Calcium-phosphate biomaterials for bone healing
practical guideline for implementation in clinical practice
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practical guideline for implementation in clinical practice

by Chris Arts
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Preface
Dear reader,

This booklet summarizes the basic terminology regarding material / mechanical properties of Ca-P ceramics and will explain their effect on biological and mechanical behavior. Also the Diamond concept for bone healing is explained and supported by illustrative cases.

The primary reason for the compilation of this book is the fact that there is little guidance about implementation of Ca-P ceramic in clinical practice. As a lecturer I have been confronted with a lot of interest in this topic of the years but unable to find an adequate summary of these topics directed towards clinical implementation.

This book is by no means intended as a comprehensive overview but aims to raise awareness and stimulation discussion regarding Ca-P ceramics for bone healing use in clinical practice. I trust you will find this a useful addition to your clinical practice and education.

Dr. Chris Arts
Definitions
Definitions
Calcium-phosphate biomaterials for bone healing
Bone is a living tissue capable of self-repair

Bone only forms when mechanical loading is present (Wolff’s law)

Bone is continuous being renewed; balance between osteoblasts forming bone and osteoclasts resorbing bone

This process of constant bone resorption and bone formation is called bone remodeling

Functions of bone

- Stabilise and support body
- Protection of internal organs and soft tissue
- Rigid parts of the human movement system
- Storage of minerals and fatty acids
- Production of blood cells through bone marrow haematopoiesis
Definitions
Calcium-phosphate biomaterials for bone healing

creeping substitution
The process of bone remodeling is also called “creeping substitution”  

The osteoclastic resorption of dead bone from the allograft and its replacement by new living bone made by osteoblasts from the host.

Gradual penetration across a fracture site by osteogenic tissue followed by bone formation.

Biomaterial

A natural or synthetic material that is suitable for introduction into living tissue.

A synthetic material used to replace part of a living system or to function in intimate contact with living tissue.

A biomaterial is a substance that has been engineered to take a form which, alone or a part of a complex system is used to direct, by control of interactions with components of living systems, the course of any therapeutic or diagnostic procedure.
## Definitions
Calcium-phosphate biomaterials for bone healing

### Scaffold

Temporary framework used to support people and material in the construction or repair of buildings.

In regenerative medicine the more commonly used definition is: “An artificial structure capable of supporting 3-D tissue formation.”

To allow bone formation a scaffold should allow: attachment, proliferation, migration, and phenotypic expression of bone cells leading to formation of new bone in direct apposition to the Ca-P biomaterial.

### Scaffold purpose

<table>
<thead>
<tr>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allow cell attachment and migration</td>
</tr>
<tr>
<td>Deliver and retain cells and biochemical factors</td>
</tr>
<tr>
<td>Enable diffusion of vital cell nutrients and expressed products</td>
</tr>
<tr>
<td>Exert certain mechanical and biological influences to modify the behaviour of the cell phase differentiation</td>
</tr>
</tbody>
</table>
A scaffold must be...⁶-⁹
- Biocompatible and biodegradable
- Mechanically stable over time
- Able to incorporate any chemical, or biological cues desired
- Adequate permeable to allow fluid flow and diffusion
- Unable to elicit an inflammatory reaction

The ideal scaffold should be...
- Implantable through a minimal surgical exposure
- Applicable for various indications
- Moldable to conform to and fill irregular defects
- In possession of roughly the same viscoelasticity as bone
- As rigid and strong as intact bone for immediate load-bearing capability
- Promote new bone formation and incorporation by host bone
- Available in large quantities
- Affordable
Bioactivity$^{2,11}$

The ability of a material to have interaction with or effect on any cell tissue in the human body.$^{2}$

The ability of a material to form a direct bonding with the host biological tissue.

Biocompatibility$^{2,11}$

The ability of a material to perform with an appropriate host response in a specific situation.

Ability of a material to be in contact with a living system without producing an adverse effect.
Biocompatibility of a material-host system

During ESB 2014 in Liverpool Prof. D.F. Williams postulated that biocompatibility of a specific material does not exist. Instead the definition should be broadened and should state: biocompatibility of a material-host system.

