Calcium Phosphate Cement: Review of Mechanical and Biological Properties

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Purpose: **Calcium phosphate cement is a bioactive and biodegradable grafting material in the form of powder and liquid, which when mixed, sets as primarily hydroxyapatite, sometimes mixed with unreacted particles and other phases. This material has been extensively investigated due to its excellent biological properties, potential resorbability, molding capabilities, and easy manipulation. Because the material can potentially be replaced with bone after a period of time, it could retain the short-term biological advantages of hydroxyapatite without the long-term disadvantages. Although little is known about this material in the dental community, in vivo and in vitro studies show calcium phosphate cement as a promising material for grafting applications. In the following article, the authors review the biological and mechanical properties of calcium phosphate cement, as well as its potential use in clinical applications.**

Materials and Methods: **A Medline search was performed (timeline: 1980 to 2003) using the following keywords: calcium phosphate cement, hydroxyapatite cement, HA cement, and hydroxyapatite. The search was limited to the English language. The patent literature as well as a limited number of master's theses and books were reviewed after using the electronic database search service from a dental school library.**

Results: **Calcium phosphate cement appears to have excellent biological properties. At only 2 weeks, spicules of living bone with normal bone marrow and osteocytes can be seen. Excellent moldability is a desired clinical characteristic; however, further research is necessary in order to improve the mechanical properties of the cement. The resorption/replacement by bone capability of the cement remains controversial. Further research is needed to clarify this issue. Due to poor mechanical properties, clinical applications are currently limited to craniofacial applications. Further research is necessary to take advantage of the excellent biological properties of this cement under clinical applications.**

Conclusion: **Further research is necessary to understand and improve the behavior of this type of cement under clinical situations.**

INDEX WORDS: implant, hydroxyapatite, bone, HA, ceramic, bioceramic

SURFACE REACTIVE ceramics have been used as grafting materials and as coatings in implant dentistry. These ceramics include the bioglasses and the calcium phosphate-based materials such as hydroxyapatite (HA), tricalcium phosphate (TCP), and others. Calcium phosphates in general have almost exactly the same composition. They can occur in both non-crystalline and crystalline forms. The presence of several crystalline forms may be affected by small variations in the composition.[1,2] The use of a bioactive material capable of releasing calcium and phosphate ions in the area adjacent to an implant may be advantageous, because bone formation can be accelerated as compared with the more inert metallic oxide surface of an implant.[3-6]

HA is the most documented calcium phosphate ceramic, and can be used in bulk form or as a coating. This material can be classified according to its porosity, form, and processing method. All forms of HA have excellent biocompatibility and are able to promote osteoconduction and osseointegration.[3,4] HA-coated implants have demonstrated higher integration rate, faster bone attachment, and higher interfacial attachment strength to bone than non-coated implants.[7-9] However, it

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has been shown that after about 6 months of being implanted, there is little difference between coated and non-coated implants in terms of stability, integration, and bone formation around the implant. Thus, short-term stabilization seems to be the only real advantage of ceramic coatings on dental implants.

Disadvantages of HA include weakness under tensile stress[10] and very slow resorbability.[11,12] Long-term complications related to the latter have been reported. Such complications include detachment of the coating from the implant (which may lead to fibrous tissue formation around the implant) and peri-implant infection, as HA is known not only as a bioactive mineral but also as an adsorbent.[13-18] In other words, HA can adsorb bacteria, causing an unfavorable tissue response, especially if exposed to the oral environment.

Calcium phosphate cement (CPC) is a bioactive cement that sets as HA when moistened.[19] The original CPC formulation was developed by Brown and Chow (US Patent No. 4,518,430).[20] Because of its great potential as a grafting material, a large number of CPC formulations have been prepared and studied for possible clinical applications.[19-36] As in other calcium phosphate preparations, slight variations in the formulation affect the presence of crystalline forms in the compositions.[1,2]

At least three formulations have been approved by the Federal Drug Administration for clinical use (Table 1). Overall, this material may overcome some of the long-term disadvantages of HA while maintaining the excellent initial stimulation of bone formation; however, further studies are necessary to improve some properties.

