INTERNATIONAL DENTAL JOURNAL 000 (2022) 1–7

Concise Review

# Bioactivity of Dental Restorative Materials: FDI Policy Statement

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ARTICLE INFO

*Article history:*
Received 9 November 2022
Accepted 20 November 2022
Available online xxx

*Key words:*
Repair
Regeneration
Caries
Pulp
Calcium silicate cement
Fluoride

ABSTRACT

The term *bioactivity* is being increasingly used in medicine and dentistry. Due to its positive connotation, it is frequently utilised for advertising dental restorative materials. However, there is confusion about what the term means, and concerns have been raised about its potential overuse. Therefore, FDI decided to publish a Policy Statement about the bioactivity of dental restorative materials to clarify the term and provide some caveats for its use in advertising. Background information for this Policy Statement was taken from the current literature, mainly from the PubMed database and the internet. Bioactive restorative materials should have beneficial/desired effects. These effects should be local, intended, and nontoxic and should not interfere with a material's principal purpose, namely dental tissue replacement. Three mechanisms for the bioactivity of such materials have been identified: purely biological, mixed biological/chemical, or strictly chemical. Therefore, when the term bioactivity is used in an advertisement or in a description of a dental restorative material, scientific evidence (in vitro or in situ, and preferably in clinical studies) should be provided describing the mechanism of action, the duration of the effect (especially for materials releasing antibacterial substances), and the lack of significant adverse biological side effects (including the development and spread of antimicrobial resistance). Finally, it should be documented that the prime purpose, for instance, to be used to rebuild the form and function of lost tooth substance or lost teeth, is not impaired, as demonstrated by data from in vitro and clinical studies. The use of the term *bioactive dental restorative material* in material advertisement/information should be restricted to materials that fulfil all the requirements as described in the FDI Policy Statement.



## Introduction

There are an increasing number of reports in the scientific literature about the bioactivity of biomaterials across the whole field of medicine; the term even appears in the name of scientific journals (eg, *Bioactive Materials*, see also below). One of the first to use this term was L.L. Hench in the 1970s when introducing bioactive glasses ("bioactive ceramics").[1–3] Such materials were used to replace or repair bone and, more recently, for bone and soft tissue engineering applications. These materials form apatite on their surfaces in contact with tissues and chemically bond to bone.[4–6] The original composition of Hench's formulation has since been modified, and materials with different compositions, particle sizes, and structures have been developed.[7]

Similarly, the terms bioactivity and bioactive material have increasingly appeared in the dental literature[4,5] and in statements from dental professional organisations such as the American Dental Association (ADA; ACE Panel Report

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https://doi.org/10.1016/j.identj.2022.11.012

Bioactive Materials. ace@ada.org; 2018). In addition, other groups, such as the Society for Biomaterials and the Academy of Dental Materials, have provided definitions of this term. The International Association for Dental Research (IADR) Dental Materials Group organised a 2016 symposium that asked "Antibacterial and Bioactive Dental Restorative Materials: Do They Really Work?"[8,9] The topic also was discussed at the 2018 Northern Lights Conference held in Oslo (see below) and during a virtual symposium, which took place during the 2022 IADR General Session. Concerns about the overuse of this term in advertisements have been raised,[10] and the term bioactivity continues as a matter of discussion in the literature.[10–13] Apparently, bioactivity means different things to different people.

Therefore, all parties (practising dentists, academia, manufacturers, and regulators) require more clarity on the meaning of bioactivity in the context of dental restorative materials to:

- Prevent misuse of the term, especially in advertisements
- Provide clarity for regulatory purposes
- Allow for future developments

Therefore, in 2022, the FDI issued a Policy Statement on this topic (https://www.fdiworlddental.org/bioactive-restorative-materials) and relevant background information for this statement is provided here. To keep the length of this Policy Statement reasonable, it was limited to "dental restorative materials." This included those used for indirect or direct restorations, adhesive procedures, and indirect and direct pulp capping. Furthermore, the term *description* was used instead of the term *definition*. According to the Britannica Dictionary (https://www.britannica.com/dictionary/definition), the term definition stands for a clear explanation of the meaning of a word, phrase, and so on, and the term description involves statements that clarify how something or someone looks, sounds, or appears. Therefore, *description* was considered to better mirror the aim of this Policy Statement.

## Target tissues and aims

The prefix *bio-* is derived from the Greek term *bios* and means life, often with a positive connotation as a "good life." Active, in this context, indicates an interaction with living structures. This can be positive (beneficial/desired) or negative. However, within the context of bioactivity, the interaction is generally meant to be beneficial/desired, and the enamel, dentin, and dental pulp are regarded as the prime target tissues for bioactive restorative materials.

