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The use of calcium phosphate-based biomaterials in implant dentistry

Cheng Xie · Hong Lu · Wei Li · Fa-Ming Chen · Yi-Min Zhao

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Abstract Since calcium phosphates (CaPs) were first proposed, a wide variety of formulations have been developed and continuously optimized, some of which (e.g. calcium phosphate cements, CPCs) have been successfully commercialized for clinical applications. These CaP-based biomaterials have been shown to be very attractive bone substitutes and efficient drug delivery vehicles across diverse biomedical applications. In this article, CaP biomaterials, principally CPCs, are addressed as alternatives/complements to autogenous bone for grafting in implant dentistry and as coating materials for enhancing the osteoinductivity of titanium implants, highlighting their performance benefits simultaneously as carriers for growth factors and as scaffolds for cell proliferation, differentiation and penetration. Different strategies for employing CaP biomaterials in dental implantology aim to ultimately reach the same goal, namely to enhance the osseointegration process for dental implants in the context of immediate loading and to augment the formation of surrounding bone to guarantee long-term success.

Abbreviations

BMP(s)	Bone morphogenetic protein(s)
CaP(s)	Calcium phosphate(s)
CPC(s)	Calcium phosphate cement(s)
DPBS	Dulbecco's phosphate buffered saline
FGF	Fibroblast growth factor
HA	Hydroxyapatite
PLA	Polylactic acid
PRP	Platelet-rich plasma
TCP	Tricalcium phosphate
TGF(s)	Transforming growth factor(s)

1 Introduction

Dental implants have been widely used in the clinic for the restoration of lost teeth as well as for the rehabilitation of maxillofacial defects in recent decades, but there remains a great challenge regarding the relatively low success rates for patients with poor quantity and quality of alveolar bone and with some diseases such as osteoporosis [1]. Atrophic maxilla and mandible bone are less tolerant to the placement of dental implants because of their reduced height and width, hence the presence of sufficient bone volume is an important prerequisite for dental implant placement [2]. There is also an increasing need to minimize the time required for prosthetic rehabilitation in order to reduce patient inconvenience and to accelerate the surrounding bone regeneration process in order to sustain the long-term fixation of implants [3]. Currently, concerted efforts are concentrated on accelerating and augmenting bone formation around dental and orthopedic implants through the

C. Xie, H. Lu and W. Li contributed equally to this manuscript.

C. Xie · Y.-M. Zhao (✉)
Department of Prosthodontics, School of Stomatology, Fourth Military Medical University, 145th West Chang-le Road, Xi'an 710032, Shaanxi, People's Republic of China
e-mail: zhaoym@fmmu.edu.cn

H. Lu · F.-M. Chen (✉)
Department of Periodontology & Oral Medicine, School of Stomatology, Fourth Military Medical University, 145th West Chang-le Road, Xi'an 710032, Shaanxi, People's Republic of China
e-mail: cfmsunhh@fmmu.edu.cn

W. Li
Department of Neurology, General Hospital of Shenyang Military Command, 83rd Wen-hua Road, Shenyang 110016, Liaoning, People's Republic of China

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implantation of various bone grafts/substitutes and/or by modifying the implant surface with osteoinductive coatings, with a view to improving and expediting the establishment of mechanical stability [4, 5]. It is now well recognized that implants with appropriate surface chemistry and surface topography are in a great demand for enhancing cell attachment, cell growth and tissue formation and the application of appropriate structural materials at dental implant defects should ultimately enhance the osseointegration process of dental implants for their immediate loading and long-term success [5–13].

Hitherto, a number of implantable materials such as autografts, allografts, xenografts and alloplastic bone substitutes have all been used to establish the structural base of osseous tissue to better support dental implants [5, 14]. Autogenous bone is always considered the 'gold standard' in reconstructive and implant surgery; however, autografts have serious drawbacks because of their limited supply, donor morbidity and unpredictability of remodeling. In addition, the process requires the graft to be harvested at a distance from the surgical site, which makes the initial operation more complicated [15, 16]. Therefore, a great variety of suitable and biocompatible bone substitutes have been proposed and developed for augmenting/inducing bone regeneration [17–24]. While these can be used as substrate alternatives, the drawbacks, especially undesirable osteoinductivity, have seriously limited their clinical applications in implant dentistry [5, 14, 15]. Alloplastic bone substitutes can be rendered osteoinductive by the introduction of osteogenic agents, namely growth factors such as bone morphogenetic proteins (BMPs) or transforming growth factors (TGFs), to their outer surfaces, inner structures and/or interfacial regions [5]. If the combination of alloplastic bone substitutes and growth factors can be an alternative/complement to autogenous bone for grafting in implant dentistry, an easier implant treatment for patients as well as for the surgeon will potentially enter clinical practice [5, 25, 26]. It should be emphasized that the use of osteoconductive agents in implant dentistry largely remains an experimental procedure because of (1) the limited knowledge regarding the clinical and biologic aspects of current bone substitute materials and (2) the insufficient vehicles available for the delivery of multiple bioactive agents in clinical implantology [5, 27–29]. Therefore, major effort in this field is focusing on developing new multifunctional materials that are capable of releasing growth factors with reproducible and predictable kinetics and providing mechanical support, serving as a substrate upon which cells can attach, proliferate and undergo differentiation [5, 8, 14, 30].

Calcium phosphate (CaP)-based materials that have been used in craniofacial surgery for more than 100 years represent an attractive candidate because of their outstanding properties as bone substitutes and as drug delivery vehicles [31–34]. These CaP biomaterials, especially calcium phosphate cements (CPCs), have also been considered good options for implant coatings that may promote accelerated bone healing around implants [30, 31]. In this article, CaP-based formulations, essentially CPCs, are briefly introduced for bone substitutes and coatings in implant dentistry, with an emphasis on their potential as an alternative/complement to autogenous bone for grafting, and their advantages as a cell/tissue scaffold as well as a growth factor vehicle in the context of a CPC coating on titanium substrates.

