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Review

A review of the bioactivity of hydraulic calcium silicate cements

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ABSTRACT

Objectives: In tissue regeneration research, the term "bioactivity" was initially used to describe the resistance to removal of a biomaterial from host tissues after intraosseous implantation. Hydraulic calcium silicate cements (HCSCs) are putatively accepted as bioactive materials, as exemplified by the increasing number of publications reporting that these cements produce an apatite-rich surface layer after they contact simulated body fluids.
Methods: In this review, the same definitions employed for establishing *in vitro* and *in vivo* bioactivity in glass–ceramics, and the proposed mechanisms involved in these phenomena are used as blueprints for investigating whether HCSCs are bioactive.
Results: The literature abounds with evidence that HCSCs exhibit *in vitro* bioactivity; however, there is a general lack of stringent methodologies for characterizing the calcium phosphate phases precipitated on HCSCs. Although *in vivo* bioactivity has been demonstrated for some HCSCs, a fibrous connective tissue layer is frequently identified along the bone–cement interface that is reminiscent of the responses observed in bioinert materials, without accompanying clarifications to account for such observations.
Conclusions: As bone-bonding is not predictably achieved, there is insufficient scientific evidence to substantiate that HCSCs are indeed bioactive. Objective appraisal criteria should be developed for more accurately defining the bioactivity profiles of HCSCs designed for clinical use.

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1. Introduction

A bioactive material may be broadly defined as "one which has been designed to induce specific biological activity".[1] Based on this generic definition, biologically active materials may include those that promote tissue regeneration by adhesion to soft and hard tissues of the human body, those that possess cell-instructive and molecular signalling properties *via* functionalized ligands or incorporating growth factors for regulating cell proliferation, migration, differentiation, protein expression and mineralization processes. Other bioactive materials include those that are designed for biosensing *via* physicochemical interactions, those that contain recognition sites for cleavage of enzymes involved in cell functions, and those that possess antimicrobial or immunoregulatory activities by incorporating antimicrobial agents or molecules that mimic natural host-defense peptides.[2–6] Along the same line of thought, bioactive materials may also include those that incorporate bioactive peptides with antithrombotic, antihypertensive, opioid or antioxidative properties for controlled release.[7]

Prior to the adoption of this contemporary interpretation of bioactivity, scientists in the field of tissue regeneration have been using a more focused definition of "bioactivity" to describe the resistance of a calcium phosphosilicate glass to be removed from the host hard and soft tissues, after it was implanted in femurs and muscles in a rat model.[8] Interfacial bonding between the implant and living tissues has subsequently been observed in other synthetic calcium phosphate ceramics, silicate-based, borate-based and phosphate-based glasses.[9,10] A bioactive material, as defined by Hench and coworkers, is one that elicits a specific biological response at the interface of the material, which results in the formation of a bond between living tissues and the material.[11] A feature commonly identified from these materials is a time-dependent kinetic modification of the material's surface *via* the formation of a carbonated apatite surface layer following its implantation *in vivo*.[12,13]

The tissue regeneration definition of bioactivity has undergone a subtle paradigm drift, after the feature of *in vivo* carbonated apatite formation[14] was found to be reproducible *in vitro* by immersing the material in a simulated body fluid (SBF) designed to mimic human blood plasma.[15] Thus, according to Kokubo and Takadama, a bioactive material is one on which bone-like carbonated apatite will form selectively after it is immersed in a serum-like solution.[16] Over the years, the scientific community at large has putatively accepted this paradigm drift, with the assumption that demonstration of "*in vitro* bioactivity" is the indirect equivalent of affirming a material's bone-bonding potential. Although *in vitro* bioactivity evaluation is appealing because of its simplicity and rapidity in data generation, a recent review cautioned the lack of adequate scientific evidence to support the assumption that a material that initiates the deposition of calcium phosphate salts on its surface after immersion in SBF will bond directly to bone following intraosseous implantation.[17] For example, a host of sol–gel reaction-derived metallic oxides, including SiO_2, TiO_2, ZrO_2, Nb_2O_5 and Ta_2O_5 were found to possess *in vitro* bioactivity after immersing in simulated body fluid[18–22]; however, the ability of these metallic oxide gels to bond to bone *in vivo* has not been demonstrated.

The introduction of hydraulic calcium (alumino) silicate cements has provided clinicians with alternative biomaterials for dentine replacement, pulp capping, pulpotomy, creation of apical barriers in teeth with open apices, repair of root perforation and resorptive defects, as well as orthograde or retrograde root canal fillings.[23–26] Among their many desirable properties, hydraulic calcium silicate cements (HCSCs) have been described as possessing bioactive properties that influence their surrounding environments.[24] A discussion of bioactivity based on its generic definition is beyond the scope of this review. Rather, the bioactivity of HCSCs will be discussed from a tissue regeneration perspective.

2. Biologically inactive *versus* bioactive inorganic materials

When a biomaterial is implanted in the human body, the host tissue reacts towards the implant in different ways depending on the tissue response along the implant surface. Accordingly, a biomaterial may be classified into 4 types based on their tissue responses: nearly inert, porous, resorbable or bioactive.[27] As HCSCs are non-resorbable and after setting, do not possess pores that are large enough for ingrowth of bone or blood vessels, only the tissue responses of nearly inert and bioactive materials will be described.

No material implanted in living tissues is completely inert. Thus, the term "bioinert" is designated to any material which, when implanted into the human body, elicits minimal interaction with its surrounding tissues. Examples of these materials are stainless steel, titanium, alumina, partially stabilized zirconia and ultrahigh molecular weight polyethylene. Following implantation of a foreign material into the body, the material's surface is immediately coated with proteins derived from blood and interstitial fluids. It is through this layer of adsorbed proteins that the cells sense foreign surfaces.[28] In response, the body's defense mechanism will stimulate the formation of a non-adherent fibrous capsule around the implant in an attempt to isolate it from the surrounding tissue. The thickness of this protective fibrous capsule depends on the chemical reactivity of the implanted material, and on the motion and fit of the material at the interface.[29] Because the interface is not chemically or biologically bonded, micro-movement of the implant will result in progressive thickening of the non-adherent fibrous capsule and eventually leads to functional deterioration of the implanted material.

By contrast, a bioactive material creates an environment compatible with osteogenesis, and in some cases, compatible with soft tissues[30] by developing a natural bonding interface between living and non-living materials. With the exception of calcite (calcium carbonate) and β-tricalcium phosphate, which are examples of resorbable bioceramics that bond directly to living bone,[31] interfacial bonding of other bioactive materials with bone is initiated *via* ion–exchange reactions between the bioactive implant and surrounding body fluids. This results in the formation of a biologically active carbonated apatite layer