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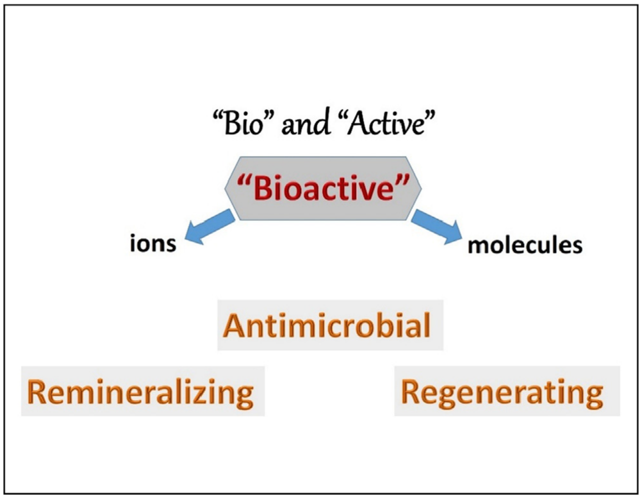
Bioactive dental materials

Developing, promising, confusing

Jack L. Ferracane, PhD[a]; Sharanbir K. Sidhu, BDS, MSc, PhD[b]; Mary Anne S. Melo, DDS, MSc, PhD, FADM[c]; In-Sung Luke Yeo, DDS, MSD, PhD[d]; Anibal Diogenes, DDS, MS, PhD[e]; Brian W. Darvell, DSc[f]

[a]Department of Restorative Dentistry, Oregon Health & Science University, Portland, OR; [b]Centre for Oral Bioengineering, Institute of Dentistry, Queen Mary University of London, London, United Kingdom; [c]Department of General Dentistry, School of Dentistry, University of Maryland, Baltimore, MD; [d]Department of Prosthodontics, School of Dentistry and Dental Research Institute, Seoul National University, Seoul, South Korea; [e]Department of Endodontics, The University of Texas Health Science Center at San Antonio, San Antonio, TX; [f]Dental Materials Science, University of Birmingham, Birmingham, United Kingdom.



Why Is This Important?

There are often different interpretations by clinicians, manufacturers, and researchers regarding what defines a bioactive material. This has led to confusion amidst varying claims by individual stakeholders. Unlike the more traditional passive materials, bioactive materials are designed to elicit a desired therapeutic or beneficial response. Such materials have been described as releasing ions or molecules to produce an antimicrobial, remineralizing, or regenerating effect within a living organism. Given the complexities of various chemistries, products, and effects, it is virtually impossible to easily identify the essential qualities that qualify a material as bioactive, and clinicians, in particular, often find it challenging to determine whether a product claiming bioactivity is clinically superior and should be used. It is difficult for clinicians to make informed decisions without clarity.

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Introduction

The term bioactivity is used frequently in the oral health field but with great latitude regarding what constitutes the specific activity. Bioactive is defined as having a biological effect or effect on a living organism, tissue, or cell. The bioactivity of certain endogenous molecules may be obvious when promoting specific cellular or tissue responses under appropriate conditions. However, is eliciting a biological response necessary to be considered bioactive? Indeed, how do we define biological response?

The biochemical term bioactive was applied to the material Bioglass by Hench,[1] the inventor and author of an excellent review of its development. Early emphasis was on materials that formed an apatitelike mineral in appropriate environments, such as simulated body fluid.[2] Throughout the literature are descriptions of bioactive materials involved in various contexts, including promoting mineralization of bone or teeth, inducing the recruitment or differentiation of cells to perform specific functions, or exerting an antimicrobial, antifouling, pH buffering, or biofilm modulating effect. However, are all these effects true evidence of bioactivity or perhaps simple chemistry or toxicity?

The rapidly emerging research into bioactive materials holds great promise for improving oral health care but also creates much confusion and potential for misinformation. These issues were the basis of presentations delivered at the 2022 International Association for Dental Research meeting in a symposium titled "Bioactive Dental Materials—Developing, Promising, Confusing."[3]

In this speaker-generated symposium summary, we aim to clarify the concept of bioactivity related to restorative and implant dentistry and dental tissue engineering and regeneration. Considering the material presented in the symposium and the previous literature, a definition closer to the reality of bioactivity is proposed.

What Does Bioactivity Imply With Dental Restorative Materials?

