BIOLOGY and BIOMECHANICS OF NORMAL & OSTEOPOROTIC BONE

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University Hospital of Patras, Orthopaedic Clinic

Objectives

- Bone structure and physiology
- Remodeling and bone metabolism
- Factors affecting bone strength and quality
- Biomechanics and damage in osteoporosis
- Future research- conclusions

Outline

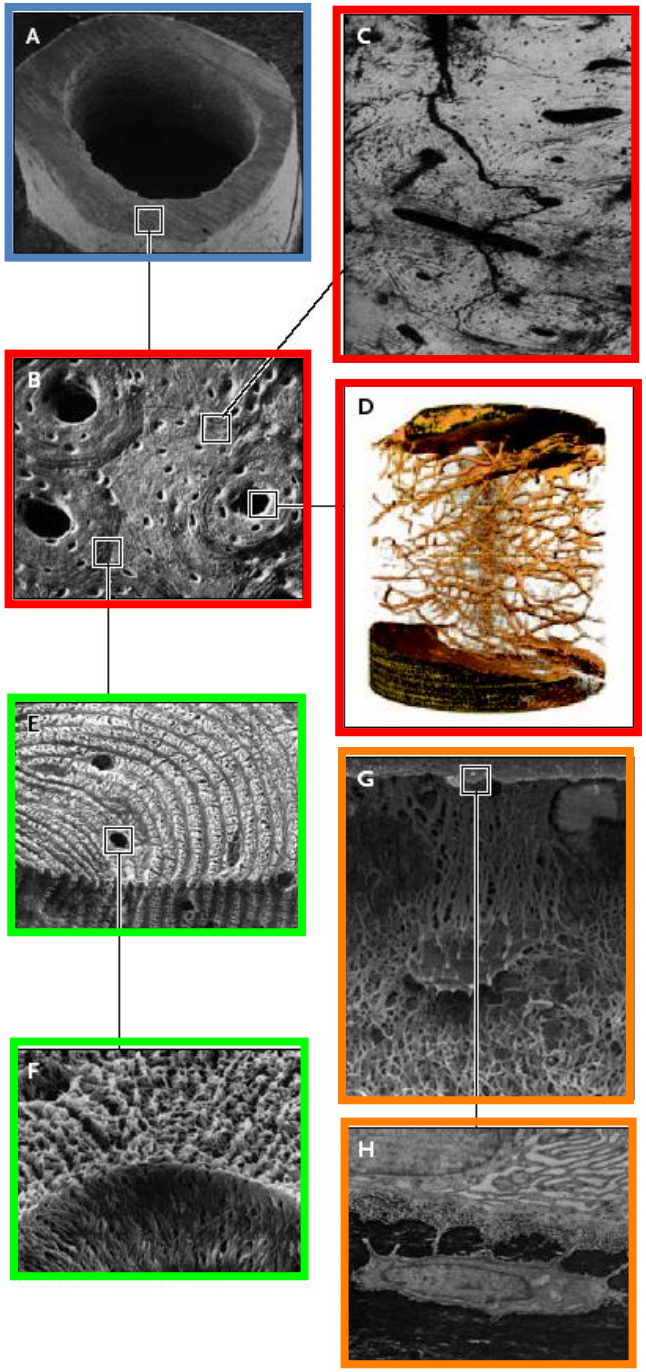
2 important **Mechanical Functions** of Bone

- 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

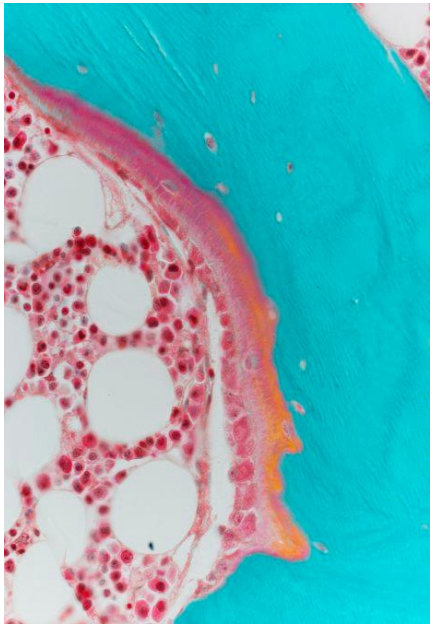
Seeman & Delmas
N Engl J Med 2006; 354:2250-61

Bone function

Properties at the cellular, matrix, microarchitectural, and macroarchitectural levels may all impact bone **mechanical properties**

These factors are interrelated and co-acting

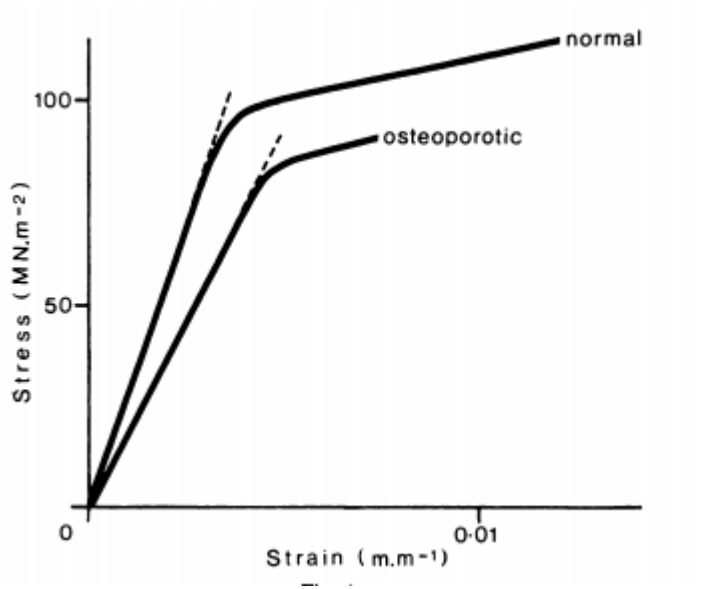
Therefore, one cannot expect that changes in a single property will be solely predictive of changes in bone mechanical behavior



THE MECHANICAL PROPERTIES OF BONE IN OSTEOPOROSIS

R. P. DICKENSON, W. C. HUTTON, J. R. R. STOTT

From the Polytechnic of Central London, and the RAF Institute of Aviation Medicine, Farnborough



Lower strength and stiffness of osteoporotic bone

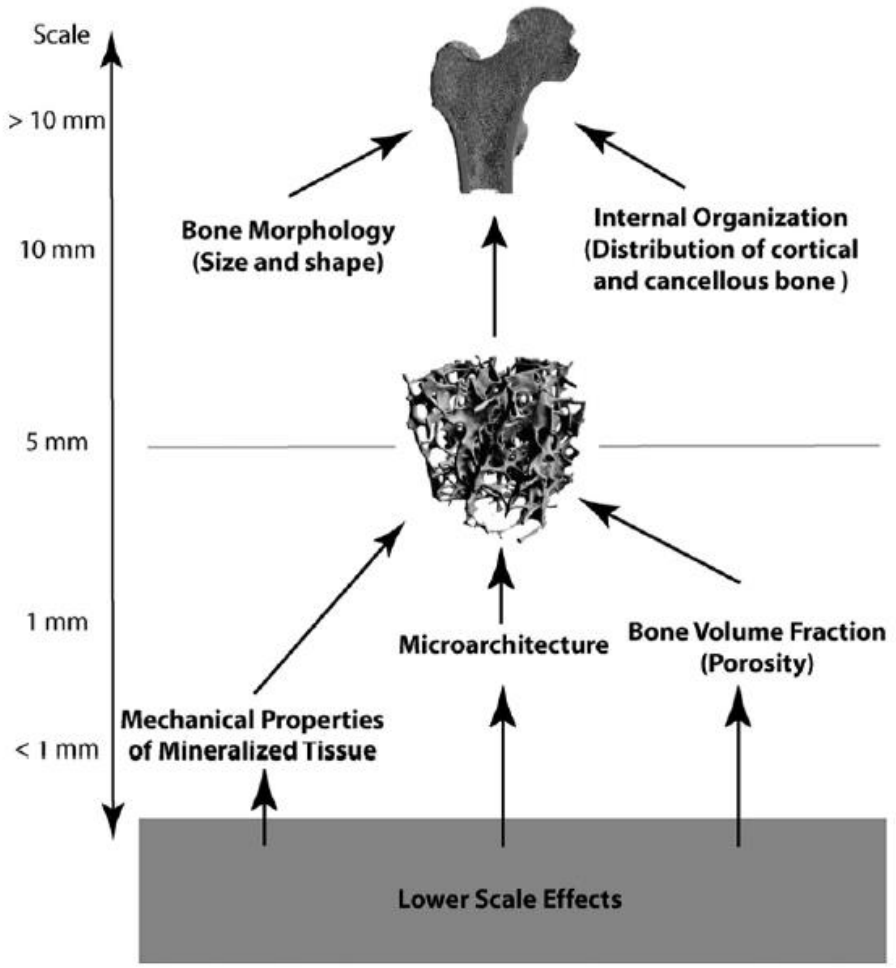
Mineral content slightly higher than that of normal bone

Published in final edited form as:
Bone. 2006 December ; 39(6): 1173–1181.

A biomechanical perspective on bone quality

C.J. Hernandez[1,*] and T.M Keaveny[1,2]

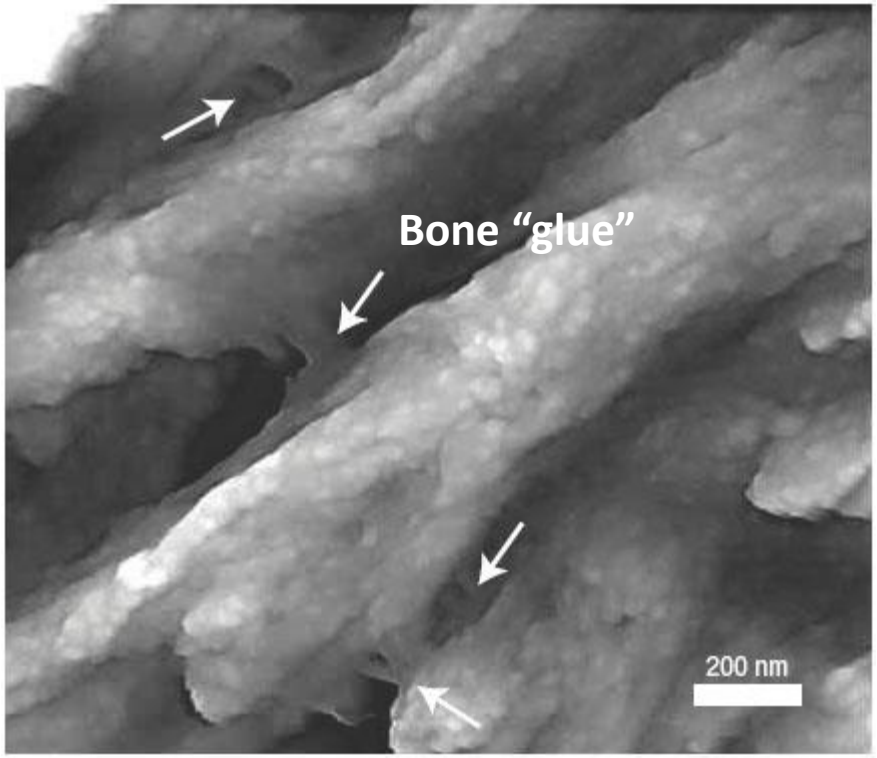
When no changes in bone quality occur at 5 mm level, probably there are no changes in lower scales also



Bone building blocks

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

Atomic Force Microscope



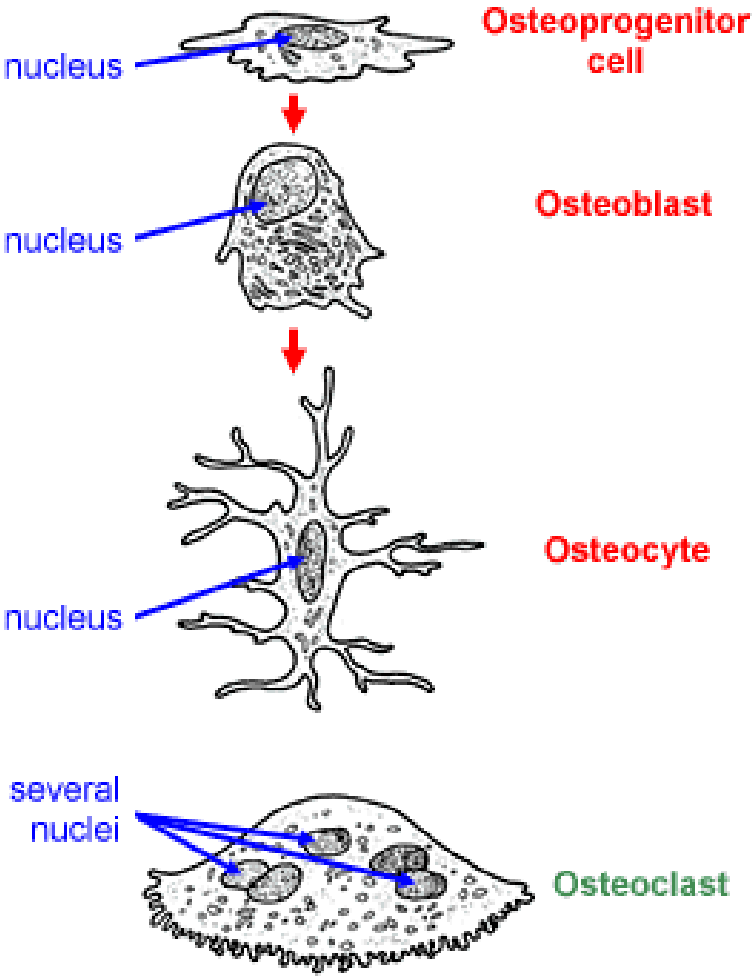
Important cells

Bone Structural Units (BSU)

