

Bioceramics in the Realm of History

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Editorial

Bioceramics have revolutionized the field of medicine by giving us the hope of generating engineered human tissues. During the past years, there have been great advances in bioceramics, glasses and glass-ceramics, and recently emphasis has shifted towards the use of this class of biomaterials especially for bone and dental tissue engineering. On this front, with the advent of advanced bioceramics, it has been speculated that the search for ideal combination of different methods and materials could result in significant advances in different areas of medicine over future years. Undoubtedly, this class of biomaterials needs further advancement and a lot of critical questions have yet to be answered. This note shortly reviews the groundbreaking work that has been performed in the field of bioceramics.

During the last four decades, there have been major developments for advanced biomaterials. Among different biomaterials, "bioceramics" have recently gained many attentions by a significant increase in the number of patents, publications, international conferences and themed meetings. Bioceramics either as "bioinert" or "bioactive" are available in different forms in the market, and now clinically used in a large number of different applications throughout the human body. The earliest attempts to substitute natural tissues with these biomaterials aimed to restore the basic function of tissues or organs without stimulating biological responses from the host tissues [1]. These bioinert materials only induced a minimal level of response from the host tissues.

For the first time, in the 1920s, de Jong [2] proposed some similarities between the natural bone minerals and hydroxyapatite. This bioceramic is the most famous synthetic calcium phosphate with a chemical formula of $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$, that has a theoretical calcium to phosphorus molar ratio of 1.667 [3]. Similarly, tricalcium phosphate with the chemical formula of $\text{Ca}_3(\text{PO}_4)_2$ has shown to be a biodegradable bioceramic with a high potential bone bonding ability [4]. It is known that different calcium phosphate bioceramics may adversely affect the biological response after implantation. Therefore, by adjusting and optimizing them, it is possible to meaningfully match the rate of resorption with bone regeneration. The mixtures of hydroxyapatite and tricalcium phosphate, known as biphasic calcium phosphate, have been investigated as bone substitutes, in which by further addition of the tricalcium phosphate content in its structure, the dissolution rate is increased [5].

In the 1960s, Raquel LeGeros [6] started to work on the characterization of carbonate-substituted calcium phosphates. For the first time, he stated that the crystal structure of calcium phosphates can accommodate substitutions by other ions [7-9]. Since then, the substitution of carbonate into the structure of synthetic hydroxyapatite has become one of the most hot topics, because carbonate is an

abundant substitution in the structure of natural bone mineral [10,11]. It has been also shown that cationic and anionic substitutions can potentially occur in the sites normally occupied by the calcium atoms and in the phosphate- or hydroxyl positions, respectively [12]. These ionic substitutions can significantly affect the lattice parameters, crystal morphology, crystallinity, solubility and thermal stability of calcium phosphate bioceramics [13,14]. Fluorapatite is the most common example of anionically substituted hydroxyapatite, in which the fluoride ions substitute for hydroxyl ions [15,16]. Many researchers are now working on the production and optimization of ionic substitutions on different bioceramics for biomedical application.

It was in the 1980s and 1990s that the number of researches in the use of different calcium phosphates for implantation *in vivo* has dramatically increased. These bioceramics are now frequently used for a variety of clinical applications such as treatment of bone defects, total joint replacement, spinal fusion, craniomaxillofacial reconstruction, revision surgery etc. [17].

Due to the large number of studies from the 1960s, there has been a particularly important period in the development of advanced bioceramics. There are a number of very important bioceramics that revolutionized this field. In the early 1970s, Hench et al. [18] suggested 45S5 Bioglass® that showed multi-stage and complex surface reactions for the formation of biologically active hydroxy-carbonate apatite layers similar to the mineral phase of natural bone mineral [19].

In the 1980s, Kokubo et al. [20] developed a new glass-ceramic material called apatite-wollastonite with the highest bending strength, fracture toughness and Young's modulus among different bioceramics. This group further developed a solution of ions with similar composition to that of human blood plasma called "simulated body fluid", in which the rate of apatite formation could be correlated with the *in vivo* activities of the sample [21]. Since then, a very large number of studies have taken place to modify the composition of the solution either as a test for the measurement of bioactivity or as method for the deposition of biomimetic bone-like apatite coatings.

Different kind of bioceramics are currently used as coatings on metallic implants, fillers in polymeric scaffolds, self-setting bone cements, granules or nanopowders. Thin film deposition techniques are also being investigated including electrophoresis, pulsed laser deposition, electrohydrodynamic spray deposition, electrochemical, sputtering, sol-gel, and biomimetic techniques. Due to the inferior mechanical properties, the clinical application of bioceramics is limited to non-load-bearing sites. Therefore, there have been always several attempts to enhance the mechanical properties of bioceramics either using different methods or materials [22].

In the 1990s, Bonfield et al. first proposed the use of bioceramics as filler in polymeric composites to improve their mechanical

performance, including a better strength, toughness and plasticity, and graded mechanical stiffness [23]. Many kinds of hybrid composite scaffolds are now being used, and the research in this field is highly active [24,25]. As a new strategy, the functionality of these constructs can be enhanced by localized delivery of appropriate biological molecules incorporated within biodegradable nanoparticles [26]. Although there are still major issues to overcome, the proponents of the use of bioceramics are optimistic as an effective approach with an increasing impact on clinical applications. Extended research in materials science and the cellular biology aspects need to be conducted to fully understand the processes involved in these systems. In addition, future in vivo and in vitro studies should systematically assess the various effects of different bioceramics. Interdisciplinary researches and effective collaborations can potentially overcome the major issues related to the improvement of mechanical properties, bioactivity for gene activation, performance of biomedical coatings, etc., and eventually make these biomaterials viable options in the treatment of bone defects in the near future.

Conclusion

Although there have been significant advances during the last few decades around the world, extended researches are still in progress to have an increasing impact in clinical applications over the next twenty years. Currently numerous research groups are working on different aspects of bioceramics for achieving significant improvements in order to make these a clinically viable strategy. Consequently, interdisciplinary researches and effective collaborations between basic scientists and clinicians could potentially overcome the major issues of such strategies and lead this treatment alternative possible in the upcoming years.

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