Refers to the ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy, but generating the most appropriate beneficial cellular or tissue response in that specific situation, and optimizing the clinically relevant performance of that therapy.
**13 Definitions**
Calcium-phosphate biomaterials for bone healing

**Osteointegration**\(^2,12\)
The property of a material that allows development of a direct, adherent and strong bond with the surrounding bone tissue.
The formation of a direct interface between an implant and bone, without intervening soft tissue.

**Osteopromotive (DBMs)**
Describes a material that promotes the de novo formation of bone. It will not contribute to de novo bone growth but serve to enhance the osteoinductivity of osteoinductive materials.

**Osteostimulative (Bioactive glasses, ceramic BGS)**
An osteostimulative material needs an osseous defect that provides nutrients (blood) to stimulate bone growth. Effectively promotes new bone growth, accelerating bone remodeling. In addition, a synthetic bone graft that is osteostimulative will not grow ectopic bone.
Osteoinductivity\textsuperscript{2,10-11}

The ability to induce new bone formation through molecular stimuli recruitment and differentiation in a controlled phenotype or particular lineage promote cellular functions leading to new bone formation.

Active process

Osteoinduction is too widely defined and often used when not supported (DBMs). It should be defined according to location in the body and timeline!

Osteoconductivity\textsuperscript{2,10-11}

The ability of a scaffold to facilitate new bone formation by allowing bone cells to adhere, proliferate, and form extracellular matrix on its surface and pores.

Primarily based on mechanical stimuli as well as chemical composition and geometry of the material.

Passive process
Ca-P ceramics properties
Ca-P ceramics

Ca-P ceramics

Refers to ancient Greek “Keramos” which means “pottery”

Made from inorganic, non-metallic materials with a crystalline structure, usually produced by sintering (processing at high >1200° C temperature)

Most ceramics are hard, porous yet brittle

The osteoconductive Ca-P biomaterials allow: attachment, proliferation, migration, phenotypic expression of bone cells leading to formation of new bone in direct apposition to the Ca-P biomaterial
Property overview of Ca-P ceramics

**Chemical properties**
composition, crystallinity, Ca-P ratio

**Structural properties**
porosity, inter-connectivity

**Biological & Mechanical characteristics of Ca-P ceramics**

**Degradation properties**
speed of resorption, chemical, cellular?

**Mechanical properties**
creep, stiffness, Young’s modulus

**Surface area**

**Particle size**
Ca-P ceramics properties

Chemical properties

Composition refers to the original base components of the material

Hydroxyapatite (HA) [Ca$_{10}$(PO$_4$)$_{6}$(OH)$_2$]

Tri-calcium phosphate (TCP) [Ca$_3$(PO$_4$)$_2$

Biphasic: percentage combination of HA & TCP in same material

Hybrid: One of the above with added material such as Si, Mg or Bioactive glass

Composition has an effect on

Mechanical properties (impactability strength, stiffness, Young’s modulus)

Biological properties (osteointegration)

Degradability speed
## Rules of thumb

<table>
<thead>
<tr>
<th>Category</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength</td>
<td>TCP less brittle in dry formulation compared to HA</td>
</tr>
<tr>
<td></td>
<td>TCP quicker loss of mechanical strength compared to HA in vivo</td>
</tr>
<tr>
<td>Resorption</td>
<td>TCP chemically less stable compared to HA</td>
</tr>
<tr>
<td></td>
<td>TCP possesses high resolution characteristics compared to HA</td>
</tr>
<tr>
<td>Degradation</td>
<td>TCP easily resorbed by osteoclasts compared to HA</td>
</tr>
<tr>
<td></td>
<td>TCP faster degradation (12-18 months) compared to HA (2-10 years)</td>
</tr>
</tbody>
</table>
Crystallinity refers to the degree of structural order in a material.