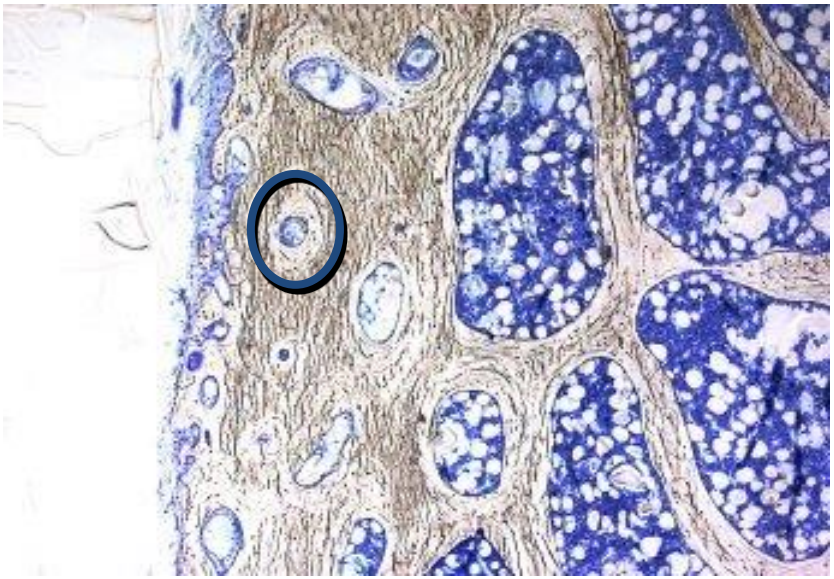
Basic Multicellular Units (BMU)

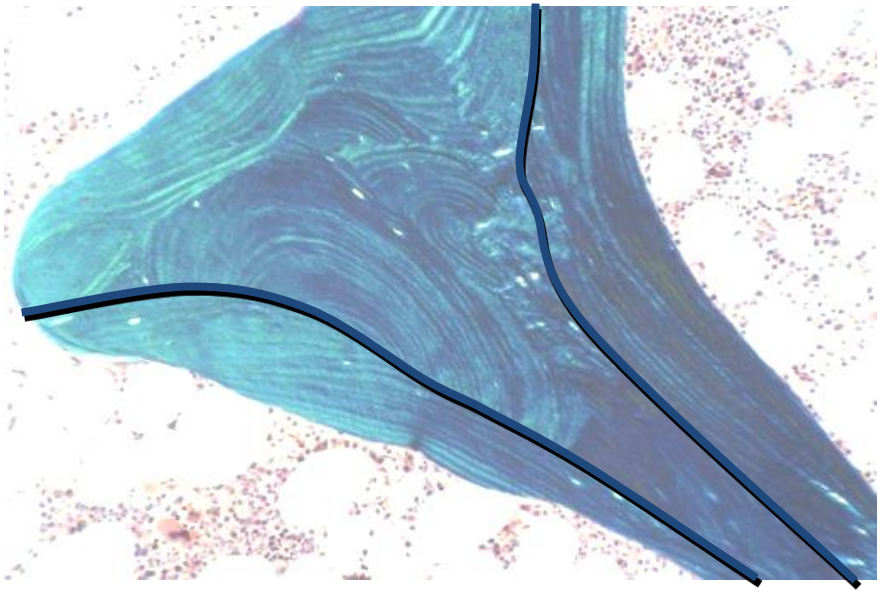
Bone remodeling

Basic regulator: osteocyte?



Bone Structural Units (BSU)



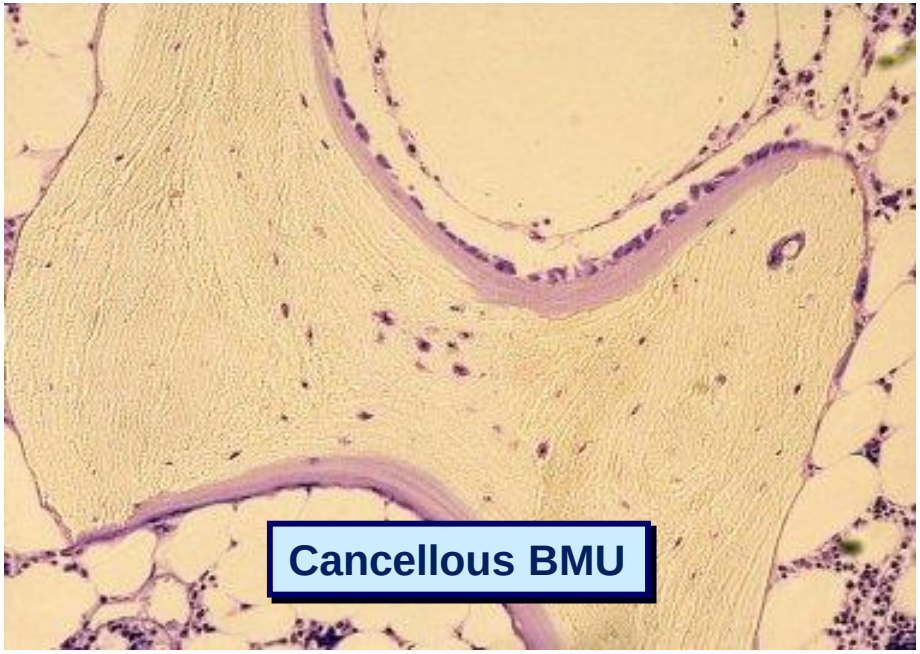


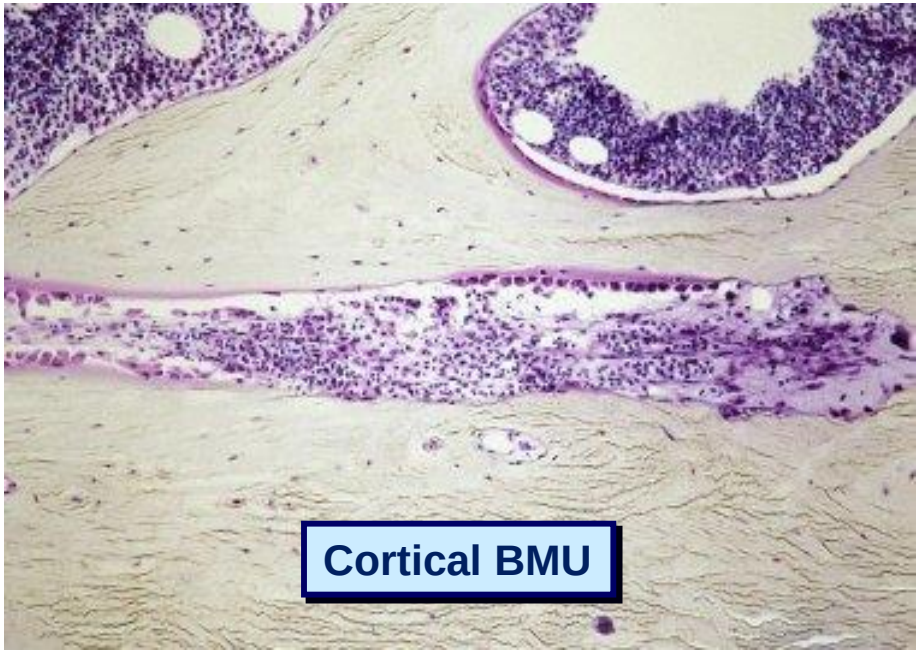
BSU (osteons) is the structural end result of a focused bone renewal

Cortical bone: concentric rings (lamellae)

Cancellous bone: flat and stacked in saucer shaped depressions

Basic Multicellular Units (BMU)

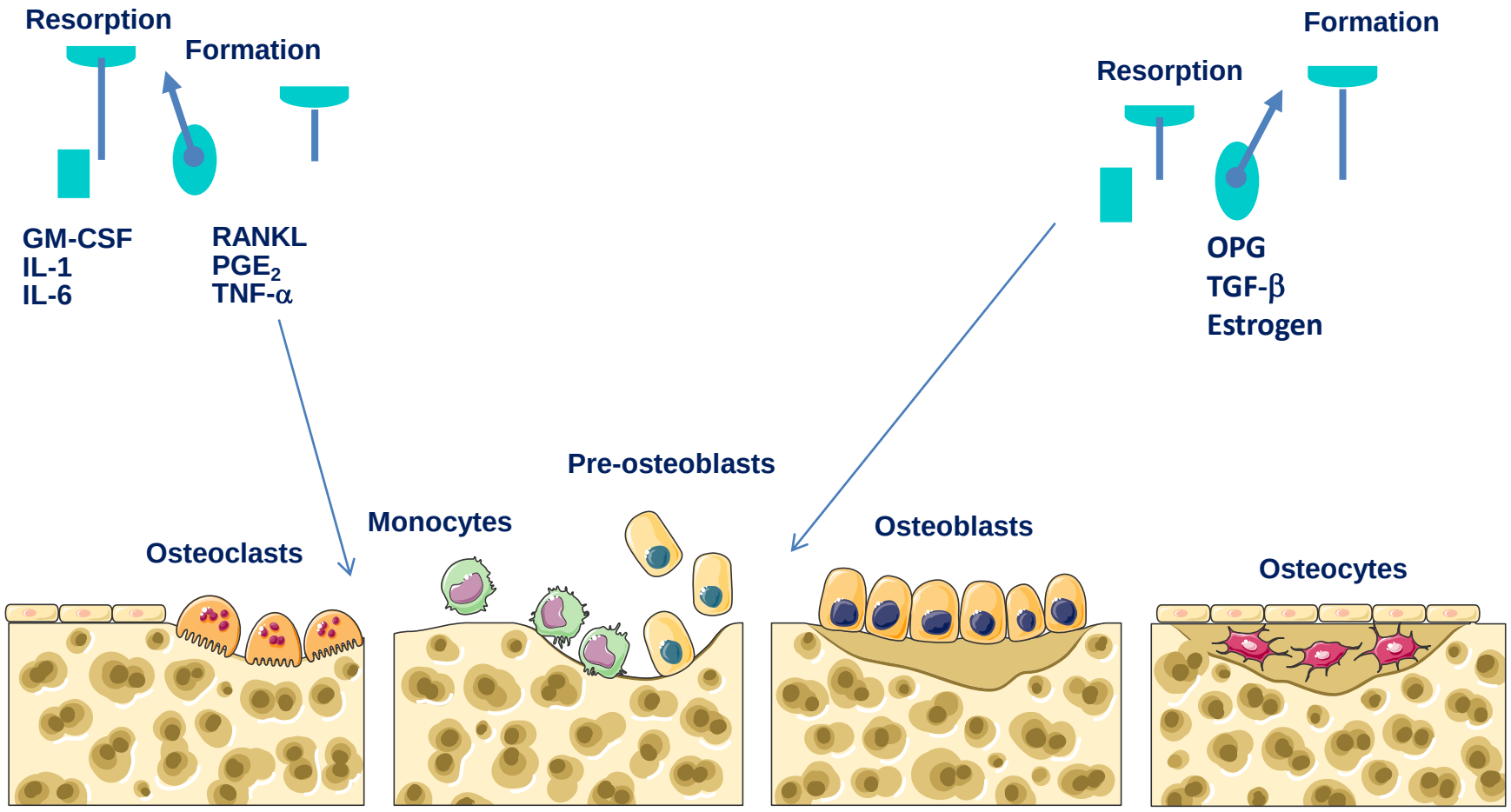




Under normal steady state conditions, the amount of bone removed is precisely replaced and there is no net change in bone mass.

