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What is Bioactive Dentistry? A Review

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What is Bioactive Dentistry? A Review

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Learning Objectives: After reading this article, the individual will learn: (1) the definition of bioactive dental materials, and (2) current dental materials that possess or claim to possess bioactivity.

About the Authors

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The biological compatibility of bioactive materials is currently a significant topic of interest in the field of restorative dental medicine. At the most recent International Association for Dental Research Meeting (2017), 68 presentations involved bioactive materials, which indicates the high level of activity in this area. The stimulation of biological tissue and cells and the incorporation of materials into tooth structures have both had a large impact on the aesthetics and clinical application of these materials.[1] Bioactive means that the body reacts to the material, as opposed to inert material.

Since the introduction of mineral trioxide aggregate (MTA) in the 1990s, restorative materials in dentistry have evolved significantly.[2] Bioactive materials now encompass new properties and functions. Nevertheless, their introduction has created debate and confusion among dental practitioners, manufacturers, and patients. To address much of what is debated, the authors will define "bioactive material" and then analyze products that claim to possess "bioactivity." ACTIVA (bioactive restorative and base/liner) (Pulpdent), Beautifil (bioactive flowable composite) (Shofu Dental), BioCem Universal Bioactive Cement (resin modified glass ionomer [RMGI]) (NuSmile), and TheraCal LC (bioactive liner) (BISCO Dental Products) have been identified by their manufacturers as bioactive.

Until recently, many restorations have failed, resulting in secondary caries. Bioactive materials may alleviate this problem via their ability to form a tight seal at the interface between tooth and restoration. The materials that have been used in the past do not provide a continuous seal, making micro-leakage more likely to occur and resulting in marginal failure of crowns, inlays, and veneers. Furthermore, these "inert" materials typically function at a continuous and constant pH, which causes the materials to fail, creating crevices where plaque can build up and secondary caries even before the restoration fails. The hope for bioactive materials is that they will prevent micro-leakage by forming apatite, which will provide a continuous seal to the margins between the restoration and tooth. Bioactive materials may also help to re-establish minerals lost to caries.[3]

In the past 20 years, the topic of bioactive materials has been given further attention, as evidenced by the change in the compositions of restorative materials away from inert "fillers" and more toward being biologically adaptive materials.[2] Biocompatible materials, such as titanium and its alloys, are generally used more often for implants, including single and multiple tooth restorations. Such materials are able to restore the form and function of the tooth, but are not influential on the activity of the oral environment. On the other hand, bioactive restorative materials, such as bioglass, glass-ceramic, calcium phosphate ceramic, composites, and coatings, are able to stimulate the biological tissue of the tooth and/or bond to living tissues.

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Figure 1. In this preoperative view, the lesion appeared small. However, that was not the case.

Figure 2. The Solea 9.3-µm CO_2 laser (Convergent Dental) preparation.

Figure 3. The use of a bioactive liner.

Figure 4. The use of a bioactive restorative material—ACTIVA, from Pulpdent—shown 3 years postoperatively.

Bioactive materials also are considerably less harmful to local and generalized tissues. Additionally, these materials have been shown to considerably enhance the aesthetic outcome of restorative dental procedures. This evolution of materials and compositions that display greater interactions with tooth structure is the drive for the future, as seen by the following trend of bioactive material compositions: zinc phosphate to polycarboxylate to glass ionomer cements.[3]

The area of regenerative dentistry has been affected more by the use of bioactive materials than by biocompatible materials. Experiences with calcium hydroxide as a lining material for restorations located close to the pulp has greatly influenced the initiative to develop bioactive materials rather than just biocompatible ones.[3] Calcium hydroxide was first introduced in the 1920s for root canal therapy and is one of the earliest bioactive materials. It is still used today to promote odontoblast differentiation, the formation of dentinal bridges, and mineralization of coronal pulp.[1] It is now understood that calcium hydroxide plays a role in inducing growth factors, which play a role in dentinogenesis. The TGF-B family of growth factors influences odontoblast differentiation in the tooth, ultimately inducing the formation of either a dentinal bridge or areas of mineralization in the coronal pulp.[4] The improved bioactive materials now all include calcium hydroxide as their active ingredient.[5] The activity of calcium hydroxide also results in the rapid release of calcium from these materials, which influences the alkaline environment required for pulpal healing, promotion of immediate bonding and sealing, stimulation of hydroxyl-apatite, and formation of secondary dentin in the affected tissues.[4]

