BIOLOGY and BIOMECHANICS OF NORMAL & OSTEOPOOROTIC BONE

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Objectives

• Bone structure and physiology

• Remodeling and bone metabolism

• Factors affecting bone strength and quality

• Biomechanics and damage in osteoporosis

• Future research- conclusions
Outline

2 important **Mechanical Functions** of Bone

- rigid **skeletal framework** that supports and protects other body tissues

- forms a **system of rigid levers** that can be moved by forces from the attaching muscles

- mineral storage
Hierarchical structure

Macrostructure

Microstructure

Matrix Properties

Cellular Composition and Activity

Seeman & Delmas
Properties at the cellular, matrix, microarchitectural, and macroarchitectural levels may all impact bone mechanical properties.

These factors are interrelated and co-acting.

Therefore, one cannot expect that changes in a single property will be solely predictive of changes in bone mechanical behavior.
Lower strength and stiffness of osteoporotic bone

Mineral content slightly higher than that of normal bone
When no changes in bone quality occur at 5 mm level, probably there are no changes in lower scales also.
Bone building blocks

- collagen fibrils
- mineral plates
- non-fibrillar protein-based organic matrix

Atomic Force Microscope

Bone “glue”
Important cells

Bone Structural Units (BSU)

Basic Multicellular Units (BMU)

Bone remodeling

Basic regulator: osteocyte?
Bone Structural Units (BSU) is the structural end result of a focused bone renewal.

**BSU** (osteons) is the structural end result of a focused bone renewal.

- **Cortical bone:** concentric rings (lamellae)
- **Cancellous bone:** flat and stacked in saucer shaped depressions
Basic Multicellular Units (BMU)

Under normal steady state conditions, the amount of bone removed is precisely replaced and there is no net change in bone mass. Only bone architecture is changed.
Bone remodeling cycle

- **GM-CSF**, **IL-1**, **IL-6**
- **RANKL**
- **PGE$_2$**, **TNF-$\alpha$**
- **OPG**, **TGF-β**, **Estrogen**

**Resorption**
- Osteoclasts
- Monocytes
- Pre-osteoblasts

**Formation**
- Osteoblasts
- Osteocytes
Osteocytes: Master Orchestrators of Bone

Osteocytes sensing and integrating mechanical and chemical signals from their environment to regulate both bone formation and resorption.
RANK Ligand is a Central Mediator in the Activation phase of bone remodeling
Luck of Wnt pathway reduces the amount of $\beta$-catenin in the cytoplasm due to high degradation. As a result important control of protein transcription in osteoblasts is lost.
Wnt pathway antagonists

- SFRP1
- WIF-1
- DKK-1
- Sclerostin

All act as inhibitors of LRP5/6

Over-expression

Reduction of osteoblastogenesis

OSTEOPOROSIS
Osteocyte-Driven Bone Remodeling

Teresita Bellido

Osteocyte-driven bone resorption & formation

- PTH/PTHr or mechanical stimuli decreased Sost/sclerostin
  - increased Wnt signaling
  - increased osteoblasts
  - bone formation

- Basal resorption osteocytic PTHR
  - RANKL/OPG M-CSF
  - increased osteoclasts
  - bone resorption

- Lactation/PTHrP/PTHR
  - lacunar/canicular remodeling
  - osteocytic Wnt/β-catenin
  - increased OPG
  - decreased osteoclasts
  - targeted osteoclast recruitment
Why Bone Remodels?

- Allows bone to respond to loads (stress)
- Maintain materials properties
- Allows repair of microdamage
- Participates in serum Ca\textsuperscript{2+} regulation
This increase in RANKL signaling is caused by the osteocyte apoptosis, not the bone microdamage itself.

