Bioceramics: From Clinic to Concept

Bryan J. Mc Entire
Amedica Corporation, Salt Lake City, USA

Introduction

It's been over 25 years since Professor Larry Hench published his seminal article entitled “Bioceramics: From Concept to Clinic” [1] and more than 40 years since he first reported the peculiar bioactive properties of glass compositions within the Na₂O-CaO-P₂O₅-SiO₂ quaternary system [2]. Curiously, the investigative ideas which led him to develop Bioglass® did not have their origin in the laboratory. They were born from the clinical need to heal the horrible wounds incurred by servicemen returning from the Vietnam War. Indeed, after a conversation with a ranking army officer, his work began under a simple hypothesis:

“The human body rejects metallic and synthetic polymeric materials by forming scar tissue because living tissues are not composed of such materials. Bone contains a hydrated calcium phosphate component, hydroxyapatite [HA] and therefore if a material is able to form a HA layer in vivo it may not be rejected by the body” [2].

Professor Hench learned early that there are no truly “bioinert” materials. Every foreign compound implanted within the human milieu solicits a response – either toxic, fibrous encapsulation, interfacial bonding, or dissolution [1]. This axiom has not changed during the past fifty years. It is therefore surprising that a significant number of today’s biomaterials engineers, scientists, and device manufacturers lack this fundamental understanding.

For instance, since its inception in the 1960s, the artificial hip joint has been developed solely for its mechanical function. This has led researchers to rely on materials that are increasingly “bioinert,” including today’s use of bioceramics and highly crosslinked vitamin-E doped polyethylene. While it is true that incorporation of “bioinert” materials into prosthetic joints has led to considerable short- and mid-term success (i.e., 10-15 years), their long-term prognosis (20+ years) remains to be determined, particularly for younger active patients [3]. Nevertheless, total hip arthroplasty (THA) is still seen to be the most innovative operation of the past century [4]. However, instead of a holistic approach to its design and use, THA innovation has stagnated with the successful introduction of various “me-too” products whose sole purpose is to provide two opposing “bioinert” counterface surfaces which minimize sliding wear. Instead of attempting to truly differentiate their products using multifaceted principles of biological innovation, manufacturers have either copied expired patents [5] or resorted to coloration schemes [6] that have little or no effect on long-term device function (Figure 1).

Perhaps designing parts solely for the purpose of minimizing friction and wear may have been excusable in an earlier era due to a lack of advanced biological engineering technologies. However, using today's sophisticated analytical tools, we now know that even ceramics once considered and still marketed as “wholly bio-inert” (e.g., alumina, Al₃O₅, and alumina-zirconia composites, ZTA) are markedly affected by the biological environment [7]. Examination of human retrievals as well as in vitro testing of Al₂O₃ and ZTA femoral heads have clearly demonstrated patterns of off-stoichiometric surface degradation and accelerated phase transformation, respectively [8–10]. The fundamental deterioration mechanism is one of surface dehydroxylation [11]. It results in the formation of an approximately 10 nm thick surface layer of oxygen vacancies, aluminum hydroxide (Al(OH)₃), and a softer spinel phase (via the substitution of calcium and magnesium ions to maintain charge neutrality) [7]. One might critically argue that the thickness of this reaction layer is inconsequential to the effective operation of the prosthetic device. However, frictional sliding eventually removes this layer; and when compounded over a decade or more of in vivo use, the synovial fluid and surrounding tissue are not only contaminated with insoluble wear debris, but also exposed to higher hydroxyl, oxygen, and aluminium ions, and an amphoteric change in the joint’s natural pH. All of these chemical species impact the tribological performance and longevity of the abiotic prosthesis; and each may be a contributor to aseptic loosening or latent infections (i.e., the dominant causes for prosthetic joint failure). Even though the presence of wear particles has been strongly correlated to aseptic loosening, it is now recognized that its etiology is in fact multifactorial [12]. It is altogether possible that even the most “bioinert” compounds contribute to prosthetic failures in the long-run. Device design may play an important role, but it is the physical chemistry of the biomaterial itself that may be the key factor in limiting device longevity.

At the opposite end of the spectrum, the use of calcium phosphates and hydroxyapatite is another example of one-dimensional bioceramic...
engineering. Although these compounds are "bioactive" as opposed to "bioinert", they are also mechanically weak. Their multiphasic chemical compositions enhance osteoconductivity and integration, but their mechanical integrity limits their useful applications. Fortunately, they have found a place as thin thermally-applied coatings onto otherwise "bioinert" prosthetic metals (e.g., titanium or cobalt-chromium alloy acetabular cups and hip stems). When properly applied, they have demonstrated excellent long-term durability and survivorship [13]. However, a large Nordic retrospective study questioned their usefulness in its entirety [14]. An analysis of over 116,000 cases demonstrated that survival rates for coated and uncoated stems were statistically equivalent. Even though these negative results appear contradictory and compelling, elimination of calcium phosphates and hydroxyapatite from medical devices would likely be a mistake. From purely a biochemical standpoint, they are markedly more effective in promoting osseointegration than their metallic substrates. So why were they not also superior in their survival statistics? Device design undoubtedly played a role; but so, did the fragile nature of the coating itself. Variations in its application (i.e., thickness, porosity, and chemical composition) may have led to delamination and particle abrasion which ultimately contributed to aseptic loosening of the stem or its associated prosthetic components. Here, the failure may not be associated with the bioceramic itself. Its processing and the integration of its metallic counterparts certainly played significant roles. Fundamentally, this is not a biomaterial issue; but one of engineering and design.

Conclusion

These examples suggest the importance of multiphysics methodologies in the processing, design, and application of bioceramics. As we proceed into the second century of modern bioceramics, one-dimensional thinking has to be abolished in favor of an integrated approach. It will necessarily involve solutions to multidisciplinary problems in physics, chemistry, mechanics, and biology. Over ten years ago, Professor Hench forecasted a third generation of biomaterials. Whereas the first two generations involved the use of "bioinert" and then "bioactive" or resorbable bioceramics, his vision of the ensuing generation was comprised of materials engineered to heal the body [15]. These compounds will not only be engineered for structural stability, wear resistance, or osseointegration, but also therapeutically designed to upregulate beneficial metabolic processes. To make this vision a reality, the methodology that led the late Dr. Hench to his invention of Bioglass® needs to be reinstated among today's biomaterial scientists and engineers. Instead of starting in the laboratory with one-dimensional approaches to prosthetic solutions, there should be renewed interest in consulting with clinicians and patients to truly understand the broad clinical requirements for abiotic biomaterials. Indeed, it is only from the clinic that the next truly innovative concepts will originate.

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