2 CaP biomaterials

CaP is the name given to a family of minerals containing calcium ions (Ca^{2+}) together with orthophosphates (PO_4^{3-}), metaphosphates or pyrophosphates ($P_2O_7^{4-}$) and occasionally hydrogen or hydroxide ions. CaP biomaterials are similar to bone in composition and having bioactive (ability to directly bond to bone, thus forming a uniquely strong interface) and osteoconductive (ability to serve as a template or guide for the newly forming bone) properties [20, 31–33]. Keeping this in mind, CaP has been suggested as a precursor of biological apatite in bone, dentin and cementum [35]. Moreover, CaPs do not cause an antigenic response when implanted in the body and can easily be tailored to the intended application. CPCs, the most popular family of CaP-based materials, are materials that are capable of self-setting to a hard mass [36]. The application of CPCs as biomedical materials for implant dentistry applications have been of great interest due to their excellent biocompatibility and bone-repair properties [37–39].

CPCs consist of a powder phase of calcium and/or phosphate salts that together with an aqueous phase react at room/body temperature and form a CaP precipitate that sets via a process that involves the entanglement of crystals. In general, all CPCs are formed by combining one or more calcium orthophosphates that, upon mixing with a liquid phase, usually water or an aqueous solution, form a paste that is able to set and harden after being implanted within the body [33, 40–43]. The precipitation of hydroxyapatite (HA) nanocrystals at body or room temperature, and the fact that those materials can be used as self-setting pastes, have for many years been the most attractive features of CPCs [43]. However, the lack of macroporosity for fast biological fluid and cell/tissue colonization are the disadvantages of CPCs, which have pushed the development of new processing routes that can develop new generation of CPCs, accommodating capabilities to sustain bone tissue ingrowth and to deliver drugs and bioactive molecules [43]. The formulation of CPCs can be classified into two types of

reactions: an acid–base reaction (called here "two-component" CPCs to simplify) or the transformation of a metastable phase into a more stable phase ("one-component" CPCs), leading to two end products that are often referred to apatite CPCs or brushite CPCs. The main difference between apatite and brushite CPCs is the pH during the reaction: neutral or basic pH for apatite CPCs and acidic pH (<6) for brushite CPCs [44]. Different studies with CPCs have shown that they are highly biocompatible and osteoconductive materials that can stimulate tissue regeneration [37–39]. Most of the apatitic cements are resorbed via cell-mediated processes. In these processes, osteoclastic cells degrade the materials layer by layer, starting at the bone-cement interphase and continuing throughout its inner part [34]. CPC coatings can provide direct bone contact at the implant-bone interface and guide bone formation along their surface, effects that are collectively termed osseoconduction [6, 13, 45].

While CPCs have been widely investigated as bone substitutes and osteoconductive coatings, the biological performance metrics of CPC bone grafts in terms of the initiation and support of bone growth are inferior of those of natural bone grafts [5, 31, 33]. However, the introduction of interconnecting porosity (macroporosity and microporosity) similar to that of bone into CaPs can be reached by chemical or physical modifications [46]. Although CaP biomaterials, by themselves, are not osteoinductive (i.e., do not have the ability to induce de novo bone formation as evidenced by bone formation nonskeletal sites such as subcutaneous or intramuscular sites), the combination of growth factors can modify the osteoinductive properties of CaP materials and therefore promote bone formation and repair [46–48]. Among the different compositions of CaP materials, beta-tricalcium phosphate (β-TCP) has attracted attention owing to its bioresorbability. There is mounting evidence that β-TCP is effective to be used as growth factor carrier in maxillary sinus floor augmentation [49, 50] and enhancing bone regeneration around titanium dental implants [51, 52]. But the release kinetics of growth factors delivered via resorbable β-TCP (a combination of purified growth factor mixed with a synthetic β-TCP) is very difficult to regulate for target application. In comparison with β-TCP, research carried out has suggested the great potential of CPCs as carriers for controlled release and vectoring of drugs and growth factors in the skeletal system [34, 53]. Recent evidence has also shown how osteoconductive CaP material coatings, especially when incorporated with growth factors, can promote bone healing and apposition, leading to the rapid biological fixation of implants. The design of CaPs with appropriate geometry, architecture and unique porosity may promote formation of a carbonate HA layer at the bone-material interface, which attracts protein to which cells bind or adhere, proliferate and differentiate, leading to matrix production and biomineralization or formation of new bone [10, 30, 45]. It is this capability that has allowed CPCs and other CaP families to find diverse applications, ranging from grafting to coatings, in implant dentistry [10, 30, 34, 45–54].

3 CaP biomaterials as bone substitutes in dental implantology

Autogenous bone, with its osteogenic, osteoinductive and osteoconductive properties, has long been considered the ideal grafting material in bone reconstructive surgery as well as in implant dentistry. However, autogenous bone is limited for grafting purposes, and its retrieval is associated with donor site morbidity [15]. Recent advances in biotechnology and bioengineering have provided the implant surgeon with access to a greater variety of bone grafting materials and hence the possibility of easier implant treatment for the patient as well as for the surgeon [5]. However, the perfect grafting material has yet to be identified. In general, the ideal alternative bone graft material would mimic the native characteristics and constituents of autologous bone, as closely as possible, by providing inductive growth and differentiation factors and an osteoconductive matrix that can act as a scaffold for vascular ingress, cellular infiltration and attachment, cartilage formation and calcified tissue deposition [55, 56]. Although implantation of bone grafts/substitutes is still the most frequently applied approach in treating bone defects around implants, the clinical usefulness of a great variety of materials for bone argumentation in implant dentistry has been seriously questioned [5]. To date, when considering a material to replace and mimic bone, synthetic CaP materials, especially CPCs, have been considered an obvious answer (though currently commercialized CPCs are still far from perfect) since they can replicate the structure and composition of bone mineral in a reproducible way and exhibit outstanding biophysical and biochemical characteristics [35, 43]:

- they have different forms, facilitating clinical application for example, dense blocks or porous solid pieces for horizontal bone loss, and granulated forms for periodontal intrabony and furcation defects [35];
- they exhibit biocompatible behavior with most cell types such as osteoblasts, osteoclasts, fibroblasts and periodontal ligament cells [20, 21];
- they have osteoconductive properties, allowing for the formation of bone on the surface via the attachment, migration, proliferation and differentiation of bone-forming cells [5, 31, 33].