Advantages of calcium phosphate cements include fast setting time, excellent moldability (the material molds like IRM cement), and excellent HA-like early biological properties. In addition, as with any other bioceramics used in bone grafting, the material provides the opportunity for bone grafting using alloplastic materials. An alloplastic material is unlimited in quantity and provides no risk of infectious disease.

The resorbability of the material is controversial. Resorbability is a key clinical property. Rapid substitution of the material by bone is desired to avoid later complications typical of alloplastic material such as HA.

Poor mechanical properties are the main disadvantage of this material. Since the material is weak under tensile forces, its use is currently limited to craniofacial applications.

In the following article, the authors review the biological and mechanical properties of this promising class of materials, as well as its potential use in clinical applications.

Materials and Methods

A Medline search was performed (timeline: 1980 to 2003) using the following keywords: calcium phosphate cement, hydroxyapatite cement, HA cement, and hydroxyapatite. Year 1980 was used as baseline considering that research involving calcium phosphate cement (as described later in this review) started in the early 1980s. The search was limited to the English language, as most of the relevant information about the material has been published in English. The patent literature was also searched at www.uspto.gov to verify the different patents concerning calcium phosphate materials. A limited number of master's theses were used because their results were never published and they provided excellent information regarding the material. The use of master's theses was also limited to accessibility to the material. Finally, books and monographs discussing calcium phosphate materials were reviewed.

Results

General Characteristics

The powder of the original calcium phosphate cement formulation (Brown and Chow) consists

Table 1. CPC Formulations Regulated by the FDA

*Product**	*Manufacturer*	*Applications**
Bone Source®**	Striker Howmedica Osteonics Rutherford, NJ	Craniofacial
Alpha-BSM®	Etex Corporations Cambridge, MA	Filling of bone defects
Skeletal repair systems (SRS)®	Norian Corporation Cupertino, CA	Skeletal distal radius fractures, craniofacial

*In Europe, other applications may apply, and the materials may be sold with a different commercial name.
**Bone Source® is the original formulation of CPC developed by Brown and Chow.

of an equimolar mixture of tetracalcium phosphate and dicalcium phosphate (anhydrous or dihydrate). The tetracalcium phosphate powder is obtained by sintering a mixture of dicalcium phosphate anhydrous powder with calcium carbonate at 1200 to 1500°C. The resulting product is later pulverized. Dicalcium phosphate (anhydrous or dihydrate) powders are ground in either distilled water or ethanol and then dried and heated at 80°C in vacuum until desiccated. Finally, the two products are mixed in a blender, sterilized by gamma radiation, and desiccated again in vacuum at 60°C. The powder is mixed with an aqueous solution in order to form a paste (similar to ZOE cement). The original aqueous solution was distilled water; however, other solutions have been proposed, as will be discussed below.

Setting Reaction

The setting reaction of calcium phosphate cements starts with dissolution of the salts in the aqueous system. This dissolution supplies Ca and P ions, which precipitate in the form of HA. The reaction occurs under isothermic conditions and at physiologic pH. After initial setting, petal or needle-like crystals enlarge epitaxially and are responsible for the adherence and interlocking of the crystalline grains, which result in hardening. After 2 hours, the crystals appear rod-like, resulting from higher crystallinity with the observation of more material at the inter-particle spaces. At 24 hours, the crystals are completely formed, being highly compacted in some areas of high density and well separated in areas with more porosity.[28,37,38] Typically, the only final product is HA, although some of the unreacted starting materials can be present in some cases.[28]

Setting time for calcium phosphate cement has been extensively studied. The setting time for the original formulation ranged from 15 to 22 minutes.[36,39,40] This setting time may be too long in many clinical applications; however, adding a neutral phosphate such as disodium hydrogen phosphate (Na_2HPO_4) or sodium dihydrogen phosphate (NaH_2PO_4) to the liquid phase (which is distilled water in the original formulation) reduces the setting time to 5 to 8 minutes.[19,41] This is possible because the formation of HA and the dissolution of dicalcium phosphate during the setting reaction occur in a linear fashion, thus avoiding early formation of HA. This is important because HA formed early during the setting reaction of the original formulation engulfs unreacted dicalcium phosphate particles.[30] Therefore, dicalcium phosphate cannot dissolve because it becomes isolated from solution and thus the setting reaction is slower.

