Dental Materials Journal 2024; 43(1): 1–10

Review

Bioactivity and remineralization potential of modified glass ionomer cement: A systematic review of the impact of calcium and phosphate ion release

Nozimjon TUYGUNOV[1], Zahra KHAIRUNNISA[1], Noor Azlin YAHYA[1,2], Azwatee ABDUL AZIZ[1,2], Myrna Nurlatifah ZAKARIA[1,2], Nigora Amanullaevna ISRAILOVA[3] and Arief CAHYANTO[1,2]

[1] *Department of Restorative Dentistry, Faculty of Dentistry, University of Malaya, Kuala Lumpur 50603, Malaysia*
[2] *Biomaterials Technology Research Groups, Faculty of Dentistry, University of Malaya, 50603, Kuala Lumpur, Malaysia*
[3] *Department of Children's Diseases in Family Medicine, Tashkent Medical Academy, Tashkent 100102, Uzbekistan*
Corresponding author, Arief CAHYANTO; E-mail: arief.cahyanto@um.edu.my

This systematic review investigates the effectiveness of calcium and phosphate ions release on the bioactivity and remineralization potential of glass ionomer cement (GIC). Electronic databases, including PubMed-MEDLINE, Scopus, and Web of Science, were systematically searched according to PRISMA guidelines. This review was registered in the PROSPERO database. Five eligible studies on modifying GIC with calcium and phosphate ions were included. The risk of bias was assessed using the RoBDEMAT tool. The incorporation of these ions into GIC enhanced its bioactivity and remineralization properties. It promoted hydroxyapatite formation, which is crucial for remineralization, increased pH and inhibited cariogenic bacteria growth. This finding has implications for the development of more effective dental materials. This can contribute to improved oral health outcomes and the management of dental caries, addressing a prevalent and costly oral health issue. Nevertheless, comprehensive longitudinal investigations are needed to evaluate the clinical efficacy of this GIC's modification.

Keywords: Glass ionomer cement, Calcium, Phosphate, Bioactive, Remineralization

INTRODUCTION

Dental decay is a prevalent disease worldwide and a major cause of tooth loss[1]. With the advancement of dentistry, minimum intervention procedures and materials have been developed to preserve remaining dental structures and limit pulp damage[2,3]. Even after removing the diseased carious layer, live bacteria can persist in the dentin cavity for months or years, independent of the restorative material used[4-6]. These bacteria can cause secondary caries, the most common reason for replacing existing restorations[7]. In the United States alone, the annual cost of replacing existing dental fillings exceeds $5 billion, accounting for more than half of all dental operative work[8]. Preventive measures, such as fluoride (F) use, are crucial in inhibiting the occurrence of secondary caries and avoiding tooth loss[9,10]. F is present in dental products like dentifrices and may be absorbed up to glass ionomer cement (GIC)[11,12], which is a versatile acid-base cement widely used in restorative and luting materials, orthodontic cement, and sealant[13].

GIC is known for its ability to remineralize hard tooth tissues, such as dentin and enamel, due to the ion release into the oral environment[14]. The F ion release from GIC is considered a clinical benefit[15,16], and studies have shown that GICs can inhibit the development of caries-causing bacteria after partial caries removal[17]. One potential strategy to enhance the remineralization process of GICs is using chemical compounds that can increase the release of specific ions[18]. Additionally, GIC is a reliable method for the clinical treatment of early-stage proximal caries[19], substantially reducing the decrease in pH caused by bacteria[20].

This systematic review investigates whether the release of calcium (Ca) and phosphate (P) ions significantly affect bioactivity properties to allow for further intervention in modified GIC powder manufacture and increase remineralization properties under *in vitro* conditions. Researchers have explored modifying dental materials with Ca and phosphate-based chemical compounds to promote the release of Ca, P and F ions[21-25]. Skrtic *et al.*[23] found that incorporating a Ca phosphate-based compound can potentially remineralize carious enamel lesions. Assessing the addition of casein phosphopeptide–amorphous calcium phosphate (CPP–ACP) to GICs, Mazzaoui *et al.* and Al Zraikat *et al.* found that modifying 3% or 5% of CPP-ACP leads to significantly decreased F release, but increased Ca and P ion release[21,22].

Another study showed that modifying 1.56% (w/w) CPP-ACP into a GIC increases mechanical properties and releases Ca, P and F ions[22]. Modifying GIC with nanohydroxyapatite, a biologically active Ca, P mineral, resulted in positive enhancements in mechanical characteristics, antibacterial properties, ion release, and reduction of microleakage and cytotoxicity[26]. Replacing CaO and CaF_2 in GIC with strontium substitutions (SrO and SrF_2) increased radiopacity and F ion release[25].

Nonetheless, according to other definitions that prioritize the ability of materials to promote remineralization, GIC is not commonly considered bioactive. These definitions that characterize a substance as bioactive indicate that it has the ability to generate a material layer, like apatite, which is intrinsic and compatible with the human body[27-30] . Regarding this topic, materials are generally considered bioactive if

Received Jun 7, 2023: Accepted Aug 25, 2023
doi:10.4012/dmj.2023-132 JOI JST.JSTAGE/dmj/2023-132

they can engage with living tissues and initiate a cellular reaction that encourages the formation of hydroxyapatite (HA)[31]. GIC and tissue connect by establishing a biologically active HA layer[32]. The capacity of a material to promote the formation of HA on its surface *in vitro* after immersion in a simulated body fluid (SBF) solution is often used to define its bioactivity[27,33,34]. Hence, bioactivity is significant for materials that are intended to promote mineral attachment to the dentine substrate at the material-tooth tissue interface. These bioactive materials must convert to HA in a controlled manner and timeframe[33]. Several *in vitro* studies have shown that GICs exhibit bioactivity by forming HA on their surface when immersed in physiological fluids such as SBF[28,31,35-38]. However, this technique has disadvantages as it can produce false positive and negative outcomes[39,40].

In addition to *in vitro* tests, additional study utilising *in vivo* testing is advised in order to validate the bioactivity results from SBF studies[28,40]. Studies conducted *in vitro* have shown that using GIC restorations can improve the resistance of both enamels[41,42] and dentin[43] to demineralization, likely due to the release of F ions that can facilitate remineralization of tooth structure. Additionally, a study over eight years found that carious lesion progression in enamel adjacent to GIC restorations in primary teeth was reduced[44]. These findings prompted a systematic literature review with the research question: "Do the release of Ca and P ions increase the bioactivity of modified GIC under *in vitro* conditions?"

MATERIALS AND METHODS

Our systematic review was focused on experimental and quasi-experimental studies published within the last decade, which aimed to investigate the bioactivity of GIC and its modification with Ca and P ions. Eligible studies were selected based on the PICOS framework, which included studies related to GIC bioactivity, with intervention focused on Ca and P ion release in GIC. We identified five studies meeting the criteria of eligibility, and the methodology is presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for transparency. Data extraction was conducted from eligible full-text manuscripts and presented in a table with relevant information on the corresponding test and statistically significant outcome(s).