Ceramic composites and scaffolds are popular implant materials in the field of dentistry, orthopedics and plastic surgery. However, the high density and slow biodegradability of ceramics are not beneficial for tissue engineering purposes. To address these issues, macroporosity can be introduced, often in combination with osteoinductive growth factors and cells. Due to the low processing temperature, CPCs do not comply with the original definition of ceramics, although the powder phase contains sintered CaP-materials such as α-TCP and HA [43]. Biodegradable polymers like polylactic acid (PLA), gelatin or chitosan can be used as matrices for ceramic particles or as adjuvants to CaP biomaterials [57–59]. The use of these polymers can introduce a tailored biodegradation to the ceramic material. It is well-recognized that growth factors play an important role in the complex cascade of tissue events in the regeneration of lost periodontal and bone tissues [27]. Hence, it is reasonable to speculate that bone healing may be improved in implant patients by the administration of osteogenic agents, such as BMPs and/or TGFs [30]. Current evidence suggests that growth factors/drugs can be added to the cement just by adding the growth factor/drug to the liquid hardener, thereby distributing it equally through the cement. However, the optimal methods of delivery, particularly through a cell/tissue CPC scaffold for tissue engineering, remain unclear [27, 30].

The use of endogenous growth factors for bone regeneration has the potential to accelerate clinical translation of new biotechnology. As a plasma fraction of autologous blood, platelet-rich plasma (PRP) has been used in various surgical fields, especially in maxillofacial and periodontal surgery, to augment bone and soft-tissue healing by placing supra-physiological concentrations of autologous platelets at the site of tissue defect [60, 61]. Although patient-derived PRP contains of a pool of endogenous growth factors, the role of PRP in combination with CaP biomaterials for bone healing enhancement remains controversial [62]. However, biological evidence as well as clinical case application do point to the modification of CaP biomaterials with PRP may serve as a clinically available strategy and warrants further investigation [63, 64]. There is evidence that a combination of PRP and CaP granules promotes bone regeneration in a metaphyseal long bone defect in mini-pigs [65], but this effect does not appear in a long-bone critical size defect in dogs [66]. It seems much more still needs to be done to evaluate this concept and to continuously optimize current techniques for PRP preparation.

4 CaP biomaterials as drug carriers in implant dentistry

The possibility of using CaP biomaterials not only as bone substitutes but also as carriers for the local and controlled supply of drugs is very attractive and may be useful in treatments of bone-related chronic diseases and bone defects in dental implantology [34]. Several formulations of CPCs with properties such as injectability or low-temperature setting allow for the incorporation of different drugs and active biomolecules, making them very attractive candidates as drug carriers [34, 67]. In general, a potential substrate that is to be used as a drug carrier must have the ability to incorporate a drug, to retain it at a specific target site and to deliver it progressively over time to the surrounding tissues. In addition, it is advantageous if the material is injectable and biodegradable [27].

When considering growth factor-based therapeutics for bone regeneration, a key issue is how to maximize growth factor access to specific bone sites and control their release in order to maintain a desired growth factor concentration level for long periods without reaching a toxic level or dropping below the minimum effective level [68]. Growth factors are normally produced by healthy cells; however, in an environment near an implant where bone regeneration does not occur naturally, growth factors need to be provided exogenously to cause the desired cell behavior and promote bone regeneration [27–29, 67]. However, the efficacy of growth factors is known to depend upon their mode of application, and the injection of this type of bioactive substance alone cannot induce tissue formation and regeneration since protein diffuses very fast away from the implantation site [4, 69]. Therefore, it is necessary to use materials that allow for the controlled administration of these factors at adequate therapeutic levels when they serve as bone substitutes in implant surgery [34]. In this regard, CPCs are good candidates until more attractive biomaterials can be developed and optimized.

While most current drug carriers are polymers [27–29, 70], inorganic materials can play a more important role than organic ones in specific fields, such as the correction of bone defects [67]. CPCs, for example, will set at room temperature and are biocompatible and osteoconductive, and they can offer additional benefits as drug carriers for bone tissue. Moreover, another relevant property of CPCs is their unique ability to adsorb different chemical species onto their surfaces [34]. Indeed, the idea of incorporating growth factors into CPCs arose with the aim of improving or increasing the osteoconductive capacity of cements for bone engineering. Drugs can be incorporated throughout the entire CPC volume by adding them to one of the two cement phases, where this can facilitate the release of drugs for more prolonged periods [34]. As the setting process can be influenced by the addition of proteins to the liquid phase, growth factors like BMP-2/TGF-β that are commonly used for bone tissue engineering purposes are only added in small amounts. Consequently, the influence of these growth factors on cement setting can be regarded as

insignificant [71]. Because of the high costs of growth factors and the wide range of concentrations of growth factors applied in in vivo research, it is important to use as little as possible in the final application. Drug release efficiencies therefore should be optimized, even though they are strongly dependent on the chemical consistency of the ceramic, the type of growth factor/carrier and the implant site. The formulation of polymer/CPC composites can compensate for brittleness and improve the biodegradation and drug release of the original ceramic; however, the compression strength and biological activity of the polymers added are often inferior. Biopolymers like chitosan, gelatin and collagen are frequently introduced to CPCs to improve the in vivo cohesion and injection properties of the cement [57–59]. These polymers can be applied to mechanically reinforce the cement, especially in the context of the compact microstructure that is formed after mixing both inorganic and organic materials.