Osteoclasts are then recruited to resorb damaged and apoptotic osteocytes during the microdamage repair process.
Nitric oxide signaling in mechanical adaptation of bone

J. Klein-Nulend · R. F. M. van Oers · A. D. Bakker · R. G. Baele

Osteocyte apoptosis (X) is caused by lack of fluid flow at the tip of the cutting cone, osteoclasts are attracted by apoptotic and RANKL producing osteocytes, and as a result, the cutting cone follows the loading direction.
Load-carrying behavior of bone

- The maximum load the material can sustain
- Initial reaction to a load
- Stored elastic energy
- The energy required to break the material

Diagram:
- Force vs. Displacement
- Strength
- Stiffness
- Resilience
- Fracture
- Toughness
Bone is a highly heterogenous material, partially because it has been adapted to resist different, complex and varying stresses.
Determinants of fragility

- BMD
- Bone Mass Distribution
- Micro-Architecture
- Mineralization
- Collagen
- Damage

- Previous FX
- Bone Turnover

Used in clinical practice: BMD, Bone Mass Distribution, Micro-Architecture, Mineralization, Collagen

- Bone Turnover

Used in clinical research: Bone Turnover

Cannot be measured non-invasively: Damage
Bone throughout the lifespan

- Pubertal Growth Spurt
- Menopause
- BMD
- Resorption
- Formation

Age (Years)

5 15 25 35 45 55 65 75 85
The Pathophysiology of the Aging Skeleton

Farhan A. Syed • Alvin C. Ng

Age-related modulation of the skeleton

**intrinsic factors**
- genetics,
- peak bone mass
- hormonal changes (FSH, GH),
- levels of oxidative stress,
- free radical generation
- changes in telomere length

**extrinsic factors**
- nutritional habits
- lifestyle choices
- lack of exercise
The influence of age on adaptive bone formation and bone resorption
Annette I. Birkhold a, b, Hajar Razi a, b, Georg N. Duda a, Richard Weinkamer c, Sara Checa d, Bettina M. Willie a, *

analogous 3D quantification
loading >> stronger effect on formation than on resorption of trabecular bone
increase of the formation surface with mechanical stimulation
the resorption thickness is independent of loading in trabecular bone in all age groups.
Osteoporosis

reduction in bone mass, disruption in bone micro-architecture

“IMBALANCE” in bone remodeling

- Excessive RANKL/RANK signaling
- Inadequate OPG production
- Inadequate Wnt/LRP-5 activity
- “Excessive” inhibition of the pathway

Changes in biomechanical strength $\rightarrow$ Fractures
Bone Quality Framework

**Structural Properties**
- Geometry
  - Size
  - Shape
- Microarchitecture
  - Trabecular architecture
  - Cortical thickness/porosity

**Material Properties**
- Mineral
  - Mineral-to-matrix ratio
  - Crystal size
- Collagen
  - Type
  - Cross-links
- Microdamage/microfracture
how bone loss in osteoporosis alters bone mechanical strength?

Bone mass
Cancellous microarchitecture
Cortical microarchitecture
Porosity
Whole bone strength
Bone tissue properties
Sequence of events in the bone loss cascade
Bone mass during osteoporosis

DEXA (preferred technology for quantifying BMD) quantitative computed tomography (QCT), absorptiometry, quantitative roentgen micro-densitometry quantitative ultrasound (QUS)

BMD do not fully explain susceptibility to bone fracture

(only 10–53% of bone fractures that occur in female post-menopausal patients over the age of 65 can be attributed to a BMD level low enough)
Cancellous micro-architecture during osteoporosis

Bone **histomorphometry - Stereology** is typically used to characterize bone micro-architecture by quantifying:

- cortical porosity,
- cortical thickness,
- trabecular number,
- trabecular thickness
- trabecular connectivity
↑ Cortical Thickness (Ct.Th)

↑ Trabecular Number (Tb.N)

↑ Trabecular Thickness (Tb.Th)

↓ Trabecular Separation (Tb.Sp)

\[
\text{Tb.Th} = \frac{1}{\text{Tb.Sp}}
\]
Cancellous micro-architecture during osteoporosis

trabecular thinning, thickening of remaining trabecula deeper resorption cavities, micro-fracture loss of trabecular connectivity

fracture risk prediction is improved by approximately 13% as compared with BMD alone
Cortical micro-architecture during osteoporosis
(41 iliac biopsies, age 19-90)

