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Review

Biphasic calcium phosphates bioceramics (HA/TCP): Concept, physicochemical properties and the impact of standardization of study protocols in biomaterials research

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A B S T R A C T

Biphasic calcium phosphates (BCP) bioceramics have become the materials of choice in various orthopedic and maxillofacial bone repair procedures. One of their main advantages is their biodegradation rate that can be modified by changing the proportional ratio of the composition phases. For enhanced bone tissue regeneration, the bioactivity of BCP should be increased by optimizing their physicochemical properties. To date, the ideal physicochemical properties of BCP for bone applications have not been defined. This is mostly related to lack of standard study protocols in biomaterial science especially with regards to their characterizations and clinical applications. In this paper we provided a review on BCP and their physicochemical properties relevant to clinical applications. In addition, we summarized the available literature on their use in animal models and evaluated the influences of different composition ratios on bone healing. Controversies in literature with regards to ideal composition ratio of BCP have also been discussed in detail. We illustrated the discrepancies in study protocols among researchers in animal studies and emphasized the need to develop and follow a set of generally accepted standardized guidelines. Finally; we provided general recommendations for future pre-clinical studies that allow better standardization of study protocols. This will allow better comparison and contrast of newly developed bone substitute biomaterials that help further progress in the field of biomaterial science.

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1. Introduction

1.1. Background

The application of biomedical materials in reconstructive surgery for repair of surgical or traumatic defects has involved significant research in the field of biomaterial science with the aim to achieve faster and better biological healing outcomes. Currently, autograft and allograft remain the gold standard for bone replacement therapy. However; disadvantages such as limited supply of donor bone graft and a secondary trauma for autograft as well as the issue of immune response of the allograft challenge their clinical applications. This has stimulated interest in the development of synthetic materials for bone replacement and more recently novel biomaterials with similar properties to native bone [1].

A major advance in biomaterial science has been the development of bioceramics as bone substitutes. The most common bioceramics in use are calcium phosphate-based (CaP) biomaterials which include: hydroxyapatite (HA), α- and β-tricalcium phosphates (α-TCP, β-TCP), octacalcium phosphate (OCP), amorphous calcium phosphate (ACP) and biphasic calcium phosphates (BCP) which is a combination of two different CaP phases [2–4]. All types of CaP biomaterials can be manufactured in both porous and dense forms as bulk, granules, and powders or in the form of coatings. Their biocompatibility, safety, availability, low morbidity and cost effectiveness are important advantages over autografts and allografts. CaP bioceramics are now in common use for different medical and dental applications such as treatment of bone defects and fracture, total joint replacement, spinal surgery, dental implants, periodontal therapy and cranio-maxillofacial reconstruction [5,6].

The majority of research on CaP based biomaterials has focused on HA ($Ca_5(PO_4)_3OH$) and β-TCP ($Ca_3(PO4)_2$) [7]. CaP based biomaterials are bioactive and have a composition and structure similar to the mineral phase of bone and can be processed to have osteoconductive properties [8]. Furthermore, they have a high affinity for protein adsorption and growth factors [9] that in turn influence osteoinductivity. The osteoinductive properties can be achieved in two ways; intrinsic and extrinsic. Intrinsic is by structural or chemical optimization of the biomaterials themselves and the extrinsic is by the addition of osteoinductive signal molecules, such as bone morphogenetic proteins (BMP) or osteogenic cells [10,11].

Although the CaP bioceramics have many advantages, they also suffer from disadvantages such as; poor mechanical strength, lack of organic phase (i.e. collagen), presence of impurities, micro-scale grain size and non-homogenous particle size and shape. Furthermore, the processing techniques for preparation of bioceramics suffer from prolonged fabrication time, low-yield final product and difficult porosity control [2]. However, over recent years, several modifications of fabrication parameters such as sintering temperature, sintering soaking time, pH and purity of the initial materials have given rise to biomaterials with improved physicochemical properties such as specific surface areas, surface energy, surface charge, surface topography and roughness, grain size and porosity [12].

Another area of recent interest in the literature is to produce bioceramics at the nanoscale level. This is because the bone matrix is also a precise composition of two major phases at the nanoscale level namely, the organic phase (proteins) and inorganic phase (minerals, mainly CaP nanocrystals). The conventional synthetic CaP ceramics are composed of large grain size at microscale level, which seems to possess different biological behaviors of bioactivity, biodegradability and mechanical properties than nanoscale alternatives. Therefore, fabrication of nanoscale bioceramics may improve the biological behavior of CaP bioceramics [13]. In addition, it has been shown that nano-HA promotes osteoblast cells adhesion, differentiation, and proliferation thereby enhancing osseointegration and deposition of calcium containing minerals on its surface better than microcrystalline HA [14]. Moreover, the superiority of biological calcified tissues (e.g., bones) are also due to the presence of biopolymers (mainly, collagen type I fibers) which confer strength and partial elasticity. Therefore, one of the most promising ideas is to apply biomaterials with similar composition and nanostructure to that of natural bone tissue. In this regard, development of composite organic–inorganic biomaterials may provide better opportunities for optimizing the conventional bone substitutes [13].

1.2. Biphasic calcium phosphate

Another major area of research on CaP based biomaterials has focused on BCP [15]. According to the definition, BCP consists of two individual CaP phases: most commonly from a more stable phase (HA) and more soluble phase (β-TCP) in different proportions. This combination has presented significant advantages over other types of CaP bioceramics by allowing a better control over bioactivity and biodegradation which guarantees the stability of the biomaterial while promoting bone ingrowth. BCP ceramics are osteoconductive with the possibility of acquiring osteoinductive properties [16,17].

Different researchers have attempted to achieve desirable biological responses by modification of different parameters during biomaterial fabrication or by incorporation of different biocompatible polymers. The biological response to BCP ceramics varies according to their chemical compositions and physical properties which can give rise to different rates and patterns of bone regeneration. To the best of our knowledge, a consensus of the ideal physicochemical properties of BCP scaffolds such as; composition ratio, pore size, total porosity and interconnected porosity has yet to be determined. In addition, there are no generally accepted standards for in vitro and in vivo studies with regards to experimental protocol and interpretation of results; this most likely appears to contribute to the variation of results and findings on the properties and effectiveness of BCP.

For the purpose of this review, it is divided into two main sections. First, Sections 3.1–3.4 provide a general overview on BCP (HA/β-TCP) elaborating the concept, synthesis and importance of physicochemical properties and characterization. This section also includes a systematic review of animal studies comparing application of different composition ratios of BCP (Section 3.4). Second, Sections 4.1–4.5. provide discussion regarding controversies on BCP composition ratio followed by general guidelines for characterization and documentation of BCP. This section also presents recommendations to help in reducing the inconsistencies in protocols and reporting strategies of future studies. Of course, the provided guidelines and recommendations can also be applied to study of other biomaterials in the field of bone tissue engineering.

2. Review of literature

It is well accepted that the best representative model of biological condition are animal studies. Therefore, for systematic review on application of different composition ratios of BCP, we restricted our search to animal studies as the best models that represent the real biological