Quality Resource Guide

A Primer for “Bioactive” Dental Materials

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Educational Objectives

Following this unit of instruction, the learner should be able to:

1. Identify the types and intended purpose of available materials for dentistry that have been referred to as “bioactive”.
2. Explain the possible modes of action for dental materials claiming to be “bioactive”.
3. Describe how certain “bioactive” materials are claimed to exert effects on bacteria.
4. Discuss how certain “bioactive” materials are claimed to contribute to the mineralization of tooth structures.
5. Compare the concept of “bioactive” materials based on chemical vs. biological vs. mixed effects.

MetLife designates this activity for **1.0 continuing education credits** for the review of this Quality Resource Guide and successful completion of the post test.

The following commentary highlights fundamental and commonly accepted practices on the subject matter. The information is intended as a general overview and is for educational purposes only. This information does not constitute legal advice, which can only be provided by an attorney.

Published August 2023. Expiration date: August 2026.

The content of this Guide is subject to change as new scientific information becomes available.

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Introduction

Dentists are moving toward a time when their demand for restorative materials is beyond those that are inert or biocompatible. Instead, they expect choices that create positive effects within the oral environment. Current commercial and experimental efforts to address that requirement involve designing materials that are antimicrobial or antifouling (inhibiting biofilm formation), mineralizing, regenerating or some combination of those outcomes. The word being applied to describe these developing materials is "bioactive", placed in quotes here and in many other publications because the actual definition is unclear, allowing the word to be used in both broad and narrow contexts and with much debate.

Controversy surrounds these materials related to understanding what constitutes "bioactivity." Materials used as sealants, adhesives, restorations, cements, vital pulp treatments and possibly in pulp regeneration are claimed to be "bioactive". However, they have different purposes and attempt to achieve results differently. Some consider certain "historical" materials to be "bioactive". Glass ionomers, used for decades in dental care, are now sometimes considered as "bioactive" because they release ions such as fluoride that can induce an antibacterial effect as well as assist in new mineral formation.

The purpose of this Quality Resource Guide (QRG) is to provide some clarity for the dental provider around the concept of "bioactive" materials used for restorative dentistry by describing and discussing:

- the types of available materials,
- their intended uses,
- their modes of action to achieve their effects, and
- differentiating materials that work by purely chemical reactions from those that induce biological interactions.

Notably, an extensive array of literature is associated with "bioactive" materials, predominantly used in bone and soft tissue regeneration. This QRG will focus solely on materials designed for restorative dentistry. Even with this restriction, searching PubMed with the terms "dental bioactive material, restorative" returns nearly 700 manuscripts.

Definition

Many definitions have been put forth for "bioactive" dental materials.[1] Most recently, an FDI World Dental Federation Policy Statement was published to clarify the term "bioactivity" and provide criteria for the use of the word in advertisements and literature for dental restorative materials.[2]

The Policy clearly provides an option for the "bioactive" effect to be biological, chemical, or mixed. In brief, the policy requires the following:

- A clearly defined and described mechanism
- A scientifically proven effect of a stated duration
- A lack of significant adverse biological side effects
- Data demonstrating that the material primarily functions in restoring form and function to the tooth

The FDI policy also makes two essential points:

"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."[2]

No doubt there will be both agreement and disagreement with this Policy's approach to describe "bioactive" materials. Nevertheless, it is with these considerations that current and future dental restorative materials that may be considered "bioactive" will be discussed in this QRG.

Note also that, as pointed out by others[2], designing and having approved a material for the primary purpose of producing a given biological effect, such as inducing mineralization, may require overcoming significant regulatory hurdles.

Abbreviations Used in this Quality Resource Guide

MTA	Mineral Trioxide Aggregate
GIC	Glass Ionomer Cement
RMGIC	Resin-Modified Glass Ionomers
SPRG	Surface pre-Reactive Glass Ionomer Particles
MDPB	Methacryloyloxdodecyl Pyridinium Bromide
QAM	Quaternary Ammonium Methacrylate
MMP	Matrix Mettalloproteinase

"Bioactive" Materials

These materials generally fall into one (or a combination) of three categories:

- ***Forming New Mineral*** - sometimes referred to as remineralizing, or potentially preventing demineralization
  - through the release of mineral promoting ions, such as fluoride, calcium, phosphate, or other molecules, that facilitate mineral formation
  - through the release of ions that raise the pH above the level for demineralization
- ***Antimicrobial***
  - through the release of ions or molecules that directly kill bacteria
  - through the contact killing of bacteria by molecules tethered to the surface
- ***Antifouling*** (or antibiofilm, *i.e.* inhibiting the formation of biofilms on surfaces)
  - through bacteria interaction with surface molecules that inhibit bacterial adhesion
  - through the release of molecules or ions that disrupt some step in the process of forming a biofilm, such as inhibition of the formation of the extracellular matrix network