For *enamel*, caries prevention is relevant to this discussion, and materials such as glass ionomer cements (GIC) may inhibit caries adjacent to restorations (secondary caries) due to the release of fluorides.[14] These, as well as active antimicrobial fillers, are added to resinous materials.[15] Fluorides from such materials may also remineralise initial enamel caries lesions.[14] However, the structure of enamel is not the result of a pure chemical precipitate from calcium, phosphates, and other molecules, but cells (ameloblasts) are required to create this specific anatomic structure.

*Dentin* in vital teeth contains odontoblast processes reaching into the dentin tubules. In addition, cell-free, intertubular dentin contains many proteins, including (fossilised) signaling molecules.[16,17] Therefore, insults that induce the release of these proteins (eg, caries) lead to intratubular deposition of apatite or the formation of tertiary dentin within the pulp. This can be considered an active cell-mediated process. Similar to enamel, prevention or retardation of caries progression adjacent to a restoration may be achieved by fluoride-releasing restorative materials. In addition, remineralisation of caries-affected dentin has been described adjacent to modified GICs or other ion-releasing materials, including antibacterial fillers.[15,18] However, remineralisation of dentin cannot be considered only as a chemical deposition of apatite. Other factors, such as the collagen fibrils, play an essential role, and substances like tannic acid for crosslinking collagen fibrils also interact chemically with dentinal tissues to improve remineralisation.[19,20] Additionally, restorative materials, such as those releasing calcium hydroxide, can induce the formation of tertiary dentin.[21,22]

The *dental pulp* contains different cell types, such as odontoblastic, neuronal, endothelial, immune, and lymphatic cells (Figure 1). These cells can be direct or indirect targets of bioactive restorative materials, for example, when supporting the healing of the inflamed or exposed pulp by calcium hydroxide-releasing materials.[21] Restorative materials are also applied during so-called pulp revitalisation treatments, for instance, to cover intracanal scaffolds.[21,23] Other oral tissues, such as periodontal tissues, contact dental restorative materials. However, little information is available regarding any potential bioactive effects.

## Definitions of bioactivity in the literature

Hench introduced the term bioactivity into material science as the property reflecting the ability of a biomaterial to form apatite-like material on its surface when immersed in a

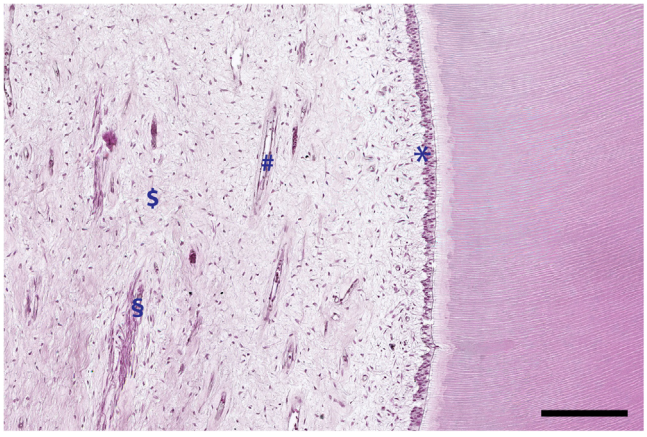


**Fig. 1 – The dental pulp is a prime target of bioactive restorative materials. Histology shows odontoblasts (*), nerve cells (§), fibroblasts ($), and blood vessels with endothelial cells (#), which are involved in pulp/dentin healing and repair (bar = 200 $\mu$m; courtesy of Dr Widbiller).**

simulated body fluid (SBF) for some time.[3–5] Since then, many modifications of this definition, both broad and narrow, and other related terms have been suggested.[24] The journal *Bioactive Materials* writes in its Aims and Scope: "Bioactive materials will feature adaptiveness to the biological environment, being designed to stimulate and/or direct appropriate cellular and tissue responses, or control interactions with microbiological species." (http://www.keaipublishing.com/en/journals/bioactive-materials).