One problem that limits the clinical use of CaP formulations is that these materials consists of only micropores with pore sizes on the order of submicrometers to a few micrometers. A lack of macropores and low porosity make its resorption rate rather slow and hence limit its use [72]. Currently, a number of CaP additives, composites and related compounds with high macro-porosity, virtually identical macroporous architectures and osteoinductive ability are being investigated [71–74]. Mastrogiacomo et al. [72], for example, used a cellulose matrix to serve as mold for a HA paste, after which the cellulose was removed by pyrolysis. After sintering, an open porous HA matrix remained [71]. A similar technique is based on an indirect rapid prototyping, where β-TCP, HA (at two sintering temperatures) and biphasic CaP scaffolds with a standardized macro-architecture were manufactured from several CPCs. The manufacturing process had little influence on the composition of the materials except for the consistent but small addition of, or increase in, a β-TCP phase [73]. In animal experiments, Vitoss, a porous β-TCP osteoconductive bone filler, performs well in comparison with other synthetic grafts, and with marrow added in various ways it rivals an autograft [75]. Release characteristics of BMPs from CPCs have been extensively studied and in many cases consist of a cement dissolution initial stage (during cement setting), followed by a diffusion-dependent release that is influenced by material characteristics. A major problem here is that when the CPC was used as the carrier of BMP, the BMP release rate was rather slow (3–13% after 2 weeks) [76]. Prolonged retention of the entrapped proteins might result in the loss of their osteoinductive potential. Moreover, the CPC setting process can be influenced by the addition of proteins to the liquid phase, and the addition of high volumes of growth factor delays cement setting and therefore causes difficulties in clinical use [71]. One possible solution is to incorporate BMP-2 loaded microspheres into CPC. The microspheres have no effect on the physicochemical character of CPCs; however, such a composite was found to be capable of releasing bioactive BMP-2 over 28 days [74]. In comparison, BMP-2 directly delivered in an injectable CPC (alpha bone substitute material) was also found to be capable of bridging critical-sized defects in the rabbit radius [77]. Its injectable properties may allow minimally invasive use.

Taken together, substantial evidence suggests that CaP biomaterials have great potential for applications such as replacement materials in bone repair and regeneration, substrates in tissue engineering and drug delivery systems (reviewed in [31–34]). Dentists have access to an increasing number of different CaP formulations for use in bone augmentation procedures prior to implant placement. However, most of these are not clinically well documented. It appears that most of these options can support excellent bone formation in the floor of the maxillary sinus. On the other hand, in some patients it is only necessary to tent the sinus membrane to build new bone for the stability of implants. Lateral bone augmentation of the alveolar ridge constitutes another important indication for this biomaterial grafting. In summary, prospective clinical studies are still lacking for many of the bone augmentation materials and techniques currently available [5].

5 CaP coatings on titanium and its alloys

There has been a growing awareness in materials science that the adaptation of natural biological processes can lead to significant progress in the controlled fabrication of advanced materials for diverse applications. Learning from, understanding and applying these natural processes to produce CaP coatings that are biologically similar to bone apatite, mimicking its properties, has been a focus of research attention in implant dentistry in recent decades [4, 10, 12, 31, 32, 45, 78, 79]. By generating an osteoinductive coating on a titanium surface that mimics the organic and inorganic components of living bone tissue, a physiological transition between the non-physiological titanium surface and the surrounding bone tissue can be established [12, 45]. Therefore, in orthopedic and dental implantology, numerous attempts have also been made to enhance the osteoconductivity, to improve the osseointegration of titanium prostheses and to improve bone formation and implant fixation by means of surface modification and coating techniques [80]. Each technique produces a unique surface and includes physicochemical methods for applying CaP-based coatings [45, 78, 79], biochemical methods using growth factors or cell attachment peptides [12], and

morphological methods for modifying implant surface area and texture [80]. With a CaP coating, metallic implants can be alternatively regarded as scaffolds for bone-forming cells that can further enhance early and strong fixation of a bone-substituting implant by stimulating bone formation starting from the implant surface [12].

Different methods have been developed to coat metal implants with CaP biomaterials: plasmaspraying, sputter-deposition, sol–gel coating, electrophoretic deposition or biomimetic precipitation. However, the most successful method to apply CaP coatings to implants to date seems to be the plasma-spraying technique, due to its high deposition rate and ability to coat large areas. It is the only coating method has been used for titanium dental implants in clinical practice [6, 10, 13, 78]. The technique by which such layers are produced has recently undergone a revolutionary change, which has had profound consequences for their potential as drug-carrier systems [4, 30]. Generally, CaP layers were deposited upon the surfaces of metal implants under highly non-physiological physical conditions, which precluded the incorporation of proteinaceous osteoinductive drugs [30]. These osteogenic agents (growth factors) could only be adsorbed, superficially, onto preformed layers. Such superficially adsorbed molecules are released too rapidly within a biological milieu to be effective in terms of osteoinductive capacity [4]. However, an implant today can be finished using biomimetic technology under physiological conditions, and thus bioactive agents can be incorporated into the three-dimensional crystal latticework from which they will be gradually released in vivo as the layer undergoes degradation [30]. This feature enhances the capacity of these coatings to act as a carrier system for osteogenic agents [32]. Liu et al. [81] provided possibly the first successful evidence that proteins can be incorporated into the latticework of CaP layers when biomimetically coprecipitated with inorganic components on the surfaces of titanium-alloy implants. These results clearly demonstrated that BMP-2 incorporated into CaP coatings was more potent in stimulating the alkaline phosphatase activity of the adhering cell layer than was the freely suspended drug in stimulating that of cell layers grown on a plastic substratum. A relatively recent study combined anodized surface and CaP deposition by electron beam evaporation. A nanostructured CaP film was deposited on the micro-arc oxidized titanium. A new apatite layer formed easily on the coated film when incubating in Dulbecco's phosphate buffered saline (DPBS) solution at 37°C. By adding basic fibroblast growth factor (bFGF) in the DPBS solution, the bFGF could be immobilized in the newly formed apatite layer. The coated film served to enhance the osseointegration of titanium implants in vivo [82]. The literature discusses a range of possible biomimetic coating routes for the laboratory and for industry [83–85]. However, these methodologies have yet to be introduced in industrial plants or in clinical practice. However, we would argue that by continuing to learn from nature and by incorporating bioactive agents into the coatings, it should eventually be possible to use these coated systems in clinical practice. Many research groups and some major companies are already pursuing this goal.

