SYNTHETIC APPROACHES TO TOOTH REGENERATION IN THE MANAGEMENT OF DENTAL CARIES

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Introduction

The purpose of this scoping review was to: analyse synthetic materials and methods of tooth regeneration utilised in the regeneration of dentinal tissues; evaluate their efficacy; and compare their mechanisms of action. Additionally, this review highlights the barriers faced when implementing these innovative procedures into clinical practices.

Gap analysis

A search was conducted across multiple databases, including Google Scholar, JBISRIR, Cochrane library, PubMed and PROSPERO which revealed no clear synthesis of evidence around this topic. It was determined that there is currently a lack of scoping and systematic reviews addressing the synthetic approaches to tooth regeneration in the management of dental caries. Given the diverse methodologies being explored, such as various synthetic biomaterials, this review synthesises existing published knowledge to clarify which materials can be used for tooth regeneration.

Methodology

This scoping review followed the Joanna Briggs Institute (JBI) methodology for evidence synthesis and was registered on the Open Science Framework platform.

Literature search questions were developed as a guide for the literature search (Fig.1).

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist and flowchart were used. A literature review was conducted from 1946 to October 2024 through OVID

Research Question	Data Collected	Type of planned analysis	Presented format
1. What are the current synthetic methods of tooth regeneraton and their associated properties?	Synthetic dental materials including: • Mineral Trioxide Aggregate (MTA) • Biodentine • Calcium hydroxide • Glass Ionomer Cement • Bioactive Glass	Qualitative – comprehensive review of the literature describing the materials effectiveness.	Table comparing the materials properties, success rate and effectiveness accompanied by a narrative synthesis to summarise the main findings.
2. What is the mechanism of action of how synthetic regenerative materials generate tertiary dentine?	Synthetic dental materials including: • Mineral Trioxide • Biodentine • Calcium hydroxide • Glass Ionomer Cement • Bioactive Glass	Qualitative – comprehensive review of the literature describing the materials effectiveness.	Conceptual framework clearly identifying the properties of each synthetic material
3. Which synthetic materials produce more tertiary dentine?	Measurable date providing quantitative results on tertiary dentine formation. Data points include dentine thickness (mm) or the percentage of tertiary dentine formed.	Quantitative – statistical comparison using descriptive statistics (mean standard deviation) and statistical tests such as t-test to evaluate significant differences between materials.	Bar chart for visualisation of comparison.
4. Which material reported the greatest percentage increase of dentinal thickness?	Numerical data from clinical and in-vitro/vivo studies reporting measured dentine thickness (mm) Standardised comparisons were based on the clinical trial conditions.	Quantitative – statistical comparison using descriptive analysis (mean, standard deviation) and inferential statistics such as t-tests to assess the significant differences in dentine formation.	Bar chart or box plot.

Figure 1: **Analysis plan including research questions.**

Patient/ Population and/ or Problem	Concept/ Exposure	Context/ Outcome
"tooth Regeneration" OR "Tooth decay" OR caries OR caries OR cariogenic OR carious	"Tertiary dentine" OR Biodentine, MTA OR "mineral trioxide aggregate" OR "Calcium hydorxide" OR "Calcium Silicate" OR "Bioactive glass"	"Dental Care" OR "dental treatment"

■ ***Figure 2:*** **Search terms created to explore the synthetic methods of tooth regeneration.**

Medline, EBSCO Web of Science, and grey literature databases with the search terms (Fig.2).

