

**UNIVERSIDADE FEDERAL DE MINAS GERAIS
FACULDADE DE ODONTOLOGIA
COLEGIADO DE PÓS-GRADUAÇÃO EM ODONTOLOGIA**

Betânia de Lourdes Canal Vasconcellos

**ESTUDO BIBLIOMÉTRICO E ANÁLISE *IN VIVO* DA
BIOCOMPATIBILIDADE E BIOATIVIDADE DE CIMENTOS
BIOCERÂMICOS NA ENDODONTIA**

**Belo Horizonte
2025**

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BIOCOMPATIBILIDADE E BIOATIVIDADE DE CIMENTOS
BIOCERÂMICOS NA ENDODONTIA**

Tese apresentada ao Colegiado de Pós-Graduação em Odontologia da Faculdade de Odontologia da Universidade Federal de Minas Gerais, como requisito parcial à obtenção do grau de Doutora em Odontologia- área de concentração em Endodontia.

Orientador: Prof. Warley Luciano Fonseca Tavares

Coorientador (a): Prof. Francine Benetti

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ESTUDO BIBLIOMÉTRICO E ANÁLISE IN VIVO DA BIOCOMPATIBILIDADE E BIOATIVIDADE DE CIMENTOS BIOCERÂMICOS NA ENDODONTIA

BETÂNIA DE LOURDES CANAL VASCONCELLOS

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Aprovada em 19 de agosto de 2025, pela banca constituída pelos membros:

Prof. Warley Luciano Fonseca Tavares - Orientador
Faculdade de Odontologia da UFMG

Profa. Francine Benetti Faria
Faculdade de Odontologia da UFMG

Profa. Daniela Augusta Barbato Ferreira
Faculdade de Odontologia da UFMG

Profa. Isabella Faria da Cunha Peixoto
Faculdade de Odontologia da UFMG

Profa. Júlia Mourão Braga Diniz
Ciências Médicas

Prof. Gustavo de Cristófaró Almeida
Ciências Médicas

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“Consagre ao Senhor tudo que você faz, e seus planos serão bem-sucedidos.”

Salomão

RESUMO

O Agregado de Trióxido Mineral (MTA) possui uma natureza bioativa e biocompatível, tendo a capacidade de interagir com o tecido receptor, estimulando seu reparo e regeneração; é o material considerado padrão de referência para tratamentos conservadores pulpares e para avaliações científicas. Este material é considerado o padrão de referência para avaliações científicas. O estudo bibliométrico é um método científico que permite mapear e fornecer uma perspectiva histórica sobre a evolução científica, além de revelar tendências de pesquisas e a interconexão entre pesquisadores e grupo de estudo. Novos materiais biocerâmicos têm sido utilizados na prática clínica, como o Biodentine e o CIMMO DTA, indicados como substitutos dentinários bioativos. O objetivo deste estudo foi identificar os principais estudos sobre cimentos biocerâmicos na endodontia e avaliar a biocompatibilidade, e a bioatividade dos cimentos Biodentine e CIMMO DTA, em comparação ao MTA branco (Angelus). Uma estratégia ampla de busca com principais termos relacionados a cimentos biocerâmicos na endodontia foi conduzida na “*Web of Science “Core Collection”*” (WoS-CC). Os dados foram recuperados e organizados em ordem decrescente do número de citações na WoS-CC, cada artigo foi comparado com o número de citações no *Scopus* e no Google Acadêmico. Para as redes de coautoria foi utilizado para a construção o *software VOSviewer*. As correlações de *Spearman* foram realizadas usando o *software Statistical Package for Social Sciences* (SPSS). Foram utilizados camundongos Balb/c para obtenção das células e para análise da biocompatibilidade e bioatividade. A pesquisa foi enviada para Comissão de Ética no Uso em Animais (CEUA) da Universidade Federal de Minas Gerais (UFMG) e foi aprovada. Para a análise *in vivo*, tubos contendo os materiais ou vazios (controle) foram inseridos de forma aleatória no tecido subcutâneo dos animais. Aos 7 e 30 dias os animais foram eutanasiados para análise do infiltrado inflamatório, pela técnica de hematoxilina e eosina; e análise da bioatividade, por meio da análise de luz polarizada e técnica de von Kossa. As análises dos dados foram feitas utilizando o programa estatístico SPSS.

Palavras-chave: Agregado de Trióxido Mineral; biocompatibilidade; cimentos biocerâmicos; endodontia; inflamação.

ABSTRACT

BIBLIOMETRIC STUDY AND IN VIVO ANALYSIS OF THE BIOCOMPATIBILITY AND BIOACTIVITY OF BIOCERAMIC CEMENTS IN ENDODONTICS

Mineral Trioxide Aggregate (MTA) has a bioactive and biocompatible nature, having the ability to interact with the recipient tissue, stimulating its repair and regeneration; it is the material considered the reference standard for conservative pulp treatments and for scientific evaluations. This material is considered the gold standard for scientific research. Bibliometric analysis is a scientific method that allows for mapping and providing a historical perspective on scientific developments, as well as revealing research trends and the interconnections between researchers and study groups. New bioceramic materials, such as Biodentine and CIMMO DTA, have been used in clinical practice, as bioactive dentin substitutes. The objective of this study was to identify the main studies on bioceramic cements in endodontics and evaluate the biocompatibility and bioactivity of Biodentine and CIMMO DTA cements compared to white MTA (Angelus). A broad search strategy using the main terms related to bioceramic cements in endodontics was conducted in the Web of Science Core Collection (WoS-CC). Data were retrieved and organized in descending order of the number of WoS-CC references, and each article was compared with the number of references in Scopus and Google Scholar. Co-authorship networks were constructed using the VOSviewer software. Spearman's correlations were performed using the Statistical Package for Social Sciences (SPSS) software. Balb/c mice were used for cell collection and biocompatibility and bioactivity analysis. Cells were analyzed using the hematoxylin and eosin technique; and bioactivity was analyzed using polarized light analysis and the von Kossa technique. Data analyses were performed using the SPSS statistical program.

Keywords: Mineral Trioxide Aggregate; biocompatibility; bioceramic cements; endodontics; inflammation.

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LISTAS DE ABREVIATURAS E SIGLAS

CEUA Comissão de Ética no Uso dos Animais

CEBIO Centro de Bioterismo

MTA Agregado de Trióxido Mineral

UFMG Universidade Federal de Minas Gerais

PVPI 5% Iodo Povidona

ICB Instituto de Ciências Biológicas

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1 CONSIDERAÇÕES INICIAIS

A polpa dentária é um tecido conjuntivo frouxo encontrado no interior dos tecidos duros dos dentes. Quando exposta a danos como cáries ou fratura dentária, ela corre risco de infecção, o que pode levar à dor, necrose e infecção do osso e tecidos circundantes (Morotomi, Washio, Kitamura, 2018). A endodontia tem sido o tratamento de escolha para exposições pulpares de origem cariosa. Porém, a terapia de polpa vital tem sido alternativa potencial ao tratamento endodôntico; ela visa tratar os dentes com polpa dentária comprometida sem a remoção e/ou sem a remoção completa do tecido pulpar saudável (Wells, Dulong, McCormack, 2019).

O sucesso da terapia de polpa vital depende de uma variedade de fatores, incluindo a quantidade de tecido infectado, um suprimento sanguíneo adequado para o dente, periodonto saudável e a oportunidade de criar um selamento coronal apropriado. Manter a vitalidade pulpar é um interesse do clínico como uma alternativa ao tratamento endodôntico, já que a capacidade de restaurar ou salvar a polpa vital pode ser benéfico para os pacientes (Wells, Dulong, McCormack, 2019). Além disso, desde que o estado da polpa seja favorável, os procedimentos de proteção pulpar com materiais bioativos podem ser realizados (Arandi, Thabet, 2021).

A terapia pulpar vital objetiva então preservar e manter a vitalidade do tecido pulpar em dentes que foram comprometidos por trauma, cárie ou procedimento restaurador. Os tratamentos mais conservadores incluem o capeamento pulpar indireto, capeamento pulpar direto, pulpotomias parcial e completa (Ghoddusi, Forghani, Parisay, 2014). Sabe-se que os cimentos biocerâmicos à base de silicato de cálcio têm sido indicados há anos e que vários tipos de células estão envolvidos em mudanças de comportamento biológico quando estes materiais são utilizados. Por exemplo, os cimentos biocerâmicos influenciam positivamente o comportamento biológico das células-tronco da polpa dentária após capeamento pulpar (Song *et al.*, 2021, Torabinejad; Chivian, 1999).