Only bone architecture is changed

Bone remodeling cycle

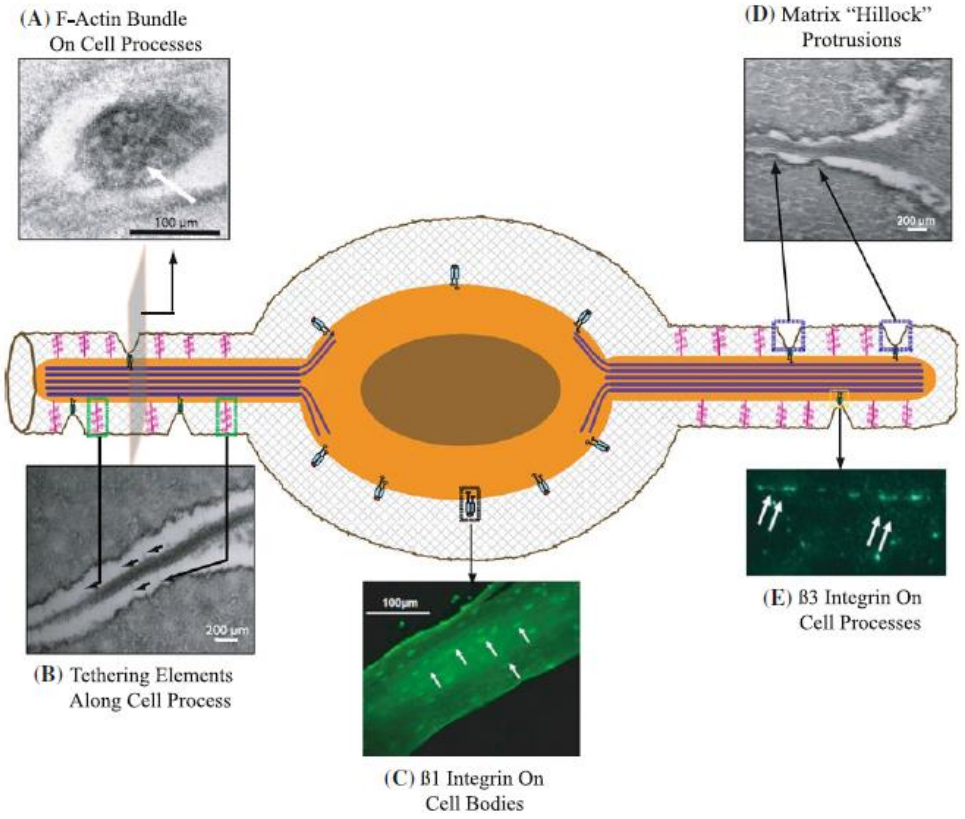


Calcif Tissue Int (2014) 94:5–24
DOI 10.1007/s00223-013-9790-y

REVIEW

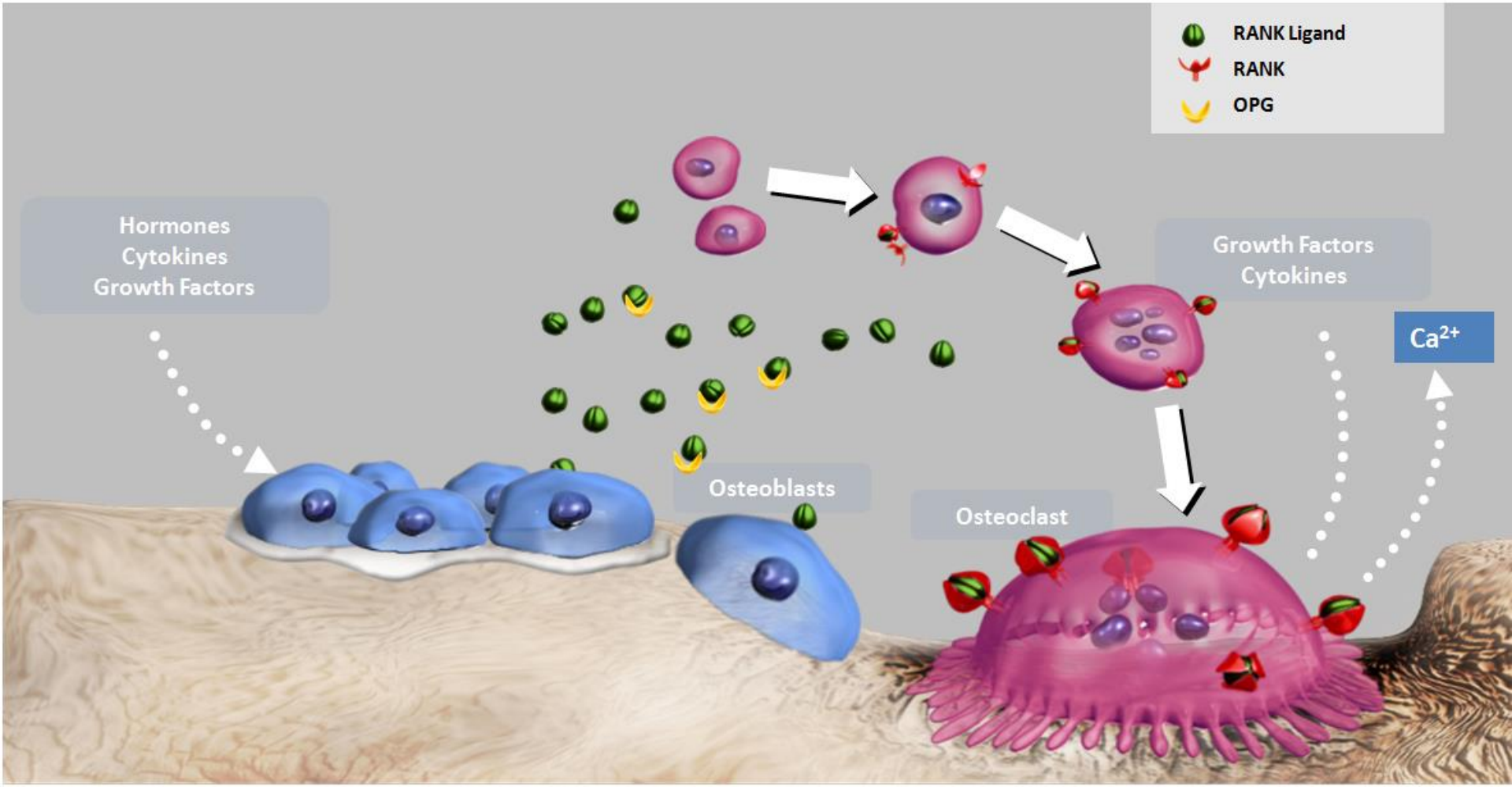
Osteocytes: Master Orchestrators of Bone

Mitchell B. Schaffler · Wing-Yee Cheung ·
Robert Majeska · Oran Kennedy

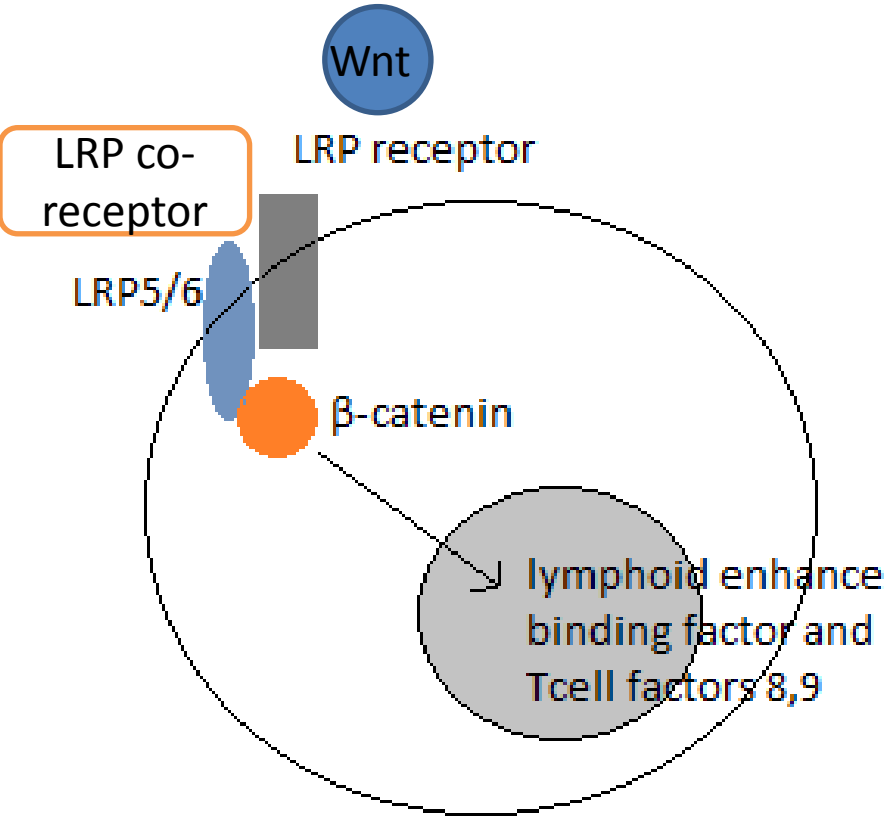


Osteocytes sensing and integrating mechanical and chemical signals from their environment to regulate both bone formation and resorption.

RANK Ligand is a Central Mediator in the Activation phase of bone remodeling



Wnt-signal pathway in osteoblasts



✓ **Luck of Wnt pathway** reduces the amount of **β-catenin** in the cytoplasm due to high degradation. As a result important control of protein transcription in osteoblasts is lost.

Wnt pathway antagonists

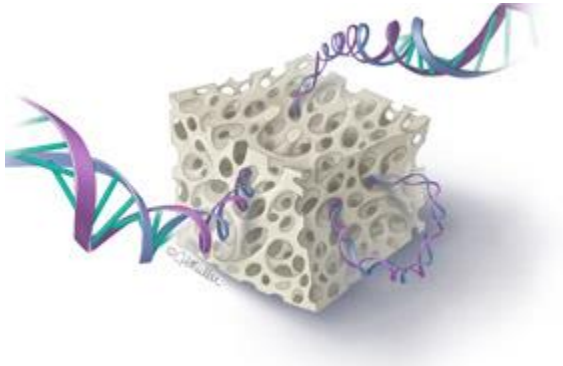
- SFRP1
- WIF-1
- DKK-1
- Sclerostin

All act as inhibitors of LRP5/6

Over-expression

Reduction of osteoblastogenesis

OSTEOPOROSIS



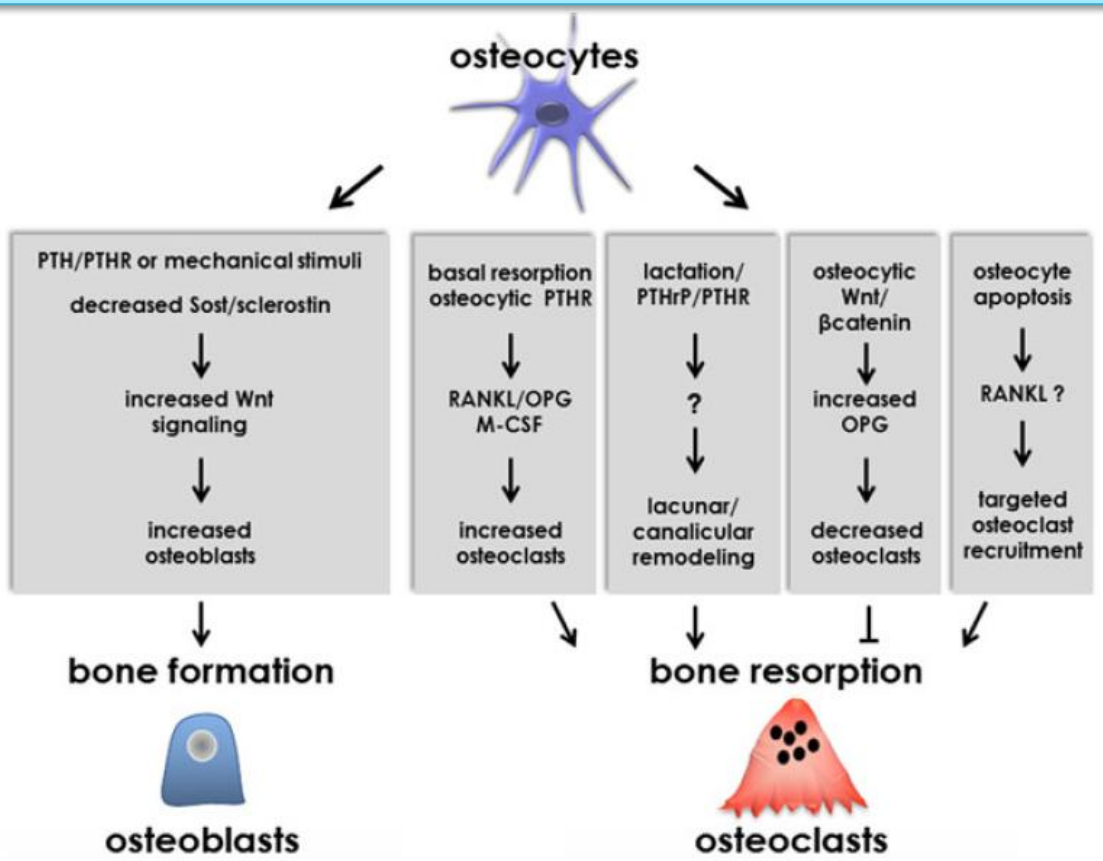
Calcif Tissue Int (2014) 94:25–34
DOI 10.1007/s00223-013-9774-y

REVIEW

Osteocyte-Driven Bone Remodeling

Teresita Bellido

Osteocyte-driven bone resorption & formation



Why Bone Remodels?

- Allows bone to respond to loads (stress)
- Maintain materials properties
- Allows repair of microdamage
- Participates in serum Ca^{2+} regulation