Whitlow et al [25] in 2016 defined bioactive materials as "materials able to elicit specific and predictable cell and tissue responses." In 2018, Vallittu et al[10] addressed the term bioactive in the context of biomineralisation and asked for stringent scientific proof of such an effect before being used in advertisements. It should be restricted to materials and material combinations that release substantial quantities of ions for specific biomineralisation in the clinical environment of the material.[10] The 2018 Northern Lights Conference concluded that "dental restorative materials may be called bioactive if, in addition to their primary function of restoring or replacing missing tooth structure, they actively stimulate or direct specific cellular or tissue responses, or both, or they can control interactions with microbiological species. Such effects should be characterised by the field of application, the effect, and how the effect was scientifically proven."[26] In the broader sense, the term bioactivity was attributed to materials that cause the formation of reparative tissue or release component(s) that have antimicrobial activity (including high-pH materials). Furthermore, materials might be included with a surface conducive to cell attachment and which nucleate the formation of calcium phosphates, including apatite-like materials, when in contact with saliva or tissue fluids.[26]

In 2015, other authors[24,27] proposed the term *biointeractive* for ion-releasing materials, such as GICs, giomers, or fluoride-releasing resin-based composites (RBCs). This definition should differentiate such materials from other materials, such as calcium silicate cements, which form apatite and induce tertiary dentin formation. However, this rather unspecific term is not frequently used, probably because the definition may include a variety of other processes, such as adhesive bonding of RBCs.

Bioactivity has also been defined in some ISO standards; however, the definition is related mainly to surgical implants. For example, in ISO 23317:2014, bioactivity is defined as the "property that elicits a specific biological response at the interface of the material, which results in the formation of a bond between tissue and material."[28] In ISO 19090:2018, bioceramics must have a direct bone bonding property when implanted into a bone defect.[29]

In summary, different definitions have been published. Some of are relatively narrow (eg, only for implant materials), and others have a broader scope that includes restorative materials and a range of different mechanisms are covered. The FDI Policy Statement takes a broad approach by combining available definitions to describe generally agreed-upon characteristics, and it also requires the mechanisms involved to be defined.

## General characteristics

*Beneficial/desired effects* from dental restorative materials comprise disease prevention, remineralisation of affected dental hard tissues, induction of new dentin or dentin-like tissue formation, and support of pulp healing.

*Local effects* comprise biological reactions that are mainly towards enamel, dentin, and the dental pulp. This is in contrast to adverse biological reactions, which can also be generalised, such as in the case of allergic reactions.[30]

*Intentionality* is also a general characteristic of bioactivity. However, the primary function ("principal intended action" according to the EU Medical Device Regulation [MDR][31]) of a dental restorative material is to replace lost tissue. This can be supported by a localised interaction of a material with enamel or dentin (eg, during a bonding procedure). Therefore, this is generally not classified as a bioactive intervention. However, the release of potentially bioactive ions, such as fluoride ions from GICs, may be regarded as a secondary effect that is potentially beneficial. Thus, medical device regulations will generally apply.

On the other end of the spectrum, when pharmaceutical agents or bone morphogenetic proteins are delivered, their bioactive effect is the primary function. Thus, regulatory systems for medicines may apply, or the product may be classified as a Class III device under the MDR.[31] This is an active area of research for restorative dental materials. Nevertheless, this shows that using the term *intentionally* in this context may also have regulatory consequences. For example, the product may be allocated to specific risk classes according to national or international medical device regulations. This may involve additional financial and time burdens for the manufacturer and the patient. Therefore, for the time being, a dental restorative material's bioactive effect is secondary to its primary purpose, which is to be used to rebuild the form and function of lost tooth substance or lost teeth.

*Repair and regeneration* are both terms that describe the endpoints of a healing process, but they cover 2 different biological events.[32] Tissue repair is associated with the formation of scar tissue, where the newly formed tissue—although often an accepted treatment outcome—may provide structural abnormalities and functional limitations compared with the original tissue.[21] On the other side, the subject of regenerative medicine aims at the replacement and regeneration of human cells, tissues, or organs.[21] For example, for enamel caries, the preventive effects of fluoride may lead to a slightly different chemical composition of the enamel (eg, partial replacement of hydroxyl-apatite by fluor-apatite) compared to the original one. The same is true for remineralising enamel and dentin.[33,34] Therefore, it should be kept in mind that the term remineralisation in this context does not mean tissue regeneration; instead, it is repair.

Tertiary dentin formation results in either reactionary dentin (with surviving primary odontoblasts) or reparative dentin after pulp capping and the formation of secondary odontoblasts (Figure 2).[32,35] In both cases, the new hard tissue lacks the clear tubular structure of the original dentin and resembles osteodentin.[35] After the healing of an inflamed pulp, structural changes can be observed, such as a reduced odontoblast layer or hard tissue formation (reactionary dentin). In summary, when describing bioactive restorative materials, the outcome is mainly repair, except for any antibacterial effects (see below), where both terms are not applicable.

