic cement: the BioRoot RCS.	It was shown that the most suitable immersion medium to test the physical properties and bioactivity of endodontic bioceramic cements (BioRoot) was pbs – a medium that was able to highlight the properties of the cement: high pH, strong evidence of potential for bioactivity.

proliferation, adhesion, and migration of human periodontal ligament stem cells in a concentration-dependent manner, while maintaining cell viability [29].

In contrast, studies showed that iRoot-BP-Plus® inhibited human periodontal ligament stem cell proliferation as well as MTA Fillapex® [4]. These results suggest that other constituent components other than calcium silicate may directly affect the induced cytotoxicity by cement [10]. They attribute the inhibition to the chemical composition that affects these materials, which may be caused by the resin component or other cement components [28].

When evaluating Total Fill BC Sealer® cement in vitro, cultured human periodontal ligament stem cells showed greater proliferation and adhesion of type I collagen compared to AH Plus® resin cement and MTA Fillapex® [4]. Biocompatibility and bioactivity of these materials are based on the induction of bone cell differentiation and proliferation and on the production of a matrix where the newly formed bone can accommodate [5].

Furthermore, adhesion to extracellular matrix proteins, such as type I collagen, and subsequent cell migration are involved in cell colonization of the surrounding tissue [12]. Adhesion and migration are two important processes to be analyzed in regenerative medicine [10,27].

These results could be attributed to the elution of components found in sealers based on calcium silicate, such as calcium ions [12].

Studies consider that the main consideration of bioceramics is the release of calcium hydroxide [8,15,27,29]. It should be noted that initially, the speed of the coagulation reaction of the sealers is high and cytotoxic effects were observed from the release of calcium hydroxide [12]. When the material reaches its final

state of coagulation, most of the alkalinity is lost, reducing Cytotoxicity [6].

The bioceramic endodontic sealants iRoot FS® and Biodentine®, on the other hand, showed considerable responses in terms of biocompatibility and low cytotoxicity [10]. These promoted the proliferation and biomineralization of cell adhesion in the periodontal ligament [14].

Biodentine®, for example, applied directly to the pulp, induces the formation of reparative dentin [28]. Resulting in the complete formation of dentin bridges without an inflammatory response from the pulp and the appearance of a well-organized layer of odontoblasts and odontoblast-like cells after 6 weeks [10,12].

The process of formation of the hard tissue bridge, also called repairing tertiary dentin [12]. This occurs through the pulp response to the capping material, triggering an inflammatory process that promotes the release of biomolecules such as growth factors (TGF), bone morphogenetic proteins (BMP), interleukins (IL) [14,22].

There is good evidence that Biodentine® has a positive effect on important cells in the dental pulp, stimulation of tertiary dentin formation and early reparative dentin formation[5,7]. The presence of human periodontal ligament stem cells near the apex causes the sealer to promote repair and bio sealing through the deposition of mineralized tissue in the apical foramen [4].

When experimental groups were analyzed, the highly reactive surface of these materials in powder form provides the ability to increase the pH by leaching Na+ and Ca2+ due to the alkaline pH providing the medium and the release of calcium ions [20,28]. Furthermore, molecular analyzes revealed that bioactive silicate dissolution products activate seven families of genes involved in the osteogenesis process [10].

However, it is known that the results obtained in ex vivo studies may not be directly extrapolated to clinical situations [24].

Other studies support the claim that Biodentine® is superior to calcium hydroxide in terms of pulp capping success [28]. Furthermore, in cell and tissue culture models, the material used during pulp capping directly affects the regenerative potential of the dental pulp, regulating the secretion of factors such as TGF-β1 [20,21].

The tissue regeneration and antimicrobial capacity of bioceramics proved to be efficient [7]. Given these characteristics, this material can be indicated as a choice in cases of interradicular or persistent infections and retrograde filling [6]. In addition, studies show that tissue regeneration capacity is seen only in this class of materials [27].

Although several new bioceramic endodontic sealants have been evaluated as root filling materials, MTA continues to be considered the gold standard material by the American Board of Endodontics and Australian endodontists [6,28].
Therefore, more research is still needed to explore the physicochemical properties of these materials in the long term to facilitate the improvement of their compositions and possibly overcome the defects that still exist.

CONCLUSION

The studies selected in this literature review showed that bioceramic endodontic sealers perform well in endodontic therapy. However, to advance in its clinical application, more in vivo and in vitro studies with precise methods are needed to obtain more reliable data on its properties.

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