6 Future perspectives

CaP biomaterials can be made with similar biological properties as those of natural bone by incorporating an osteogenic agent [30]. However, the natural tissue repair process involves multiple growth factors and signaling molecules, in a time and concentration-dependent fashion, as has been clearly established for bone repair [1, 86–88]. The double potential roles of bone substitutes, as systems for growth factor release and as scaffolds for bone regeneration, could be combined by using loaded growth factors to improve the dynamics of bone tissue regeneration [5]. To make CaP substitute and growth factors an alternative to autogenous bone for grafting in implant dentistry, the next step in the evolution process of this kind of bone substitute is the transition from single growth factor-adsorption to multiple growth factor-incorporation [28]. However, we note that the industrial use of CaP biomaterials for drug delivery is not easy for two main reasons. First, implant companies selling CaPs do not have the expertise to deal with drugs and growth factors, whereas pharmaceutical companies do not have any knowledge of the materials and often do not have any interest in working with such small markets. Second, the growth factors of interest are not always the same for different end requirements [35]. Therefore, it would be appropriate to propose a product using CaPs that could be combined with many different growth factors very easily, in such a way that the surgeon could choose the growth factors just before implantation. Much work remains to be done to establish the general laws that control the release kinetics of different growth factors from CPC substitutes, in order to be able to fine-tune them for different therapeutic needs and clinical applications [89–92].

A growing number of biomaterials of natural and/or synthetic origin has been described and considered as vehicles for the delivery of bioactive compounds (growth factors or genes) into different tissue sites [29, 68, 69, 71]. Considering the application of biologically active coatings, various approaches have been extensively investigated that use inorganic (e.g., CPCs) and organic (extracellular matrix components, growth factors, enzymes, etc.) components of natural bone tissue to directly influence the local response

of surrounding tissues and improve the apposition of newly formed bone around implants. The combination of both organic and inorganic constituents into composite coatings is believed to result in truly bone-resembling coatings, leading to improved functionality and biological efficacy [12]. However, to date, there has been no data regarding the delivery of dual/multiple growth factors from implant coatings. Delivering pharmacological doses of short half-life factors and maintaining an environment with an appropriate combination of molecular signals that induce proper cell function and regenerate clinically useful amounts of new bone tissue in vivo around the implants have been critical challenges [28]. Therefore, the development of methodologies that optimize growth factor release and manage multiple growth factors to maximize the therapeutic outcome of clinical regenerative procedures in dental implantology is an area still in need of substantial research attention.

7 Conclusion

Due to their self-hardening and appropriate mechanical properties, high osteoconductivity, excellent surface chemistry and surface topography to bone defect surfaces, CaP-based biomaterials can be used with outstanding results in a number of dental applications, including ridge augmentation, implant coating, bone defect fill and sinus lift [5, 13]. They are available as granules, porous blocks, CaP/polymer composites, cements, and as coatings on orthopedic or dental implants [93–95]. They can also be used as scaffolds in tissue engineering for dentin or bone regeneration. However, research efforts have been somewhat unfocused so that despite a wealth of knowledge gained, clinical uses of CaP-based biomaterials remain restricted to a relatively narrow area [36]. In particular, clinical use of CPCs for dental and intraoral applications has been substantially lacking. In seeking a break-through in the clinical use of CPCs in implant dentistry, the material property requirements for a specific clinical application (e.g., grafting or coating) should first be thoroughly analyzed and well understood. In addition, the development of the "ready to use" CPCs and the optimization their capability for delivering drugs and bioactive molecules are of critical importance, whereas it should not be anticipated that a CPC formulation can be universally efficacious. It would seem a realistic goal that in the foreseeable future CPC type materials with the necessary attributes can replace many of the autografts that are currently used in implant dentistry.

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Conflict of interest The authors declare that there is no conflict of interest

References

1. Gaetti-Jardim EC, Santiago-Junior JF, Goiato MC, Pellizer EP, Magro-Filho O, Jardim EG Jr. Dental implants in patients with osteoporosis: a clinical reality? J Craniofac Surg. 2011;22:1111–3.
2. Chiapasco M, Casentini P, Zaniboni M. Bone augmentation procedures in implant dentistry. Int J Oral Maxillofac Implant. 2009;24 Suppl:237–59.
3. Gapski R, Wang HL, Mascarenhas P, Lang NP. Critical review of immediate implant loading. Clin Oral Implants Res. 2003;14:515–27.
4. Liu Y, de Groot K, Hunziker EB. Osteoinductive implants: the mise-en-scène for drug-bearing biomimetic coatings. Ann Biomed Eng. 2004;32:398–406.
5. Hallman M, Thor A. Bone substitutes and growth factors as an alternative/complement to autogenous bone for grafting in implant dentistry. Periodontol 2000. 2008;47:172–92.
6. Liu X, Chub PK, Ding C. Surface modification of titanium, titanium alloys and related materials for biomedical applications. Mater Sci Eng Rep. 2004;47:49–121.
7. Esposito M, Grusovin MG, Coulthard P, Thomsen P, Worthington HV. A 5 year follow-up comparative analysis of the efficacy of various osseointegrated dental implant systems: a systematic review of randomized controlled clinical trials. Int J Oral Maxillofac Implants. 2005;20:557–68.
8. Esposito M, Grusovin MG, Coulthard P, Worthington HV. The efficacy of various bone augmentation procedures for dental implants: a Cochrane systematic review of randomized controlled clinical trials. Int J Oral Maxillofac Implants. 2006;21:696–710.
9. Zhang Y, Song J, Shi B, Wang Y, Chen X, Huang C, Yang X, Xu D, Cheng X, Chen X. Combination of scaffold and adenovirus vectors expressing bone morphogenetic protein-7 for alveolar bone regeneration at dental implant defects. Biomaterials. 2007;28:4635–42.
10. Le Guéhennec L, Soueidan A, Layrolle P, Amouriq Y. Surface treatments of titanium dental implants for rapid osseointegration. Dent Mater. 2007;23:844–54.
11. Clark PA, Moioli EK, Sumner DR, Mao JJ. Porous implants as drug delivery vehicles to augment host tissue integration. FASEB J. 2008;22:1684–93.
12. de Jonge LT, Leeuwenburgh SC, Wolke JG, Jansen JA. Organic-inorganic surface modifications for titanium implant surfaces. Pharm Res. 2008;25:2357–69.
13. Paital SR, Dahotre NB. Calcium phosphate coatings for bio-implant applications: materials, performance factors, and methodologies. Mater Sci Eng R. 2009;66:1–70.
14. Aghaloo TL, Moy PK. Which hard tissue augmentation techniques are the most successful in furnishing bony support for implant placement? Int J Oral Maxillofac Implants. 2007;22:S49–70.
15. Chen FM, Jin Y. Periodontal tissue engineering and regeneration: current approaches and expanding opportunities. Tissue Eng Part B Rev. 2010;16:219–55.