Other factors that could influence setting time are particle size, temperature of the liquid phase, and presence of HA in the solid phase;[36] however, in vitro studies have demonstrated that these parameters do not affect setting time significantly.[27,28]

CPC-Bone Interaction

Different studies have reported the progress of bone formation around calcium phosphate cements, and these materials have demonstrated both osteoconductive and osteoinductive properties in certain cases. Histologically, at 2 weeks, spicules of living bone with normal bone marrow and osteocytes in lacunae can be seen in the cement. At 8 weeks, the cement is almost totally surrounded by mature bone. At this stage, no resorption of the cement is typically observed.[42]

As seen with other bioactive ceramics, calcium phosphate cements form an apatite layer on the surface shortly after implantation in bone. However, a unique feature of this material is that the apatite particles are mixed with each other and the force linking them is weak; therefore, these particles can easily detach from the cement body, especially after some dissolution has occurred. When this happens, the particles are easily ingested by osteoclast-like cells or by giant cells.[43]

Resorption and Replacement of the Cement by Bone

In theory, calcium phosphate cement may be substituted by bone depending on its formulation and particle size.[43] This is an important property, as the cement could provide short-term biologically desirable properties and then be replaced by a new bone. However, there is controversy regarding this property, as mixed results have been reported from in vitro and animal studies. It seems that the overall dissolution behavior of calcium phosphate cement is a combination of a solution-mediated process (the implant dissolves in physiologic solutions) and a cell-mediated process (phagocytosis).[12] Bone substitution depends

on age, sex, and general metabolic health of the recipient and anatomic site, porosity, bulk site, crystallinity, chemical composition, particle size, and P/L ratio of the cement. Considering these factors, it may take 3 to 36 months for the cement to be completely resorbed and replaced by bone. Further studies are necessary to assure resorbability of the material in clinical applications.

Mechanical Properties

A critical problem that limits wider clinical application of these ceramic cements is their mechanical properties, as they are brittle and have low impact resistance and relatively low tensile strength (6 to 10 MPa).[34,41,44] On the other hand, the compressive strength of this cement is still significantly higher than that of normal bone at 12 weeks after implantation (60 to 70 MPa).[45]

One of the main reasons for the weakness of these materials is their porosity, which makes it easier for micro and macro cracks to run throughout the mass. The pores are approximately 8 to 12 μm in diameter, and after the cement is set, about 43% of the mass is porosity.[39] Porosity may be controlled to a certain extent by adjusting particle size and P/L (powder/liquid) ratio. The authors measured density of the cement as a function of method of preparation and found that density was higher when using an amalgamator to mix the cement as compared with mixing the cement by hand with a cement spatula. The use of the amalgamator allowed for a higher P/L ratio without altering consistency; however, this method of mixing did not improve the mechanical strength of the cement.[34]

Ishikawa calculated that if the porosity of the cement was zero, then the diametral tensile strength could be 103 MPa;[44] however, higher density may compromise the initial desirable biological properties of the material if bone is not able to grow into the pores of the mass and continue growing while dissolution of the material occurs. In any case, there is no practical way to get zero porosity in a clinical setting, even if desired.

