Comparison of the biocompatibility of calcium silicate-based materials to mineral trioxide aggregate: Systematic review

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ABSTRACT

The objective of this systematic review was to evaluate the biocompatibility and interaction of bioceric materials with animal and human mesenchymal cells in vitro and in vivo and to compare them with mineral trioxide aggregate (MTA). Two independent researchers conducted PubMed/Medline, Web of Science, and Scopus searches to identify studies published in English, without restrictions on year of publication using the following keywords: “root canal sealer,” “root repair material,” “cytotoxicity,” and “biocermics.” The articles were selected following the PRISMA statement. A total of 1486 titles were identified in the initial search. However, only 18 studies met the inclusion and exclusion criteria. The results showed that bioceramic materials have biological properties similar to those of MTA, including low cytotoxicity as well as promoting cell proliferation and adhesion, low expression of inflammatory cytokines, and reduced pulp inflammation. This systematic review therefore suggests that the choice of repair bioceric materials or MTA based on biocompatibility should be the professional’s decision.

Key words: Biocermics, cytotoxicity, root canal sealer, root repair material

INTRODUCTION

Complete filling of root canal systems after chemo-mechanical preparation is critical to the success of endodontic treatment, as well as to sealing of the root apex since many materials exhibit limited contact with vital tissues in the apical region. However, in some procedures such as pulp capping/pulpotomy, perforation repair, apexification, and obturation itself, the materials are placed in proximity to pulp and apical periodontal tissues. Root repair materials must therefore have excellent characteristics such as biocompatibility and stability of physical and chemical properties. In addition to these characteristics, the repair material should stimulate tissue regeneration, especially after endodontic treatment or apical pathology.

Mineral trioxide aggregate’s (MTA’s) success as a repairing material is undeniable, although there are...
some limitations regarding its use. Limitations of MTA include color alteration, manipulation difficulties, the need of specific instruments, and delayed setting time. A reduction of the setting period has a beneficial effect on patient’s relief and on bacterial infection. Based on these limitations, it is necessary to search for new materials that have better properties.

Bioceramic root canal sealers have recently been introduced into endodontics, with the same indications of the MTA, that is, or use in obturation and repair procedures. These cement contain tri- and di-calcium silicate, calcium phosphate, calcium hydroxide, as well as zirconium oxide as radiopacifier. Bioceramic materials are indicated as an alternative to MTA, due to their excellent physical, chemical, and biological properties, for example, they have been shown to induce cell differentiation, to have osteoconductive effects, and to reduce inflammation.

The objective of this systematic review was to evaluate the biocompatibility and interaction of bioceramic materials with animal and human mesenchymal cells in vitro and in vivo and to compare them with MTA, since there are no randomized clinical trials that perform this type of comparison. Since it is a relatively new material in the endodontic market, it is necessary to compare its biocompatibility with materials such as MTA, which are considered the gold standard of endodontics. The hypothesis tested is that bioceramic materials are more biocompatible than MTA.

**METHODOLOGY**

**Procedure**

This systematic review was conducted according to the guidelines of the PRISMA statement. The review protocol was registered at PROSPERO (CRD42017056232). The studies were selected according to the inclusion and exclusion criteria reported below. All abstracts and full texts were reviewed. None of the manuscript author was contacted during this process. Disagreements between authors were evaluated and the studies were eliminated through discussion among researchers until a consensus was reached.

**Inclusion and exclusion criteria**

The inclusion criteria for this review included studies published in English, without restrictions on year of publication, and studies which evaluated biocompatibility, comparing the cytotoxicity of bioceramic materials to MTA. The types of studies were in vitro and in vivo laboratory studies using animal (no species restriction, either small or large) and human cells, prospective studies, retrospective studies, and randomized clinical trials. Excluded were studies that compared the cytotoxicity of bioceramic materials only, studies that compared bioceramic materials with cement other than MTA, or studies comparing bioceramic endodontic sealers, since the biocompatibility requirements of a repairing material are much greater than that of a sealer.

