Calcium-phosphate biomaterials for bone healing
practical guideline for implementation in clinical practice
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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 ceramics in clinical practice. As a lecturer I have been confronted with a lot of interest in this topic over 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 stimulate 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.

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Definitions
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.

Definitions
Calcium-phosphate biomaterials for bone healing

Functions of bone
Stabilise and support body
Protection of internal organs and soft tissue
Rigid part of the human movement system
Storage of minerals and fatty acids
Production of blood cells through bone marrow haematopoiesis
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.

Definitions
Calcium-phosphate biomaterials for bone healing

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 as 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
- Allow cell attachment and migration
- Deliver and retain cells and biochemical factors
- Enable diffusion of vital cell nutrients and expressed products
- Exert certain mechanical and biological influences to modify the behaviour of the cell phase differentiation

A scaffold must be...
- 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 visco-elasticity 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
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.

Bioactivity

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

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

Biocompatibility

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.

**Definition:**

Calcium-phosphate biomaterials for bone healing.
**Definitions**

*Calcium-phosphate biomaterials for bone healing*

**Osteointegration**

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 osteointuctivity 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**

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**

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
17 Ca-P ceramics properties

Calcium-phosphate biomaterials for bone healing

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, interconnectivity

Biological & Mechanical characteristics of Ca-P ceramics

Mechanical properties
creep, stiffness, Young’s modulus

Degradation properties
speed of resorption, chemical, cellular?
**Ca-P ceramics properties**

**Chemical properties**

**Composition refers to the original base components of the material**

- Hydroxyapatite (HA) \([\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2]\)
- Tri-calcium phosphate (TCP) \([\text{Ca}_3(\text{PO}_4)_2]\)
- 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 (osteoconduction)
- Degradability speed

**Rules of thumb**

- Strength
- TCP less brittle in dry formulation compared to HA
- HA quicker loss of mechanical strength compared to TCP in vivo
- TCP chemically less stable compared to HA
- TCP possesses high resolution characteristics compared to HA
- TCP easily resorbed by osteoclasts compared to HA
- TCP faster degradation (12-18 months) compared to HA (2-10 years)
**Ca-P ceramics properties**

**Structural properties**

**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 (osteoconduction)
- 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 degradability due to resistance in dissolution
Ca-P ceramics properties

**Calcium-phosphate (Ca/P) ratio** refers to 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>Ca₄(PO₄)₂O</td>
<td>2.0</td>
</tr>
<tr>
<td>Hydroxyapatite</td>
<td>Ca₁₀(PO₄)₆(OH)₂</td>
<td>1.67</td>
</tr>
<tr>
<td>Calcium deficient hydroxyapatite</td>
<td>Ca₉(HPO₄)(PO₄)₅(OH)</td>
<td>&lt;1.67</td>
</tr>
<tr>
<td>Tricalcium phosphate (α,β)</td>
<td>Ca₃(PO₄)₂</td>
<td>1.5</td>
</tr>
<tr>
<td>Dicalcium phosphate dihydrated (Brushita)</td>
<td>CaHPO₄·2H₂O</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)

**Ca/P ratio Ca-P granules**
- between 1.67 (HA) and 1.5 (TCP)

**Ca/P ratio Ca-P cements**
- between 2.0 (TTCP) and 1.0 (DCPH)
**Porosity**\(^{2,16-17}\) refers to the fraction of the volume of voids within the material over the total material volume

<table>
<thead>
<tr>
<th>Macro porosity</th>
<th>Micro porosity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pores &gt; 100 (\mu)m -400 (\mu)m</td>
<td>Pores &lt; 10 (\mu)m</td>
</tr>
<tr>
<td>Provides a scaffold for bone cell colonization</td>
<td>Allows body fluid circulation (proteins)</td>
</tr>
<tr>
<td></td>
<td>Allows blood vessel ingrowth</td>
</tr>
<tr>
<td></td>
<td>(&lt; 30 (\mu)m decreased tissue infiltration)</td>
</tr>
</tbody>
</table>

**Ca-P ceramics properties**

**Structural properties**

- **Porosity**
  - **Surface Porosity**
    - pores only on surface area
    - mechanically stronger
  - **Interconnective Porosity**
    - pores throughout entire structure
    - mechanically weaker

- **Regulates cell reactions**
  - Interconnective porosity allows for mechanical interlocking between the implant biomaterials and host bone.
  - Surface porosity only on surface area, mechanically stronger.

- **Degradability**
  - Interconnective porosity degrades faster compared to surface porosity.
  - Surface porosity degrades slower compared to interconnective porosity.

**Rules of thumb**

- **Strength**
  - Interconnective porosity is mechanically weaker compared to surface porosity.

- **Resorption**
  - Interconnective porosity resorbs faster compared to surface porosity.

- **Degradation**
  - Interconnective porosity degrades faster compared to surface porosity.
Creep refers to the permanent deformation under influence of mechanical stress.

**Ca-P ceramics properties**

**Mechanical properties**

**Strength** refers to the load carrying capacity of a material.

**Stiffness** refers to the resistance to elastic deformation.

**Strain** refers to the deformation of a material by a force acting on the material. Strain can be tensile or compressive (plastic or viscoelastic deformation).

**Young’s Modulus** (modulus of elasticity) refers to the unique property of a material; measure of a material to resist deformation and return to its original shape.

<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>
Ca-P ceramics properties

Mechanical properties

**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. 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). 11

**Rules of thumb**

- Material strength primarily dependent on composition, structure, porosity and elasticity
- Ca-P ceramics strong under compression and weak under torsion loads
- Ca-P cement compressive modulus stronger compared to Ha or TCP granules
- TCP quicker loss of mechanical strength compared to HA in vivo
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 (osteoconduction)
- Degradability speed

Rules of thumb:
- TCP chemically less stable compared to HA due to high resolution characteristics
- TCP easily resorbed by osteoclasts compared to HA
- TCP faster degradation (12-18 months) compared to HA (2-10 years)
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.