Bioactive restorative dental materials are designed specifically to bioengineer lost tissue and possess clinically applicable benefits due to their unique composition. The design includes a biocompatible matrix material, bioactive molecules, or additive molecules and ions. The biocompatible matrix material functions as the frame or structure for the new tissue to grow within. The bioactive molecules play a role in promoting temporal regeneration of new tissue at the site to which the molecules are recruited. Lastly, additive molecules and ions are incorporated into the bioactive materials, which provide the antimicrobial, tissue-anabolic, and remineralization potential to the tooth.[3]

Although this is a new, interesting, and exciting topic in dental medicine, the clinical relevance of these bioactive materials has not yet been defined. Further research is required to determine the clinical impact of these materials that have been shown to adhere to tooth structure, produce hydroxyapatite, release fluoride, protect the tooth from secondary caries, and have other bioactive properties.[2] Nonetheless, dentists should keep an open mind when it comes to emerging materials that will be extremely beneficial, particularly for the high-risk patients with deep restorations and individuals who have dealt continuously with composite or amalgam restorative failures.

Evolving bioactive materials have a strong influence on the biological environment of the tooth by adhering to tooth structure, releasing fluoride, and ultimately providing protection against secondary caries.[2] These properties will benefit both adult and pediatric patients, as illustrated by the clinical cases described herein. For pediatric patients, the ease of use of these materials is particularly beneficial because of their dual-cure and bulk-fill capabilities. As recently shown by a group at the University of Alabama at Birmingham, dual-cured bulk-fill materials such as ACTIVA produce significantly less micro-leakage compared to conventional, light-cured composite materials.[6]

For pediatric and adult patients, these bioactive materials are more preventative of recurrent caries, which is a leading cause of restorative replacement. This can be attributed to the fact that the bioactive materials are able to self cure and light cure. Self curing allows for more of the material to integrate into the tooth structure, resulting in less polymerization shrinkage and reduced

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Figure 5. Pre-op view showing the appearance of rampant caries.

Figure 6. Preparation for the bioactive liner.

Figure 7. The use of the bioactive ACTIVA liner.

Figure 8. Two restored teeth following the use of bioactive ACTIVA restorative.

Figure 9. The use of ACTIVA Liner and ACTIVA Restorative, post-op view.

stress. ACTIVA, for example, can be light cured up to a thickness of 4 mm and self cured at any depth. In applying ACTIVA, time should be allotted for self curing before placing the material and after mixing it.[7]

Clinicians will also appreciate how biocompatible and antimicrobial these materials are, which is due to their highly alkaline pH. After the setting reaction, the pH rises to become more alkaline as a result of the calcium hydroxide formed from the calcium ions and fluoride ions that are continuously released and recharged from the material.[6] In fact, bioactive materials may provide greater antimicrobial resistance to *Streptococcus mutans* biofilm adhesion, as shown recently by a group at Oregon Health & Sciences University.[8]

Another important property is the strong bond strength between the material and the tooth, enabling greater adherence. This relies on apatite-forming biocompatibility between the bioactive material and enamel or dentin. After immersion of the material into a solution containing inorganic phosphate, a precipitated solid layer of hydroxyapatite is formed at the tooth-material interface.[9] The formation of this layer promotes the creation of a chemical bond that forms between the material and tooth. The clinical success of this property was previously studied on MTA and Portland cement. After immersion of the materials in phosphate-buffered saline (PBS) solution for 2 months, they were shown by the Push-Out Test for bond strengths to have increased adhesion to dentin.[10] More recently, ACTIVA Bioactive Restorative was shown to have significantly greater shear bond strength compared to an RMGI material (ie, GC Fuji Ortho LC Automix [GC America]) and less demineralization than the RMGI and composite resin materials (Transbond XT light cure adhesive [3M]).[11]

What Defines a Bioactive Dental Restorative?