**Criteria for selection of the studies**

First, studies were selected by analysis of the titles. If the title indicated inclusion, the abstract was evaluated carefully and articles considered eligible for review (or in case of doubt) were selected for reading. Disagreements among researchers were resolved by discussion with a third researcher (MVC). The kappa level of agreement between authors was 0.81. Due to the lack of randomized clinical trials and prospective and retrospective studies, this review included in vitro studies using animal and human cells and in vivo animal studies. For this reason, the patient-intervention-comparison-outcome (PICO) system was adapted: population (studies that evaluated animal and human mesenchymal cells), intervention (evaluation of the biocompatibility of bioceramic materials), comparison (MTA), and outcomes (cell viability, changes in cell morphology, inflammatory responses, cytokine production, and cell adhesion).

**Search strategy**

Two independent researchers (NGO and PRSA) conducted searches in PubMed/Medline, Web of Science, and Scopus to identify studies published in English without restriction on year of publication. The keywords used were “root repair material,” “root canal sealer,” “cytotoxicity,” and “bioceramics.” The search details were Root repair material (all fields) AND root canal sealer (all fields) OR (root repair material [all fields] AND cytotoxicity [All Fields]) OR root repair material (all fields) AND biocermics (all fields) OR root canal sealer (all fields) AND cytotoxicity (all fields) OR root canal sealer (all fields) AND biocermics (all fields) OR cytotoxicity (all fields) AND biocermics (all fields). This electronic search was complemented by a manual search conducted from March 1, 2016, to January 8, 2017, in high-impact journals in endodontics, such as the Journal of Endodontics and International Endodontics Journal.

**Assessment of risk of bias**

Since no specific evaluation exists for in vitro studies, this review critically evaluated the selected studies.
using an adapted version of the CONSORT checklist, which consists of 25 items; however, only 15 items were used in this study (presence of the first author’s name, type of study being identified in the title, presentation of a structured abstract, introduction containing a scientific context, clearly describing the rationale, objectives, and hypothesis tested, methodology showing study type, cell type, intervention, statistical analysis, evaluation time between groups studied, if materials were used according to the manufacturers, main results from each experiment being described, if in the discussion section the results and their clinical implications were interpreted, whether these results could be translated into other species or systems, relevance to human biology, and the existence of funding. If the authors reported the information analyzed, a yes (Y) answer was assigned to the specific parameter. If the information could not be found, a no (N) answer was given. Articles reporting 1–5 items were classified as high risk, 6–10 as medium risk, and 11–15 as low risk of bias. All the 18 presented low risk of bias.

RESULTS

The flowchart of the systematic review is depicted in Figure 1. A total of 1486 titles were identified in the initial search. Eighteen studies were included in this review and processed for data extraction in the following order: first author, year of publication, type of study (in vitro or in vivo), type of sealer, type of laboratory analysis, type of biocompatibility test, type of cell used (animal or human), incubation time or experimental period, and the main results found in each study according to the methodology applied [Table 1].

As a response to the possible results established in PICO, in general, the bioceramic materials exhibited similar biological properties when compared to MTA, including good biocompatibility, cell proliferation and adhesion, low cytotoxicity, low expression of inflammatory cytokines, and reduced inflammation of human pulp cells.

Eight (44%) of the eighteen studies analyzed used the MTT or MTS assay for laboratory analysis [Table 1]. Only one study[18] evaluated tissue reactions through histological analysis in subcutaneous tissues of rats (Wistar rats).

Eleven studies evaluated cytotoxicity, in which, in eight studies, the cytotoxicity of bioceramic materials was similar to that of MTA.[9,10,13,15,16,20,22,24] In one study, the results obtained with the bioceramic materials were superior.[12] In contrast, two studies demonstrated greater biocompatibility of the MTA[21,23] [Table 1].

Two of the studies included in this review evaluated the inflammatory responses and production and expression of cytokines (interleukin [IL]-1β, tumor necrosis factor-alpha [TNF-α], IL-6, and IL-8) induced by these materials when in contact with mesenchymal cells.[13,17] None of the materials produced a severe inflammatory response [Table 1].