Table 1 - Applications for Current and Future "Bioactive" Materials for Dentistry

Application	"Bioactive" Material or Component	Mechanism of Action
Pulp Capping and Vital Pulp Therapy	• Calcium hydroxide • MTA* (mineral trioxide aggregate) • Bioceramics (calcium silicates) • Bioceramics with resins (light-cured)	• Release of calcium ions for: ◊ mineral formation ◊ pH regulation ◊ bactericidal effect
Restoratives Adhesives Sealants Cements	• Fluoride releasing glass	• Release of fluoride for: ◊ mineral formation ◊ bactericidal effect
	• Bioactive glass • Calcium phosphates	• Release of calcium, phosphate and other ions for: ◊ mineral formation ◊ pH regulation ◊ bactericidal effect
	• Antimicrobial monomers/molecules (releasable)	• Release of monomers or molecules for direct killing of bacteria
	• Antimicrobial monomers/molecules (tethered, not releasable)	• Presence of monomers tethered to surface and within material that: ◊ kill bacteria on contact ◊ prevent biofilm adhesion
	• Antibiofilm/Antifouling monomers/molecules (releasable or tethered)	• Release of molecules that prevent or disrupt a step in the process of biofilm formation

This QRG will describe "bioactive" materials used in vital pulp therapy, restorations, adhesives, sealants and cements. Many of the same types of "bioactive" components can be incorporated into each of these materials (**Table 1**).

Pulp Capping Agents and Cavity Liners/Bases for Vital Pulp Therapy

Calcium hydroxide is perhaps the first truly "bioactive" dental material. While it was previously thought that the primary mechanism of action for calcium hydroxide to promote reactionary dentin formation was related to irritation caused by its alkalinity, more recent evidence suggests that the interaction of the material with dentin, mobilizing the release of natural bioactive molecules sequestered within the tissue, contributes to its beneficial effects of reparative dentin formation.[3,4] Similar behavior has been demonstrated by Mineral Trioxide Aggregate (MTA).[5] MTA is a biocompatible mixture of metal oxides and silicates (similar to Portland cement) that forms calcium hydroxide during setting. Therefore, it is alkaline and has a similar mechanism of action as calcium hydroxide.[6] Both materials also have a potential antibacterial effect due to their alkalinity and release of calcium ions.

The chemical formulation of MTA consists of tricalcium oxide, silicon oxide, bismuth oxide, tricalcium silicate and tricalcium aluminate, which hardens in the presence of humidity, similar to calcium hydroxide.[7] Because the set MTA is less soluble than calcium hydroxide and produces similar benefits, and because clinical studies have shown its superiority to calcium hydroxide,[8] it has become the material of choice as a direct pulp capping agent or for pulpotomies, despite its higher cost.[9] Although MTA offered improvements over calcium hydroxide, its slow setting rate, potential discoloring of the tooth, and still limited mechanical properties were considered significant limitations. To address these concerns, other "bioactive" materials for vital pulp therapy have been produced based on tricalcium silicate. These materials are labeled as hydraulic cements,[10] a term also suggested for MTA.[11] Hydraulic cements have demonstrated improved physical properties and nearly equivalent success as pulp capping agents for permanent teeth and primary molars.[9,12]

These pulp capping materials and similar endodontic sealers have become referred to as "bioceramics", a term used routinely in the endodontic literature.[10,13] Other bioceramics have been developed that are designed for fast setting by incorporating resin components to enable rapid hardening by light-curing. However, the literature suggests they may produce a level of toxicity that exceeds that of the non-resin materials.[14]

Some suggest that MTA should be the preferred pulp-capping agent over the more recently developed calcium silicate bioceramics due to MTA's longer history of safety until further evidence is accumulated for the resin-containing systems to support their use.[15-17] These materials are considered "bioactive" because of their potential dual action of promoting mineral formation and being antimicrobial. The fact that they have shown to be capable of releasing cell-stimulating dentin matrix components (natural bioactive molecules) from dentin suggests that they may be considered "bioactive" in the strictest sense.

