Lecture 1: Anatomy and physiology of normal bone healing

Dr. Chris Arts
Associate Professor Translational biomaterials research
Dept. Orthopaedic surgery
Maastricht University Medical Centre+, the Netherlands

Dept Orthopaedic biomechanics
Eindhoven University of technology TU/e
j.j.c.arts@tue.nl

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Bone

* Function
* Anatomy
* Cells: osteoblast / osteoclast / osteocyte
* Formation: endochondral/intramembranous
* Regulation: Ca^{2+}
* Healing
* Pharmacology
* Bone strength
* Take home messages
Bone function

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
  - osteoclasts resorbing bone
Bone function

- 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 anatomy

- Cortical/Compact Bone
- Cancellous/Trabecular/Spongy Bone
Bone anatomy

- Diaphysis (shaft)
- Epiphysis
  - * Proximal
  - * Distal
- Compact bone
- Spongy bone
- Periosteum
- Medullary cavity
- Articular/hyaline cartilage
- Nutrient V/A/N
- Epyphyseal (growth) plates
## Bone anatomy

<table>
<thead>
<tr>
<th>Physical Description</th>
<th>Cortical</th>
<th>Cancellous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dense protective shell</td>
<td>Rigid lattice designed for strength; Interstices are filled with marrow</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td>Around all bones, beneath periosteum; Primarily in the shafts of long bones</td>
<td>In vertebrae, flat bones (e.g. pelvis) and the ends of long bones</td>
</tr>
<tr>
<td>% of Skeletal Mass</td>
<td>80%</td>
<td>20%</td>
</tr>
<tr>
<td>First Level Structure</td>
<td>Osteons</td>
<td>Trabeculae</td>
</tr>
<tr>
<td>Porosity</td>
<td>5-10%</td>
<td>50-90%</td>
</tr>
<tr>
<td>Circulation</td>
<td>Slow circulation of nutrients and waste</td>
<td>Haversian system allows diffusion of nutrients and waste between blood vessels and cells</td>
</tr>
<tr>
<td>Strength</td>
<td>Withstand greater stress</td>
<td>Withstand greater strain</td>
</tr>
<tr>
<td>Direction of Strength</td>
<td>Bending and torsion, e.g. in the middle of long bones</td>
<td>Compression; Young’s modulus is much greater in the longitudinal direction</td>
</tr>
<tr>
<td>Stiffness</td>
<td>Higher</td>
<td>Lower</td>
</tr>
<tr>
<td>Fracture Point</td>
<td>Strain&gt;2%</td>
<td>Strain&gt;75%</td>
</tr>
</tbody>
</table>
Bone cells

Osteoclast
• Degrade and resorb bone for remodeling

Osteoblast
• Make and deposit components of bone extracellular matrix

Osteocyte
• “watcher cells” Sit in bone and monitor its current status
Bone cells

Osteoclast
• Degrade and resorb bone for remodeling
• “Dig holes” with hydrochloric acid
• Degrades calcium
• Phagocytize collagen fibers and dead osteocytes

Osteoblast
• Make and deposit components of bone extracellular matrix
• Line tubes (Haversian canals) left by osteoclasts
• Lay down new bone in circular concentric lamellae

Osteocyte
• “watcher cells” Sit in bone and monitor its current status
Bone formation

Endochondral bone formation

1. Formation of bone collar around hyaline cartilage model
2. Cavitation of the hyaline cartilage within the cartilage model
3. Invasion of internal cavities by the periosteal bud and spongy bone formation
4. Formation of the medullary cavity as ossification continues
5. Ossification of the epiphyses

endochondral ossification in a long bone
1. Cartilage model

2. Bone collar forms in diaphysis (dense bone)
   - Cartilage chondrocytes in center of diaphysis die and cartilage disintegrates

3. Periosteal bud enters diaphysis
   - Makes spongy bone at ends of diaphysis (primary ossification center)

4. Epiphysis begins to ossify (secondary ossification center)

5. Hyaline cartilage remains only at
   - Epiphyseal surfaces (articular surfaces of joints)
   - Epiphyseal growth plates between diaphysis and epiphysis (primary and secondary ossification centers on either side)
Bone regulation