16. Hanes PJ. Bone replacement grafts for the treatment of periodontal intrabony defects. Oral Maxillofac Surg Clin N Am. 2007;19:499–512.
17. Le Nihouannen D, Daculsi G, Saffarzadeh A, Gauthier O, Delplace S, Pilet P, Layrolle P. Ectopic bone formation by microporous calcium phosphate ceramic particles in sheep muscles. Bone. 2005;36:1086–93.
18. Le Nihouannen D, Guehennec LL, Rouillon T, Pilet P, Bilban M, Layrolle P, Daculsi G. Micro-architecture of calcium phosphate granules and fibrin glue composites for bone tissue engineering. Biomaterials. 2006;27:2716–22.
19. Le Nihouannen D, Saffarzadeh A, Gauthier O, Moreau F, Pilet P, Spaethe R, Layrolle P, Daculsi G. Bone tissue formation in sheep muscles induced by a biphasic calcium phosphate ceramic and fibrin glue composite. J Mater Sci Mater Med. 2008;19:667–75.
20. Saldaña L, Sánchez-Salcedo S, Izquierdo-Barba I, Bensiamar F, Munuera L, Vallet-Regí M, Vilaboa N. Calcium phosphate-based particles influence osteogenic maturation of human mesenchymal stem cells. Acta Biomater. 2009;5:1294–305.
21. Ergun C, Liu H, Webster TJ. Osteoblast adhesion on novel machinable calcium phosphate/lanthanum phosphate composites for orthopedic applications. J Biomed Mater Res A. 2009;89:727–33.
22. Lee SB, Jung UW, Choi Y, Jamiyandorj O, Kim CS, Lee YK, Chai JK, Choi SH. Investigation of bone formation using calcium phosphate glass cement in beagle dogs. J Periodontal Implant Sci. 2010;40:125–31.
23. Cheng L, Ye F, Yang R, Lu X, Shi Y, Li L, Fan H, Bu H. Osteoinduction of hydroxyapatite/beta-tricalcium phosphate bioceramics in mice with a fractured fibula. Acta Biomater. 2010;6:1569–74.
24. Jegoux F, Aguado E, Cognet R, Malard O, Moreau F, Daculsi G, Goyenvalle E. Alveolar ridge augmentation in irradiated rabbit mandibles. J Biomed Mater Res A. 2010;93:1519–26.
25. Bateman J, Intini G, Margarone J, Goodloe S, Bush P, Lynch SE, Dziak R. Platelet-derived growth factor enhancement of two alloplastic bone matrices. J Periodontol. 2005;76:1833–41.
26. Mooren RE, Dankers AC, Merkx MA, Bronkhorst EM, Jansen JA, Stoelinga PJ. The effect of platelet-rich plasma on early and late bone healing using a mixture of particulate autogenous cancellous bone and Bio-Oss: an experimental study in goats. Int J Oral Maxillofac Surg. 2010;39:371–8.
27. Chen FM, Shelton RM, Jin Y, Chapple IL. Localized delivery of growth factors for periodontal tissue regeneration: role, strategies and perspectives. Med Res Rev. 2009;29:472–513.
28. Chen FM, Zhang M, Wu ZF. Toward delivery of multiple growth factors in tissue engineering. Biomaterials. 2010;31:6279–380.
29. Lee K, Silva EA, Mooney DJ. Growth factor delivery-based tissue engineering: general approaches and a review of recent developments. J R Soc Interface. 2011;8:153–70.
30. Liu Y, Huse RO, de Groot K, Buser D, Hunziker EB. Delivery mode and efficacy of BMP-2 in association with implants. J Dent Res. 2007;86:84–9.
31. Daculsi G. Biphasic calcium phosphate concept applied to artificial bone, implant coating and injectable bone substitute. Biomaterials. 1998;19:1473–8.
32. Suzuki O, Kamakura S, Katagiri T. Surface chemistry and biological responses to synthetic octacalcium phosphate. J Biomed Mater Res B Appl Biomater. 2006;77:201–12.
33. Bohner M, Gbureck U, Barralet JE. Technological issues for the development of more efficient calcium phosphate bone cements: a critical assessment. Biomaterials. 2005;26:6423–9.
34. Ginebra MP, Traykova T, Planell JA. Calcium phosphate cements as bone drug delivery systems: a review. J Control Release. 2006;113:102–10.
35. Vallet-Regí M. Revisiting ceramics for medical applications. Dalton Trans. 2006;28:5211–20.
36. Chow LC. Next generation calcium phosphate-based biomaterials. Dent Mater J. 2009;28:1–10.
37. Aral A, Yalçin S, Karabuda ZC, Anil A, Jansen JA, Mutlu Z. Injectable calcium phosphate cement as a graft material for maxillary sinus augmentation: an experimental pilot study. Clin Oral Implants Res. 2008;19:612–7.
38. Arisan V, Ozdemir T, Anil A, Jansen JA, Ozer K. Injectable calcium phosphate cement as a bone-graft material around periimplant dehiscence defects: a dog study. Int J Oral Maxillofac Implants. 2008;23:1053–62.
39. Arisan V, Anil A, Wolke JG, Ozer K. The effect of injectable calcium phosphate cement on bone anchorage of titanium implants: an experimental feasibility study in dogs. Int J Oral Maxillofac Surg. 2010;39:463–8.
40. Markovic M, Takagi S, Chow LC. Formation of macropores in calcium phosphate cements through the use of mannitol crystals. Key Eng Mater. 2001;192–195:773–6.
41. Takagi S, Chow LC. Formation of macropores in calcium phosphate cement implants. J Mater Sci Mater Med. 2002;12:135–9.
42. Barralet JE, Grover L, Gaunt T, Wright AJ, Gibson IR. Preparation of macroporous calcium phosphate cement tissue engineering scaffold. Biomaterials. 2002;23:3063–72.
43. Ginebra MP, Espanol M, Montufar EB, Perez RA, Mestres G. New processing approaches in calcium phosphate cements and their applications in regenerative medicine. Acta Biomater. 2010;6:2863–73.
44. Bohner M, van Landuyt P, Merkle HP, Lemaitre J. Composition effects on the pH of a hydraulic calcium phosphate cement. J Mater Sci Mater Med. 1997;8:675–81.
45. Narayanan R, Seshadri SK, Kwon TY, Kim KH. Calcium phosphate-based coatings on titanium and its alloys. J Biomed Mater Res B Appl Biomater. 2008;85:279–99.
46. LeGeros RZ. Calcium phosphate-based osteoinductive materials. Chem Rev. 2008;108:4742–53.
47. Sohier J, Daculsi G, Sourice S, de Groot K, Layrolle P. Porous beta tricalcium phosphate scaffolds used as a BMP-2 delivery system for bone tissue engineering. J Biomed Mater Res A. 2010;92:1105–14.
48. Son JS, Appleford M, Ong JL, Wenke JC, Kim JM, Choi SH, Oh DS. Porous hydroxyapatite scaffold with three-dimensional localized drug delivery system using biodegradable microspheres. J Control Release. 2011;153:133–40.
49. Stavropoulos A, Becker J, Capsius B, Açil Y, Wagner W, Terheyden H. Histological evaluation of maxillary sinus floor augmentation with recombinant human growth and differentiation factor-5-coated β-tricalcium phosphate: results of a multicenter randomized clinical trial. J Clin Periodontol. 2011;38:966–74.
50. Koch FP, Becker J, Terheyden H, Capsius B, Wagner W. A prospective, randomized pilot study on the safety and efficacy of recombinant human growth and differentiation factor-5 coated onto β-tricalcium phosphate for sinus lift augmentation. Clin Oral Implants Res. 2010;21:1301–8.
51. Weng D, Poehling S, Pippig S, Bell M, Richter EJ, Zuhr O, Hürzeler MB. The effects of recombinant human growth/differentiation factor-5 (rhGDF-5) on bone regeneration around titanium dental implants in barrier membrane-protected defects: a pilot study in the mandible of beagle dogs. Int J Oral Maxillofac Implants. 2009;24:31–7.
52. Choo T, Marino V, Mark Bartold P. Effect of PDGF-BB and beta-tricalcium phosphate (β-TCP) on bone formation around dental implants: a pilot study in sheep. Clin Oral Implants Res. 2011. doi:10.1111/j.1600-0501.2011.02345.x.
53. Luvizuto ER, Tangl S, Zanoni G, Okamoto T, Sonoda CK, Gruber R, Okamoto R. The effect of BMP-2 on the osteoconductive properties of β-tricalcium phosphate in rat calvaria defects. Biomaterials. 2011;32:3855–61.