Calcif Tissue Int (2014) 94:5–24
DOI 10.1007/s00223-013-9790-y

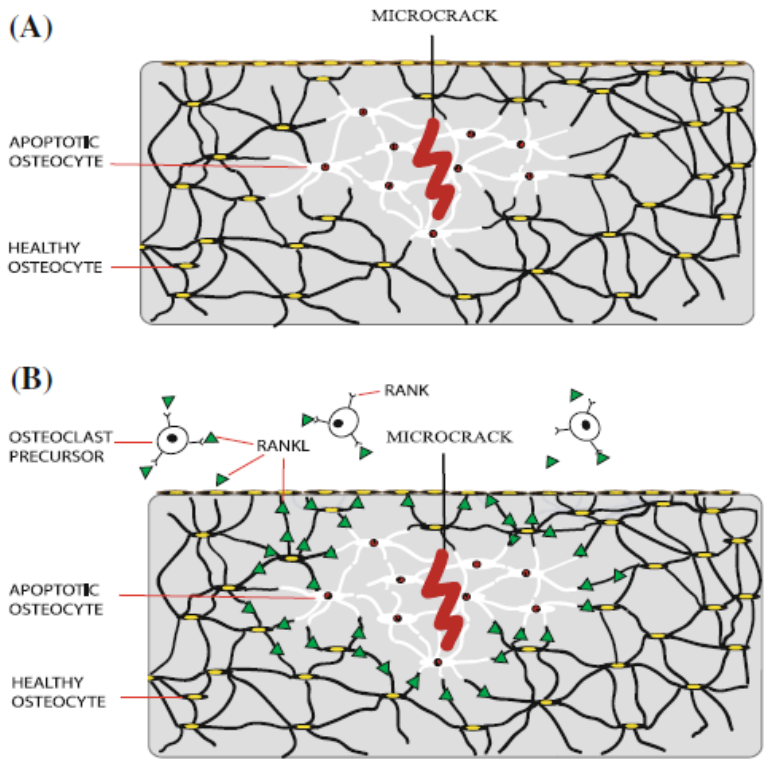
REVIEW

Osteocytes: Master Orchestrators of Bone

Mitchell B. Schaffler · Wing-Yee Cheung · Robert Majeska · Oran Kennedy

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

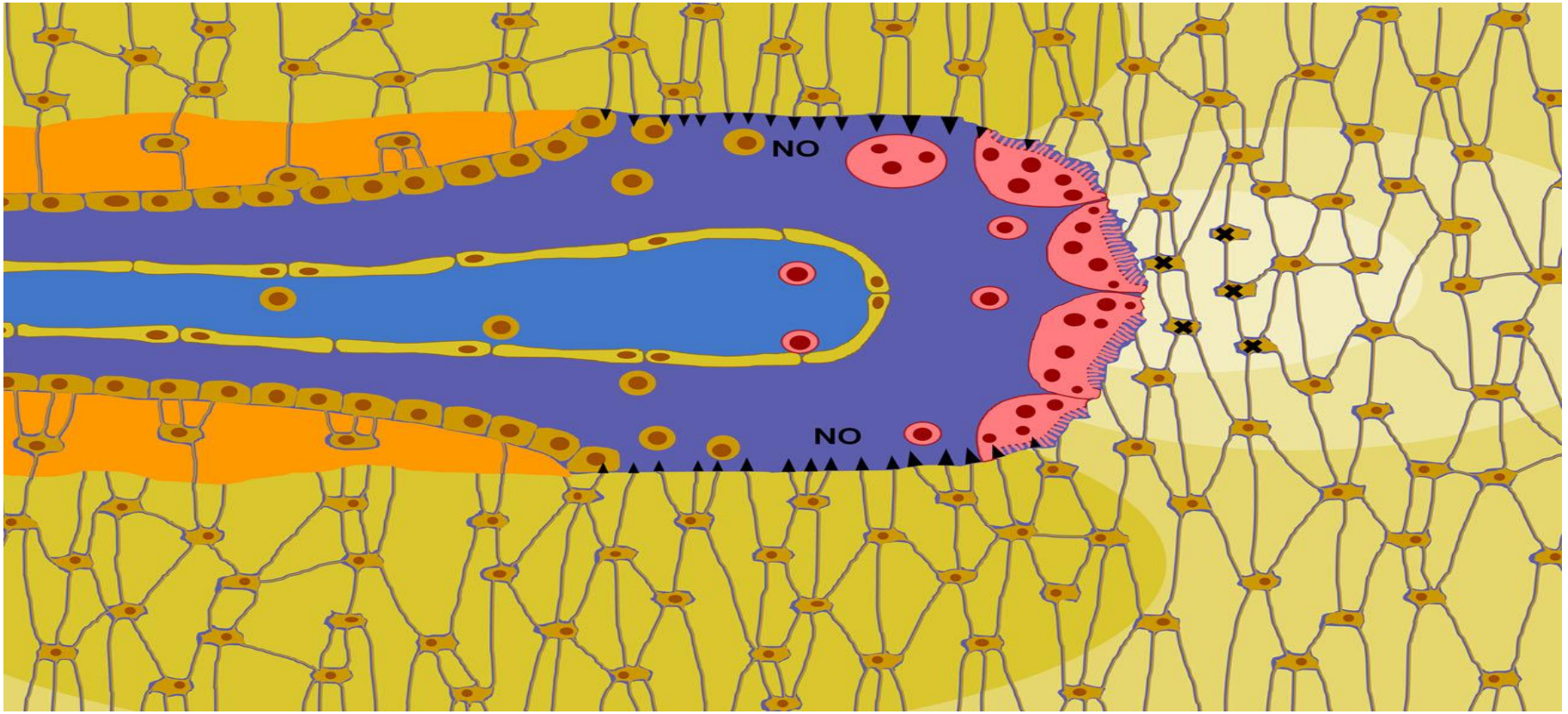


Osteoporos Int (2014) 25:1427–1437
DOI 10.1007/s00198-013-2590-4

REVIEW

Nitric oxide signaling in mechanical adaptation of bone

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

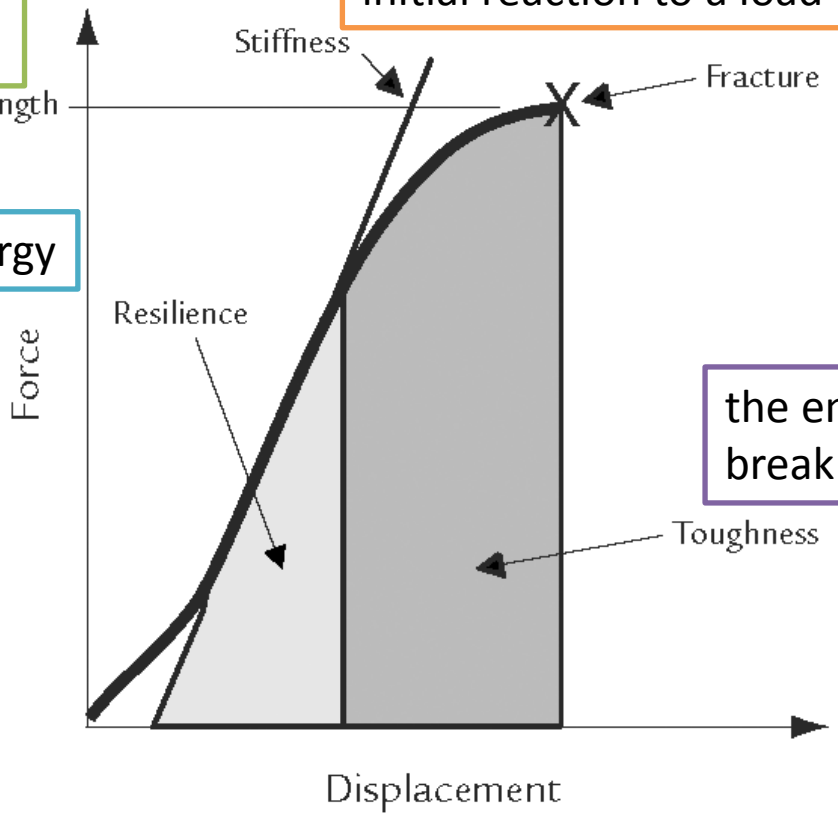


Osteocyte apoptosis (X) is caused by lack of fluid flow at the tip of the cutting cone, osteoclasts are attracted by apoptotic and RANKL producing osteocytes, and as a result, the cutting cone follows the loading direction.

Load-carrying behavior of bone

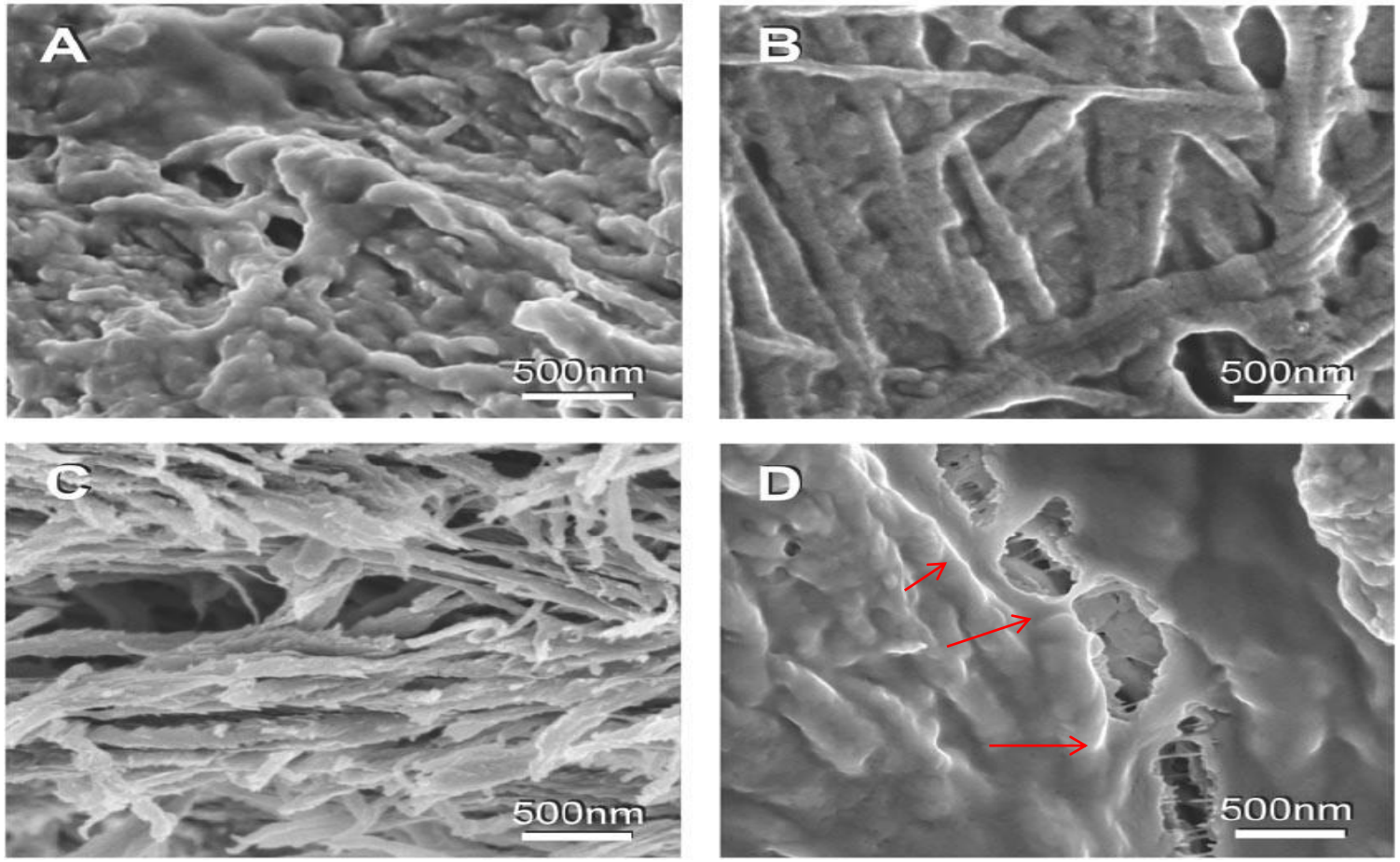
the maximum load the material can sustain

initial reaction to a load



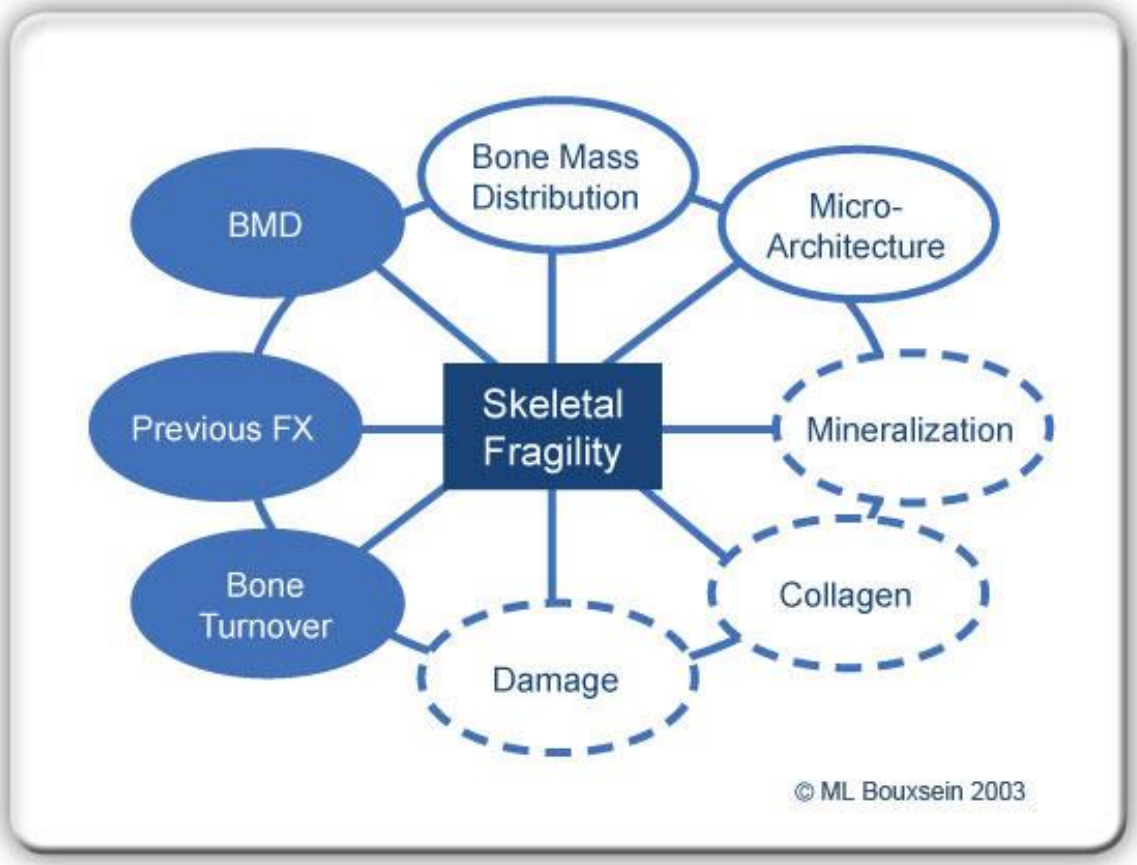
stored elastic energy

the energy required to break the material



Bone is a highly heterogenous material, partially because it has been adapted to resist different, complex and varying stresses