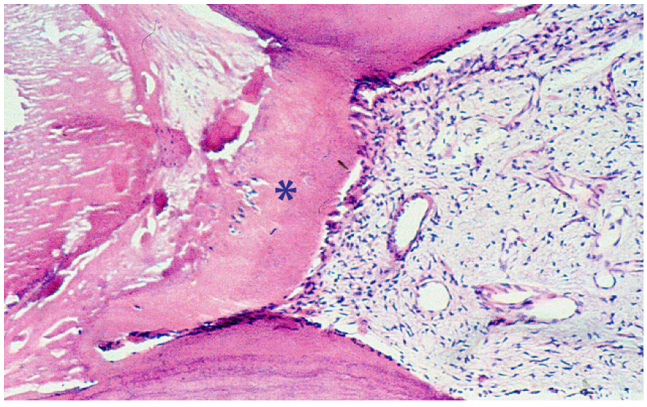

**Fig. 2 – Bridge formation (* = osteodentin) after capping the exposed pulp with a calcium hydroxide releasing preparation (60×).[30]**

*Antibacterial effects* play an essential role because most oral diseases are associated with the presence of a biofilm. For example, a possible bioactive effect of dental restorative materials is to prevent caries and gingivitis adjacent to restorations through antibacterial properties.[36] Such effects may be due to substances released from the restorative material or via a surface-repellent effect (eg, the lotus effect).[36] Recently, materials have been investigated that use pH-sensitive carriers that release antibacterial substances only at or below a critical pH level.[37]

Numerous potential products and substances have been investigated,[36] but only a few products have made it to market.[38] An essential point is the problem of determining when the antibacterial effect measured in a laboratory test is clinically relevant. Another point is the duration of such an effect because the release of substances from restorative materials will likely decrease over time.[39] Therefore, activities in the ISO Technical Committee 106 – Dentistry are underway to standardise such experiments, setting limits that define when a material can be termed antibacterial and determining the duration of this effect.[39]

*Combined effects* for one bioactive material may occur. For instance, calcium hydroxide induces tertiary dentin formation and exerts antibacterial effects.[21,40] For materials containing so-called bioglasses as fillers, long-term antibacterial actions have been shown, and there is also a long-lasting Ca and phosphate ion release from the product. This indicates some potential for remineralisation.[41]

## Mechanism of action

Different mechanisms of action have been attributed to bioactive dental restorative materials. In the FDI Policy Statement, the following mechanisms of action are listed:

- Solely biological
- Mixed biological and chemical
- Purely chemical

The *solely biological mechanisms* involve molecules such as exogenous growth factors, enzymes, or pharmaceuticals,[21,23,42,43] which specifically interact with the cell metabolism, being investigated in the context of pulp regeneration and potential incorporation into dental restorative materials in the future.[44] Restorative materials that contain antibiotics or antibiotic conjugates[45] can also be included in this group. However, such an unspecific use of antibiotics (for antiseptics, see below) is viewed critically due to the problem of creating antibacterial resistance and dysbiosis.[46] From a regulatory point of view, such materials may fall under systems for medicines, or they may be classified as Class III devices, under the MDR.[31]

Products that release calcium hydroxide are an example of a *mixed biological and chemical mechanism* (Figure 2). A typical material based on Portland cement (MTA) induces tertiary dentin formation after pulp capping in laboratory and clinical studies.[47–50] Calcium hydroxide leads to a chemical burn due to its high pH when in direct contact with living tissue. However, it also releases and activates fossilised signaling molecules from dentin, such as transforming growth factor beta 1, which then initiate tertiary dentin formation.[44,51]

Materials based on synthetic tri/dicalcium silicates, such as Biodentine (Septodont), have been marketed. Similar to MTA, they release calcium hydroxide, which then initiates the above-described tissue reactions.[52,53] Combinations of calcium silicate (Portland cement) and acrylates release calcium ions,[54] but no calcium hydroxide,[55] and thus the clinical reactions are equivocal. Although some authors report positive results and some bridge formation in animal studies, this was not confirmed in clinical studies.[56] This exemplifies that release studies alone may be insufficient to demonstrate that clinically relevant bioactivity exists. Little information exists about a modified version of calcium silicate material combined with acrylates.[57] Different so-called bioglasses releasing ions (eg, calcium and phosphate ions) and raising the pH have been investigated[6,58,59] and proposed for pulp capping.[7] However, scientific information is again limited.