A bioactive dental restorative is defined as a material that forms a layer of hydroxyapatite when immersed in a simulated body fluid or a solution containing inorganic phosphate (eg, a phosphate-buffered saline solution).[12] The concept of bioactivity was first introduced in 1969 and later defined by Cao and Hench[13] in 1996. In general, it refers to a specific property of a material that will induce a response from a living tissue or cell, such as inducing the formation of hydroxyapatite. The direct function of the bioactive material is to induce growth factors and stimulate natural mineralization.[14]

ACTIVA

ACTIVA was reported by the manufacturer, Pulpdent, to be the first bioactive dental material with an ionic resin matrix, shock-absorbing resin component, and bioactive glass fillers that display similar chemical and physical properties to natural teeth.[15] Hydration of this cement results in the formation of hydroxyapatite on the tooth surface, binding the resin to the tooth.[16] A recent study by Epstein et al[17] at Tufts University School of Dental Medicine introduced the clinical relevance of ACTIVA. ACTIVA was shown to have greater compressive strength than the nonbioactive liners, Vitrebond and Fuji Liner. This indicates that the bioactive material can potentially withstand compressive strength and, therefore, more occlusal stress than the others.[17] The comprehensive strength of ACTIVA is attributable to its ability to form calcium and phosphorus on the surface after immersion in PBS, ie, its bioactivity.[18] Therefore, ACTIVA is bioactive by definition, as it is able to produce hydroxyapatite on the tooth after mixing with PBS.

The benefits of this bioactive restorative over nonbioactive materials have also been evaluated as discussed in a review article by Kugel and Eisen in 2017. In the first study reviewed, ACTIVA Bioactive Restorative demonstrated sustained fluoride release when brushed with fluoridated toothpaste compared to other nonbioactive materials that showed decreased fluoride

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release.[19] The continuous release of fluoride may contribute to stronger enamel and greater resistance to acid in the bioactive restored teeth compared to nonbioactive restorations.

Two common pediatric restorative techniques are interim therapeutic restorations (ITR) and atraumatic restorative technique (ART). Although the techniques of these procedures are similar, their therapeutic goals are quite different. ITR is primarily for patients who are very young, who are uncooperative, or who require special care because conventional procedures are not achievable at the time. ITR is also used for caries control (prior to restoration) in children with multiple open carious lesions. On the other hand, the purpose of ART is to restore and prevent caries specifically in populations with little access to dental care.[20] A recent case report by Ewoldsen[21] (2015) described a modified ART technique using ACTIVA in the management of caries. The author concluded that the bioactive materials exceed the service of the previously classified interim or temporary materials as demonstrated by their ionic properties and remineralization potential. Thus, bioactive materials may indeed provide long-term therapeutic restorations with aesthetics and durability comparable to today's complex composite restoratives.[21]

More recently, ACTIVA has been shown to alleviate the difficult challenge that ankylosed primary second molars with no premolar successor present to dentists. One treatment option for this is the re-establishment of proper occlusion and mesio-distal contacts for retained primary molars with infra-occlusion. Croll and Cavanaugh[22] (2016) published a case report on the treatment of an ankylosed, carious mandibular primary second molar that had no succedaneous premolar by placing an occlusal platform using ACTIVA restorative material on the primary molar. After 14 months, the authors reported the platform had virtually identical contact with the opposing premolar, with no evidence of wear or marginal chipping or staining.[22]

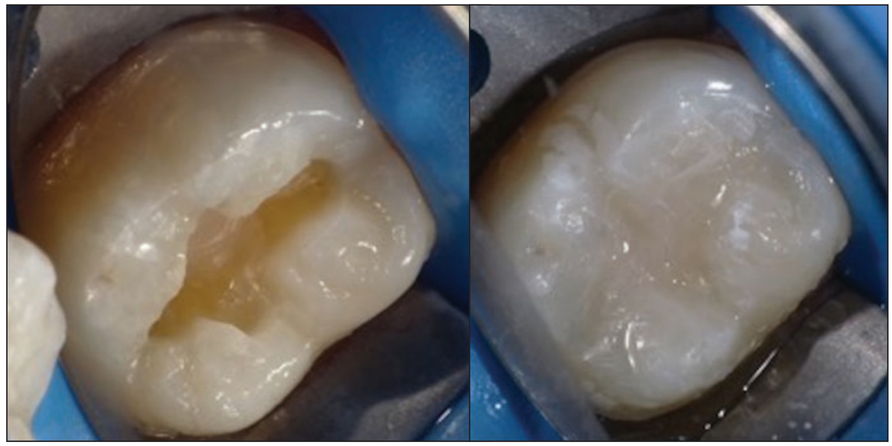

Figure 10. The use of Beautifil II LS (Shofu Dental) as a posterior occlusal restoration on tooth No. 1, cavity preparation and post-op views.