4-fold increase in cortical porosity from age 20 to 80
Increased heterogeneity with age

Brockstedt et al. Bone 1993; 14:681-91
Related changes in geometry

Adaptation to maintain whole bone strength
## Related changes in mechanical properties

<table>
<thead>
<tr>
<th></th>
<th>Cortical bone (% loss 30-80 yrs)</th>
<th>Cancellous bone (% loss 30-80 yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elastic modulus, $E$</td>
<td>-8%</td>
<td>-64%</td>
</tr>
<tr>
<td>Ultimate strength, $S$</td>
<td>-11%</td>
<td>-68%</td>
</tr>
<tr>
<td>Toughness</td>
<td>-34%</td>
<td>-70%</td>
</tr>
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Related changes in bone strength

![Bar chart showing whole bone strength (in Newtons) for young and old individuals for femoral neck (sideways fall) and lumbar vertebrae (compression).]

Age-related changes in femoral neck cortex and association with hip fracture

Those with hip fractures have:

- Preferential thinning of the inferior anterior cortex
- Increased cortical porosity

Jordan et al. Bone, 2000; 6:305-13
Bone tissue properties during osteoporosis

**Organic phase** (collagen, non-collagenous proteins and cells) accounts for 35% of bone mass and provides post-yield behaviour and strength.

**Mineral phase** (calcium and phosphorus in the form of hydroxyapatite crystals) allows the tissue to resist deformation under applied loading, which is known as the stiffness of the tissue.

Overall bone mass and BMD are reduced during oestrogen deficiency, but the yield strength and elastic modulus of the remaining tissue increased by 40–90% of control values.

↓ elastic deformation capacity of the bone
↑ type I collagen synthesis
↓ VI and III collagen synthesis
↑ hydroxylation of lysine residues

increase fracture susceptibility by altering the strength of the collagen network
Non Collagenous Proteins (NCPs)

- act as mineral crystal nucleation sites on the organic matrix

- indirectly regulate the mechanical properties of the collagen–mineral interface

NCPs are altered during post-menopausal osteoporosis.

- Osteocalcin
- Osteopontin
- Osteonectin
- Fibronectin
- Thrombospondin-2
NCPs influence bone fracture independently from bone mass.

play a significant role in the formation of specific morphologies of microdamage.

Nonenzymatic **glycation** is an important variable in analysis of bone’s fracture resistance, because it significantly alters bone’s organic matrix.
conflicting data exist from previous studies; some studies report a decrease in tissue mineral content and others reveal an increase in the mineral content.

These findings have been shown to differ for trabecular and cortical bone.
Decreased degree of mineralization

- increased HA crystal size and perfection
- carbonate content is increased,
- acid phosphate content is decreased

infrared imaging spectroscopy
sequence of events in the bone loss cascade
Updated Factors affecting fractures

Bone remodeling

Bone density

H₂O

Mineralization degree

Collagen

Fatigue damage

Crystallinity

Non-collagen proteins

Collagen

Bone micro-architecture

Bone strength

Bone geometry

Fracture

Falls Trauma

...etc
Future research and conclusions
Toward Mechanical Systems Biology in Bone

Andreas Trüssel, Ralph Müller, and Duncan Webster
Molecular biology of bone remodeling: Implications for new therapeutic targets for osteoporosis

J. Chris Gallagher*, A.J. Sai
bone fracture during post-menopausal osteoporosis has not yet been eliminated.

Future research studies should include multi-disciplinary analyses at **multiple time points** to comprehensively characterize the sequence of changes in molecular signalling, cell physiology, tissue composition, micro-architecture, damage and bone mass.
Connecting mechanics and bone cell activities in the bone remodeling process: an integrated finite element modeling

Ridha Hamblin

Bone adaptation:
1. Evolution of material properties, damage growth and repair, mineralization
2. Evolution of bone mass
3. Cell accommodation: change of setpoint value

1. Modulate the factors produced by osteoclasts that regulate osteoblast formation (g12).
2. Modulate the factors produced by osteoblasts that regulate osteoclast formation (g21).
Improving fixation methods in osteoporotic bones