Regarding the evaluation of differentiation of odontoblasts, one study[14] used cell counting kit-8, alkaline phosphatase (ALP) activity, and quantitative reverse-transcriptase-polymerase chain reaction (qRT-PCR); a second study evaluated osteoblast differentiation by qRT-PCR;[19] and a third study evaluated the odontogenic differentiation, through flow cytometry and scanning electron microscopy (SEM).[9]

Regarding cell viability, growth, morphology, and cell adhesion modifications, both materials obtained similar favorable responses.[2,11,12,16,17,25]
Table 1: Data summary of the articles selected

<table>
<thead>
<tr>
<th>First author</th>
<th>Year of study</th>
<th>Type of study</th>
<th>Type of Sealer</th>
<th>Type of laboratorial analysis</th>
<th>Type of biocompatibility test</th>
<th>Type of cell or human</th>
<th>Experimental period</th>
<th>Summary</th>
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<tbody>
<tr>
<td>1. Zhou[9]</td>
<td>2013</td>
<td>In vitro</td>
<td>MTA (Dentsply Tulsa Dental, Tulsa, OK, USA)</td>
<td>Flow cytometry, SEM</td>
<td>Cytotoxicity</td>
<td>Gingival fibroblast</td>
<td>Human</td>
<td>1, 3 and 7 days</td>
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<td>Glass ionomer (GC Fuji IX GP, Japan)</td>
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<td>Odontogenic differentiation</td>
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<td>Biodentine* (Septodont, Saint-Maur-des -Fossés, France)</td>
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<td>2. Coaguila -Llerena[10]</td>
<td>2016</td>
<td>In vitro</td>
<td>MTA (Angelus, Londrina, PR, Brazil)</td>
<td>MTT assay</td>
<td>Cytotoxicity</td>
<td>PDL</td>
<td>Human</td>
<td>1, 3 and 7 days</td>
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<td>ERRM* (Brasseler, Savannah, GA, USA)</td>
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<td>Super EBA (Bosworth, Skokie, IL, USA)</td>
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<td>3. Willershausen[11]</td>
<td>2013</td>
<td>In vitro</td>
<td>White MTA (Angelus, Londrina, PR, Brazil)</td>
<td>Alamar blue, fluorescence staining</td>
<td>Proliferation cellular morphology</td>
<td>Fibroblasts and osteoblasts</td>
<td>Human</td>
<td>6, 24, 72 and 96 h</td>
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<td>Grey MTA (Angelus, Londrina, PR, Brazil)</td>
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<td>ProRoot MTA (Dentsply/ Maillefer, Ballaigues, Switzerland)</td>
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<td>ERRM* (Brasseler, Savannah, GA, USA)</td>
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<tr>
<td>4. Jiang[12]</td>
<td>2014</td>
<td>In vitro</td>
<td>iRoot BP Plus* (Innovative Bioceramix, Vancouver, BC, Canada)</td>
<td>MTT assay, SEM and SEM analysis</td>
<td>Cytotoxicity</td>
<td>Osteoblasts (MG63)</td>
<td>Human</td>
<td>1, 3, 7, and 14 days</td>
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<td>iRoot FS* (Innovative Bioceramix. Vancouver, BC, Canada)</td>
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<td>ProRoot MTA (Tulsa Dental, Johnson City, TN, USA)</td>
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<td></td>
<td>Super-EBA (Bosworth, Skokie, IL, USA)</td>
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Table 1: Contd...