A introdução dos cimentos à base de silicato de cálcio causou mudança de paradigma no tratamento conservador de cáries profundas na terapia pulpar vital. No passado, o material de escolha era apenas o hidróxido de cálcio, já que ele é capaz

de estimular a formação de dentina terciária, porém este material tem demonstrado grandes desvantagens pela sua dissolução ao longo do tempo (Arandi, Thabet, 2021).

O Agregado de Trióxido Mineral (MTA) foi desenvolvido na universidade de Loma Linda por Mahmoud Torabinejad, em 1993. Foi o primeiro material à base de silicato de cálcio, formulado a partir de cimento Portland comercial, combinado a um radiopacificador. Este cimento possui natureza bioativa e biocompatível, tendo a capacidade de interagir com o tecido receptor, estimulando seu reparo e regeneração; é o material considerado padrão de referência para tratamentos conservadores pulpares e para avaliações científicas (Reyes-Carmona *et al.*, 2009, Scarparo, Haddad; Acasigua, 2010, Torabinejad; Chivian, 1999).

No entanto, o MTA apresenta algumas desvantagens, como a dificuldade de manipulação, falta de escoamento, e escurecimento da coroa dentária (Rezende *et al.*, 2007, Vasconcellos *et al.* 2022). Além do MTA, novos cimentos à base de silicato de cálcio estão sendo desenvolvidos com o objetivo de manter as propriedades do seu precursor, porém, superando suas desvantagens, dentre eles estão os cimentos Biodentine e CIMMO DTA.

O Biodentine (Septodont, Saint-Maurdes-Fossés, França) foi introduzido no mercado em 2011, e de acordo com o fabricante, é indicado como um substituto dentinário bioativo podendo ser utilizado na dentística restauradora, na endodontia e na odontopediatria. É utilizado para capeamento pulpar direto e indireto, pulpotomias, base de restaurações, e lesões cervicais ou radiculares profundas. Foi relatado que esse material demonstra melhores propriedades mecânicas, melhor estabilidade de cor, menos escurecimento do dente, fácil aplicação, e tempo de presa adequado (Arandi, Thabet, 2021). Outro material desenvolvido recentemente para base e forramento de restaurações é o cimento CIMMO DTA. De acordo com o fabricante, é indicado como dessensibilizante dentinário, para proteção pulpar direta e indireta, adequação do meio para dentes decíduos e permanentes e como substituto de dentina perdida.

A análise bibliométrica é um método científico que permite mapear e fornecer uma perspectiva histórica sobre a evolução científica, além de revelar tendências de pesquisas e a interconexão entre pesquisadores e grupo de estudo (Andrade-Maia *et al.*, 2024). Nessa metodologia pode ser identificado os principais estudos sobre um determinado tópico revelando tendências de pesquisa além de outros dados como os

principais autores, periódicos e países com maior atividade de publicação (Mourão *et al.*, 2024).

Considerando que ainda existem informações limitadas sobre o novo cimento biocerâmico CIMMO DTA, são necessários estudos laboratoriais, para conhecer suas propriedades, sendo assim evidências científicas poderão respaldar o uso clínico desse material. O objetivo deste estudo será identificar através de estudo bibliométrico os 100 principais estudos sobre cimentos biocerâmicos em endodontia revelando tendências de pesquisa, além de outros dados com maior atividade de publicação. E avaliar a biocompatibilidade e a bioatividade dos cimentos Biodentine e CIMMO DTA, comparados ao MTA branco (Angelus).

2 OBJETIVOS

2.1 Objetivo geral

- Constatar os 100 artigos mais citados sobre cimentos biocerâmicos em endodontia;
- Avaliar a biocompatibilidade e bioatividade de cimentos biocerâmicos.

2.2 Objetivos específicos

- Avaliar a biocompatibilidade dos cimentos MTA, Biodentine e CIMMO DTA em camundongos, através da coloração de hematoxilina e eosina;
- Analisar a capacidade de bioatividade destes materiais por meio da técnica de luz polarizada em von Kossa.

3 METODOLOGIA EXPANDIDA

3.1 Estudo Bibliométrico

Uma busca de artigos sobre o tema principal foi conduzida na *Web of Science "Core Collection"* (WoS-CC) em 30 de maio de 2025, usando uma ampla estratégia de busca com principais termos relacionados a cimentos biocerâmicos em endodontia. Uma equipe formada por cinco pesquisadores realizou a busca e seleção dos artigos até que os 100 artigos mais citados sobre o tema foram identificados.

Os dados foram recuperados e foram organizados em ordem decrescente do número de citações na WoS-CC, que foi o principal critério para classificar a posição final dos artigos nesta lista dos 100 melhores. No mesmo dia da busca, o número de citações recebidas por artigos *Scopus* e no Google Acadêmico foi coletado. Em caso de empate, a posição de um artigo na lista foi baseada na maior densidade de citações do WoS-CC (número de citações por ano), seguida pelo maior número de citações no *Scopus*. Foram estabelecidos critérios de elegibilidade: 1- critérios de inclusão: artigos com foco principal no estudo de cimentos biocerâmicos na área de endodontia e 2- critérios de exclusão: editoriais e artigos de conferência.

Para cada artigo incluído na lista dos 100 mais citados, os seguintes dados foram extraídos: título do artigo, número de citações, densidade de citações, tema do estudo, autoria, periódico, tipo de biocerâmico, desenho do estudo, objetivo do estudo, ano de publicação, instituição, país e continente (com base na afiliação do autor correspondente) da publicação.

Os dados foram analisados e qualquer discordância na extração foi resolvida por meio de discussão e consenso dos autores. Todos os artigos foram revisados e classificados de acordo com as categorias definidas.

Para as redes de coautoria foi utilizado para a construção o *software VOSviewer*. Os nomes dos autores foram introduzidos como uma unidade de análise, já as proporções de itens foram determinadas pelo número de artigos de autoria. Os *clusters* nas redes são compostos por um grupo de nós intimamente relacionados e os círculos maiores indicam termos mais importantes. As linhas conectam itens que designam um relacionamento existente, com linhas mais grossas indicando uma forte conexão entre dois itens e os termos com relacionamentos fortes são posicionados próximos uns dos outros (Adrade-Maia *et al.*, 2024, Mourão *et al.*, 2023). As

correlações de *Spearman* foram realizadas usando o *software Statistical Package for Social Sciences (SPSS 22.0)*.

3.2 Áreas de estudo e Universo

A pesquisa foi desenvolvida na cidade de Belo Horizonte, MG, na Faculdade de Odontologia da Universidade Federal de Minas Gerais (UFMG) no Laboratório de Gnotobiologia e Imunologia (ICB/UFMG) em parceria com o biotério da UFMG seguindo as normas e regras da Comissão de Ética no uso de Animais (CEUA).

3.3 Animais

A pesquisa foi enviada para o CEUA e foi aprovada. Foram utilizados 16 camundongos Balb/c machos de 8 semanas. Os animais foram mantidos com barreiras, em gaiolas de 20cm x 30cm x 20cm, com controle de luminosidade, temperatura, ração e água *ad libitum* no biotério do ICB.

3.3.1 Divisão dos grupos

Grupo 1: Cimento MTA (Angelus, Londrina, Paraná, Brasil);

Grupo 2: Cimento Biodentine (Septodont, Saint-Maurdes-Fossés, França);

Grupo 3: CIMMO DTA (CIMMO, Pouso Alegre, Minas Gerais, Brasil);

Grupo 4: Vazios (controle).

3.4 Análise *in vivo*

3.4.1 Procedimento cirúrgico

Os animais foram anestesiados, via intraperitoneal (80 mg/Kg de cetamina, e 10 mg/Kg de xilazina), e em seguida foi feita a tricotomia da região dorsal e a antisepsia da região com Iodo Povidona PVPI 5% com a finalidade de evitar contaminação do campo cirúrgico. Para o procedimento foi feita incisão com lâmina de bisturi número 15, no dorso do animal, (tendo a coluna vertebral como linha média de marcação). Após a divulsão do tecido subcutâneo para o lado esquerdo e direito

da porção cranial e caudal, foi formado uma bolsa. Logo em seguida foi inserido um tubo com material em cada bolsa formada com auxílio de uma pinça reta. Cada animal recebeu dois tubos preenchidos com os materiais a serem estudados. O tecido foi suturado com fio de seda 4.0 e antissepsia final foi realizada com solução de PVPI 5%.