Search strategy

This systematic review was conducted using a research protocol that refers to PRISMA guidelines[45]. A thorough search for the literature was carried out from November 2022 to January 2023 using electronic databases, including PubMed-MEDLINE, Scopus and Web of Science. The following keywords were used to search relevant articles: ("Calcium" OR "Ca") AND ("phosphate" OR "P" OR "PO4") AND "calcium phosphate" AND "release" AND ("glass ionomer cement" OR "GIC") AND ("fluoride" OR "F") AND "bioactive".

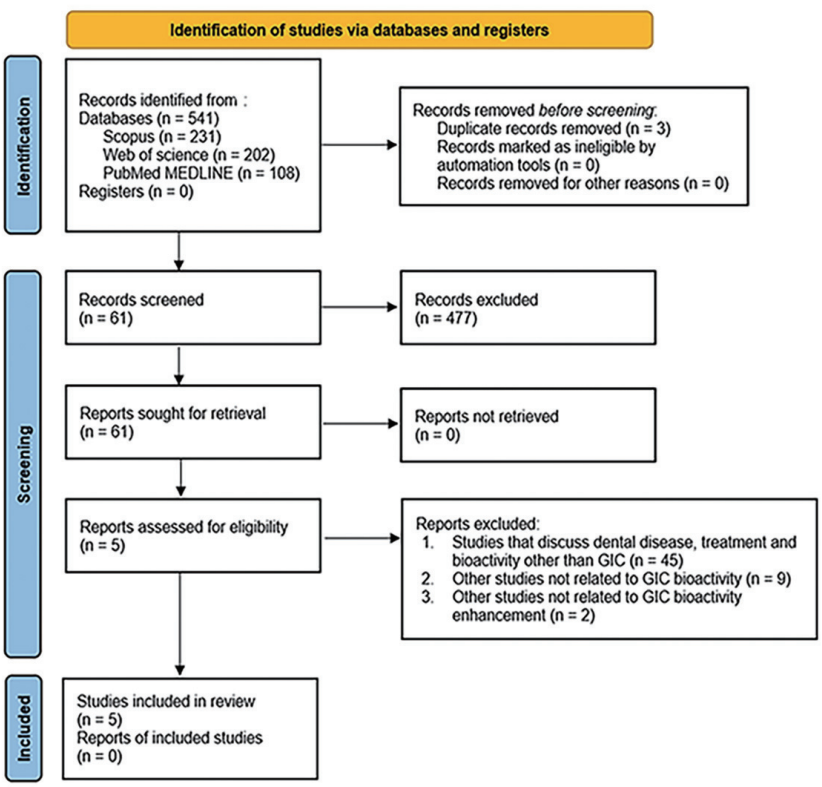

Fig. 1 PRISMA flow diagram in this study.

Study selection

The search across multiple databases resulted in 541 articles, screened by two reviewers (TN and KZ) based on title, abstract and full text. Disagreements were resolved through discussion, and ultimately, five studies met the eligibility criteria and were included in the systematic review. The search process and article selection are presented in a PRISMA flow diagram Fig. 1[45].

Eligibility criteria

This systematic review followed the PICOS (Problem/Population, Intervention, Comparison, Objective, and Study design) framework to establish inclusion criteria[46]. Population (P) included studies related to GIC bioactivity, and intervention (I) comprised studies on Ca and P ion release in GIC. As bioactive materials, comparison (C) evaluated conventional GIC and GIC modified with Ca and P. Outcome (O) research on GIC bioactivity augmentation *in vitro* and *in vivo* were the focus of this outcome.. Experimental and quasi-experimental studies published over the last ten years were included in the study design (S). The review is registered at PROSPERO with registration number CRD42023388399. Exclusion criteria comprised studies that discussed dental disease, treatment, and bioactivity other than GIC; studies not related to GIC bioactivity; comparisons with other restoration materials; studies not related to GIC bioactivity enhancement; reviews, systematic reviews, books or book chapters; conference papers; articles not published in English, and articles published over ten years ago.

Table 1 Summary of studies included in this systematic review

Authors, Year	Sample	Release of ions	Methodology	Outcome
Par *et al*. 2022[48]	Reinforced glass ionomer cement (ChemFil Rock, Dentsply Sirona, Konstanz, Germany; shade: A2, LOT: 1903000819)	1. Calcium (Ca^{2+}) 2. Phosphate (PO_4^{3-}) 3. Fluoride (F^-)	1. Atomic absorption spectrometry for calcium; 2. UV–Vis spectrometry for phosphate; 3. Ion-selective electrode for fluoride.	1. The resinous adhesive layer can act as a barrier for ion release and diminish the beneficial effects of remineralizing restorative materials; 2. Sufficient water absorption is necessary to release ions from the fillers.
Allam and Abd El-Geleel 2018[56]	Glass-ionomer cement (AquaCem, Dentsply, Konstanz, Germany)	1. Calcium (Ca^{2+}) 2. Fluoride (F^-)	1. Atomic absorption spectrometry for calcium; 2. Ion-selective electrode for fluoride. *The release of phosphate ions has not been studied.*	Modification of conventional GIC with Chicken Eggshell Powder: 1. Enhances the mechanical properties; 2. Not significant effects on fluoride and calcium release.
Zalizniak *et al*. 2013[47]	Glass ionomer cement, Fuji VIITM (F7) and Fuji VIITM EP (F7EP)	1. Calcium (Ca^{2+}) 2. Phosphate (PO_4^{3-}) 3. Fluoride (F^-)	1. Atomic absorption spectrometry for calcium; 2. UV–Vis spectrometry for phosphate; 3. Ion-selective electrode for fluoride.	Incorporation of 3% (w/w) CPP–ACP into GIC: 1. Enhances calcium and phosphate ion release; 2. Not significantly changes fluoride ion release; 3. Not significant effects on surface hardness and change in mass.
Nicholson *et al*. 2021[55]	Glass ionomer cement AquaCem (Dentsply)	1. Calcium (Ca^{2+}) 2. Phosphate (PO_4^{3-})	1. Inductively coupled plasma-optical emission spectroscopy for calcium; 2. Inductively coupled plasma-optical emission spectroscopy for phosphate. *The release of fluoride ions has not been studied.*	1. In neutral conditions, calcium ions do not release, however in acid, significant amounts are released; 2. The phosphate is released in neutral and acid conditions, with greater amounts of acid.
De Caluwe *et al*. 2017[28]	Conventional aluminosilicate glass (prepared by the researcher)	1. Calcium (Ca^{2+}) 2. Phosphate (PO_4^{3-})	1. Atomic absorption spectrometry for calcium; 2. UV–Vis spectrometry for phosphate. *The release of fluoride ions has not been studied.*	1. The addition of bioactive glass improves the bioactivity by apatite formation; however, it decreases the strength 2. Adding Al^{3+} to the bioactive glass composition improves strength, but bioactivity decreases.