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<th>First author</th>
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<th>Type of study</th>
<th>Type of Sealer 1</th>
<th>Type of laboratory analysis</th>
<th>Type of biocompatibility test</th>
<th>Type of cell or human</th>
<th>Animal</th>
<th>Experimental period</th>
<th>Summary</th>
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<tbody>
<tr>
<td>5. Ciasca[13]</td>
<td>2012</td>
<td>In vitro</td>
<td>ProRoot MTA (MTA; Dentsply Tulsa Dental, Johnson City, TN, USA) ERRM* (Brasseler, Savannah, GA, USA) AH-26 (Dentsply, De Trey, Konstanz, Germany)</td>
<td>Photomicrograph images and qRT-PCR</td>
<td>Cytotoxicity Cytokine expression</td>
<td>Osteoblasts (MG63)</td>
<td>Human</td>
<td>24, 36 and 48 h</td>
<td>ERRM and MTA showed similar cytotoxicity and cytokine expressions</td>
</tr>
<tr>
<td>6. Chen[2]</td>
<td>2016</td>
<td>In vitro</td>
<td>ERRM* (Brasseler, Savannah, GA, USA) ProRoot MTA (Dentsply Tulsa Dental, Tulsa, OK, USA)</td>
<td>MTT assay and SEM</td>
<td>Cell proliferation Cell survival Cellular surface morphology</td>
<td>Mesenchymal, Human PDL, and dental pulp stem cells</td>
<td>Human</td>
<td>1, 3, 5, and 7 days</td>
<td>MTA and ERRM are biocompatible and promote cell proliferation and survival in an ERK-signaling pathway Bioaggregate and iRoot BP Plus were no toxic and able to induce mineralization and odontoblastic differentiation</td>
</tr>
<tr>
<td>7. Zhang[14]</td>
<td>2013</td>
<td>In vitro</td>
<td>Bioaggregate* (Innovative Bioceramix, Vancouver, BC, Canada) iRoot BP Plus* (Innovative Bioceramix, Vancouver, BC, Canada) MTA (Dentsply Tulsa Dental, Tulsa, OK, USA)</td>
<td>CCK-8, ALP activity, and qRT-PCR</td>
<td>Cell proliferation Cell differentiation Expression of odontoblast differentiation</td>
<td>Dental pulp</td>
<td>Human</td>
<td>1, 3, 5, and 7 days</td>
<td>Bioaggregate and iRoot BP Plus were no toxic and able to induce mineralization and odontoblastic differentiation</td>
</tr>
<tr>
<td>8. Jovanovic[15]</td>
<td>2014</td>
<td>In vitro</td>
<td>Amalgam (Ekstrakap-D III, ICN Galenika, Serbia) MTA (Angelus, Londrina, PR, Brazil) Biodentine* (Septodont, Saint Maur-des-Fossés, France)</td>
<td>DET, MTT assay, and agar diffusion test</td>
<td>Cytotoxicity</td>
<td>Fibroblasts (MRC-5 and mouse L929)</td>
<td>Human and animal</td>
<td>24, 48, and 72 h</td>
<td>Biocompatibility tests showed high level of cell compatibility of all the three tested materials</td>
</tr>
<tr>
<td>9. Ma[16]</td>
<td>2011</td>
<td>In vitro</td>
<td>ERRM* (Brasseler, Savannah, GA, USA) MTA (Dentsply Tulsa Dental, Tulsa, OK, USA) IRM (Dentsply Caulk, Milford, DE) Cavit G (3M ESPE AG, Seefeld, Germany)</td>
<td>MTT assay and scanning electron microscope</td>
<td>Cytotoxicity Cell viability Cell adhesion</td>
<td>Fibroblasts</td>
<td>Human</td>
<td>1, 3 and 7 days</td>
<td>ERRM putty and paste displayed similar in vitro biocompatibility to MTA</td>
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<th>First author</th>
<th>Year</th>
<th>Type of study</th>
<th>Type of Sealer</th>
<th>Type of laboratory analysis</th>
<th>Type of biocompatibility test</th>
<th>Type of cell or human</th>
<th>Experimental period</th>
<th>Summary</th>
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<tbody>
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<td>Corral Nuñez</td>
<td>2014</td>
<td><em>In vitro</em></td>
<td>Biodentine*</td>
<td>Alamar blue, SEM, and qRT-PCR</td>
<td>Cell viability, Morphology cellular, Cytokine expression</td>
<td>Fibroblasts</td>
<td>Animal</td>
<td>3, 6, 24 and 72 h</td>
</tr>
<tr>
<td>Khalil</td>
<td>2015</td>
<td><em>In vivo</em></td>
<td>MTA (Dentsply Tulsa Dental, Tulsa, OK) ERRM* (Brasseler, Savannah, GA, USA)</td>
<td>Histological evaluation</td>
<td>Tissue reactions</td>
<td>Subcutaneous Animal (Wistar rats)</td>
<td>7 and 30 days</td>
<td>Both ERRM and MTA cause an injurious effect when implanted in rat subcutaneous tissues after 7 and 30 days, ERRM is significantly less injurious to tissues than MTA</td>
</tr>
<tr>
<td>Rifaey</td>
<td>2016</td>
<td><em>In vitro</em></td>
<td>ProRoot MTA (Dentsply Tulsa Dental Specialties, Tulsa, OK) ERRM* (Brasseler, Savannah, GA, USA)</td>
<td>qRT-PCR</td>
<td>Osteoblast differentiation</td>
<td>Osteoblasts</td>
<td>Animal</td>
<td>7, 14, and 21 days</td>
</tr>
<tr>
<td>De-Deus</td>
<td>2012</td>
<td><em>In vitro</em></td>
<td>iRoot BP Plus* (Innovative Bioceramix, Vancouver, BC, Canada) ProRoot MTA (Dental, Tulsa, Ok, USA)</td>
<td>XTT, NR, and CVDE</td>
<td>Cytotoxicity</td>
<td>Osteoblast</td>
<td>Human</td>
<td>24 or 48 h</td>
</tr>
<tr>
<td>Modareszadeh</td>
<td>2012</td>
<td><em>In vitro</em></td>
<td>ERRM* (Brasseler, Savannah, GA, USA) ProRoot MTA (Dentsply Tulsa Dental, Tulsa, OK)</td>
<td>MTS and p-NPP assay</td>
<td>Cytotoxicity</td>
<td>Saos-2 Osteoblast-like</td>
<td>Human</td>
<td>1, 3 and 7 days</td>
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<tr>
<td>Damas</td>
<td>2011</td>
<td><em>In vitro</em></td>
<td>MTA (Angelus, Londrina, PR, Brazil) ERRM* (Brasseler, Savannah, GA, USA)</td>
<td>MTT assay</td>
<td>Cytotoxicity</td>
<td>Fibroblasts</td>
<td>Human</td>
<td>24 h</td>
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DISCUSSION