54. Lind M, Overgaard S, Nguyen T, Ongpipattanakul B, Bunger C, Soballe K. Transforming growth factor-β stimulates bone ongrowth. Hydroxyapatite-coated implants studied in dogs. Acta Orthop Scand. 1996;67:611–6.
55. LeGeros RZ. Calcium phosphate materials in restorative dentistry: a review. Adv Dent Res. 1988;2:164–80.
56. Ambard AJ, Mueninghoff L. Calcium phosphate cement: review of mechanical and biological properties. J Prosthodont. 2006;15:321–8.
57. Lee HH, Sang Shin U, Lee JH, Kim HW. Biomedical nanocomposites of poly(lactic acid) and calcium phosphate hybridized with modified carbon nanotubes for hard tissue implants. J Biomed Mater Res B Appl Biomater. 2011;98:246–54.
58. Xu Z, Neoh KG, Lin CC, Kishen A. Biomimetic deposition of calcium phosphate minerals on the surface of partially demineralized dentine modified with phosphorylated chitosan. J Biomed Mater Res B Appl Biomater. 2011;98:150–9.
59. Barbieri D, Yuan H, de Groot F, Walsh WR, de Bruijn JD. Influence of different polymeric gels on the ectopic bone forming ability of an osteoinductive biphasic calcium phosphate ceramic. Acta Biomater. 2011;7:2007–14.
60. Plachokova AS, Nikolidakis D, Mulder J, Jansen JA, Creugers NH. Effect of platelet-rich plasma on bone regeneration in dentistry: a systematic review. Clin Oral Implants Res. 2008;19:539–45.
61. Intini G. The use of platelet-rich plasma in bone reconstruction therapy. Biomaterials. 2009;30:4956–66.
62. Chen FM, Zhang J, Zhang M, An Y, Chen F, Wu ZF. A review on endogenous regenerative technology in periodontal regenerative medicine. Biomaterials. 2010;31:7892–927.
63. Kasten P, Vogel J, Beyen I, Weiss S, Niemeyer P, Leo A, Lüginbuhl R. Effect of platelet-rich plasma on the in vitro proliferation and osteogenic differentiation of human mesenchymal stem cells on distinct calcium phosphate scaffolds: the specific surface area makes a difference. J Biomater Appl. 2008;23:169–88.
64. Tözüm TF, Keçeli HG. Treatment of peri-implant defect with modified sandwich bone augmentation. Case report and follow-up. N Y State Dent J. 2008;74:52–7.
65. Jungbluth P, Wild M, Grassmann JP, Ar E, Sager M, Herten M, Jäger M, Becker J, Windolf J, Hakimi M. Platelet-rich plasma on calcium phosphate granules promotes metaphyseal bone healing in mini-pigs. J Orthop Res. 2010;28:1448–55.
66. Rabillard M, Grand JG, Dalibert E, Fellah B, Gauthier O, Niebauer GW. Effects of autologous platelet rich plasma gel and calcium phosphate biomaterials on bone healing in an ulnar ostectomy model in dogs. Vet Comp Orthop Traumatol. 2009;22:460–6.
67. Matsumoto T, Okazaki M, Nakahira A, Sasaki J, Egusa H, Sohmura T. Modification of apatite materials for bone tissue engineering and drug delivery carriers. Curr Med Chem. 2007;14:2726–33.
68. Arkfeld DG, Rubenstein E. Quest for the Holy Grail to cure arthritis and osteoporosis: emphasis on bone drug delivery systems. Adv Drug Deliv Rev. 2005;57:939–44.
69. Lieberman JR, Daluiski A, Einhorn TA. The role of growth factors in the repair of bone. Biology and clinical applications. J Bone Joint Surg Am. 2002;84-A:1032–44.
70. Sokolsky-Papkov M, Agashi K, Olaye A, Shakesheff K, Domb AJ. Polymer carriers for drug delivery in tissue engineering. Adv Drug Deliv Rev. 2007;59:187–206.
71. Habraken WJ, Wolke JG, Jansen JA. Ceramic composites as matrices and scaffolds for drug delivery in tissue engineering. Adv Drug Deliv Rev. 2007;59:234–48.
72. Mastrogiacomo M, Scaglione S, Martinetti R, Dolcini L, Beltrame F, Cancedda R, Quarto R. Role of scaffold internal structure on in vivo bone formation in macroporous calcium phosphate bioceramics. Biomaterials. 2006;27:3230–7.
73. Wilson CE, van Blitterswijk CA, Verbout AJ, Dhert WJ, de Bruijn JD. Scaffolds with a standardized macro-architecture fabricated from several calcium phosphate ceramics using an indirect rapid prototyping technique. J Mater Sci Mater Med. 2011;22:97–105.
74. Fei Z, Hu Y, Wu D, Wu H, Lu R, Bai J, Song H. Preparation and property of a novel bone graft composite consisting of rhBMP-2 loaded PLGA microspheres and calcium phosphate cement. J Mater Sci Mater Med. 2008;19:1109–16.
