Relationship Between Bone Morphometry (Trabecular And Cortical Bone) And Strength – Part 1

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IMVS

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SUB CRUCE LUMEN

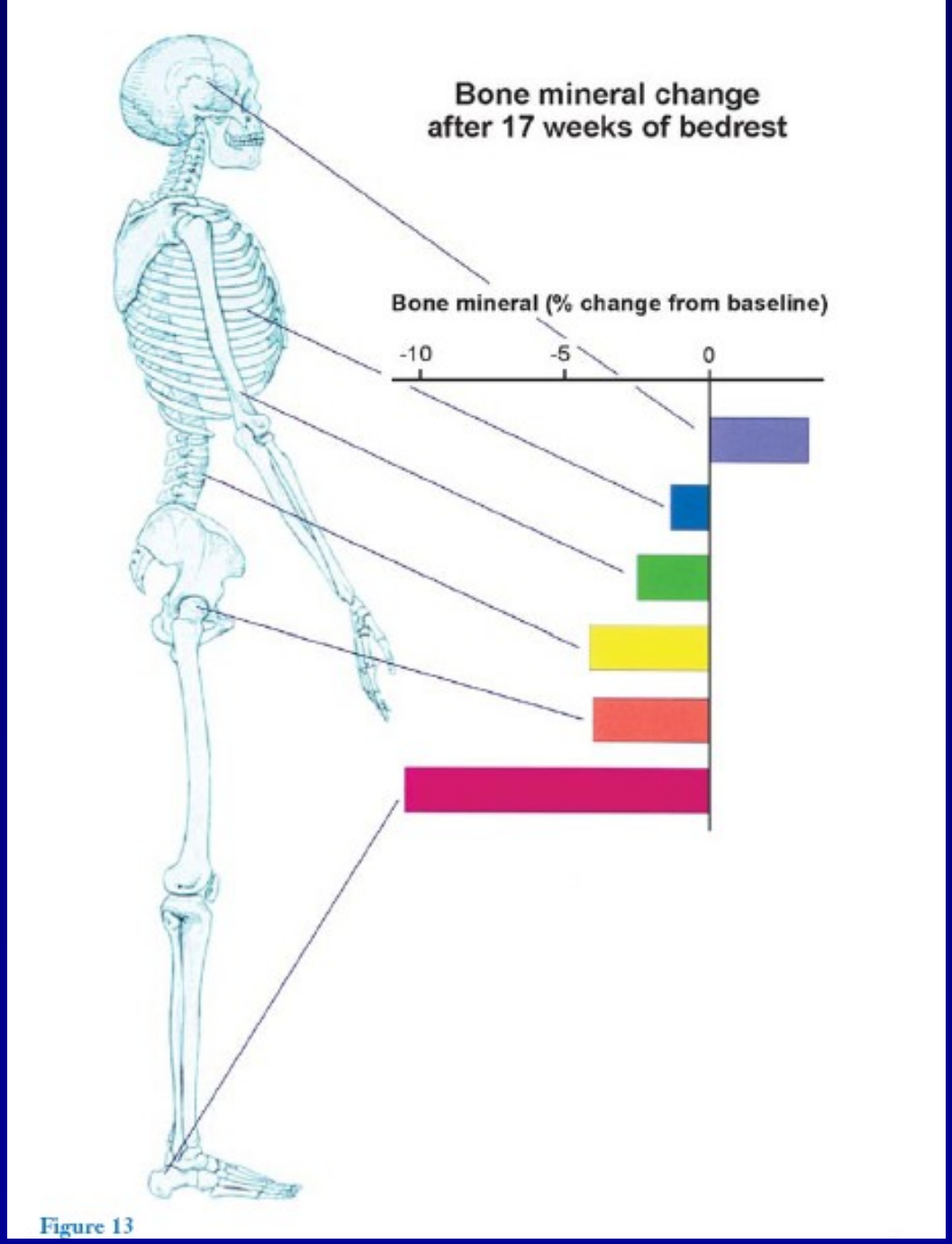

Figure 13

Robling et al. Ann Rev Biomed Eng 8:455-98, 2006

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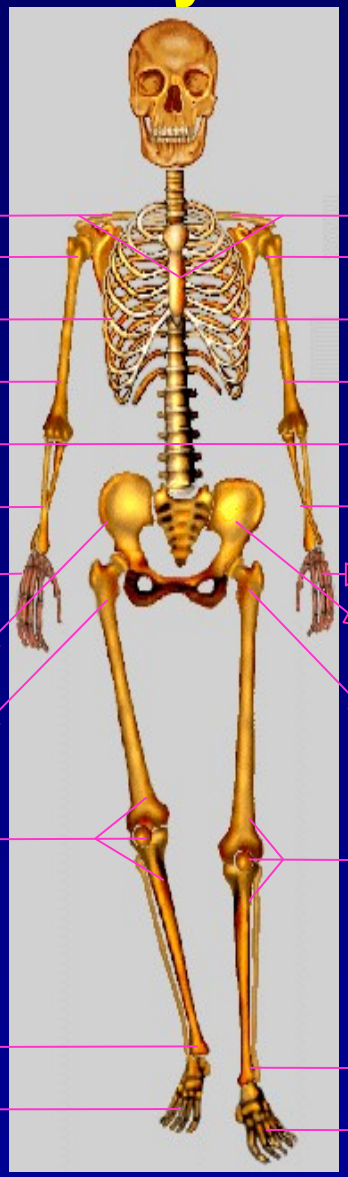
Osteoporotic fractures by site in Dubbo: 1989-2000

Men, n = 306		Women, n = 809
7	Clavicle/Sternum	13
16	Proximal Humerus	58
52	Ribs	52
1	Distal Humerus	13
78	Spine	201
25	Forearm/Wrist	156
7	Hand	22
25	Pelvis	25
54	Hip	175
11	Distal Femur, Knee Proximal Tibia	41
20	Ankle	40
10	Foot	33



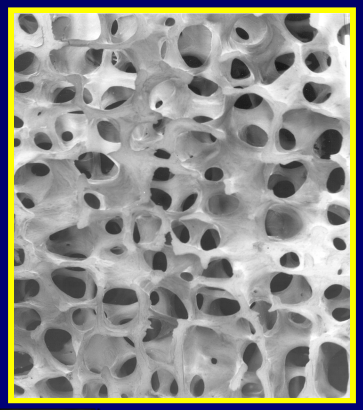
Chang et al, 2004
JBMR 19:532-536

Bone Organisation: From the cell to the whole bone

Molecular

Cellular

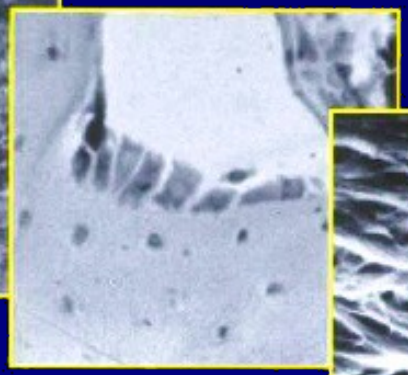
Micro architecture



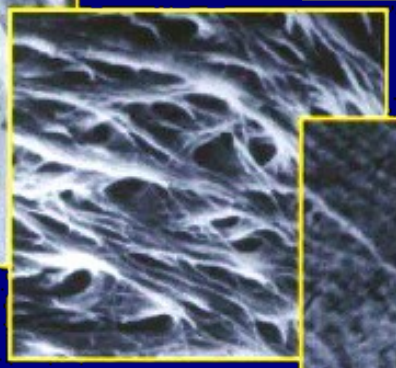
Macro architecture

Fibrils

Cells

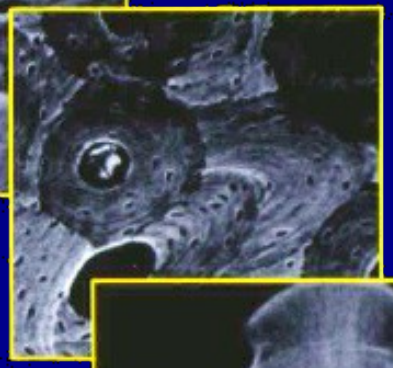


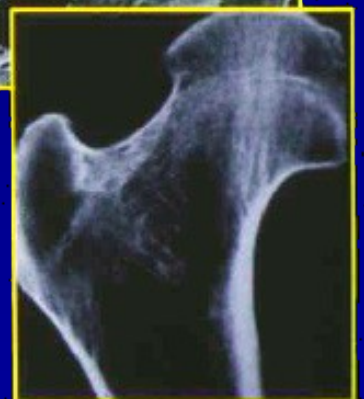
Matrix



Lamellae

Tissue





Whole Bone

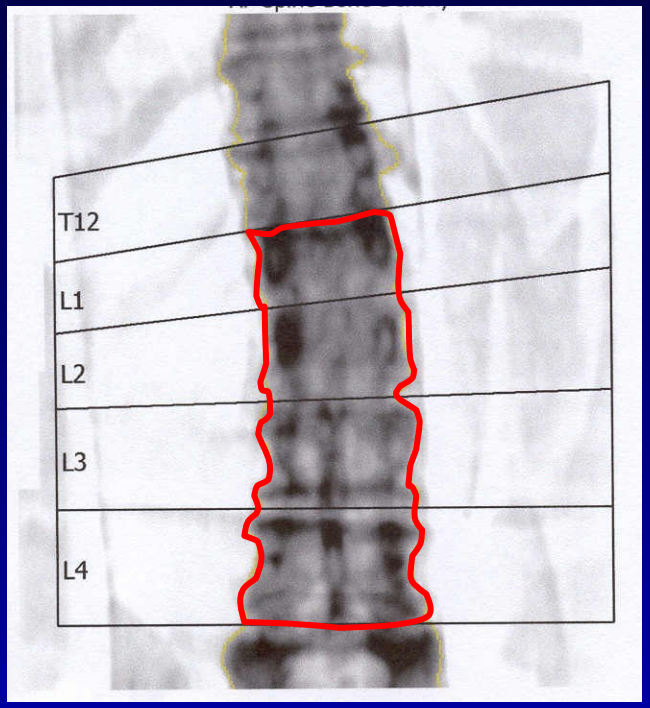
Our objective

To further elucidate an integrated understanding of the hierarchical structures in bone and ultimately contribute to the well being of our ageing community.

Adapted from Jepsen. 1994

Dual Energy X-ray Absorptiometry

Dual Energy X-ray Absorptiometry



Bone Mineral 'Density' (BMD):

BMD = Bone Mineral Content (BMC) / Area

BMC: The amount of calcium in the two-dimensional region of interest

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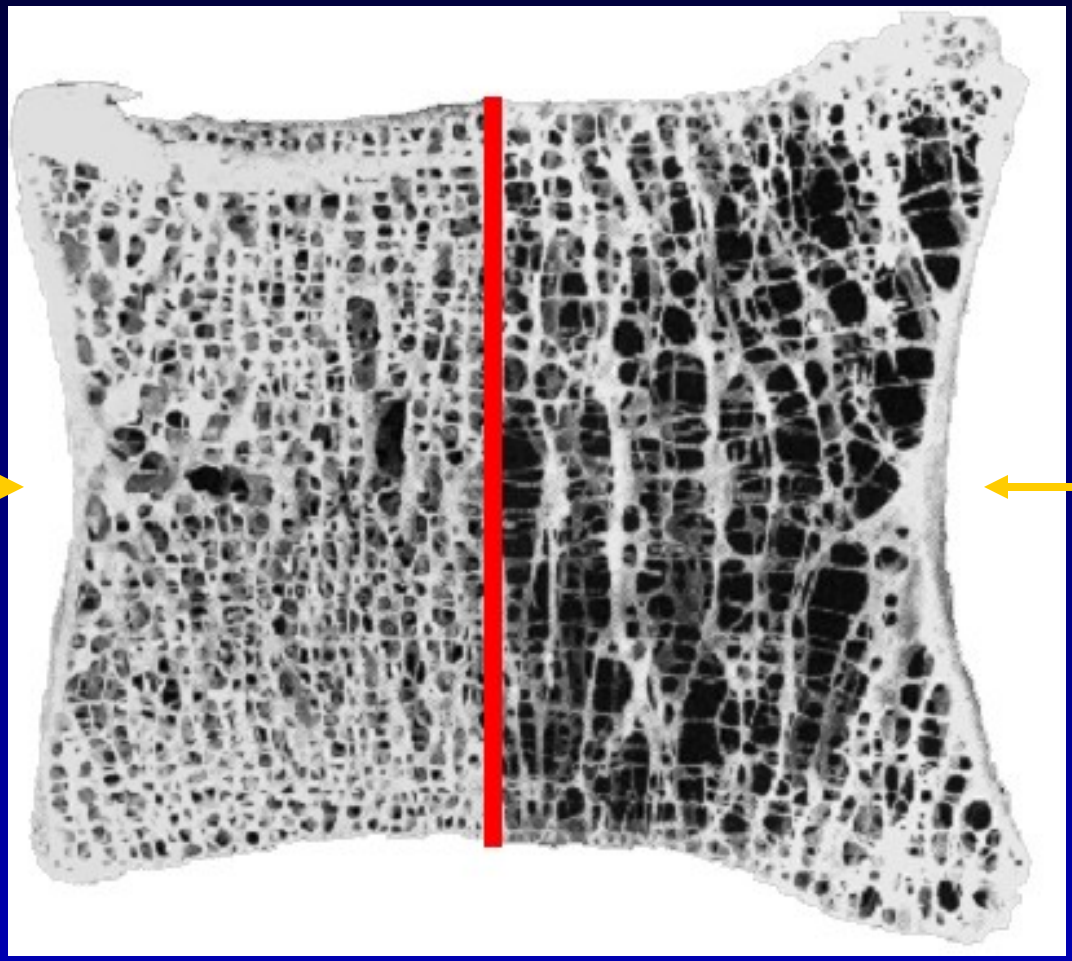
Motivation



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Dual Energy X-ray Absorptiometry

- BMD accounts for 30 - 80% of mechanical characteristics of bone
- Not a good predictor of ‘bone quality’
- Measures areal density not true volumetric density
- Sensitive to size
- Only accounts for one aspect of ‘bone quality’

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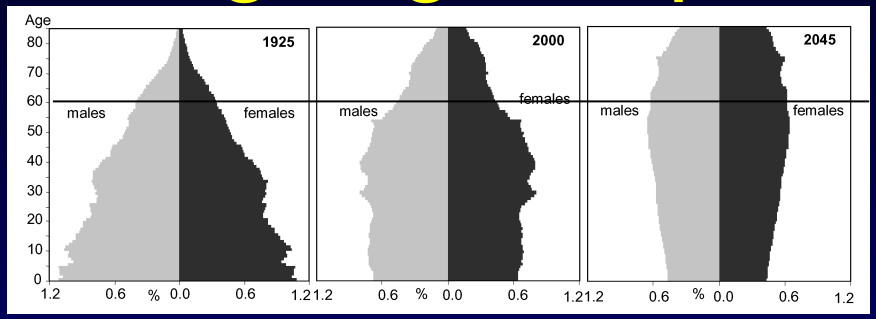
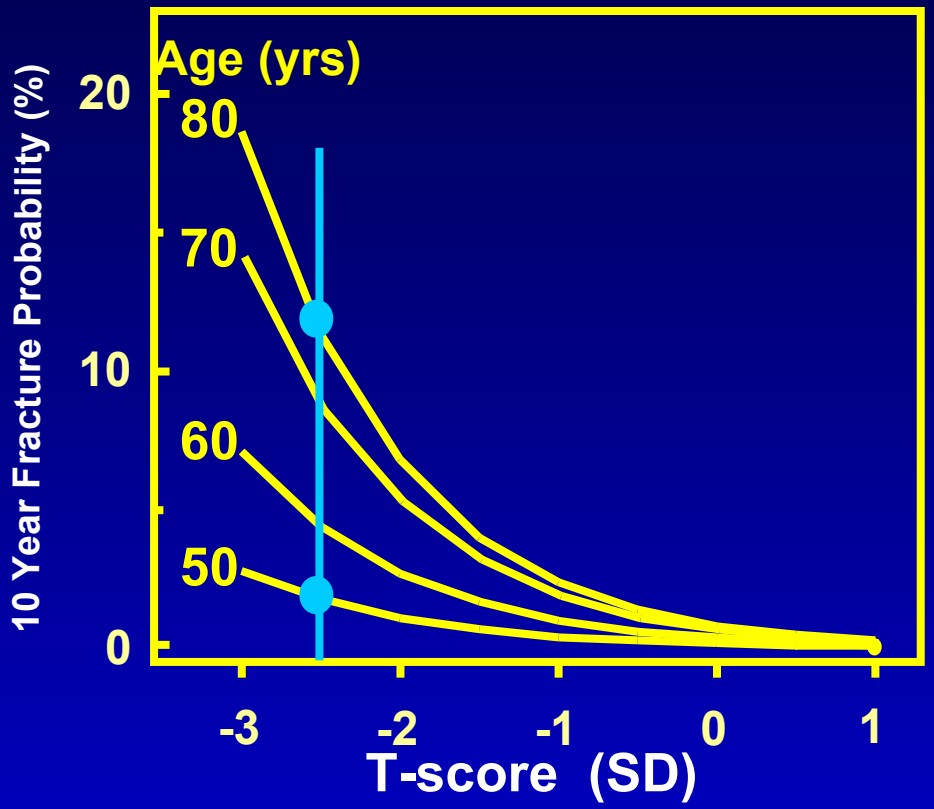
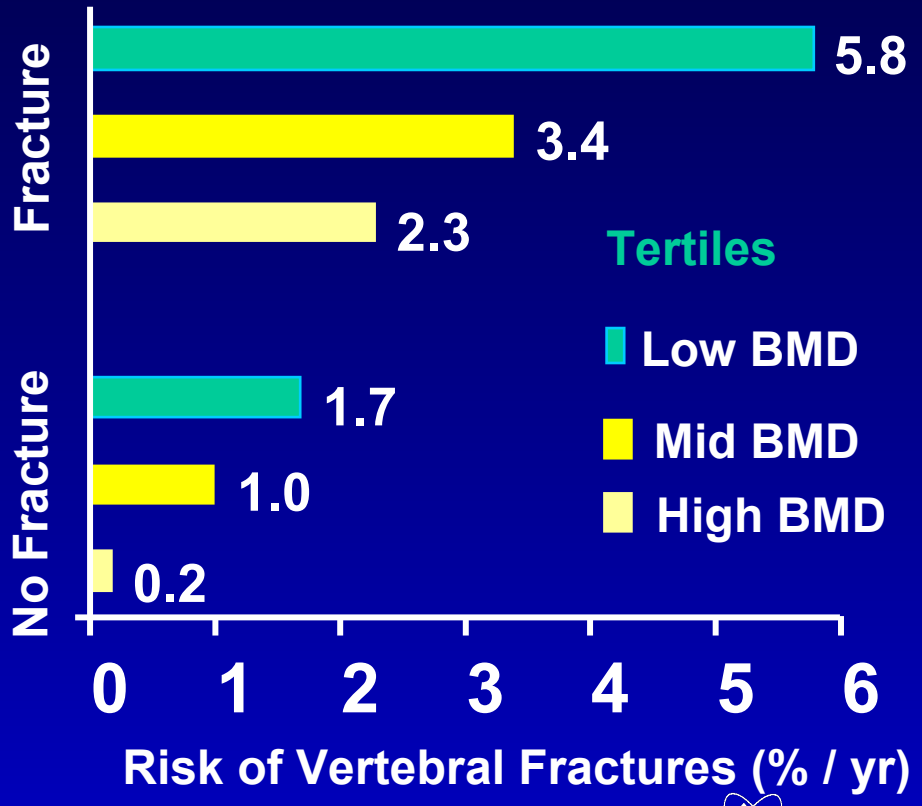
Fracture risk – Ageing and previous fracture





Kanis et al. *Osteoporos Int* 2002; 13: 527-636



Ross PD et al. *Osteoporos Int* 1993; 3: 120-26

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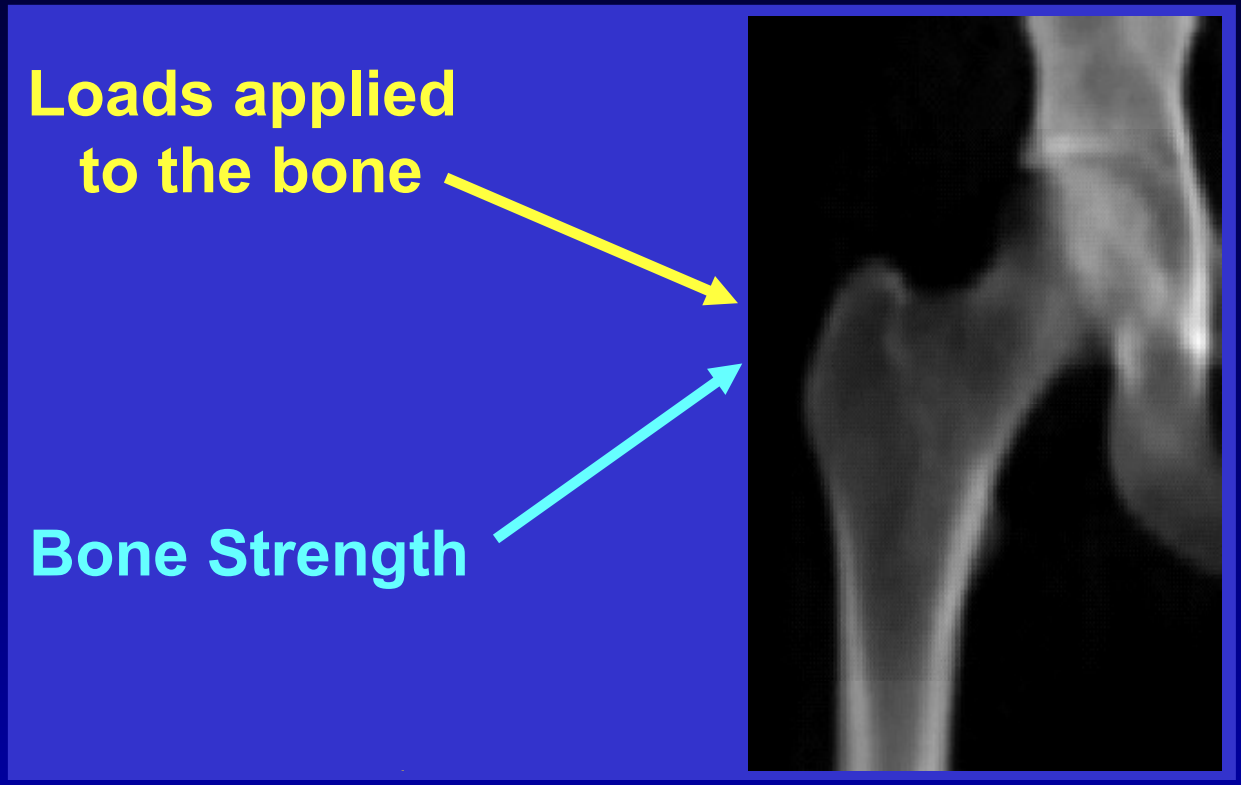
Why do bones break?



$$\text{If } \frac{\text{Applied Load}}{\text{Bone Strength}} > 1 \quad \text{Fracture will then occur}$$

Bouxsein. 2001

B[illegible] FRACTURE [illegible]H

STRUCTURAL PROPERTIES

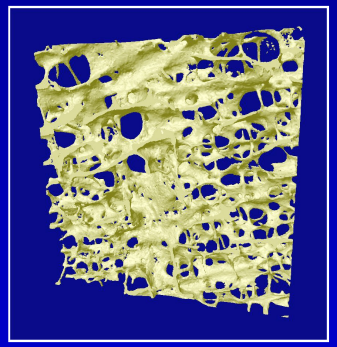
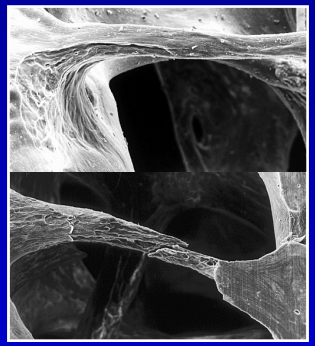
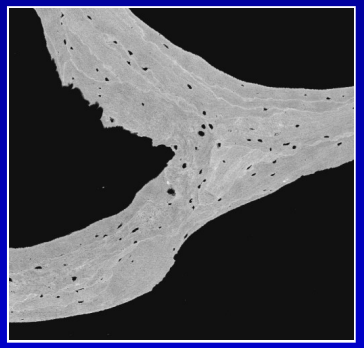
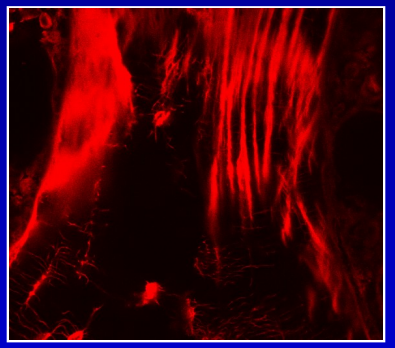
- bone mass
- geometry
- microarchitecture

MATERIAL PROPERTIES

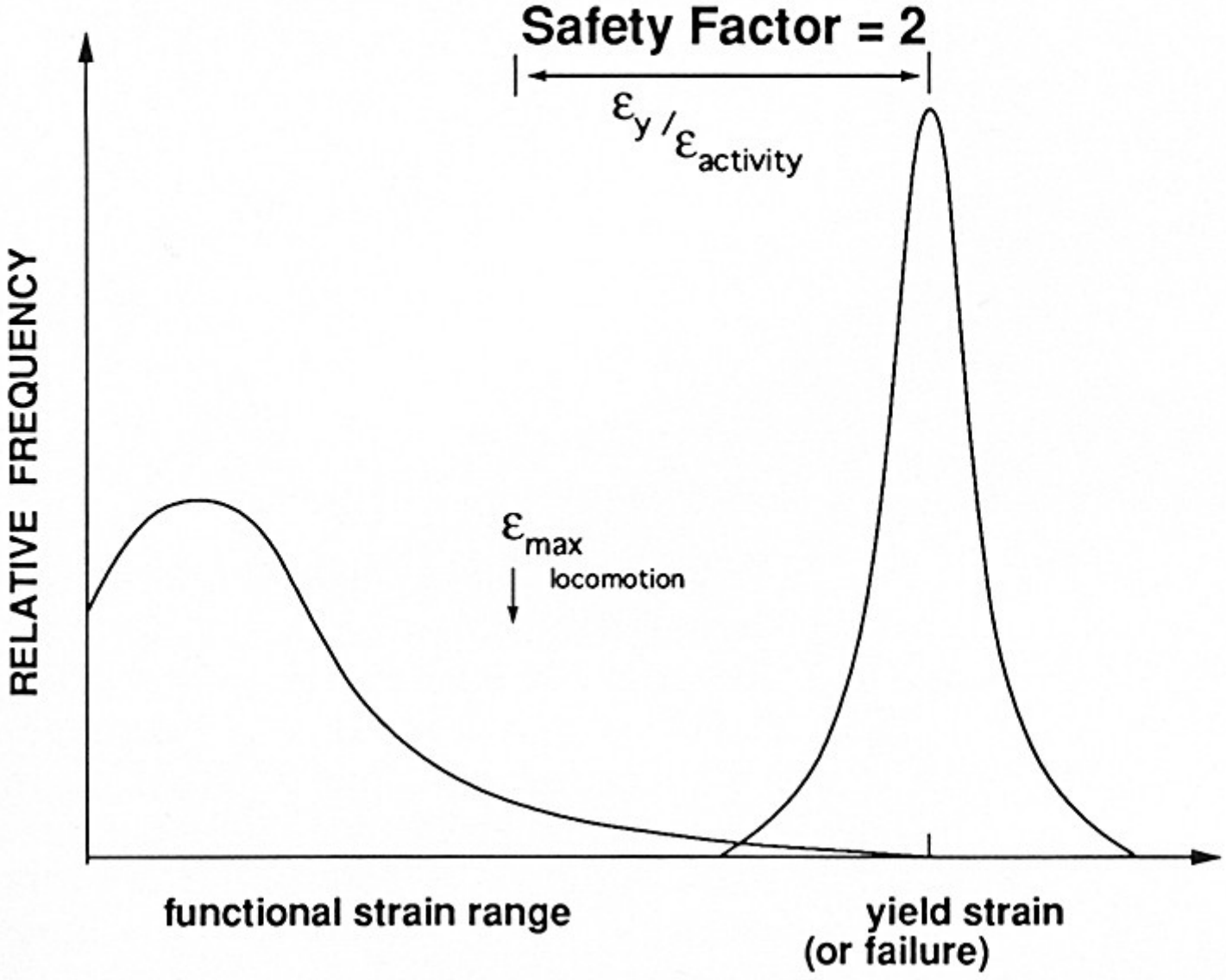
- mineralisation
- collagen
- microdamage