Após 7 e 30 dias, os animais foram anestesiados com sobredose anestésica seguida do deslocamento cervical. Logo após, tendo a linha média como marcação, foi realizada uma nova incisão com lâmina de bisturi número 15 no dorso do animal, e trinta e dois tubos de polietileno (n = 8 tubos/grupo) (Abbot Lab. Do Brasil Ltda., São Paulo) foram localizados, removidos juntamente com os tecidos que os envolvem e foram fixados em solução formalina neutra por até 24h (Benetti *et al.*, 2018). As peças foram lavadas em água corrente por 12h, para a remoção de toda solução de fixação. Posteriormente, foram desidratadas em álcool, diafanizadas em xilol e incluídas em parafina. As peças foram cortadas com cortes semi-seriados em micrótomo (Leica - RM 2045, Buffalo Grove, IL, USA), em cortes de 5µm para análise do infiltrado inflamatório em hematoxilina-eosina, e 10µm para análise da bioatividade sob luz polarizada e von Kossa. As análises foram realizadas por um avaliador cego e previamente calibrado.

3.4.2 Análise dos resultados

A reação tecidual em contato com o material na extremidade dos tubos foi avaliada por meio de escores, sendo: 0, células inflamatórias ausentes ou em número desprezível; 1, menos de 25 células por campo/inflamação leve; 2, entre 25 e 125 células por campo/ inflamação moderada; e 3, mais que 125 células por campo/ inflamação severa (examinados em aumento de 400x) (Cintra *et al.*, 2017; Benetti *et al.*, 2018). A cápsula fibrosa foi considerada fina se menor que 150µm, e espessa se igual ou maior a 150µm. Para bioatividade, estruturas birrefringentes à luz polarizada e von Kossa foram registradas como presentes ou ausentes.

3.5 Análise estatística

Para o estudo bibliométrico os dados foram recuperados e organizados em ordem decrescente do número de citações na WoS-CC, cada artigo foi comparado

com o número de citações no *Scopus* e no Google Acadêmico. Para as redes de coautoria foi utilizado para a construção o *software VOSviewer*. As correlações de *Spearman* foram realizadas usando o *software Statistical Package for Social Sciences* (SPSS 22.0).

Para o estudo em animais os dados foram avaliados pelos testes de Kruskal-Wallis seguido pelo teste de Dunn ($p < 0,05$). As comparações entre os grupos nos diferentes períodos experimentais foram submetidas à análise estatística com o programa estatístico SPSS (SPSS 14.0).

4 ARTIGO 1

Bioceramic Cements in Endodontics: a bibliometric analysis of the 100 most cited articles

Betânia de Lourdes Canal Vasconcellos, Luna Chagas Clementino, Thiago César da Silva Lima, Caroline Andrade Maia, Gabriele Andrade-Maia, Paulo Antônio Martins-Júnior, Francine Benetti, Warley Luciano Fonseca Tavares

Abstract

Introduction: This study analyzes the characteristics of the 100 most cited articles on bioceramic cements in endodontics.

Methods: A search strategy using terms related to bioceramic cements in endodontics was conducted in the Web of Science – Core Collection (WoS-CC). Data were retrieved and organized in descending order of the number of submissions in the WoS-CC. Each article was compared with the number of requests in the Scopus and Google Scholar databases. VOSviewer software was used to identify co-authorship networks. Spearman's correlations were performed using the Statistical Package for Social Sciences (SPSS 22.0).

Results: The article with the most requests was "Physical and Chemical Properties of a New Root Canal Filling Material" by Torabinejad et al. (1995), with 821 restrictions in the WoS-CC. Of the 100 articles, the corresponding authors were predominantly from the United States (n=37). Most were published in the first decade of the 2000s (n=44). The institution of origin for most articles was Loma Linda University (USA) (n=15). Experimental laboratory studies were the most common study design among the included articles (58%), and MTA predominated in most studies (73%). Most studies focused on evaluating material properties (48%). The VOSviewer co-authorship and density map demonstrated clusters of author collaboration.

Conclusions: This list of the most cited articles can provide a reference point to guide research and material selection in clinical practice in endodontics.

Keywords: Bibliometrics, bioceramics, endodontics, biocompatibility, bioactivity.

Introduction

Calcium silicate cements were developed over 20 years ago and their composition was based on Portland cement components combined with a radiopacifier. These materials possess valuable properties, such as the ability to set and seal in humid and blood-contaminated environments, enabling their use in a variety of clinical applications. Their main limitations are their long setting time, low radiopacity, and difficult handling (1).

Mineral Trioxide Aggregate (MTA) was the first calcium silicate-based material developed. This cement was developed at Loma Linda University by Mahmoud Torabinejad in 1993. The cement is bioactive and biocompatible in nature and has the ability to interact with the recipient tissue, stimulating its repair and regeneration. It is considered the reference standard for scientific evaluations (2, 3, 4).

MTA was initially indicated as a filling material and was subsequently used for various clinical applications, such as pulp capping, pulpotomy, perforation repair, and apical barrier formation in teeth with open apices, among others. In addition to MTA, the introduction of calcium silicate cements caused a paradigm shift in endodontics (9). Bibliometric analysis is a scientific method that allows mapping and providing a historical perspective on scientific developments, in addition to revealing research trends and the interconnections between researchers and study groups (5). This methodology can identify the main studies on a given topic, revealing research trends, as well as other data such as the main authors, journals, and countries with the highest publication activity (6, 7, 8).

No bibliometric study has addressed the topic of biceramic cements in endodontics. Therefore, the present study was designed to review the scientific literature and evaluate the characteristics of the 100 most cited articles on this topic, gathering high-quality evidence for the clinician's decision-making process regarding the use of bioceramics in clinical practice, in addition to providing a historical perspective on these materials.

Methodology

A search for articles on the main topic was conducted in the Web of Science "Core Collection" (WoS-CC) on May 30, 2025, using a broad search strategy with key terms related to bioceramic cements in endodontics. A team of five researchers conducted the search and selection of articles until the 100 most cited articles on the topic were identified. Eligibility criteria were established: 1) Inclusion criteria: articles focusing primarily on the study of bioceramic cements in endodontics; 2) Exclusion criteria: editorials and conference papers.

The data were retrieved and organized in descending order of the number of citations in WoS-CC, which was the main criterion for classifying the final position of the articles in this list of the 100 most cited. On the same day of the search and selection in WoS-CC, the number of citations received by the articles in Scopus and Google Scholar databases was also recorded. In the event of a tie, an article's position

in the list was based on the highest WoS-CC citation density (number of citations per year), followed by the highest number of citations in Scopus.

For each article included in the top 100 most cited list, the following data were extracted: article title, number of citations, citation density, study topic, authorship, journal, type of bioceramic cement, study design, study objective, year of publication, institution, country, and continent (based on the affiliation of the corresponding author of the publication). The data were analyzed, and any disagreements during extraction were resolved through discussion and consensus among the authors. All articles were reviewed and classified according to the defined categories.

VOSviewer software was used to construct the co-authorship networks. Author names were introduced as the unit of analysis, while item proportions were determined by the number of articles authored. Clusters in the networks are composed of a group of closely related nodes, and larger circles indicate more important terms. Lines connect items that designate an existing relationship, with thicker lines indicating a strong connection between two items, and terms with strong relationships are positioned close to each other (5, 6). Descriptive analyses of frequencies and percentages were performed using the Statistical Package for Social Sciences (SPSS 22.0).

Results

The WoS-CC search strategy yielded a total of 5,560 articles. After displaying the list in descending order by number of citations, two articles were excluded and replaced because they did not focus on the area of interest. The 100 most cited articles on the use of bioceramic cements in endodontics are listed in Table 1. These articles received a total of 22,188 citations in WoS-CC. Additionally, the 100 most cited articles received 27,151 citations in Scopus and 59,861 citations in Google Scholar; the oldest article was published in 1993 and the most recent in 2020.

Before applying the correlation tests, the normality of the distributions was assessed using the Kolmogorov-Smirnov test. The results indicated a violation of normality for all variables analyzed—Web of Science, Scopus, and Google Scholar—with significance values below 0.001 in both tests ($p < 0.001$), justifying the use of nonparametric methods.

Therefore, Spearman's correlation test was applied to investigate the association between the three databases. A strong and statistically significant positive correlation was observed between all variables: Web of Science versus Scopus ($p < 0.001$), Web of Science versus Google Scholar ($p < 0.001$), and Scopus versus Google Scholar ($p < 0.001$). These findings suggest strong agreement in data measurement across the different scientific databases. The Spearman's rho value was 0.280 ($p = 0.005$), indicating a weak positive correlation between the number of WoS-CC citations and altimetry (95% CI: 0.083 to 0.457).