Restorative Materials

"Bioactive" restorative dental materials have been available for almost five decades; however, the original materials were not called "bioactive". Traditional Glass Ionomer Cements (GIC) harden by an acid-base reaction between the ionic polymer and the di-and tri-valent cations released from the glass particles due to the acidification of the polymer in the presence of water.[18] The addition of polymerizable monomers rendered the materials curable by blue light and produced materials known as Resin-Modified Glass Ionomers (RMGIC). GICs and RMGICs are now considered "bioactive" by the standard of releasing fluoride, calcium and potentially other ions.[18] GICs have been shown to inhibit adjacent enamel and dentin demineralization at restoration/tooth interfaces[19-21] and potentially on adjacent proximal tooth surfaces.[22]

Glass ionomers may be effective for moderate caries challenges. However, evidence suggests they are less so when exposed to a more severe challenge, such as for xerostomic patients when additional fluoride protections are not provided.[23] Bioactive glass has been added to glass ionomers to enhance their potential "bioactive" effect. This combination has been shown in vitro to release fluoride, calcium and phosphate[24] and to deposit minerals near tooth-composite margins,[25] though no known commercially available product has been produced at this time.

These ionomer materials are often the first-choice restorative material in caries control situations, especially class V lesions. However, they are considered to be limited as definitive restorative materials in load-bearing surfaces due to relatively low wear and fracture resistance during mastication. To address these issues, other types of "hybrid" restorative materials were created, the so-called compomers and giomers. These are a resin composite material with some glass ionomer features, such as fluoride release and/or the inclusion of Surface Pre-Reactive Glass Ionomer particles (SPRG) for ion release.[18]

Others have incorporated ionic resins and calcium phosphate compounds to create potential adhesion to the tooth and beneficial ion release to promote mineralization.[26] While these materials are considered intermediate between resin composite and GIC, they are much closer to composites and require adhesive bonding agents to succeed. Clinicians must read and follow the manufacturer's instructions for material placement. The "bioactive" label would only apply to these materials based on the release of fluoride and potentially other ions, such as calcium and phosphate.

Literature reviews chronicle many attempts to create resin composites with enhanced ion release as a mineralization strategy for adjacent tissues or to fill interfacial gaps, mainly by incorporating calcium phosphate, hydroxyapatite and calcium silicate compounds, or bioactive glasses.[27,28] Particulates in these compounds may be micro-sized, similar to the fillers in most composites. However, the inclusion of nano-sized (1-100 nm) particles of calcium fluoride[29] or amorphous calcium phosphate[30,31] has shown the benefit of greater particle surface area and potentially increased release of ions.

A commercial product, Cention N (Ivoclar-Vivadent), is called an alkasite resin composite with silicate glasses that releases fluoride, calcium and phosphate. This material has significant positive in vitro evidence, with one clinical study showing it is equivalent to GIC for class V restorations, at least up to one year [32] Since the goal of such materials is to saturate the surrounding environment with calcium and phosphate to facilitate the precipitation of minerals, or at least to neutralize the pH, maximizing ion release is essential for the "bioactive" effect. However, it is important to recognize that these are purely chemical processes and, as such, would not be considered "bioactive" by many definitions.[1] Additional issues with these materials are the uncontrolled formation of apatite mineral on the surface of the restorative material,[33] and the fact that composites with calcium phosphate, or hydroxyapatite, fillers show reduced physical properties over time as the particles erode.[34]

Experimental composites containing up to 15% bioactive glass have been shown to have equivalent properties to current commercial dental composites and remained mechanically stable for up to two months.[35] Composites containing nanoparticles as ion releasers and delivery systems for drugs, such as chlorhexidine, are being studied as anti-caries materials.[36]

Several groups have attempted to incorporate organic molecules into resin-based composite restorative materials to create antimicrobial or antibiofilm qualities.[37] The problem with this approach is that simply incorporating molecules that may diffuse out of the composite and into the surrounding environment may impart its antimicrobial activity at some distance from the material, affecting microbes that have yet to become part of a biofilm.[38] This is a different outcome from that achieved by molecules that are co-polymerized within the polymer framework. Those are non-mobile and remain within the material (tethered) and on its surface.[39,40] The antibacterial effect of tethered molecules is either through direct contact killing of bacteria, such as with Methacryloyloxdodecyl Pyridinium Bromide (MDPB) (described in the next section) or through the inhibition of the biofilm formation (antifouling). Many of these materials have shown some evidence for their claims in vitro, and one commercial restorative product (Nobio's Infinix), based on a silica nanoparticle with tethered Quaternary Ammonium Methacrylate (QAM), has been evaluated in an in situ gap model and showed to be superior to conventional composite in reducing demineralization.[41]