Eligibility Criteria

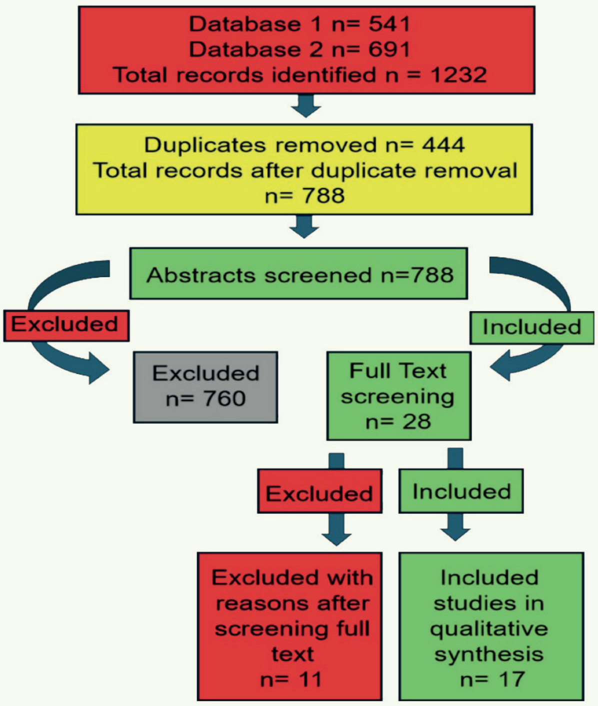
The search focused on teeth in the human dentition affected by natural, and artificially induced dental caries, but also included regenerative mechanisms involving the pulpal tissues through stem cells. No limitations were applied regarding age, location or study design.

Data Extraction

The extracted data included author names, publication years, study details, population demographics, key concepts, methodologies, dentine regeneration techniques, materials used, results and study limitations. This was tabulated using Microsoft Excel 2017.

Results

The PRISMA-flow chart demonstrates the papers found using the search criteria (Fig.3).

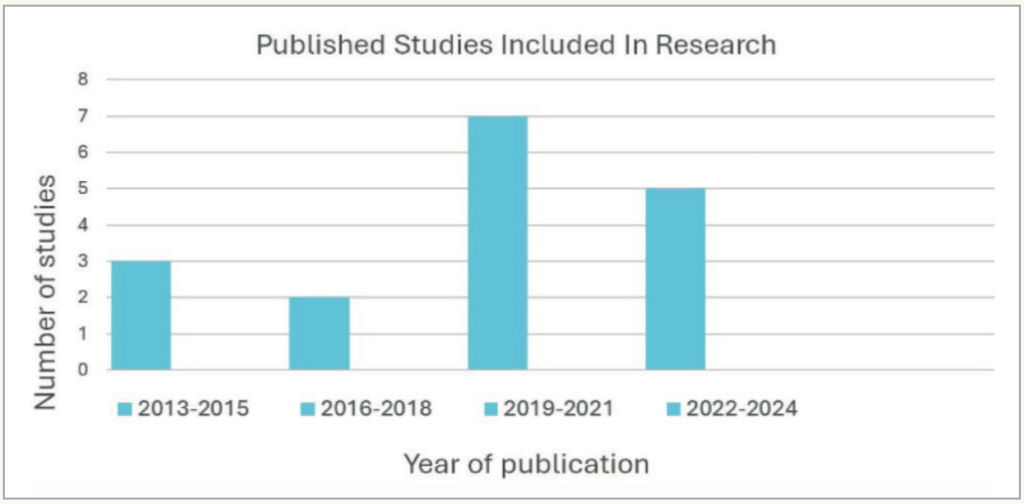


■ ***Figure 3:*** **PRISMA flow-chart displaying included and excluded studies following screening**