75. Damron TA. Use of 3D beta-tricalcium phosphate (Vitoss) scaffolds in repairing bone defects. Nanomedicine. 2007;2:763–75.
76. Ruhé PQ, Kroese-Deutman HC, Wolke JG, Spauwen PH, Jansen JA. Bone inductive properties of rhBMP-2 loaded porous calcium phosphate cement implants in cranial defects in rabbits. Biomaterials. 2004;25:2123–32.
77. Seeherman HJ, Azari K, Bidic S, Rogers L, Li XJ, Hollinger JO, Wozney JM. rhBMP-2 delivered in a calcium phosphate cement accelerates bridging of critical-sized defects in rabbit radii. J Bone Joint Surg Am. 2006;88:1553–65.
78. de Groot K, Wolke JG, Jansen JA. Calcium phosphate coatings for medical implants. Proc Inst Mech Eng H. 1998;212:137–47.
79. Yang Y, Kim KH, Ong JL. A review on calcium phosphate coatings produced using a sputtering process–an alternative to plasma spraying. Biomaterials. 2005;26:327–37.
80. Shalabi MM, Gortemaker A, Van't Hof MA, Jansen JA, Creugers NH. Implant surface roughness and bone healing: a systematic review. J Dent Res. 2006;85:496–500.
81. Liu Y, Hunziker EB, Layrolle P, De Bruijn JD, De Groot K. Bone morphogenetic protein 2 incorporated into biomimetic coatings retains its biological activity. Tissue Eng. 2004;10:101–8.
82. Li Y, Lee IS, Cui FZ, Choi SH. The biocompatibility of nanostructured calcium phosphate coated on micro-arc oxidized titanium. Biomaterials. 2008;29:2025–32.
83. Schliephake H, Scharnweber D, Roesseler S, Dard M, Sewing A, Aref A. Biomimetic calcium phosphate composite coating of dental implants. Int J Oral Maxillofac Implants. 2006;21:738–46.
84. Reyes CD, Petrie TA, Burns KL, Schwartz Z, García AJ. Biomolecular surface coating to enhance orthopaedic tissue healing and integration. Biomaterials. 2007;28:3228–35.
85. Salemi H, Behnamghader A, Afshar A, Ardeshir M, Forati T. Biomimetic synthesis of calcium phosphate materials on alkaline-treated titanium. Conf Proc IEEE Eng Med Biol Soc. 2007;2007:5854–7.
86. Suzuki O, Kamakura S, Katagiri T, Nakamura M, Zhao B, Honda Y, Kamijo R. Bone formation enhanced by implanted octacalcium phosphate involving conversion into Ca-deficient hydroxyapatite. Biomaterials. 2006;27:2671–81.
87. Peattie RA, Rieke ER, Hewett EM, Fisher RJ, Shu XZ, Prestwich GD. Dual growth factor-induced angiogenesis in vivo using hyaluronan hydrogel implants. Biomaterials. 2006;27:1868–75.
88. Riley CM, Fuegy PW, Firpo MA, Shu XZ, Prestwich GD, Peattie RA. Stimulation of in vivo angiogenesis using dual growth factor-loaded crosslinked glycosaminoglycan hydrogels. Biomaterials. 2006;27:5935–43.
89. Jones AA, Buser D, Schenk R, Wozney J, Cochran DL. The effect of rhBMP-2 around endosseous implants with and without membranes in the canine model. J Periodontol. 2006;77:1184–93.
90. Salata LA, Burgos PM, Rasmusson L, Novaes AB, Papalexiou V, Dahlin C, Sennerby L. Osseointegration of oxidized and turned implants in circumferential bone defects with and without adjunctive therapies: an experimental study on BMP-2 and autogenous bone graft in the dog mandible. Int J Oral Maxillofac Surg. 2007;36:62–71.

91. Hayashi K, Kubo T, Doi K, Tabata Y, Akagawa Y. Development of new drug delivery system for implant bone augmentation using a basic fibroblast growth factor-gelatin hydrogel complex. Dent Mater J. 2007;26:170–7.
92. Han D, Liu W, Ao Q, Wang G. Optimal delivery systems for bone morphogenetic proteins in orthopedic applications should model initial tissue repair structures by using a heparin-incorporated fibrin-fibronectin matrix. Med Hypotheses. 2008;71:374–8.
93. Perez RA, Del Valle S, Altankov G, Ginebra MP. Porous hydroxyapatite and gelatin/hydroxyapatite microspheres obtained by calcium phosphate cement emulsion. J Biomed Mater Res B Appl Biomater. 2011;97:156–66.
94. LeGeros RZ, LeGeros JP. Calcium phosphate biomaterials: an update. Int J Oral-Med Sci. 2006;4:117–23.
95. Verron E, Khairoun I, Guicheux J, Bouler JM. Calcium phosphate biomaterials as bone drug delivery systems: a review. Drug Discov Today. 2010;15:547–52.