Adhesives

The most common reason to make a dental adhesive "bioactive" is to provide antibacterial properties. This is logical, considering that recurrent caries is considered the main reason for the failure of bonded composite restorations.[42] To date, there is one commercial dental adhesive that would be considered "bioactive" by virtue of its antibacterial effect (Clearfil Protect Bond, Kuraray). This adhesive contains MDPB, a compound containing QAM.[43] MDPB is claimed to be antibacterial through bacteriolysis, where negatively charged bacteria are attracted to the positively charged MDPB causing bacterial cell membrane destruction. The exact mechanism of action is still debated. Many similar QAM-containing compounds have been investigated.[44]

Other adhesives have been attempted to create antibacterial properties by adding silver, glutaraldehyde, chlorhexidine, or other compounds (alone or in combinations).[45,46] Experimental "bioactive" adhesives also have been proposed containing fluoride, calcium and phosphate. They are designed to reduce demineralization of adjacent tooth structure.[47,48] Others have tried incorporating various ion-releasing glasses designed to be antimicrobial or inhibiting bond-degrading Matrix Metalloproteinases (MMPs) within the adhesion region.[49,50] No commercial products have come from these attempts for resin-dentin bonding, though adhesive cements for orthodontic bonding applications have been derived.

Sealants

Fluoride ion-releasing sealants, including resin-based and glass ionomer-type materials, have been available for decades. While the concept of fluoride release from these sealants is not detrimental, clinical studies have yet to show a significant improvement due to fluoride release compared to standard resin-based sealants.[51,52] A novel way of incorporating fluoride, calcium and phosphate into permeable microcapsules has been commercialized in at least one sealant, which has shown beneficial effects on remineralizing tissue in vitro.[53] However, no clinical benefits of this technology have been shown.

Another "bioactive" sealant is based on the SPRG fillers noted in the restorative materials section. It has been clinically shown to produce an equivalent anti-caries effect when compared with a fluoride-containing sealant. However, it demonstrates a significantly greater loss of material over time.[54] One may expect that as "bioactive" materials continue to be developed, sealants will provide an excellent vehicle for additional investigation, primarily due to their less-invasive nature.

Cements

The first "bioactive" cements were the silicates, which inhibited caries formation due to their high fluoride content. Glass ionomer and resin-modified glass ionomers, as described previously, would by some definitions be considered bioactive cements by virtue of their potential dual effect of fluoride release. Fluoride has a toxic effect on bacteria and has demonstrated some clinical evidence[53] that it promotes tooth remineralization or, at least, inhibits demineralization.

Other cements have been studied, including calcium phosphates, calcium aluminates, calcium silicates, and other silicates, and have been called bioceramics or "bioactive". These may be considered "bioactive" because they release additional mineralizing ions, such as calcium and phosphate. They harden by a mechanism similar to glass ionomers or may be more composite-like, depending primarily on a polymerization reaction. These cements are designed to adhere to the tooth in some cases, but also to aid in new mineral formation. Often the claim is that they protect against recurrent caries by sealing gaps with new mineral formation, though these claims are yet to be clinically proven. A recent in vitro study suggested that ion-releasing cements may protect crown margins from secondary caries.[55]

Activa BioActive Cement (Pulpdent) is a resin-modified GIC-type material with polyacrylic acid polymer liquid, but the inclusion of significant dimethacrylate resins makes it similar to a compomer as well. The resin is mixed with fluoroaluminosilicate glass fillers that release ions for potential mineralization. Ceramir is called a bioceramic by its manufacturer (Doxa Dental). It is composed of calcium aluminate with fluoroaluminosilicate glass mixed with polyacrylic acid, similar to glass ionomer. A three-year clinical study has shown the material to perform well with complete retention, absence of secondary caries or sensitivity, and no marginal discoloration or loss of marginal integrity.[56] Calibra Biocement (Dentsply), called a bioceramic, is a glass ionomer-type cement with added calcium aluminate and strontium fluoride. Biocem (NuSmile) is a resin-modified glass ionomer cement that claims to release calcium, phosphate and fluoride. It is primarily marketed for pediatric dentistry.

Theracem (Bisco) is a resin cement-type system of adhesive monomers with calcium and silica glass fillers. Predicta (Parkell) is a resin-based self-adhesive cement composed of various monomers and claims to release calcium, phosphate and fluoride. In contrast, Infinix (Nobio) is a resin-based dental cement containing quaternary ammonium compounds tethered to silica particles to make the cement antimicrobial on contact. In this way, it claims to inhibit demineralization by preventing biofilm formation.