■ ***Figure 4:*** **Papers selected for analysis**

Papers selected for analysis	
Paper 1	Dai LL, Mei ML, Chu CH, Lo ECM. Mechanisms of bioactive glass on caries management: a review. Materials. 2019;12(24):4183. www.ncbi.nlm.nih.gov/pmc/articles/PMC6947261/, https://doi.org/10.3390/ma12244183. (Accessed 26 Feb. 2025).
Paper 2	Nowicka A, Wilk G, Lipski M, Kotecki J, Buczkowska-Radlinska J. Tomographic evaluation of reparative dentin formation after direct pulp capping with Ca(OH)2, MTA, Biodentine, and Dentin Bonding System in human teeth. J Endodont. 2015;41(8):1234–1240. PubMed, pubmed.ncbi.nlm.nih.gov/26031301/, https://doi.org/10.1016/j.joen.2015.03.017. (Accessed 26 Feb. 2025).
Paper 3	Schwendicke F, Al-Abdi A, Moscardo AP, Cascales AF, Sauro S. Remineralization effects of conventional and experimental ion-releasing materials in chemically or bacterially-induced dentin caries lesions. Dent Mat. 2019;35(5):772–779. PubMed, pubmed.ncbi.nlm.nih.gov/30853209/, https://doi.org/10.1016/j.dental.2019.02.021. (Accessed 26 Feb. 2025).
Paper 4	Chandak M, Chandak MSS, Rathi CH, Chandak P, Relan K. The mineral trioxide aggregate in vital pulp therapy of permanent teeth - a systematic review. J Evolution Med Dent Sci. 2021;10(1):34-38. https://doi.org/10.14260/jemds/2021/7. (Accessed 26 Feb. 2025).
Paper 5	Eftimoska M, Apostolska S, Rendzhova V, Gjorgievska E, Stevanovic M, Ivanovski K et al. Clinical and histological analyzes of the response of the pulp after its direct capping with Calxyl, MTA and biodentine. Res J Pharmaceut Biolog Chem Sci. 2015;6(4):1097-1111. (Accessed 26 Feb. 2025).
Paper 6	Pires PM, Santos TP, Fonseca-Goncalves A, Pithon MM, Lopes RT, Neves AA. Mineral density in carious dentine after treatment with calcium silicates and polyacrylic acid-based cements. Int Endodont J. 2018;51(11):1292-1300. https://doi.org/10.1111/iej.12941. (Accessed 26 Feb. 2025).
Paper 7	Roma M, Gupta R, Hegde S. A prospective clinical study with one year follow up of deep caries management using a novel biomaterial. BMC Res Notes. 2022;15(1):150. https://doi.org/10.1186/s13104-022-06041-z (Accessed 26 Feb. 2025).
Paper 8	Dammaschke T, Nowicka A, Lipski M, Ricucci D. Histological evaluation of hard tissue formation after direct pulp capping with a fast-setting mineral trioxide aggregate (RetroMTA) in humans. Clin Oral Investigat. 2019;23:4289–4299. https://doi.org/10.1007/s00784-019-02876-2. (Accessed 26 Feb. 2025).
Paper 9	Pires PM, Ionescu AC, Perez-Garcia MT, Vezzoli E, Soares IPM, Brambilla E, et al. Assessment of the remineralisation induced by contemporary ion-releasing materials in mineral-depleted dentine. Clin Oral Investigat. 2022;26:6195-6207. https://doi.org/10.1007/s00784-022-04569-9. (Accessed 26 Feb. 2025).
Paper 10	Swanson WB, Gong T, Zhang Z, Eberle M, Niemann D, Dong R, et al. Controlled release of odontogenic exosomes from a biodegradable vehicle mediates dentinogenesis as a novel biomimetic pulp capping therapy. J Control Release. 2020;324:679–694. https://doi.org/10.1016/j.jconrel.2020.06.006. (Accessed 26 Feb. 2025).
Paper 11	Grewal N, Salhan R, Kaur N, Patel HB. Comparative evaluation of calcium silicate-based dentin substitute (Biodentine®) and calcium hydroxide (Pulpdent) in the formation of reactive dentin bridge in regenerative pulpotomy of vital primary teeth: triple blind, randomized clinical trial. Contem Clin Dent. 2016;7(4):457-463. https://doi.org/10.4103/0976-237x.194116 (Accessed 26 Feb. 2025).
Paper 12	Paper 12: Manzoor K, Manzoor S, Qazi Z, Ghaus S, Saleem M, Kasif M. Remineralization effect of bioactive glass with and without fluoride and casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) on artificial dentine caries: an in vitro study. Cureus. 2024;16(10):e70801. https://doi.org/10.7759/cureus.70801. (Accessed 26 Feb. 2025).
Paper 13	Kuru E, Eronat N, Turkun M, Cogulu D. Comparison of remineralization ability of tricalcium silicate and of glass ionomer cement on residual dentin: an in vitro study. BMC Oral Health. 2024;24:732. https://doi.org/10.1186/s12903-024-04475-4. (Accessed 26 Feb. 2025).
Paper 14	Bhatt RA, Patel MC, Bhatt R, Patel C, Kaushal J, Disha M. A comparative evaluation of light cure calcium silicate and resin-modified glass ionomer as indirect pulp capping agent in primary molars: a randomized clinical trial. Dent Res J. 2023;20(1):18. https://doi.org/10.4103/1735-3327.369620. (Accessed 26 Feb. 2025).
Paper 15	Elchaghaby MA, Moheb DM, El Shahawy OI, Abd Alsamad AM, Rashed MAM. Clinical and radiographic evaluation of indirect pulp treatment of young permanent molars using photo-activated oral disinfection versus calcium hydroxide: a randomized controlled pilot trial. BDJ Open. 2020;6:4. https://doi.org/10.1038/s41405-020-0030-z. (Accessed 26 Feb. 2025).
Paper 16	Stafuzza TC, Vitor LLR, Rios D, Cruvinel T, Neto NL, Sakai VT et al. A randomized clinical trial of cavity liners after selective caries removal: one-year follow-up. J Applied Oral Sci. 2019; 27. https://doi.org/10.1590/1678-7757-2018-0700. (Accessed 26 Feb. 2025).
Paper 17	Petrou M A, Alhamoui FA, Welk A, Altarabulsi MB, Alkilzy M, Splieth CH. A randomized clinical trial on the use of medical Portland cement, MTA and calcium hydroxide in indirect pulp treatment. Clin Oral Investigat. 2013;18:1383-1389. https://doi.org/10.1007/s00784-013-1107-z. (Accessed 26 Feb. 2025).

