20 Ca lcium-phosphate **biomaterials** *for bone healing*

practical guideline for implementation in clinical practice

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

by **Chris Arts**

Colofon

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Contents

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 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 intented 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 usefull addition to your clinical practice and education.

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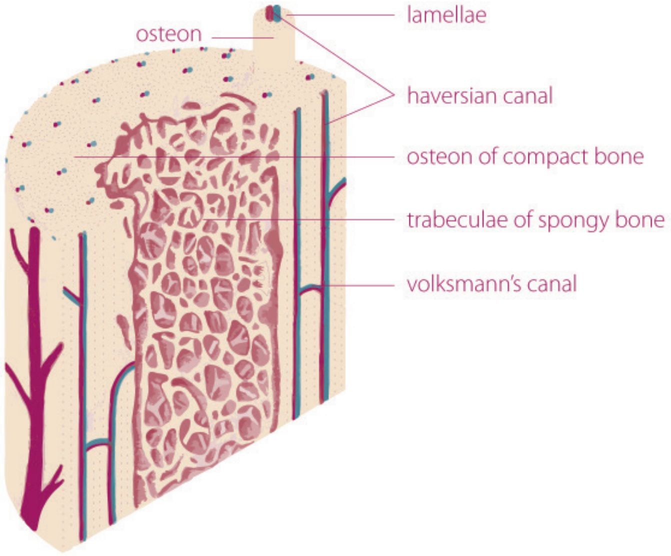
Definitions

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

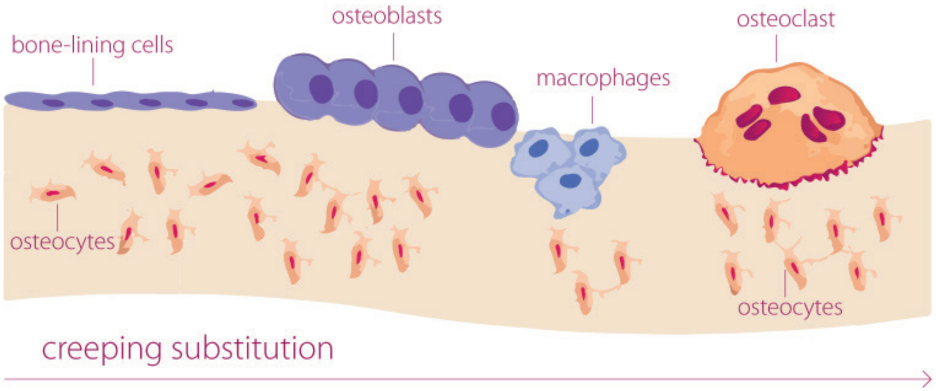
Stabilise and support body

Protection of internal organs and soft tissue

Rigid 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"*[17]

The osteoclastic resorption of dead bone from the allograft and it's 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[1]

A synthetic material used to replace part of a living system or to function in intimate contact with living tissue.[2]

A biomaterial is a substance that has been engineered to take a form which, alone or a 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.[3]

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."[4]

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.[2,5]

Scaffold purpose[6-9]

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...[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 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

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[5]

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.[5]

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 [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 [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 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)

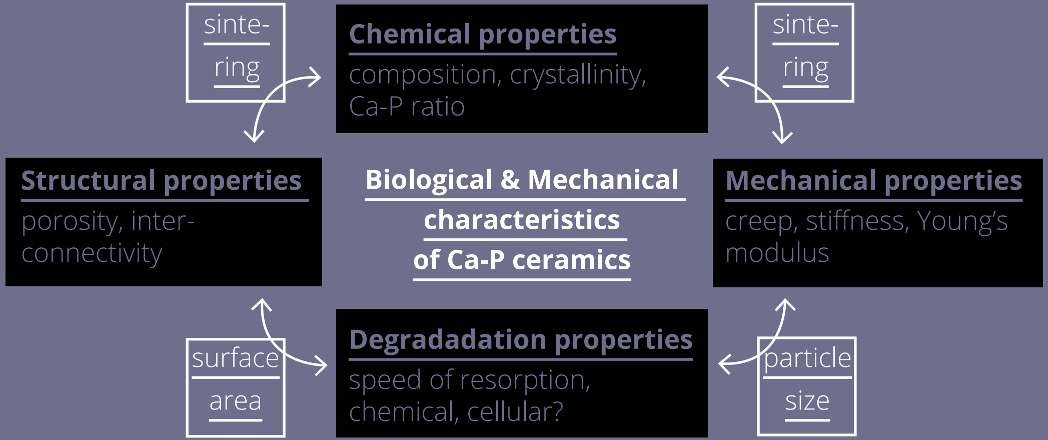
Most ceramics are hard, porous yet brittle