Determinants of fragility

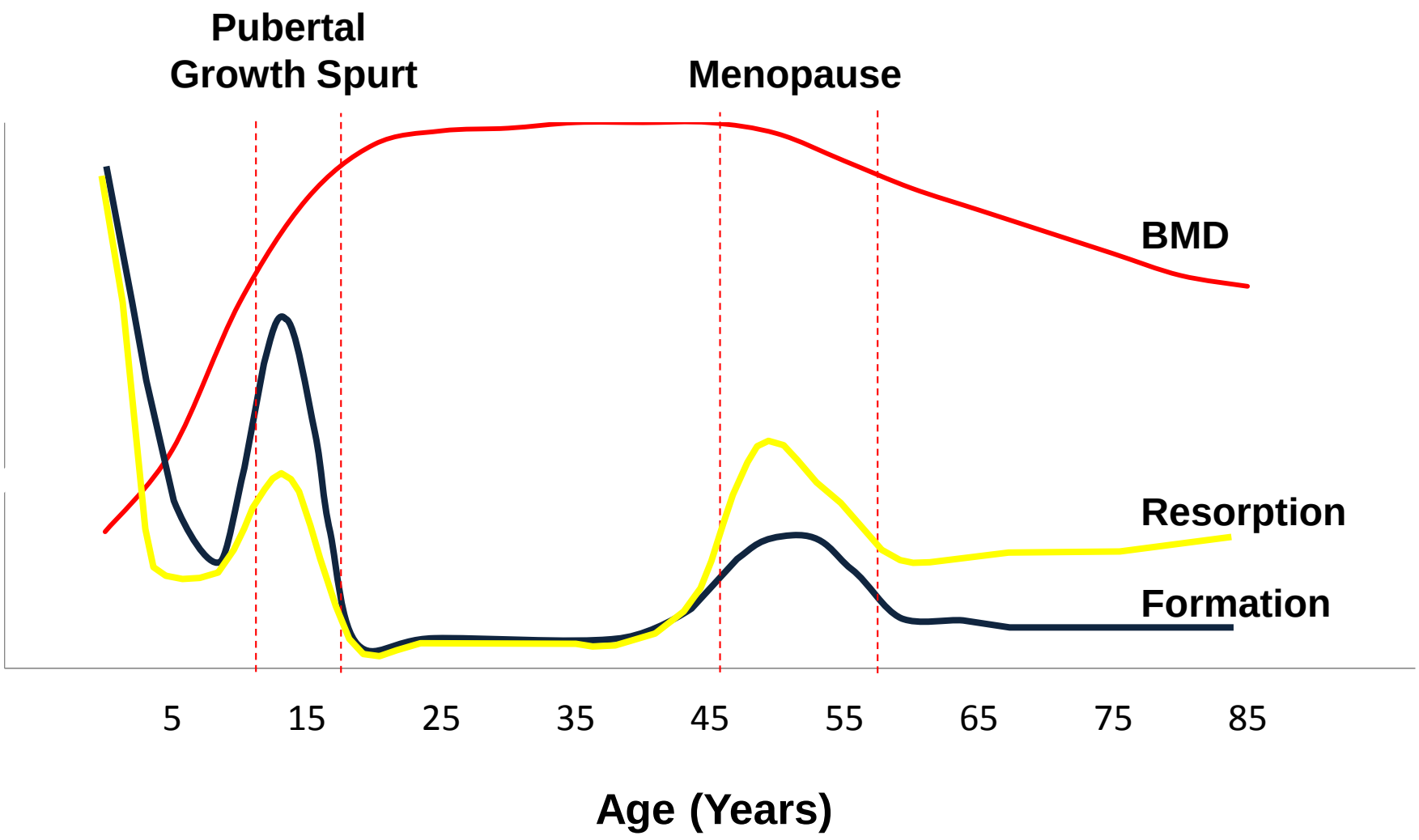


used in clinical practice

used in clinical research

cannot be measured non-invasively

Bone throughout the lifespan



Aging

Curr Osteoporos Rep (2010) 8:235–240
DOI 10.1007/s11914-010-0035-y

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

Biomaterials 35 (2014) 9290–9301

Contents lists available at ScienceDirect

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials

The influence of age on adaptive bone formation and bone resorption

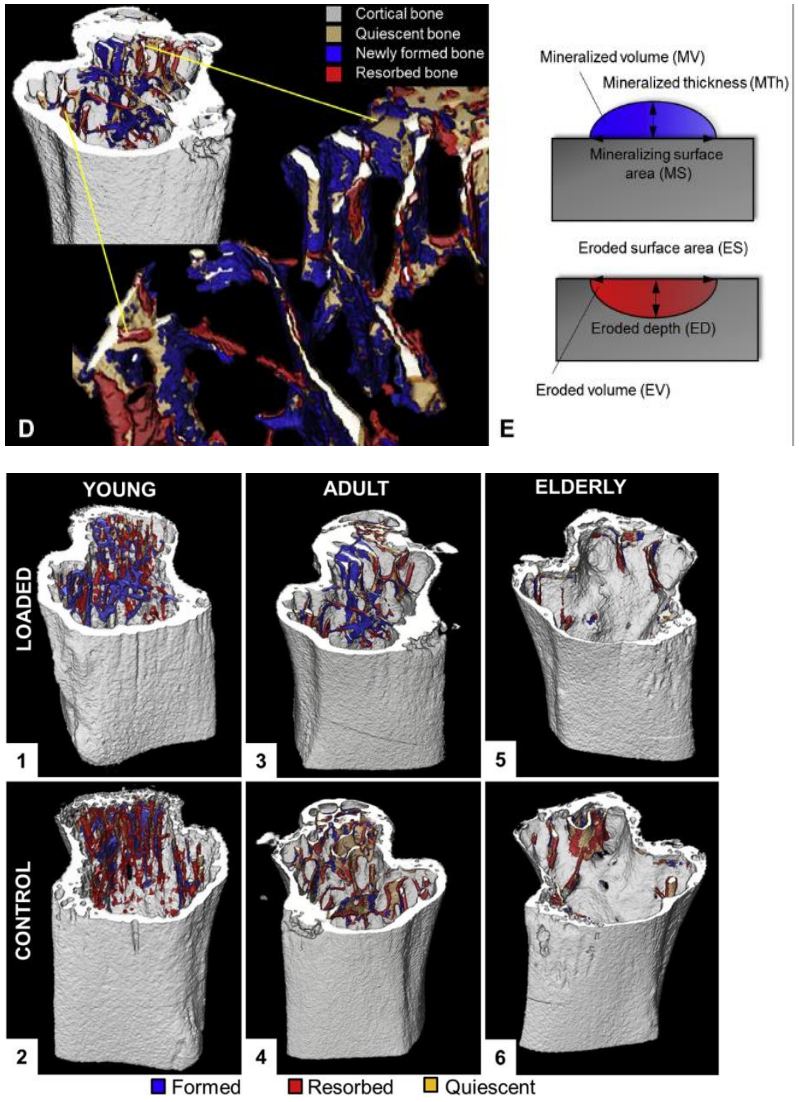
Annette I. Birkhold [a, b], Hajar Razi [a, b], Georg N. Duda [a], Richard Weinkamer [c], Sara Checa [a], Bettina M. Willie [a, *]

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

CHANGES in BIOMECHANICAL STRENGTH →→→ FRACTURES

"IMBALANCE" in bone remodeling

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

Bone Quality Framework

Structural Properties

- Geometry

-Size

-Shape

- Microarchitecture

-Trabecular architecture

-Cortical thickness/porosity

Material Properties

- Mineral

-Mineral-to-matrix ratio

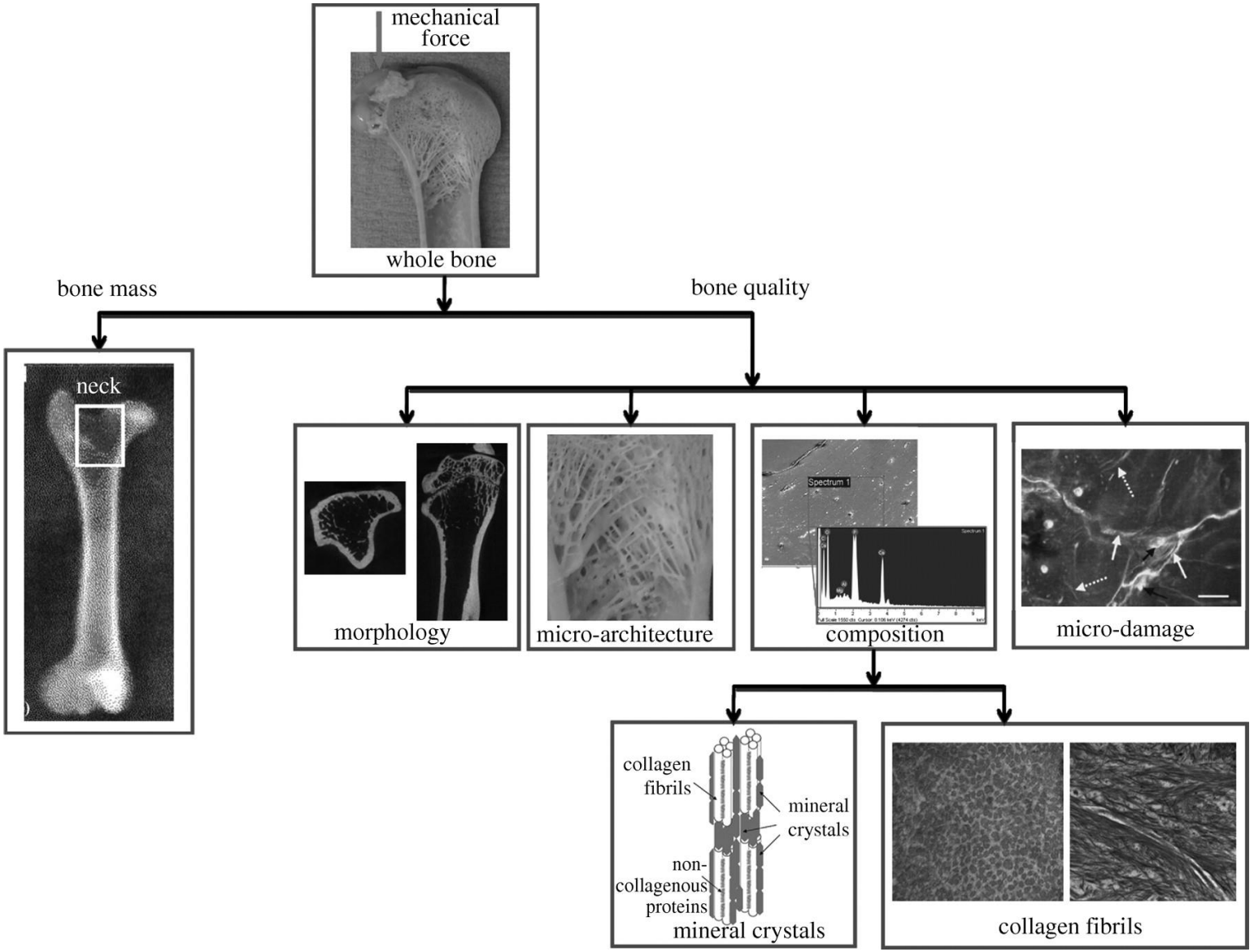
-Crystal size

- Collagen

-Type

-Cross-links

- Microdamage/microfracture



McNamara L M J. R. Soc. Interface 2010;7:353-372

how bone loss in osteoporosis alters bone mechanical strength?

Bone mass

Cancellous microarchitecture

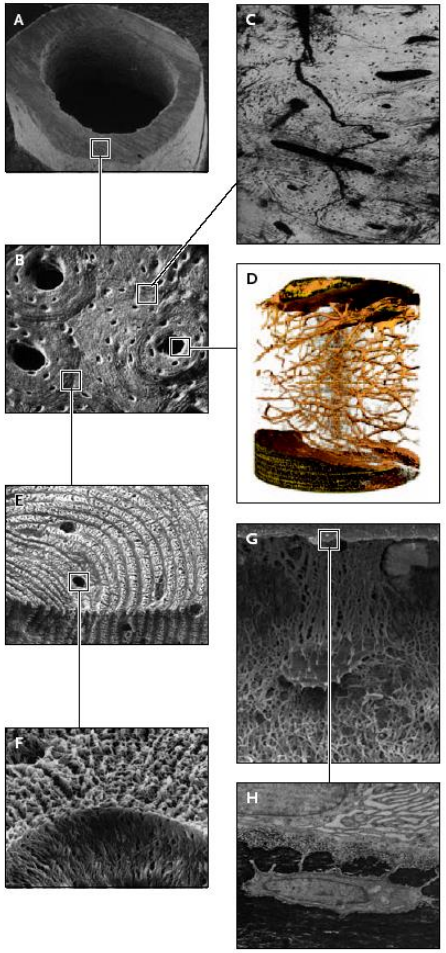
Cortical microarchitecture

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)

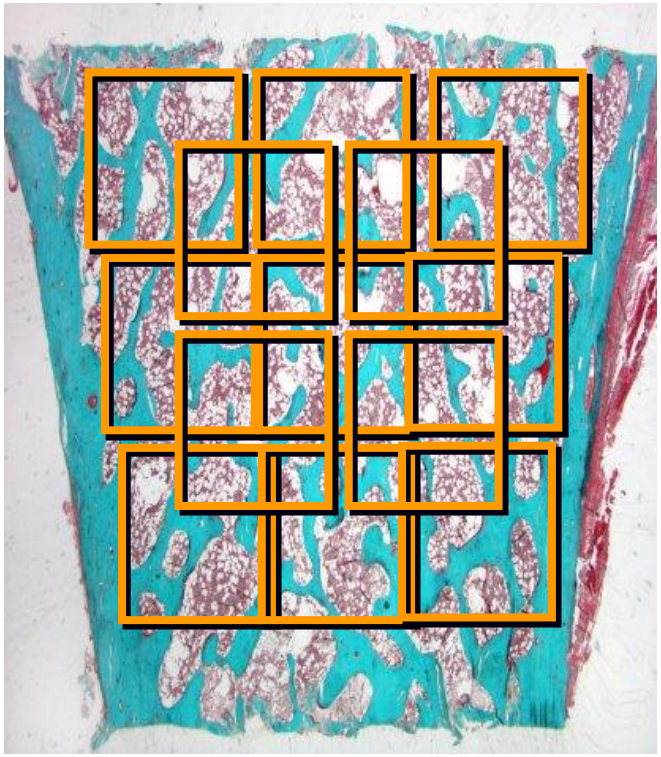
BMD do not fully explain susceptibility to bone fracture

(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)