Table 1- List of the 100 most cited articles on bioceramic cements in endodontics in the databases: Web of Science, Scopus, Google Scholar and average cit

Rank	Paper	Web of Science	Scopus	Google Scholar	Mean citations
1	Physical And Chemical-Properties of a New Root-End Filling Material	821	1034	2562	1472,33
2	Mineral Trioxide Aggregate: A Comprehensive Literature Review-Part III: Clinical Applications, Drawbacks, and Mechanism of Action	794	983	1999	1258,66
3	Clinical applications of mineral trioxide aggregate	720	892	2305	1305,66
4	Mineral Trioxide Aggregate: A Comprehensive Literature Review-Part I: Chemical, Physical, and Antibacterial Properties	703	894	1867	1154,66
5	Sealing Ability Of A Mineral Trioxide Aggregate When Used As A Root End Filling Material	598	753	1972	1107,66
6	Mineral Trioxide Aggregate: A Comprehensive Literature Review-Part II: Leakage and Biocompatibility Investigations	545	687	1428	886,66
7	Sealing Ability of a Mineral Trioxide Aggregate For Repair of Lateral Root Perforations	502	636	1724	954,00
8	Physicochemical basis of the biologic properties of mineral trioxide aggregate	486	609	1400	831,66
9	Calcium silicate bioactive cements: Biological perspectives and clinical applications	356	412	661	476,33
10	The constitution of mineral trioxide aggregate	324	367	836	509,00
11	Mineral trioxide aggregate material use in endodontic treatment: A review of the literature	312	356	853	507,00
12	Mineral trioxide aggregate and other bioactive endodontic cements: an updated overview - part I: vital pulp therapy	303	341	604	416,00
13	Investigation of Mineral Trioxide Aggregate For Root-End Filling In Dogs	291	351	888	510,00
14	Histologic assessment of mineral trioxide aggregate as a root-end filling in Monkeys	289	357	833	493,00
15	Investigation of the hydration and bioactivity of radiopacified tricalcium silicate cement, Biodentine and MTA Angelus	288	344	733	455,00
16	Response of Human Dental Pulp Capped with Biodentine and Mineral Trioxide Aggregate	286	372	733	463,66
17	Mahidol Study 1: Comparison of Radiographic and Survival Outcomes of Immature Teeth Treated with Either Regenerative Endodontic or Apexification Methods: A Retrospective Study	285	339	616	413,33
18	Histologic Characterization of Regenerated Tissues in Canal Space after the Revitalization/Revascularization Procedure of Immature Dog Teeth with Apical Periodontitis	273	339	601	404,33
19	Using mineral trioxide aggregate - As a pulp-capping material	268	398	28	231,33
20	Mineral trioxide aggregate and other bioactive endodontic cements: an updated overview - part II: other clinical applications and complications	265	310	604	393,00
21	Mineral trioxide aggregate (MTA) and calcium hydroxide as pulp-capping agents in human teeth: a preliminary report	264	323	665	417,33

22	Histological, ultrastructural and quantitative investigations on the response of healthy human pulps to experimental capping with mineral trioxide aggregate: a randomized controlled trial	257	62	692	337,00
23	Bacterial Leakage of Mineral Trioxide Aggregate As A Root-End Filling Material	254	314	892	486,66
24	Comparison of the physical and mechanical properties of MTA and Portland cement	252	310	717	426,33
25	Dye Leakage Of 4 Root End Filling Materials - Effects Of Blood Contamination	249	312	874	478,33
26	Direct pulp capping with mineral trioxide aggregate - An observational study	239	293	612	381,33
27	Biominerization Ability and Interaction of Mineral Trioxide Aggregate and White Portland Cement With Dentin in a Phosphate-containing Fluid	237	299	600	378,66
28	Use of Mineral Trioxide Aggregate For Repair Of Furcal Perforations	233	298	798	443,00
29	Investigation of the physical properties of tricalcium silicate cement-based root-end filling materials	224	279	635	379,33
30	The effects of various additives on setting properties of MTA	223	285	569	359,00
31	Antibacterial Activity of Endodontic Sealers by Modified Direct Contact Test Against Enterococcus faecalis	222	279	663	388,00
32	Evaluation of Radiopacity, pH, Release of Calcium Ions, and Flow of a Bioceramic Root Canal Sealer	213	268	600	360,33
33	Cytotoxicity Of 4 Root End Filling Materials	212	244	668	374,66
34	Bioceramic-Based Root Canal Sealers: A Review	209	268	662	379,66
35	Response of the pulp of dogs to capping with mineral trioxide aggregate or a calcium hydroxide cement	201	245	604	350,00
36	Comparative Investigation Of Marginal Adaptation of Mineral Trioxide Aggregate And Other Commonly Used Root-End Filling Materials	200	254	670	374,66
37	Tooth discoloration induced by endodontic materials: a laboratory study	193	236	562	330,33
38	A Review on Biodentine, a Contemporary Dentine Replacement and Repair Material	191	236	451	292,66
39	Uptake of calcium and silicon released from calcium silicate-based endodontic materials into root canal dentine	190	252	571	337,66
40	Setting Properties and Cytotoxicity Evaluation of a Premixed Bioceramic Root Canal Sealer	188	226	508	307,33
41	Chemical modification of ProRoot MTA to improve handling characteristics and decrease setting time	188	226	416	276,66
42	Apatite-forming ability (bioactivity) of ProRoot MTA	187	215	356	252,66
43	A prospective clinical study of Mineral Trioxide Aggregate and IRM when used as root-end filling materials in endodontic surgery	186	218	493	299,00
44	Calcium silicate and calcium hydroxide materials for pulp capping: biointeractivity, porosity, solubility and bioactivity of current formulations	185	229	404	272,66
45	Comparison of CaOH with MTA for Direct Pulp Capping: A PBRN Randomized Clinical Trial	185	239	409	277,66

46	Antibacterial Effects Of Some Root End Filling Materials	182	236	681	366,33
47	Biodentine Induces Immortalized Murine Pulp Cell Differentiation into Odontoblast-like Cells and Stimulates Biom mineralization	181	227	493	300,33
48	A comparative study of root-end induction using osteogenic protein-1, calcium hydroxide, and mineral trioxide aggregate in dogs	180	238	600	339,33
49	Effects of physiological environments on the hydration behavior of mineral trioxide aggregate	179	216	468	287,66
50	Repair of root perforations using mineral trioxide aggregate: A long-term study	178	224	578	326,66
51	The sealing ability and retention characteristics of mineral trioxide aggregate in a model of apexification	177	224	536	312,33
52	Regenerative Potential of Immature Permanent Teeth with Necrotic Pulps after Different Regenerative Protocols	176	218	364	252,66
53	Dissolution of bio-active dentine matrix components by mineral trioxide aggregate	175	209	371	251,66
54	Cell and tissue reactions to mineral trioxide aggregate and Portland cement	168	207	530	301,66
55	Effect of a Calcium-silicate-based Restorative Cement on Pulp Repair	161	200	406	255,66
56	Properties of a new root-end filling material	161	197	420	259,33
57	Mineral Trioxide Aggregate Obturation: A Review and Case Series	160	185	445	263,33
58	Effect of bismuth oxide radioopacifier content on the material properties of an endodontic Portland cement-based (MTA-like) system	159	187	375	240,33
59	The use of mineral trioxide aggregate in one-visit apexification treatment: a prospective study	159	209	537	301,66
60	Effect of mineral trioxide aggregate on proliferation of cultured human dental pulp cells	158	175	315	216,00
61	Long-term evaluation of pulpotomy in primary molars using mineral trioxide aggregate or formocresol	156	181	423	253,33
62	Apatite formation on bioactive calcium-silicate cements for dentistry affects surface topography and human marrow stromal cells proliferation	155	175	254	194,66
63	MTA-An Hydraulic Silicate Cement: Review update and setting reaction	154	182	379	238,33
64	Mineral Trioxide Aggregate or Calcium Hydroxide Direct Pulp Capping: An Analysis of the Clinical Treatment Outcome	152	196	365	237,66
65	pH and calcium ion release of 2 root-end filling materials	152	188	495	278,33
66	Clinical Outcome of Non-Surgical Root Canal Treatment Using a Single-cone Technique with Endosequence Bioceramic Sealer: A Retrospective Analysis	151	163	294	202,66
67	Bioactivity evaluation of three calcium silicate-based endodontic materials	151	190	420	253,66
68	The chemical constitution and biocompatibility of accelerated Portland cement for endodontic use	151	194	423	256,00