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

Top sintering production of large HA blocks at high temperature

Down ceramic TCP-HA granules with macro-porosity

Property overview of Ca-P ceramics



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, stiffnes, Young's modulus)

Biological properties (osteoconduction)

Degradability speed

Rules of thumb

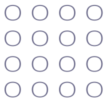
Strength	TCP less brittle in dry formulation compared to HA
Strength	TCP quicker loss of mechanical strength compared to HA in vivo
Resorption	TCP chemically less stable compared to HA
Resorption	TCP possesses high resolution characteristics compared to HA
Degradation	TCP easily resorbed by osteoclasts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

Ca-P ceramics properties

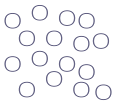
Structural properties

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 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

Name	Formula	Ca/P
Tetracalcium phosphate	$Ca_4(PO_4)_2O$	2.0
Hydroxyapatite	$Ca_{10}(PO_4)_6(OH)_2$	1.67
Calcium deficient hydroxyapatite	$Ca_9(HPO_4)(PO_4)_5(OH)$	<1.67
Tricalcium phosphate (α,β)	$Ca_3(PO_4)_2$	1.5
Dicalcum phosphate dihydrated (Brushita)	$CaHPO_4{\cdot}2H_2O$	1.0

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)

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)

25 Ca-P ceramics properties

Structural properties

Porosity [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 ...	Surface Porosity ...	Interconnective Porosity ...
allows for mechanical interlocking between the implant biomaterials and host bone	pores only on surface area	pores throughout entire structure
regulates cell reactions	mechanically stronger	mechanical weaker
effects degradability		direction dictates pathway for ingrowing cells

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Rules of thumb

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

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

Creep refers to the permanent deformation under influence of mechanical stress

Mechanical property	Cortical bone	Cancellous bone	Ca-P ceramics
Tensile strength (MPa)	50-150	10-100	40-100
Elastic modulus (GPa)	3-20	8	
Compressive strength (MPa)	130-230	2-12	100-900
Young's modulus (GPa)	15-42	0,02 - 0,5	70-120

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

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

Ca-P ceramics properties

Degradation properties

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, stiffnes, Young’s modulus)

Biological properties (osteoconduction)

Degradability speed

Rules of thumb

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

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 [2,11]

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.

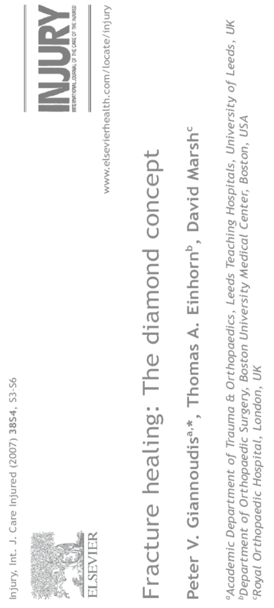
Bone healing

Bone healing

Diamond & Pentagon concept

Diamond concept **Bone healing is a multidimensional process requiring all elements of the Diamond concept** [18-19]

Pentagon concept **Multidimensional process requiring all elements of the Diamond concept combined with mechanical stability and vascularization** [18-19]



Injury, Int. J. Care Injured (2007) 38S4, S3-S6

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Fracture healing: The diamond concept

Peter V. Giannoudis[a,*], Thomas A. Einhorn[b], David Marsh[c]