■ ***Figure 5:*** **Bar-graph representing publication dates of studies.**



Data Analysis

Data extraction was conducted by the investigators in pairs and the studies were categorised as qualitative or quantitative. The results were visually represented using flow charts, pie charts, and graphs. Recurring themes across the studies were identified and systematically categorised.

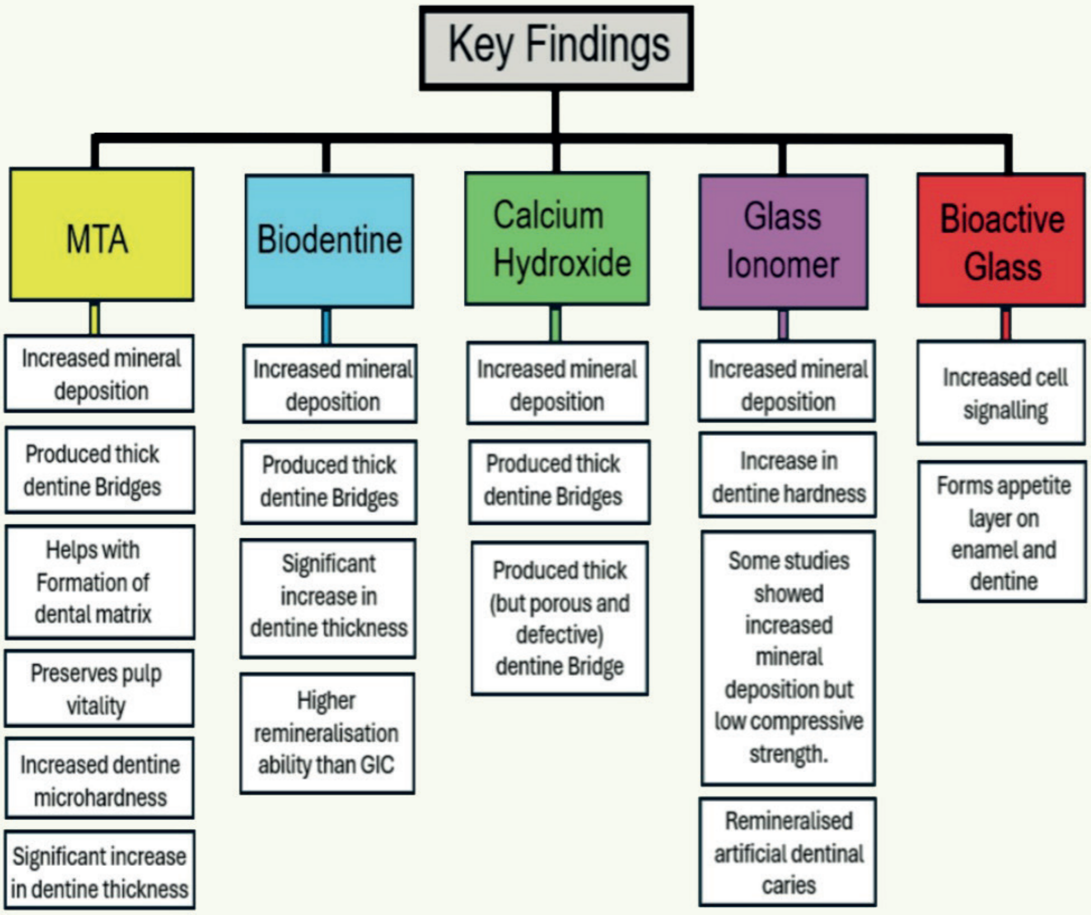
Research question 1

What are the current synthetic methods of tooth regeneration and their associated properties?