A *purely chemical mechanism of action* is the basis of bioactive restorative materials which release different ions, and the bioactive effect (for caries prevention and remineralisation) is due to chemical reactions such as some form of precipitation/deposition. A typical example of this group of dental restorative materials is GIC, which releases fluoride ions, especially after setting. However, this material can be "recharged" by applying topical fluoride to the surface. The extent of the caries preventive effect is a matter of discussion, but some effect has been described.[14] In addition, several substances have been added to GIC, such as silver alloys or silver alloys fused to the glass particles, which exhibit some antibacterial activity.[60]

Resin-modified glass ionomers (RMGIC) also release fluoride, but to a lesser extent than the original GICs. Amorphous calcium phosphate has also been added to RBCs, resulting in the release of calcium and phosphate ions.[61] Resin-based composite materials containing so-called reactive fillers, such as bioglasses, release ions like calcium, phosphate, or fluoride or raise the pH of the surrounding fluids , resulting in some remineralising and antibacterial effects.[58,59] However, differences between different products exist, and despite the release of calcium ions from one material, no apatite formation was observed.[62] This again shows that the simple demonstration that ions are released is insufficient to demonstrate bioactivity.

Also, in this group, materials containing antiseptic substances can be listed, such as chlorhexidine, cetylpyridium chloride, copper, zinc, or silver, because—in contrast to antibiotics—their action is unspecific and not directed to a particular metabolic pathway.[63] Also, the inactivation of enzymes like matrix metalloproteinases is based on a chemical reaction.[64]

Depending upon the intended effect, one material may act through several mechanisms. For instance, bioglass-containing RBCs can exert a purely chemical effect that prevents caries adjacent to restorations,[58] and also a mixed effect when inducing tertiary dentin formation.[7]

In summary, although the release of different ions from restorative materials may be considered a prerequisite for bioactivity, this release is insufficient to demonstrate any actual bioactive effect, such as remineralisation, tertiary dentin formation, or other antibacterial effects. Instead, the influence of other factors, such as proteins, must also be addressed.

## Impairment of principal material properties/ adverse effects

The claimed bioactive effects of restorative materials are primarily caused by substances eluted from the material into a mainly aqueous environment. This solubility may interfere with the material's physical properties and also increase water sorption.[5,65] In addition, incorporating bioactive substances into restorative materials with the intent to have a slow release may also interfere with the setting reaction. Thus, other substances may be eluted in higher amounts than the original materials.[66] The possibility of bacterial resistance formation should always be addressed when considering the addition and slow release of antibacterial substances, such as antibiotics or antiseptics.[46,67]

Substances with antibacterial effects, such as disinfectants like copper, zinc, or silver, may be incorporated, but cytotoxic effects may be caused by eluted substances, which must be investigated. Silver nanoparticles may be beneficial, but the concentrations used in the products are particularly important.[63,68]

Finally, the fulfillment of the principal purpose of the dental restorative material to be used in the context of restoring lost dental tissue must be shown by clinical studies. In the past, a material termed *smart* was marketed, which released fluoride and calcium ions. However, after only 1 year of clinical service, increasing hypersensitivity and tooth crack formation occurred. This was apparently due to increased water uptake and material swelling.[69] More recently, another material advertised as bioactive was used in a clinical trial following the manufacturer's instructions (placed after a short phosphoric acid pretreatment, but without an adhesive system). Unfortunately, the material had an unacceptably high failure rate (24.1%) after 1 year.[70] After this study was published, the manufacturer's instructions for use were changed. This demonstrates the need to prove that adding bioactive substances to a product does not impair the primary function of the restorative material before the product is marketed.

## Proof of an effect

The FDI Policy Statement asks for scientific evidence before a restorative material is called bioactive in advertisements. This evidence should be based on in vitro, in situ, or preferably clinical studies. These studies must be designed according to the anticipated effect. Single in vitro studies demonstrating the release of ions or a cell/bacterial reaction towards a material are only considered screening tools. Properly conducted clinical studies are most relevant, proving that certain effects occur clinically, such as enamel or dentin remineralisation. However, such studies are both challenging and costly. In situ experiments can be an alternative for testing remineralising effects[36] or test batteries for pulp studies, where different end points are included when evaluating the effect on dentin formation.[7] Finally, it must be demonstrated that the primary function of restorative materials is not impaired, for which clinical studies are essential.

## Conclusions

The term bioactive comprises an extensive array of intended material properties in the product. This term is frequently used as a marketing tool, and concerns have been expressed about its overuse. Therefore, FDI asks in its policy statement to limit the use of the term *bioactive dental restorative material* in product advertisements/information to those materials that meet all five of the following criteria:

- the mechanism is clearly defined and described (biological, mixed, chemical),
- a scientifically proven bioactive effect in vitro or in situ and preferably also in clinical studies,
- a stated duration of the effect, especially for antibacterial effects,
- no significant adverse biological side effects (including the development and spread of antimicrobial resistance), and
- the prime purpose, for instance, to be used to rebuild the form and function of lost tooth substance or lost teeth, is not impaired, as demonstrated by data from in vitro *and* clinical studies.