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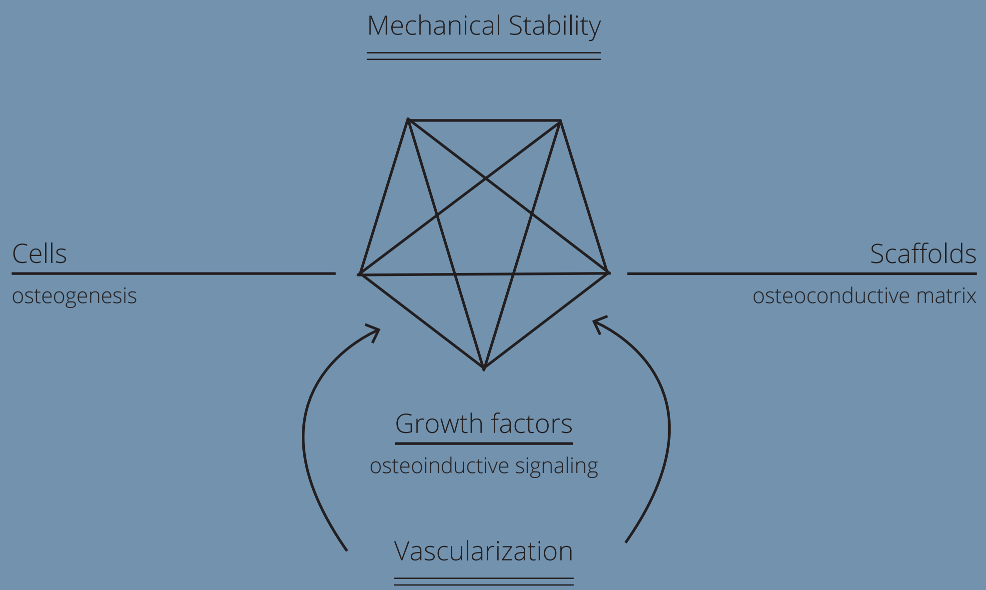


Stepwise assessment of bone defect

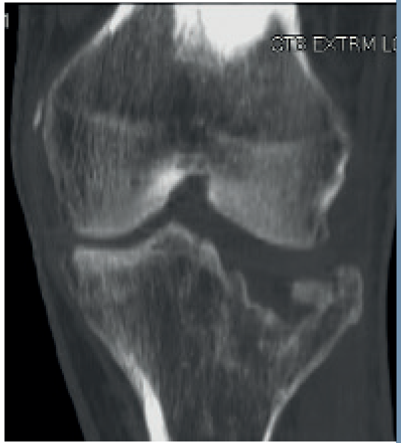
What would you do with this patient... And why?

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

2. Think
3. Plan

} structure

4. Operate
5. Clinical follow-up of cases

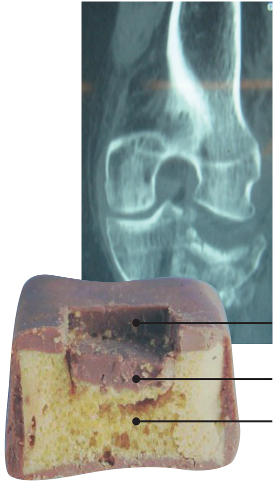


Stepwise bone defect assessment considerations

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

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

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

2. Small contained bone defects

Filling of small Ø <2cm non-load bearing defects/voids

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

3. Smaller non-load bearing defects

Filling of larger Ø <2cm 'unloaded' defects when fixation/stabilisation is absent

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

4. Lager stabilisated defects

tibia plateau #, distal radius #, distal/ proximal femur #, open wedge osteotomy

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

5. Weight-bearing defects

Bone impaction grafting in TKA & THA, large acetabular #, segmental defects

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

6. Infected defects

in general Ca-P materials as standalone are a contra-indication

Local and systemic antibiotic therapy must be used

Bone healing

Take home messages [10,21]

message **Bone substitute materials vary in composition, mechanical strength and biological mechanism of function, each having their own advantages and disadvantages**

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

message **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**

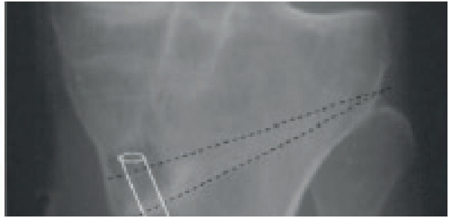
message **The choice of the optimal bone substitutes is therefore not always an easy one, and largely depends on the clinical application and its associated biological and mechanical needs. Mechanical stability should primarily always be the predominant factor**