Research question 2

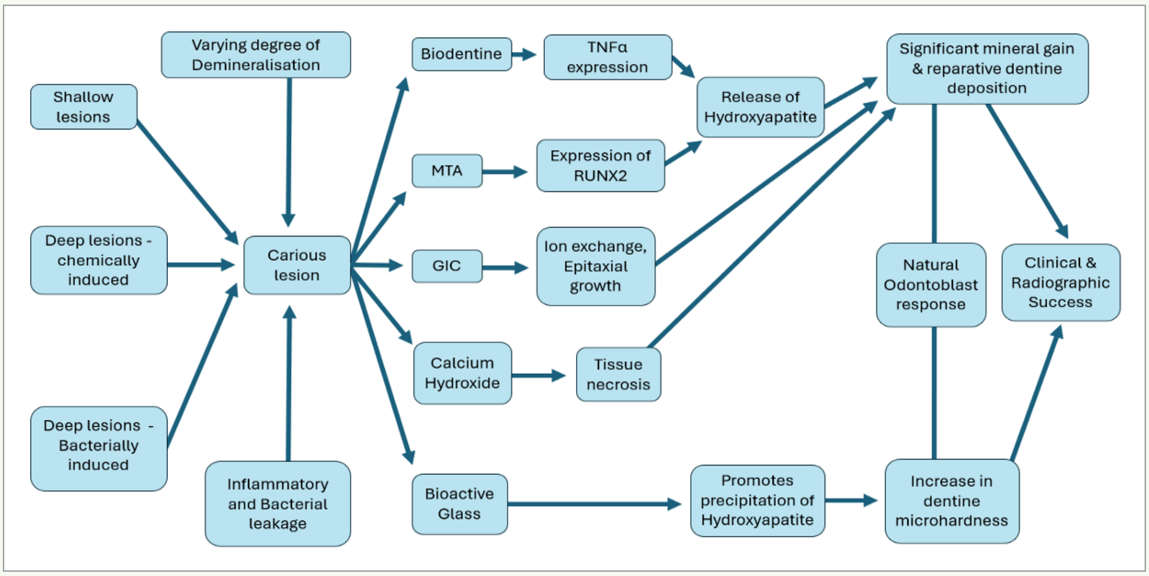
What is the mechanism of action of how synthetic regenerative materials generate tertiary dentine?

This conceptual framework was created with data extracted from the selected papers. The flowchart demonstrates the different mechanisms each material initiates in the sequence of dentine regeneration. More research into the specific sequence of tooth regeneration would allow for the creation of a detailed framework. MTA and Biodentine demonstrated the ability to induce anti-inflammatory cytokines



■ ***Figure 6:*** **Flow chart exploring the synthetic methods of tooth regeneration to determine which materials have shown promising results regarding the formation of reactionary and or reparative dentine.**

Figure 7: Conceptual framework.



(TNF-alpha and RUNX2), to enhance reparative dentine formation, stimulate natural odontoblast responses, and ultimately contribute to both clinical and radiographic success in dentine deposition, and enamel remineralisation.

Research question 3

Which synthetic materials produce more tertiary dentine?