Less order provides a more amorphous material

| crystalline structure | amorphous structure |

Crystallinity has an effect on

- Mechanical properties (hardness, density)
- Biological properties (osteococonduct)
- Degradation properties (speed and type of degradation)
Rules of thumb

**Strength**
High crystallinity provides better stiffer material

**Resorption**
Amorphous porous materials enhance bone ingrowth but also biological degradation

**Degradability**
High crystallinity leads to slower degradablity due to resistance in dissolution
## Ca-P ceramics properties

### Structural properties

**Calcium-phosphate (Ca/P) ratio** refers to be a measurement of Ca-P ceramics composition.

<table>
<thead>
<tr>
<th>Name</th>
<th>Formula</th>
<th>Ca/P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracalcium phosphate</td>
<td>( \text{Ca}_4(\text{PO}_4)_2\text{O} )</td>
<td>2.0</td>
</tr>
<tr>
<td>Hydroxyapatite</td>
<td>( \text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2 )</td>
<td>1.67</td>
</tr>
<tr>
<td>Calcium deficient hydroxyapatite</td>
<td>( \text{Ca}_9(\text{HPO}_4)(\text{PO}_4)_5(\text{OH}) )</td>
<td>&lt;1.67</td>
</tr>
<tr>
<td>Tricalcium phosphate (( \alpha,\beta ))</td>
<td>( \text{Ca}_3(\text{PO}_4)_2 )</td>
<td>1.5</td>
</tr>
<tr>
<td>Dicalcium phosphate dihydrated (Brushita)</td>
<td>( \text{CaHPO}_4.2\text{H}_2\text{O} )</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Rules of thumb

Strength
High Ca/P ratio provides higher strength when compared to low Ca-P ratio

Degradability
High Ca/P ratio 1,67 (HA) leads to slower degradability as compared to Ca/P ratio of 1,5 (TCP)
Porosity\textsuperscript{2,16-17} refers to the fraction of the volume of voids within the material over the total material volume

Macro porosity
- Pores > 100 µm - 400 µm
- Provides a scaffold for bone cell colonization

Micro porosity
- Pores < 10 µm
- Allows body fluid circulation (proteins)
- Allows blood vessel ingrowth
- (< 30 µm decreased tissue infiltration)

Porosity ... allows for mechanical interlocking between the implant biomaterials and host bone
- regulates cell reactions
effects degradability
**Rules of Thumb**

<table>
<thead>
<tr>
<th>Surface Porosity</th>
<th>Interconnective Porosity</th>
</tr>
</thead>
<tbody>
<tr>
<td>pores only on surface area</td>
<td>pores throughout entire structure</td>
</tr>
<tr>
<td>mechanically stronger</td>
<td>mechanically weaker</td>
</tr>
<tr>
<td>direction dictates pathway for ingrowing cells</td>
<td></td>
</tr>
</tbody>
</table>

**Strength**

- Interconnective porosity mechanical weaker compared to surface porosity

**Resorption**

- Interconnective porosity resorbs faster compared to surface porosity

**Degradation**

- Interconnective porosity degrades faster compared to surface porosity
## Ca-P ceramics properties

### Mechanical properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strength</strong></td>
<td>Refers to the load carrying capacity of a material.</td>
</tr>
<tr>
<td><strong>Stiffness</strong></td>
<td>Refers to the resistance to elastic deformation.</td>
</tr>
<tr>
<td><strong>Strain</strong></td>
<td>Refers to the deformation of a material by a force acting on the material.</td>
</tr>
<tr>
<td></td>
<td>Strain can be tensile or compressive (plastic or viscoelastic deformation)</td>
</tr>
<tr>
<td><strong>Young’s Modulus</strong></td>
<td>(Modulus of elasticity) refers to the unique property of a material;</td>
</tr>
<tr>
<td></td>
<td>Measure of a material to resist deformation and return to its original shape</td>
</tr>
</tbody>
</table>
Creep refers to the permanent deformation under influence of mechanical stress