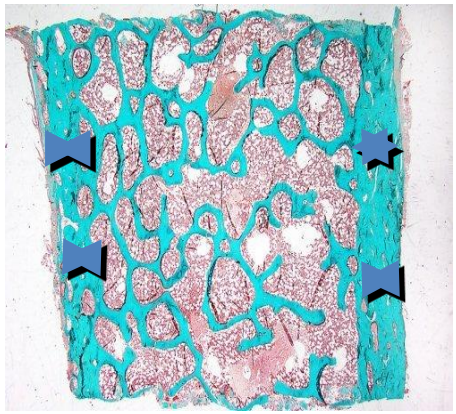
Cancellous micro-architecture during osteoporosis

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

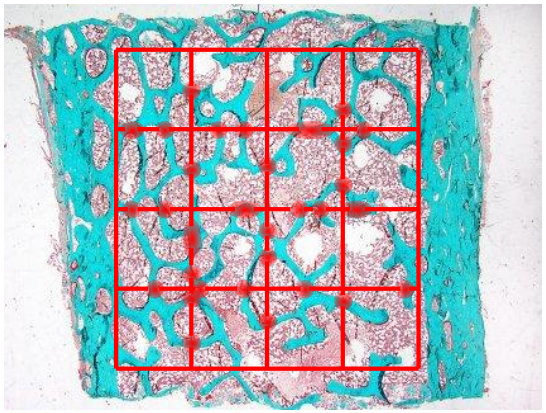
- cortical porosity,
- cortical thickness,
- trabecular number,
- trabecular thickness
- trabecular connectivity



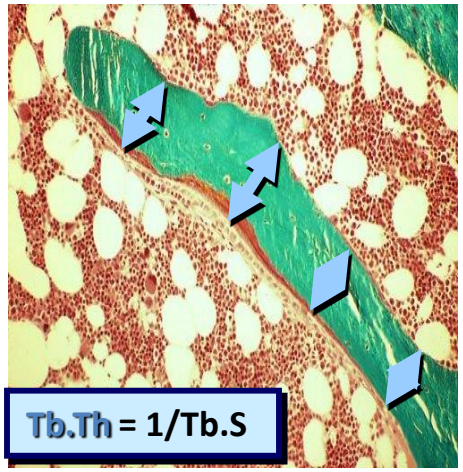
↑ Cortical Thickness (Ct.Th)



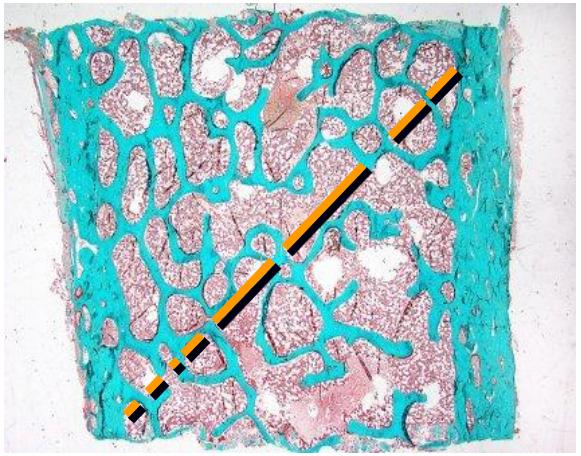
↑ Trabecular Number (Tb.N)



↑ Trabecular Thickness (Tb.Th)

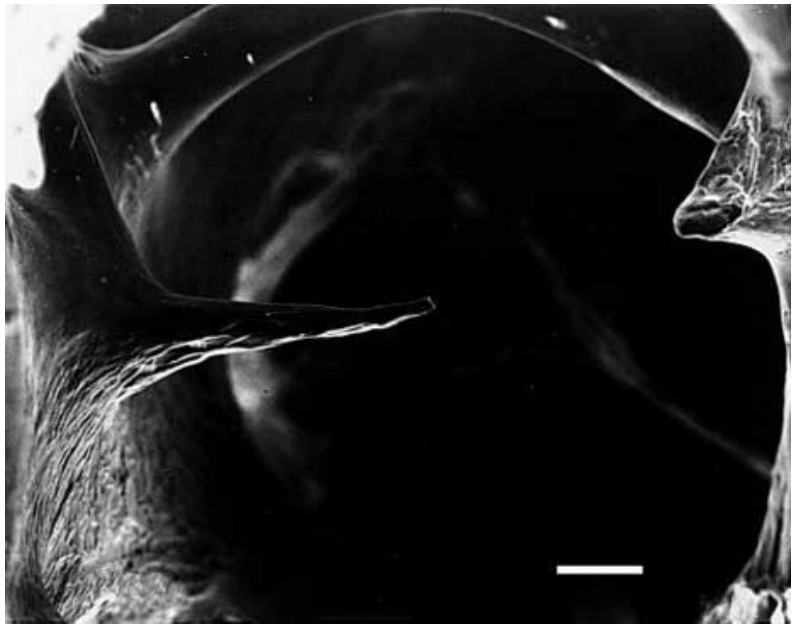


↓ Trabecular Separation (Tb.Sp)



Cancellous micro-architecture during osteoporosis

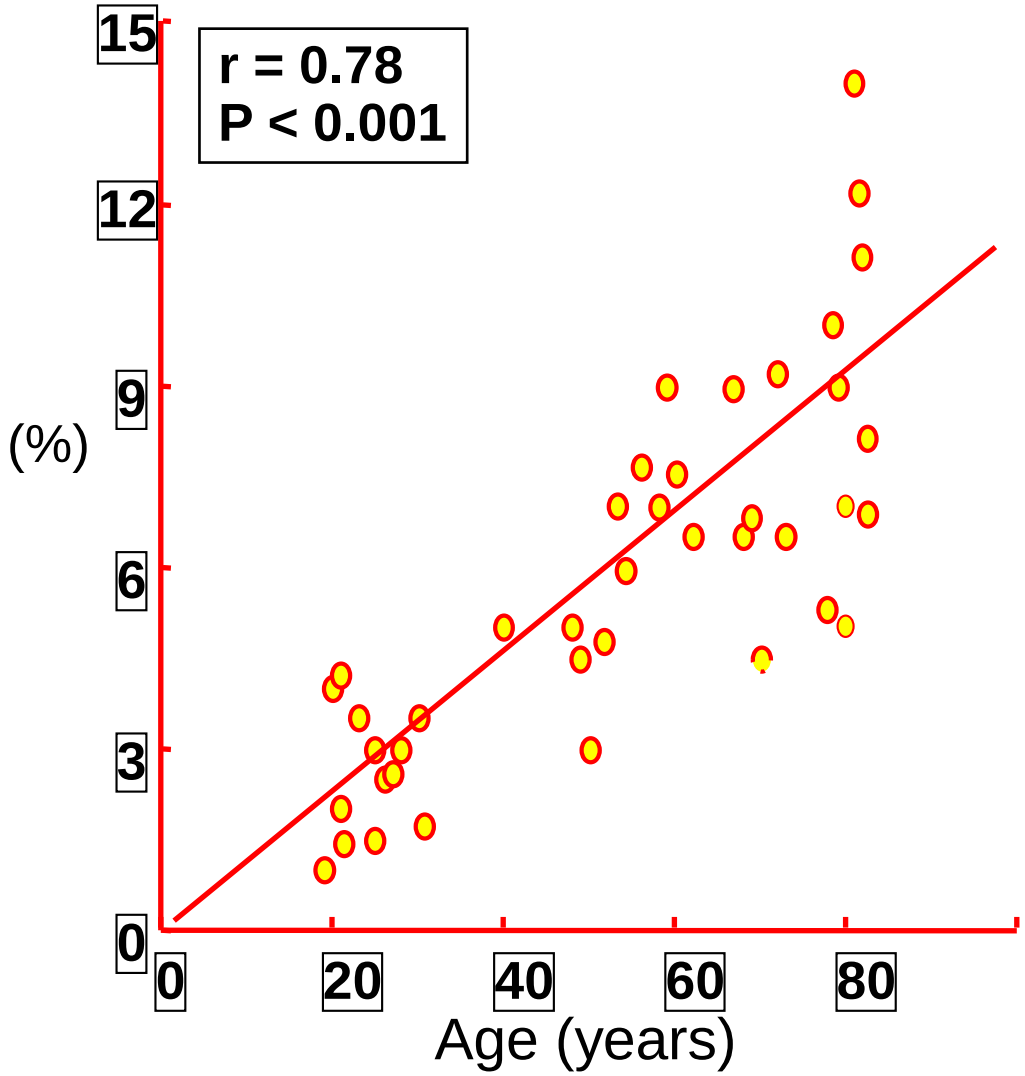
trabecular thinning,
thickening of remaining trabecula
deeper resorption cavities,
micro-fracture
loss of trabecular connectivity



fracture risk prediction is improved by approximately 13% as compared with BMD alone

Cortical micro-architecture during osteoporosis

(41 iliac biopsies, age 19-90)