Data extraction
Two reviewers (TN and KZ) independently extracted data from the eligible full-text manuscripts using the specified data items. Any disagreements or uncertainties were resolved through discussion until a consensus was reached.

Data items
The data relevant to the research question was extracted from the included studies and tabulated into the following fields for qualitative synthesis: author (year), sample, methodology, and outcome. The data extracted from the included studies are presented in Table 1, which includes the brand name, manufacturer, country of manufacture and ex., pertinent information on the corresponding test and variable(s) measured, and the statistically significant outcome(s) of the experiment(s) unless specified otherwise.

RESULTS

Study characteristics
This review comprised five non-randomized *in vitro* experimental investigations. Only five of the 541 articles retrieved in the databases matched the inclusion requirements. All studies chosen were published within the last ten years and were Q1 and Q2 indexed based on rank by journal citation indicator. The studies were released in 2013, 2017, 2018, 2021, and 2022. Table 2 presents the characteristics of the included studies.

Qualitative study and outcome measures
Two studies in this systematic review investigated Ca, P and F release using atomic absorption spectrometry (for Ca), ultraviolet–visible (UV–Vis) spectroscopy (for P), and ion-selective electrode analysis (for F)[47,48]. Par *et al*. reported that the resinous adhesive layer could act as a barrier for ion release, significantly reducing the remineralization properties of restorative materials. Sufficient water absorption is also necessary to release ions from the fillers[48]. Similarly, Wang *et al*. examined the effects of coating on initial F release from resin-modified GIC[49]. Furthermore, Kelić *et al*. reported that the presence of a dental adhesive system or GIC coating significantly reduced the recharge capacity compared to uncoated materials[50].

In contrast to previous findings, Tay *et al*. proposed that adhesives could act as permeable membranes and aid in remineralizing tooth structure, halting the caries process[51]. While the inner surface of the restoration, adjacent to the cavity wall, may hinder ion release, the outer surface is exposed to saliva and dynamic changes in acidity, leading to increased porosity and potential for ion uptake and surface adsorption due to enhanced roughness over time[52].

Zalizniak *et al*. found that adding 3% (w/w) CPP-ACP to GIC enhances the release of F, Ca and P ions without significant effects on the surface hardness or changes in mass[47]. The distribution of CPP-ACP nano complexes throughout the set cement leads to sustained ion release and protects against acid demineralization of adjacent tooth tissue, as demonstrated in previous studies[21,22,47]. The highly charged/polar nature of CPP-ACP also alters the surface properties of set GIC, inhibiting bacterial adherence and biofilm development[53]. Additionally, Shen *et al*. discovered that applying CPP-ACP/F paste to GIC recharges ion release and increases surface hardness[54].

Table 2 Characteristics of studies

Authors, Year	Country	Title	Journal/Index	Method	Citations
Par *et al*. 2022[48]	Croatia	Effect of adhesive coating on calcium, phosphate, and fluoride release from experimental and commercial remineralizing dental restorative materials	Sci Rep 2022; 12: 10272. Q2	*In vitro* experimental study	1
Allam and Abd El-Geleel 2018[56]	Egypt	Evaluating the mechanical properties, and calcium and fluoride release of glass-ionomer cement modified with chicken eggshell powder	Dent J 2018; 6: 40. Q2	*In vitro* experimental study	8
Zalizniak *et al*. 2013[47]	Australia	Ion release and physical properties of CPP-ACP modified GIC in acid solutions	J Dent 2013; 41: 449-454. Q1	*In vitro* experimental study	28
Nicholson *et al*. 2021[55]	UK	Kinetics of ion release from a conventional glass-ionomer cement	J Mater Sci Mater Med 2021; 32: 30. Q2	*In vitro* experimental study	8
De Caluwe *et al*. 2017[28]	Belgium	Addition of bioactive glass to glass ionomer cement: Effect on the physicochemical properties and biocompatibility	Dent Mater 2017; 33: e186-e203. Q1	*In vitro* experimental study	76

Two articles in this systematic review investigated Ca and P ion release using different spectroscopy techniques[28,55]. However, F ion release was not assessed in either article. Nicholson *et al.*'s study, discovered that Ca ions do not release in neutral conditions, but significant amounts are released in acid. In contrast, P ions are released in neutral and acid conditions, with more significant amounts in acid[55].

The study by Allam and Abd El-Geleel found enhanced mechanical properties of GIC modified with chicken eggshell powder without significant effect on Ca and F release. Ca ion release was evaluated using atomic absorption spectrometry, and F release was evaluated using ion-selective electrode analysis[56]. Other recent studies investigated the use of nano-sized eggshell powder to enhance the bioactivity and Ca ion release of a chemically-cured Ca hydroxide cement[57]. The eggshell powder was also found to reduce the surface roughness of denture base resin and was studied as a pulp capping material[58,59]. Table 1 presents a summary of the selected articles' data analysis.

One research out of five included in this systematic review article investigated bioactivity properties with SBF incubation. De Caluwe *et al.* found that incorporating bioactive glass (BAG) such as 45S5F (based on the commercial Na^+ containing Bioglass® [29,30]) and CF9 (sodium-free BAG[60,61]) into GIC improves Ca and P ion release, but reduces strength. However, adding Al^{3+} to the bioactive glass composition increases strength while decreasing ion release. Despite the reduction in strength, adding bioactive glass to GIC enhances its remineralization properties[28,59,62,63]. A recent advancement in this area is using bioactive glass nanoparticles to modify GIC. Incorporating these nanoparticles increases the material's bioactivity and improves its mechanical properties, including compressive, tensile, and flexural strengths[35]. It is shown that SBF incubation positively affects cell viability for the CF9-containing GICs, and the viability of cells containing GICs with CF9 is notably improved when exposed to SBF, mainly when the concentration of CF9 is at 10%. Upon incubation in SBF, the surfaces of these cements were observed to form a HA layer, as evidenced by the combined use of Fourier-transform infrared spectroscopy (FT-IR) and scanning electron microscope (SEM) imaging along with energy-dispersive X-ray spectroscopy (EDX) analysis. After being immersed in SBF for one day, HA precipitation was observed on hybrid GICs containing 5 wt% and 10 wt% bioglass[28,64,65]. After three days of immersion in SBF, the surface became smoother, possibly due to formation of HA layer on the surfaces[64]. The growth of these precipitates into different HA morphologies over time can be partially attributed to the gradual incorporation of carbonate ions into the HA structure[28,64]. With longer immersion times, discrete islands of HA in three dimensions appeared on the surface of the GICs[66].