Bioactivity is a relatively new term for direct restorative materials, interpreted in many ways by dentists and researchers. As the first-choice material for direct restorations, resin composites have experienced relatively high failure rates because of secondary caries and interfacial bond degradation, requiring frequent replacements. Based on this deficiency, the desire for materials that provide additional benefits to maintain oral health has led to intensive research into what has been called bioactive resin-based restorative materials.[4]

The use of the term bioactive in clinical dentistry is much broader than is implied by the medical-based description of materials that have a biological effect or are biologically active and form a bond between material and tissue.[5]

From the biomaterials' perspective, the ability to form a surface apatite-containing material, including hydroxyapatite, in a simulated body fluid is defined as bioactivity. From a dental restorative perspective, bioactivity describes a dynamic, positive interaction between the restorative materials and the tooth, promoting health. For example, a bioactive restorative material could modulate the cariogenic biofilm growth over its surface and prevent massive bacterial acid production that could result in the degradation of the tooth-adhesive interface. With this in mind, a bioactive restorative material would need to retain satisfactory mechanical performance to rebuild the tooth form, provide proper shade and translucency to reestablish an esthetic appearance, and provide bioactivity by releasing specific components that modulate cariogenic species and biofilm formation, stimulate specific interactions to control or restore mineral loss, or both (Figure 1).[6]

Do Surface Treatments Make Dental Implants Bioactive?

Bioactive has been defined by 1 source as "having an effect upon a living organism, tissue, or cell."[7] In dental implantology, is it possible to have an implant surface that is really

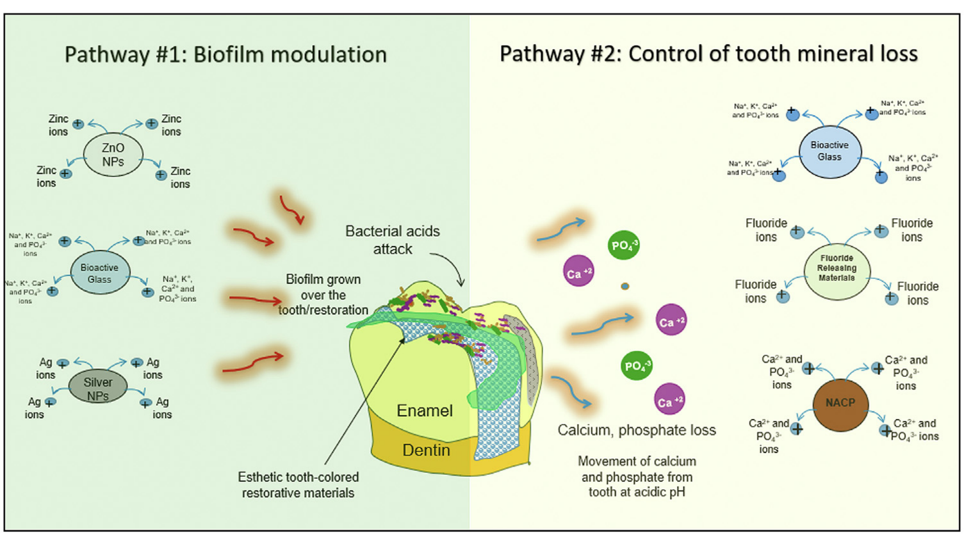

Figure 1 Illustration of the restorative concept of bioactivity toward caries prevention by dental restorative materials. Pathway no. 1: the release of relevant ions, such as calcium ions, to assist in the chemical equilibrium of the mineral net into the hard dental tissues, such as enamel and dentin. Pathway no. 2: the release or contact with bioactive agents that can modulate or suppress bacterial metabolism, consequentially reducing biofilm growth, such as metallic ions provided by nanoparticles. Ag, Silver. Ca^{2+}, Calcium ion. K^{+}, Potassium ion. Na^{+}, Sodium ion. NACP, Nanoparticles of amorphous calcium phosphate. NPs, Nanoparticles. PO_4^{3-}, Phosphate ion. ZnO, Zinc oxide.