BONE REMODELLING/TURNOVER

JS Kuliwaba
Bone & Jt Lab, IMVS

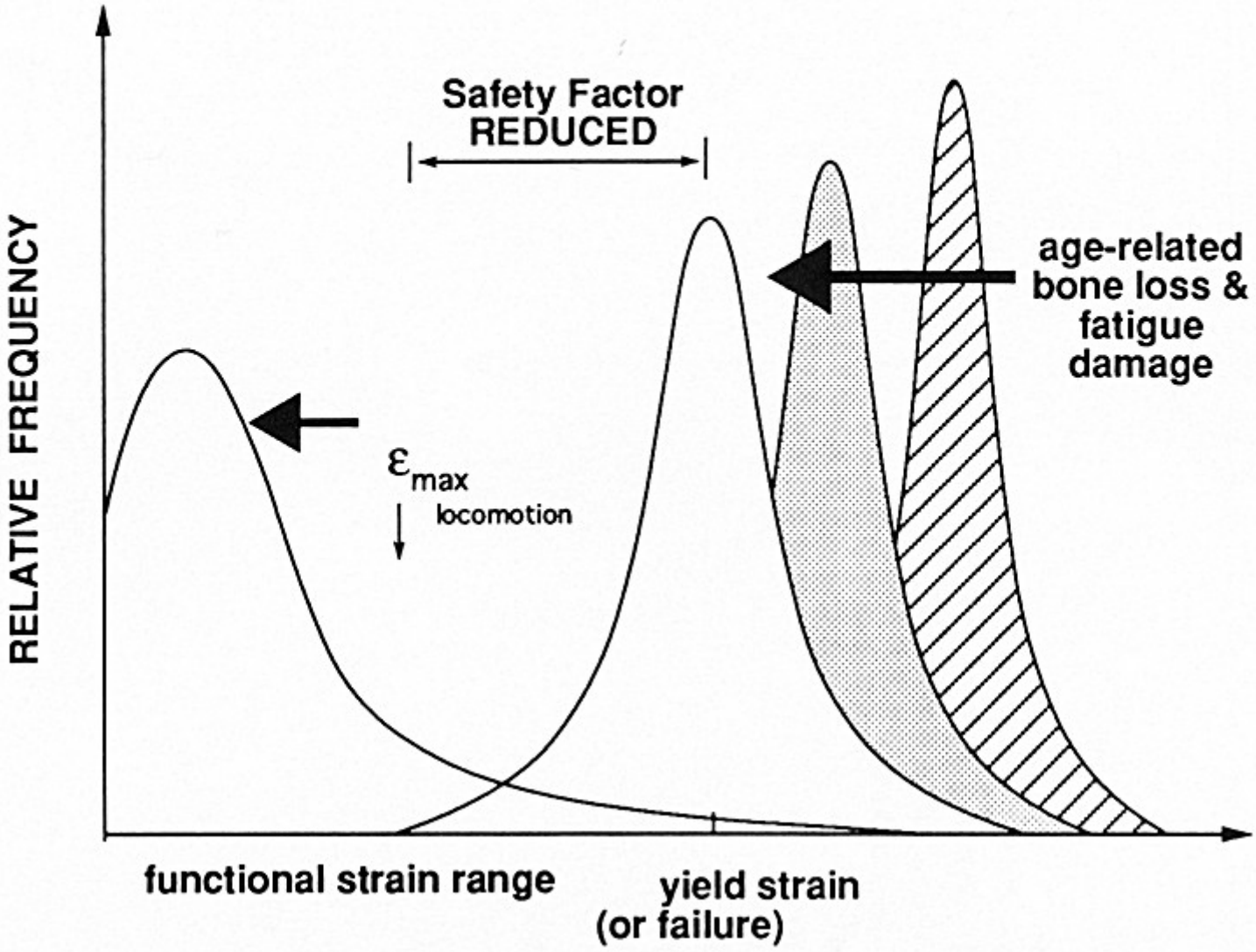





A. YOUNG ADULT



Biewener. Calcif Tissue Int 53S:S68-S74;1993

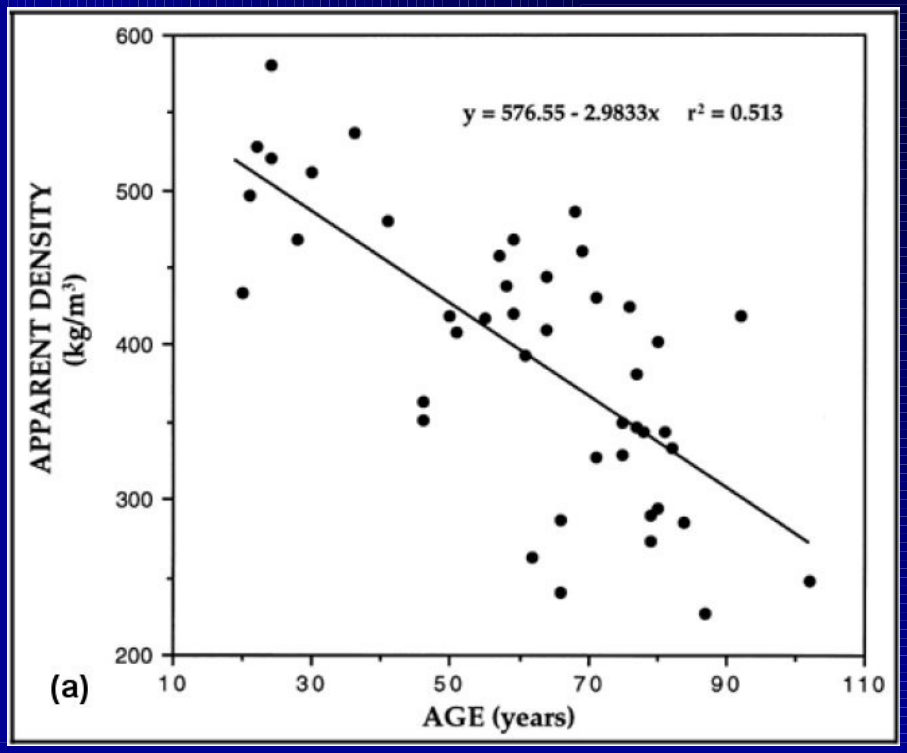
B. AGING

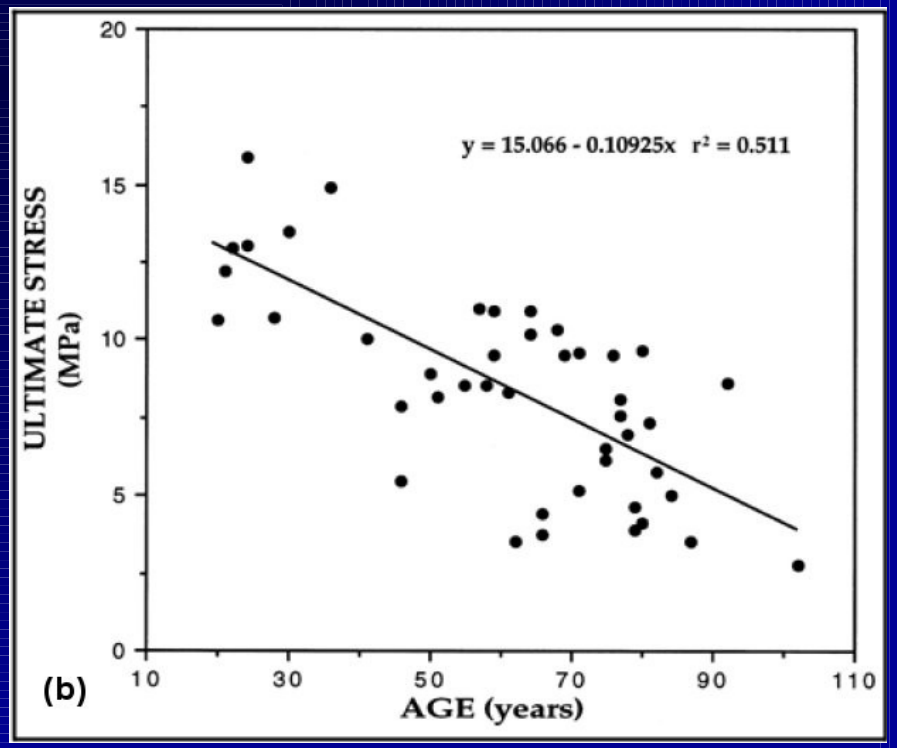


Biewener. Calcif Tissue Int 53S:S68-S74;1993

Consequences of aging on cancellous bone

- ✓ For normal bone, age-dependencies of the mechanical properties.
- ✓ Consequences of aging: <u>decrease</u> of cancellous <u>bone density</u> and <u>stress to failure</u>





Curry

Intermediary organisation of the skeleton

- Growth
- Modelling
- Remodelling

To characterise the spatial structure of cancellous bone as it ‘emerges’ from the growth plate

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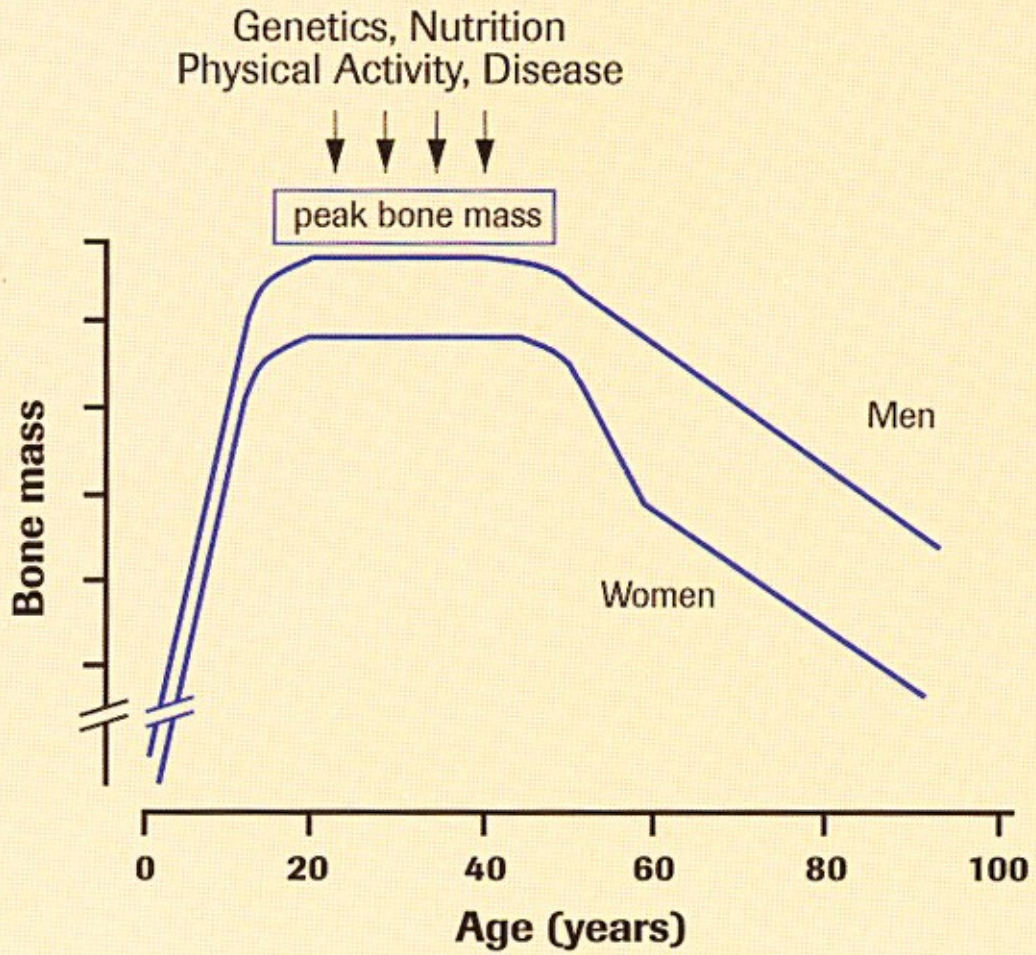
Figure: Bone Mass in Relation to Age and Gender



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The skeleton

- “a record of past events and an oracle of future behaviour”
- “studying the skeleton by measuring the bone mineral density does not relate to what is actually going on inside the skeleton”

Johnson 1964, Brown and Haglund 1995

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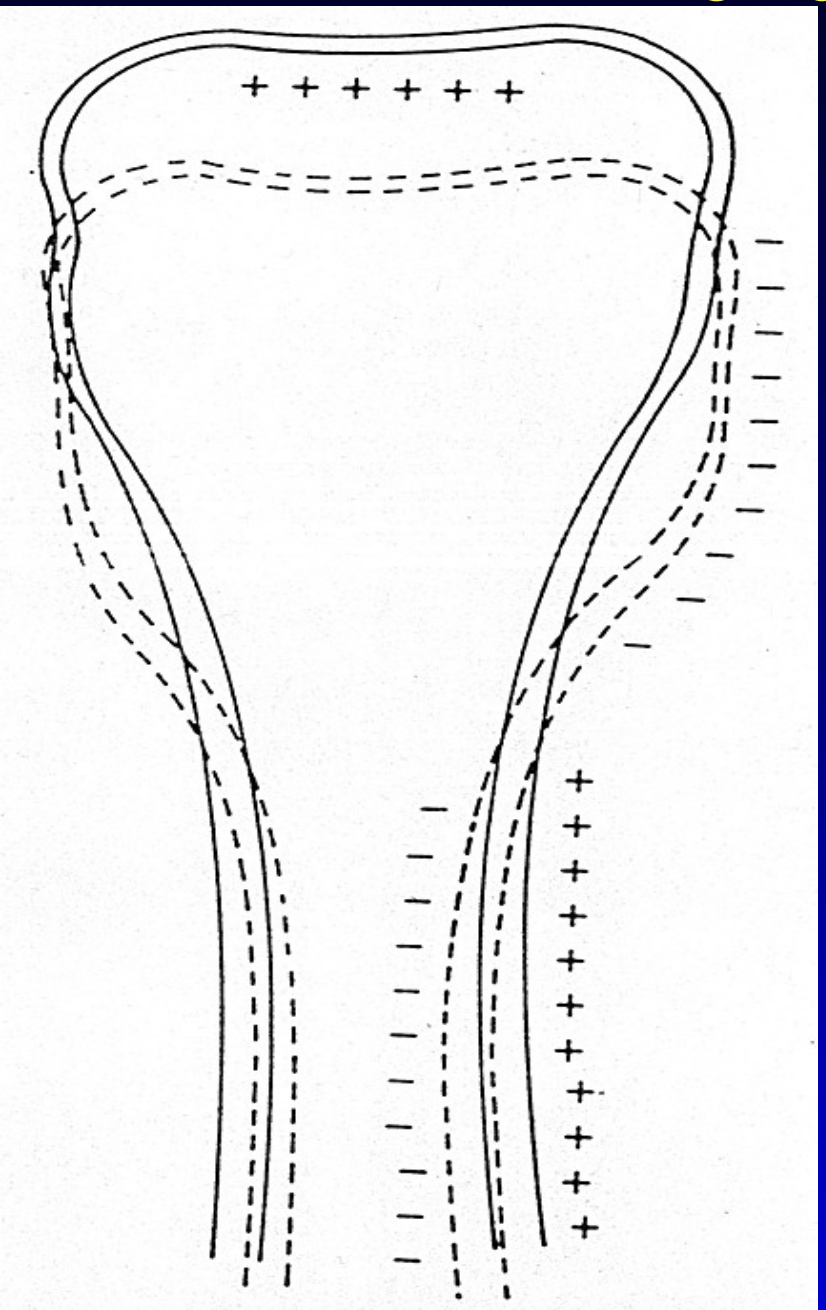
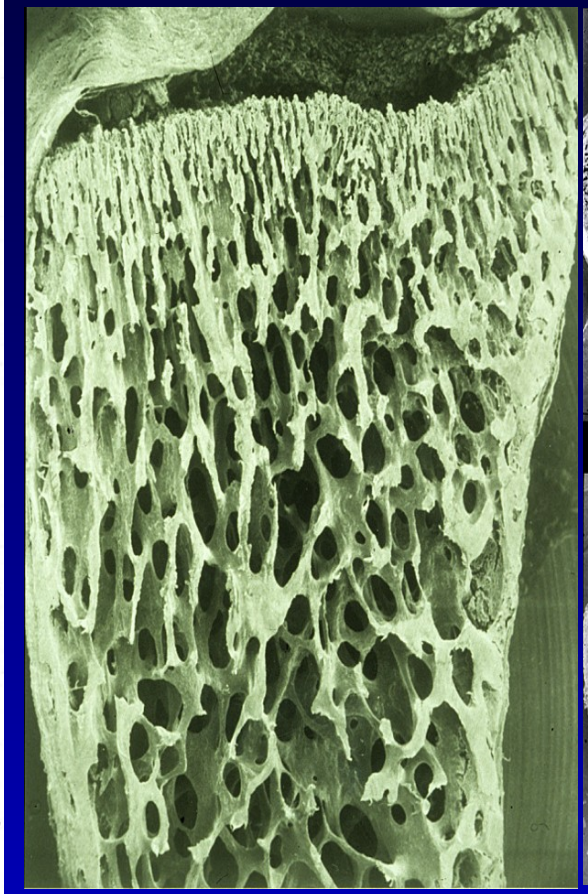
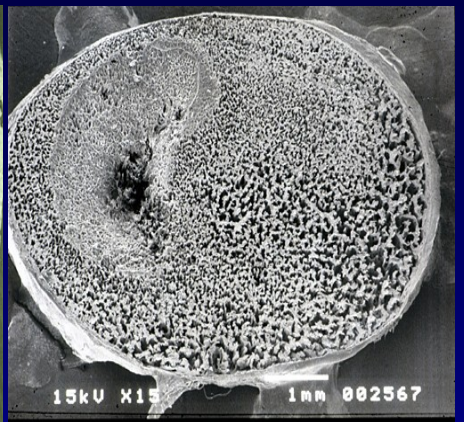
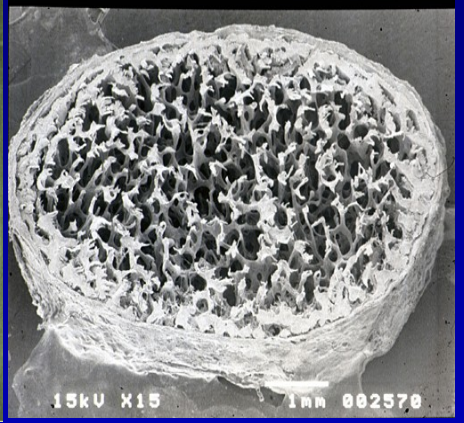
Bone modelling









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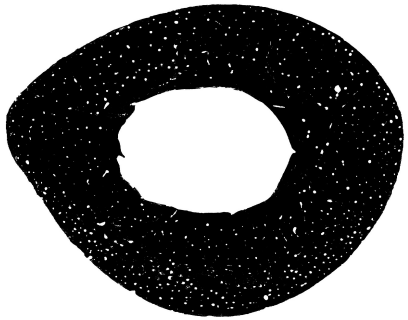
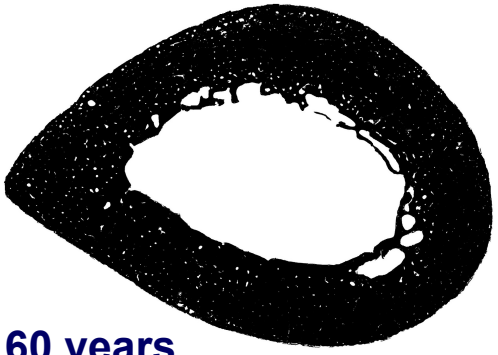
The Ageing Wrist

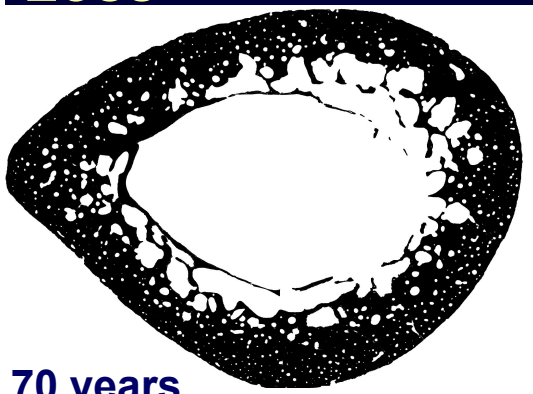
Endosteal Intracortical Bone Loss



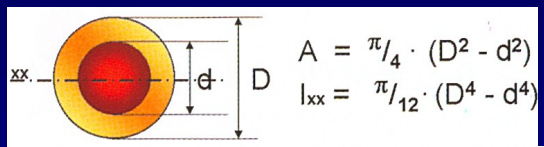
50 years

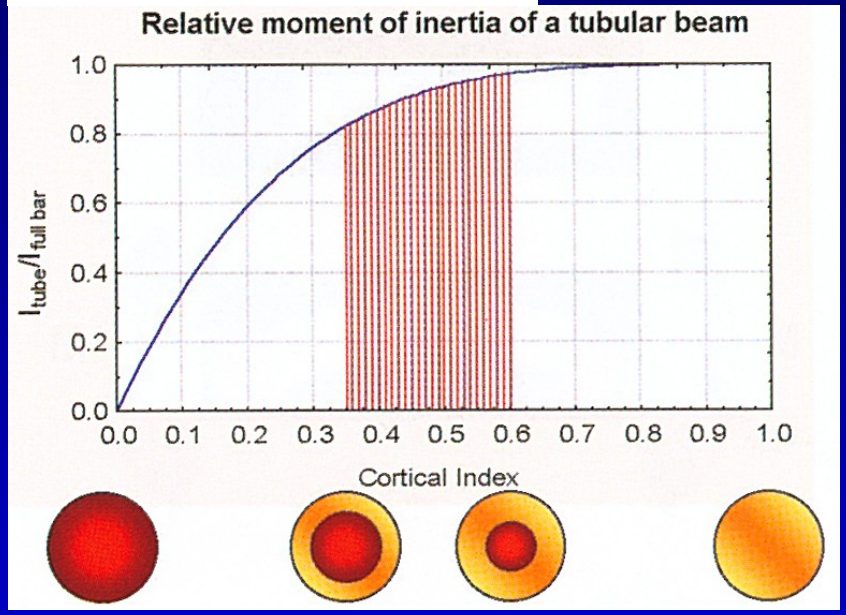


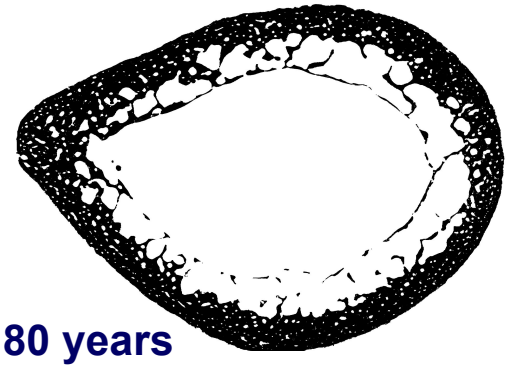
60 years



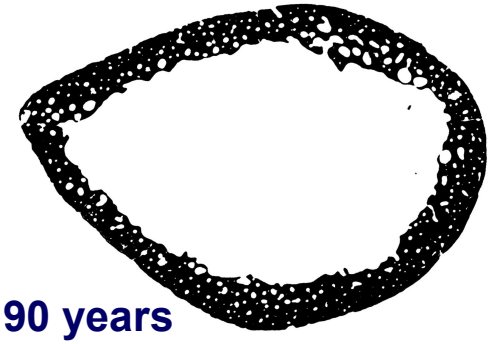
70 years







80 years



90 years

Provided by Jepsen 2005

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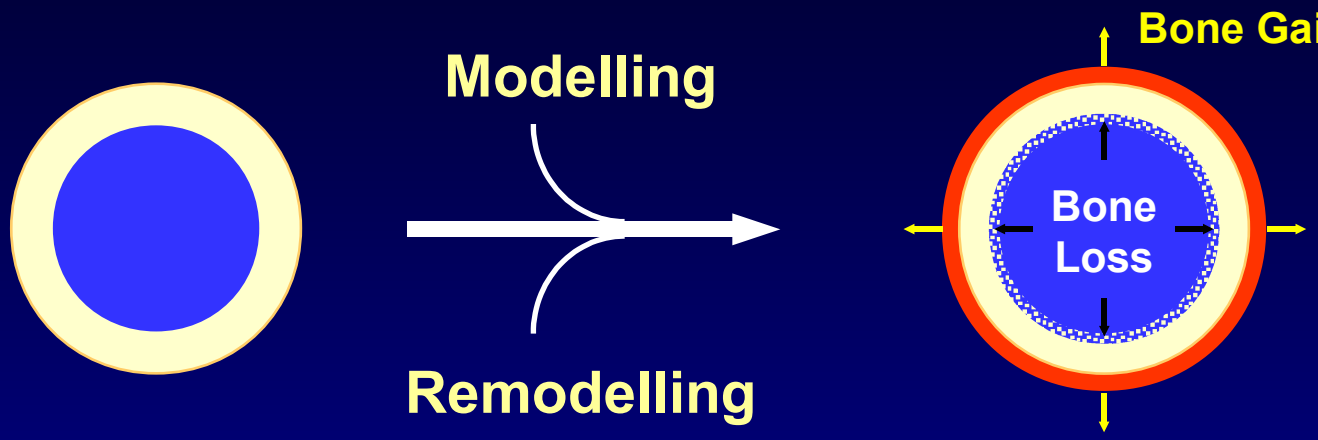
Maintain bone strength



Smith and Walker, Science 1964

35% increase in marrow width → 15% decrease in strength

35% increase in marrow width + 3% increase periosteal width → Maintain Strength

Provided by Jepsen 2005

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Modelling gone wrong

Metaphyseal modelling in children treated with bisphosphonates

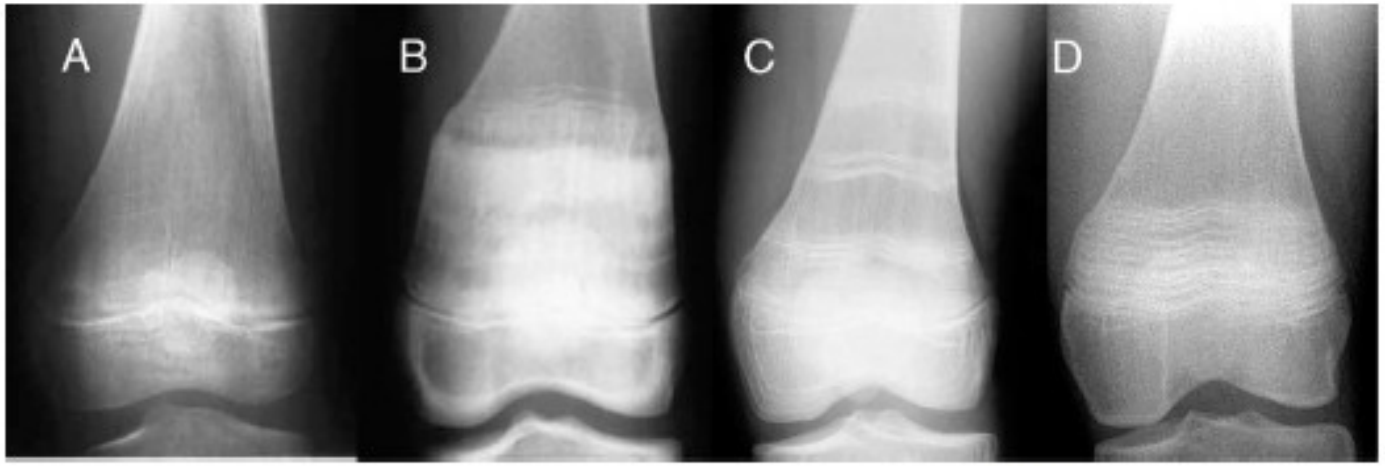

Fig. 3. Representative radiographs from specific patient cases. (A) Patient from report of Whyte et al. [10] before pamidronate treatment. The *Z* score for metaphyseal index is 2.5. (B) Patient from report of Whyte et al. [10] post-pamidronate therapy. The *Z* score for metaphyseal index is 9.0. (C) Patient who received intermittent pamidronate therapy totaling 16.5 mg/kg. The *Z* score for metaphyseal index is 0.2. (D) Patient who received regular pamidronate therapy totaling 12.6 mg/kg. The metaphyseal index *Z* score is 0.3.

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Remodelling

- Remodelling is the localized removal of bone and its replacement with newly formed bone.
- This process requires interactions of osteoclasts (bone resorption cells) and osteoblasts (bone formation cells)
- The roles of remodelling include
    - The repair of microdamage and maintenance of skeletal strength

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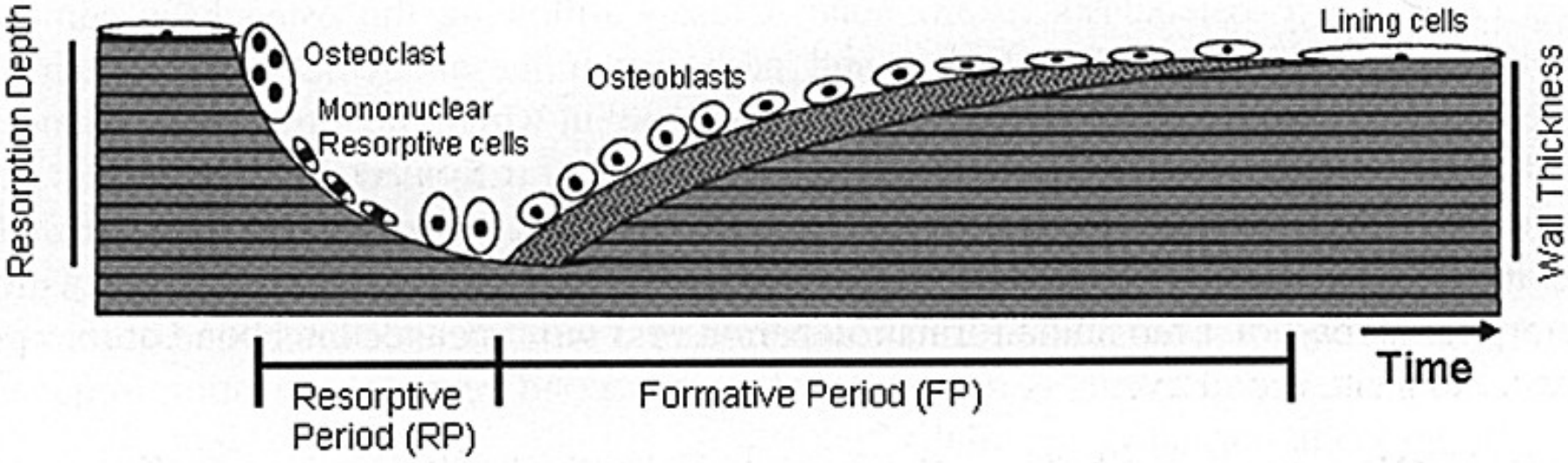
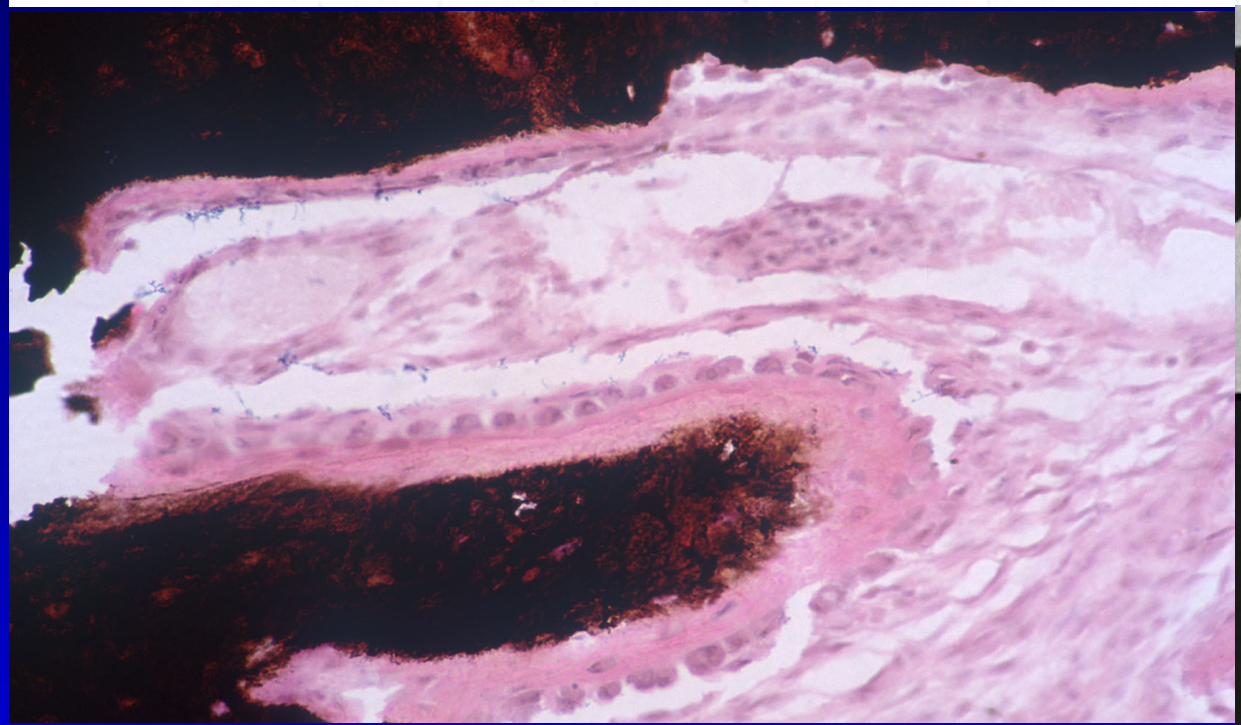
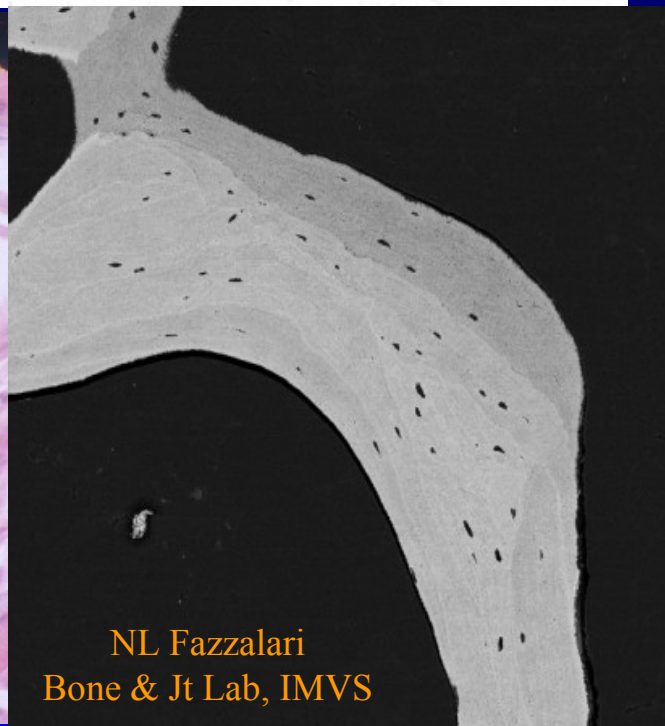
Cancellous Bone Remodeling Sequence