HA microcrystals adhere to the crystallites of human tooth tissue[67]. Recently published data validates HA particles to establish bridges between enamel crystallites through mineral-mineral interactions[68,69]. Firstly, Enax *et al.*[70] proposed remineralization mechanisms with action between HA and the tooth surface. Furthermore, clinical studies have shown that HA has the potential to shield teeth against dental caries, and there are several randomized controlled trials (RCTs) research suggesting that HA possesses anti-caries properties[24,71-76]. Figure 2 shows how HA is formed, prevents enamel demineralisation, and promotes remineralization[77-80].

Bibliometric analyses

Articles on GIC bioactivity have been published in dental, pharmaceutical, and chemistry journals. A search of PubMed-MEDLINE, Scopus, and Web of Science databases conducted in November 2022 yielded a total of 541 articles. The ten most frequently published journals are shown in Table 3.

The last decade has seen a surge in research focusing on the bioactivity of GIC, likely driven by the need to develop dental materials that offer improved biocompatibility and tissue regeneration. This shift from biocompatibility to bioactivity may be due to advancements in dental materials science and a better understanding of the importance of tissue regeneration[81]. The distribution of publications concerning GIC bioactivity by year and origin is depicted in Fig. 3.

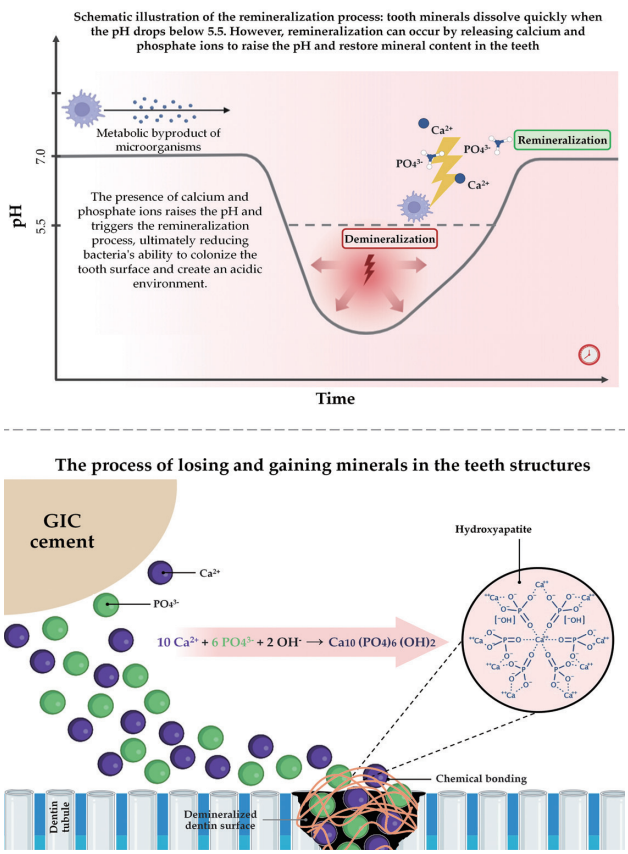

Fig. 2 The mechanisms of the formation of HA and its interactions with tooth structure[77-80].

Table 3 Distribution of articles related to GIC bioactivity by journals

Source title	Publications	Citations	Citations per publications	Source normalized impact per paper (SNIP)	Cite score 2021	Journal impact factor (2021)
Journal of Dentistry	23	462	20.1	1.917	6.8	4.991
Clinical Oral Investigations	16	172	10.8	1.779	5.8	3.607
Dental Materials Journal	13	122	9.4	1.209	3.5	2.418
Scientific Reports	10	127	12.7	1.389	6.9	4.997
Molecules	9	194	21.5	1.267	5.9	4.927
BMC Oral Health	8	39	4.9	1.785	3.6	3.747
Ceramics International	8	155	19.4	1.192	8.0	5.532
Dental Materials	8	383	47.8	2.219	9.2	5.687
Polymers	8	44	5.5	1.061	7.1	4.967
Nanomaterials	7	66	9.4	1.094	6.6	5.719

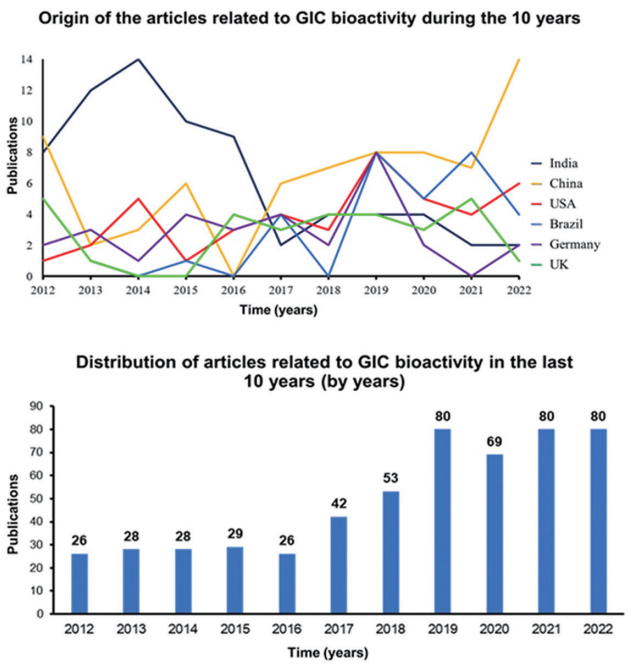

Fig. 3 Distribution of articles related to GIC bioactivity.

Numerous studies have been conducted on the bioactivity of GIC across different countries. Among these countries, India (72), China (69), USA (42), Brazil (31), Germany (31) and the UK (30) have published a significant number of articles on the topic. These countries boast active research communities and have made valuable contributions to the knowledge base surrounding GIC bioactivity and its potential use in restorative dentistry. Through their research efforts, these countries have enhanced our understanding of GIC and the unique properties that make it a promising dental material. GIC's bioactivity and remineralization properties have been studied extensively, and incorporating Ca and P ions into the material has been shown to improve its effectiveness.

The increased interest in the bioactivity of GIC over the last decade was a significant rise in published articles between 2012 and 2022. This trend may be due to advancements in dental materials science, a better understanding of the importance of promoting tissue regeneration, and a shift towards bioactivity. However, there was a slight decrease in the number of published articles related to GIC bioactivity in 2020, which can be attributed to the COVID-19 pandemic's significant impact on scientific research and publishing.

Risk of bias and quality assessment

The risk of bias (RoB) analysis for this systematic review article has been performed using a RoBDEMAT tool —developed by a broad panel of dental materials experts to assess the quality of laboratory dental materials studies[82]. This tool includes the following sources of bias: bias in planning and allocation (proper randomization and sample size calculation), bias in sample/specimen preparation, bias in outcome assessment and bias in data treatment and outcome reporting. Each signaling question was answered as "sufficiently reported", "insufficiently reported", "not reported" or "not applicable". Answering "sufficiently reported" will indicate that the article under evaluation correctly reports the item being judged, whereas "insufficiently reported" would indicate that not enough details were given. Finally, judging as "not reported" indicates that no detail or explanation was given. An overall summary RoB score was not produced as it was kept as a simple checklist.