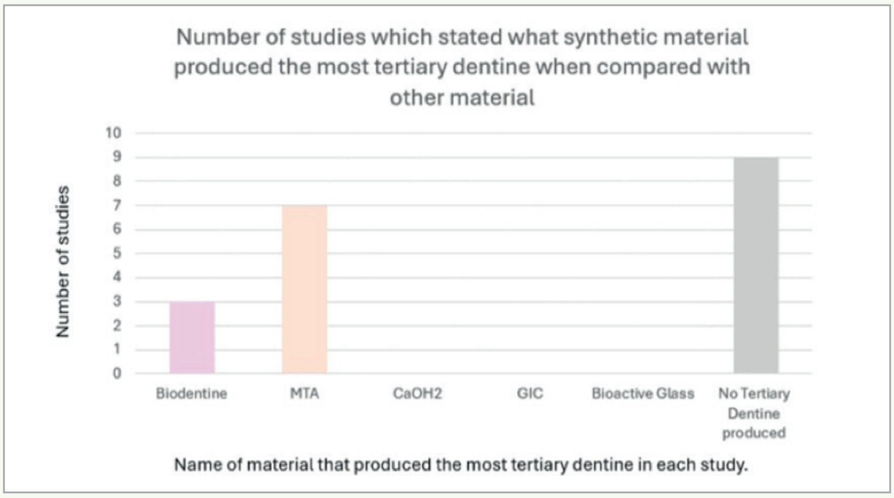


Figure 8: Bar-chart displaying which synthetic material produced more tertiary dentine compared to any other material.

Research question 4

Which materials reported the greatest percentage increase of dentinal thickness?

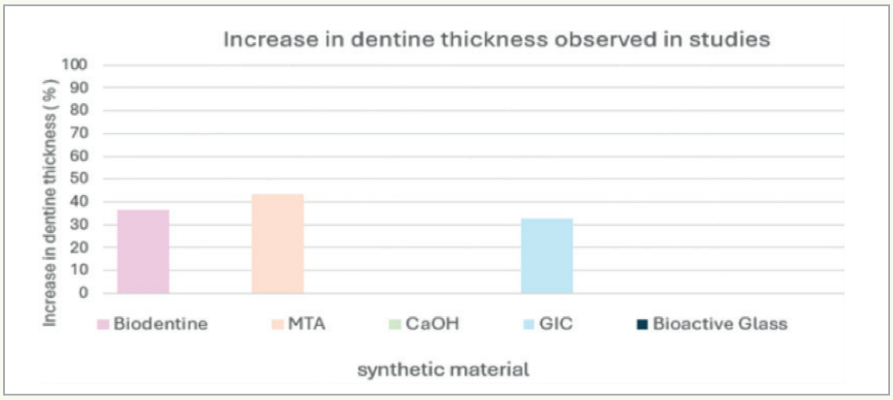


Figure 9: Bar-chart displaying which synthetic material reported the greatest percentage increase in dentine thickness.

Findings

Mineral Trioxide Aggregate

Papers 2, 3, 4, 5, 6, 7, 9, 14, 16,17 focused on the use of MTA in the formation of reparative dentine in several clinical scenarios including: pulp capping; pulpotomies; and the management of deep carious lesions. Papers 4, 7 and 17 highlight MTA's significant reduction of Streptococcus mutans and Lactobacilli species, underscoring its antimicrobial properties. Paper 4 described MTA as eliciting a non-toxic inflammatory response while providing pro-healing effects. Paper 16 observed that MTA facilitated reparative dentine formation with an increase of 0.12mm in dentinal thickness three months post-application. Papers 3 and 9 further demonstrated MTA's role in enhancing microhardness.[7,8] Overall, MTA has been shown to be a highly favourable material for its regenerative effects with papers 5 and 7 reporting a: '100% human tissue acceptance rate'.

Biodentine

Papers 2, 3, 5, 6, 11, 13 examined biodentine in the treatment of dentine caries, consistently demonstrating its remineralisation capabilities. Papers 2 and 5 highlighted its effectiveness in forming dentine bridges, with paper 2 showing biodentine has significantly higher stimulatory activity on pulpal cells than MTA, resulting in thicker dentine bridges. Papers 6 and 13 further confirmed its remineralisation properties with paper 6 reporting the mineral density in enamel and dentine to increase by 36 - 40%. Additionally, paper 13 found that Biodentine's high alkalinity led to the denaturation of intratubular dentinal collagen fibrils, creating a porous structure to enhance bonding, ion exchange and overall remineralisation of dentinal tubules.

