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Review article

Biphasic calcium phosphate ceramics for bone reconstruction: A review of biological response

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ABSTRACT

Autologous bone graft is considered as the gold standard in bone reconstructive surgery. However, the quantity of bone available is limited and the harvesting procedure requires a second surgical site resulting in severe complications. Due to these limits, scientists and clinicians have considered alternatives to autologous bone graft. Calcium phosphates (CaPs) biomaterials including biphasic calcium phosphate (BCP) ceramics have proven efficacy in numerous clinical indications. Their specific physico-chemical properties (HA/TCP ratio, dual porosity and subsequent interconnected architecture) control (regulate/condition) the progressive resorption and the bone substitution process.

By describing the most significant biological responses reported in the last 30 years, we review the main events that made their clinical success. We also discuss about their exciting future applications as osteoconductive scaffold for delivering various bioactive molecules or bone cells in bone tissue engineering and regenerative medicine.

Statement of Significance

Nowadays, BCPs are definitely considered as the gold standard of bone substitutes in bone reconstructive surgery. Among the numerous clinical studies in literature demonstrating the performance of BCP, Passuti et al. and Randsford et al. studies largely contributed to the emergence of the BCPs. It could be interesting to come back to the main events that made their success and could explain their large adhesion from scientists to clinicians. This paper aims to review the most significant biological responses reported in the last 30 years, of these BCP-based materials. We also discuss about their exciting future applications as osteoconductive scaffold for delivering various bioactive molecules or bone cells in bone tissue engineering and regenerative medicine.

Contents

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1. Introduction

1.1. Clinical context

Despite the benefits that minimally invasive osteosynthesis and surgery have brought to fracture and bone healing, there are still many circumstances where achieving bone healing may prove challenging. Autologous bone grafts are still considered the gold standard in bone repair and regeneration because of their osteogenicity, osteoinductivity and osteoconductivity [1]. But in human medicine, some instances clearly demonstrated the clinical equivalence of synthetic bone substitutes over autografts which then are no longer recommended as they are time consuming in the OR expansive in terms of hospitalization and available in limited quantity. They induce morbidity and chronic pain and can be associated with unpredictable outcomes [2–7]. The harvesting procedure requires a second surgical site, with which complications have been reported, and the quantity of bone graft is limited. In addition, autologous bone grafts may be too rapidly resorbable as they can be degraded before bone healing has been completed [8].

Allogenic and xenogenic bone substitutes have also been proposed and are still used in some clinical applications [9]. But viral transmission and a lack availability of native bone have led to the development of synthetic bone substitution biomaterials whose use dramatically increased in the last 15 years, because of their reliable manufacturing process and the possibility of combining them with bioactive molecules, therapeutic agents and cells for tissue engineering, cell-therapy and gene-therapy applications.

1.2. Biomaterials as bone graft substitutes

Synthetic bone graft materials available as alternatives to autogenous bone for repair, substitution or augmentation include: metals; resorbable and non-resorbable polymers; inert ceramics (e.g., alumina, zirconia); special glass ceramics described as bioactive glasses; calcium sulfates, calcium carbonates and calcium phosphates (CaP). These inorganic materials differ in composition and physical properties from each other and from bone [10–12].

Since bone mineral is made of non-stoichiometric and polysubstituted CaP apatite, CaP materials were rapidly preferred as they can be part of the bone remodeling process. Based on composition, synthetic calcium phosphates presently used as biomaterials are classified as calcium hydroxyapatite (HA), $Ca_{10}(PO_4)_6(OH)_2$; alpha- or beta-tricalcium phosphate (α- or β-TCP), $Ca_3(PO4)_2$; biphasic calcium phosphates (BCPs) for mixtures of HA and β-TCP; and unsintered apatites or calcium-deficient apatites (CDA). HA and β-TCP ceramics can be prepared by grounding CaO and P_2O_5 powders with Ca/P equals to 1.67 and 1.5 respectively. These mixtures have to be subsequently sintered over than 1100 °C and generally submitted to further grounding/sintering processes until the final powder presents a homogeneous final Ca/P. CDAs can be prepared either by aqueous precipitation from calcium and phosphate salts or alkaline hydrolysis of acidic calcium phosphates [13–15]. BCPs, with varying β-TCP/ HA ratios can be prepared by sintering precipitated CDAs of varying Ca/P ratio [16–18]. Calcium phosphate biomaterials differ in their solubility or extent of dissolution in acidic buffer which may reflect the comparative dissolution or degradation *in vivo* [14]. The comparative extent of dissolution is α-TCP ≫ CDAs > β-TCP ≫ HA. For BCPs, extent of dissolution depends on the β-TCP/HA ratio, the higher the ratio, the higher the extent of dissolution [14,19]. BCP have been described for the first time in 1985 at the 11th Annual Meeting of the Society for Biomaterials [20,21]. They were used by Nery et al. in 1975 [22] but the preparation was wrongly described as 'tricalcium phosphate' which was corrected by these authors in 1986 [23] and confirmed by LeGeros in 1988 [18].

- Nowadays, BCPs are definitely considered as the gold standard of bone substitutes in bone reconstructive surgery. Among the numerous clinical studies in literature demonstrating the performance of BCPs [4,6,7,24,25], Passuti et al. [26] and Randsford et al. [27] studies largely contributed to the emergence of the BCPs. It could be interesting to come back to the main events that made their success and could explain their large adhesion from scientists to clinicians. This paper aims to review the most significant biological responses reported in the last 30 years, of these BCP-based materials.

2. The biological responses of BCP ceramics

2.1. The role of HA/β-TCP ratios

Chemical properties of ceramics may influence the resorption activity by osteoclasts. Among the chemical properties, solubility of ceramic is probably one of the most important to control. It is irrelevant to affirm that by increasing the solubility of ceramic, the resorption activity would be optimal. By contrast, synthesis of a ceramic too soluble might create an important gradient of calcium ions extremely deleterious for the activity of osteoclasts. Given that solubility of ceramic is mainly dependant on the ratio HA/β-TCP, some studies were interested in determine which is the best selected ratio [28–30].

In this attempt, Yamada et al. have tested CaP ceramics with various degrees of solubility according to HA/β-TCP ratios [30]. Resorption activity was observed on pure β-TCP and BCP 25/75 (25% HA/75% β-TCP). Osteoclasts did not resorb BCP 75/25 (75% HA/25% β-TCP) or pure HA. Interestingly, they observed that solubility influences the pattern of osteoclastic resorption in terms of shape and distribution of resorption lacunae. For example, on pure β-TCP, lacunae appear discontinuous like a chain of small islands whereas they are large and continuous on BCP 25/75 (25% HA/75% β-TCP). resembling those on bone. In addition, the shift in functional phases from resorption to migration seems to occur earlier on β-TCP than on BCP 25/75 (25% HA/75% β-TCP). Data in literature are often contradictory considering the various ceramics tested. Their properties tend to vary depending on the mode and sintering processes which induce different phases in ceramics and various amounts of lattice defects crystals and even when the