The risk of bias and the factors considered for the analysis are presented in Table 4. For the five studies

Table 4 Risk of bias analysis for the five studies included in this systematic review paper

Study ID	Bias in planning and allocation (Domain 1)			Bias in sample/specimen preparation (Domain 2)		Bias in outcome assessment (Domain 3)		Bias in data treatment and outcome reporting (Domain 4)	
	1.1. Control group	1.2. Randomization of samples	1.3. Sample size rationale and reporting	2.1. Standardization of samples and materials	2.2. Identical experimental conditions across groups	3.1. Adequate and standardized testing procedures and outcomes	3.2. Blinding of the test operator	4.1. Statistical analysis	4.2. Reporting study outcomes
Par *et al.* 2022[48]	Sufficiently reported	Not reported	Not reported	Sufficiently reported	Insufficiently reported	Sufficiently reported	Not reported	Sufficiently reported	Sufficiently reported
Allam and Abd El-Geleel 2018[56]	Sufficiently reported	Not reported	Sufficiently reported	Sufficiently reported	Insufficiently reported	Sufficiently reported	Not reported	Sufficiently reported	Sufficiently reported
Zalizniak *et al.* 2013[47]	Sufficiently reported	Not reported	Not reported	Sufficiently reported	Sufficiently reported	Sufficiently reported	Not reported	Sufficiently reported	Sufficiently reported
Nicholson *et al.* 2021[55]	Insufficiently reported	Not reported	Not reported	Insufficiently reported	Insufficiently reported	Insufficiently reported	Not reported	Insufficiently reported	Insufficiently reported
De Caluwe *et al.* 2017[28]	Sufficiently reported	Not reported	Sufficiently reported	Sufficiently reported	Sufficiently reported	Sufficiently reported	Not reported	Sufficiently reported	Sufficiently reported

included in this systematic review, a control group was present and reported in all, while randomization of sample size was not reported in any of them. Further, regarding bias in planning and allocation, the sample size rationale and reporting were not reported in three of them[47,48,55]. Blinding of1 the testing operators was not reported in any of the studies. Doubts concerning sufficient reporting of the study expected outcomes were raised in all studies.

DISCUSSION

Dental materials have made significant advancements in recent decades, yet researchers still strive to develop techniques to prevent secondary caries progression beneath restorations and enhance materials' bioactivity properties. There is a growing trend towards using bioactive and remineralizing restorative materials to address these issues, improving bonded restoration longevity. Dental restorative materials with enhanced bioactivity properties have been associated with decreased caries due to interactions with the oral environment and improved remineralization. This is achieved by releasing various ions and introducing HA deposition[83].

Recent advancements in dental materials have led to the development of restorative materials with enhanced bioactivity properties. These materials release various ions that interact with the oral environment and improve the longevity of bonded restorations[84]. The release of ions can eliminate microorganisms, encourage the accumulation of apatite-like substances, and enhance the tooth's resistance to acid attacks. The accumulation of apatite-like substances also reacts to changes in the pH levels of the oral cavity by absorbing or discharging Ca, P, and F ions, which helps maintain the tooth structure's integrity[85]. As a result, the durability of restorations is improved, and the frequency of recurrent decay is reduced.

Bioactive materials have the ability to react to environmental changes, which is beneficial for maintaining oral health[86]. For example, when pH levels decrease within the oral cavity, bioactive materials can discharge hydroxyl ions to neutralize the acid generated by the biofilm and increase the alkalinity of the environment. This mechanism eradicates bacteria and prevents the demineralization of teeth. Moreover, alkalizing the oral environment promotes remineralization, restoring lost minerals in teeth.

Several studies have investigated the modification of GIC by various additives to improve their F, Ca, P, and other ion releases[21-23,25,26,28,47,48,56]. When placed on wet dentin, an ion exchange occurs between the freshly mixed GIC and the underlying dentin, releasing aluminium, F, Ca, or strontium ions from the cement and Ca and P ions from the dentin[87,88]. This results in forming an intermediate layer containing ions from both substrates[88-90]. However, for the ion exchange process to promote remineralization, the restoration must create a complete seal against the external environment and have direct contact with the partly demineralized dentin[91]. The release of ions from GICs can potentially promote the (re-)establishment of HA and remineralization of tooth structure, contributing to developing a healthier tooth structure[91,92].

The limitation of our study is the small number of eligible studies that met our inclusion criteria, which was limited to only five non-randomized *in vitro* experimental studies. Additionally, most studies investigated only one type of ion release from GIC, with

only two studies investigating Ca, P, and F release using different analytical techniques. Furthermore, most studies were published in the last decade and had a limited follow-up period. Despite the studies' promising results, the clinical significance of the findings is unclear, and further research is needed to assess their efficacy in clinical practice. Finally, the bibliometric analysis showed a considerable increase in the number of studies published in the last decade, likely due to advancements in dental materials science and the importance of tissue regeneration, with a slight decrease in 2020 due to the COVID-19 pandemic's impact on scientific research and publishing.

CONCLUSIONS

The increased bioactivity of GICs due to ion release is essential in promoting long-term oral health outcomes. In this systematic review, all studies consistently demonstrated that releasing Ca and P ions from GIC significantly enhances its bioactivity. The release of these ions can initiate the remineralization process, leading to the restoration of lost minerals and the promotion of a stronger and healthier tooth structure. Additionally, the ability of GICs to release F ions can contribute to the inhibition of bacterial growth, further promoting the tooth's overall health. Therefore, the release of Ca, P and F ions by GICs is crucial in enhancing their bioactivity and promoting overall oral health.

PERSPECTIVES AND FUTURE DIRECTIONS

In dentistry, researchers continually explore the optimal chemical composition of dental materials to enhance their efficacy in restoring and protecting teeth and oral tissues. The release of F, Ca, and P ions from GIC is a critical property that makes them useful in dentistry. This property is affected by several factors, including the cement's composition, the surrounding environment's pH, and the presence of other ions in the mouth.

Exploring new materials and additives that enhance the cement's ability to remineralize tooth structure is a promising avenue. For future studies, enhancing the bioactivity of GIC and developing new applications are essential. Firstly, it is crucial to develop a new formulation of GIC that can release higher levels of Ca and P ions. Secondly, there may be other applications where GIC's remineralization properties could also be useful, such as treating dental erosion. Thirdly, using GIC combined with other dental treatments, such as F treatments, could enhance their remineralization properties and lead to new treatment protocols that are more effective at preventing tooth decay and other dental problems.