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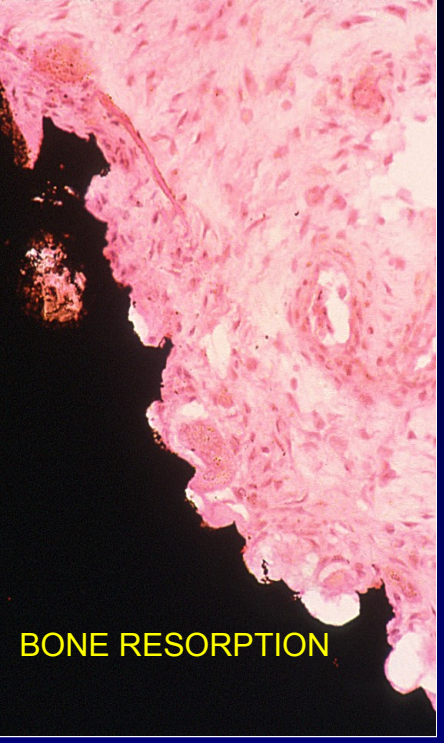
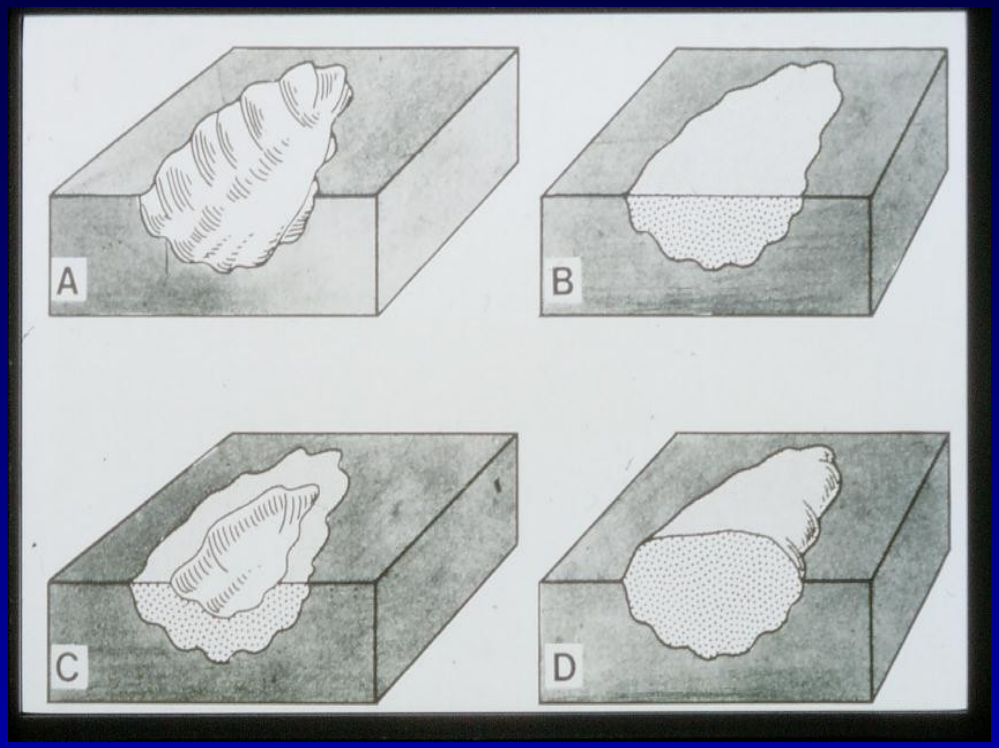
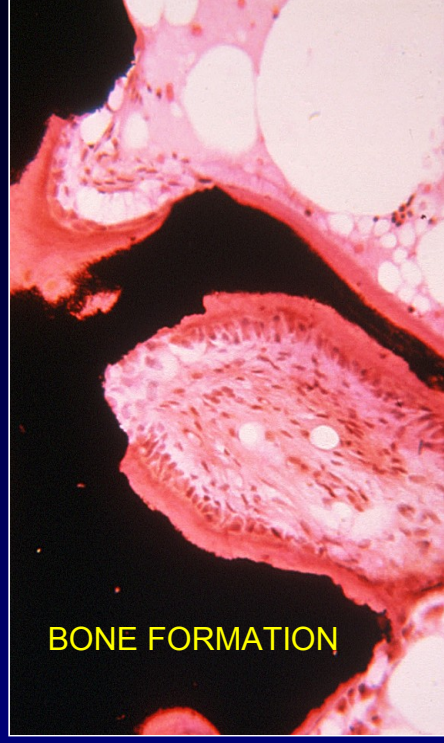
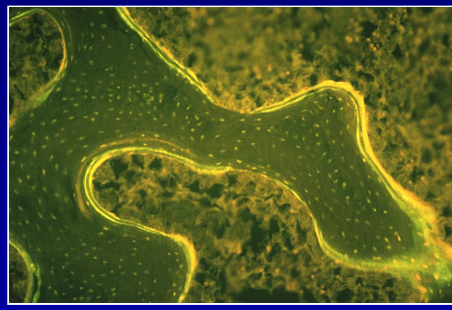
Bone remodelling:
bone cell activity









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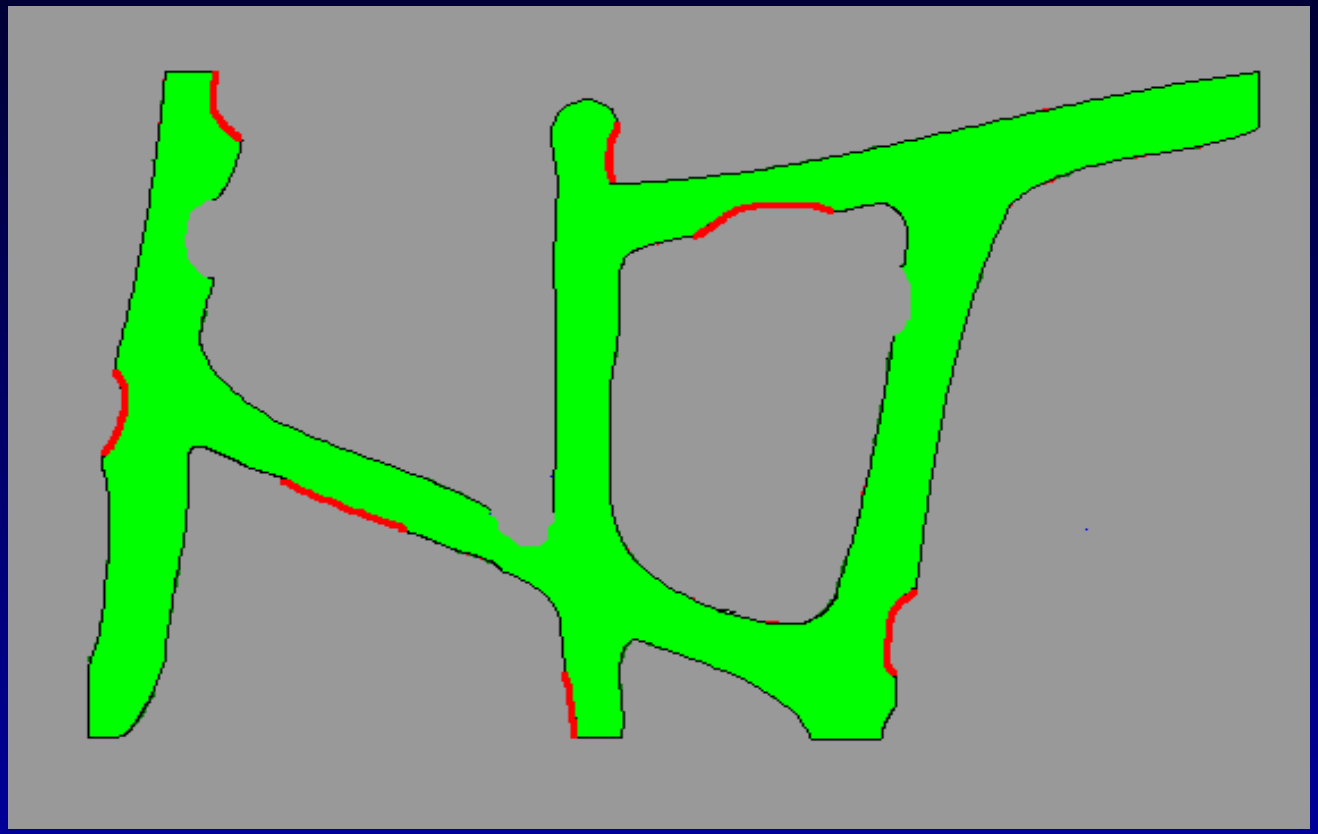
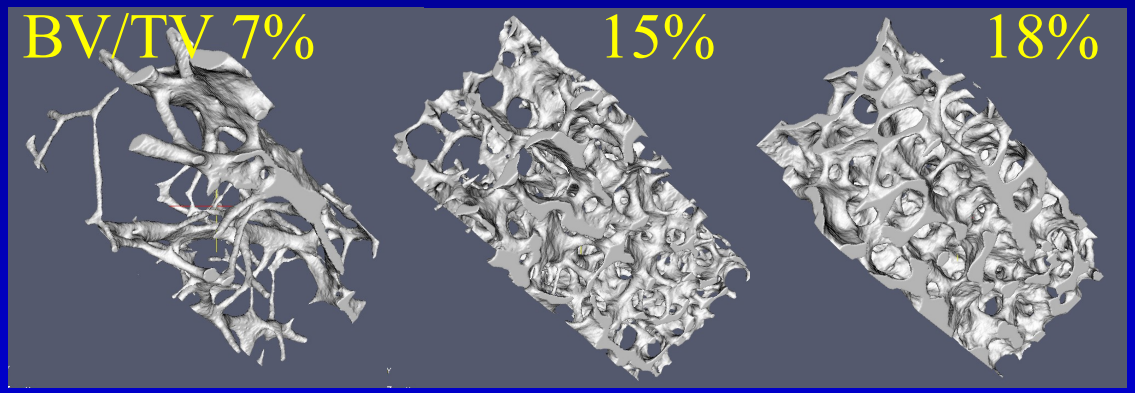
Dynamics of the BMU

Remodelling





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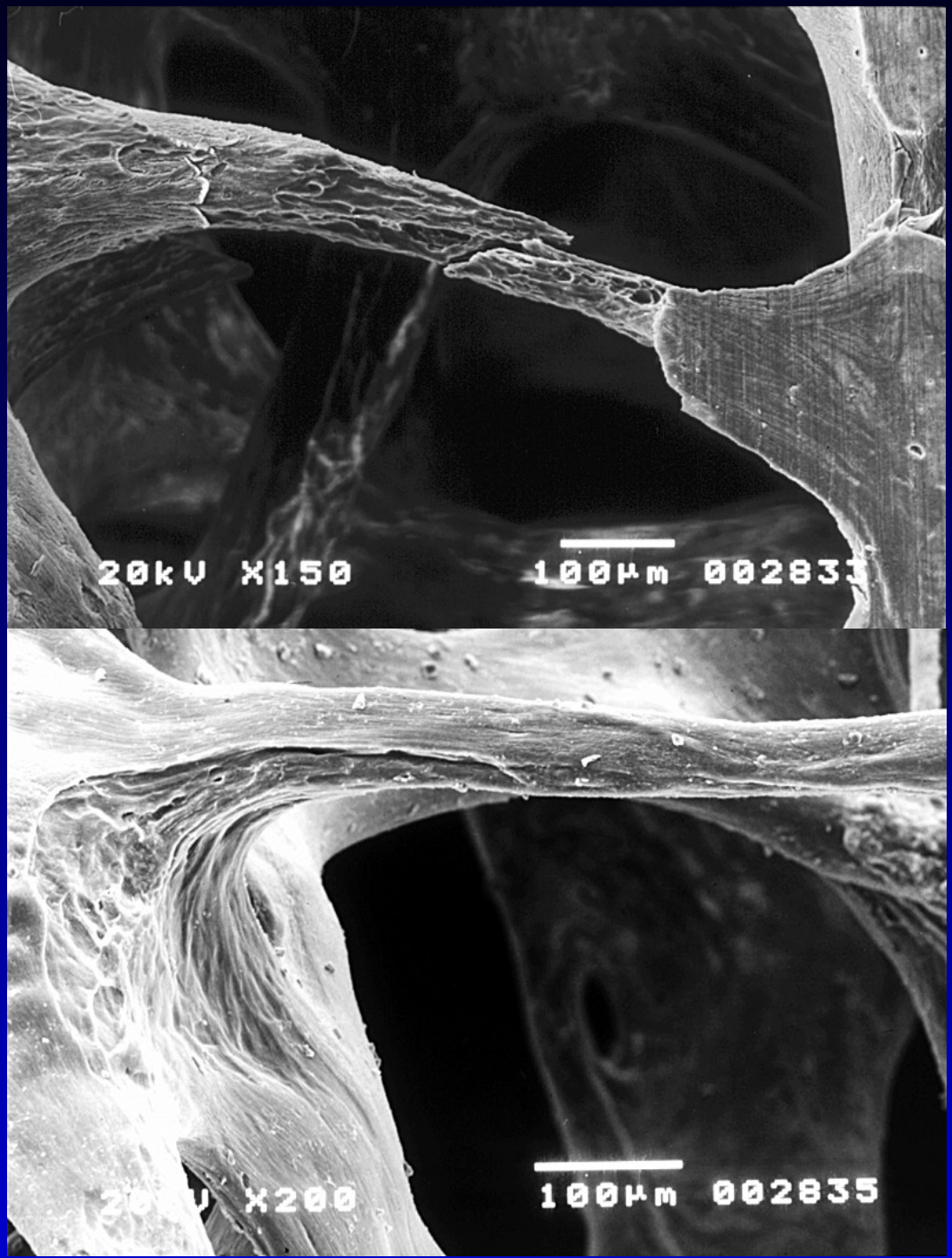

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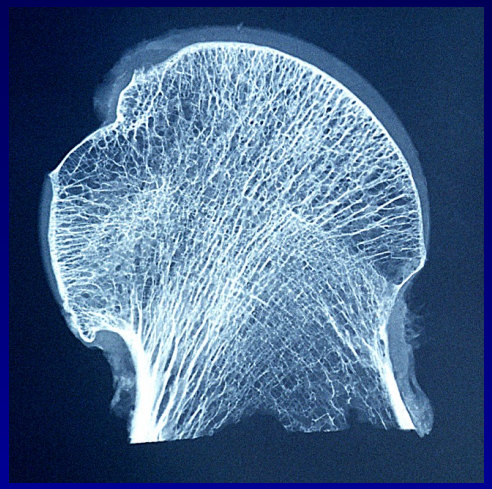
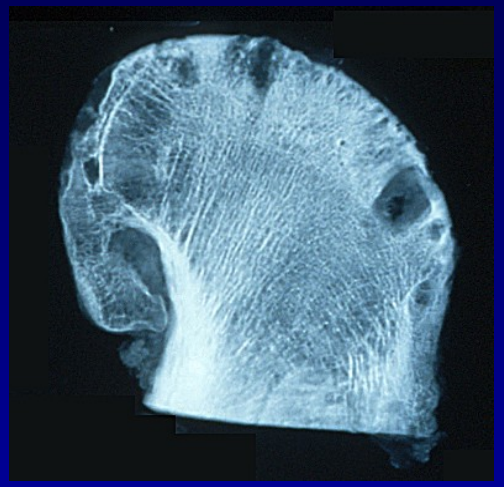
Remodelling gone wrong





Osteoporosis ⟷ Normal ⟷ Osteoarthritis

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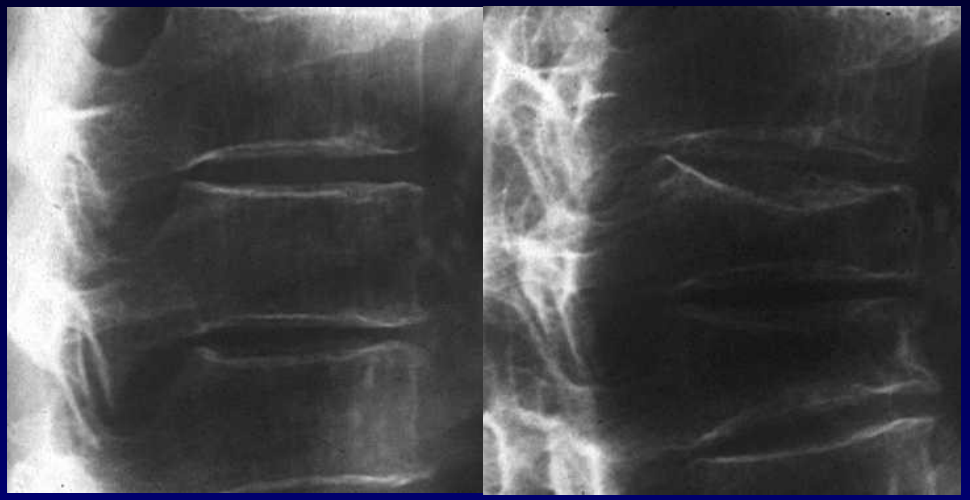
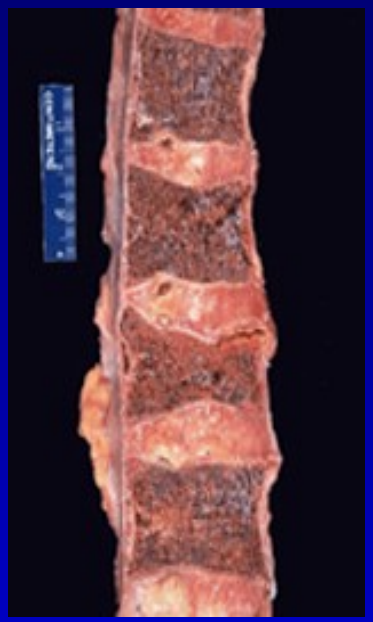
Vertebral fractures





Wedging

Concavity

Specific compression

Evans et al. 1993

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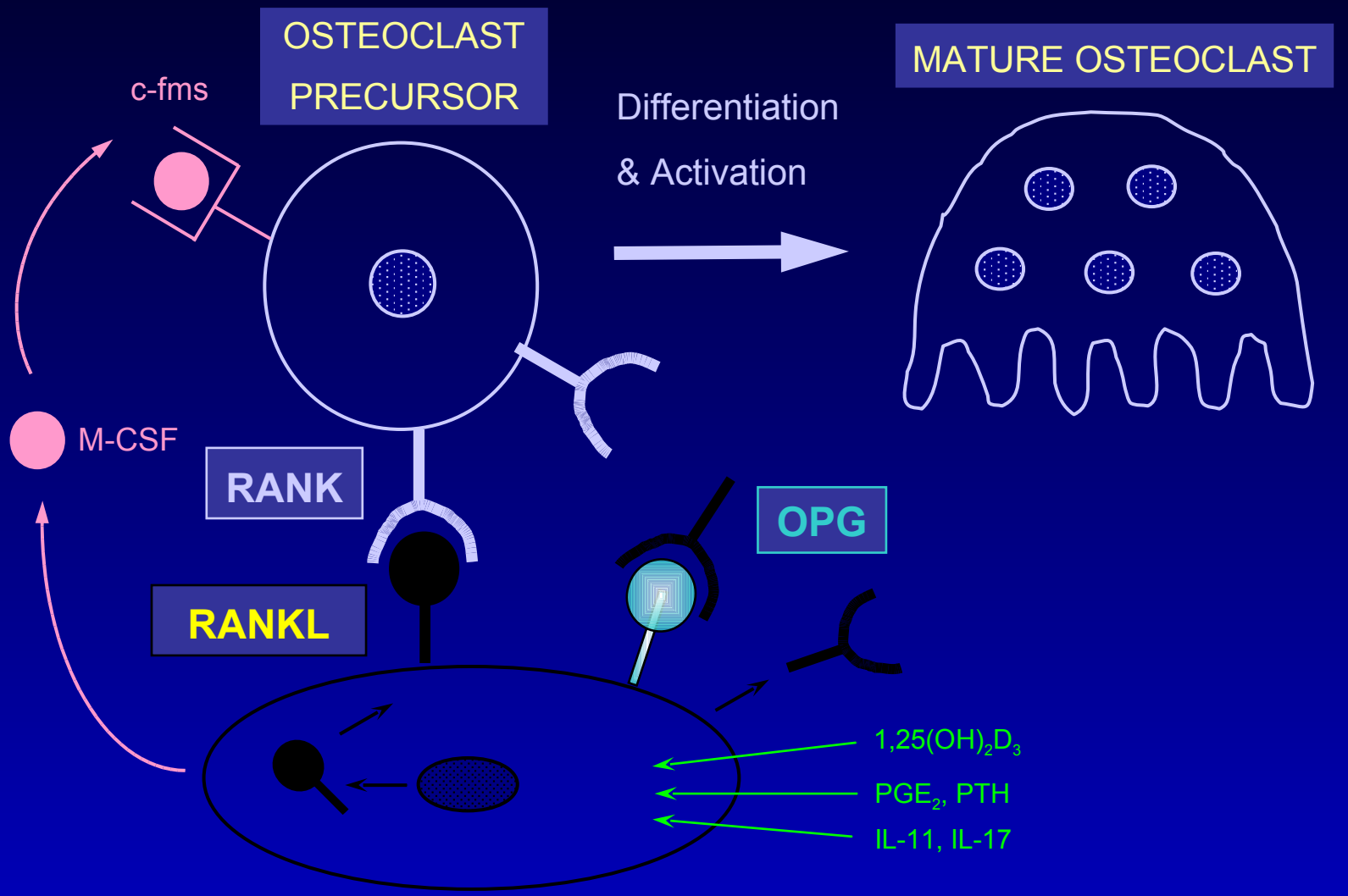
TABLE 4. *Comparison of modeling and remodeling*

	Remodeling	Modeling
Location	Spatially related	Different surfaces
Coupling	A → R → F	A → F; A → R
Timing	Cyclical	Continuous
Extent	Small (<20%)[a]	Large (>90%)
Apposition rate	Slow (0.3–1.0 μm/day)	Fast (2–10 μm/day)
Balance	No change or net loss	Net gain

Source: From Jee (5).

[a] Of available surface.

OSTEOCLASTOGENESIS



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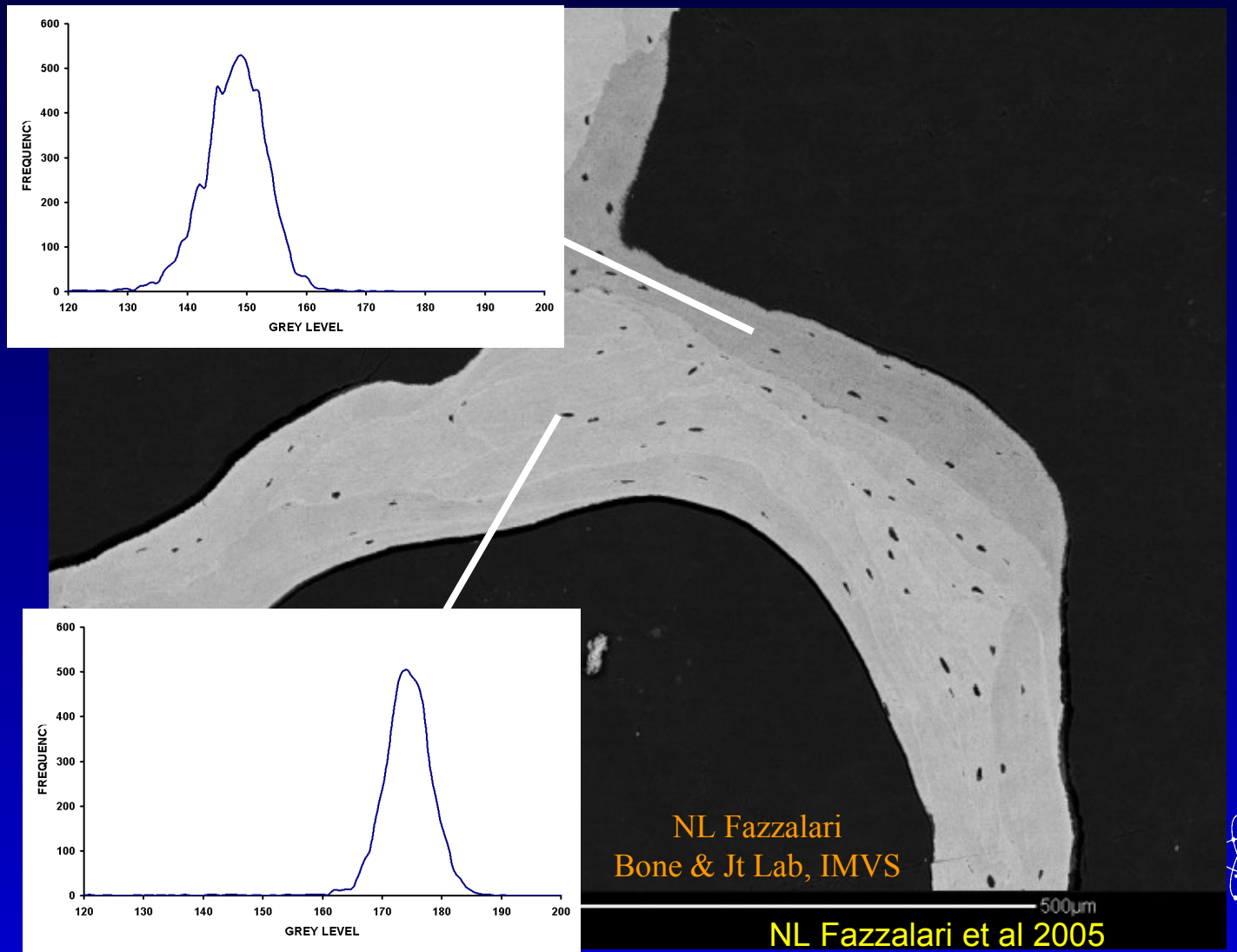
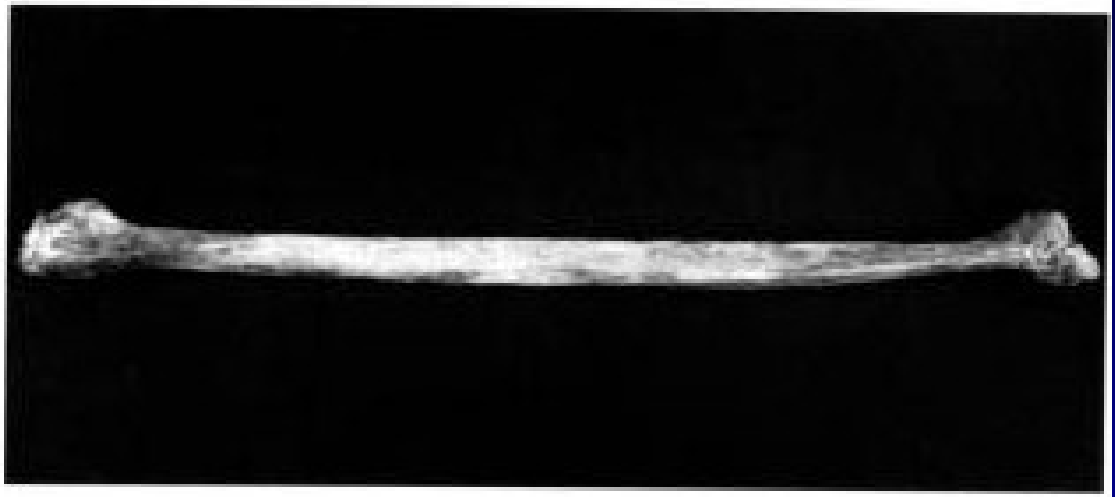
Bone Remodelling and Mineralisation

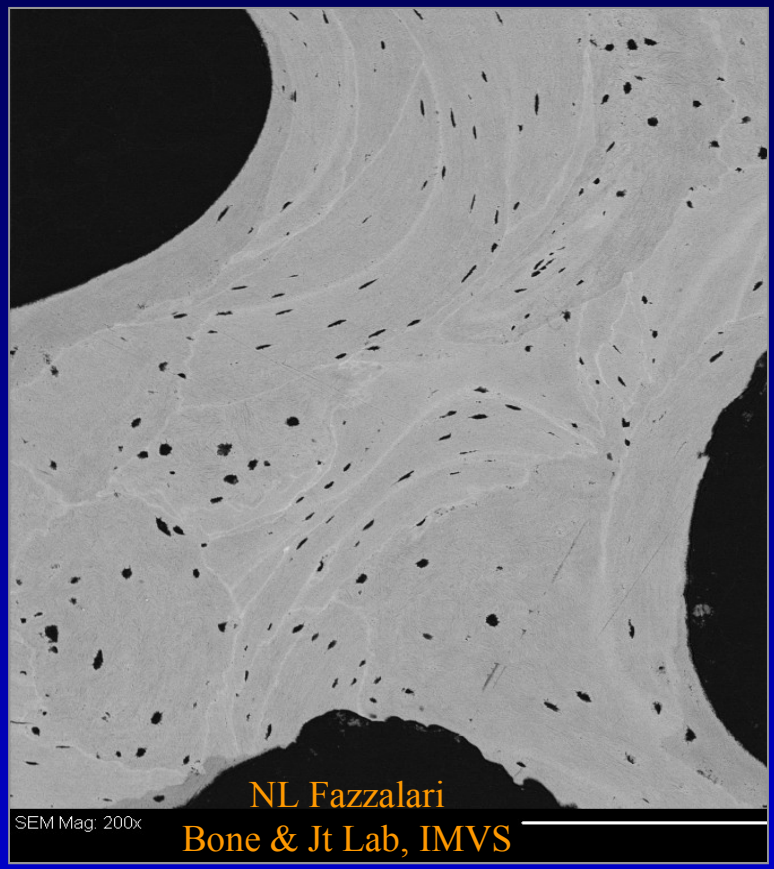
The higher the remodelling rate, the younger and less mineralised the bone