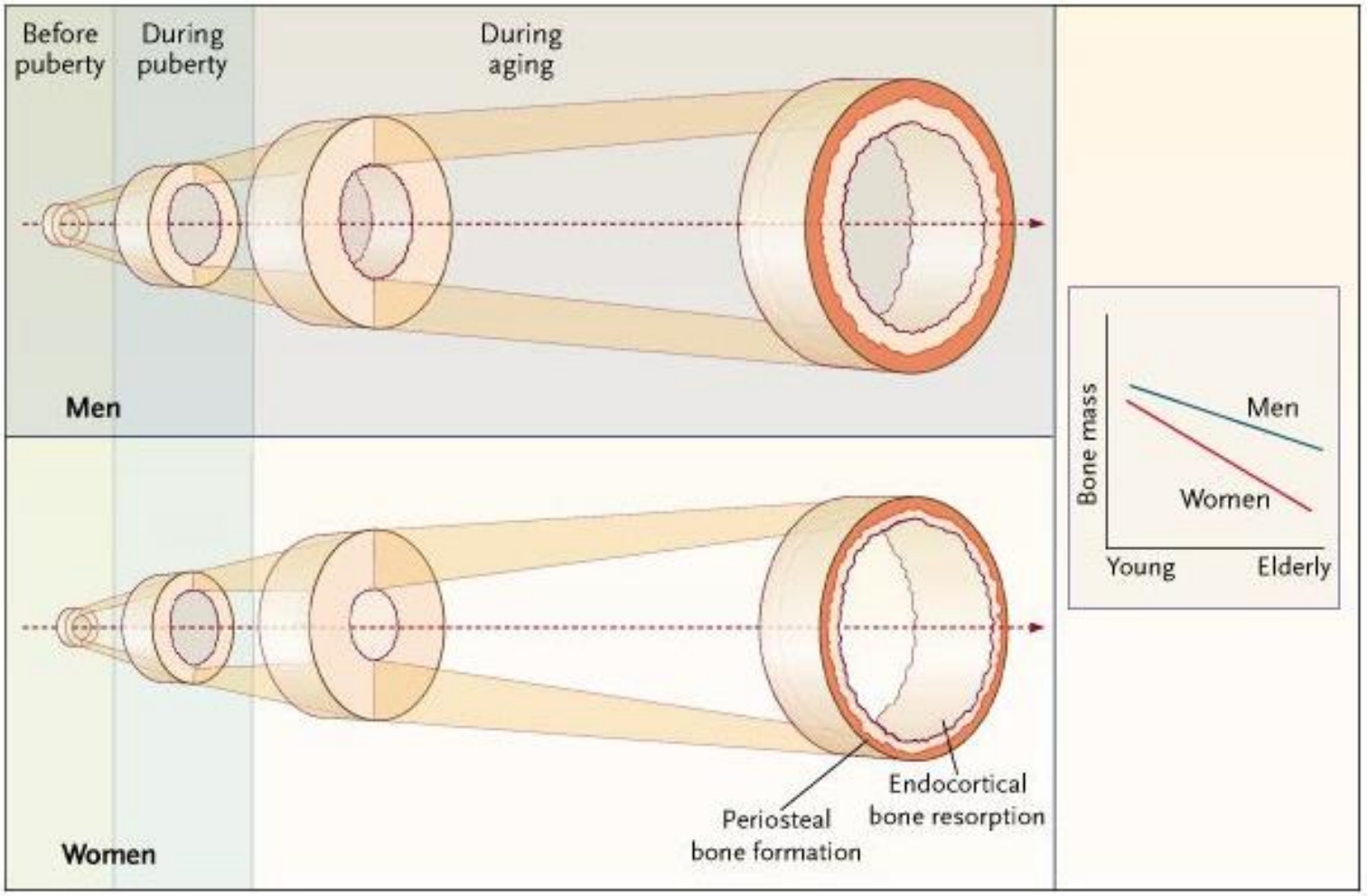


4-fold increase in cortical porosity from age 20 to 80

Increased heterogeneity with age

Brockstedt et al. Bone 1993; 14:681-91

Related changes in geometry



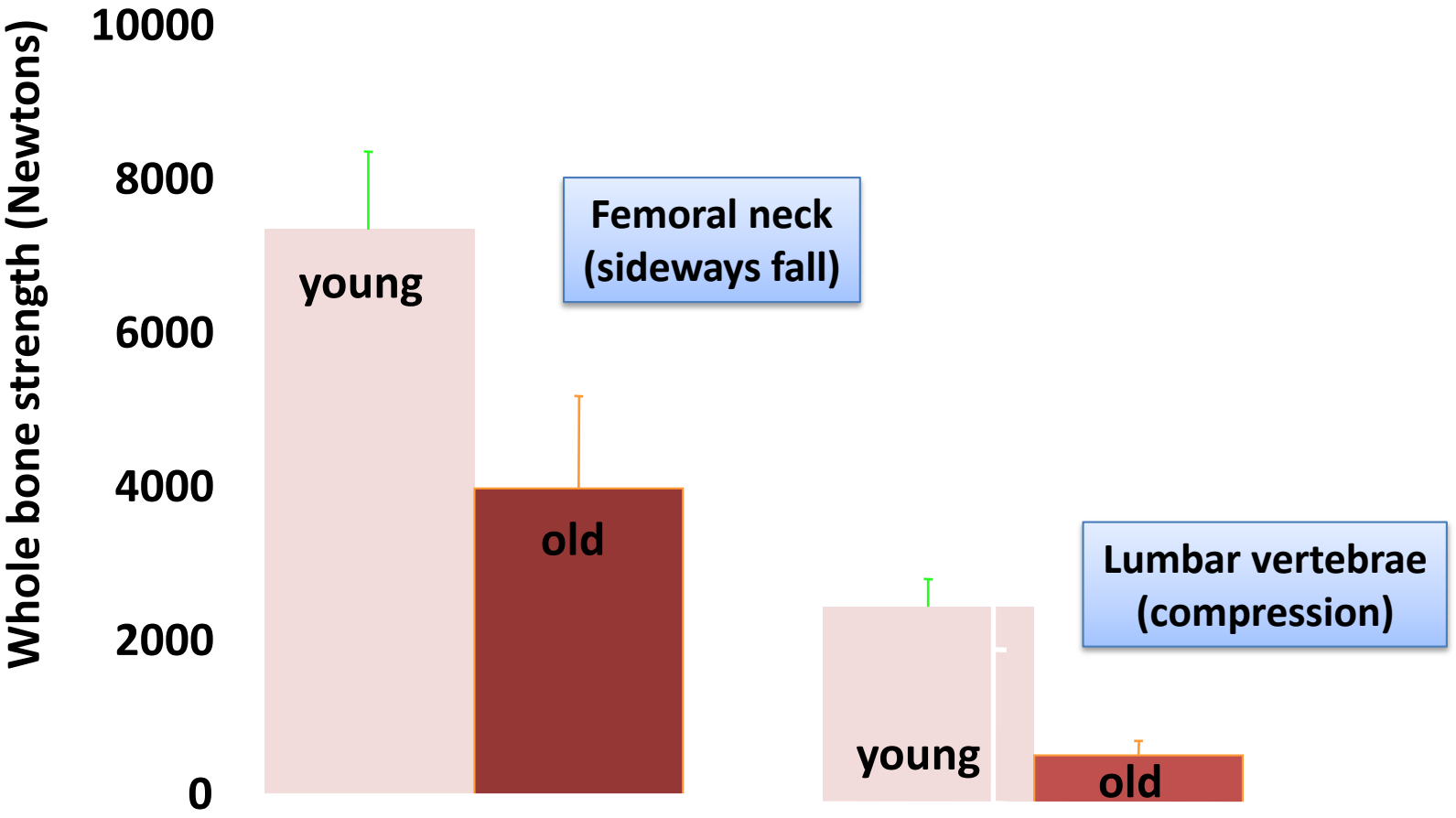
Adaptation to maintain whole bone strength

Related changes in mechanical properties

	Cortical bone (% loss 30-80 yrs)	Cancellous bone (% loss 30-80 yrs)
Elastic modulus, E	-8%	-64%
Ultimate strength, S	-11%	-68%
Toughness	-34%	-70%

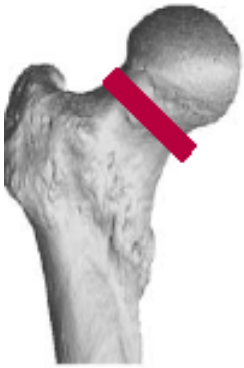
Bouxsein & Jepsen, Atlas of Osteoporosis, 2003

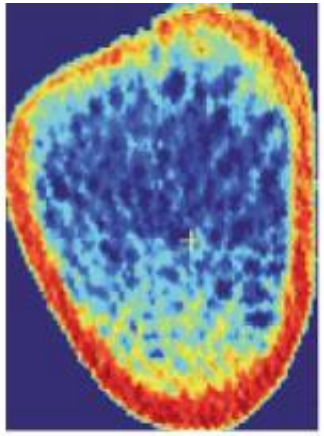
Related changes in bone strength

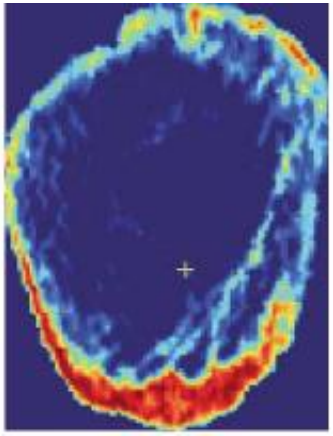


Courtney et al. J Bone Joint Surg Am. 1995; 77:387-95
Mosekilde. Technology and Health Care 1998; 6:287-97

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







Mayhew et al,
Lancet 2005

20-year-old **80-year-old**

Those with hip fractures have:

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

Bell et al. Osteoporos Int 1999; 10:248-57
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

McNamara L. 2005. Musculoskelet. Neuronal Interact. 5, 342–343

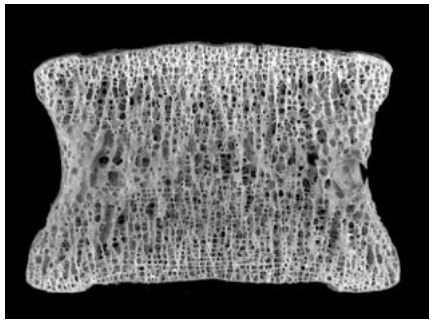
Collagen

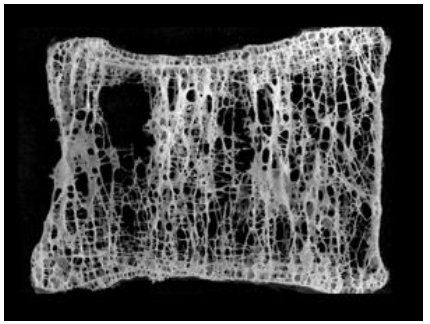
↓ elastic deformation capacity of the bone

↑ 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*

Published in final edited form as:
Curr Osteoporos Rep. 2012 June ; 10(2): 141–150. doi:10.1007/s11914-012-0103-6.

Effects of Bone Matrix Proteins on Fracture and Fragility in Osteoporosis

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

Mineral

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

Clin Orthop Relat Res. 2006 February ; 443: 28–38.

Mineral Changes in Osteoporosis *A Review*

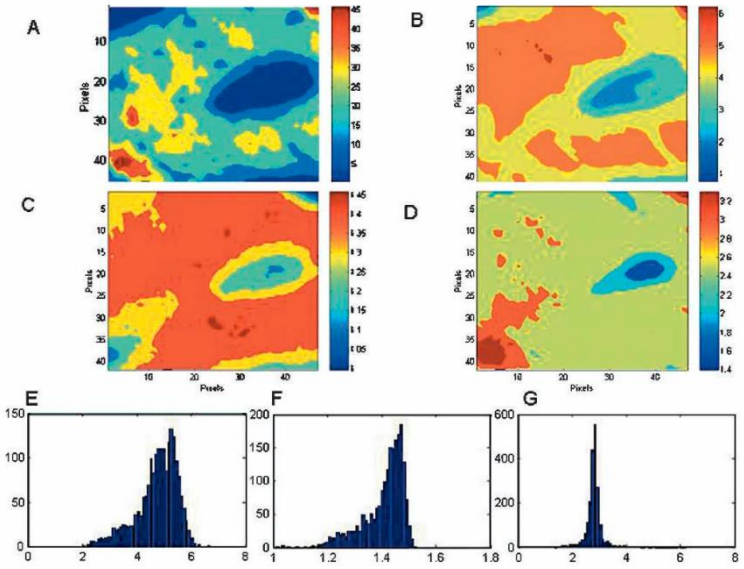
Dan Faibish, DMD[*], **Susan M. Ott, MD**[†], and **Adele L. Boskey, PhD**[*]
**Musculoskeletal Integrity Program, Hospital for Special Surgery, New York, NY*