Ongoing research and development in dentistry are focused on the potential of GIC to release Ca and P ions and promote remineralization. However, it is also essential to study the long-term effects of this modification of GIC to determine how they hold up in the mouth and whether they continue to promote remineralization over the long term. Understanding the long-term effects of this modification of GIC and its potential applications will be instrumental in developing more effective restorative materials and enhancing oral health.

ACKNOWLEDGMENTS

The authors would like to thank the University of Malaya for supporting this study and providing the data via the Central Library of the University of Malaya. The authors also declared that no financial support was received for the completion of this study.

REFERENCES

1) Heng C. Tooth decay is the most prevalent disease. Fed Pract 2016; 33: 31-33.
2) Bjørndal L, Larsen T. Changes in the cultivable flora in deep carious lesions following a stepwise excavation procedure. Caries Res 2000; 34: 502-508.
3) Maltz M, Oliveira EF, Fontanella V, Carminatti G. Deep caries lesions after incomplete dentine caries removal: 40-month follow-up study. Caries Res 2007; 41: 493-496.
4) Duque C, Negrini Tde C, Sacono NT, Spolidorio DM, de Souza Costa CA, Hebling J. Clinical and microbiological performance of resin-modified glass-ionomer liners after incomplete dentine caries removal. Clin Oral Investig 2009; 13: 465-471.
5) Weerheijm KL, Kreulen CM, de Soet JJ, Groen HJ, van Amerongen WE. Bacterial counts in carious dentine under restorations: 2-year in vivo effects. Caries Res 1999; 33: 130-134.
6) Mjör I, Moorhead J, Dahl J. Reasons for replacement of restorations in permanent teeth in general dental practice. Int Dent J 2001; 50: 361-366.
7) Jokstad A, Bayne S, Blunck U, Tyas M, Wilson N. Quality of dental restorations FDI Commission Project 2–95*. Int Dent J 2001; 51: 117-158.
8) Comar LP, Wiegand A, Moron BM, Rios D, Buzalaf MA, Buchalla W, *et al*. In situ effect of sodium fluoride or titanium tetrafluoride varnish and solution on carious demineralization of enamel. Eur J Oral Sci 2012; 120: 342-348.
9) Bonetti D, Clarkson JE. Fluoride varnish for caries prevention: Efficacy and implementation. Caries Res 2016; 50 Suppl 1: 45-49.
10) Kucukyilmaz E, Savas S. Evaluation of shear bond strength, penetration ability, microleakage and remineralisation capacity of glass ionomer-based fissure sealants. Eur J Paediatr Dent 2016; 17: 17-23.
11) Yönel N, Bikker FJ, Lagerweij MD, Kleverlaan CJ, van Loveren C, Özen B, *et al*. Anti-erosive effects of fluoride and phytosphingosine: an in vitro study. Eur J Oral Sci 2016; 124: 396-402.
12) Shen C, Rawls HR, Esquivel-Upshaw JF. In; Shen C, Rawls HR, Esquivel-Upshaw JF, editor. Phillips' Science of Dental Materials. 13th ed. St. Louis: Elsevier; 2021.
13) Khoroushi M, Keshani F. A review of glass-ionomers: From conventional glass-ionomer to bioactive glass-ionomer. Dent Res J (Isfahan) 2013; 10: 411-420.
14) Wilson AD, Kent BE. A new translucent cement for dentistry. The glass ionomer cement. Br Dent J 1972; 132: 133-135.
15) Crisp S, Lewis BG, Wilson AD. Glass ionomer cements: Chemistry of erosion. J Dent Res 1976; 55: 1032-1041.
16) Gruythuysen RJ, van Strijp AJ, Wu MK. Long-term survival of indirect pulp treatment performed in primary and permanent teeth with clinically diagnosed deep carious lesions. J Endod