69	Evaluation of mineral trioxide aggregate and calcium hydroxide cement as pulp-capping agents in human teeth	150	178	381	236,33
70	Treatment Outcome of Mineral Trioxide Aggregate or Calcium Hydroxide Direct Pulp Capping: Long-term Results	149	170	323	214,00
71	Cytotoxicity of endodontic materials	149	177	445	257,00
72	Endodontic sealers based on calcium silicates: a systematic review	148	167	315	210,00
73	Chemical-physical properties of TheraCal, a novel light-curable MTA-like material for pulp capping	144	192	420	252,00
74	Comparison of mineral trioxide aggregate and formocresol as pulp-capping agents in pulpotomized primary teeth	144	176	402	240,66
75	Partial Pulpotomy in Mature Permanent Teeth with Clinical Signs Indicative of Irreversible Pulpitis: A Randomized Clinical Trial	143	166	283	197,33
76	Mineral trioxide aggregate: A new material for endodontics	143	190	601	311,33
77	The dentinogenic effect of mineral trioxide aggregate (MTA) in short-term capping experiments	142	171	428	247,00
78	Retrospective analysis of open apex teeth obturated with mineral trioxide aggregate	138	166	383	229,00
79	The properties of a new endodontic material	138	246	508	297,33
80	Calcium silicate-based cements: composition, properties, and clinical applications	136	156	321	204,33
81	Direct Pulp Capping with Calcium Hydroxide or Mineral Trioxide Aggregate: A Meta-analysis	136	168	300	201,33
82	Color Stability of White Mineral Trioxide Aggregate in Contact with Hypochlorite Solution	135	168	293	198,66
83	Dentin Moisture Conditions Affect the Adhesion of Root Canal Sealers	135	173	391	233,00
84	Adhesion of human osteoblasts on root-end filling materials	135	158	386	226,33
85	Radiopacity of Portland Cement Associated With Different Radiopacifying Agents	134	168	322	208,00
86	Comprehensive review of current endodontic sealers	133	169	361	221,00
87	The effect of mineral trioxide aggregate on the apexification and periapical healing of teeth with incomplete root formation	133	168	418	239,66
88	Regenerative Endodontic Treatment or Mineral Trioxide Aggregate Apical Plug in Teeth with Necrotic Pulp and Open Apices: A Systematic Review and Meta-analysis	132	166	295	197,66
89	Coronal Tooth Discoloration and White Mineral Trioxide Aggregate	132	163	319	204,66
90	Treatment of Tooth Discoloration after the Use of White Mineral Trioxide Aggregate	132	164	309	201,66
91	The Biomineralization Ability of Mineral Trioxide Aggregate and Portland Cement on Dentin Enhances the Push-out Strength	132	163	333	209,33
92	Clinical outcomes of artificial root-end barriers with mineral trioxide aggregate in teeth with immature apices	129	154	351	211,33
93	Bio-Inductive Materials in Direct and Indirect Pulp Capping-A Review Article	128	157	260	181,66

94	Radiographic and Clinical Outcomes of the Treatment of Immature Permanent Teeth by Revascularization or Apexification: A Pilot Retrospective Cohort Study	126	159	295	193,33
95	Changes in the surface of four calcium silicate-containing endodontic materials and an epoxy resin-based sealer after a solubility test	126	166	356	216,00
96	Mineral trioxide aggregate pulpotomies - A case series outcomes assessment	126	148	356	210,00
97	Histological and scanning electron microscopy assessment of various vital pulp-therapy materials	126	146	309	193,66
98	Effect of Various Endodontic Irrigants on the Push-out Bond Strength of Biodentine and Conventional Root Perforation Repair Materials	123	148	370	213,66
99	Properties of BioRoot RCS, a tricalcium silicate endodontic sealer modified with povidone and polycarboxylate	122	151	286	186,33
100	Five-Year Longitudinal Assessment of the Prognosis of Apical Microsurgery	122	134	231	162,33

The most cited article was "Physical and chemical properties of a new root-end filling material," by Torabinejad et al. (1995), with 821 citations in WoS-CC, 1,034 in Scopus, and 2,562 in Google Scholar. The Journal of Endodontics published in 1995 cited the most frequently cited articles.

Most of the most cited articles came from Anglo-Saxon America (38 articles; 10,520 citations), followed by Europe (28 articles; 5,248 citations) and Asia (20 articles; 3,819 citations). Latin America was represented by Brazil (9 articles; 1,478 citations) and Venezuela (1 article; 149 citations), totaling 10 articles; 1,627 citations. Africa (1 article; 176 citations) also accounted for the most frequently cited articles. Furthermore, Oceania (28 articles; 5,248 citations) was the country with the most frequently cited articles (Figure 1).

Loma Linda University, in the United States of America (15 articles; 6216 citations) was the institution with the most articles among the top 100, followed by the University of Bologna, in Spain (6 articles; 1149 citations) and the University of Malta, Europe (four articles; 798 citations) (Table 2).

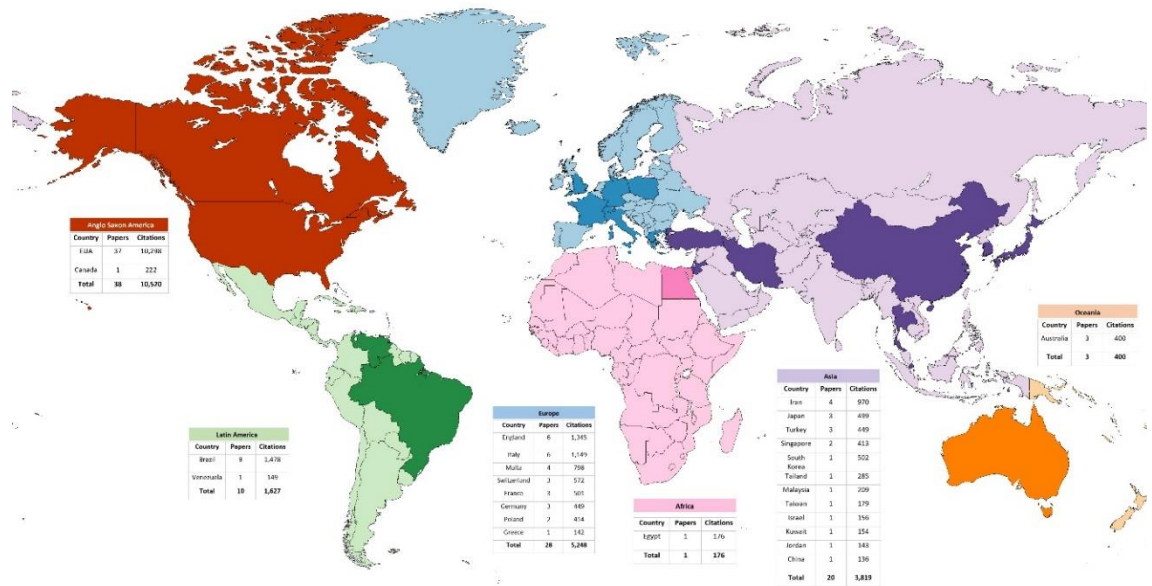


Figure 1. Global distribution of the 100 most cited articles on bioceramic cements in endodontics.

Table 2. List of institutions where two or more of the most published articles on bioceramic cements in endodontics were developed.

Institution (country)	Number of articles	Number of citations WoS-AD
Loma Linda University (USA)	15	6,216
University of Bologna (Italy)	6	1,149
University of Malta (Malta)	4	798
Federal University of Santa Catarina (Brazil)	3	502
Texas A&M University (USA)	3	500
University of Melbourne (Australia)	3	400
Kerman University of Medical Sciences (Iran)	2	568
King's College London (England)	2	510
United States Air Force (USA)	2	455
National University of Singapore (Singapore)	2	413
Shahid Beheshti University (Iran)	2	402
University of Birmingham (England)	2	334
Niigata University (Japan)	2	341
INSERM (France)	2	340
University of Texas Center at San Antonio (USA)	2	306
University of Connecticut (USA)	2	303
Ruprecht-Karls-University of Heidelberg (Germany)	2	301
Sagrado Coração University (Brazil)	2	286

Analysis of studies published between 1993 and 2020 revealed a predominance of laboratory experimental designs (in vitro, in vivo, and ex vivo), which accounted for 58% of the sample, especially in the first two decades. A progressive methodological expansion was observed over the years, with the emergence of non-systematic reviews (14%), observational studies (11%), and clinical trials (10%), especially since the 2000s.

This diversification was accompanied by a gradual shift in the type of cement evaluated: while MTA predominated in 73% of studies, the presence of other bioactive cements intensified after 2009, representing 17% of publications, with 10% of studies involving comparisons between MTA and other materials. Starting in 2011, this balance became more evident, particularly in 2015 and 2016, when there was a more even distribution among the different methodologies and materials analyzed.