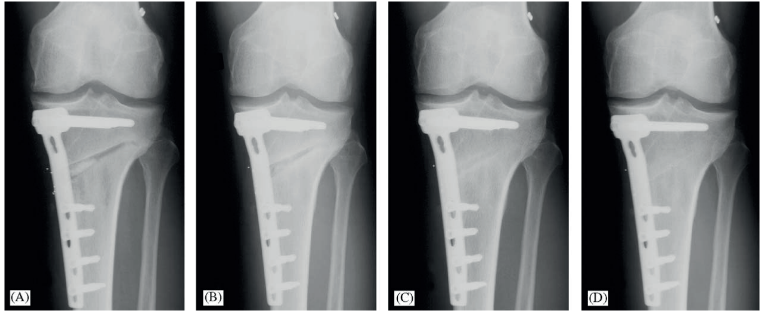
message **Pentagon / Diamond concepts are useful tools for planning surgery with bone substitute materials**

Cases

Cases

Case 1 Tibia Osteotomy [20]





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.

Details

- Porous β-TCP ($Ca3(PO4)2$ 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

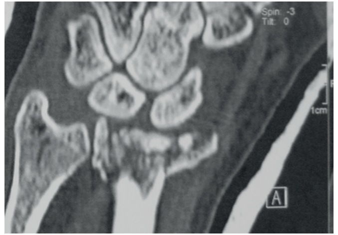
Results

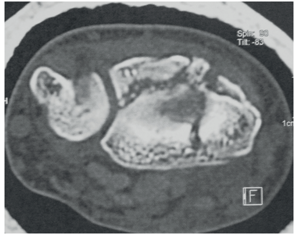
- Complete consolidation at 12 months in all cases
- 16 patients (17 osteotomies) : core biopsies at different follow-up periods
- Note: although the B-TCP wedge is almost completely resorbed at 12 months and bone is remodeling, the plate is still providing mechanical stability
- The newly formed bone is a mixture of woven and lamellar bone and it’s not as strong as completely remodeled bone

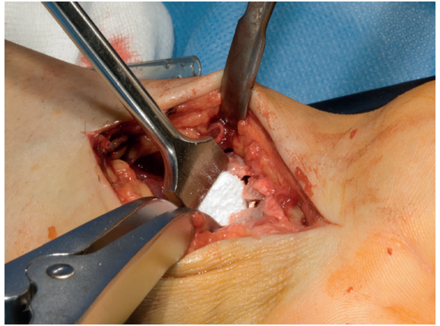
Lessons learned

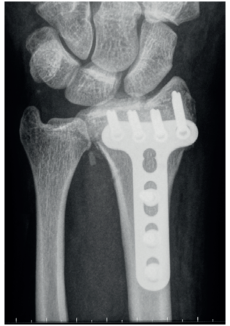
- This case illustrates the importance of the element mechanical stability of the Pentagon concept

Case 2 Distal Radius Fracture **









Details

- Porous bi-phasic ceramic strip) 80% β-TCP [Ca_3 $(PO_4)_2$] 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

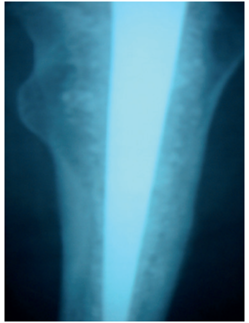
**Courtesy to Prof. Dr. Med. G.Zimmerman, Theresien krankenhaus Mannheim, Germany for sharing the case

150 Acta Orthopaedica 2009; 80 (2): 150–154

Impaction bone grafting of the acetabulum at hip revision using a mix of bone chips and a biphasic porous ceramic bone graft substitute

Good outcome in 43 patients followed for a mean of 2 years

Ashley W Blom[1,2], Vikki Wylde[1], Christine Livesey[1], Michael R Whitehouse[1,2], Steve Eastaugh-Waring[2], Gordon C Bannister[2], and Ian D Learmonth[1]

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

Results

- 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

Lessons learned

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

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