<table>
<thead>
<tr>
<th>Mechanical property</th>
<th>Cortical bone</th>
<th>Cancellous bone</th>
<th>Ca-P ceramics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tensile strength (MPa)</td>
<td>50-150</td>
<td>10-100</td>
<td>40-100</td>
</tr>
<tr>
<td>Elastic modulus (GPa)</td>
<td>3-20</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Compressive strength (MPa)</td>
<td>130-230</td>
<td>2-12</td>
<td>100-900</td>
</tr>
<tr>
<td>Young’s modulus (GPa)</td>
<td>15-42</td>
<td>0,02 - 0,5</td>
<td>70-120</td>
</tr>
</tbody>
</table>
Strength refers to the load carrying capacity of a material

Elastic modulus, compressive strength and tensile strength are highly dependent on the position of the body and the condition of the individual.\textsuperscript{11}

Mechanical properties of bone vary with depending on load orientation with respect to the orientation of tissue (anisotropy) and the speed to which the load is applied (viscoelasticity).\textsuperscript{11}
## Rules of thumb

<table>
<thead>
<tr>
<th>Strength</th>
<th>Material strength primarily dependent on composition, structure, porosity and elasticity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength</td>
<td>Ca-P ceramics strong under compression and weak under torsion loads</td>
</tr>
<tr>
<td>Strength</td>
<td>Ca-P cement compressive modulus stronger compared to Ha or TCP granules</td>
</tr>
<tr>
<td>Strength</td>
<td>TCP quicker loss of mechanical strength compared to HA in vivo</td>
</tr>
</tbody>
</table>
Degradation refers to a chemical process resulting in the cleavage of covalent bonds due to hydrolysis, oxidation or enzymatic processes.

(Bio)degradation or resorption is chemical breakdown of an implant by a chemical agent (enzyme, cell, organism).

Erosion refers to physical changes in size, shape or mass due to degradation, dissolution, ablation or wear.

Erosion can be distinguished into surface erosion and bulk erosion.

Degradation has an effect on:

Mechanical properties (impactability strength, stiffness, Young’s modulus)

Biological properties (osteoconductivity)

Degradability speed
### Rules of thumb

<table>
<thead>
<tr>
<th>Degradation</th>
<th>TCP chemically less stable compared to HA due to high resolution characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degradation</td>
<td>TCP easily resorbed by osteoclasts compared to HA</td>
</tr>
<tr>
<td>Degradation</td>
<td>TCP faster degradation (12-18 months) compared to HA (2-10 years)</td>
</tr>
</tbody>
</table>
In vitro dissolution of Ca-P materials depends on

- Composition
- Crystallinity
- Ca/P ratio
- Interconnectivity
- Degradability / type and speed of resorption
- Mechanical properties
- Particle size
- Surface area
- Production process
- Patient characteristics: age, gender, health status, co-morbidities

Ca-P bone substitutes have to be intact long enough for bone ongrowth to occur and to maintain stability.

To achieve balanced bone remodeling, slow bone remodeling and to fast biomaterial resorption should be prevented.
Ca-P ceramics design considerations

Mechanical properties: mechanical properties such as elastic modulus, tensile strength, fracture toughness, fatigue, and elongation percentage should be as close as possible to the replaced tissue (mechanical compatibility) in order to prevent bone loss, osteopenia, or "stress shielding".

Ca-P ceramics must have enough mechanical strength to retain its structure in order to comply with its mechanical function after its implantation in the case of hard, load-bearing tissues as bone.

Pore size and porosity: a 3-D design affects the spatial distribution and location of cells, nutrients, and oxygen, thus affecting the viability of the new formed tissue. Porous scaffolds facilitate the migration and proliferation of cells, providing an appropriate microenvironment for cell proliferation and differentiation and allowing the mass transfer of nutrients, oxygen, and waste metabolic products within the structure.