Regarding the objectives of the studies, most focused on evaluating material properties (chemical, physical, and biological), representing 48% of the total, with greater frequency between 2005 and 2013. Vital pulp therapy was the second most common objective (21%), distributed evenly throughout the years, while topics such as filling (11%), drilling (4%), and endodontic surgery (6%) were less explored. In this study, research on the treatment of immature teeth (10%) appeared after the year 2000. It was also noted that studies with multiple simultaneous clinical applications represented a small fraction (2%). These findings indicate a trajectory that, over the decades, has evolved consistently, incorporating different methodological designs, broader clinical objectives, and diversity in the selection of materials analyzed.

Table 3. Objective of the study of the most cited articles on bioceramic cements in endodontics.

Study Objective	%
Material Properties	48,0
Vital Pulp Therapy	21,0
Filling	11,0
Treatment of immature teeth	8,0
Endodontic surgery	6,0
Perforations	4,0
More than one clinical application	2,0
Total	100,0

Table 4. Materials studied from the most cited articles on bioceramic cements in endodontics.

Material	%
MTA	73,0
Bioactive cements	17,0
More than one material	10,0
Total	100,0

Discussion

This bibliometric study identified and analyzed the 100 most cited articles on the use of bioceramics in endodontics. This scientific method was applied to classify citations in several well-known databases and to provide a better understanding of global research in this field. Furthermore, a concurrent analysis was conducted to investigate collaboration networks, research groups, and the most productive countries and universities on the topic. In terms of absolute citation numbers, the top 100 articles received a total of 22,188 citations in the WoS-CC. Comparing this finding with that of other bibliometric studies in dentistry, this number is similar to that of other fields, such as laser use (10) and quality of life (7).

The most productive decade was from 2000 to 2010. These results may be associated with advances in technologies and materials that drove scientific growth during this period, which was considered the era of exponential growth in scientific publications. Citations generally depend on the time of publication; therefore, older articles have been in global circulation for a longer period and are more likely to receive additional citations, even without considering their scientific value. In this case, it is necessary to consider not only total citations but also citation density; this strategy was also used in this bibliometric study (5, 6, 7).

The country with the highest number of publications was the United States, with Mahmoud Torabinejad, the author who published the most on the topic, developing the first bioceramic cement (4). This attests to the leadership and tradition of American institutions in this area (11, 12). Brazil appears as the second country with the most publications, with its centers and research groups on bioceramic cements in endodontics demonstrating the productivity of Brazilian articles (13, 14, 15). The

intense collaboration between institutions in the publication of the 100 most cited articles, evidenced in the authorship maps (Figures 2 and 3), was also highlighted.

As the use of bioceramic cements has become more common, their chemical, physical, and biological properties were relevant in this investigation, as evidenced by the large number of laboratory studies (11, 12, 16). These studies allow for well-controlled environments and reduce confounding factors, and are important models for testing new materials and protocols (17). Articles cited at least 400 times are considered classics (17). In this study, the most cited article received 821 citations in WoS-CC, identifying its relevance in the research environment (16, 18).

The results found in this study reinforce the growing need for rigorous clinical trials, as the positive physicochemical and biological properties observed *in vitro* require validation under clinical conditions. Clinical trials are essential to demonstrate the efficacy, safety, and durability of these materials in various clinical applications. Therefore, incorporating robust clinical data is essential to consolidate the use of bioceramic cements as a therapeutic standard, while also guiding the development of improved formulations and clinical application strategies (19, 20).

To date, no bibliometric study has been conducted based on the analysis of the most cited articles on bioceramic cements in endodontics in consolidated databases. Therefore, this work fills this gap by offering a comprehensive and descriptive overview of the scientific literature related to these materials. This analysis is essential to guide future research, identify emerging trends, and consolidate a reference point for scholars and professionals in the field, contributing to advancement and innovation in the field of endodontic materials.

Conclusion

This bibliometric analysis highlighted the characteristics of the 100 most cited articles on bioceramic cements in endodontics, demonstrating that these materials have brought about a paradigm shift and offered alternatives for adverse clinical situations. This list of the most cited articles can provide a reference point to guide future research and material selection in clinical practice in endodontics.

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4 ARTIGO 2

Biocompatibility and bioactivity of new formulations of CIMMO DTA and Biodentine bioceramic materials

Betânia de Lourdes Canal Vasconcellos, Caroline Andrade Maia, Larissa Fassarella Marquiore, Francine Benetti, Warley Luciano Fonseca Tavares.

Abstract

The aim of this study was to evaluate the biocompatibility and bioactivity of the bioceramic cements CIMMO DTA and Biodentine, in comparison with the white mineral trioxide aggregate (MTA) (Angelus). For this purpose, 32 polyethylene tubes (n = 8 tubes/group) were filled with the materials or remained empty for control, and were randomly implanted in the back of 16 Balb/c mice, with 2 tubes per animal (CEUA-UFMG 332/2023). After 7 and 30 days (n = 4), the animals were euthanized and the samples processed for analysis of biocompatibility, in hematoxylin-eosin, and bioactivity, under polarized light and von Kossa. Data were analyzed using the Kruskal-Wallis and Dunn tests ($p < 0.05$). At 7 days, most specimens in the Control, MTA, Biodentine, and CIMMO DTA groups showed moderate inflammation ($p > 0.05$). At 30 days, a reduction in inflammation was observed in all groups, with predominantly mild inflammation in Control, MTA, and Biodentine, while CIMMO DTA showed mild to moderate inflammation, but with no significant difference between groups ($p > 0.05$). Furthermore, at 7 days, the fibrous capsule was thick in all Biodentine and CIMMO DTA specimens and in half of the MTA and Control specimens, and at 30 days, the fibrous capsule was thin for all specimens in all groups. Regarding bioactivity, all materials presented birefringent structures under polarized light and von Kossa positivity at 7 and 30 days. It was concluded that CIMMO DTA and Biodentine were biocompatible and promoted bioactivity similar to white MTA (Angelus).

Keywords: biocompatibility, bioactivity, mineral trioxide aggregate, bioceramic, inflammation.

Introduction

Endodontics has been the treatment of choice for pulp exposures of carious origin. As long as the pulp condition is favorable, pulp protection procedures with bioactive materials can be performed (Arandi & Thabet 2021). It is known that calcium silicate-based bioceramic cements have been indicated for years and that several cell types are involved in changes in biological behavior when these materials are used. For example, bioceramic cements positively influence the biological behavior of dental pulp stem cells after pulp capping (Song et al., 2021; Torabinejad & Chivian 1999).

Vital pulp therapy aims to preserve and maintain the vitality of pulp tissue in teeth that have been compromised by trauma, caries or restorative procedures. More conservative treatments include indirect pulp capping, direct pulp capping, partial and complete pulpotomies (Ghoddusi et al., 2014). The introduction of calcium silicate-based cements caused a paradigm shift in the conservative treatment of deep caries in vital pulp therapy. In the past, the material of choice was only calcium hydroxide, as it is capable of stimulating the formation of tertiary dentin, however, this material has shown major disadvantages due to its dissolution over time (Arandi & Thabet 2021).

Mineral Trioxide Aggregate (MTA) was developed at Loma Linda University by Mahmoud Torabinejad in 1993. It was the first calcium silicate-based material, formulated from commercial Portland cement combined with a radiopacifier. This cement is bioactive and biocompatible in nature and has the ability to interact with the recipient tissue, stimulating its repair and regeneration; MTA is considered the gold standard material for conservative pulp treatments, and is a reference for scientific evaluations (Torabinejad & Chivian 1999; Reyes-Carmona et al., 2011, Scarparo et al., 2010)

However, MTA has some disadvantages, such as difficulty in handling, lack of flow, and in the past, darkening of the dental crown (Rezende et al., 2007). In addition to MTA, new calcium silicate-based cements are being developed with the aim of maintaining the properties of their precursor, but overcoming their disadvantages, among them are Biodentine and CIMMO DTA cements.

Biodentine was introduced to the market in 2011. According to the manufacturer, it is indicated as a bioactive dentin substitute and can be used in restorative dentistry, endodontics, and pediatric dentistry. It is used for direct and indirect pulp capping, pulpotomies, restoration bases, and deep cervical or root lesions. It has been reported that this material demonstrates better mechanical properties, better color stability, less tooth darkening, easy application, and adequate setting time (Arandi & Thabet 2021). Another material recently developed for restoration bases and linings is Cimmo DTA cement. It is indicated as a dentin desensitizer, for direct and indirect pulp protection, adaptation of the environment for deciduous and permanent teeth, and as a substitute for lost dentin.