Calcium hydroxide

Papers 2, 7, 10, 11, 15, 16, 17 investigated the use of calcium hydroxide for pulp capping and pulpotomies, focusing on its role in tertiary dentine formation. Papers 11, 15 and 16 confirmed its effectiveness with paper 11 reporting a significant increase in dentine thickness and 15 and 16 presenting reparative dentine formation. Papers 11 and 15 described calcium hydroxide as "gold standard" for pulpotomies in primary teeth and pulp capping. Calcium hydroxide's antimicrobial properties were highlighted in paper 15, emphasising its role in protecting the pulp from noxious stimuli. However, paper 2 noted key drawbacks with calcium hydroxide including mineral dissolution over time, dentinal bridge tunnel defects and an uneven dentine thickness.[9] Additionally, calcium hydroxide was found to produce a porous dentine bridge with structural weakness, increasing susceptibility to harmful ion penetration, which has been demonstrated to compromise long-term tooth durability.[10]

Glass Ionomer Cement

Papers 3, 6, 9, 10, 13 examined Glass Ionomer Cement (GIC) and its abilities to induce hard tissue remineralisation in artificially induced dentine lesions. GIC showed limited dentine bridge formation with one study documenting a 32.54% increase in dentine mineral deposition, along with improvements in microhardness, and remineralisation of the dentinal layer.

Bioactive glass

Papers 1 and 12 focused on utilising bioactive glass for the remineralisation of carious lesions in enamel and dentine. It was found to exchange ions between bioactive glass and the alveolar bony surfaces, forming hydroxyapatite crystals. Overall, it was found to significantly increase root dentine microhardness whilst being anticariogenic and prohibiting mineral demineralisation and promoting enamel and dentine remineralisation. No figures were provided in this study.

Dentine bonding systems

Paper 2 focused on utilising dentine bonding systems in pulp capping which was found to a form a significantly weak reparative dentine bridge. Single universal bond was significantly less active for dentine bridge formation. No decision was concluded regarding its efficacy.

Propolis

Paper 5 focused on Propolis. The literature states that Propolis presented with a high clinical success rate of around 91.7%. Not only does the material form a dentine bridge (in 58.3% of the participants included in this study), but it was also found to have antibacterial and anti-inflammatory properties. However, this material was found to induce calcification in direct pulp capping.

RetroMTA

Papers 8 and 9 focused on RetroMTA and its effects as a pulp capping material. This material demonstrated beneficial results, forming a complete mineralised barrier in 3 out of 7 cases after a 7-month period post-application (paper 8). The remaining cases exhibited either channels or direct contact between the material and pulp, indicating unpredictable barrier formation. The newly formed calcified tissues were irregular, atubular and varied in thickness. Paper 9 concludes that RetroMTA was an effective material in hydroxyapatite deposition.

Portland Cement

Papers 16 and 17 focused on Portland Cement. It was found that Portland Cement (with added zirconium oxide) provides effective treatment of primary teeth after selective caries removal, with reparative dentine evidently being laid down after reassessment. Additionally, the material was found to have antimicrobial properties with a significant reduction in Streptococcus mutans and Lactobacilli species.

Zinc Polycarboxylate

Paper 6 focused on zinc polycarboxylate and its ability to remineralize artificial dentine. The literature described how zinc polycarboxylate had significantly increased the mineral density of artificially demineralised dentine, thus promoting its remineralisation abilities.

Bioengineering pulpal stem cells

Paper 10 highlighted primary human dental pulp stem cells isolated from adult human teeth cultured under odontogenic conditions for two weeks. This displayed exosomes rapidly being taken up into the cytoplasm of pulpal cells to rapidly increase mineralisation after 14 days, stimulating a rapid proliferation of tertiary dentine. There have been several systematic reviews published within the grey literature concerning in vitro stem cell dentinal regeneration.4-6 This underpins the need for knowledge and a deeper understanding of the cellular and molecular interactions, between bioactive restorative dental materials, and the dentine-pulp complex.

Discussion

Tooth regeneration has been described as a revolutionary and developing field that aims to biologically restore damaged teeth from infectious dental diseases such as dental caries through bioactive molecule activation (cytokines), synthetic bioactive materials and growth factors. There is still an unmet clinical need for tooth regenerative materials which is particularly important for patients with various degrees of enamel and dentine breakdown. The goal of tooth regeneration for diseased teeth is to restore the natural structure and function of the tooth.[1]

Several systematic reviews[1-3] have explored synthetic tooth regeneration mechanisms. These studies identified various methods to initiate tooth regeneration, including the use of synthetic biomaterials, pulpal stem cell stimulation and enamel and dentine remineralisation. Additionally tooth regenerative mechanisms have shown to induce the successful regenerative capabilities of the dental pulp and dentinal layers which requires optimal conditions for its long-term success'.[4-6] This scoping review incorporated additional studies based on specific eligibility criteria. By analysing a broader dataset, it aimed to provide more up-to-date insights into the capabilities and limitations of current tooth regeneration techniques.