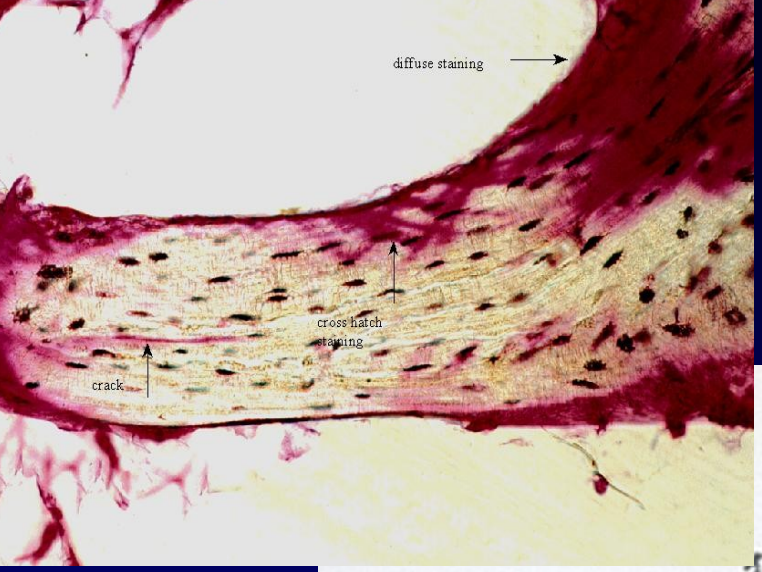
Bone is a composite material

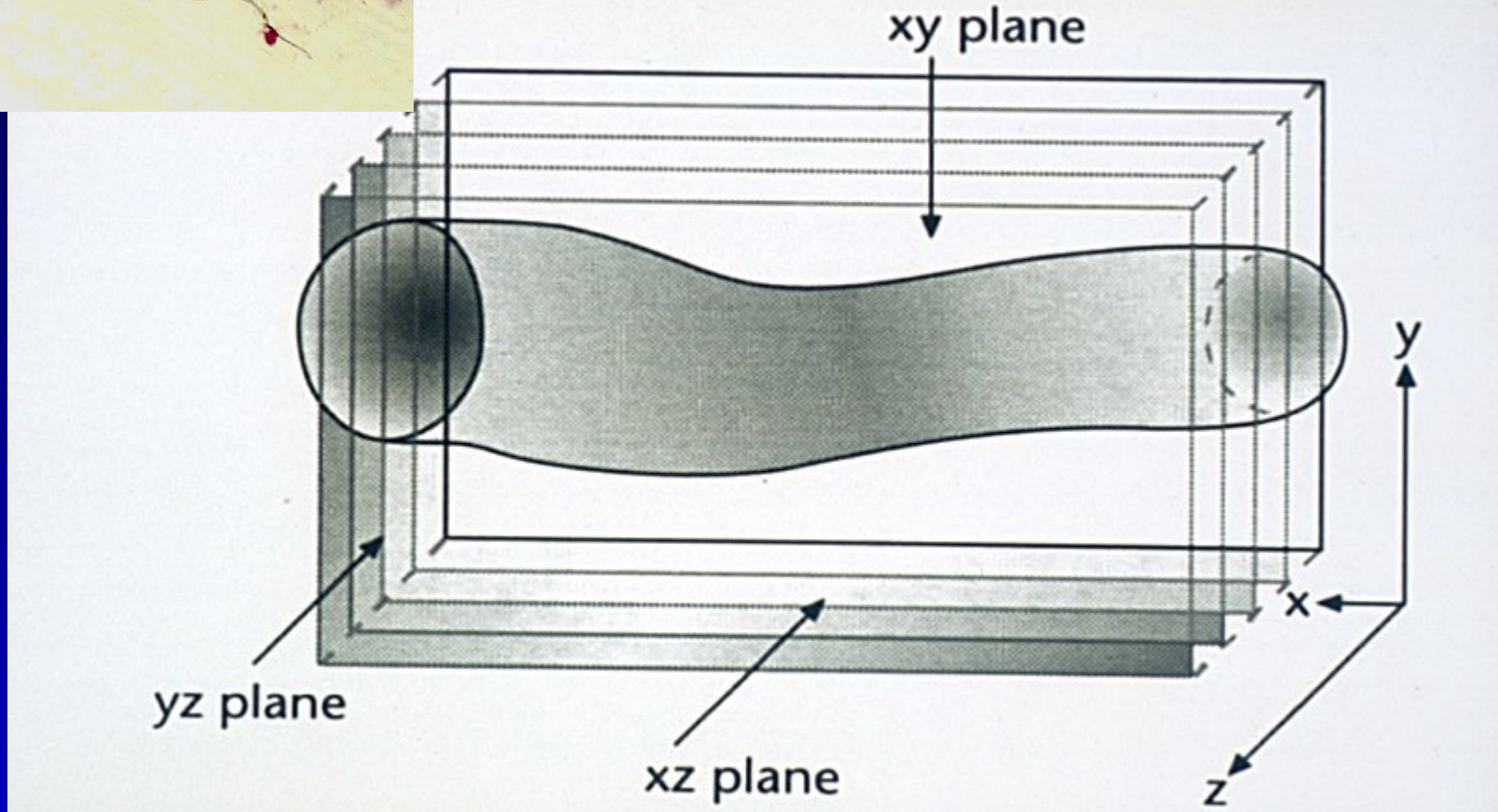


Mineralisation ⇨ degree of bone matrix mineralisation



Confocal microscopy



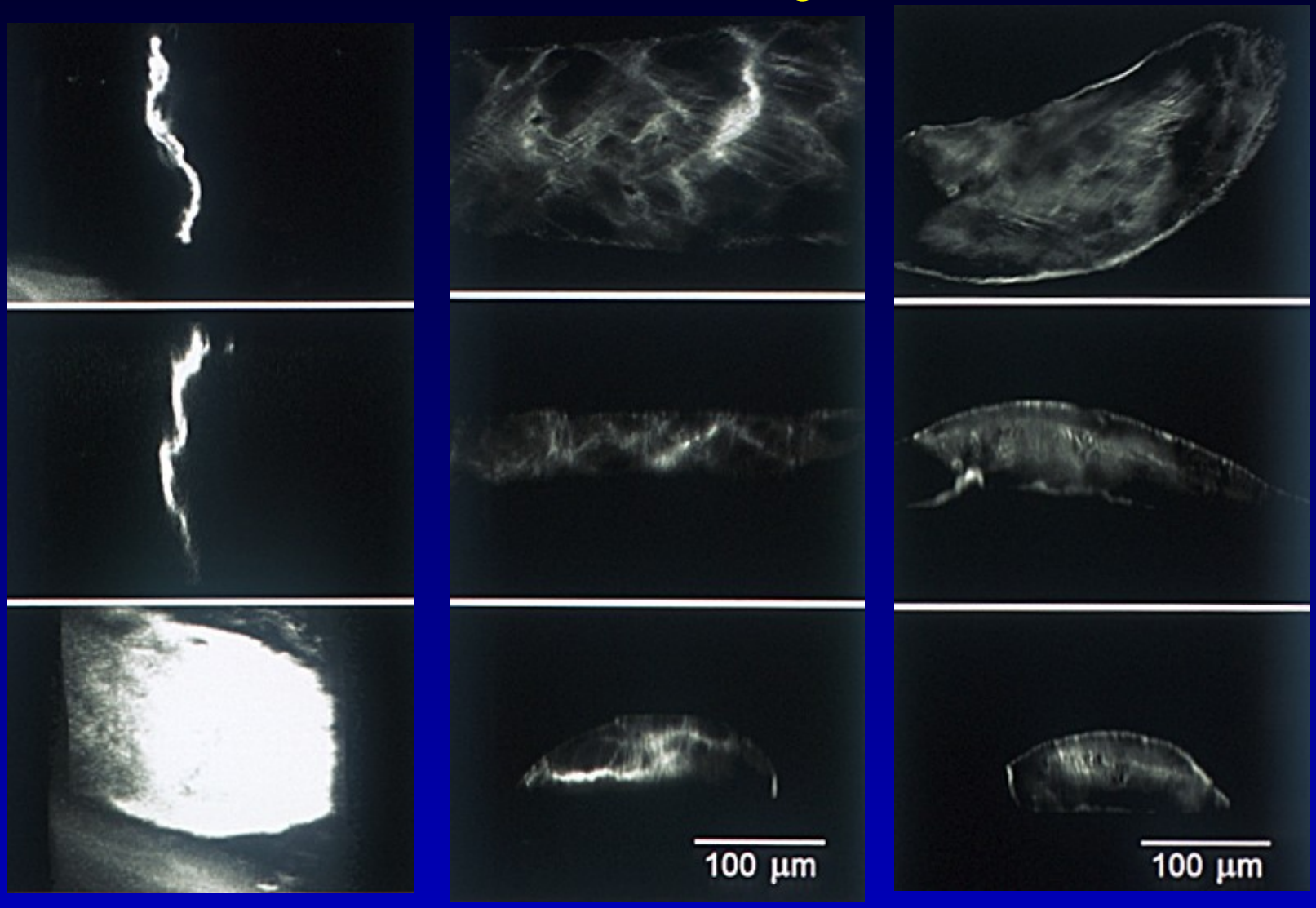


NL Fazzalari et al Bone 1998
Bone & Jt Lab, IMVS

Microcrack

Cross hatch damage

Diffuse damage

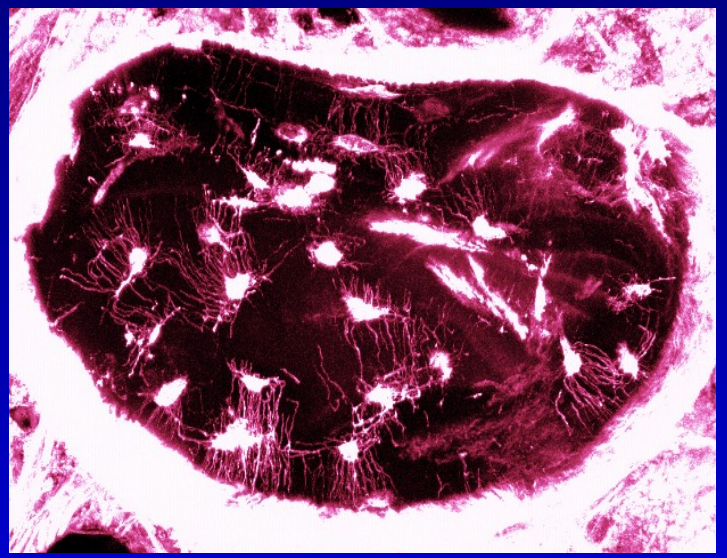


NL Fazzalari et al Bone 1998

Bone & Jt Lab, IMVS

Osteocytes

- Send an inhibitory signal in response to mechanical loading to inhibit bone lining cells from activating remodelling.
  - Remodelling increases in the disuse state because strain-generated inhibitory signals diminish
  - Remodelling is activated by mechanical damage along with osteocyte apoptosis, which interferes with both signal generation and transmission



Martin 2000

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Osteocyte, microdamage and repair

- Physiological strains continually produce fatigue damage in bone
- Damage weakens bone and is associated with osteocyte apoptosis and the activation of remodelling
- Remodelling is the only means by which microdamage can be removed and repaired

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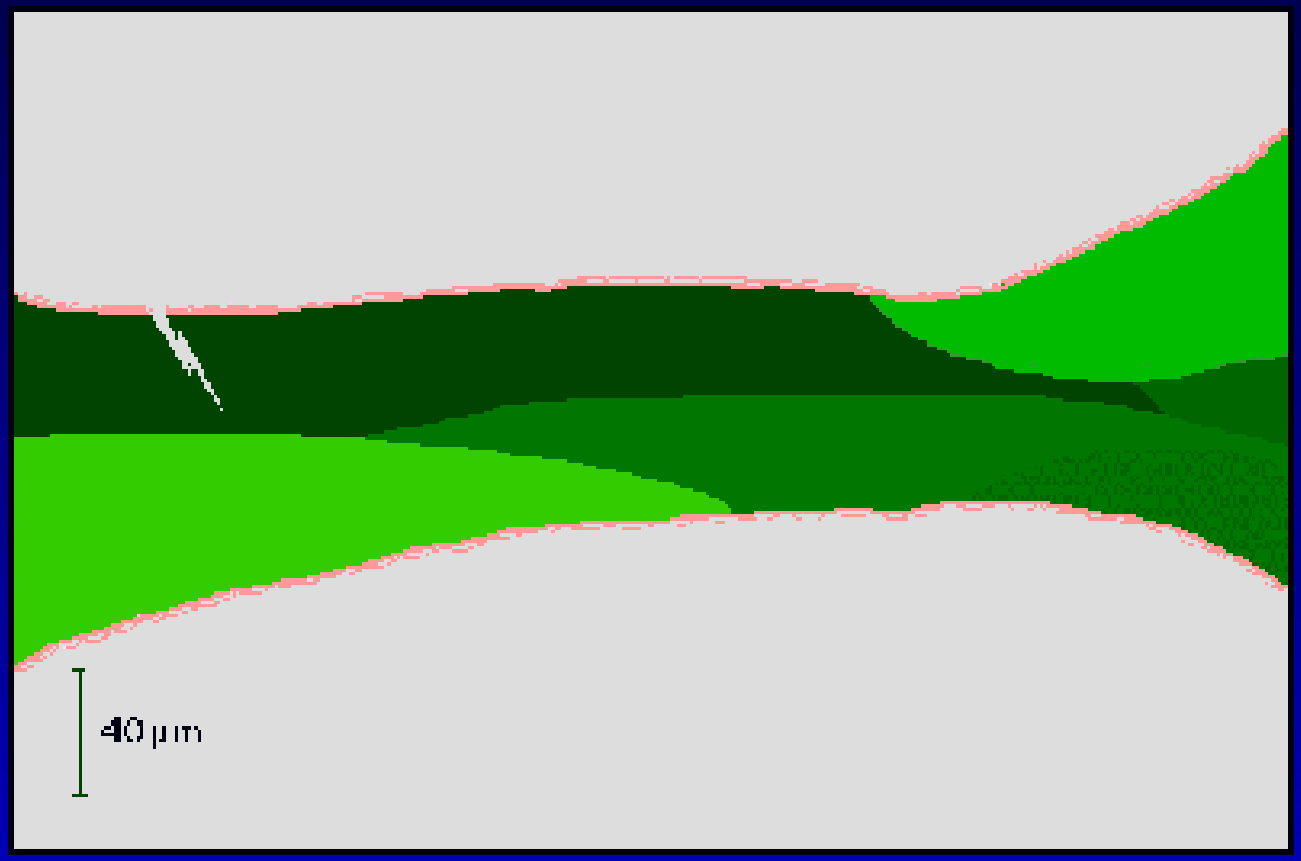
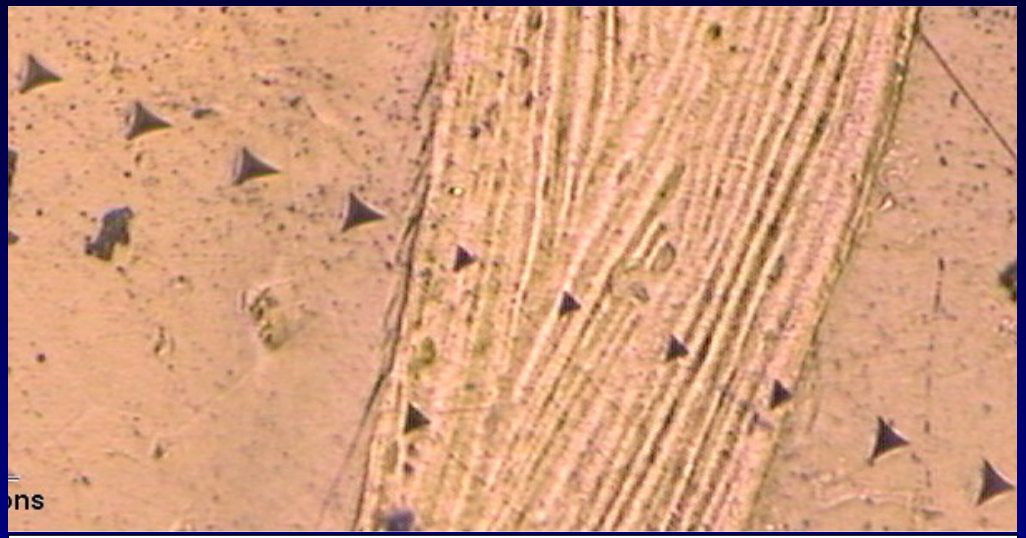
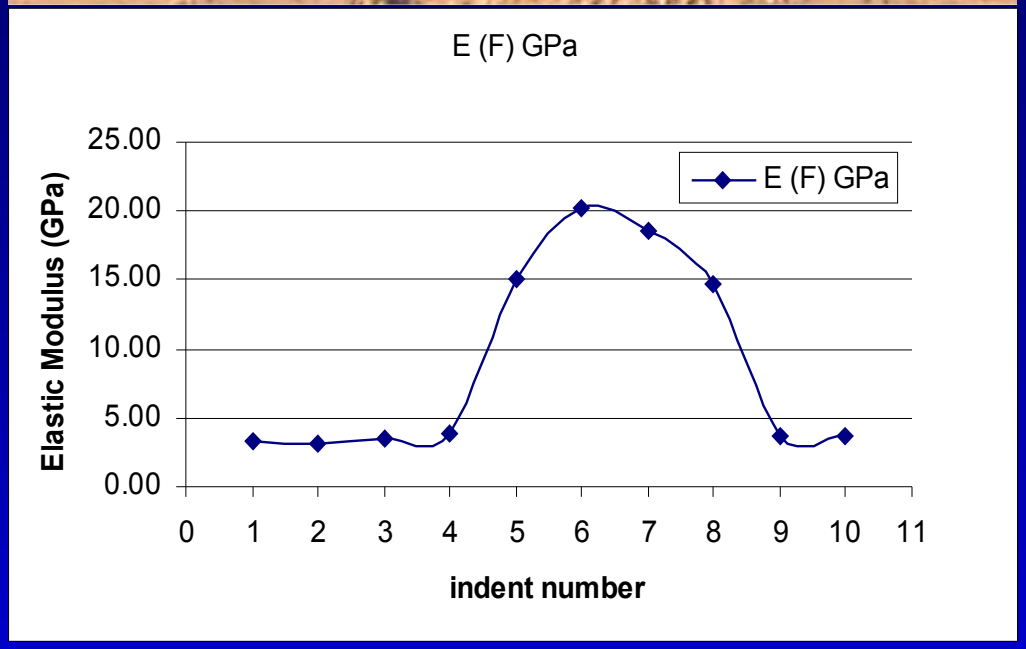
Remodelling - Microdamage repair



Micromechanics of bone





Norman et al 2009

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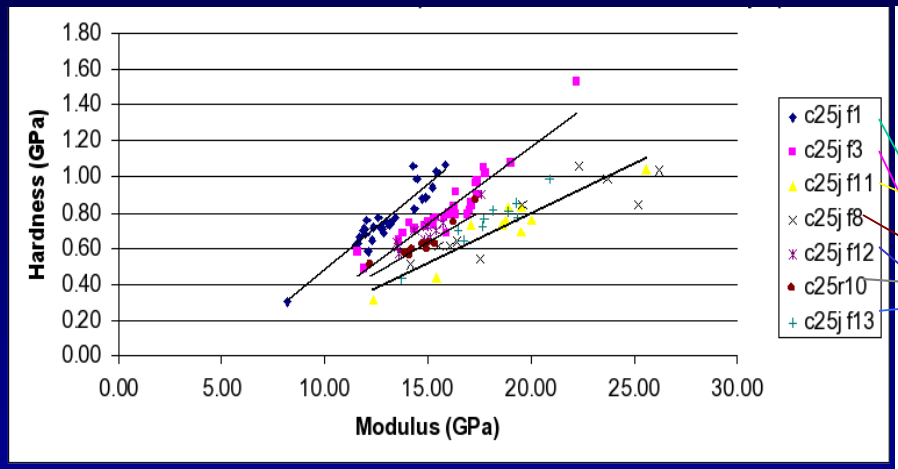
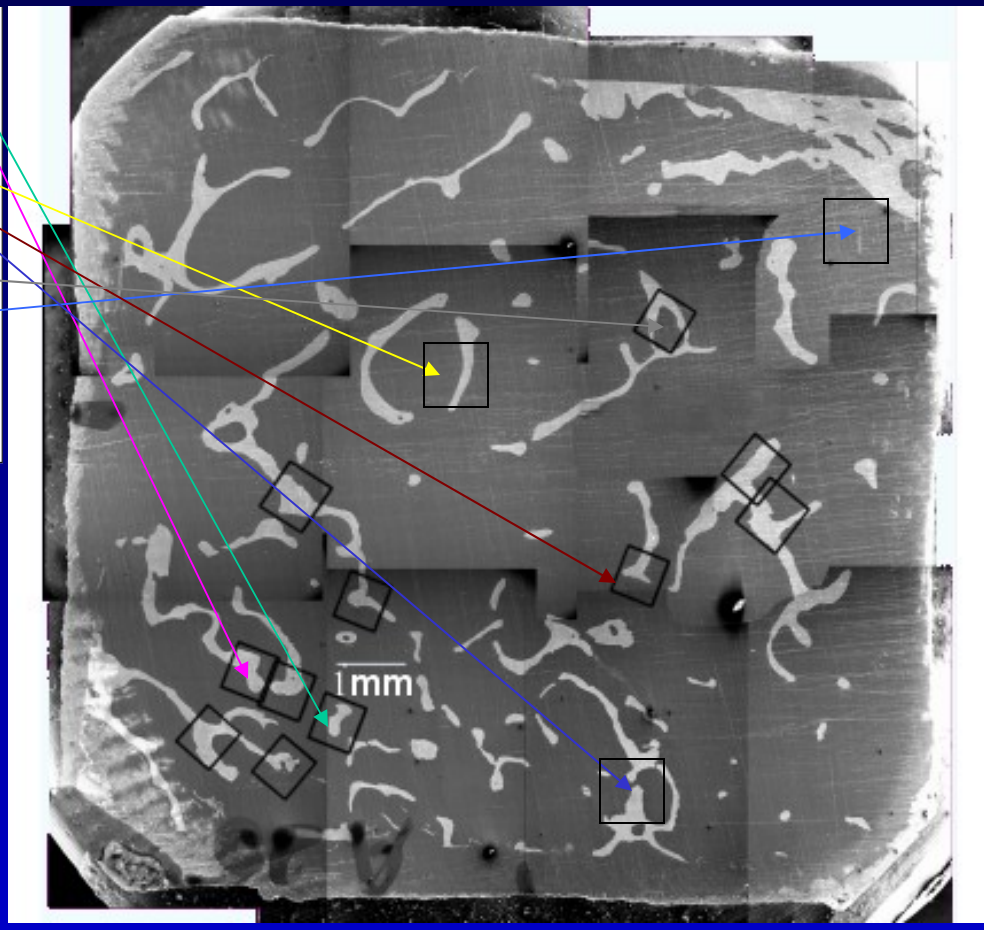
Micromechanics of bone





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Norman et al 2009

Summary

Bone:

- is a composite material
- has heterogeneous material properties
- is self healing
- is a hierarchical material/structure
- derangement can occur at various levels in the hierarchy
- properties change with age and disease

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Relationship Between Bone Morphometry (Trabecular And Cortical Bone) And Strength – Part 2

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Bone and Joint Research Laboratory
Institute of Medical and Veterinary Science and
Hanson Institute

Discipline of Pathology
The University of Adelaide

Adelaide, South Australia, AUSTRALIA

IMVS

HANSON INSTITUTE

THE UNIVERSITY OF ADELAIDE AUSTRALIA
SUB CRUCE LUMEN

Talk

1. Genesis of trabecular structure during growth
2. Trabecular structure in OP and OA
3. Average (population) vs Individual distributions.
4. Direction of loading and structural failure
5. Mineralisation and nano mechanical properties
6. Conclusion/Discussion

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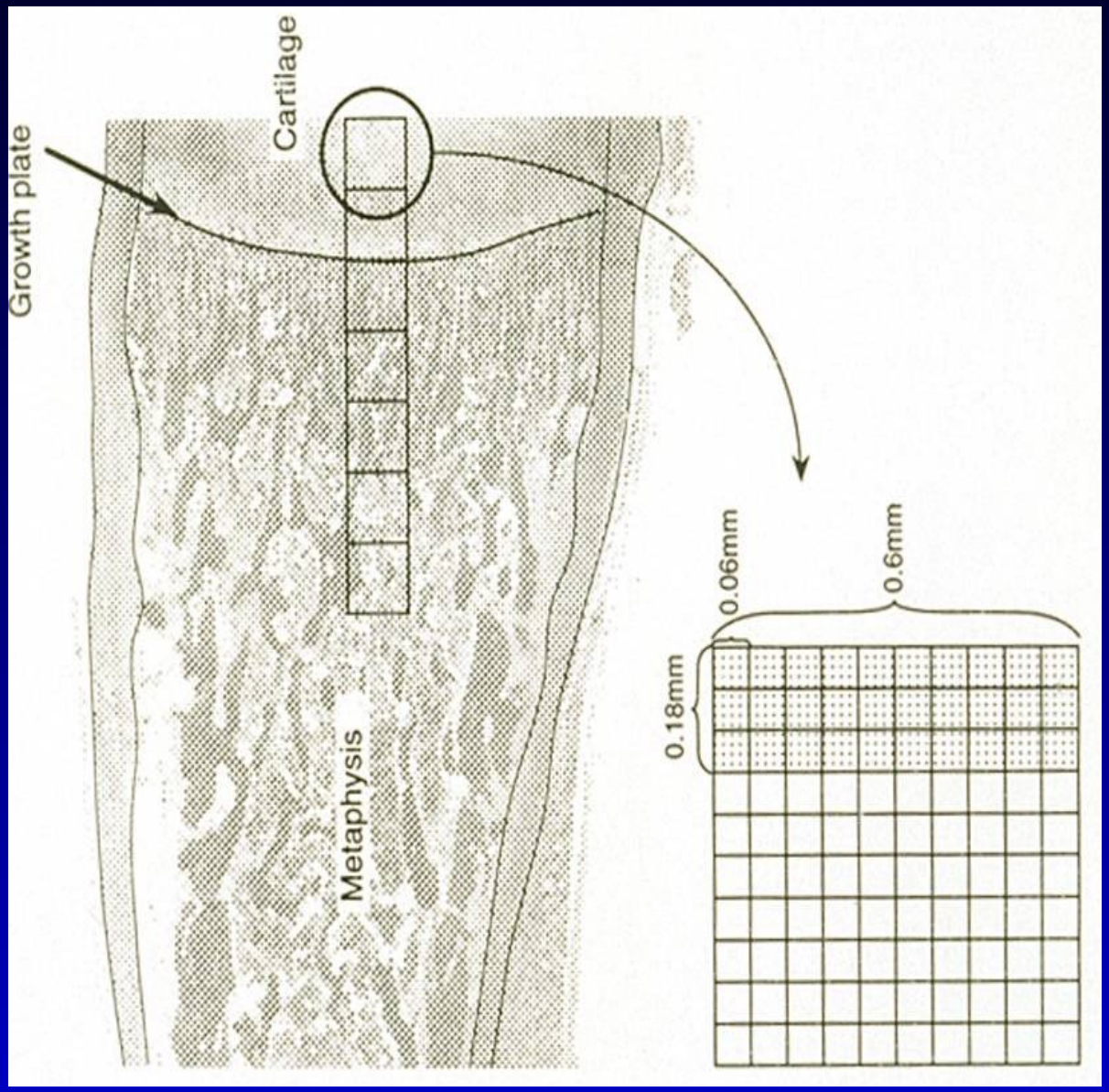
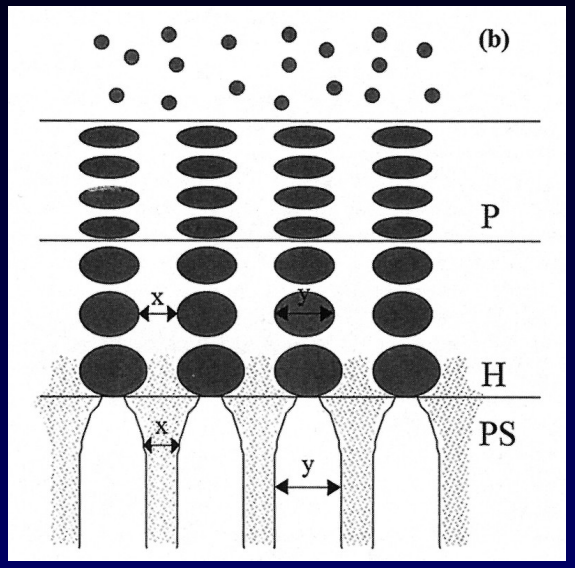
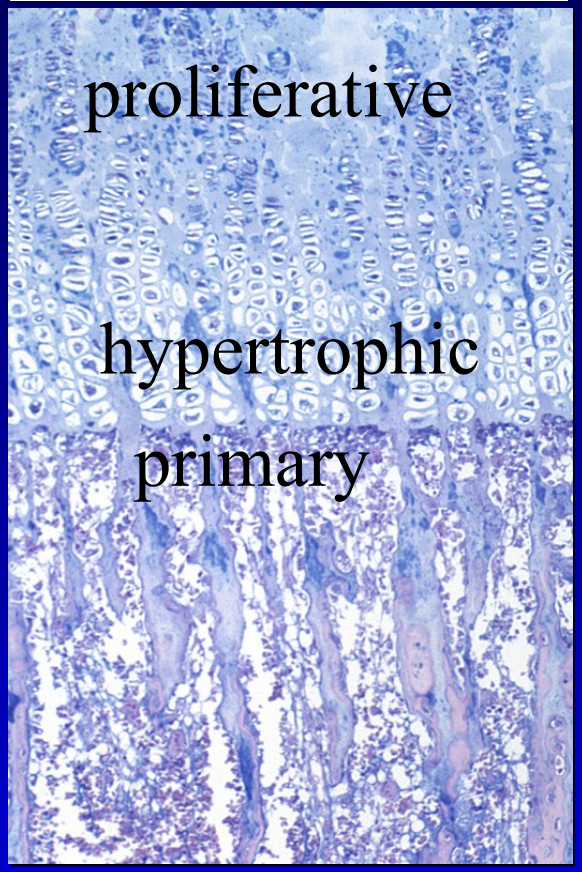






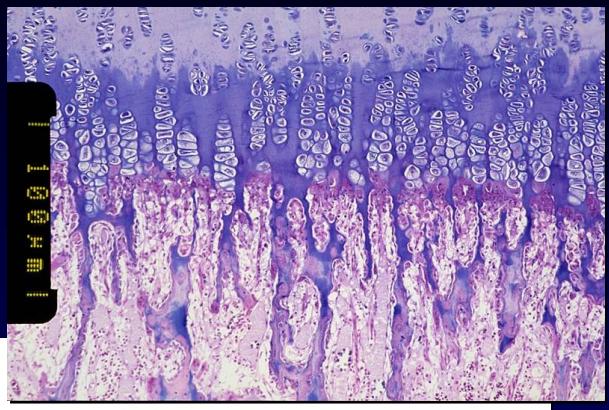
NL Fazzalari et al 1997
Bone & Jt Lab, IMVS

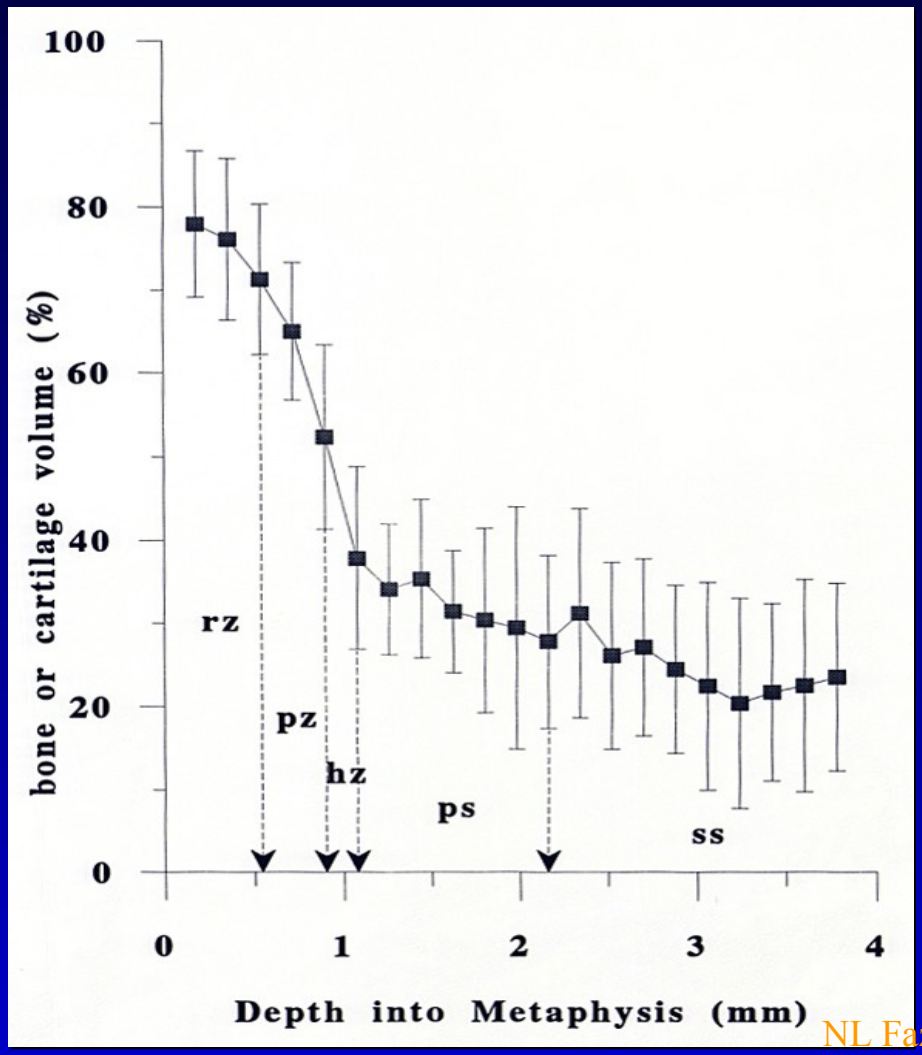
Volume

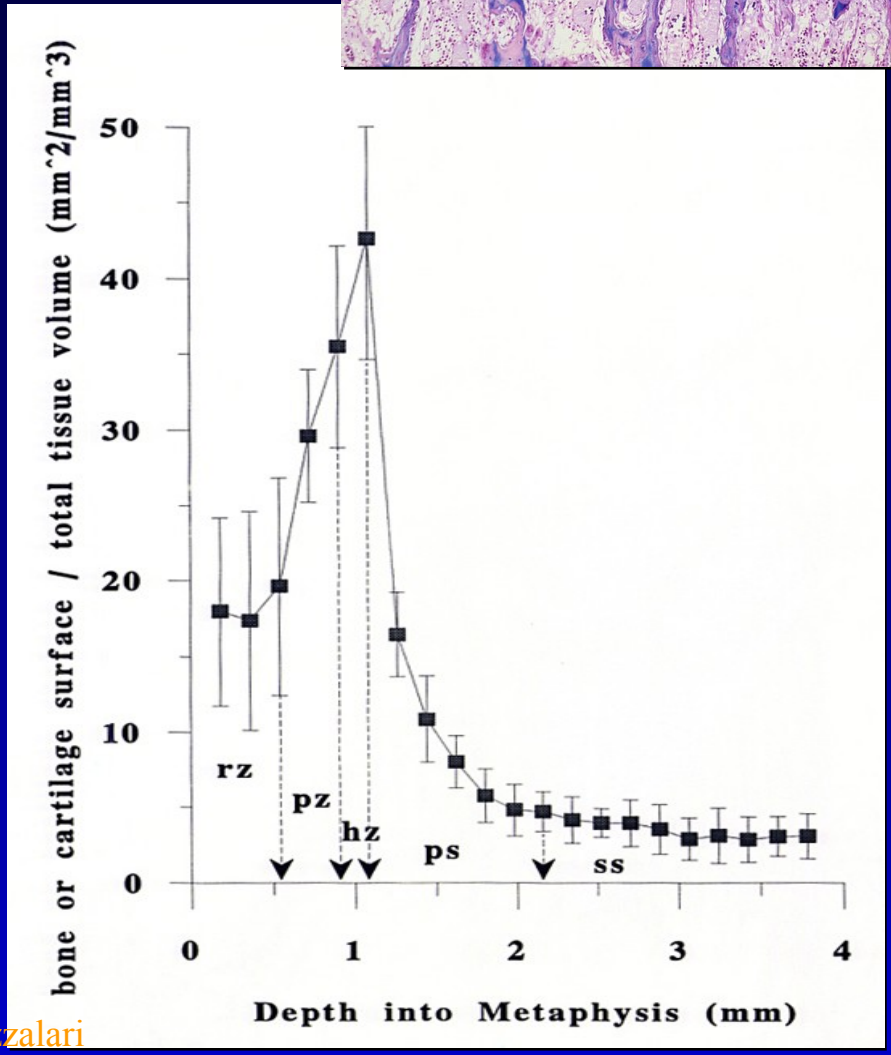
Cartilage matrix volume and bone volume fraction