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.

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

Diamond & Pentagon concept page 37
Stepwise assessment of bone defect page 39
Biomaterial choice page 41
Clinical indications page 43
Take home messages page 45
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

Growth factors
osteinductive signaling

Vascularization

Scaffolds
osteconductive matrix

Fracture healing: The diamond concept
Peter V. Glavindou*, Thomas A. Elhenni, David MacE"
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

3. Plan

4. Operate

5. Clinical follow-up of cases

Stepwise bone defect assessment considerations

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

2. Instability
   - 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

Biomaterial choice considerations

**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

<table>
<thead>
<tr>
<th>Biomaterial choice considerations</th>
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</thead>
<tbody>
<tr>
<td>1. Material</td>
</tr>
<tr>
<td>2. Surgical</td>
</tr>
<tr>
<td>3. Mechanical</td>
</tr>
<tr>
<td>4. Biological</td>
</tr>
<tr>
<td>5. Patient</td>
</tr>
<tr>
<td>6. Literature</td>
</tr>
<tr>
<td>7. Surgeon</td>
</tr>
</tbody>
</table>

- biocompatibility/ osteoconductivity / osteoinductivity
- mechanical properties material and mechanical load on bone defect
- resorption speed
- containment in defect (metal, periost flap, muscle, bone)
- connection (interdigitation) with host tissue
- mechanical stability
- adequate fixation (preferably dynamic)
- availability of stem cells
- availability of vascularisation
- co-morbidity
- post-op compliance
- large differences in level of evidence between products
- personal preference
- experience
- training and education

Articular cartilage damage
Depressed intra articular fracture
Compressed metaphyseal bone
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

4. Larger 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 structional 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

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 structional 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

Can use 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
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.

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.
Cases

Case 1 Tibia Osteotomy  page 49
Case 2 Distal Radius Fracture  page 51
Case 3 THA Impaction Grafting  page 53
Cases
Case 1 Tibia Osteotomy

Details
• Porous β-TCP (Ca$_3$(PO$_4$)$_2$) with 70% interconnected macropores with a size of 100–500 μm and micropores of 1–10 μm (ChronOS, Synthes)
• 16 patients (17 osteotomies): core biopsies for histology of bone remodeling at different follow-up periods
• X-rays at 6 weeks, 3 months, 6 months and 1 year postoperative
• Complete consolidation at 12 months in all cases
• 16 patients (17 osteotomies): core biopsies at different follow-up periods
• Note: although the B-TCP wedge is almost completely resorbed at 12 months and bone is remodeling, the plate is still providing mechanical stability
• The newly formed bone is a mixture of woven and lamellar bone and it’s not as strong as completely remodeled bone
• This case illustrates the importance of the element mechanical stability of the Pentagon concept

Results
• Complete consolidation at 12 months in all cases
• 16 patients (17 osteotomies): core biopsies at different follow-up periods
• Note: although the B-TCP wedge is almost completely resorbed at 12 months and bone is remodeling, the plate is still providing mechanical stability
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Lessons learned
• Porous β-TCP (Ca$_3$(PO$_4$)$_2$) with 70% interconnected macropores with a size of 100–500 μm and micropores of 1–10 μm (ChronOS, Synthes)
• 16 patients (17 osteotomies): core biopsies for histology of bone remodeling at different follow-up periods
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Top (left): B-TCP wedge and (right) location of osteotomy and biopsy.
Down: Bone remodeling at different follow-up times after open wedge osteotomy filled with TCP. (A) at 6 weeks, (B) at 3 months, (C) at 6 months, (D) at 12 months.
Case 2 Distal Radius Fracture

Details
- Porous bi-phasic ceramic strip) 80% β-TCP \([\text{Ca}_3(\text{PO}_4)_2]\) and type-1 bovine collagen (VitossStrip, Stryker)
- Single patient n=1 case
- X-rays at 12 weeks

Results
- Fracture stabilized with plate > osteosynthesis must come first!
- Bone vid filled with TCP strip (Vitoss)
- Bone healing at 12 weeks follow-up
- The newly formed bone is a mixture of woven and lamellar bone and its not as strong as completely remodeled bone

Lessons learned
- This case illustrates the importance of the element scaffold of the Pentagon concept

**Courtesy to Prof. Dr. Med. G. Zimmerman, Theresien krankenhaus Mannheim, Germany for sharing the case**
Details

- Porous bi-phasic TCP-HA granule (80% β-TCP [Ca$_3$(PO$_4$)$_2$], 20% HA [Ca$_{10}$(PO$_4$)$_6$(OH)$_2$]) with not interconnected macropores with a size of 300–600μm and micropores of 2–80μm (BoneSave, Stryker)
- Revision total hip arthroplasty > TCP-HA granules as bone void filler in load-bearing bone defect
- Biphasic TCP-HA (BoneSave) granules are strong enough to be used in load-bearing applications
- Gradual remodeling into a new bone structure over time
- Advise: neo vascularisation cannot span a graft layer thickness larger than 12-14 mm within 6 months
- This case illustrates the importance of the element scaffold of the Pentagon concept

Results

- Impaction bone grafting of the acetabulum at hip revision using a mix of bone chips and a bi-phasic porous ceramic bone graft substitute
- Good outcome in 43 patients followed for a mean of 2 years

Lessons learned

- Case 3 THA Impaction Grafting

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References


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