CASE 1

A 21-year-old, healthy college student presented with what appeared to be a small, incipient lesion on tooth No. 16 (Figure 1). A CO_2 laser was used to remove the caries (Figure 2). The lesion was more extensive than indicated by either the radiograph or clinical observation. A bioactive liner was placed, followed by etching of the enamel and placement of the ACTIVA bioactive restorative with shade A1 (Figures 3 and 4).

CASE 2

A 40-year-old, male, dental-phobic patient who had not received dental care for a long period of time was referred for emergency treatment. The patient presented with rampant caries and was treated like a caries control case in an attempt to save the teeth. The caries were removed and TheraCal was placed over the pulp, followed by an ACTIVA liner, and filled with ACTIVA restorative. After polishing, the patient was sent home (Figures 5 to 9). The patient returned asymptomatic at the followup 3 months later and discontinued treatment.

Beautifil

Another product that is claimed to be bioactive by the manufacturer (but lacks extensive data) is Beautifil. The clinical success of this material in high-caries patients has been shown by a group at the University of Florida.[23] Nonetheless, further research evaluating the bioactive properties of this material is still needed.

CASE 3

A 16-year-old, healthy female patient with multiple caries presented for restorative treatment. Due to the patient's high caries risk, tooth No. 31, which had an occlusal lesion, was restored with Beautifil II LS (Shofu Dental) (Figure 10).

BioCem

BioCem Universal BioActive Cement is a fairly new cement manufactured for NuSmile. This new cement is similar to some other products on the market. The chemistry, packaging, and characteristics are analogous to ACTIVA cement. It is classified as an RMGI cement specifically designed for pediatric dental patients. The manufacturer claims that this material

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contains bioactive components that form hydroxyapatite, which integrates and regenerates the tooth structure.[24]

This material is used as a luting agent, as it has been shown to create bonds between the dentin of teeth and stainless steel, preveneered, or zirconia crowns. The secure bond is created due to the vast amount of phosphate ions released from the material. The effect of this bond creates a passive gingival fit of the crown, in which no expansion or contraction occurs after the crown is placed. BioCem Universal BioActive Cement acts as a shock absorber for tooth movement after the crown has been cemented.[25] Milman et al[26] from the University of Texas at Houston recently showed BioCem to have significantly greater "flexural strength, diametrical tensile strength, and comprehensive strength" compared to RMGI and glass-ionomer luting cements.

Further research is needed to validate the manufacturer's claim that this material is in fact bioactive. Therefore, it cannot be concluded at this time that BioCem Universal BioActive Cement is bioactive because it has not been shown to form hydroxyapatite when immersed in a simulated body fluid or PBS.

TheraCal LC

TheraCal LC (BISCO Dental Products) is a resin-modified, calcium silicate cement. It is a light-cured, resin-based material that has a chemistry similar to MTA and is bioactive. This material has an indicated use as a radiopaque protective liner for pulp capping (direct and indirect) to be used under a variety of bases, such as composites and amalgams. It acts to insulate and protect the dentin-pulp complex. In the pulp-capping procedure, a thin layer of TheraCal can be placed after any bleeding has stopped. The application of this material in a thin layer is extremely important for shading because it is opaque and its white color can alter the desired color choice when placing the translucent composite over it. Since TheraCal contains a photo-initiator, it can be easily light cured, which sets the material hard.

TheraCal is similar to MTA in its clinical application. However, it has higher calcium release and no solubility. Its role in dentinal bridging, dentin remineralization, and protection of the pulpal tissue is due to its bioactivity. When hydrated by dentinal fluids, calcium and hydroxide ions are released, resulting in the formation of a layer of hydroxyapatite under the material surface.[27] A study from the Hokkaido University Graduate School of Dental Medicine recently showed MTA-based products such as TheraCal produced significantly better results in pulp capping than calcium hydroxide-based products such as Dycal (Dentsply Sirona).[28]

TheraCal differs from some of the earlier silicate cements because it possesses a hydrophilic monomer that allows interaction of the calcium hydroxide and the calcium in the tooth with the TheraCal via ionic exchange. Some of the earlier silicate cements were hydrophobic and prevented the entry of water and ionic exchange and were not very bioactive or regenerative.[11]

CLOSING STATEMENTS

Bioactivity refers to a specific property of a material to induce a response from a living tissue or cell, such as the formation of hydroxyapatite. As opposed to inert materials, bioactive materials are able to induce growth factors and stimulate natural mineralization. The stimulation of biological tissue and cells and the incorporation of materials into tooth structures has a large impact on the aesthetic outcome and clinical application of the material.[1]