Surface

Surface of cartilage matrix bordered by chondrocyte lacunae and mineralised bone surface







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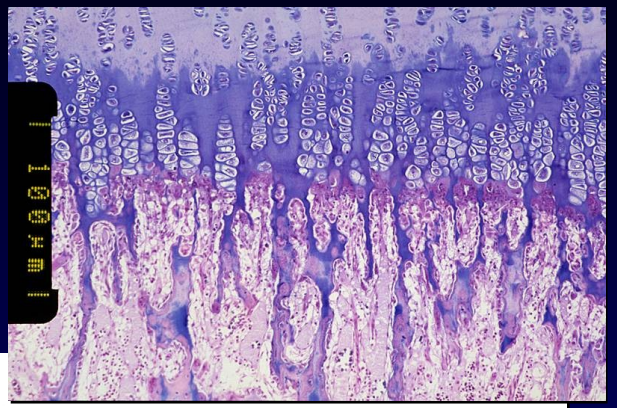
Fazzalari et al. The Anatomical Record 1997;248:1–12

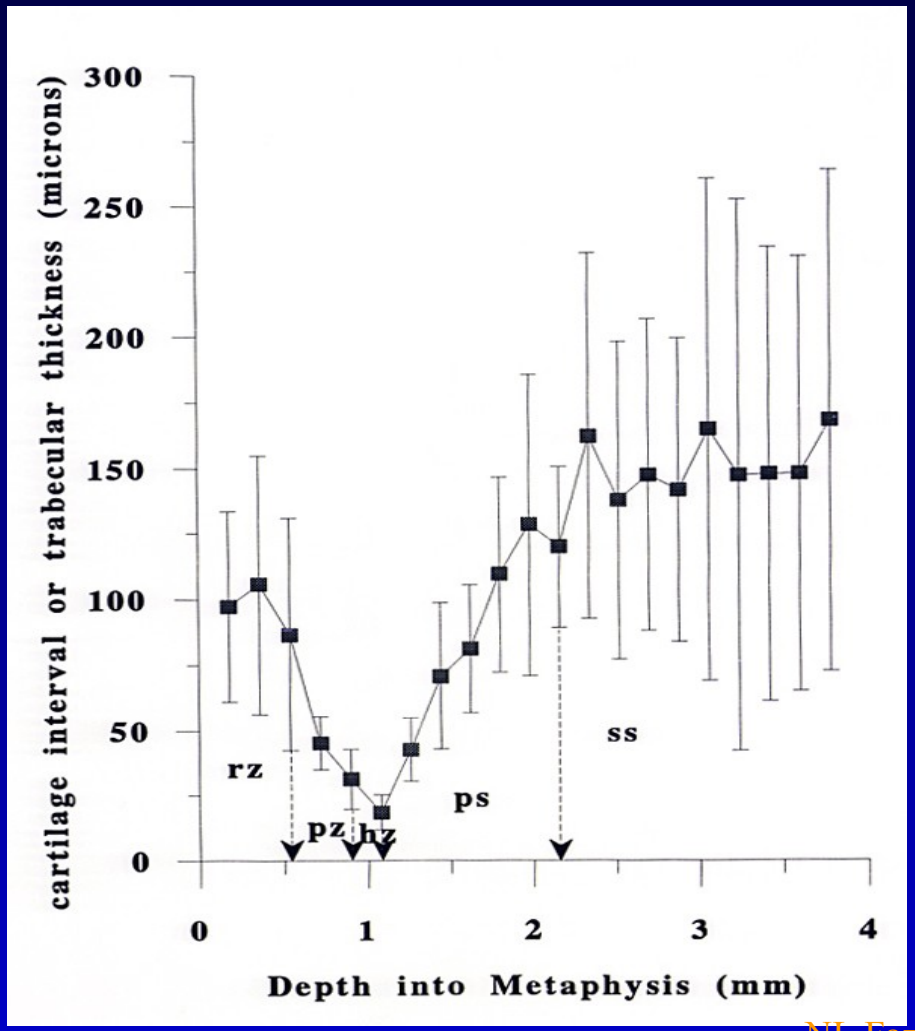
Thickness

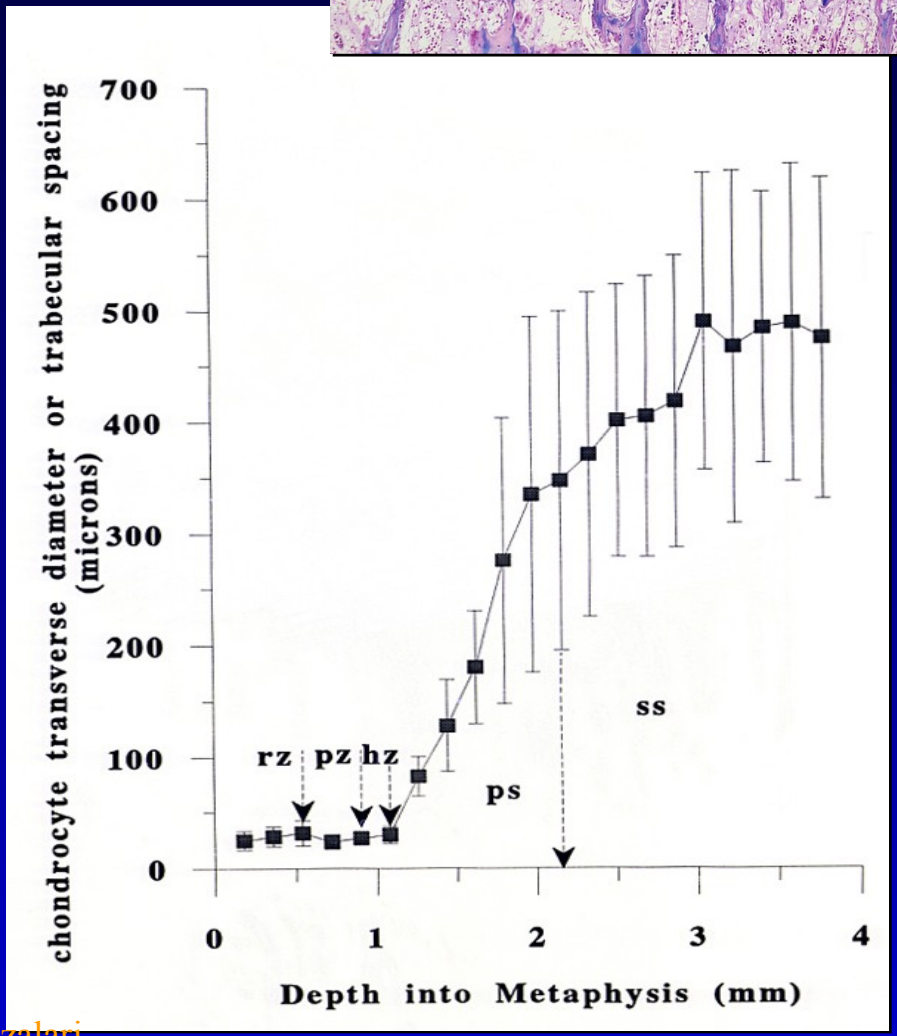
Cartilage matrix between chondrocyte lacunae, cartilage septa, individual trabeculae

Separation

Chondrocyte lacunae dimeter, trabecular separation

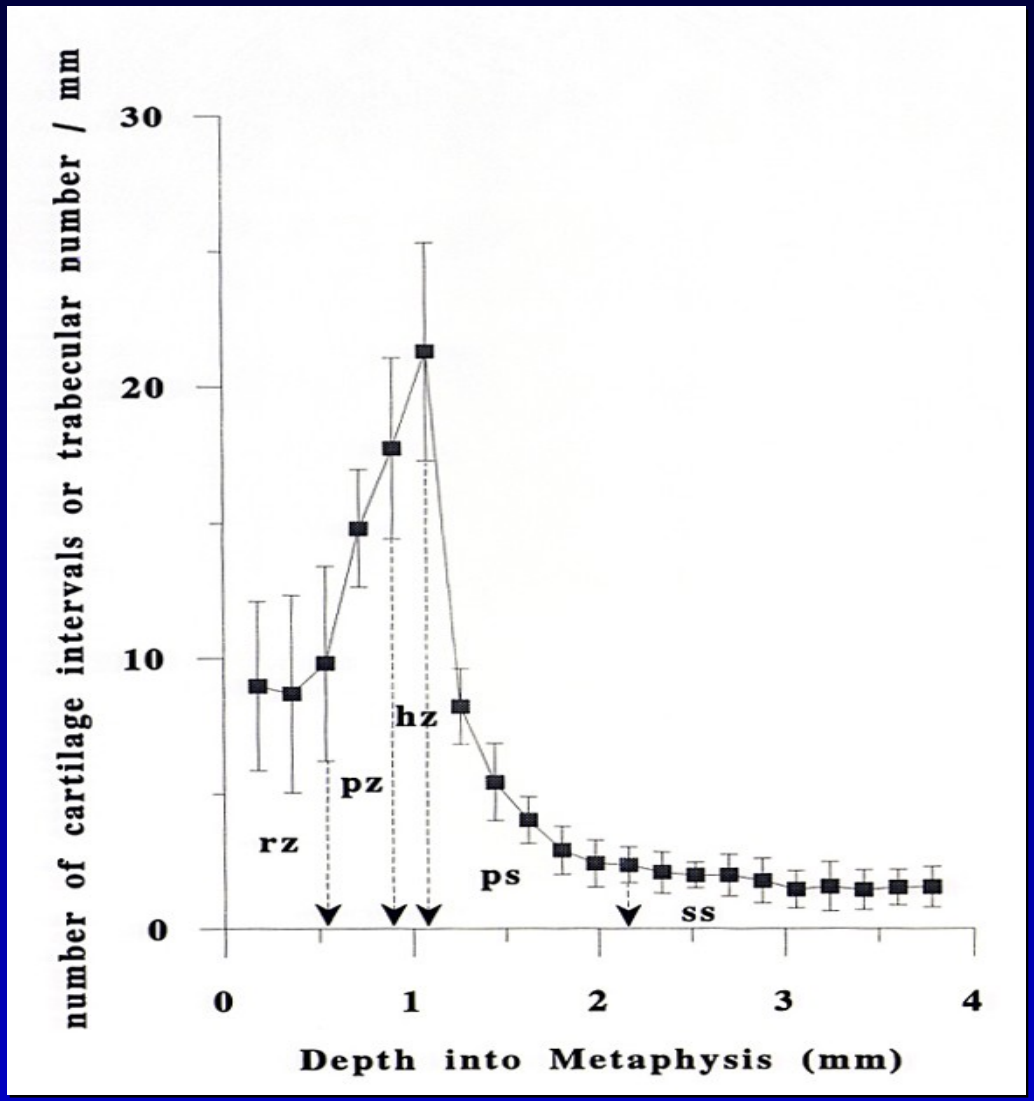


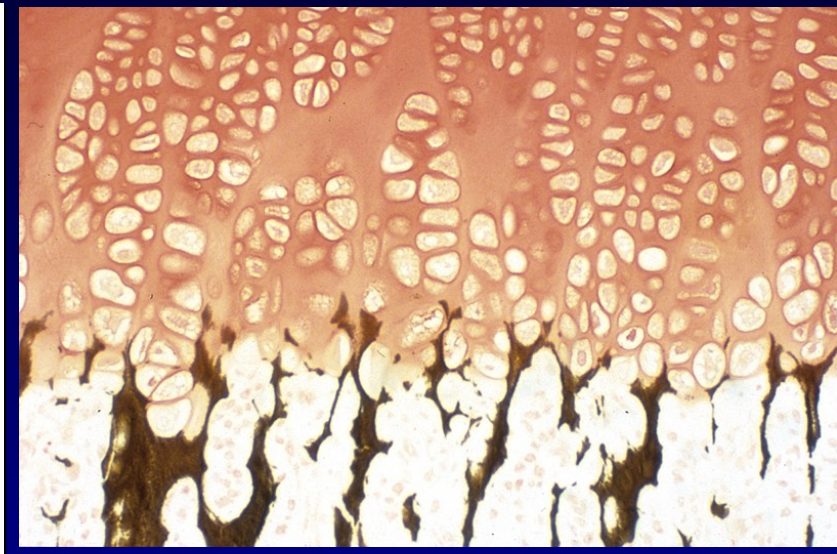




Fazzalari et al. The Anatomical Record 1997;248:1–12

Number
Cartilage septa and trabecular elements





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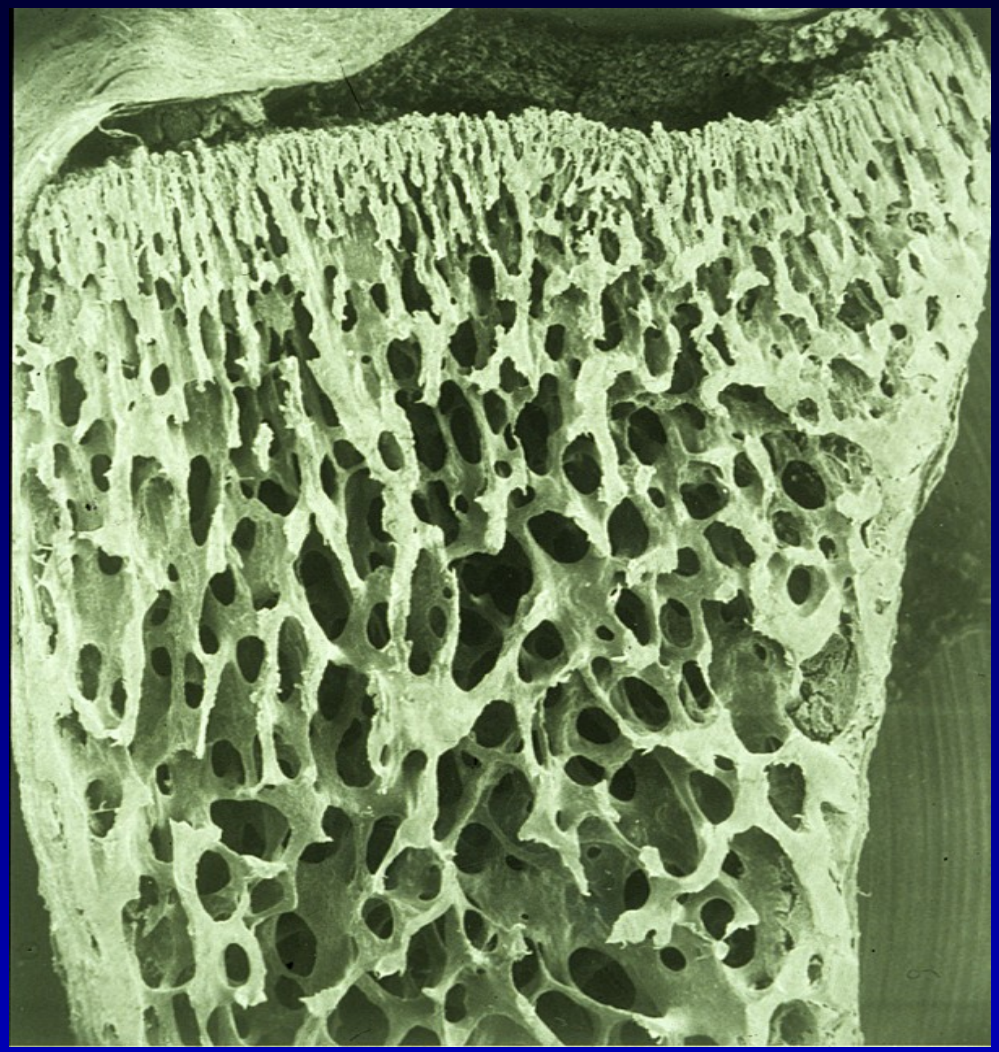
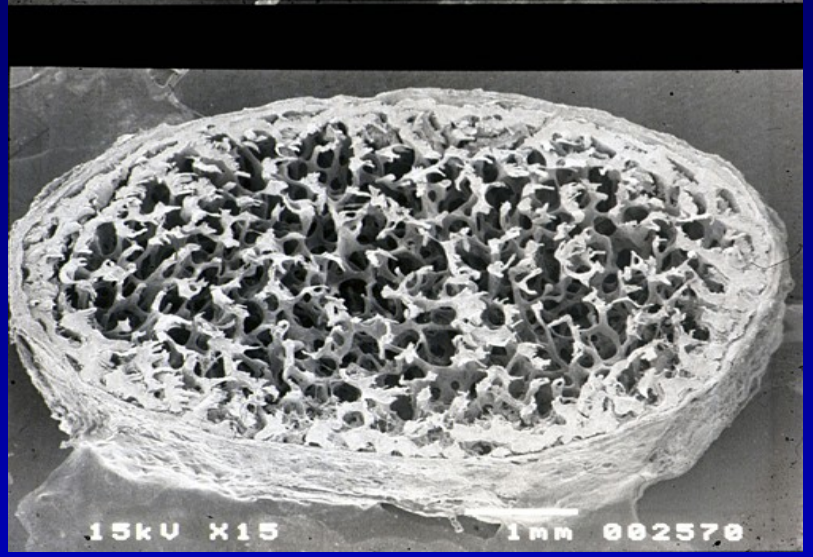
Fazzalari et al. The Anatomical Record 1997;248:1–12





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Fazzalari et al. The Anatomical Record 1997;248:1–12

Conclusions

- Trabecular bone spatial structure conforms to a design specification
- The matrix framework of the cartilage in the hypertrophic zone determines the architectural plan or template for the formation of cancellous bone
- Bone mineral surface and trabecular number vary or regulate spatial trabecular structure

NL Fazzalari
Bone & Jt Lab, IMVS

Fazzalari et al. The Anatomical Record 1997;248:1–12

Significance

- Analysis of growth stress or specific bone growth defects may improve our understanding of bone disease aetiology
- Examine features which may predispose an individual to bone disorders later in life
- The geometrical structure of trabecular bone following osteoporotic and osteoarthritic changes may be influenced by the original structure

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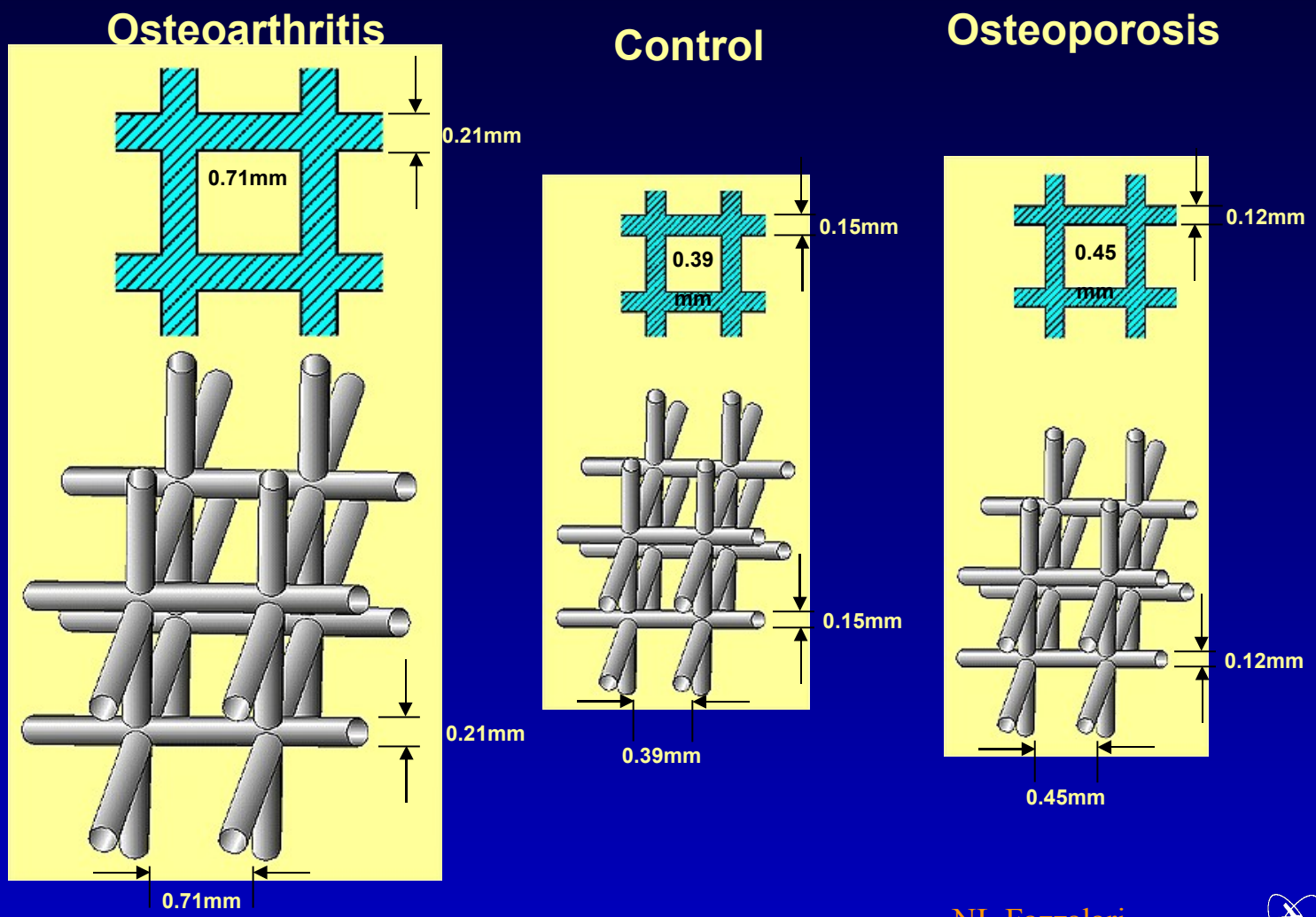
Relative Difference in Trabecular Bone Structure



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Fazzalari et al. Bone 1985;6(3):125-33

Geometric Relationships between Trabecular Bone Structure

$$\text{Sp ratio (OP/C)} = (2*(Th_{op} - Th_c) + Sp_{op})/Sp_c$$

$$= (2*(0.12 - 0.15) + 0.45)/0.39$$

$$= (2*(-0.03) + 0.45)/0.39$$

$$= (-0.06 + 0.45)/0.39$$

$$= 0.39/0.39 = 1$$

$$\text{Sp ratio (OA/C)} = (2*(Th_{OA} - Th_c) + Sp_{OA})/Sp_c$$

$$= (2*(0.21-0.15) + 0.71)/0.39$$

$$= (2*(0.6) + 0.71)/0.39$$

$$= (0.12 + 0.71)/0.39$$

$$= 0.83/0.39 = 2.13$$

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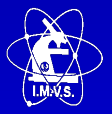
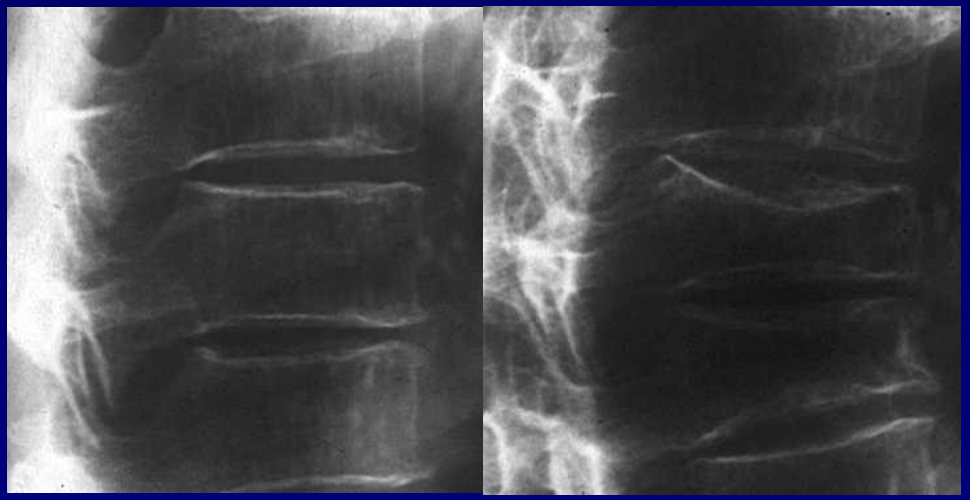
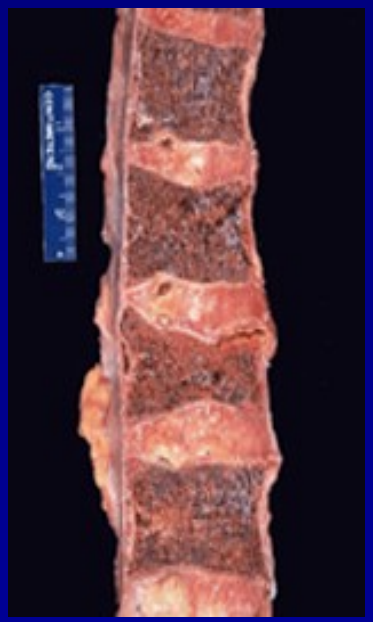


Fazzalari et al. Bone 1985;6(3):125-33

Vertebral fractures





Wedging

Concavity

Specific compression

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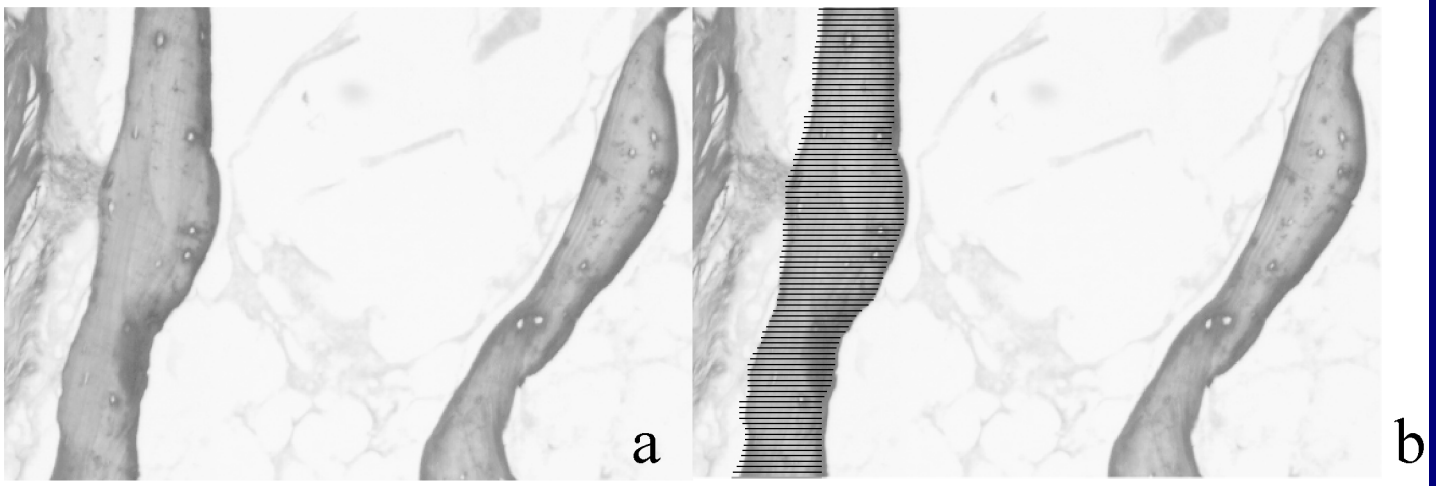
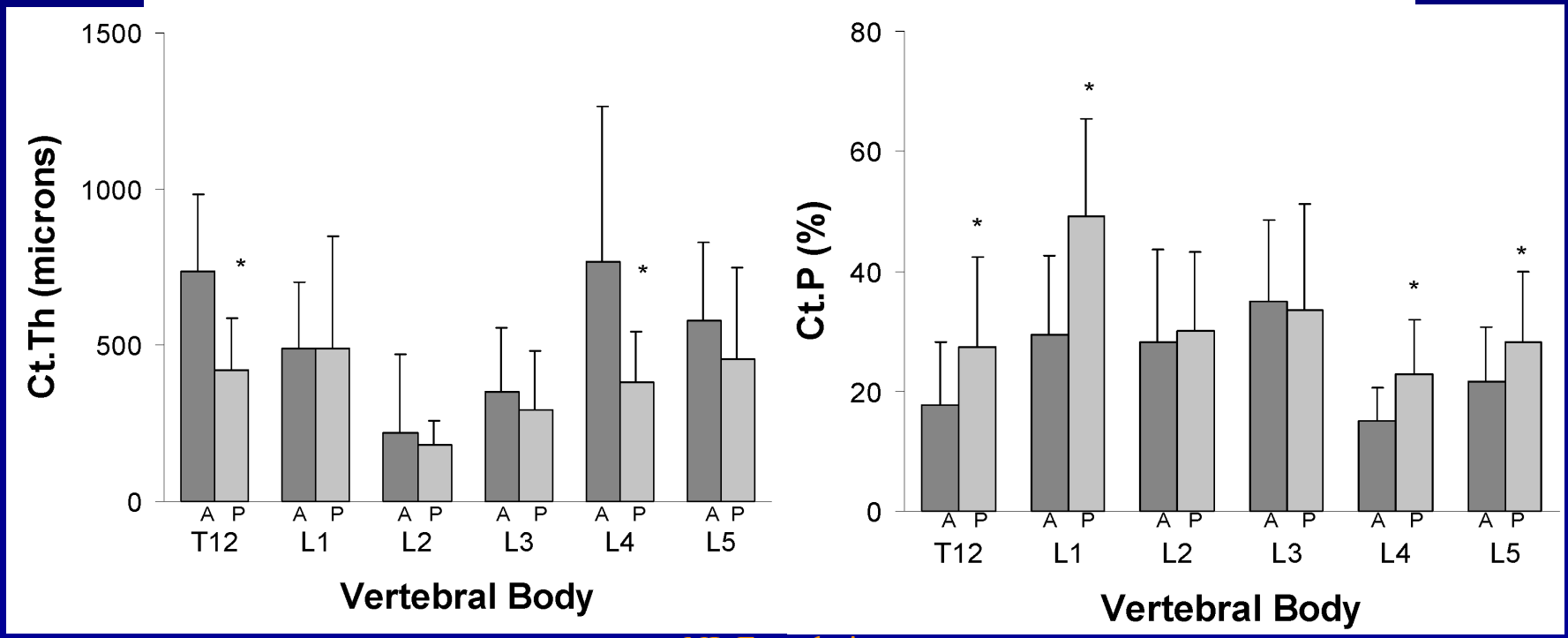
Evans et al. 1993