Few studies have compared the cytocompatibility and cell interactions between bioceramic materials and MTA and other conventional sealers, such as containing calcium hydroxide, zinc oxide and eugenol, and resins. Based on the current literature, there are no systematic reviews that make this kind of comparison.

The cytotoxic potential is one of the most common features investigated in in vitro studies to determine the biocompatibility of root repair materials before testing them in clinical studies. The cytotoxicity of materials can be due to the presence of toxic or soluble compounds in their composition. Jiang et al.\(^{[12]}\) compared the cytotoxicity in vitro of iRoot BP Plus, iRoot FS, ProRoot MTA, and Super-EBA in fibroblasts and human osteoblasts. All materials, with the exception of Super-EBA, exhibited insignificant cytotoxicity. In addition, iRoot FS demonstrated great potential in other clinical
applications due to its rapid setting time (1 h) and better cell adhesion capacity when compared to other studied materials.

Rifaey et al.,[19] investigating the gene expression levels of bone sialoprotein, ALP, and Osterix, found that endosequence root repair material (ERRM) increased the differentiation of osteoblasts when compared to MTA. The results obtained for the bioceramics can be explained by the presence of nontoxic compounds in their composition, including calcium and phosphorus.[20] The biocompatibility of these materials can be attributed to the formation of hydroxyapatite in the presence of Ca²⁺ ion during the setting reaction.[21] Another explanation for this result, according to the study, was the use of not so frequent biocompatibility test, the three-dimensional culture system (Alvetex scaffold), which best resembles clinical conditions, where the cells are not placed in contact with materials. Instead, they are attracted to the proximity of the studied material.[19]

On the other hand, in the study of Modareszadeh et al.,[22] ERRM significantly reduced the bioactivity of human osteoblasts. Samyuktha et al.[23] found that MTA was less toxic to periodontal ligament fibroblasts than ERRM and biodentine. The bioactivity of the MTA is dependent on its high pH, which results in the release of calcium ions after setting.[24] These divergent results may be due to differences in the cell lines (osteoblasts and fibroblasts), type of laboratory analysis (MTT assay, Trypan blue dye assay), concentrations and dilutions, and duration of the experiments used to evaluate these bioceramic materials (ERRM and biodentine).

The contact of cells with the surface of the material is a good indicator that the materials are biocompatible. In addition, if the materials stimulate cell proliferation or survival, they are likely to promote the repair process.[25] In many studies, bioceramic materials promoted cell proliferation and viability and their performance was similar or better than that of MTA. In contrast, De-Deus et al.[26] found clear differences in cell viability in the XTT assay: tetrazolium dye 2,3-bis-(2-methoxy-4-nitro-5-sulphenyl)-(2H)-tetrazolium-5-carboxanilide between iRoot BP Plus and ProRoot MTA after 48 h of exposure. The bioceramic material reduced cell viability significantly more than that observed in the other groups (zinc oxide- and eugenol-containing cement and control, in which the cells were exposed to unconditioned medium). However, iRoot BP Plus did not induce critical cytotoxic effects. Thus, the biocompatibility of the bioceramic sealer was comparable to that of MTA.