Before choosing which material to use in practice, the clinician should be aware that the clinical relevance of these bioactive materials has not yet been defined. More research is required to be sure of the clinical impact of these materials, even those that have shown to produce hydroxyapatite, release fluoride, and have other bioactive properties. For instance, some believe that human saliva is a suitable environment for hydroxyapatite growth. Human saliva does typically contain inorganic phosphate sources, and could potentially replace the use of PBS for hydroxyapatite formation, which was shown in a study by Engstrand et al[9] in 2012. The authors of that study, however, also explained that the natural formation of hydroxyapatite promoted by saliva may not result in a stable and durable system that assists in the prevention of secondary caries.[9]

The mechanisms of adhesion, integration, and sealing of dentin for these new bioactive materials are still being understood and require more research before we can fully understand and prove whether bioactive materials are able to restore the form and function of the natural tooth.[2] More specifically, further clinical studies in humans are indicated in the ability of ACTIVA PC (a new pulp capping material) to form thicker dentinal bridges compared to MTA.[29]

Once more research is conducted, a new wave of materials will arise, and it is extremely important for dentists to keep an open mind to new restorative materials that may provide better protection of patients' oral health.✦

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POST EXAMINATION QUESTIONS

1. "Bioactive" means that the body reacts to the material, as opposed to inert material.
a. True.
b. False.

2. Inert dental materials typically function at a continuous and constant pH. This creates crevices where plaque can build up and cause secondary caries.
a. The first statement is true, the second is false.
b. The first statement is false, the second is true.
c. Both statements are true.
d. Both statements are false.

3. The following is/are bioactive restorative material(s):
a. Bioglass.
b. Glass-ceramic.
c. Calcium phosphate ceramic.
d. All of the above.

4. Which material was first introduced in the 1920s and is one of the earliest bioactive materials?
a. Titanium alloys.
b. Mineral trioxide aggregate.
c. Calcium hydroxide.
d. None of the above.

5. The TGF-B family of growth factors influences odontoblast differentiation in the tooth. This ultimately induces the formation of either a dentinal bridge or areas of mineralization in the coronal pulp.
a. The first statement is true, the second is false.
b. The first statement is false, the second is true.
c. Both statements are true.
d. Both statements are false.

6. For both pediatric and adult patients, bioactive dental materials are more preventative of recurrent caries. This can be attributed to the fact that bioactive materials can be both self-cured and light-cured.
a. The first statement is true, and second is false.
b. The first statement is false, the second is true.
c. Both statements are true.
d. Both statements are false.

7. The direct function of a bioactive material is to:
a. Induce growth factors.
b. Stimulate natural mineralization.
c. Both a and b.
d. None of the above.

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8. ACTIVA is a bioactive material that contains:
- **a.** An ionic resin matrix.
- **b.** A shock-absorbing resin component.
- **c.** Bioactive glass fillers.
- **d.** All of the above.

9. Bioactivity refers to a specific property of a material to induce a response from a living tissue or cell, such as the formation of hydroxyapatite.
- **a.** True.
- **b.** False.

10. TheraCal LC is a resin-modified, calcium silicate cement. It is light-cured, resin-based and similar in chemistry to MTA, and is bioactive.
- **a.** The first statement is true, the second is false.
- **b.** The first statement is false, the second is true.
- **c.** Both statements are true.
- **d.** Both statements are false.

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ANSWER FORM: COURSE #: 217

Please check the correct box for each question below.

1.	❑ True	❑ False		
2.	❑ a	❑ b	❑ c	❑ d
3.	❑ a	❑ b	❑ c	❑ d
4.	❑ a	❑ b	❑ c	❑ d
5.	❑ a	❑ b	❑ c	❑ d
6.	❑ a	❑ b	❑ c	❑ d
7.	❑ a	❑ b	❑ c	❑ d
8.	❑ a	❑ b	❑ c	❑ d
9.	❑ True	❑ False		
10.	❑ a	❑ b	❑ c	❑ d

PROGRAM EVAUATION FORM

Please complete the following activity evaluation questions.
Rating Scale: Excellent = 5 and Poor = 0

Course objectives were achieved. ________
Content was useful and benefited your clinical practice. ________
Review questions were clear and relevant to the editorial. ________
Illustrations and photographs were clear and relevant. ________
Written presentation was informative and concise. ________
How much time did you spend reading the activity and completing the test? ________
What aspect of this course was most helpful and why? ________

What topics interest you for future *Dentistry Today* CE courses?