Vertebral body cortical thickness



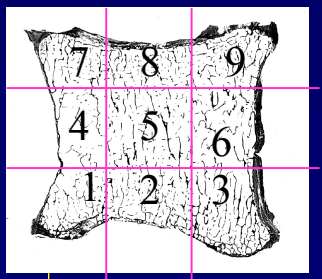


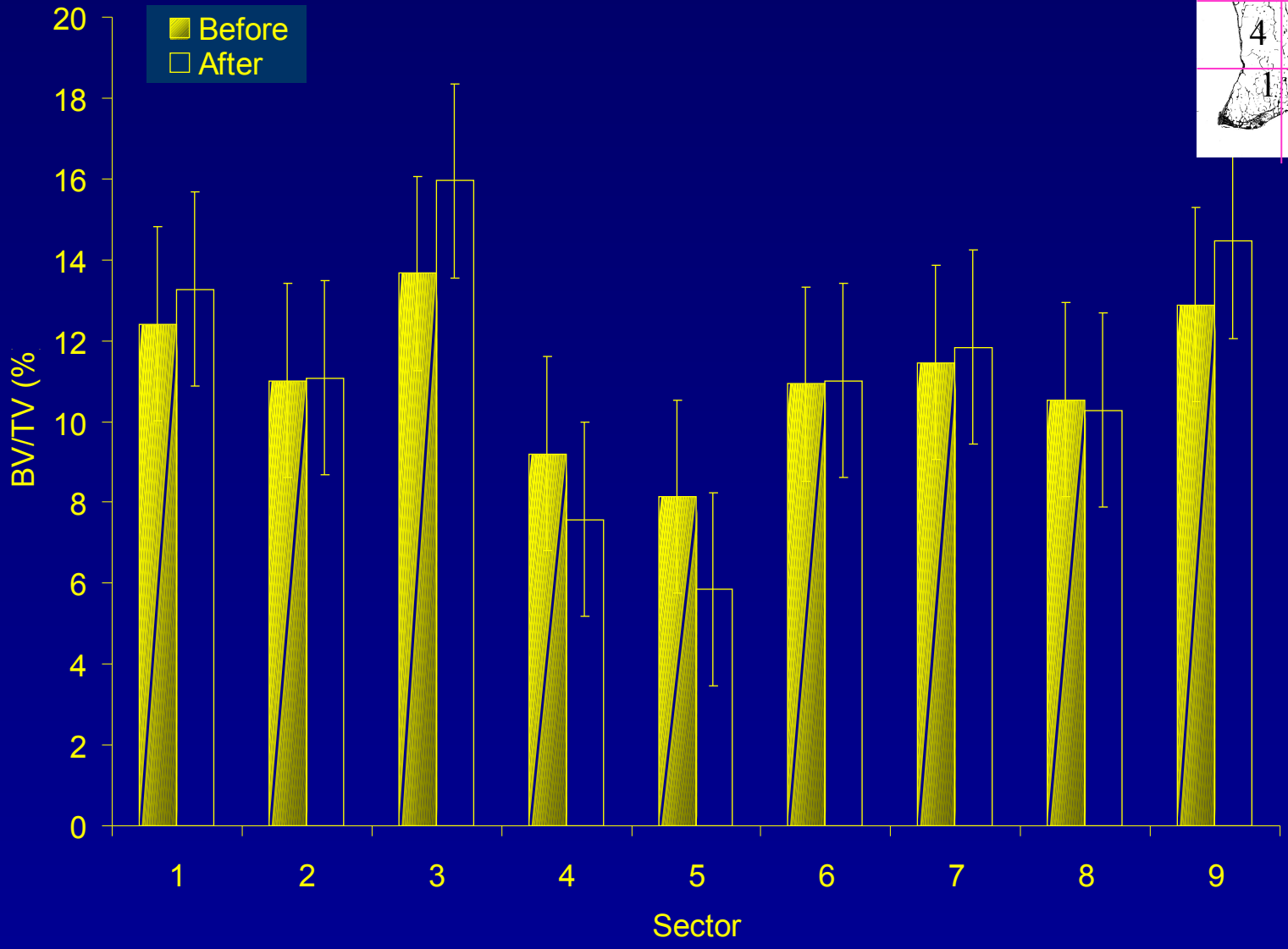
Fazzalari et al. Joint Bone Spine 2006;73:293–7

Adjusted for age

Bone volume fraction

Anterior





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Simpson et al. JBMR 2001;16:681-7

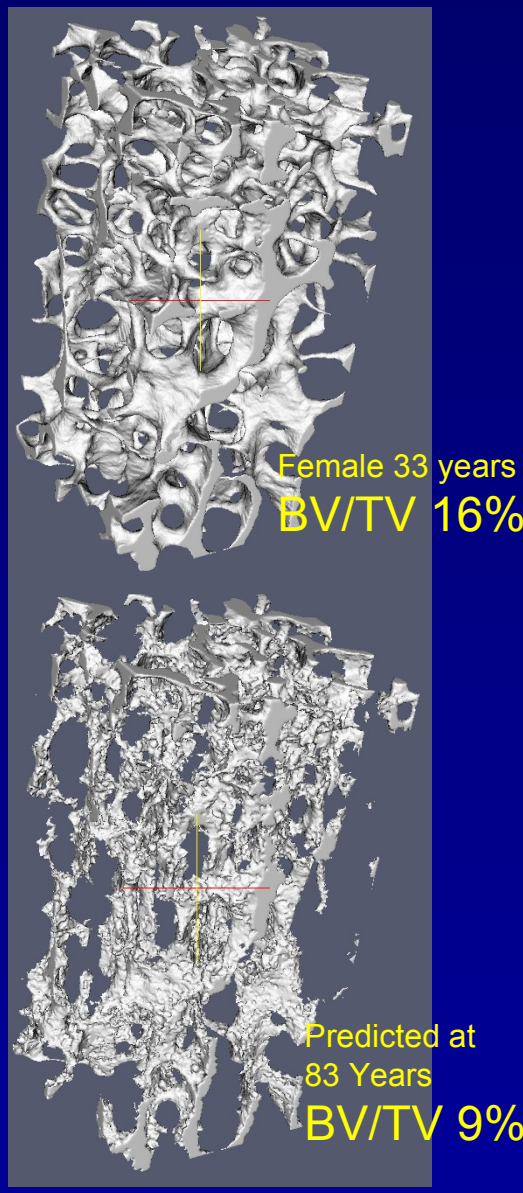
Microarchitectural changes that influence bone strength

Euler buckling and structural instability

Slender column will buckle (bend) at critical load as function of:

$$P_c \propto EI / L^2$$

- Column material (E)
- Cross-sectional moment of inertia area (I)
- *1 / Length* of column^2



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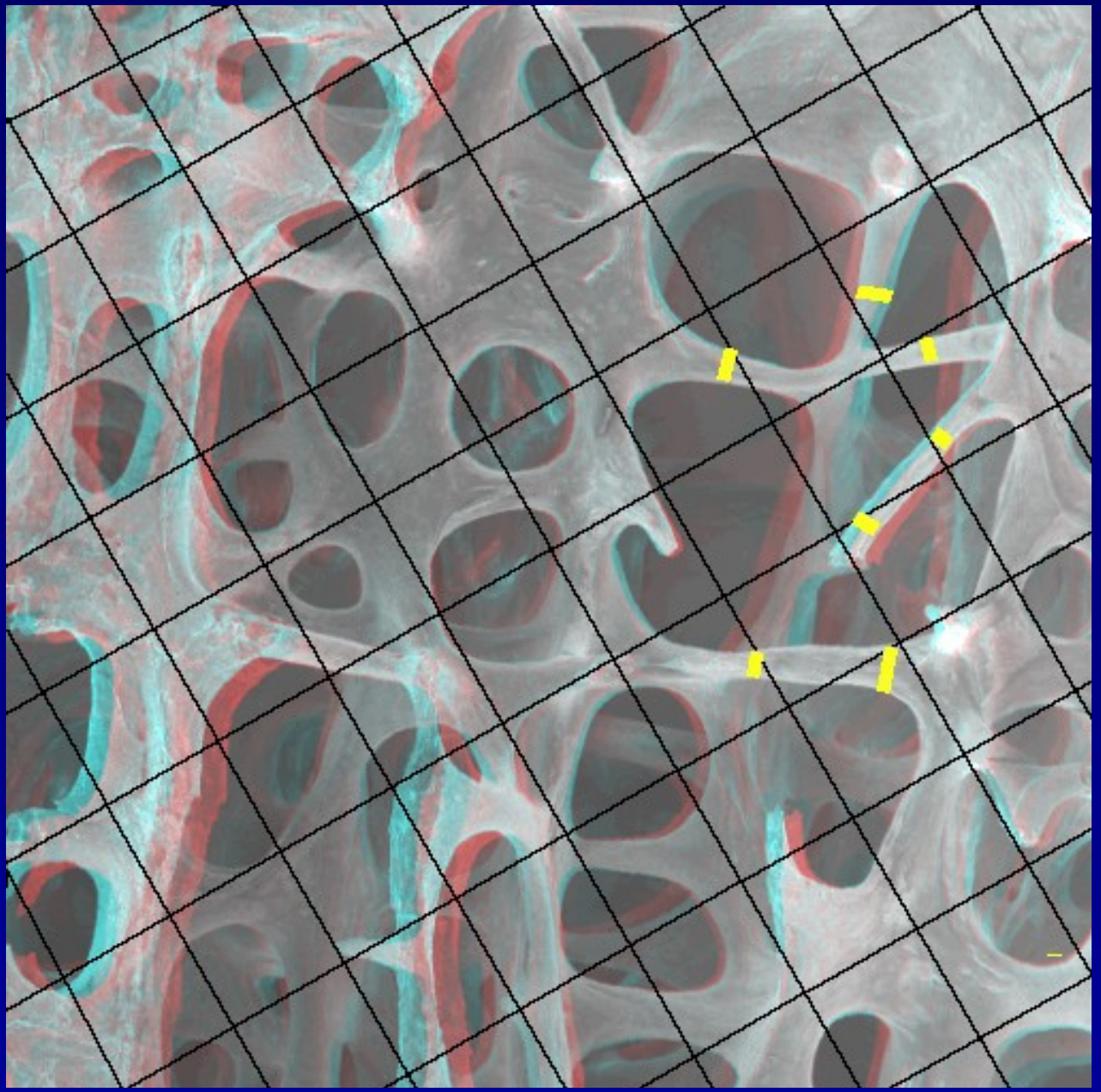
Bone & Jt Lab, IMVS

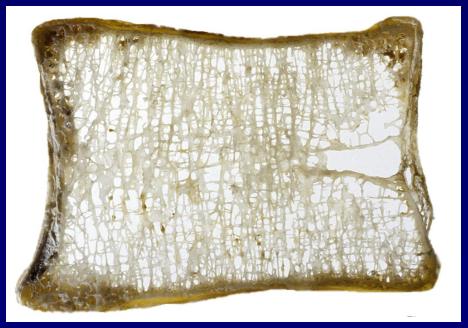
Mosekilde Bone 1988;9:195-9

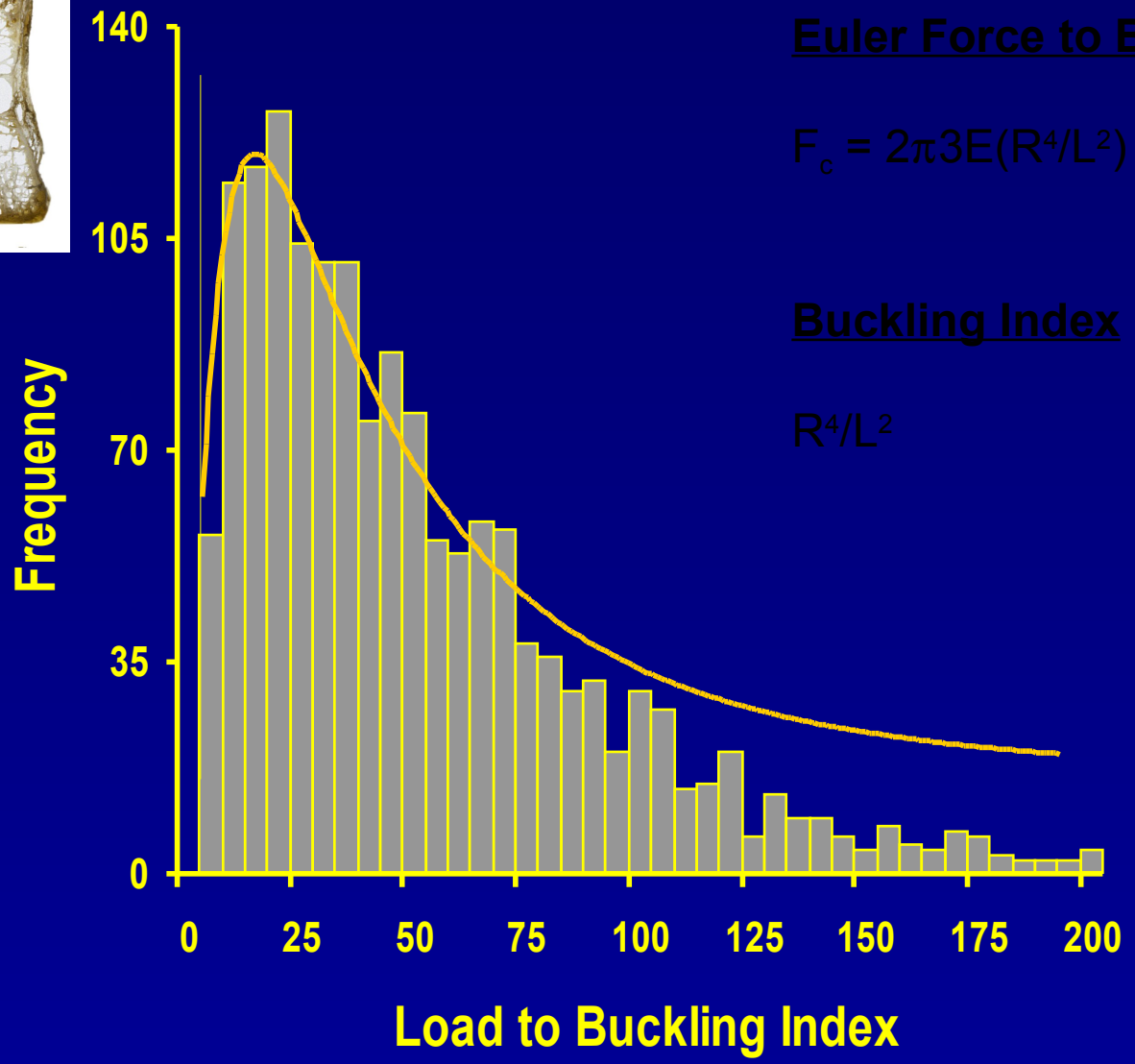
Vertebral body - anaglyph



NL Fazzalari
Bone & Jt Lab, IMVS

Buckling index distribution





Euler Force to Buckling

$F_c = 2\pi 3E(R^4/L^2)$

Buckling Index

R^4/L^2

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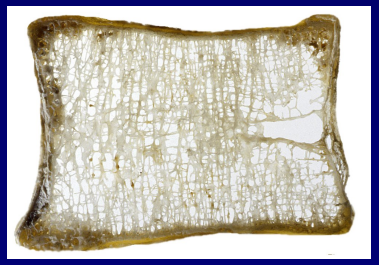
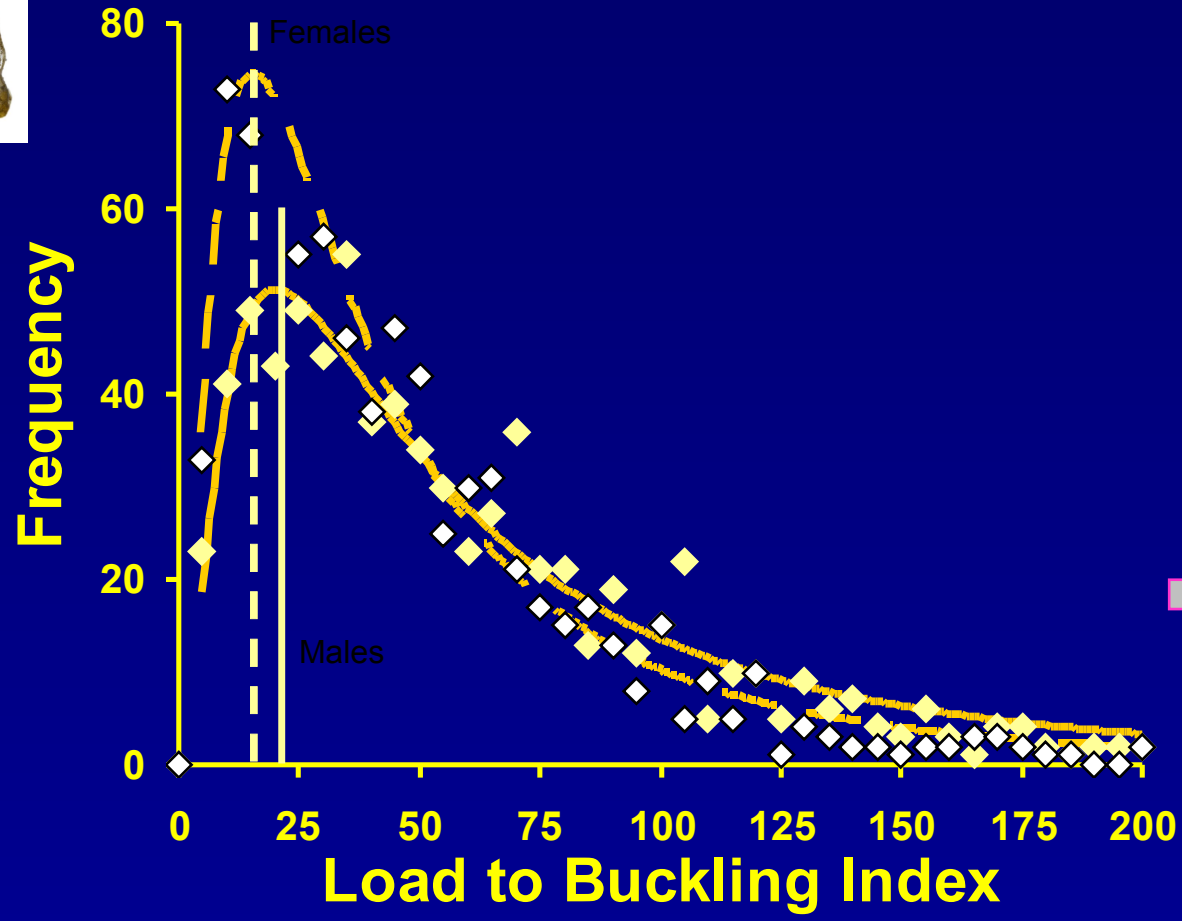
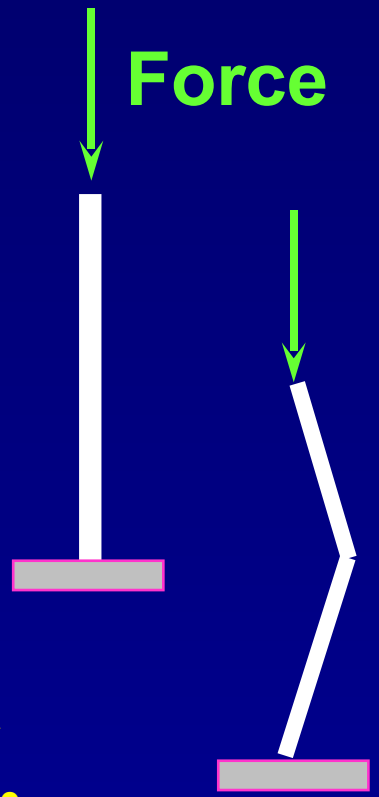
Bone & Jt Lab, IMVS

Sutton-Smith et al. Clinical Anatomy 2006;19:12–8

Buckling index distribution by sex







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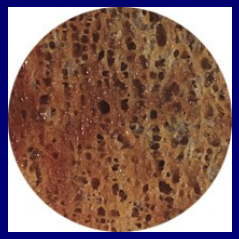
Sutton-Smith et al. Clinical Anatomy 2006;19:12–8

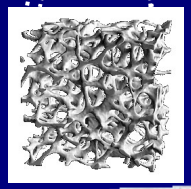
Mechanical test

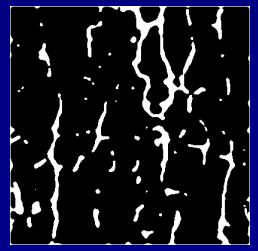
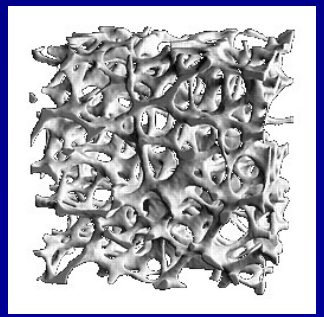
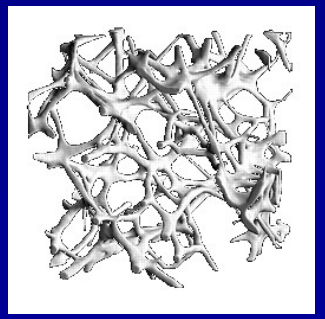
Aim

Investigate the effects of overload in orthogonal directions on longitudinal and transverse mechanical integrity in human vertebral trabecular bone.

Protocol





Badiei et al. JBMR 2007;22(11):1690-9

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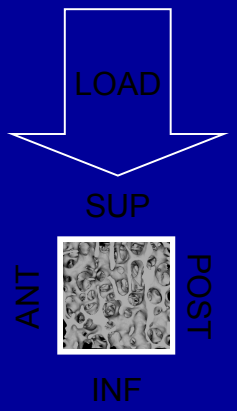
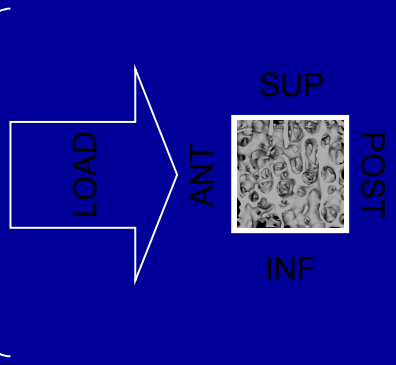
Test protocol

SI GROUP

1ST OVERLOAD (SI)



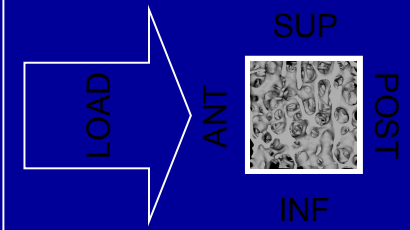
2ND OVERLOAD (S/A)



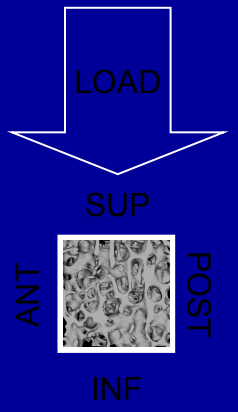
BV/TV = 10.70 ± 1.47
n = 12

AP GROUP

1ST OVERLOAD (AP)



2ND OVERLOAD (A/S)



BV/TV = 10.79 ± 1.43
n = 12

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Badiei et al. JBMR 2007;22(11):1690-9

Mechanical Anisotropy

Differences in superoinferior to anteroposterior mechanical properties (UFS, E and u) were greater than differences resulting from overloading orthogonal structures.

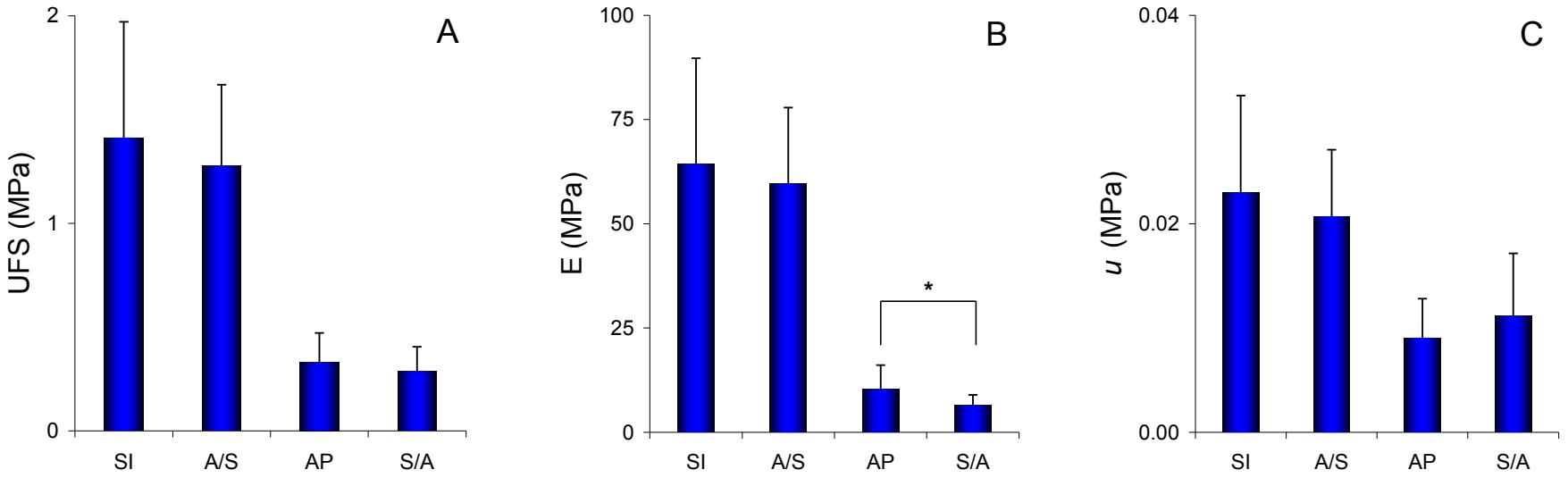
SI Versus AP → UFS: 76%*, E: 84%* and u: 61%*

A/S Versus S/A → UFS: 77%*, E: 89%* and u: 46%*

SI Versus A/S → UFS: 9%#, E: 10%# and u: 10%#

AP Versus S/A → UFS: 15%#, E: 35%** and u: 20%#

#: N.S., *: p < 0.01, **: p = 0.03



Thus, AP elements may have a significant role in the dissipation of energy during trauma acting as sacrificial elements, allowing dissipation of energy away from SI elements, thereby minimising damage, analogous to the crumple zone in vehicles.

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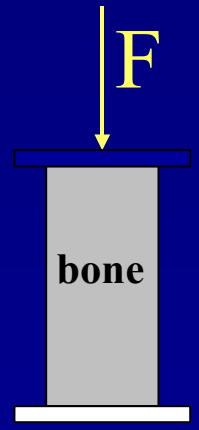
Badiei et al. JBMR 2007;22(11):1690-9

Mechanical test

Aim

- To investigate whether local variations in bone morphometric parameters are linked to localized failure regions of cancellous bone

Protocol



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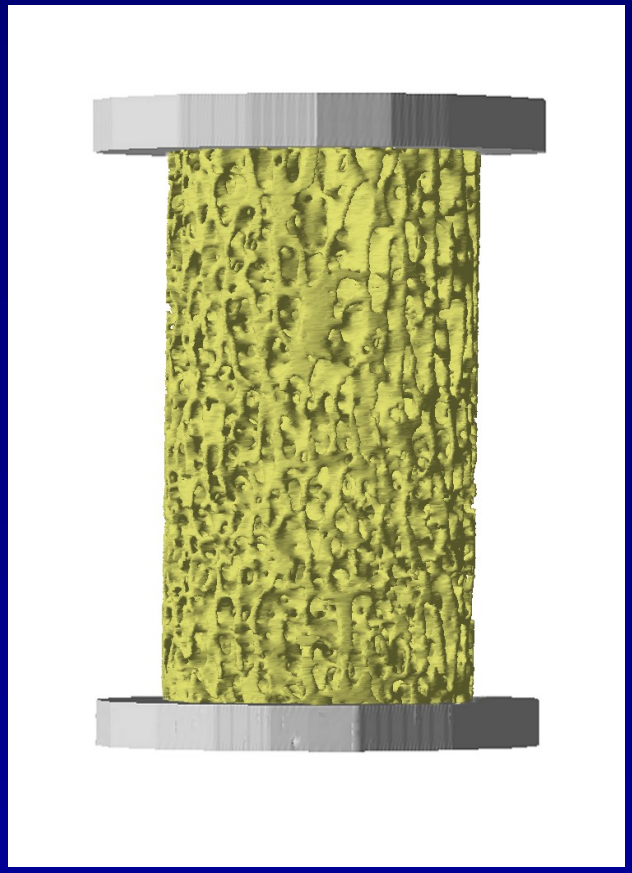
Perilli et al. J Biomech. 2008;41(2):438-46.

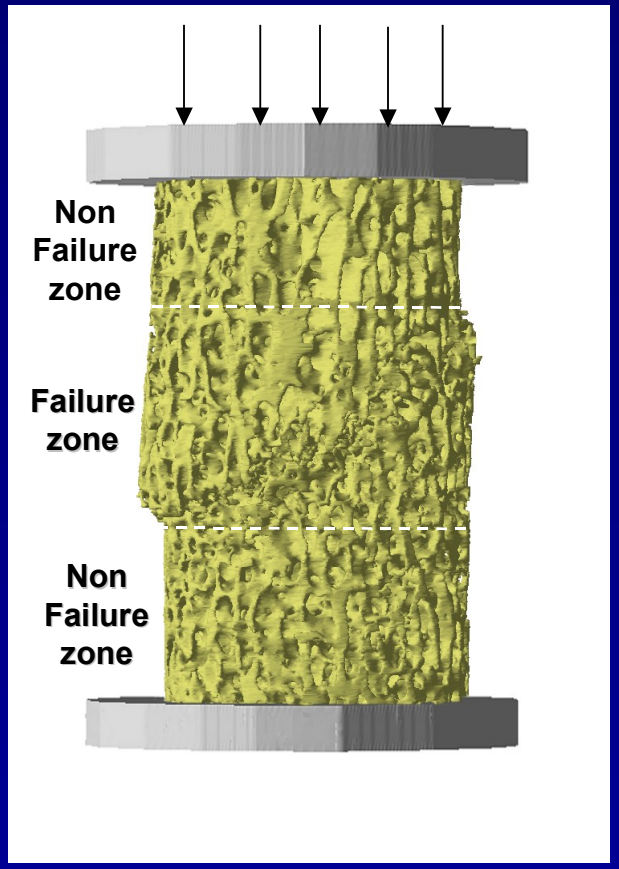
MicroCT imaging

3D reconstructions

Cancellous Bone cylinder before compression test



Cancellous Bone cylinder after compression test



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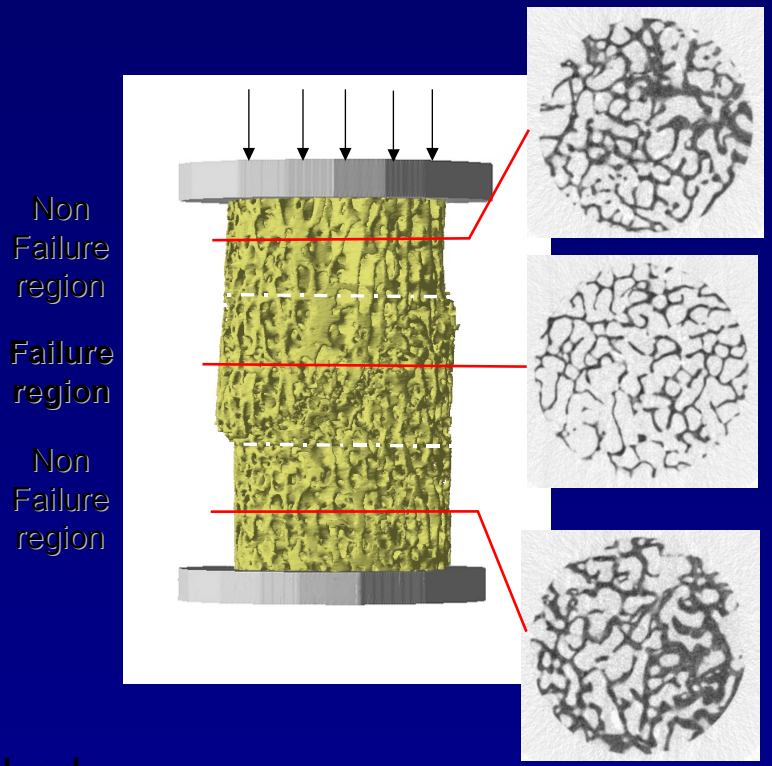
Failure vs non-failure region

	Failure regions Mean ± SD	Non-Failure regions Mean ± SD
BV/TV (%):	24.5±7.8	28.5 ± 9.1
Tb.Th (µm):	125 ± 29	133 ± 27
Tb.Sp (µm):	423 ± 147	369 ± 129
Tb.N (1/mm):	1.93 ± 0.43	2.11± 0.46



- The failure region and the non-failure region had significant differences in bone structure parameters

(T-test, P <0.01 for all differences) N= 35

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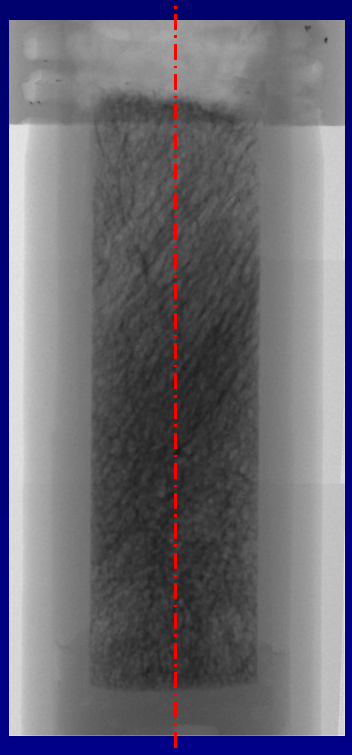
Perilli et al. J Biomech. 2008;41(2):438-46.