2010; 36: 1490-1493.
17) Tiveron AR, Delbem AC, Gaban G, Sassaki KT, Pedrini D. Effect of resin composites with sodium trimetaphosphate with or without fluoride on hardness, ion release and enamel demineralization. Am J Dent 2013; 26: 201-206.
18) Trairatvorakul C, Itsaraviriyakul S, Wiboonchan W. Effect of glass-ionomer cement on the progression of proximal caries. J Dent Res 2011; 90: 99-103.
19) Mayanagi G, Igarashi K, Jumpei W, Nakajo K, Domon H, Takahashi N. Evaluation of pH at the bacteria-dental cement interface. J Dent Res 2011; 90: 1446-1450.
20) Imazato S, Ma S, Chen JH, Xu HH. Therapeutic polymers for dental adhesives: Loading resins with bio-active components. Dent Mater 2014; 30: 97-104.
21) Al Zraikat H, Palamara JE, Messer HH, Burrow MF, Reynolds EC. The incorporation of casein phosphopeptide-amorphous calcium phosphate into a glass ionomer cement. Dent Mater 2011; 27: 235-243.
22) Mazzaoui SA, Burrow MF, Tyas MJ, Dashper SG, Eakins D, Reynolds EC. Incorporation of casein phosphopeptide-amorphous calcium phosphate into a glass-ionomer cement. J Dent Res 2003; 82: 914-918.
23) Skrtic D, Antonucci JM, Eanes ED. Amorphous calcium phosphate-based bioactive polymeric composites for mineralized tissue regeneration. J Res Natl Inst Stand Technol 2003; 108: 167-182.
24) Grocholewicz K, Matkowska-Cichocka G, Makowiecki P, Droździk A, Ey-Chmielewska H, Dziewulska A, *et al*. Effect of nano-hydroxyapatite and ozone on approximal initial caries: A randomized clinical trial. Sci Rep 2020; 10: 11192.
25) Shahid S, Hassan U, Billington RW, Hill RG, Anderson P. Glass ionomer cements: Effect of strontium substitution on esthetics, radiopacity and fluoride release. Dent Mater 2014; 30: 308-313.
26) Murugan R, Yazid F, Nasruddin NS, Anuar NNM. Effects of nanohydroxyapatite incorporation into glass ionomer cement (GIC). Minerals 2022; 12: 9.
27) Toledano M, Osorio R, Vallecillo-Rivas M, Osorio E, Lynch CD, Aguilera FS, *et al*. Zn-doping of silicate and hydroxyapatite-based cements: Dentin mechanobiology and bioactivity. J Mech Behav Biomed Mater 2021; 114: 104232.
28) De Caluwé T, Vercruysse CWJ, Ladik I, Convents R, Declercq H, Martens LC, *et al*. Addition of bioactive glass to glass ionomer cements: Effect on the physico-chemical properties and biocompatibility. Dent Mater 2017; 33: e186-e203.
29) Jones JR. Review of bioactive glass: From Hench to hybrids. Acta Biomater 2013; 9: 4457-4486.
30) Hench LL, Xynos ID, Polak JM. Bioactive glasses for in situ tissue regeneration. J Biomater Sci Polym Ed 2004; 15: 543-562.
31) Hamdy T. Bioactivity: A new buzz in dental materials. EC Dental Science 2018; 17: 8.
32) Holzapfel BM, Reichert JC, Schantz J-T, Gbureck U, Rackwitz L, Nöth U, *et al*. How smart do biomaterials need to be? A translational science and clinical point of view. Adv Drug Deliv Rev 2013; 65: 581-603.
33) Vallittu PK, Boccaccini AR, Hupa L, Watts DC. Bioactive dental materials —Do they exist and what does bioactivity mean? Dent Mater 2018; 34: 693-694.
34) Kokubo T, Takadama H. How useful is SBF in predicting in vivo bone bioactivity? Biomaterials 2006; 27: 2907-2915.
35) Kim DA, Lee JH, Jun SK, Kim HW, Eltohamy M, Lee HH. Sol-gel-derived bioactive glass nanoparticle-incorporated glass ionomer cement with or without chitosan for enhanced mechanical and biomineralization properties. Dent Mater 2017; 33: 805-817.
36) Makanjuola JO, Essien ER, Bolasodun BO, Umesi DC, Oderinu OH, Adams LA, *et al*. A new hydrolytic route to an experimental glass for use in bioactive glass-ionomer cement. J Mater Res Technol 2022; 18: 2013-2024.
37) Moraes JF, Gomes de Moraes T, Nunes FRS, Carvalho EM, Nunes GS, Carvalho CN, *et al*. Formation of hydroxyapatite nanoprecursors by the addition of bioactive particles in resin-modified glass ionomer cements. Int J Adhes Adhes 2021; 110: 102933.
38) Ana ID, Anggraeni R. Development of bioactive resin modified glass ionomer cement for dental biomedical applications. Heliyon 2021; 7: e05944.
39) Mozafari M, Banijamali S, Baino F, Kargozar S, Hill RG. Calcium carbonate: Adored and ignored in bioactivity assessment. Acta Biomater 2019; 91: 35-47.
40) Bohner M, Lemaitre J. Can bioactivity be tested in vitro with SBF solution? Biomaterials 2009; 30: 2175-2179.
41) Hatibovic-Kofman S, Suljak JP, Koch G. Remineralization of natural carious lesions with a glass ionomer cement. Swed Dent J 1997; 21: 11-17.
42) Attar N, Onen A. Artificial formed caries-like lesions around esthetic restorative materials. J Clin Pediatr Dent 2002; 26: 289-296.
43) Jang KT, Garcia-Godoy F, Donly KJ, Segura A. Remineralizing effects of glass ionomer restorations on adjacent interproximal caries. ASDC J Dent Child 2001; 68: 125-128, 142.
44) Qvist V, Laurberg L, Poulsen A, Teglers PT. Eight-year study on conventional glass ionomer and amalgam restorations in primary teeth. Acta Odontol Scand 2004; 62: 37-45.
45) Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al*. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021; 372: n71.
46) Mehrdad A-B, Ali J. Population, Intervention, Comparison, Outcomes and Study (PICOS) design as a framework to formulate eligibility criteria in systematic reviews. Emerg Med J 2020; 37: 387.
47) Zalizniak I, Palamara JEA, Wong RHK, Cochrane NJ, Burrow MF, Reynolds EC. Ion release and physical properties of CPP–ACP modified GIC in acid solutions. J Dent 2013; 41: 449-454.
48) Par M, Gubler A, Attin T, Tarle Z, Tarle A, Prskalo K, *et al*. Effect of adhesive coating on calcium, phosphate, and fluoride release from experimental and commercial remineralizing dental restorative materials. Sci Rep 2022; 12: 10272.
49) Wang L, Buzalaf MA, Atta MT. Effect of one-bottle adhesive systems on the fluoride release of a resin-modified glass ionomer. J Appl Oral Sci 2004; 12: 12-17.
50) Kelić M, Kilić D, Kelić K, Šutej I, Par M, Peroš K, *et al*. The fluoride ion release from ion-releasing dental materials after surface loading by topical treatment with sodium fluoride gel. J Funct Biomater 2023; 14: 102.
51) Tay FR, Pashley DH, Suh B, Carvalho R, Miller M. Single-step, self-etch adhesives behave as permeable membranes after polymerization. Part I. Bond strength and morphologic evidence. Am J Dent 2004; 17: 271-278.
52) Gao W, Smales RJ. Fluoride release/uptake of conventional and resin-modified glass ionomers, and compomers. J Dent 2001; 29: 301-306.
53) Dashper SG, Catmull DV, Liu SW, Myroforidis H, Zalizniak I, Palamara JE, *et al*. Casein phosphopeptide-amorphous calcium phosphate reduces Streptococcus mutans biofilm development on glass ionomer cement and disrupts established biofilms. PLoS One 2016; 11: e0162322.
54) Shen P, Zalizniak I, Palamara JEA, Burrow MF, Walker GD, Yuan Y, *et al*. Recharge and increase in hardness of GIC with CPP-ACP/F. Dent Mater 2020; 36: 1608-1614.
55) Nicholson JW, Coleman NJ, Sidhu SK. Kinetics of ion release from a conventional glass-ionomer cement. J Mater Sci Mater Med 2021; 32: 30.
56) Allam G, Abd El-Geleel O. Evaluating the mechanical properties, and calcium and fluoride release of glass-ionomer