Decreased degree of mineralization

increased HA crystal size and perfection

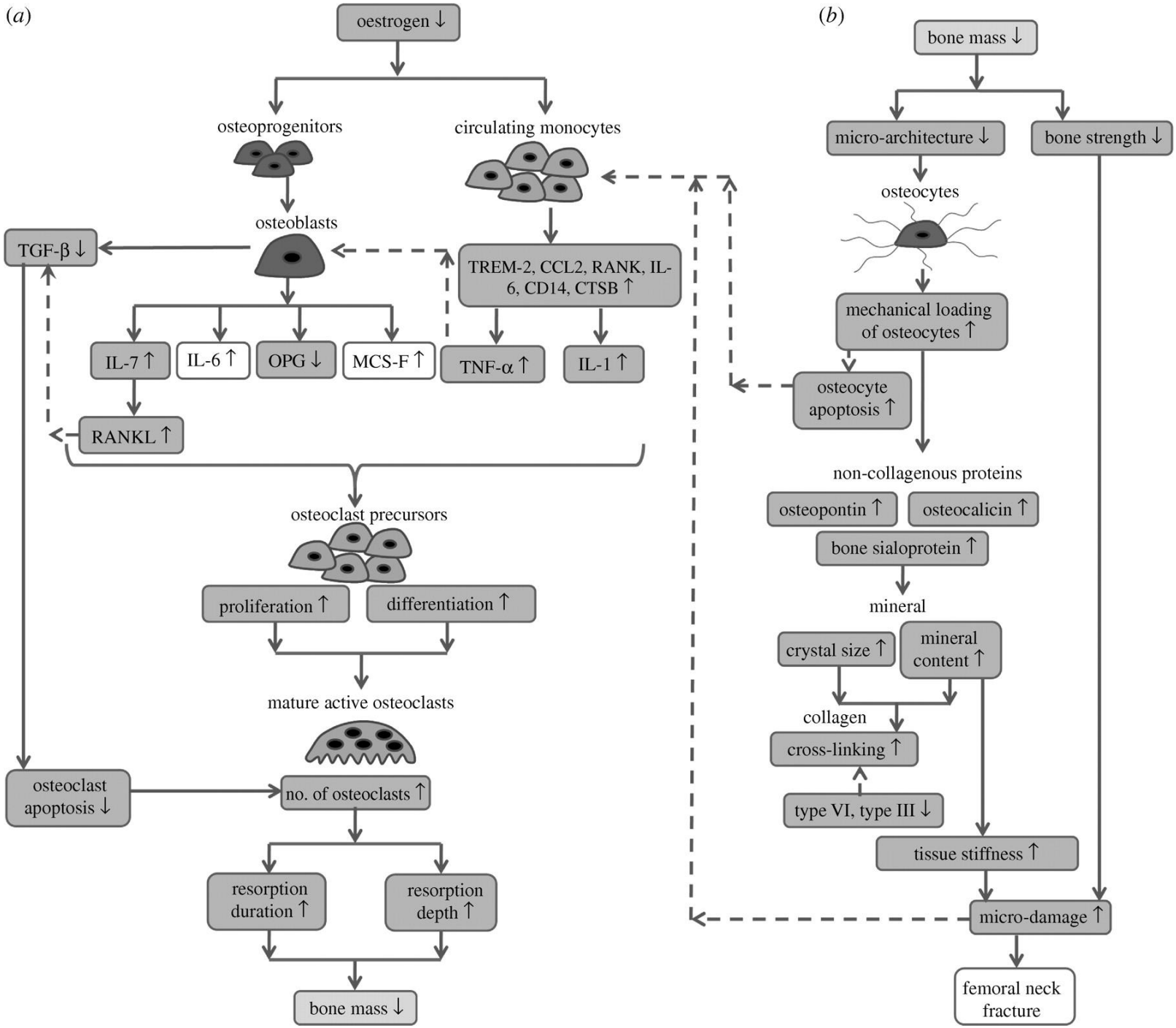
- carbonate content is increased,

- acid phosphate content is decreased

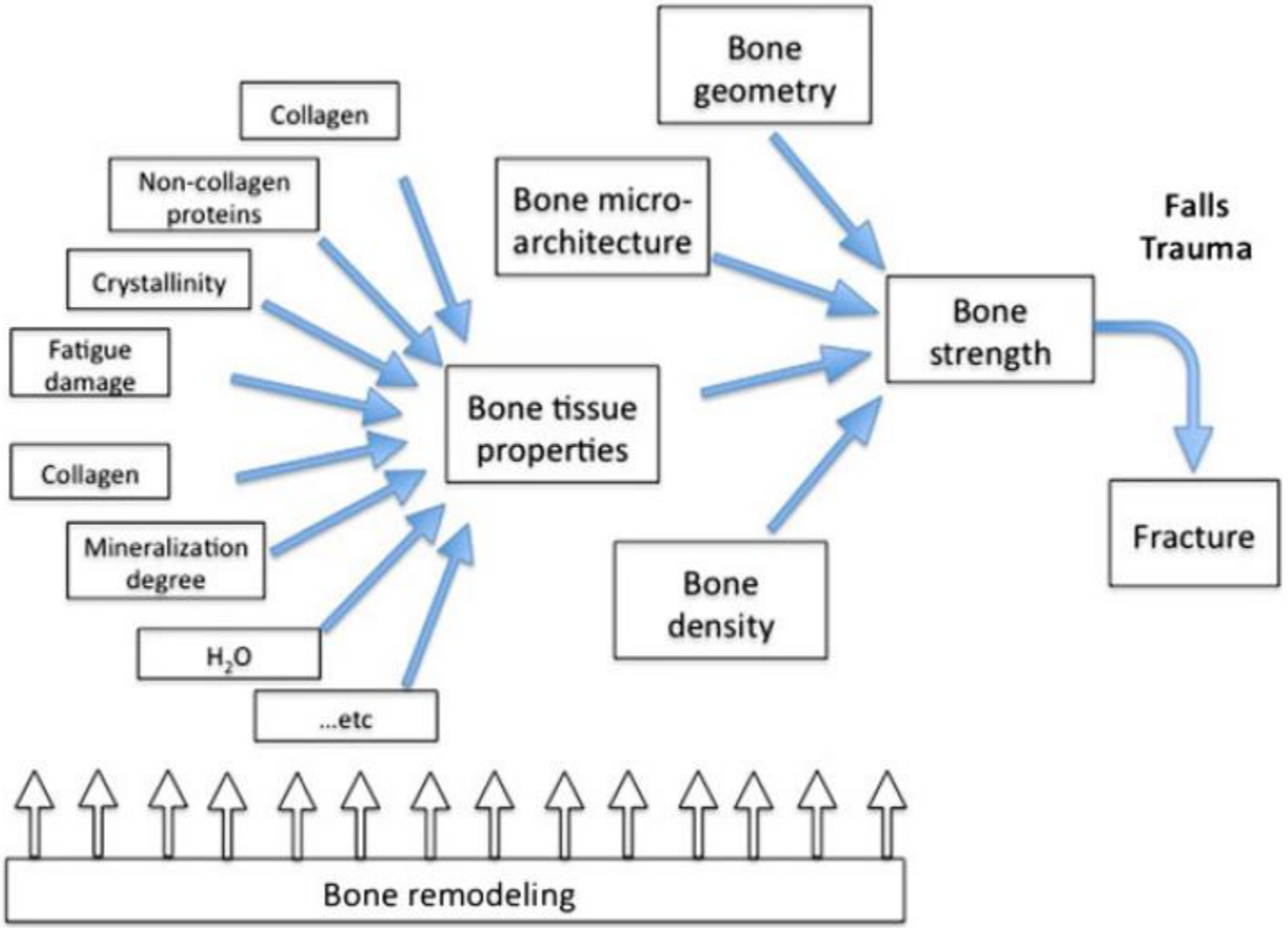


infrared imaging spectroscopy

sequence of events in the bone loss cascade


(a)
oestrogen ↓
osteoprogenitors
circulating monocytes
osteoblasts
TGF-β ↓
TREM-2, CCL2, RANK, IL-6, CD14, CTSB ↑
IL-7 ↑
IL-6 ↑
OPG ↓
MCS-F ↑
TNF-α ↑
IL-1 ↑
RANKL ↑
osteoclast precursors
proliferation ↑
differentiation ↑
mature active osteoclasts
osteoclast apoptosis ↓
no. of osteoclasts ↑
resorption duration ↑
resorption depth ↑
bone mass ↓
(b)
bone mass ↓
micro-architecture ↓
bone strength ↓
osteocytes
mechanical loading of osteocytes ↑
osteocyte apoptosis ↑
non-collagenous proteins
osteopontin ↑
osteocalicin ↑
bone sialoprotein ↑
mineral
crystal size ↑
mineral content ↑
collagen
cross-linking ↑
type VI, type III ↓
tissue stiffness ↑
micro-damage ↑
femoral neck fracture

Updated Factors affecting fractures

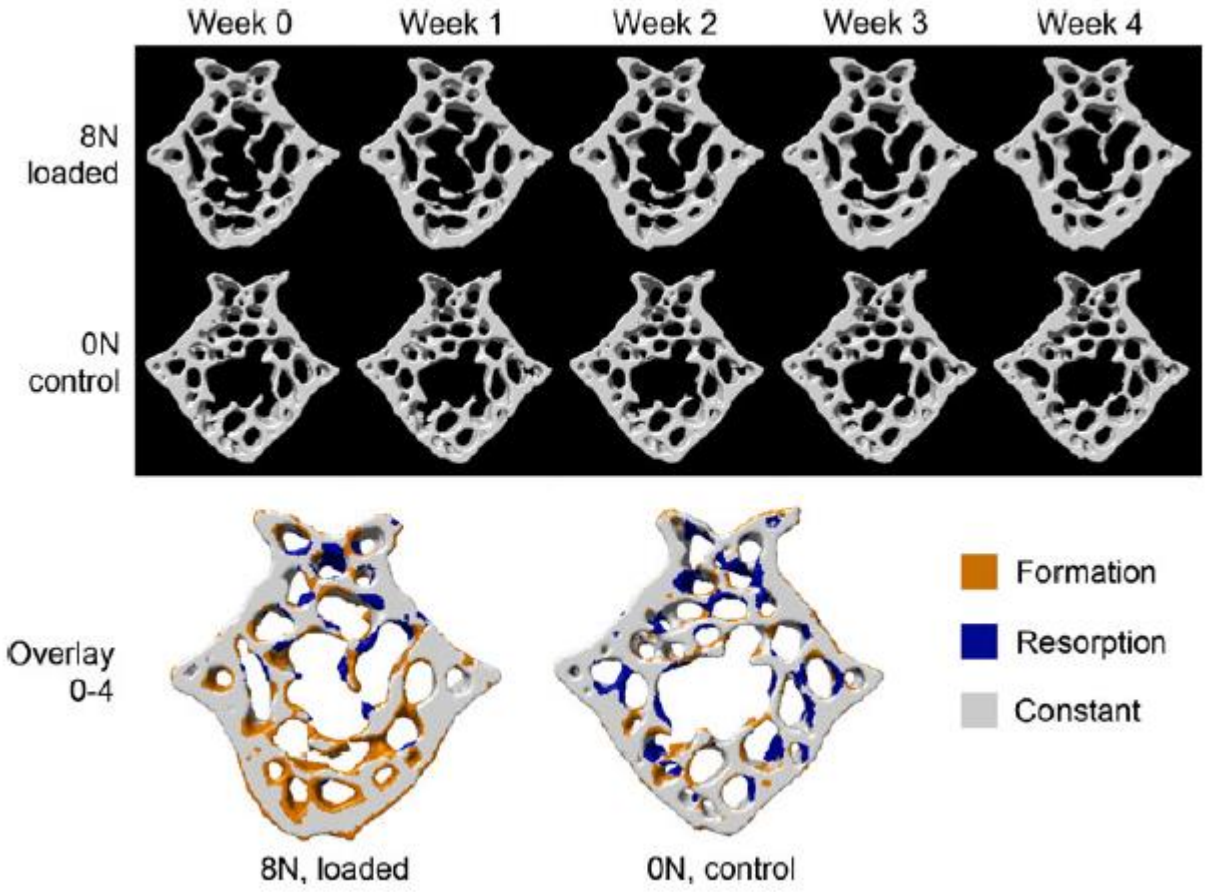


Future research and conclusions

Annals of Biomedical Engineering, Vol. 40, No. 11, November 2012 *(© 2012)* pp. 2475–2487
DOI: 10.1007/s10439-012-0594-4

Toward Mechanical Systems Biology in Bone

ANDREAS TRÜSSEL, RALPH MÜLLER, and DUNCAN WEBSTER



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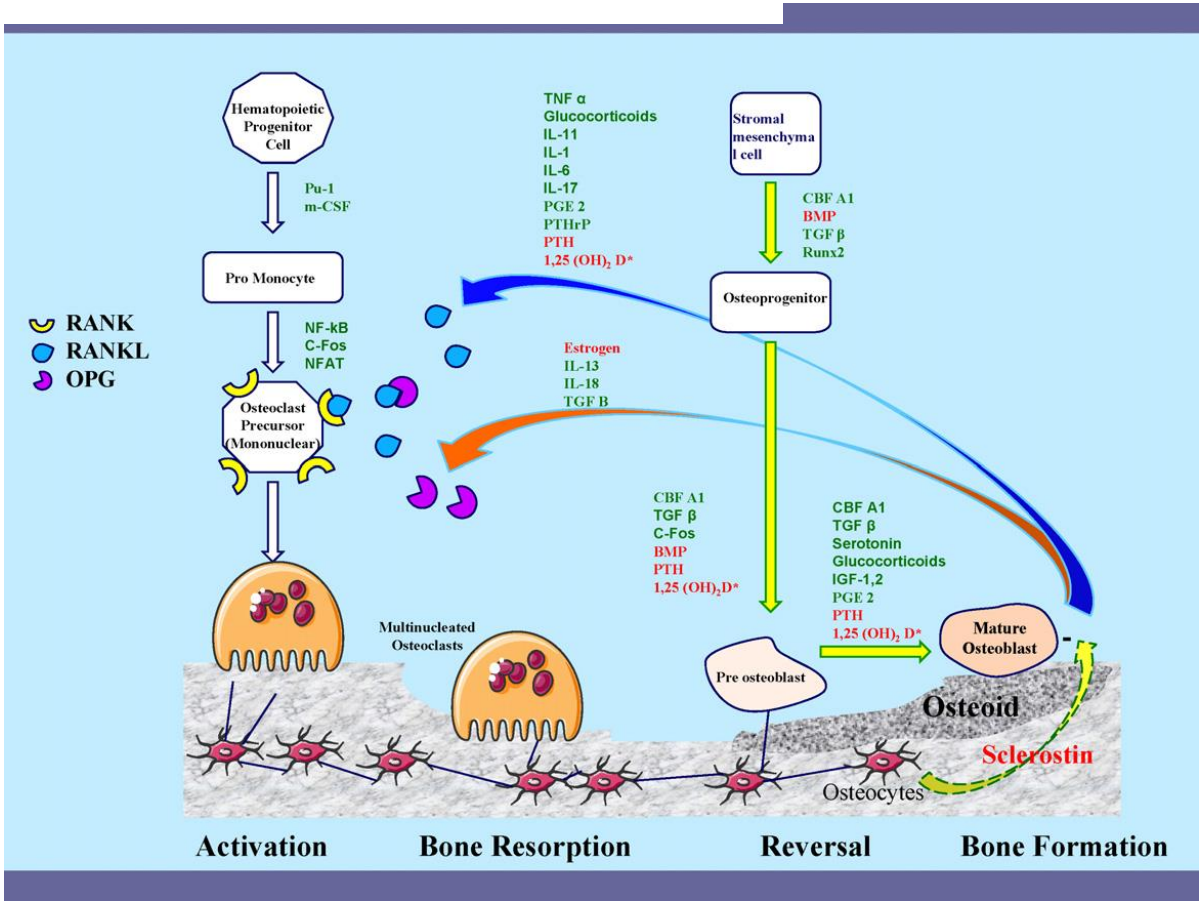
Review

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.

frontiers in
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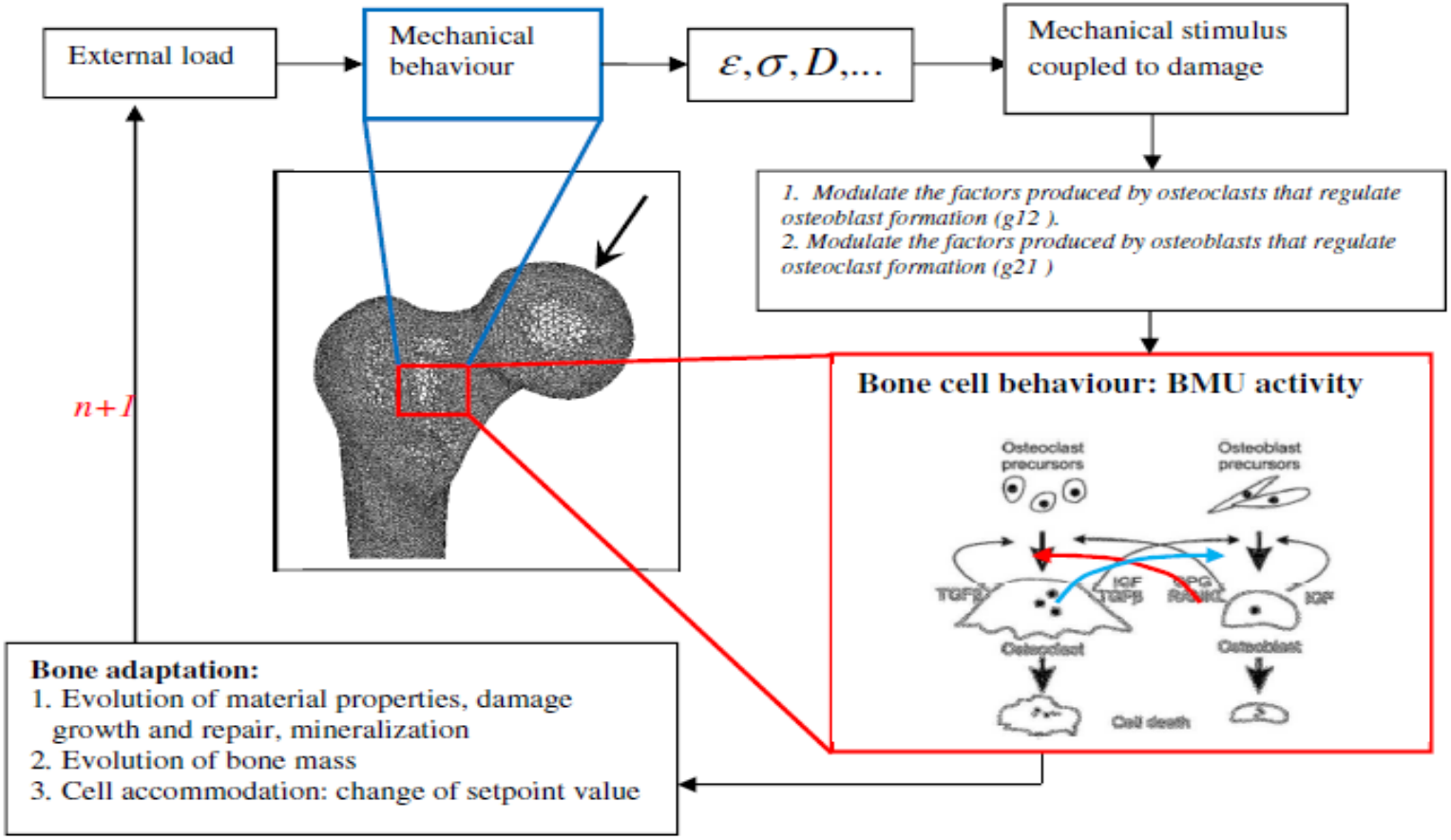
Connecting mechanics and bone cell activities in the bone remodeling process: an integrated finite element modeling

Ridha Hambli [1,2] *



Improving fixation methods in osteoporotic bones