With respect to morphology and the capacity of root canal sealers to promote cell adhesion, bioceramic materials were also found to be similar or better than MTA. In the study of Jiang et al.,[27] iRoot FS promoted better cell–cell adhesion (L929 and MG63). Previous studies have shown that cell adhesion is highly dependent on cell morphology and on the surface characteristics of the materials.[28,29] These characteristics influence the behavior, migration, adhesion, and differentiation of cells.[28]

Chen et al.[2] found only minimal differences between the surface characteristics of MTA and ERRM by SEM. Ma et al.[16] still visually confirmed, through the same method, a positive cellular interaction between the two cement. Both materials promoted cell proliferation and survival. The similar granular surface characteristics of MTA and ERRM may therefore explain the similar biological activities of these materials.

On the other hand, Corral Nuñez et al.[17] found changes in cell viability during fibroblast exposure to biodentine and MTA. After 24 h of exposure to biodentine, the study showed an increase in cell viability, which was not observed with MTA. This result can be explained by differences in the composition between the two materials, such as the presence of the radiopacifier. The radiopacifier for MTA is bismuth oxide. Its use has been questioned for not promoting cell growth. In addition, calcium phosphate crystals, produced by the reaction of MTA with the SEM preparation, can generate distorted images. However, over time, it appears that the cells can repair themselves. Although SEM is the most widely used method for assessing cell viability in direct contact with calcium silicate-based materials, studies have shown that sample processing may affect morphology and consequent cell viability[30] and may contribute to the controversial results.

Regarding inflammatory responses and the production of pro-inflammatory mediators and cytokines, Ciasca et al.[13] reported similar effects for ERRM putty, flow, and ProRoot MTA, including the expression of IL-1β, IL-6, and IL-8 in all samples with minimal expression of TNF-α determined by RT-PCR. A slight difference was observed between the levels of cytokine expression, in which the ERRM putty showed higher levels during the first 24 h. One explanation for this would be based on the use of different types of vehicles applied
to create ERRM flow, although the difference was not significant. Many studies have shown that the interaction between the components of bioceramics and osteoblasts increases the production of cytokines, such as ILs and TNF. The high expression of these bone resorption cytokines has a beneficial effect on bone formation. Thus, these materials present high repairing potential.

In contrast to most studies that reported similar characteristics for bioceramic materials and MTA, Khalil and Abunasef\(^{[18]}\) showed more tissue injury with MTA than ERRM, after their applications in rat subcutaneous tissues. The authors observed areas of necrosis and abscesses that were attributed to the setting of MTA. An exothermic reaction occurs during this process in which tissues are exposed to high temperatures that can cause ischemia, cell death, and tissue necrosis.

One of the challenges of this research was the lack of standardization of the biocompatibility tests and evaluation times used in each study between the bioceramic materials and MTA. Different methods were likely responsible for the conflicting results. It is very important that root canal sealers exhibit acceptable biocompatibility and cytotoxicity and good biological properties. Therefore, the hypothesis tested in this review was not accepted, since the bioceramic materials showed biological properties similar to those of MTA such as good biocompatibility indicated by low cytotoxicity as well as the induction of cell proliferation and adhesion, adequate expression of inflammatory cytokines, and reduced pulp inflammation after the acute phase.

**CONCLUSION**

This systematic review therefore suggests that the choice of repair bioceramic materials or MTA based on biocompatibility should be the professional’s decision.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

In vitro comparison of induction capacity and biomineralization ability 
of mineral trioxide aggregate and a bioceramic root canal sealer. Int 
27. Hansen SW, Marshall JG, Sedgley CM. Comparison of intracanal 
EndoSequence root repair material and ProRoot MTA to induce pH 
changes in simulated root resorption defects over 4 weeks in matched 
28. Roach P, Eglin D, Rohde K, Perry CC. Modern biomaterials: 
A review – Bulk properties and implications of surface modifications. 
29. Berry CC, Campbell G, Spadiccino A, Robertson M, Curtis AS. The 
influence of microscale topography on fibroblast attachment and 
30. Camilleri J, Montesin FE, Papaioannou S, McDonald F, Pitt Ford TR. 
Biocompatibility of two commercial forms of mineral trioxide 