## Author contributions

G. Schmalz, R. Hickel, R.B. Price, and J.A. Platt contributed to conception, design, and data acquisition and interpretation and drafted and critically revised manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

## Conflict of interest

None disclosed.

## Funding

The publication costs of this review were covered by the FDI World Dental Federation.

## REFERENCES

[1]. Hench LL, Splinter RJ, Allen WC. Greenlee TK. Bonding mechanisms at the interface of ceramic prosthetic materials. J Biomed Mater Res 1971;5(6):117–41.
2. Hench LL. Bioactive ceramics. Ann N Y Acad Sci 1988;523:54–71.
3. Hench LL. The story of Bioglass. J Mater Sci Mater Med 2006;17 (11):967–78.
4. Jefferies SR. Bioactive and biomimetic restorative materials: a comprehensive review. Part I. J Esthet Restor Dent 2014;26 (1):14–26.
5. Jefferies SR. Bioactive dental materials. Inside Dentistry. 2016;12(2).
6. Ciraldo FE, Boccardi E, Melli V, Westhauser F, Boccaccini AR. Tackling bioactive glass excessive in vitro bioreactivity: preconditioning approaches for cell culture tests. Acta Biomater 2018;75:3–10.
7. Mocquot C, Colon P, Fernando D, et al. The influence of experimental bioactive glasses on pulp cells behavior in vitro. Dent Mater 2020;36(10):1322–31.
8. Chan DC, Sadr A. Special issue foreward. Am J Dent 2018;31 (B):2b.
9. Chan DC, Hu W, Chung KH, et al. Reactions: antibacterial and bioactive dental restorative materials: do they really work? Am J Dent 2018;31 (B):32b–6b.
10. Vallittu PK, Boccaccini AR, Hupa L, Watts DC. Bioactive dental materials-do they exist and what does bioactivity mean? Dent Mater 2018;34(5):693–4.
11. Pan H, Zhao X, Darvell BW, Lu WW. Apatite-formation ability –predictor of "bioactivity"? Acta Biomater 2010;6(11):4181–8.
12. Darvell BW, Smith AJ. Inert to bioactive - a multidimensional spectrum. Dent Mater 2022;38(1):2–6.
13. Spagnuolo G. Bioactive dental materials: the current status. Materials 2022;15:2016.
14. Hill R. Glass ionomer polyalkenoate cements and related materials: past, present and future. Br Dent J 2022;232(9):653–7.
15. Makvandi P, Gu JT, Zare EN, et al. Polymeric and inorganic nanoscopical antimicrobial fillers in dentistry. Acta Biomater 2020;101:69–101.
16. Widbiller M, Schweikl H, Bruckmann A, et al. Shotgun proteomics of human dentin with different prefractionation methods. Sci Rep 2019;9(1):4457.
17. Zhao S, Sloan AJ, Murray PE, Lumley PJ, Smith AJ. Ultrastructural localisation of TGF-beta exposure in dentine by chemical treatment. Histochem J 2000;32(8):489–94.
18. Shoji M, Kurokawa H, Takahashi N, et al. Evaluation of the effect of a glass ionomer cement containing fluoro-zinc-silicate glass on dentin remineralization using the ultrasonic pulse-echo method. Dent Mater J 2022;41(4):560–6.
19. Niu LN, Zhang W, Pashley DH, et al. Biomimetic remineralization of dentin. Dent Mater 2014;30(1):77–96.
20. Kong W, Du Q, Qu Y, et al. Tannic acid induces dentin biomineralization by crosslinking and surface modification. RSC Adv 2022;12(6):3454–64.
21. Widbiller M, Schmalz G. Endodontic regeneration: hard shell, soft core. Odontology 2021;109(2):303–12.
22. Anselmi C, Mendes Soares IP, Leite ML, Kitagawa FA, de Souza Costa CA, Hebling J. Cytocompatibility and bioactivity of calcium hydroxide-containing nanofiber scaffolds loaded with fibronectin for dentin tissue engineering. Clin Oral Investig 2022;26(5):4031–47.
23. Schmalz G, Widbiller M, Galler KM. Clinical perspectives of pulp regeneration. J Endod 2020;46(9S):S161–S74.