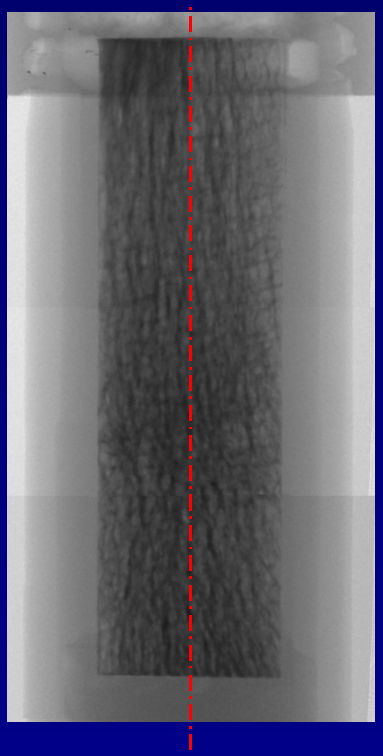
Orientation of the trabeculae has to be aligned with the loading axis for maximum UFS



Misalignment

Misalignment:

Off-axis angle measured with the Mean Intercept Length



Correct Alignment

	Misalignment	Correct Alignment
BV/TV (%)	26.4 ± 8.3	26.6 ± 7.6
UFS (MPa)	11.2 ± 6.4	18.0 ± 6.4

Turner & Cowin. J. Biomech. Eng. 1988;110:213-5.

Öhman, C., et al. J Biomech. 2007;40 (11):2426-33

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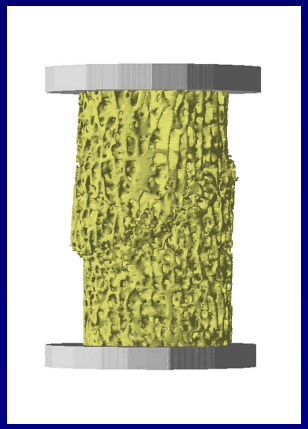
Ultimate stress vs. Average and Failure region BV/TV

Determination coefficients (r^2) of the power regressions between ultimate stress and BV/TV



	Average	Failure region
σ_u vs BV/TV	0.84	0.95

- r^2 increases when failure region BV/TV is used
- BV/TV_{min} is overall best predictor of ultimate stress.

Due to the heterogeneity of human cancellous bone, inside the specimen there is microarchitecture where cancellous bone is more likely to fail.

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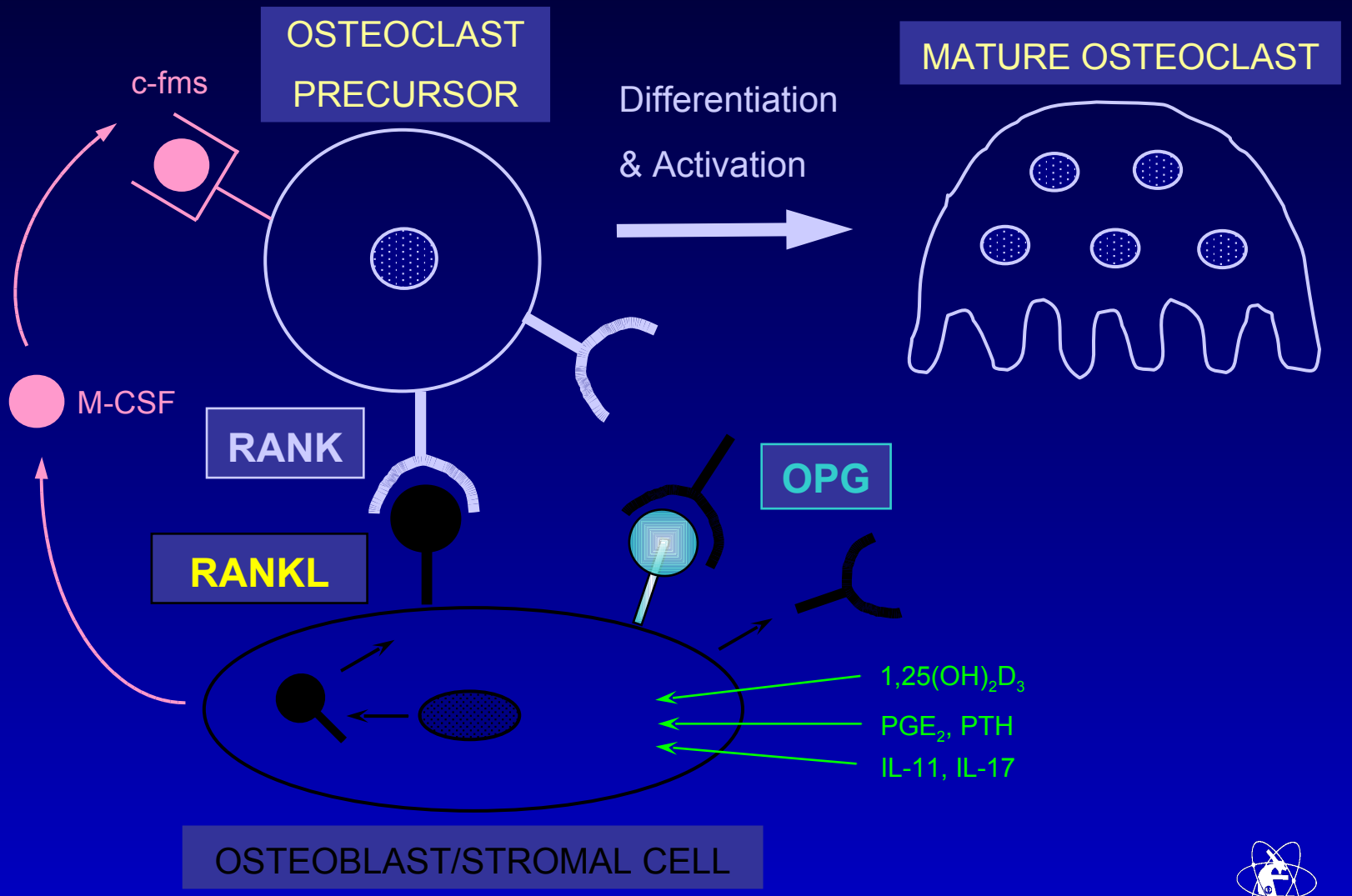
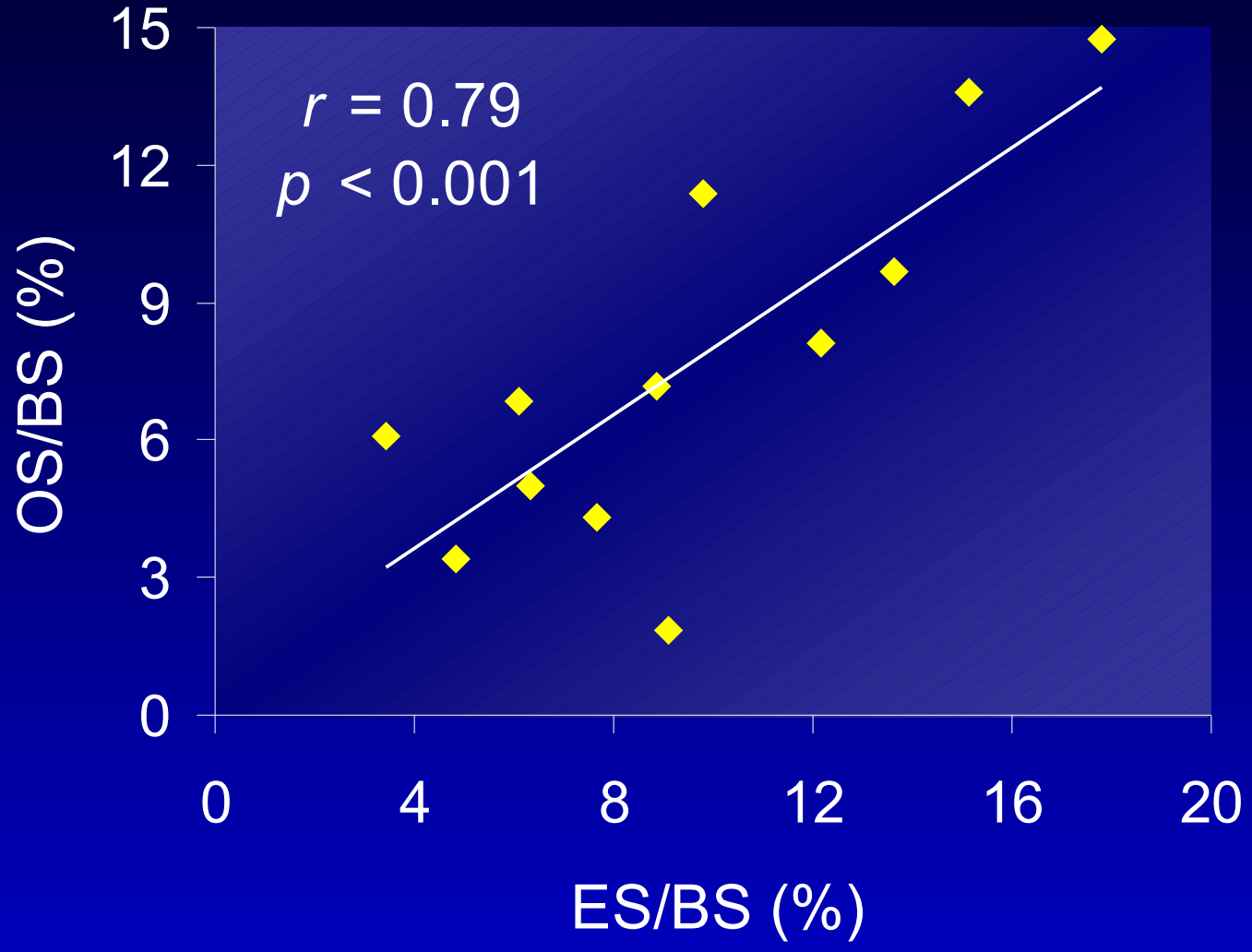
Perilli E. et al. J Biomech 2008;41(2):438–46

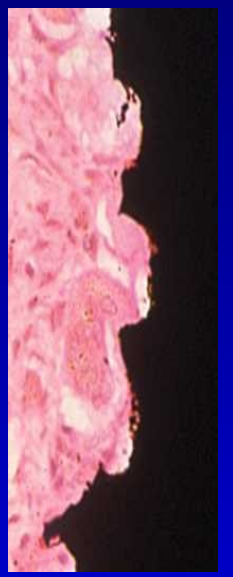
OSTEOCLASTOGENESIS and BONE REMODELLING



JS Kuliwaba
Bone & Jt Lab, IMVS

Osteoid surface vs Eroded surface





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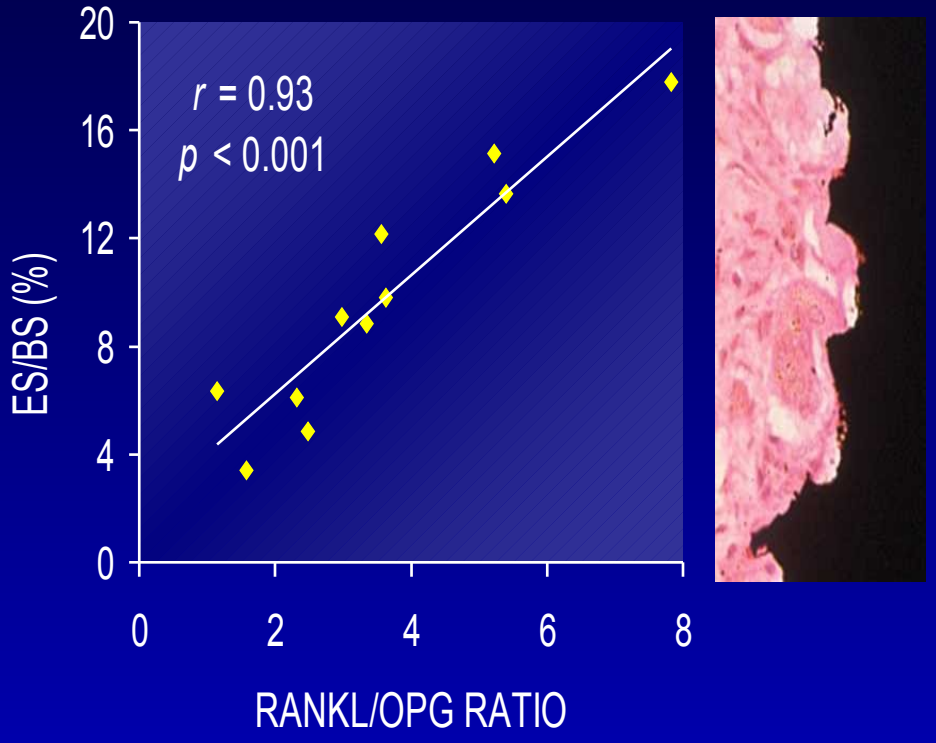
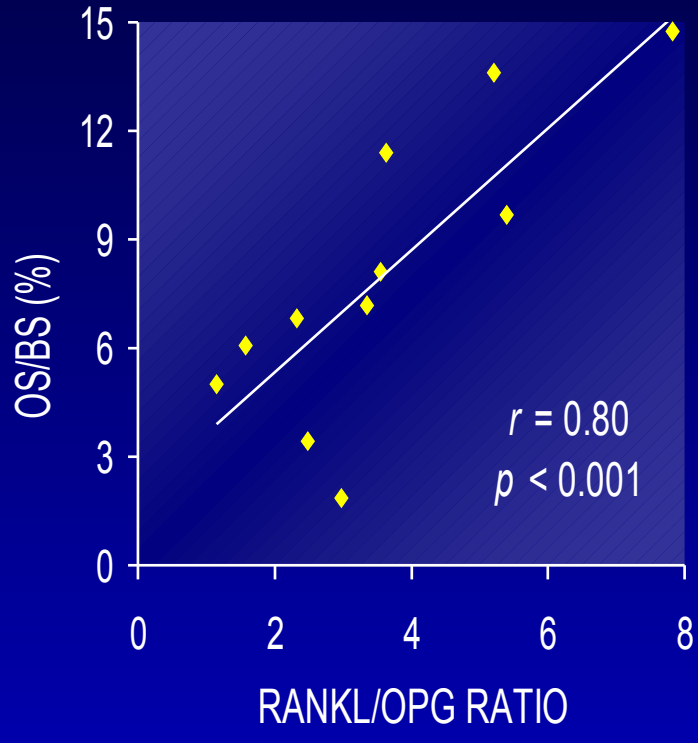
Remodelling bone surface vs RANKL/OPG mRNA





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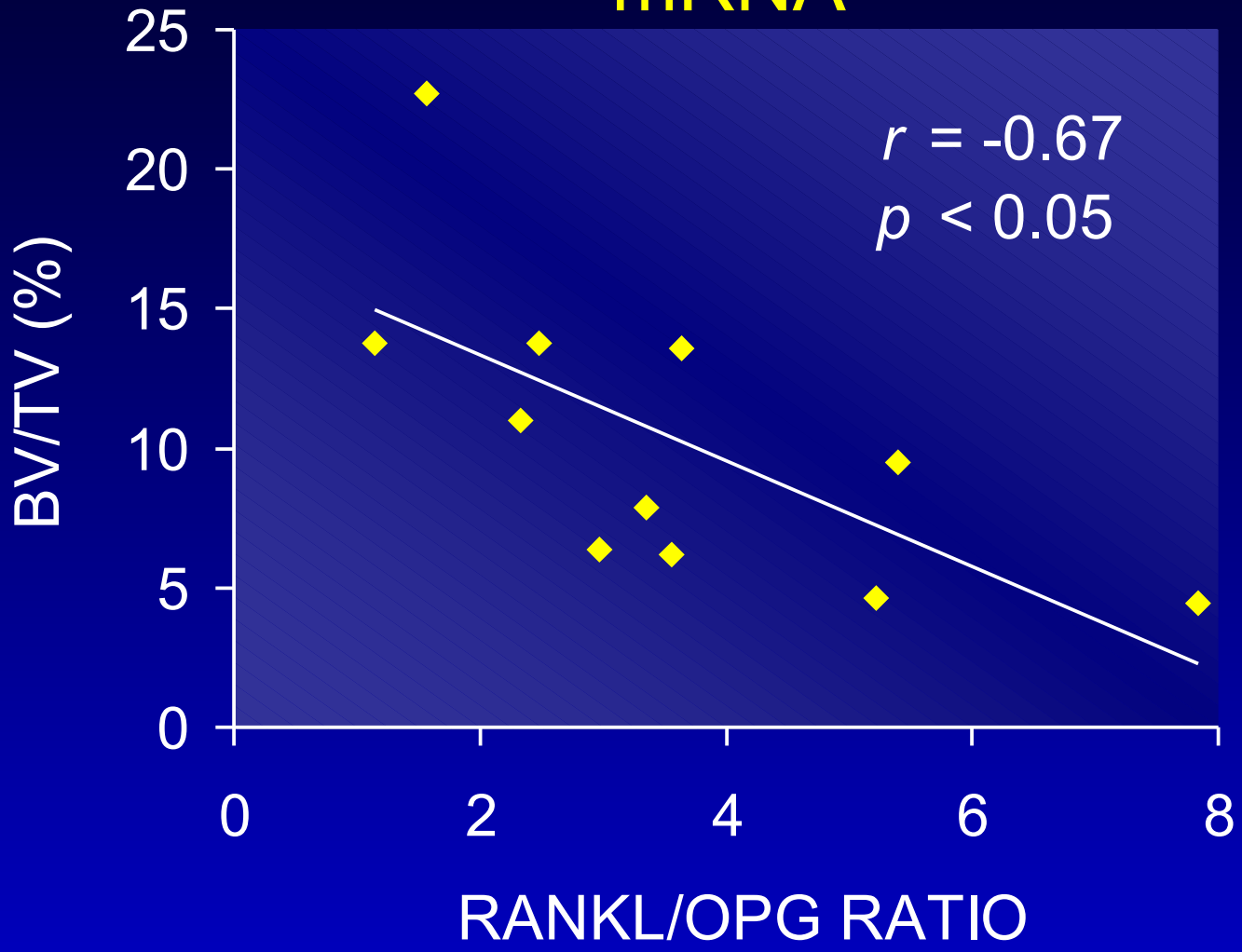
Trabecular bone volume vs RANKL/OPG mRNA



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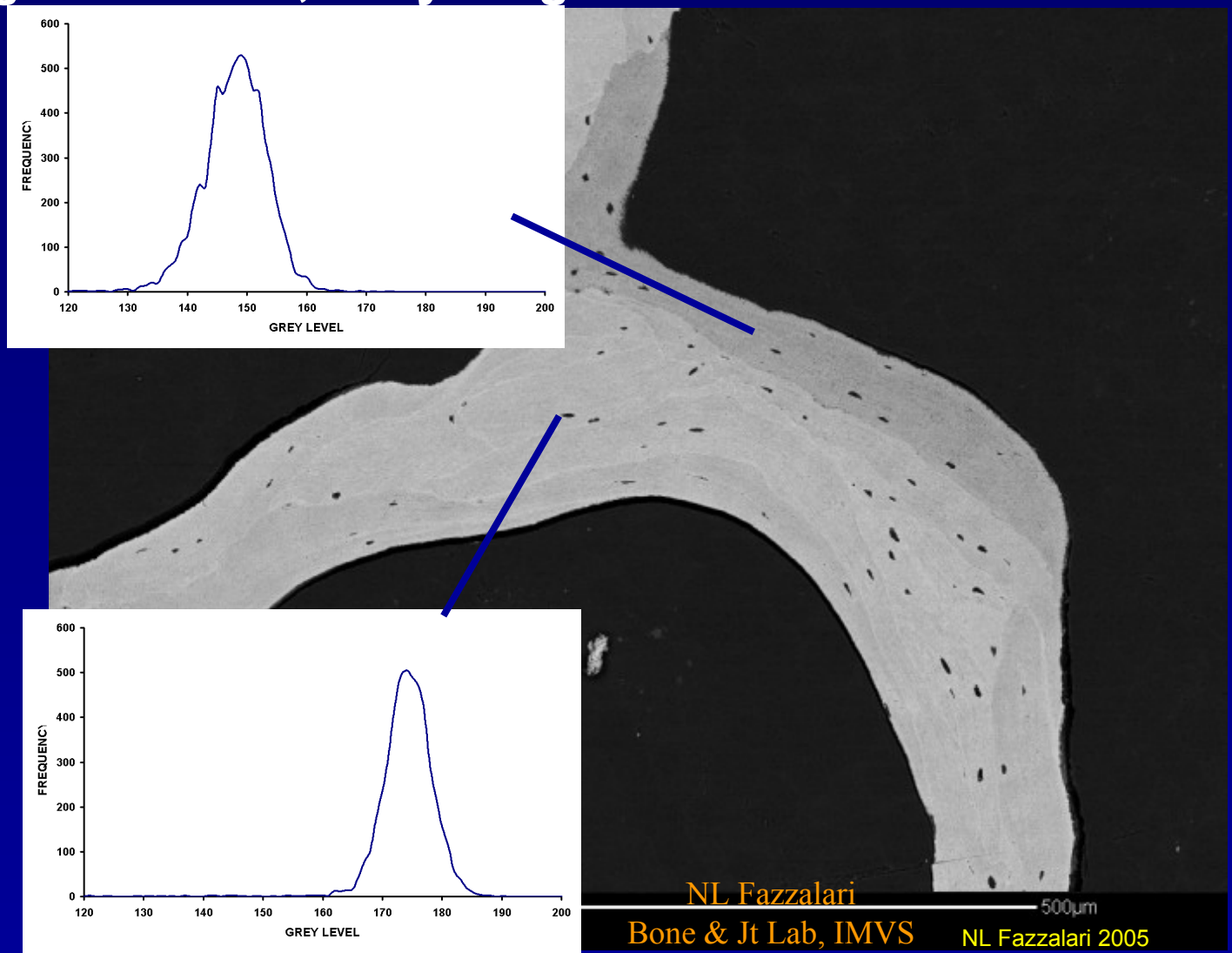
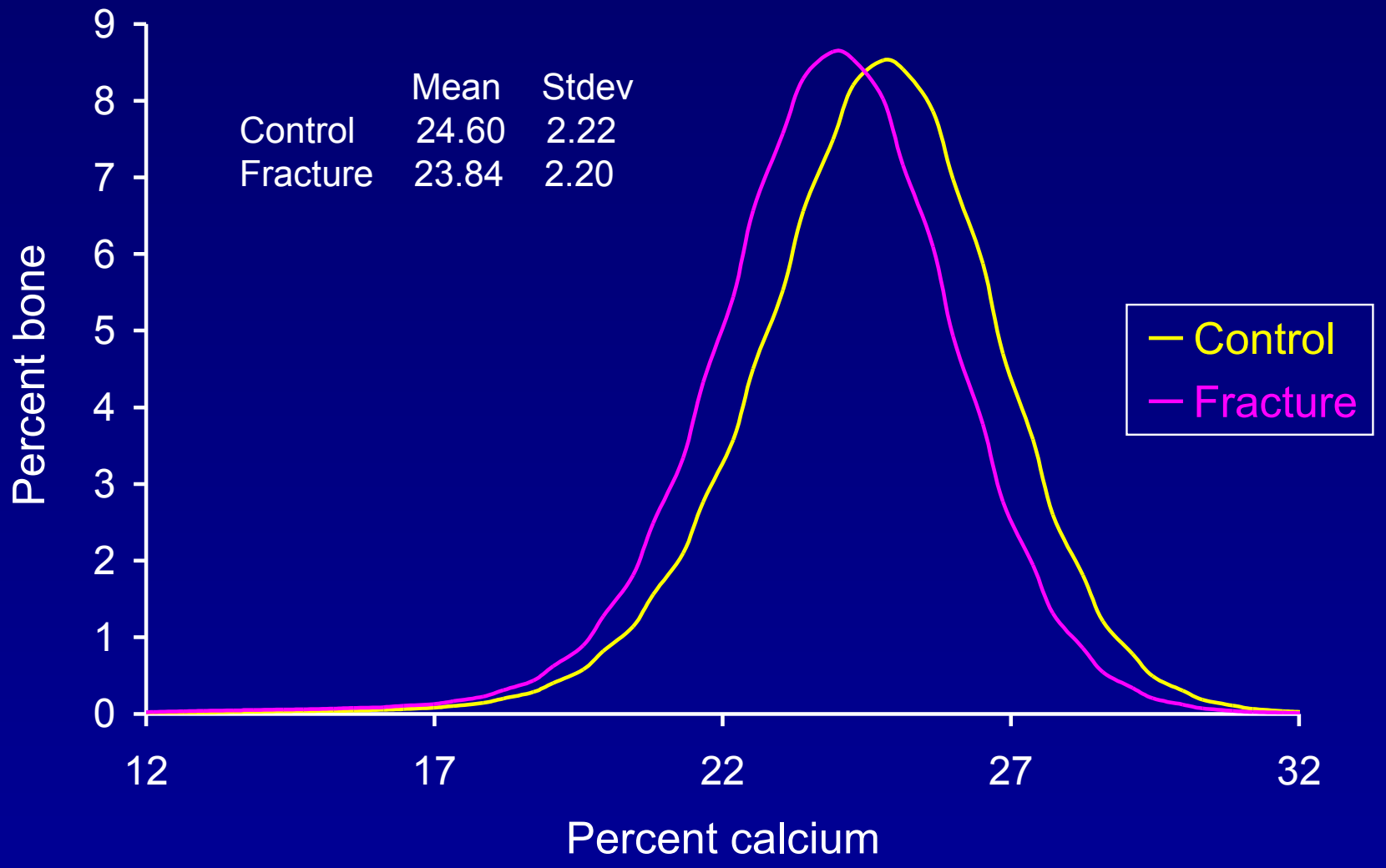
Bone Remodelling and Mineralisation

The higher the rate, the younger and less mineralised the bone



Bone Mineralisation



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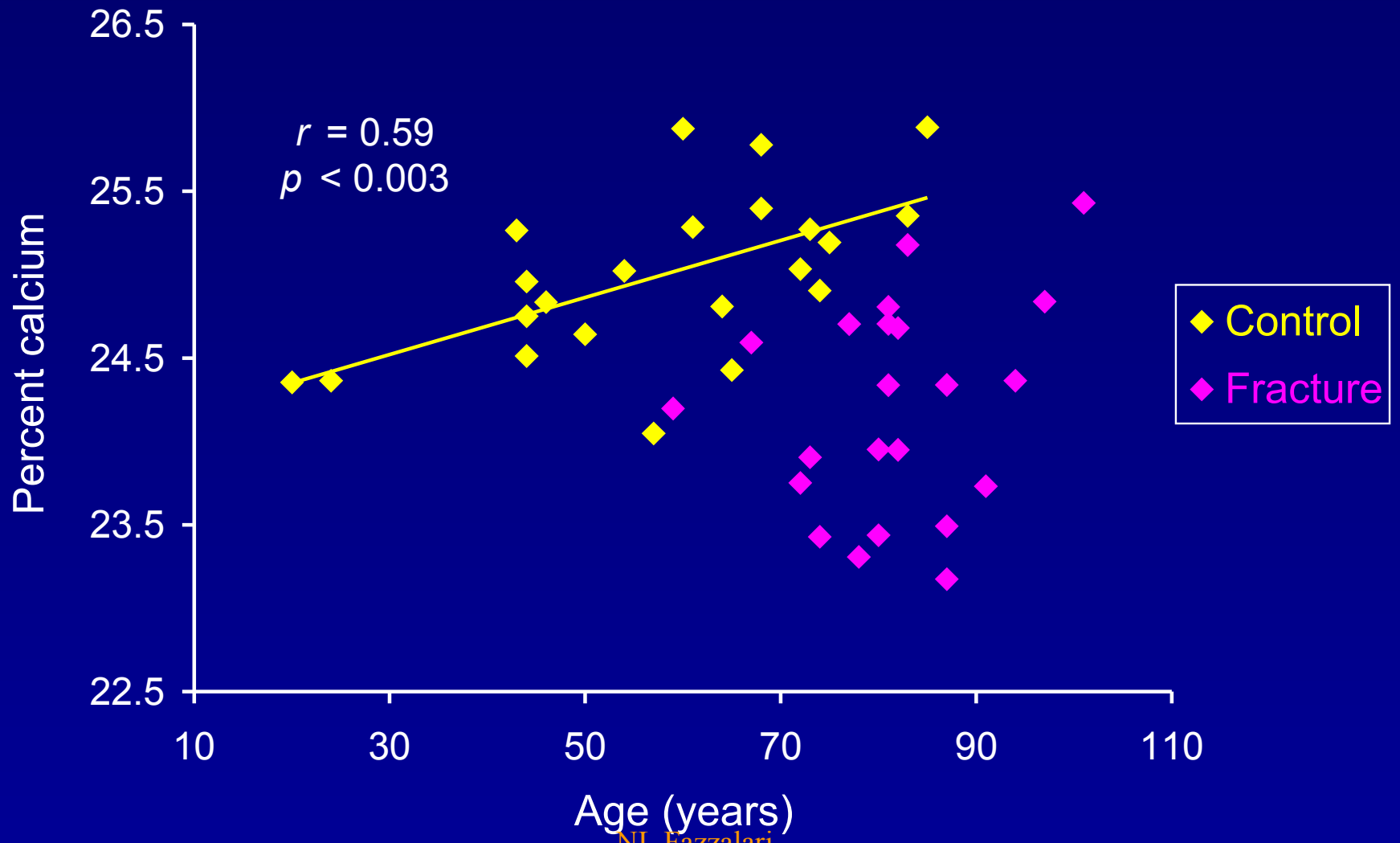
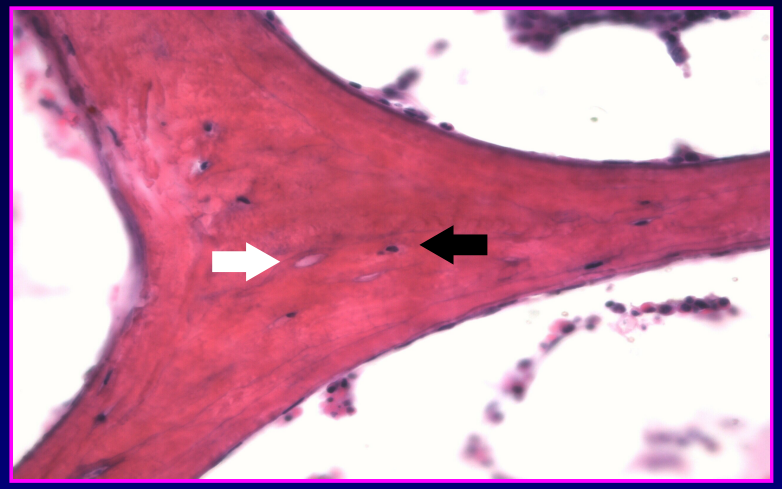
Mineralisation vs. Age

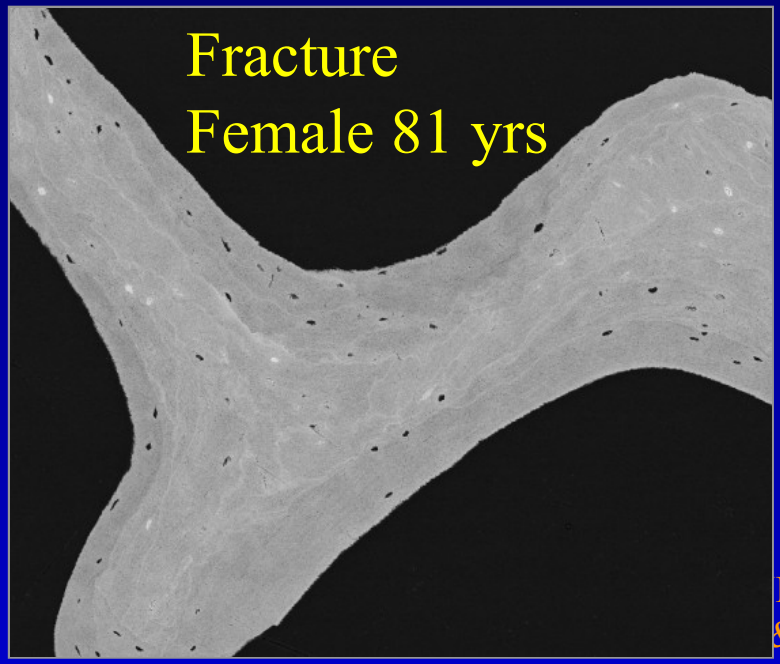


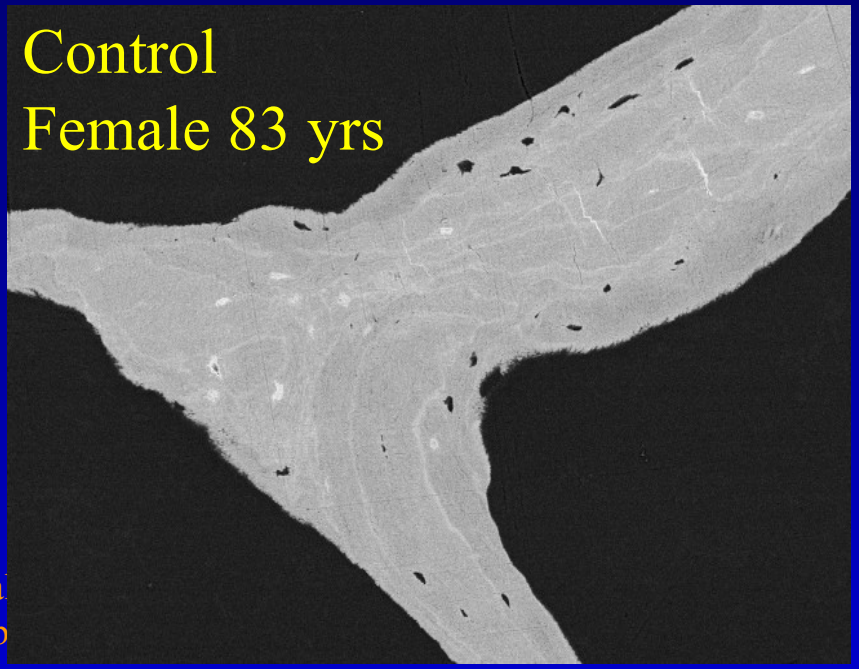
Sutton-Smith et al J Microscopy

Micropetrosis



- qBEI reveals regions of micropetrosis (hypermineralised lacunae) in femoral bone from both fragility hip fracture patients and non-fracture controls.





