Lecture 5:
Basic properties of biomaterials

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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
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**
- This process is also called “**creeping substitution**” 17
  - 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

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 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. ³

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
Definitions

**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

Depending on application 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:

- Should be implantable through a minimal surgical exposure
- Applicable for various indications
- Should be moldable to conform to and fill irregular defects
- Should posses roughly the same visco-elasticity as bone
- Should be as as rigid and strong as intact bone for immediate load-bearing capability
- Should promote new bone formation and incorporation by host bone
- Should be available in large quantities and it should be cheap

**DOES NOT EXIST!**
Definitions

**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** \(^5\)
- 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 \cite{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.

Osteoconductivity \cite{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

Osteoinductivity \cite{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
Osteopromotive (DBMs), Osteostimulative (Bioactive glasses, ceramic BGS), Osteosupportive

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.

Osteosupportive ...
- No definition found in literature.
Osteoinductivity (critical look)

- Osteoinduction is too widely defined and often used when not supported (DBMs)
- It should be defined according to location in the body and timeline!
- **Example:**
  Calcium phosphate materials have an intrinsic affinity to bind BMPs. If these materials are implanted in an ectopic location (such as a muscle) they might initiate bone formation directly or they might accumulate BMPs which when in sufficient numbers initiate bone formation at a later time-point on in a very friendly environment (availability of stem cells and good blood supply).
- Are both processes osteoinduction?
Ca-P ceramics properties

Ca-P ceramics

• Refers Ancient Greek “Keramos” 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

Left: ceramic TCP-HA granules with macroporosity. Right: Sintering production of large HA blocks at high temperature.
Ca-P ceramics properties overview

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

- **CHEMICAL PROPERTIES**
  - Composition crystallinity / Ca-P ratio

- **STRUCTURAL PROPERTIES**
  - Porosity
  - Interconnectivity

- **MECHANICAL PROPERTIES**
  - Creep/ stiffness
  - Young’s modulus

- **DEGRADABILITY**
  - Speed of resorption
  - Chemical / cellular?

- **sintering**
  - Surface area
  - Particle size

- **sintering**
  - Particle size
  - Surface area

**Notes:**

- Porosity and Interconnectivity affect structural properties.
- Creep and stiffness impact mechanical properties.
- Composition and crystallinity influence chemical properties.
- Degradability is influenced by the speed of resorption and chemical or cellular interaction.
**Ca-P ceramics 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 (osseoconduction)
  - 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)
Crystallinity

- Refers to the degree of structural order in a material, less order provides a more amorphous material.

- 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 degradation.
Ca-P ceramics chemical properties

Calcium-phosphate (Ca/P) ratio

- Refers to be a measurement of Ca-P ceramics composition
- 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)

**Table 1. Ca/P ratio of some of the calcium phosphates used in medical applications**

<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
- **Degradability:** High Ca/P ratio 1.67 (HA)
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 \(\mu m\) - 400 \(\mu m\)
  - Provides a scaffold for bone cell colonization

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

- Porosity allows for mechanical interlocking between the implant biomaterials and host bone.

- Porosity regulates cell reactions

- Porosity effects degradability
Porosity interconnection

• **Surface porosity**
  - Pores only on surface area
  - Mechanically stronger

• **Interconnective porosity**
  - Pores throughout entire structure
  - Mechanical weaker

Porosity allows for mechanical interlocking between the implant biomaterials and host bone.

Interconnective porosity direction possibly can dictate pathway for ingrowing cells

**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 mechanical properties

**Strength**
- The load carrying capacity of a material

**Stiffness**
- The resistance to elastic deformation

**Strain**
- 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)
- Unique property of a material; measure of a material to resist deformation and return to its original shape

**Creep**
- 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>
Ca-P ceramics mechanical properties

**Strength**

- 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 degradation properties

Degradation

- 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/resorption has an effect on:
  - Mechanical properties (impactability, strength, stiffness, Young’s modulus)
  - Biological properties (ossteoconduction)
  - 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 degradation properties

In vitro & in vivo 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.

Creeping substitution: TRAP stained osteoclasts (red cells and arrows) degrade the surface of a Ca-P ceramic (BS) and behind them a osteblast front (blue nuclei) is forming.
Ca-P ceramics properties: bone remodeling

- **Initial stability**
- **Failure limit**
- **Safety margin**

**Total stability**

**Balanced bone remodeling**

**Slow bone remodeling**

**Fast biomaterial resorption**
Ca-P ceramics properties

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.