Other factors affecting strength are the materials used in the solid phase, particle size, incorporation of filler materials in the solid phase, P/L ratio, and various liquid phases.[28] Aware of the excellent advantages of the material, researchers have been focused on trying to overcome the mechanical weakness of the cement. More than 20 formulations have been studied for this purpose.[23]

Several investigators have used different filler materials to improve the mechanical properties.[23-25,32,34,45] The idea behind the use of filler particles is that if a strong filler is present in the matrix, it may stop crack propagation; however, by adding fillers, porosity decreases, as does the ability of the material to allow bone ingrowth into the pores. A more dense cement would have slower resorption and thus slower bone substitution as explained previously. Therefore, it seems difficult to increase the strength of the material without reducing its excellent bioactivity.[44]

In an attempt to enhance the rate of bone substitution for the ceramic material, a group of investigators added demineralized bone to the cement in the solid phase. They observed better ingrowth of vascularized tissue; however, the setting time increased and the mechanical properties decreased.[25] Other groups have added polymers and composites and have improved the mechanical strength of the cement up to 30 MPa, but decreased the HA formation, and thus the bioactivity of the material.[26,33]

The authors mixed the cement with two types of bioglass using different particle sizes in an attempt to increase strength; however, bioglass negatively influenced the diametral tensile strength in three of the four groups studied. The remaining group was not stronger than the control group.[34] Other investigators have tried different formulations in an attempt to increase the mechanical properties of the material without success.[45-47]

Target values have not been determined for CPC. Obviously, the targets would depend on the location where the graft would be under loading, the type of bone, and the amount and direction of the forces applied. As a minimum, it appears logical to say that the material should match the mechanical properties of the substance being replaced.

Clinical Applications

The combination of its self-setting nature, moldability, biocompatibility, lack of any by-products, and potential for being replaced by bone make calcium phosphate cements promising materials for dental and orthopedic applications. The ability to be molded in place is an important property of

calcium phosphate cements, because the material can easily be delivered in the desired place and can be made to fit perfectly with the bone surface.[22]

1. *Dental and Orthopedic Applications*
   Tri-dimensional complex load is probably applied during orthopedic and dental applications as a result of a combination of forces that may include bending, torsion, tension, and compression. Unfortunately, CPC is strong at compression only. For example, diametral tensile strength values for CPC materials are usually lower than 20 MPa. Implants consisting of zirconium oxide, which have more than 30 times higher values of diametral tensile strength, may still fail under high stress concentrations when used in orthopedic applications. Despite poor mechanical properties, further studies to determine the efficacy for dental application of these calcium phosphate cements are worthwhile.
   Recent studies have reported optimistic results in relation to the clinical application of calcium phosphate cements. A group of investigators extracted all mandibular premolar teeth from Beagles. After one month of healing, alveolar bone was reduced to make space for a previously fabricated CPC block. After an additional month, 8-mm HA implants were placed in such a manner that the apical half was embedded into alveolar bone and the coronal half in the CPC block. The investigators observed that the CPC block was gradually replaced by bone, and histopathologic features of the CPC area were similar to that of natural bone. Moreover, the area previously surrounded by the CPC block was firmly attached by natural bone. In a second study, the authors used fluorescent labeling analysis and electron microanalysis to measure the extent of new bone formation and elemental (Ca, P, Mg) distribution. Results indicated the presence of newly formed bone at 1 month after surgery and similar elemental distributions in the CPC and natural bone areas at 6 months after surgery.[48,49]
   Comuzzi injected CPC as bone filler for gaps around oral implants placed on the medial femoral condyles of six goats and found excellent bone formation around the graft material; however, the degradation rate of the cement was very slow, and no breakdown of the cement was observed during the time of implantation.[50]
2. *Craniofacial/Maxillofacial Applications*
   The use of CPC for craniofacial applications seems logical, as there is little or no stress generated under these conditions. Moreover, the ability to mold the material at placement is an enormous advantage from a cosmetics standpoint. Losee and coworkers presented excellent results using the material combined with an underlying resorbable mesh in calvarian defects of Yorkshire pigs. They found progressive bone ingrowths in all defects at 180 days with nearly complete replacement by host bone.[51] Friedman reported excellent results in over 100 human patients when using the cement in cranial defects. The success rate of the cement after 6 years was 97%.[22]
3. *Application in Osteonecrotic Sites*
   One study by Aponte[52] involved the use of biodegradable calcium phosphate cement for the treatment of osteonecrotic lesions near articulating joints. In that study the author created an osteonecrotic lesion in the cancellous bone of the distal femur of a rabbit by forming a drill hole in conjunction with local freezing of the site with a cryoprobe. The calcium phosphate cement used as a filler material was easy to manipulate (3/1 P/L ratio) and provided good support to the articular surface and the subchondral bone, even when the cartilage zone was degraded due to the freezing/thawing process. Structural alteration of the subchondral bone was observed within 3 months, with normal bone observed for longer-term specimens. The articular cartilage appeared normal in most specimens, and the interfacial zone showed minimal foreign body response. The cement penetrated into trabecular bone during condensation of the material using a technique that minimized macroporosities within the cement. Microfractures observed in the specimens were primarily along the bone-to-cement interface. After 3 to 12 months, specimens demonstrated osteoconduction, and bone had replaced much of the cement at 12 months. Further studies are highly encouraged in this area.
4. *Other Dental Applications*
   One group of investigators used the cement on artificially created periodontal defects, but they did not find a significant difference between cement and control groups. However, they concluded that the results warranted further