To date, literature is scarce regarding the new bioceramic cement CIMMO DTA. The aim of this study was to evaluate the biocompatibility and biomineralization of CIMMO DTA and Biodentine, compared to white MTA-Ang. The null hypothesis was

that there would be no difference between the materials in relation to (1) biocompatibility and (2) bioactivity.

Material and Methods

The manuscript of this animal study has been written according to Preferred Reporting Items for Animal studies in Endodontology (PRIASE) guidelines.

Subcutaneous implants

Sixteen 8-week-old BALB/c male mice (weighing approximately 20g) were used in this study and were kept in an environment with temperature (22-24 °C) and light control (12 h light-dark cycle) and were provided with water and food ad libitum. The study was approved by the local ethical committee (CEUA-UFMG 332/2023) and conducted according to the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health (Bethesda, MD, USA).

Thirty two polyethylene tubes (n = 8 tubes/group) (Abbot Lab. Do Brasil Ltda., São Paulo), were randomly implanted in the back of 16 Balb/c mice, 2 tubes per animal. With 1.0 mm internal diameter, 1.6 mm external diameter and 10.0 mm length (ISO 10993-6:2007), the tubes were filled with white-MTA, CIMMO DTA or Biodentine, prepared according to the manufacturer's recommendations; and empty tubes were used as control group.

After anaesthesia, the animals had their dorsa shaved, and after the antisepsis with 5% iodine solution, a 2-cm incision was made in a head-to-tail orientation with a blade of #15. The skin was reflected to create one pocket in each side of the incision. Two tubes were randomly implanted into the pockets and the skin was sutured with 4-0 silk sutures (Benetti et al., 2018).

Tissue processing and histological analysis

At 7 and 30 days (n = 4), the animals were euthanized by anesthesia overdose, and the implanted tubes, along with the surrounding tissues, were removed and fixed in 10% buffered formalin at pH 7.0. The samples were processed and included in paraffin. The paraffin blocks were serially sectioned in 5 µm for staining with haematoxylin and eosin, while 10 µm histological sections remain without staining to be observed under polarised light and von Kossa (Benetti et al., 2018; Benetti et al.,

2020).

Histological analyses were performed by a single, calibrated operator in a blinded manner, using light microscopy (DM 4000 B; Leica Microsystem, Wetzlar, Germany). The tissue inflammation was scored as follows: “1”, no or minimal inflammatory cells and no reaction; “2”, fewer than 25 cells and a mild reaction; “3”, between 25 and 125 cells and a moderate reaction; and “4”, 125 or more cells and a severe reaction (Benetti et al., 2018). Fibrous capsules were classified as thin when the thickness was less than 150 μm and thick when equal or greater than 150 μm . Birefringent structures to polarized light and von Kossa were observed and classified as present or absent in the material groups (Benetti et al., 2020).

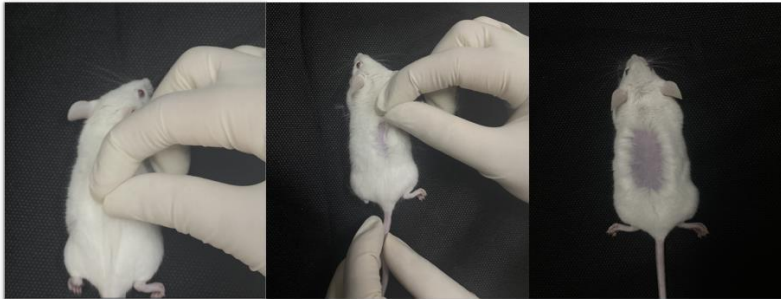


Figure 1. Antisepsis with 5% iodine solution, animals with shaved back, 2 cm incision in the head-to-tail direction with blade no. 15.

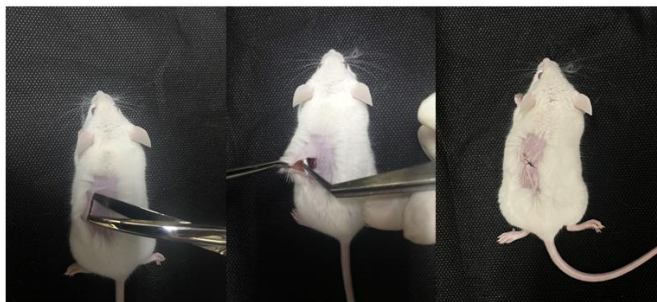


Figure 2. The skin was spread to create a pocket on each side of the incision, two tubes were randomly implanted into the pockets, the skin was sutured with 4-0 silk sutures.

Statistical Analysis

SPSS 17.0 software (SPSS Inc, Chicago IL, USA) was used. Data from *in vivo* analysis were analysed using the Kruskal-Wallis and Dunn tests. $P < 0.05$ was

considered statistically significant.

Results

Representative images of in vivo analysis can be observed in Figure 3 and data of analysis in Table 1. At 7 days, specimens from Biodentine, CIMMO DTA, MTA and control had moderate inflammation, with no significant difference between groups ($P > 0.05$); the fibrous capsule was thick for all Biodentine and CIMMO DTA samples and in half of the MTA and control samples.

At 30 days, most of the control, Biodentine and MTA specimens showed mild inflammation, while CIMMO DTA, mild to moderate inflammation, but with no significant difference between groups ($P > 0.05$); the fibrous capsule was thin for all specimens from the control, Biodentine, MTA and CIMMO DTA.

In both analysis periods, structures birefringent to polarized light and positive for von Kossa were observed in the material groups (Figure 4 and Table 1).

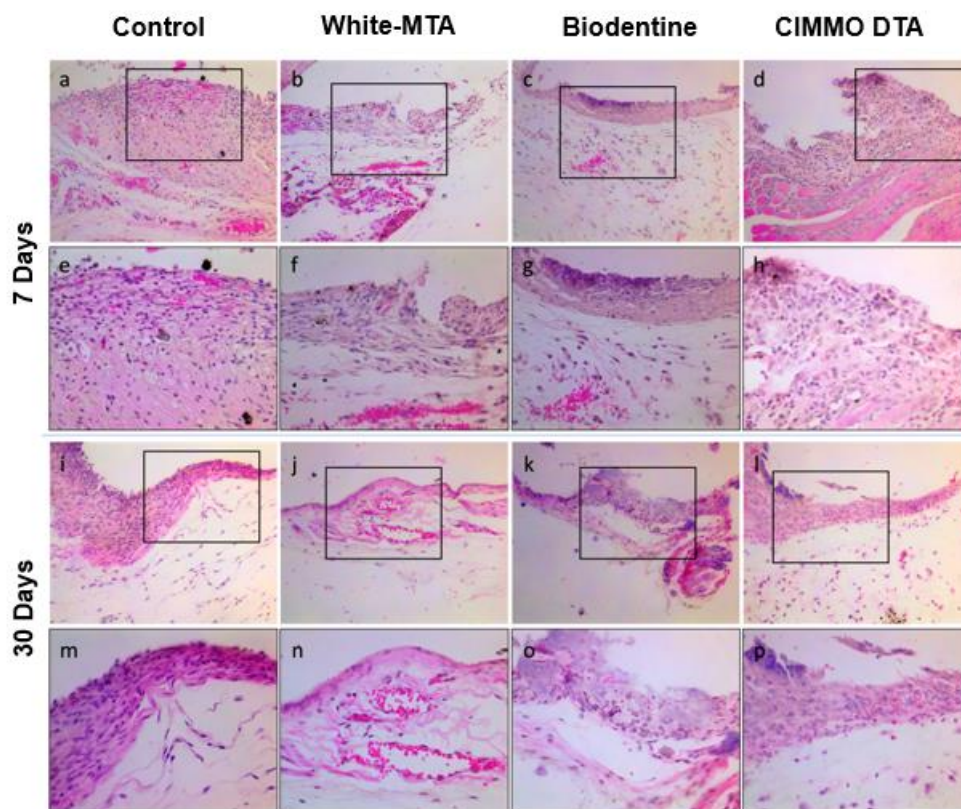


Figure 3. Images of the biocompatibility each group. The cells of the inflammatory infiltrate, thick fibrous capsule at 7 days and moderate inflammatory infiltration and thin fibrous capsule at 30 days. Hematoxylin-eosin staining, 250x, 400x.