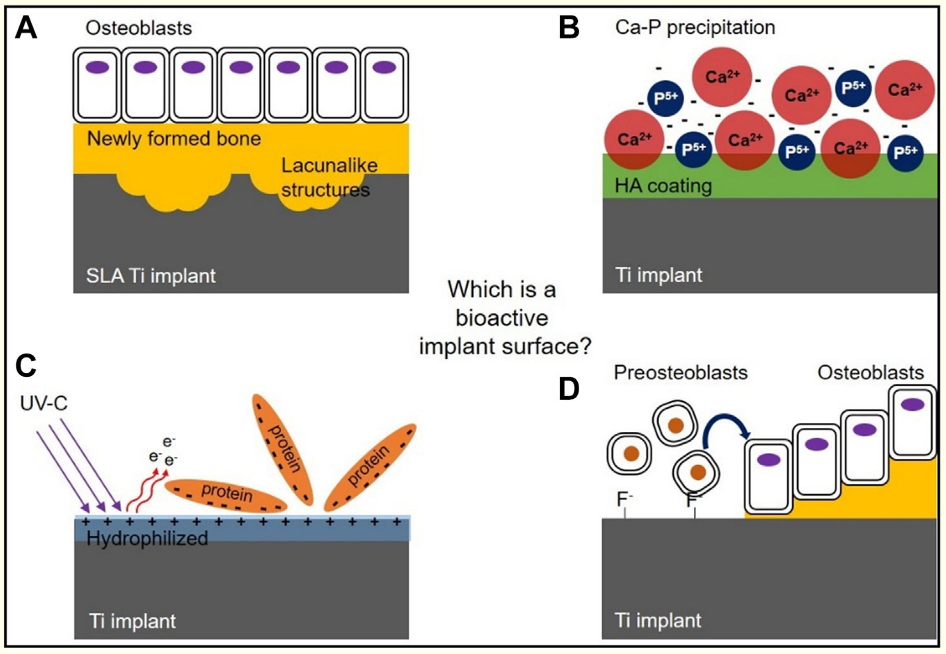

Figure 2 The osteoblast response to the sandblasted large-grit acid-etched (SLA) implant surface, interpreted as the response to structures morphologically similar to Howship lacunae (**A**). Accelerated mineralization on the hydroxyapatite (HA)-coated surface (**B**) and improved protein adsorption to the ultraviolet (UV-C) treated surface (**C**) are chemical reactions, not cellular biological responses. The fluoride-treated surface (**D**) is bioactive to modulate cellular behavior, stimulating osteoblast differentiation. Ca^{2+}, Calcium ion. Ca-P, Calcium-phosphate. e^{-}, Electron. F^{-}, Fluoride ion. P^{5+}, Phosphate ion. Ti, Titanium.

bioactive? Topographic, physical or chemical modifications of grade 4 commercially pure titanium implant surfaces appear to modulate cell behavior and tissue response, leading to osseointegration, though exactly how this happens remains undetermined.[8]

Pure titanium is an inert material. However, microtopographic modification of the surface, for example, a sandblasted large-grit acid-etched surface, mimics Howship lacunae formed by osteoclasts, thus resulting in contact osteogenesis that allows de novo bone formation on the surface.[9] However, this phenomenon is difficult to describe as evidence of bioactivity because this topographical feature does not modulate normal osteogenic cell behavior. Similarly, a hydroxyapatite-coated implant surface contributes to calcium phosphate precipitation and bone mineralization,[10] and ultraviolet irradiation of the implant surface increases surface hydrophilicity and surface attraction to plasma proteins (Figure 2).[9] However, these effects are chemical and do not modulate cellular behavior. Therefore, carefully interpreting the data showing improved osseointegration to a modified implant surface is important in evaluating an actual bioactive effect. In this light, applying fluoride to an implant surface to stimulate osteoblast differentiation or attaching core peptides derived from endogenous cytokines probably make the inert implant surface bioactive because these molecules modulate osteogenic cell responses.[8] However, every surface modification of dental implants used in the clinic is unlikely to render them bioactive.

Does Successful Engineering and Regeneration of the Pulp-Dentin Complex Rely on Bioactivity?

Regenerative endodontics focuses on replacing damaged cells and tissue in part or the entirety of the pulp-dentin complex through vital (pulp capping, pulpotomies) or nonvital procedures (revitalization, stem cell transplant). It has been shown that growth factors are fossilized or trapped in the dentin matrix during tooth development, and these noncollagenous proteins can be released on dentin demineralization caused by caries or certain materials used in vital pulp therapies (Figure 3).[11] Once released, dentin-derived growth factors are sufficient to drive the recruitment and differentiation of mesenchymal stem cells into an odontoblastlike phenotype and increase their mineralization potential.[11] Their reparative potential, in this case, may be attributed to the indirect effect of material placement on dentin.

Regenerative endodontic therapies aim to resolve apical periodontitis and reestablish root development, pulp immune, and sensory functions. Despite high success rates ($>85\%$) of apical periodontitis healing, continued root development and responses to pulp sensitivity (vitality) testing are less predictable,[12] and histologic studies show that the tissue formed does not resemble native dental pulp.[13]

Clinical trials with transplantation of autogenous and allogenic mesenchymal stem cells, such as that by Xuan et al.[14] using autogenous transplantation of cells into disinfected