24. Primus C, Gutmann JL, Tay FR, Fuks AB. Calcium silicate and calcium aluminate cements for dentistry reviewed. JACerS 2022;105(3):1841–63.
25. Whitlow J, Paul A, Polini A. Bioactive materials: definitions and application in tissue engineering and regeneration therapy. In: Marchi J, editor. Biocompatible glasses: from bone regeneration to cancer treatment. editor Cham: Springer International Publishing; 2016. p. 1–17.
26. Price JBR. The value of consensus conference: peer review by 50 key opinion leaders. Stoma Edu J 2018;5(5):202–4.
27. Gandolfi MG, Siboni F, Botero T, Bossù M, Riccitiello F, Prati C. Calcium silicate and calcium hydroxide materials for pulp capping: biointeractivity, porosity, solubility and bioactivity of current formulations. J Appl Biomater Funct Mater 2015;13 (1):43–60.
28. ISO 23317:2014 Implants for surgery — In vitro evaluation for apatite-forming ability of implant materials. International Organization for Standardization: Chemin de Blandonnet 2014;8:1214. Vernier, Genève, Switzerland.
29. ISO 19090:2018 Tissue-engineered medical products — Bioactive ceramics — Method to measure cell migration in porous materials. International Organization for Standardization: Chemin de Blandonnet 2018;8:1214. Vernier, Genève, Switzerland.
30. Schmalz G, Arenholt-Bindslev D. Biocompatibility of dental materials. Berlin Heidelberg: Springer; 2009.
31. European Commission. REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC. Official Journal of the European Union; 2017. Available from: https://eur-lex.europa.eu/legal-content/DE/TXT/?uri=CELEX%3A32017R0745 Accessed October 1, 2022.
32. Goldberg M, Schmalz G. Toward a strategic plan for pulp healing: from repair to regeneration. Clin Oral Investig 2011;15 (1):1–2.
33. ten Cate JM. Current concepts on the theories of the mechanism of action of fluoride. Acta Odontol Scand 1999;57(6):325–9.
34. Li X, Wang J, Joiner A, Chang J. The remineralisation of enamel: a review of the literature. J Dent 2014;42(Suppl 1): S12–20.
35. Goldberg M, Smith AJ. Cells and extracellular matrices of dentin and pulp: a biological basis for repair and tissue engineering. Crit Rev Oral Biol Med 2004;15(1):13–27.
36. Schmalz G, Cieplik F. Biofilms on restorative materials. Monogr Oral Sci 2021;29:155–94.
37. Peng X, Han Q, Zhou X, et al. Effect of pH-sensitive nanoparticles on inhibiting oral biofilms. Drug Deliv 2022;29(1):561–73.
38. Imazato S. Bio-active restorative materials with antibacterial effects: new dimension of innovation in restorative dentistry. Dent Mater J 2009;28(1):11–9.
39. Cieplik F, Aparicio C, Kreth J, Schmalz G. Development of standard protocols for biofilm-biomaterial interface testing. JADA Foundational Science 2022;1:100008.
40. Sharma G, Ahmed HMA, Zilm PS, Rossi-Fedele G. Antimicrobial properties of calcium hydroxide dressing when used for long-term application: a systematic review. Aust Endod J 2018;44(1):60–5.
41. AlSahafi R, Mitwalli H, Alhussein A, et al. Novel rechargeable nanostructured calcium phosphate crown cement with long-term ion release and antibacterial activity to suppress saliva microcosm biofilms. J Dent 2022;122:104140.
42. Schmalz G, Widbiller M, Galler KM. Signaling molecules and pulp regeneration. J Endod 2017;43(9S):S7–11.
43. Neves VC, Babb R, Chandrasekaran D, Sharpe PT. Promotion of natural tooth repair by small molecule GSK3 antagonists. Sci Rep 2017;7:39654.
44. Schmalz G, Smith AJ. Pulp development, repair, and regeneration: challenges of the transition from traditional dentistry to biologically based therapies. J Endod 2014;40(4 Suppl):S2–5.