Scaffolds should have a large internal surface area due to overall porosity and pore size. The surface to volume ratio of porous scaffolds depends on the size of the pores. A large surface area allows cell adhesion and proliferation, whereas a large pore volume is required to contain and later deliver a cell population sufficient for healing or regeneration process.
Bone healing
Bone healing is a multidimensional process requiring all elements of the Diamond concept

Multidimensional process requiring all elements of the Diamond concept combined with mechanical stability and vascularization
Mechanical Stability

Cells
- osteogenesis

Scaffolds
- osteoconductive matrix

Growth factors
- osteoinductive signaling

Vascularization
39 Bone healing
Stepwise assessment of bone defect

**Stepwise assessment of bone defect**
What would you do with this patient... And why?

1. Observe
   - Changed anatomy -> correct
   - Instability -> stabilise
   - Bone loss, CT? -> restore 3-D

2. Think
   - structure

3. Plan

4. Operate

5. Clinical follow-up of cases
## Stepwise bone defect assessment considerations

1. **Changed anatomy**
   - > correct
     - alignment mechanical/anatomical axis
     - articular surface

2. **Instability**
   - > stabilise
     - rigid or dynamic fixation
     - minimal invasive or open exposure
     - choice fixation

3. **Biological capacity**
   - > assess regenerative capacity
     - availability of stem cells
     - availability of vascularisation

4. **Patient**
   - > assess regenerative capacity
     - co-morbidity
     - post-op compliance
Bone healing

Rules of Thumb

> defect location, size, local mechanical (loading regime, stability) and biological environment (cells, osteoinductive signaling, vascularisation)

> determine what bone substitute material can be used
Biomaterial choice considerations

1. Material
   - biocompatibility/ osteoconductivity / osteoinductivity
   - handling (injectability)
   - mechanical properties material and mechanical load on bone defect
   - resorption speed

2. Surgical
   - containment in defect (metal, periost flap, muscle, bone)
   - connection (interdigitation) with host tissue

3. Mechanical
   - mechanical stability
   - adequate fixation (preferably dynamic)

4. Biological
   - availability of stem cells
   - availability of vascularisation

5. Patient
   - co-morbidity
   - post-op compliance

6. Literature
   - large differences in level of evidence between products

7. Surgeon
   - personal preference
   - experience
   - training and education
Bone healing

Clinical indications

1. **Bone graft extender**
   In case insufficient bone graft volume is available

2. **Small contained bone defects**
   Filling of small Ø <2cm non-load bearing defects/voids

3. **Smaller non-load bearing defects**
   Filling of larger Ø <2cm ‘unloaded’ defects when fixation/stabilisation is absent

   Autograft, Allograft, DBM and Ca-P granules can be used
   Ca-P bone substitute: TCP resorption time < HA
   Ca-P cement, BMP should not be used

   Autograft, Allograft, DBM and Ca-P granules can be used
   Ca-P bone substitute: TCP resorption time < HA
   Ca-P ceramic/bone graft mixtures result in a more homogeneous mixture
   Ca-P cement, BMP should not be used

Can use allograft/autograft (provide structural integrity)
Use of DBM is not advocated, due to lack of structural integrity
Ca-P weight bearing granules made of HA (resorb faster than Ca-P cement)
Ca-P cements. Stable but slow resorption
BMP should not be used
4. Lager stabilised defects
- Tibia plateau #, distal radius #, distal/proximal femur #, open wedge osteotomy

5. Weight-bearing defects
- Bone impaction grafting in TKA & THA, large acetabular #, segmental defects

6. Infected defects
- In general Ca-P materials as standalone are a contra-indication

Can use allograft/autograft (provide structural integrity)
Do not use DBM (no structural integrity/stability of fragments)
Ca-P weight bearing granules made of HA if rotational forces/shear is present
Can use Ca-P cements. Stability for fragments but slow resorption

Osteosynthesis must come first
Use materials that provide structural integrity (bone grafts or Ca-P ceramics)
Defect closure for material containment is essential

Local and systemic antibiotic therapy must be used
Bone substitute materials vary in composition, mechanical strength and biological mechanism of function, each having their own advantages and disadvantages.

Large variance in bone substitute materials, material properties, indications and level of evidence.

Not all bone graft substitutes will perform the same way, and their performance in one clinical site may not necessarily predict their performance in another site.
The choice of the optimal bone substitutes is therefore not always an easy one, and largely depends on the clinical application and its associated biological and mechanical needs. Mechanical stability should primarily always be the predominant factor.

Pentagon / Diamond concepts are useful tools for planning surgery with bone substitute materials.