Conclusions

Products claiming "bioactivity" have been designed to be antimicrobial, antifouling, mineralizing and inhibiting of demineralization. Examples exist of materials whose mechanism of action involves an authentic biological action, one that is purely chemical, or some mixed mode. While the specific definition of "bioactive" dental restorative materials will likely remain a topic of debate for some time, it is clear is that the group is evolving rapidly.

It was not possible within the context of this guide to discuss all of the research efforts being dedicated to the different types of "bioactive" restorative materials. As is typical, the introduction of these materials will proceed at a far greater rate than the evidence for their effectiveness can be ascertained. However, this is an exciting and rapidly progressing area of restorative dentistry. Dental providers can look forward to many promising materials coming to market for years to come but must be vigilant in assessing the basis of their evidence for efficacy.

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POST-TEST

Internet Users: This page is intended to assist you in fast and accurate testing when completing the "Online Exam." We suggest reviewing the questions and then circling your answers on this page prior to completing the online exam.

(1.0 CE Credit Contact Hour) Please circle the correct answer. 70% equals passing grade.

1. For which application are "bioactive" dental materials NOT currently available or being developed?
a. Adhesives
b. Crowns
c. Restorative Materials
d. Cements

2. "Bioactive" restorative materials typically contain all of the following, EXCEPT:
a. Releasable antibacterial monomers
b. Ion releasing fillers
c. Antifouling monomers
d. Antimicrobial pigments

3. Glass ionomer restoratives may be considered "bioactive" because they:
a. Chemically adhere to apatite
b. Harden through an acid-base reaction
c. Release fluoride ions
d. Can be used for temporary restorations

4. Which of the following is NOT a designed mechanism of action for bioactive materials?
a. Promote chemical precipitation of mineral
b. Stimulate resident cells to produce mineral
c. Kill inflammatory cells to prevent rejection
d. Kill bacteria and promote mineral formation

5. Which of the following is NOT true of bioceramics?
a. Often used for occlusal restorations
b. Have an alkaline pH
c. Release calcium and other ions
d. Are effective pulp capping agents

6. Dentin contains bioactive molecules that can be released when dentin is directly exposed to all of the following EXCEPT:
a. Resin composite
b. Phosphoric acid etching
c. MTA
d. Dentin adhesive

7. According to the FDI policy, a "bioactive" material must exert effects that are:
a. Systemic
b. Toxic
c. Intended
d. Multifactorial

8. Which direct pulp capping agent has shown the best success in clinical studies?
a. Calcium Hydroxide
b. Mineral Trioxide Aggregate (MTA)
c. Dentin adhesives
d. Glass Ionomer

9. Materials containing bioactive glass may be considered beneficial because they:
a. Have a sedative effect on the pulp
b. Encourage healthy gingival tissue
c. May promote mineral formation in interfacial gaps
d. Produce restorations with excellent wear resistance

10. Which ions/molecules are NOT typically released from "bioactive" cements?
a. Eugenol
b. Calcium
c. Phosphate
d. Fluoride

Registration/Certification Information (Necessary for proper certification)

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Date of Birth: _____ Email: _____

State(s) of Licensure: _____ License Number(s): _____

Preferred Dentist Program ID Number: _____ ☐ Check Box If Not A PDP Member

AGD Mastership: ☐ Yes ☐ No

AGD Fellowship: ☐ Yes ☐ No Date: _____

Please Check One: ☐ General Practitioner ☐ Specialist ☐ Dental Hygienist ☐ Other

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Evaluation - A Primer for "Bioactive" Dental Materials 1st Edition

Providing dentists with the opportunity for continuing dental education is an essential part of MetLife's commitment to helping dentists improve the oral health of their patients through education. You can help in this effort by providing feedback regarding the continuing education offering you have just completed.

Please respond to the statements below by checking the appropriate box, using the scale on the right.

	1 = POOR 1	2	3	4	5 = Excellent 5	
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2. How would you rate the quality of the content?	☐	☐	☐	☐	☐	
3. Please rate the effectiveness of the author.	☐	☐	☐	☐	☐	
4. Please rate the written materials and visual aids used.	☐	☐	☐	☐	☐	
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6. How relevant was the course material to your practice?	☐	☐	☐	☐	☐	
7. The extent to which the course enhanced your current knowledge or skill?	☐	☐	☐	☐	☐	
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10 **9** **8** **7** **6** **5** **4** **3** **2** **1** **0**

extremely likely — neutral — not likely at all

What is the primary reason for your 0-10 recommendation rating above?

11. Please identify future topics that you would like to see:

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