45. Zhang R, Jones MM, Moussa H, et al. Polymer-antibiotic conjugates as antibacterial additives in dental resins. Biomater Sci 2018;7(1):287–95.
46. Thompson W, Sandoe J, Pavitt S, Walsh T, Byrne-Davis L. Co-developing an antibiotic stewardship tool for dentistry: shared decision-making for adults with toothache or infection. Antibiotics 2021;10(11).
47. Torabinejad M, Nosrat A, Verma P, Udochukwu O. Regenerative endodontic treatment or mineral trioxide aggregate apical plug in teeth with necrotic pulps and open apices: a systematic review and meta-analysis. J Endod 2017;43 (11):1806–20.
48. Camilleri J, Pitt Ford TR. Mineral trioxide aggregate: a review of the constituents and biological properties of the material. Int Endod J 2006;39(10):747–54.
49. Dammaschke T, Stratmann U, Wolff P, Sagheri D, Schäfer E. Direct pulp capping with mineral trioxide aggregate: an immunohistologic comparison with calcium hydroxide in rodents. J Endod 2010;36(5):814–9.
50. Hilton TJ, Ferracane JL, Mancl L. Northwest practice-based research collaborative in evidence-based d. comparison of CaOH with MTA for direct pulp capping: a PBRN randomized clinical trial. J Dent Res 2013;92(7 Suppl):16S–22S.
51. Tomson PL, Grover LM, Lumley PJ, Sloan AJ, Smith AJ, Cooper PR. Dissolution of bio-active dentine matrix components by mineral trioxide aggregate. J Dent 2007;35(8):636–42.
52. Laurent P, Camps J, About I. Biodentine(TM) induces TGF-beta1 release from human pulp cells and early dental pulp mineralization. Int Endod J 2012;45(5):439–48.
53. Giraud T, Jeanneau C, Rombouts C, Bakhtiar H, Laurent P. About I. Pulp capping materials modulate the balance between inflammation and regeneration. Dent Mater 2019;35(1):24–35.
54. Gandolfi MG, Siboni F, Prati C. Chemical-physical properties of TheraCal, a novel light-curable MTA-like material for pulp capping. Int Endod J 2012;45(6):571–9.
55. Camilleri J. Hydration characteristics of Biodentine and Theracal used as pulp capping materials. Dent Mater 2014;30 (7):709–15.
56. Bakhtiar H, Nekoofar MH, Aminishakib P, et al. Human pulp responses to partial pulpotomy treatment with TheraCal as compared with Biodentine and ProRoot MTA: a clinical trial. J Endod 2017;43(11):1786–91.
57. Rodríguez-Lozano FJ, López-García S, García-Bernal D, et al. Cytocompatibility and bioactive properties of the new dual-curing resin-modified calcium silicate-based material for vital pulp therapy. Clin Oral Investig 2021;25(8):5009–24.
58. Khvostenko D, Hilton TJ, Ferracane JL, Mitchell JC, Kruzic JJ. Bioactive glass fillers reduce bacterial penetration into marginal gaps for composite restorations. Dent Mater 2016;32(1):73–81.
59. Khvostenko D, Mitchell JC, Hilton TJ, Ferracane JL, Kruzic JJ. Mechanical performance of novel bioactive glass containing dental restorative composites. Dent Mater 2013;29(11):1139–48.
60. Nicholson JW, Sidhu SK, Czarnecka B. Enhancing the mechanical properties of glass-ionomer dental cements: a review. Materials (Basel) 2020;13(11).
61. Marović D, Šariri K, Demoli N, et al. Remineralizing amorphous calcium phosphate based composite resins: the influence of inert fillers on monomer conversion, polymerization shrinkage, and microhardness. Croat Med J 2016;57(5):465–73.
62. Tiskaya M, Al-Eesa NA, Wong FSL, Hill RG. Characterization of the bioactivity of two commercial composites. Dent Mater 2019;35(12):1757–68.
63. Schmalz G. Strategies to improve biocompatibility of dental materials. Curr Oral Health Rep 2014;1:222–31.
64. Neves JG, Marcato PD, de Paula ESFWG, et al. Synthesis and characterization of an experimental primer containing chitosan nanoparticles - effect on the inactivation of metalloproteinases, antimicrobial activity and adhesive strength. Arch Oral Biol 2021;127:105148.
65. Marovic DPM, Posavec K, Marić I, et al. Long-term assessment of contemporary ion-releasing restorative dental materials. Materials 2022;15:4042.
66. Durner J, Stojanovic M, Urcan E, Hickel R, Reichl FX. Influence of silver nano-particles on monomer elution from light-cured composites. Dent Mater 2011;27(7):631–6.
67. Muehler D, Mao X, Czemmel S, et al. Transcriptomic stress response in *Streptococcus mutans* following treatment with a sublethal concentration of chlorhexidine digluconate. Microorganisms 2022;10(3).
68. Schmalz G, Hickel R, van Landuyt KL, Reichl FX. Scientific update on nanoparticles in dentistry. Int Dent J 2018;68(5):299–305.
69. Braun AR, Frankenberger R, Krämer N. Clinical performance and margin analysis of ariston pHc versus Solitaire I as posterior restorations after 1 year. Clin Oral Investig 2001;5(3):139–47.
70. van Dijken JWV, Pallesen U, Benetti A. A randomized controlled evaluation of posterior resin restorations of an altered resin modified glass-ionomer cement with claimed bioactivity. Dent Mater 2019;35(2):335–43.