cement modified with chicken eggshell powder. Dent J (Basel) 2018; 6: 40.
57) Nahla A. Elsalamony DMA-H, Nahed G. Bakir. Bioactivity of ananoeggshell-modified calcium hydroxide dental cement: An in-vitro study. IOSR J Dent Med Sci (IOSR-JDMS) 2018; 17: 70-80.
58) Onwubu SC, Vahed A, Singh S, Kanny KM. Reducing the surface roughness of dental acrylic resins by using an eggshell abrasive material. J Prosthet Dent 2017; 117: 310-314.
59) Salah M, Kataia MM, Kataia EM, El Din EA, Essa ME. Evaluation of eggshell powder as an experimental direct pulp capping material. Futur Dent J 2018; 4: 160-164.
60) Brauer DS, Anjum MN, Mneimne M, Wilson RM, Doweidar H, Hill RG. Fluoride-containing bioactive glass-ceramics. J Non-Cryst Solids 2012; 358: 1438-1442.
61) Mneimne M, Hill RG, Bushby AJ, Brauer DS. High phosphate content significantly increases apatite formation of fluoride-containing bioactive glasses. Acta Biomater 2011; 7: 1827-1834.
62) Kim H-J, Bae HE, Lee J-E, Park I-S, Kim H-G, Kwon J, *et al*. Effects of bioactive glass incorporation into glass ionomer cement on demineralized dentin. Sci Rep 2021; 11: 7016.
63) De Caluwé T, Vercruysse CW, Declercq HA, Schaubroeck D, Verbeeck RM, Martens LC. Bioactivity and biocompatibility of two fluoride containing bioactive glasses for dental applications. Dent Mater 2016; 32: 1414-1428.
64) Nourmohammadi J, Sadrnezhaad SK, Behnamghader A. In vitro bioactivity of novel cured ionomer cement based on iron oxide. Ceram Int 2010; 36: 1645-1651.
65) Landi E, Celotti G, Logroscino G, Tampieri A. Carbonated hydroxyapatite as bone substitute. J Eur Ceram Soc 2003; 23: 2931-2937.
66) Sarig S. Aspartic acid nucleates the apatite crystallites of bone: A hypothesis. Bone 2004; 35: 108-113.
67) Tschoppe P, Zandim DL, Martus P, Kielbassa AM. Enamel and dentine remineralization by nano-hydroxyapatite toothpastes. J Dent 2011; 39: 430-437.
68) Fabritius-Vilpoux K, Enax J, Herbig M, Raabe D, Fabritius H-O. Quantitative affinity parameters of synthetic hydroxyapatite and enamel surfaces in vitro. Bioinspired Biomim Nanobiomaterials 2018; 8: 1-40.
69) Fabritius-Vilpoux K, Enax J, Mayweg D, Meyer F, Herbig M, Raabe D, *et al*. Ultrastructural changes of bovine tooth enamel and dentin surfaces and the influence of biomimetic hydroxyapatite crystallites under chemical erosion. SSRN Electron J 2020; 10.2139/ssrn.3681039.
70) Enax J, Fabritius H-O, Fabritius-Vilpoux K, Amaechi B, Meyer F. Modes of action and clinical efficacy of particulate hydroxyapatite in preventive oral health care —State of the art. Open Dent J 2019; 13: 274-287.
71) Limeback H, Enax J, Meyer F. Biomimetic hydroxyapatite and caries prevention: A systematic review and meta-analysis. Can J Dent Hyg 2021; 55: 148-159.
72) O'Hagan-Wong K, Enax J, Meyer F, Ganss B. The use of hydroxyapatite toothpaste to prevent dental caries. Odontology 2022; 110: 223-230.
73) Paszynska E, Pawinska M, Gawriolek M, Kaminska I, Otulakowska-Skrzynska J, Marczuk-Kolada G, *et al*. Impact of a toothpaste with microcrystalline hydroxyapatite on the occurrence of early childhood caries: A 1-year randomized clinical trial. Sci Rep 2021; 11: 2650.
74) Schlagenhauf U, Kunzelmann KH, Hannig C, May TW, Hösl H, Gratza M, *et al*. Impact of a non-fluoridated microcrystalline hydroxyapatite dentifrice on enamel caries progression in highly caries-susceptible orthodontic patients: A randomized, controlled 6-month trial. J Investig Clin Dent 2019; 10: e12399.
75) Badiee M, Jafari N, Fatemi S, Ameli N, Kasraei S, Ebadifar A. Comparison of the effects of toothpastes containing nanohydroxyapatite and fluoride on white spot lesions in orthodontic patients: A randomized clinical trial. Dent Res J (Isfahan) 2020; 17: 354-359.
76) Kani T, Kani M, Isozaki A, Shintani H, Ohashi T, Tokumoto T. Effect to apatite-containing dentifrices on dental caries in school children. J Dent Health 1989; 39: 104-109.
77) Chen L, Al-Bayatee S, Khurshid Z, Shavandi A, Brunton P, Ratnayake J. Hydroxyapatite in oral care products —A review. Materials (Basel) 2021; 14: 4865.
78) Hannig M, Hannig C. Nanomaterials in preventive dentistry. Nat Nanotechnol 2010; 5: 565-569.
79) White DJ. The application of in vitro models to research on demineralization and remineralization of the teeth. Adv Dent Res 1995; 9: 175-193; discussion 94-97.
80) Buzalaf MA, Hannas AR, Magalhães AC, Rios D, Honório HM, Delbem AC. pH-cycling models for in vitro evaluation of the efficacy of fluoridated dentifrices for caries control: Strengths and limitations. J Appl Oral Sci 2010; 18: 316-334.
81) Spagnuolo G. Bioactive dental materials: The current status. Materials (Basel) 2022; 15: 2016.
82) Delgado AH, Sauro S, Lima AF, Loguercio AD, Della Bona A, Mazzoni A, *et al*. RoBDEMAT: A risk of bias tool and guideline to support reporting of pre-clinical dental materials research and assessment of systematic reviews. J Dent 2022; 127: 104350.
83) Alrahlah A. Diametral tensile strength, flexural strength, and surface microhardness of bioactive bulk fill restorative. J Contemp Dent Pract 2018; 19: 13-19.
84) Diane RB, Anthony AG, Drago S. Amorphous Calcium Phosphate as Bioactive Filler in Polymeric Dental Composites. In: David GC, Maja Dutour S, Božana Č, Helga Füredi M, editors. Contemporary Topics about Phosphorus in Biology and Materials. Rijeka: IntechOpen; 2019. p. Ch. 8.
85) Imazato S, Kohno T, Tsuboi R, Thongthai P, Xu HH, Kitagawa H. Cutting-edge filler technologies to release bio-active components for restorative and preventive dentistry. Dent Mater J 2020; 39: 69-79.
86) Bhadra D, Shah NC, Rao AS, Dedania MS, Bajpai N. A 1-year comparative evaluation of clinical performance of nanohybrid composite with Activa™ bioactive composite in Class II carious lesion: A randomized control study. J Conserv Dent 2019; 22: 92-96.
87) Sennou HE, Lebugle AA, Grégoire GL. X-ray photoelectron spectroscopy study of the dentin–glass ionomer cement interface. Dent Mater 1999; 15: 229-237.
88) Yiu CKY, Tay FR, King NM, Pashley DH, Sidhu SK, Neo JCL, *et al*. Interaction of glass-ionomer cements with moist dentin. J Dent Res 2004; 83: 283-289.
89) Tanumiharja M, Burrow MF, Cimmino A, Tyas MJ. The evaluation of four conditioners for glass ionomer cements using field-emission scanning electron microscopy. J Dent 2001; 29: 131-138.
90) Watson T. Bonding of glass-ionomer cements to tooth structure. In: Davidson CL, Mjör IA, editors. Advances in glass-ionomer cements. Chicago: Quintessence Publishing Co; 1999. p. 121-136
91) Ngo HC, Mount G, Mc Intyre J, Tuisuva J, Von Doussa RJ. Chemical exchange between glass-ionomer restorations and residual carious dentine in permanent molars: An in vivo study. J Dent 2006; 34: 608-613.
92) Ten Cate JM, Buus MJ, Damen JJM. The effects of GIC restorations on enamel and dentin demineralization and remineralization. Adv Dent Res 1995; 9: 384-388.