Table 2. Potential Advantages and Disadvantages of Calcium Phosphate Cements

Advantages	*Disadvantages*
Osteoconduction and osteoinduction: Initial biological properties similar to those of HA	Mechanical weakness: Limited use due to potential collapse of material followed by soft tissue formation instead of bone formation (loaded areas)
Can be replaced by newly formed bone after a period of time. Therefore, HA-related long-term disadvantages may be avoided*	Can washout from surgical defect if excess of blood. Compression during setting reaction is recommended. Formulations containing sodium alginate have been studied to solve this problem
Moldability: Easy to place in surgical site	
Excellent biocompatibility	
Can be used to deliver growth factors, antibiotics, morphogenic proteins at local site*	
Excellent material for maxillofacial/craniofacial applications (non-loaded areas)	

*Further studies are necessary.

investigation since the cement acted as a scaffold for bone formation and provided histocompatible healing of periodontal tissues.[53]

Other investigators used the cement for direct pulp capping and compared it to calcium hydroxide. They found that both materials were equally capable of producing secondary dentin at 24 weeks.[54]

5. *Other Clinical Considerations*

Disintegration, or washout, of calcium phosphate cements has been reported as a potential clinical problem.[19,44] This could perhaps be solved by putting pressure on the paste during the setting period. To avoid this problem, another possibility is the use of a proposed formulation containing sodium alginate; however, the mechanical properties (strength) of this formulation are still poor.[31]

Antibiotics can be delivered in a controlled manner using this same formulation. This same group of investigators added flomoxef sodium to the formulation and found that the release of antibiotic could be easily controlled in vivo by adjusting the content of sodium alginate in the formula.[19]

Recently, Blom added recombinant human transforming growth factor beta-1 to the cement and found that after 8 weeks the addition of growth factors stimulated and increased bone formation (50% volume) and bone contact (65%) in comparison to control calvarian defects in an animal study. In addition, the growth factor group reduced the remaining volume of cement by 20%.[35] Additional animal studies using growth factors are encouraged based on these results.

Conclusions

Despite decades of research efforts, a perfect grafting material does not exist. Calcium phosphate cements are no exception to this statement. While possessing excellent biological properties (osteoconduction, osteoinduction), adequate setting time, excellent moldability for surgical applications, and the capability to deliver different bone-enhancing proteins/antibiotics at local level, the material lacks adequate mechanical properties for applications other than non-loaded surgical sites (craniofacial). In addition, as the literature is conflicting in this matter, it is not clear whether the material has adequate resorbability properties (Table 2). However, in vitro and in vivo studies have demonstrated some interesting and promising qualities in this material.

Further research is necessary to understand and improve the behavior of this type of cement under clinical situations.

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