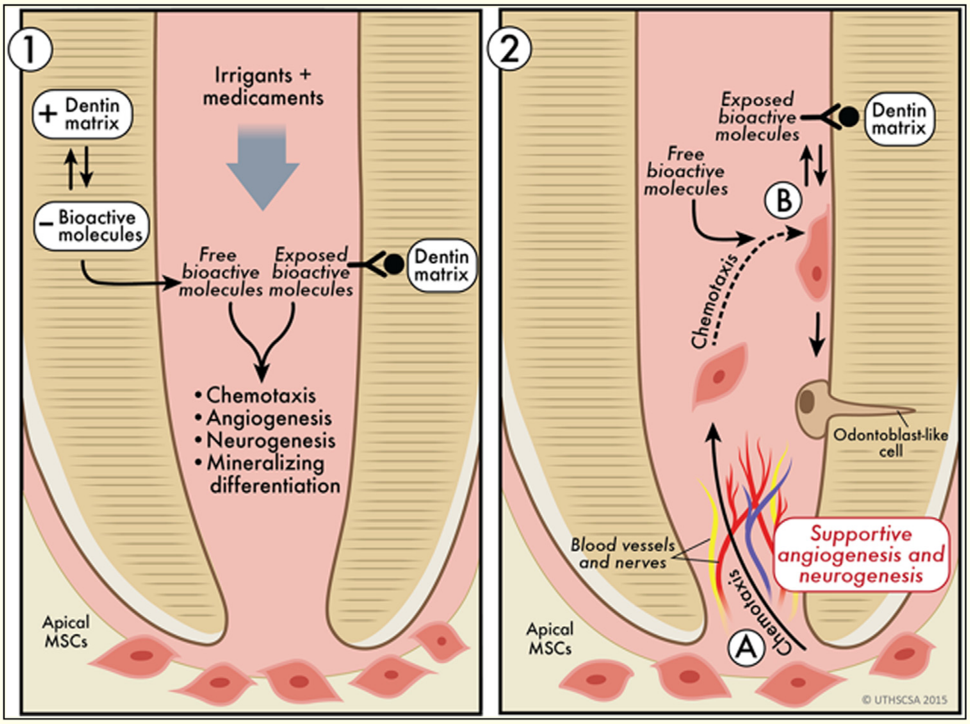

Figure 3 Schematic illustrating the potential actions of irrigants and medicaments in the release or exposure of bioactive molecules sequestered in dentin and their influences on regenerative events, including chemotaxis, odontoblastlike cell differentiation, mineralization, angiogenesis, and neurogenesis. Adapted with permission of the publisher from Smith et al.[11] MSCs, mesenchymal stem cells.

root canal systems, have shown results with histology assessment showing remarkable organization of the tissue with a circumferential cell layer resembling odontoblasts. The bioactivity observed in this trial can only be attributed to dentin-derived growth factors, an autogenous scaffold (blood clot), and factors released by the transplanted cells, and not to a single bioactive material. Therefore, the bioactivity observed in pulp tissue engineering is primarily mediated indirectly by the release of growth factors and the exposure of the dentin matrix favoring cellular attachment, signaling and differentiation.

Bioactivity: an Overview of the Current Situation

The symposium nicely illustrated the nature of the problem: the term bioactivity has been devalued almost to the point of uselessness by being applied indiscriminately to include all simple chemistry arising in even vaguely biological contexts as well as inappropriately to all biological defensive responses to insults and challenges.[15,16] Many definitions suffer from lack of precision, a narrow focus on forming a bond between the material and tissue, merely dissolution to release supposedly useful ions or even the appearance of hydroxyapatite, whether in vivo or in vitro.[10] Including microbial control, nutrients and pharmaceuticals is questionable and perhaps unhelpful,[16] as is the prejudicial use of the term remineralization when there can be no tissuelike structure in the calcium phosphates precipitated[15]; likewise, the application to any so-called reparative process occasioned by toxicity is injudicious. Similarly, cellular responses to topography were shown to be overstated.

The only clear demonstration of true bioactivity presented was that of sequestered substances released by damage to or destruction of dentin, but properly it applies to those substances themselves, not the agent that did the damage, as was pointed out in the "Does Successful Engineering and Regeneration of the Pulp-Dentin Complex Rely on Bioactivity?" section. Nevertheless, an indirect effect may still be valuable, using such substances in a nondestructive material to induce beneficial biological processes.

The 1 suggestion of true bioactivity using nonbiological means was that of the implant surface doped with fluoride. If verified, this would indeed count and indicates another avenue for investigation.

The definition of a bioactive material as one that intentionally modulates a specific, targeted biological process for beneficial effect may be used to establish the veracity of a claim of bioactivity. The 2 examples cited above would pass this test.

It may be too late to rescue the term bioactivity in general use. However, it remains to be seen that for students, researchers, and clinicians, a clear understanding of what is happening is essential for meaningful study, properly directed research, and realistic treatment design. Truly bioactive materials would indeed make a difference.

Email ferracan@ohsu.edu. Address correspondence to Dr Ferracane.

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ORCID Numbers. Jack L. Ferracane: https://orcid.org/0000-0002-6511-5488; Sharanbir K. Sidhu: https://orcid.org/0000-0001-8362-385X. For information regarding ORCID numbers, go to http://orcid.org.

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