Intra-membranous bone formation

1. An ossification center appears in the fibrous connective tissue membrane
2. Bone matrix (osteoid) is secreted within the fibrous membrane
3. Woven bone and periosteum form
4. Bone collar of compact bone forms and red marrow appears

intramembranous bone formation
Bone mass, peak bone mass and bone loss
Bone mass regulation and healing

Bone mass evolution

- Higher bone peak mass
- Later and less bone loss

Age (Years)

Bone mass %

male

female
Bone Ca\(^{2+}\) homeostasis

3 tissues and 3 hormones are important

- **Calcium Homeostasis:**
  - **Input: diet**
  - **Gut:**
    - *Calcium* → *Bone*
    - Loss: Faeces, urine
  - **Kidney:**
    - Decreases calcium excretion (clearance), Increases phosphorus excretion
  - **Gastrointestinal Tract:**
    - Increases calcium and phosphorus absorption. Indirect effect via 1,25-D
  - **Blood:**
    - Increases calcium. Decreases phosphorus

**Effects PTH Calcium and Skeletal Metabolism**

- **Bone:** Increases resorption, Increases formation, especially at low and intermittent concentrations
- **Kidney:** Decreases calcium excretion (clearance), Increases phosphorus excretion
- **Gastrointestinal Tract:** Increases calcium and phosphorus absorption. Indirect effect via 1,25-D
- **Blood:** Increases calcium. Decreases phosphorus

- **Calcium Homeostasis:**
  - 3 Hormones
    - Parathyroid Hormone (PTH)
    - 1,25(OH)\(_2\) vitamin D\(_3\) (Calcitriol)
    - Calcitonin
Bone $Ca^{2+}$ homeostasis

**Low serum calcium $\Rightarrow$ PTH secretion increased**

**Bone:**
- Increases bone resorption
- Increases serum Ca (especially at continuous concentrations)

**Kidney**
- Increases tubular Ca reabsorption
- Decreases Ca excretion (clearance)
- Increases secretion of 1,25-D

**Gastrointestinal Tract:**
- Increases Ca absorption.
- Indirect effect via 1,25-D production
Low serum Calcium

Kidney: Calcium reabsorption ↑

Gut: Calcium absorption ↑

Bone: Calcium resorption ↑

PTH ↑

1.25(OH)₂D₃ ↑

SERUM CALCIUM ↑
“The mechanism of action in bone healing points to the hierarchical role of creating a vascular network before bone can be formed.”

Creating a microenvironment with vascular sufficiency is a critical first step in bone formation since impaired angiogenesis results in impaired bone formation.
Bone healing

1. Hematoma formation
   0 - 2 weeks

2. Soft callus formation
   2 - 3 weeks

3. Hard callus formation
   3 - 6 weeks

4. Bone remodeling
   8 weeks - 2 years

fracture healing
Bone healing

Bone remodeling

- pre-osteoclasts
- active osteoclasts
- mononuclear cells
- pre-osteoblasts
- osteoblasts
- osteocytes

resting bone surface → resorption → reversal → bone formation → mineralization

bone remodeling circle
Bone strength

Response to Mechanical Stress

Load here (body weight)

Head of femur

Tension here

Compression here

Point of no stress
Bone strength

How to quantify bone strength?

• Bone mineral density (BMD)
• Bone micro-architecture

• High-Resolution pQCT scanners have the potential to assess in-vivo 3-D bone micro-architecture and bone density and its changes over time in clinical patients

Healthy

Osteoporotic
Take home messages

• 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
• Bone consists of cortical (compact) and cancellous (spongy) tissue
• Endochondral bone formation and intramembranous bone formation
• Bone homeostasis
  3 hormones (PTH / vitamin D₃ / Calcitonine) are important
  3 cells (osteoblast/osteocyt/osteoclast) are important
  3 tissues (gut, kidney, bone) are important
• Quantification of bone strength with both BMD and micro-architecture
Questions