Comprehensive literature evaluation of the 17 studies identified a comprehensive overview into the associated properties of: Mineral Trioxide Aggregate (MTA); Biodentine; Calcium hydroxide; Glass Ionomer Cement; Bioactive glass; Dentine bonding systems; Propolis; RetroMTA; Resin Modified GIC; Portland Cement; and Zinc Polycarboylate.

Comparison of Methods and Findings in Literature

The findings of this scoping review identified MTA as the most effective synthetic material for dentine bridge formation closely followed by Biodentine, correlating with grey literature.[11] Others, however, have found no significant difference between MTA and Biodentine in this regard.[12] Calcium hydroxide was observed to induce dentine formation which was however found to be highly porous, raising concerns about its long-term structural integrity and ability to maintain protection against bacterial ingress.[9] In contrast, GIC and bioactive glass primarily enhanced enamel and dentine remineralisation (by 28.8% with bioactive glass), rather than directly promoting odontoblastic stimulation and dentine bridge formation.[10]

Further research is needed to test the formulated conceptual framework and create a comparison between MTA, Biodentine, Calcium Hydroxide, and Bioactive Glass to efficiently guide their optimal selection and application in clinical practice. Further developing studies around these synthetic materials regarding and their properties will allow for clinicians to make more informed decisions when selecting the most appropriate synthetic material in clinical practice.

Barriers

In vitro studies utilising artificial caries face significant challenges, particularly due to the absence of a host immune response, microbiome interactions, and the structural complexity of the oral microbiome and its influence on dentine repair. In vitro studies also struggle to replicate the structural complexity of dental tissues, long-term stability and the chemical variability of the oral cavity. While these studies provide valuable preliminary insights, in vivo and clinical validation remain essential for translating findings into real-world applications. Economic factors also influence dental material availability with high-income countries having the accessibility to more financially significant materials including bioactive glass and MTA. However, low-middle income countries rely on a more limited selection, often dictated by cost and resource availability[13] which can be noted from the publications in this scoping review.

Implications for Practice

The historical use of dental materials plays a significant role in the clinician's material selection process which may come down to time constraints, cost and availability, suggesting that decisions may be influenced by factors unrelated to the tooth's best suited material and patient variabilities.[14] Calcium hydroxide remains the most common choice in clinical practice as a synthetic tertiary dentine stimulating material due to faster preparation.[15] Dycal (a brand of calcium Hydroxide) remains popular due to its rapid mixing time of 10 seconds and setting within 2.5-3.5 minutes. In contrast MTA is more difficult to handling and requires 3 - 4 hours of setting time.[16] Biodentine, combining benefits of both, triturates in under 30 seconds but requires 12 minutes of setting time.[17]

While efficiency is key in clinical practices, material selection should be evidence-based. Understanding the properties of newer materials can enhance treatment longevity and support a more conservative approach to dentistry whilst maximising patient outcomes and care.

Conclusion

This review highlights the need for further research on the synthetic materials, their associated properties and in-vitro stem-cell biomechanical engineering. While research on organic biomolecules for tooth regeneration is ongoing, this study focused primarily on synthetic biomaterials. Findings indicate that MTA and Biodentine are the most effective pulp capping agents due to their bioactivity. Although calcium hydroxide promotes dentine bridge formation, its long-term stability is compromised by porosity and degradation. Bioactive glass is biocompatible but lacks substantial evidence supporting dentine formation. GIC demonstrated limited dentine regeneration potential but contributed to enamel and dentine remineralisation.

Overall, MTA and Biodentine remain the most promising synthetic materials for tertiary dentine regeneration, warranting further clinical research to refine their clinical applications.

Authors: The authors have recently graduated as DTH students from the university of Plymouth. This scoping review was undertaken in their final year.

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