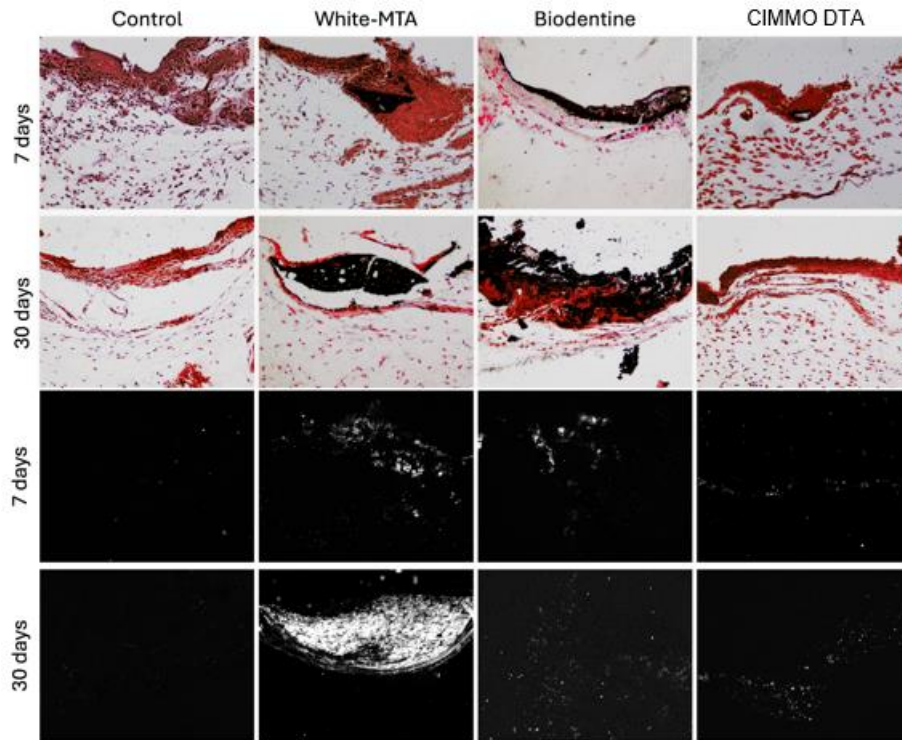


Figure 4. Representative images of bioactivity analysis at 7 and 30 days.

Table 1. Scores applied to the inflammatory infiltrate in the different groups, thickness of the fibrous capsule, and analysis of bioactivity, in each analysis period.

Period/ <i>p</i> value	Material*	Scores				Median	Fibrous capsule (%)		PL/ VK (%)
		1	2	3	4		Thick	Thin	
<i>p</i> =0.8593	Cont ^a	0/8	4/8	4/8	0/8	2,5	50	50	0
	MTA-Ang ^a	0/8	6/8	2/8	0/8	2	50	50	100
	Biodentine ^a	0/8	8/8	0/8	0/8	2	100	0	100
	CIMMO DTA ^a	0/8	6/8	2/8	0/8	2	100	0	100
<i>p</i> =0.3714	Cont ^a	6/8	2/8	0/8	0/8	1	0	100	0
	MTA-Ang ^a	8/8	0/8	0/8	0/8	1	0	100	100
	Biodentine ^a	8/8	0/8	0/8	0/8	1	0	100	100
	CIMMO DTA ^a	4/8	2/8	0/8	0/8	1,5	0	100	100

* Equal lowercase letters indicate no significant difference between groups in each analysis period. PL= polarized light. VK= von Kossa. (Kruskal-Wallis and Dunn statistical tests; $P > 0.05$).

Discussion

Healthy pulp has the innate ability to repair and restore the diseased state. With the advent of standardized operating procedures using new bioactive materials, a tooth that was previously diagnosed with the need for endodontic treatment, depending on the state of the pulp, can now undergo more conservative treatment and present a good prognosis (Sharma et al., 2020, Montwani et al., 2021).

Bioceramic cements are used in close contact with mineralized and non-mineralized tissues. MTA has been considered the material of choice for years for different endodontic procedures due to its well-known physicochemical properties (Coaguila-Llerena et al., 2020), cytocompatibility, biocompatibility and ability to allow the formation of hard tissue (Benetti et al., 2018; Benetti et al., 2020, Vasconcellos et al., 2022). However, new bioceramic compositions based on calcium silicate have been constantly developed. The current study evaluated the biological response of new bioceramic materials, CIMMO DTA and Biodentine, in comparison with white MTA (Angelus).

An ideal pulp capping material should preserve tooth vitality and stimulate the formation of reparative dentin. The compromised results of pulp capping in the past can be attributed to inadequate case selection, incorrect diagnosis, incomplete removal of carious tissue, and the lack of suitable materials to enable the formation of reparative dentin and regenerative potential (Motwani et al., 2021). A success rate of 88.5% has been reported using MTA and Biodentine in pulp capping procedures (Suhag et al., 2019). The improved results after the use of these materials can be attributed to the improved and biocompatible composition of these cements.

Despite the superiority of Biodentine cement in relatively easier manipulation and predictable outcome, a correlation of *in vitro* and *in vivo* data revealed that the most validated material for pulp capping procedures is still MTA (Kunert et al., 2020). More long-term clinical studies on Biodentine as a pulp capping agent are needed.

In this study, at 7 days, the Biodentine, CIMMO DTA, MTA and Control samples presented moderate inflammation, and the fibrous capsule was thick for all Biodentine and CIMMO DTA samples and in half of the MTA and Control samples. The association between *in vitro* tests, with histological analysis using animals can determine, in a preliminary way, the safety of a new material under test, predicting its clinical response (Wataha et al., 2012, De Souza et al., 2014). The implantation of polyethylene tubes

with materials in the subcutaneous tissue of animals is a standardized method, recommended by ISO 10993-6 for biocompatibility research. This method is validated by clinical studies, being able to show whether a material is irritating to connective tissues. The measure of the fibrous capsule thickness is an additional indicator of biocompatibility, also allowing the evaluation of bioactivity. The thinner the fibrous capsule, the more biocompatible the material. (Benetti et al., 2018)

In the present study, at 30 days, most specimens of the Control, Biodentine and MTA-Ang presented mild inflammation, while CIMMO DTA presented mild to moderate inflammation. In this period, the fibrous capsule was thin for all of the Control, Biodentine, MTA and CIMMO DTA groups. Inflammation was also observed in the Control group, where the polyethylene tubes were empty. It is known that surgical trauma causes inflammation in the area of tube insertion, resulting in the presence of inflammatory infiltrate (Valentim et al., 2017). The inflammation was moderate at 7 days and became mild over time at 30 days. Other previous studies corroborate our results (Valentim et al., 2017, Cintra et al., 2017).

Furthermore, in both analysis periods, birefringent structures under polarized light and von Kossa were observed in the material groups. The MTA and calcium silicate-based materials released a considerable amount of calcium ions, which can induce the formation of hard tissue (Cosme-Silva et al., 2019, Gomes-Filho et al., 2010). In the subcutaneous tissue of mice, the formation of calcite crystals and the mineralization of nuclei indicate the bioactivity capacity of the materials (Cintra et al., 2017). In the present study, the analysis under polarized light and von Kossa showed the presence of calcite crystals in all groups evaluated.

Despite the need for prospective clinical studies to determine the biological performance of the tested biomaterials, these data can contribute significantly to the understanding of the biocompatibility and bioactivity of the materials when in contact with living cells and tissues. Biodentine and CIMMO DTA cements showed biocompatibility and bioactivity as similar as white MTA.

This was the first study to evaluate the biocompatibility and bioactivity of CIMMO DTA *in vivo*. Although bioactivity was identified, further studies should be performed, mainly using animal models. White MTA had its bioactivity confirmed again.

Conclusion

The CIMMO DTA and Biodentine were biocompatible and promoted bioactivity similar to white MTA-Angelus.

Conflict of Interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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5 CONSIDERAÇÕES FINAIS

- No estudo bibliométrico foi realizado uma visão abrangente e descritiva da produção científica relacionada aos cimentos biocerâmicos na endodontia; essa lista dos artigos mais citados pode fornecer um ponto de referência para orientar futuras pesquisas, escolha de materiais na prática clínica na endodontia e serviços em saúde bucal.
- O cimento CIMMO DTA apresentou biocompatibilidade e bioatividade semelhante ao MTA branco (Angelus);
- O cimento Biodentine apresentou biocompatibilidade e bioatividade semelhante ao MTA branco (Angelus);
- Novos materiais bioativos indicados como substitutos dentinários podem ser utilizados para tratamento da polpa vital;
- São necessários mais estudos para corroborar com os resultados desse trabalho, principalmente estudos em animais;
- Espera-se que clinicamente os tecidos respondam positivamente quando em contato com esses materiais;
- Os resultados encontrados nesse estudo reforçam a crescente necessidade de ensaios clínicos rigorosos, visto que as propriedades físico-químicas e biológicas positivas observadas *in vitro* e *in vivo* necessitam de validação em condições clínicas.

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