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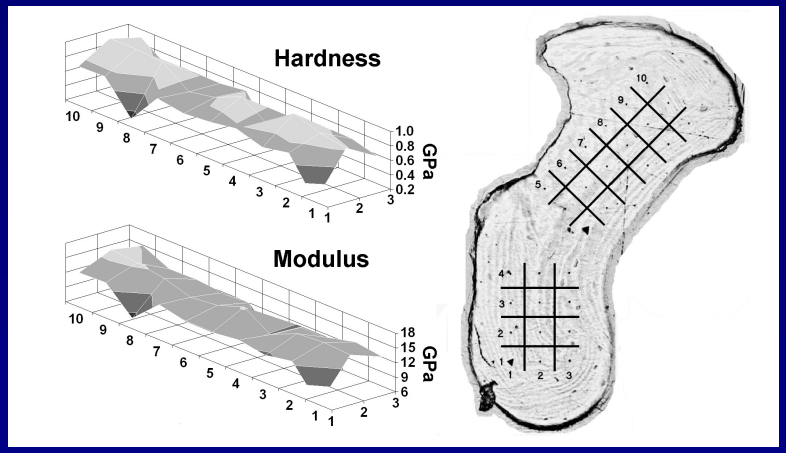
& Jt Lab

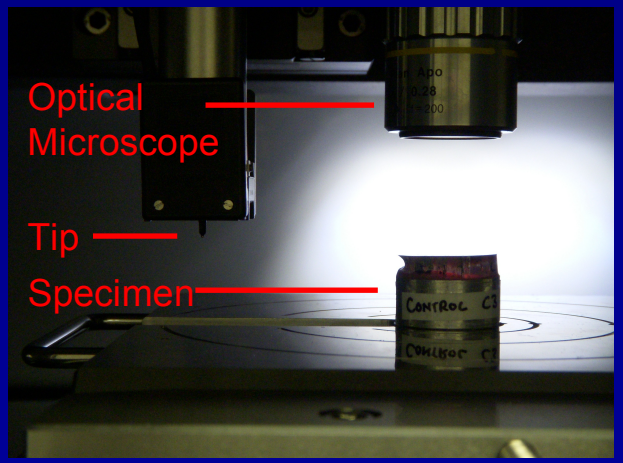
Why nanoindentation?

Recent studies have demonstrated that microhardness and elastic modulus also exhibit significant spatial variation across the areas of individual bone spicules. *(Norman et al., 2008; Mulder et al., 2007)*



Aim

To investigate potential inter-relationships between calcium content and micromechanical properties in human trabecular bone.



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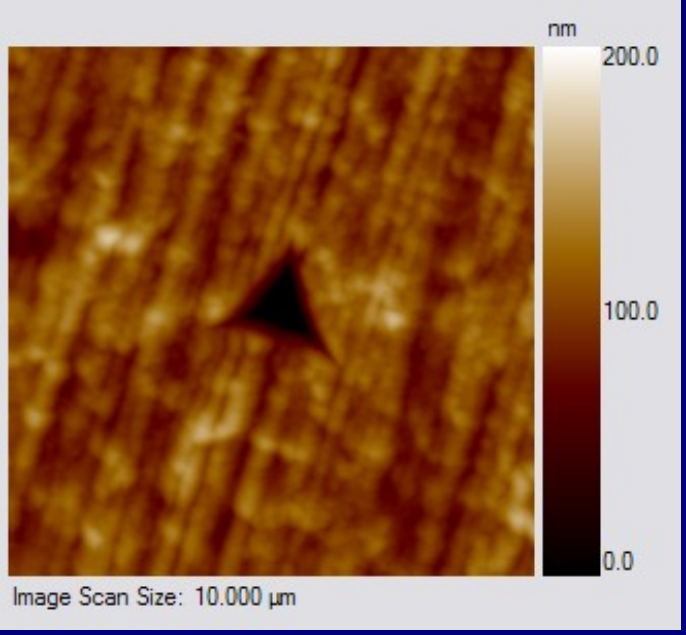
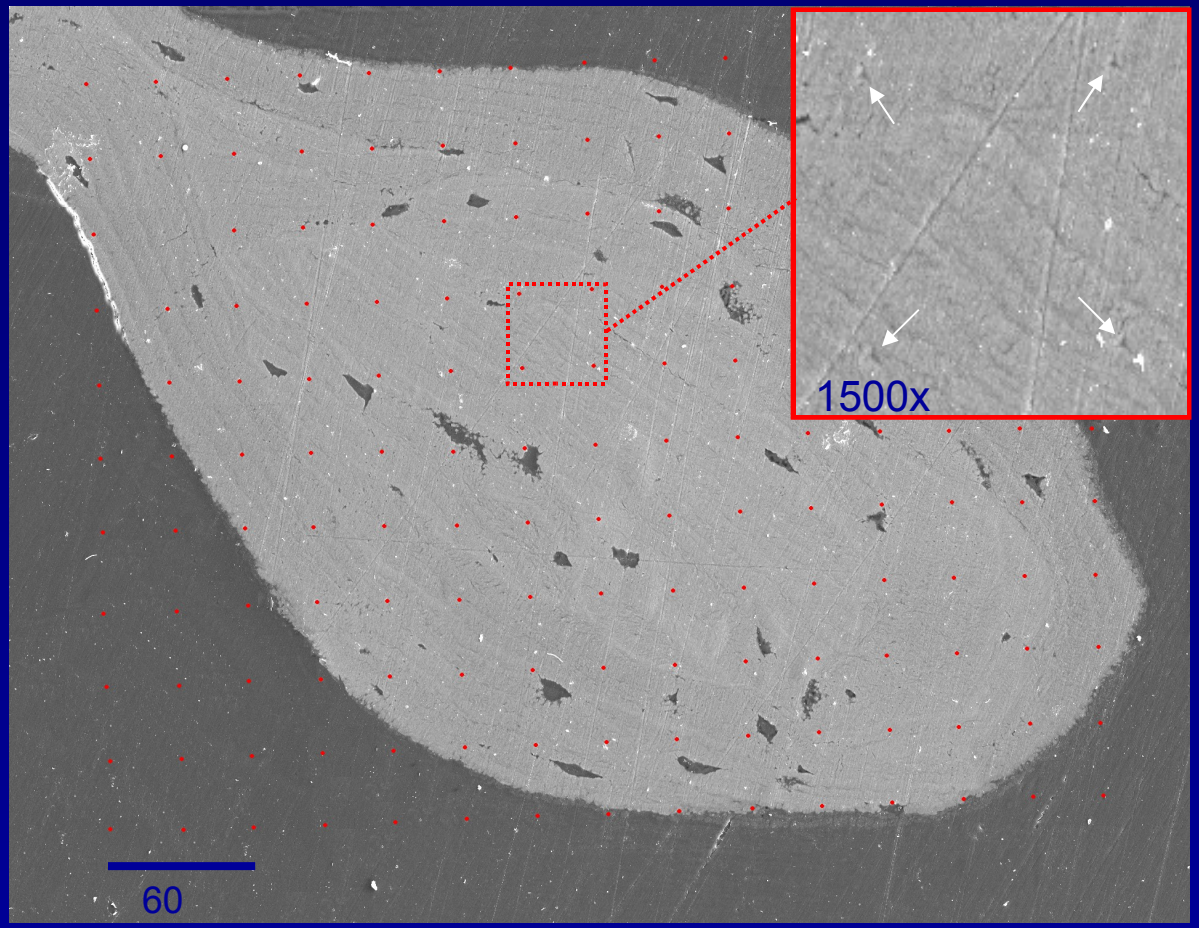
Nanoindentation





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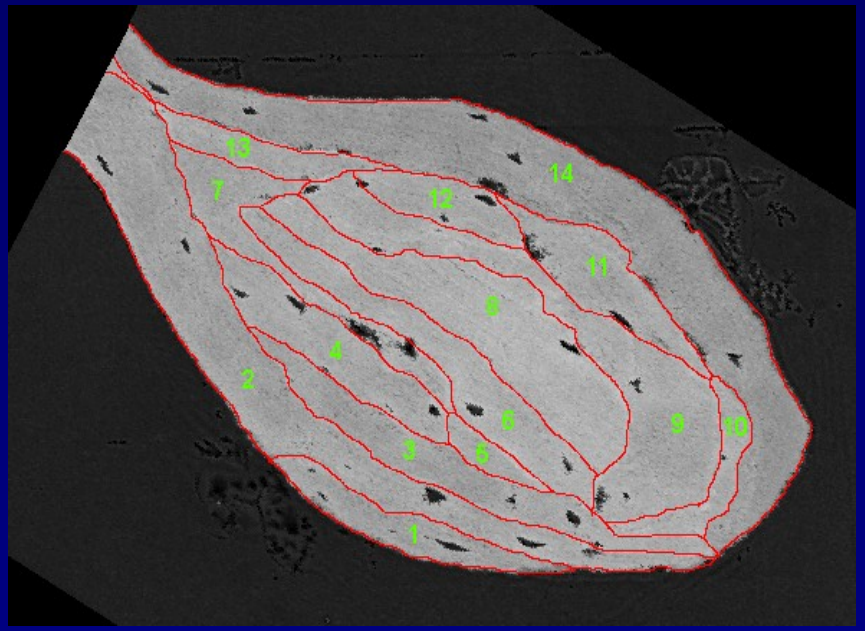
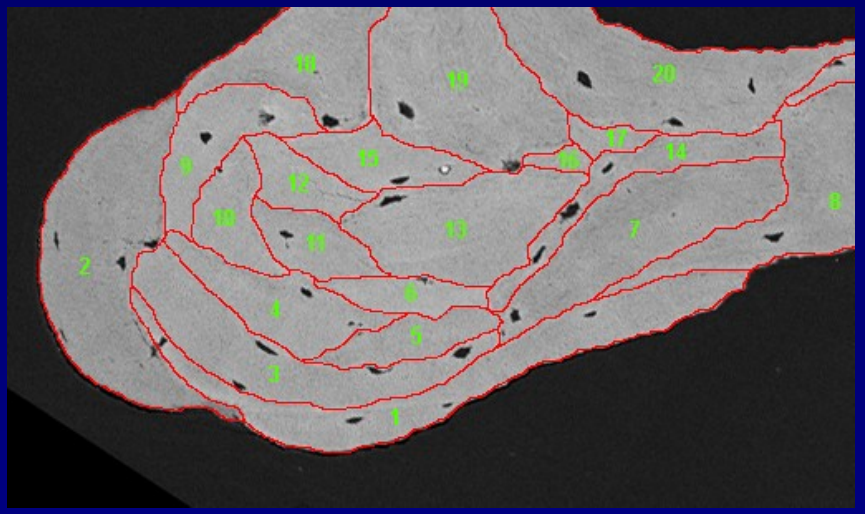
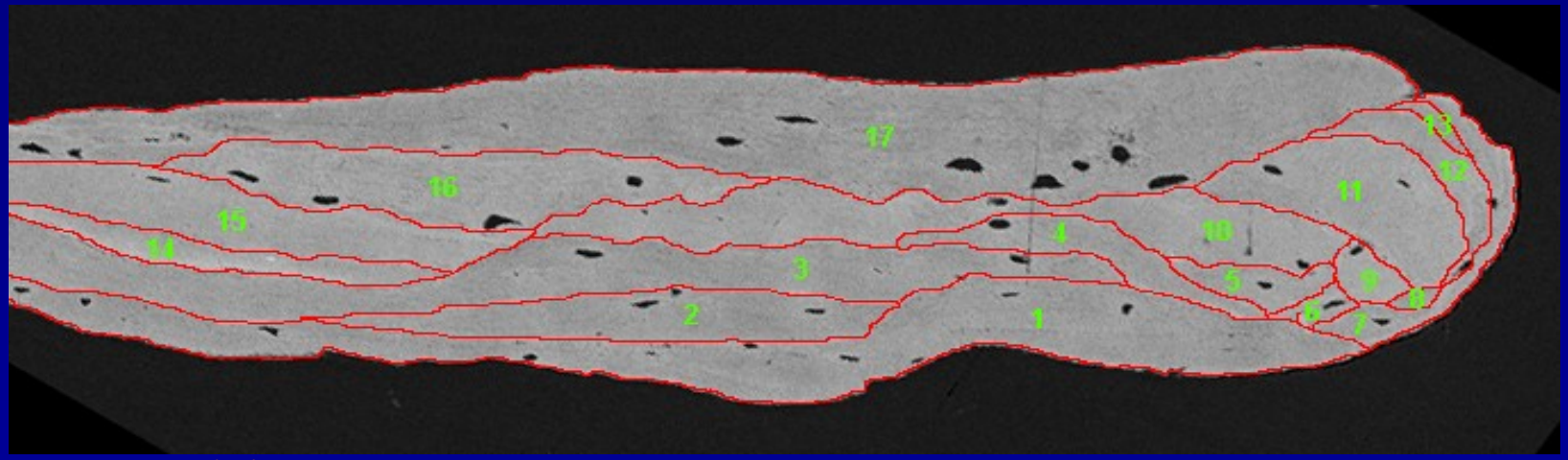
Remodelling packets



Spicule 1 – 14 packets



Spicule 2 – 20 packets



Spicule 3 – 17 packets

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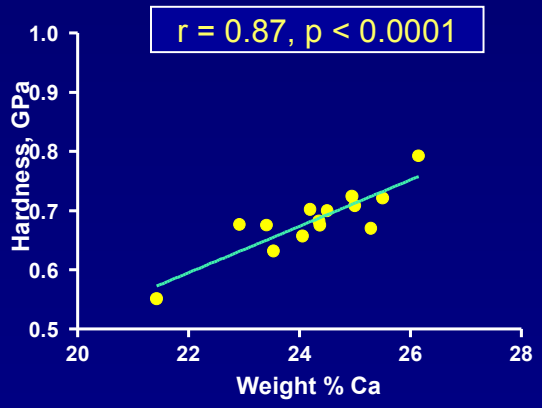
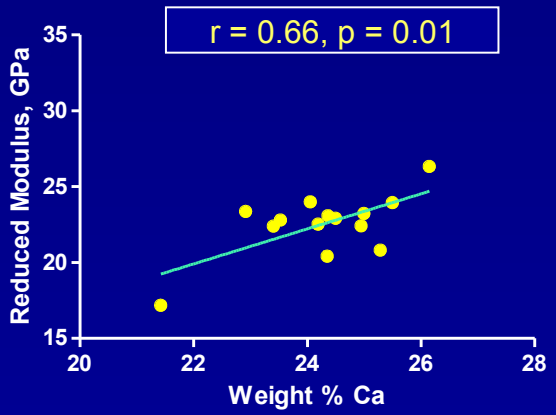
Control case: 44 year old female

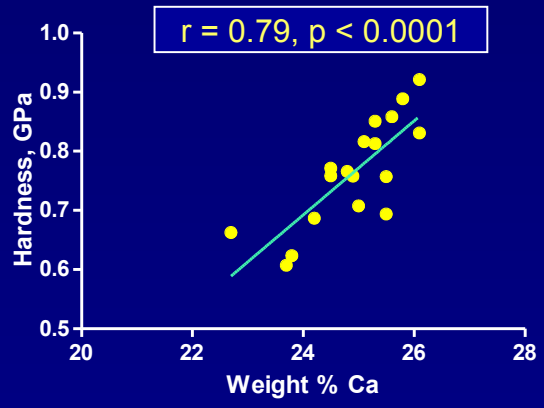
Relationships between calcium content and micromechanical properties for individual bone packets

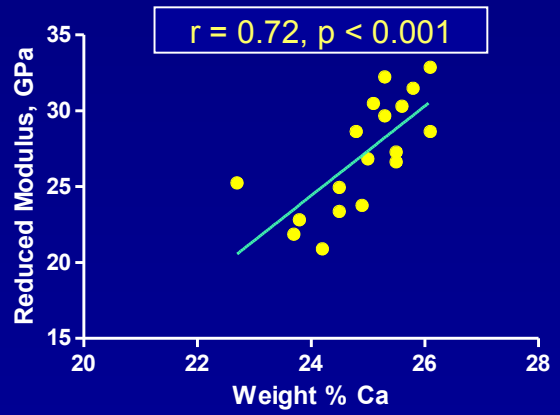
Spicule 1



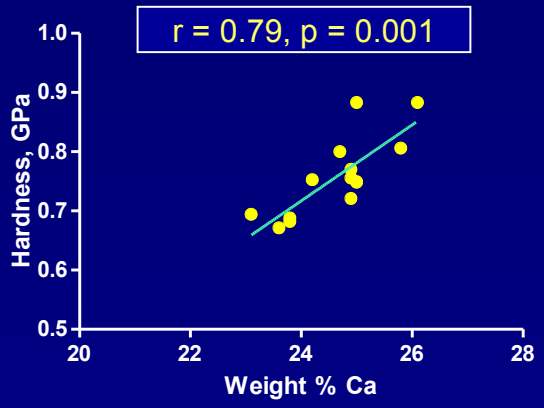


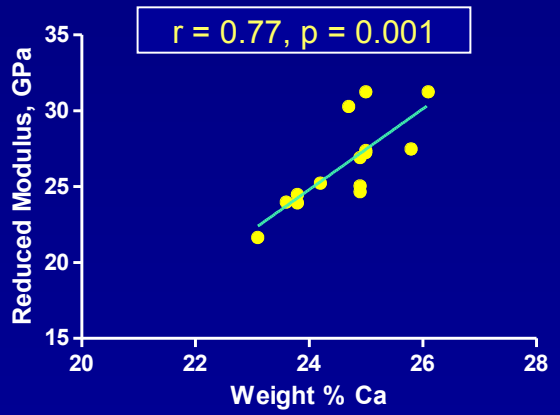
Spicule 2





Spicule 3





(Average of 8 indents per packet across the 3 spicules)

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Fazzalari et al. 2008

Conclusions and Discussion

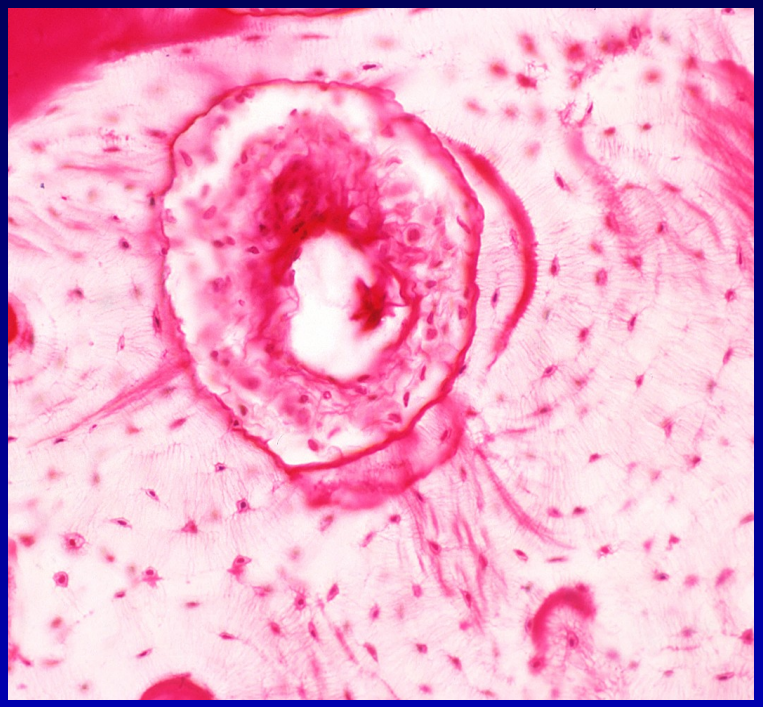
- Hardness and modulus are heterogeneous across the area of individual trabecular bone spicules (confirming previous findings).
- Calcium content correlates significantly with both hardness and modulus for individual bone packets.
- Calcium content appears to correlate more strongly with hardness than with modulus.
- Results will assist analytical and FE model development at the sub-spicule level.
- To build on these preliminary results, further work is planned including investigating how relationships between micromechanical properties and mineralisation may vary following fragility fracture and anti-resorptive therapy.

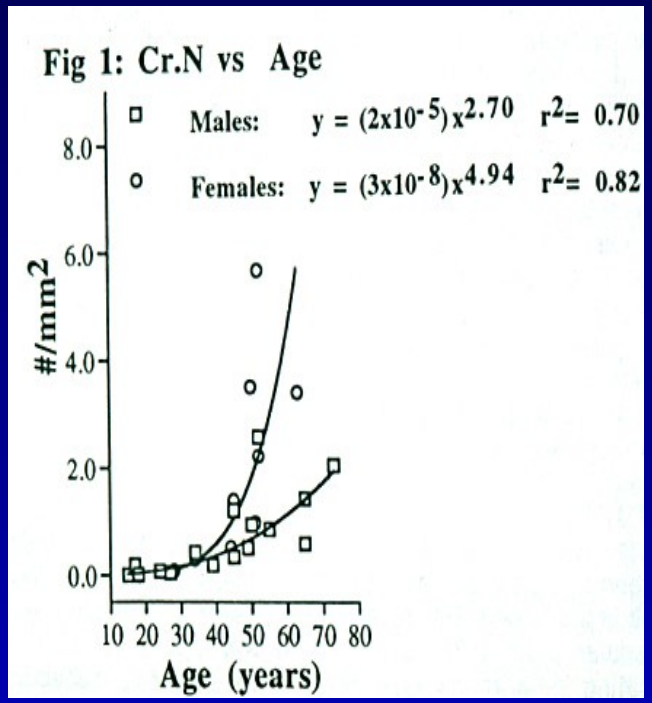
Osteocyte, microdamage and repair

- Physiological strains continually produce fatigue damage in bone
- Damage weakens bone and is associated with osteocyte apoptosis and the activation of remodelling
- Remodelling is the only means by which microdamage can be removed and repaired

Microdamage

Cortical bone





NL Fazzalari
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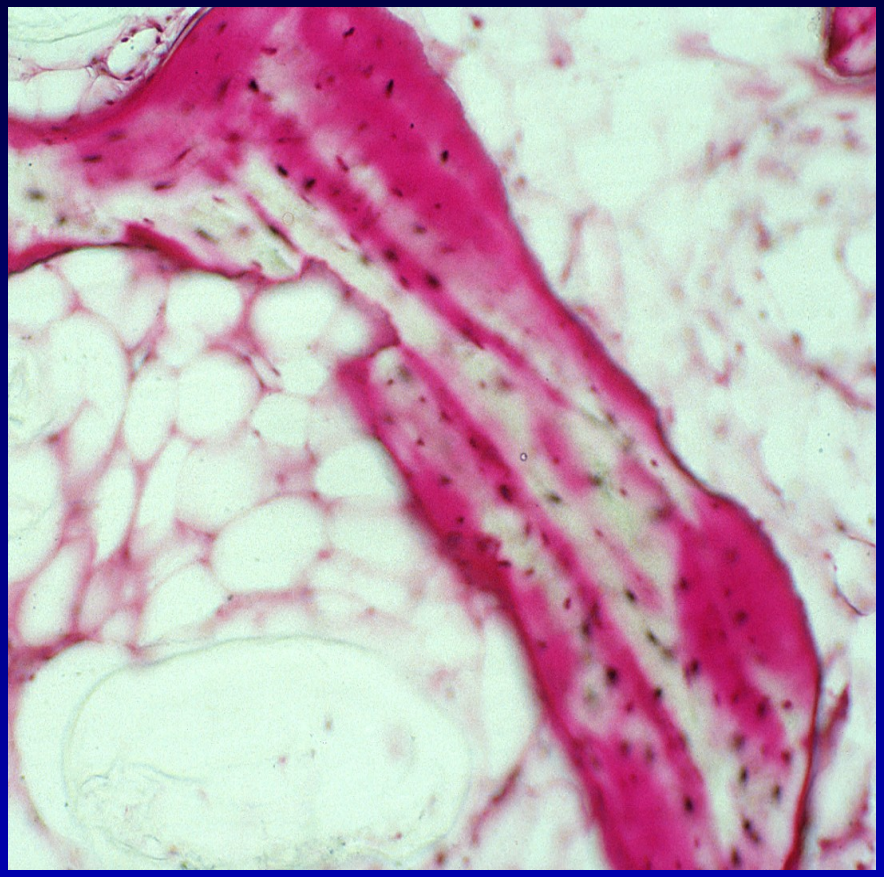
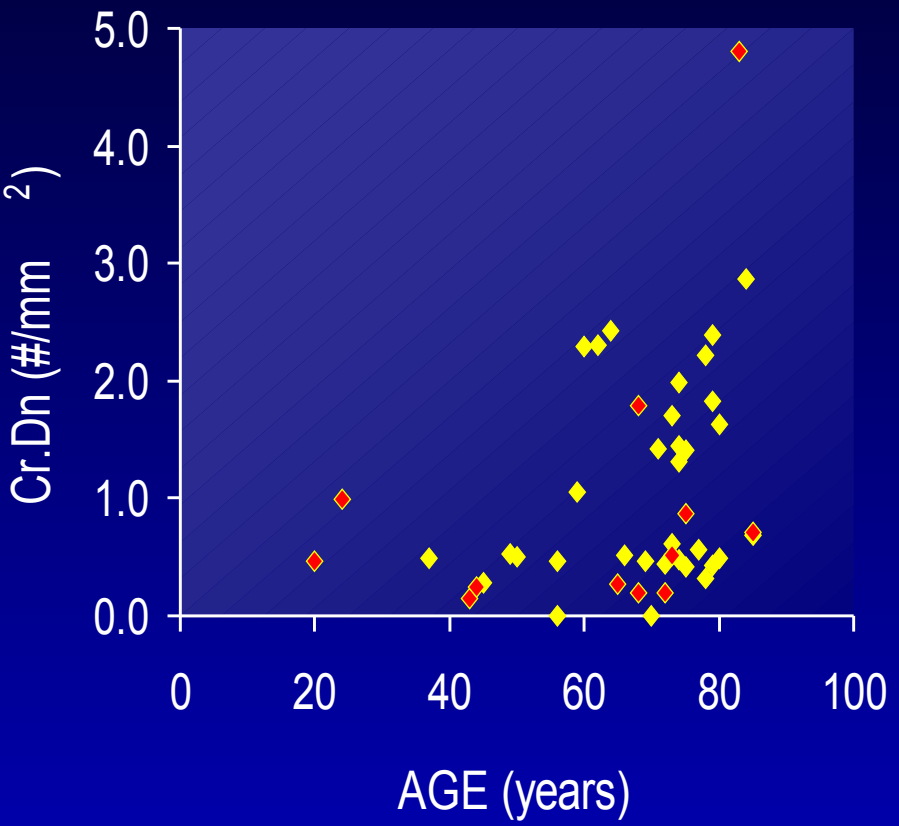
Schaffler et. al., 1995

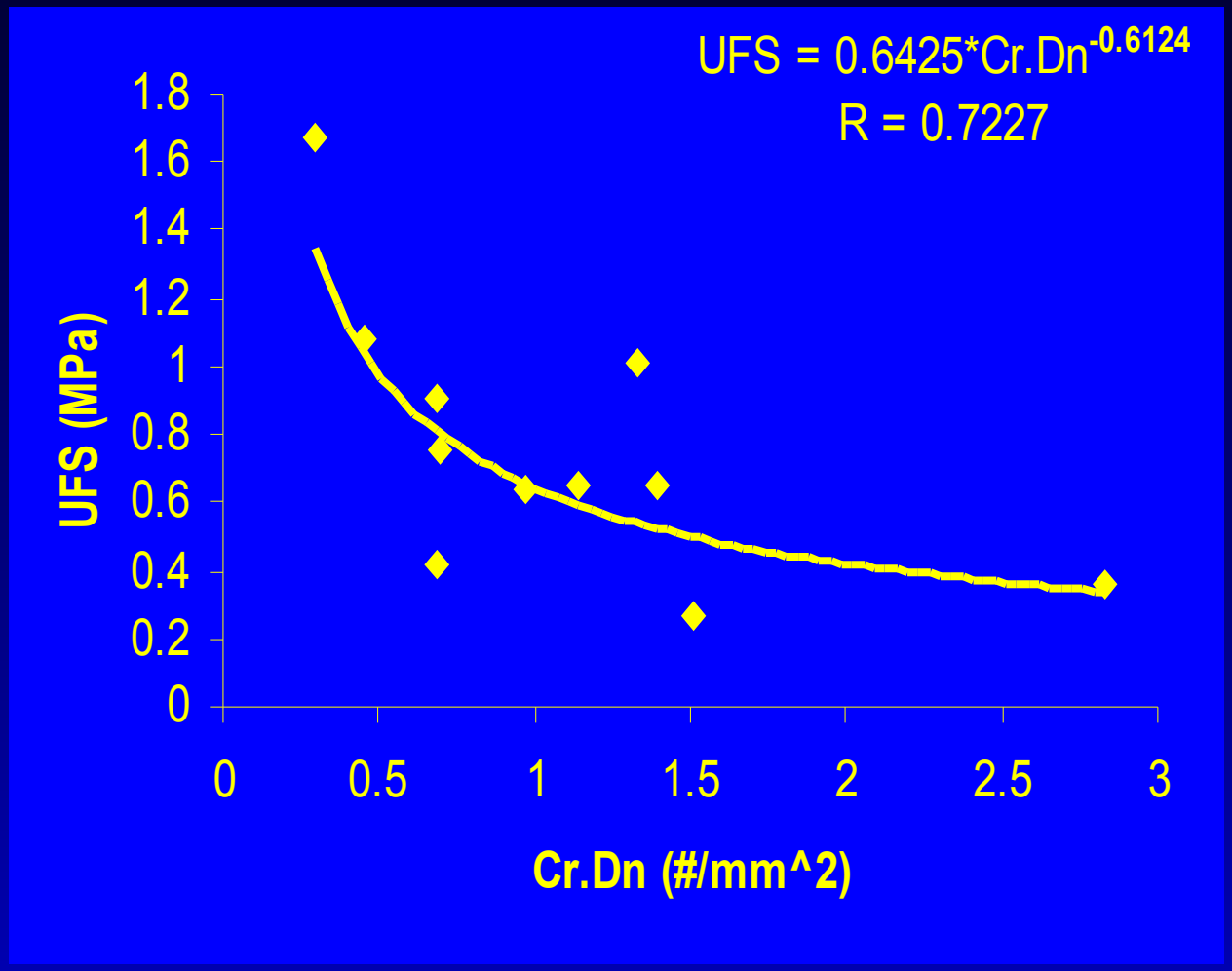
Trabecular bone microdamage



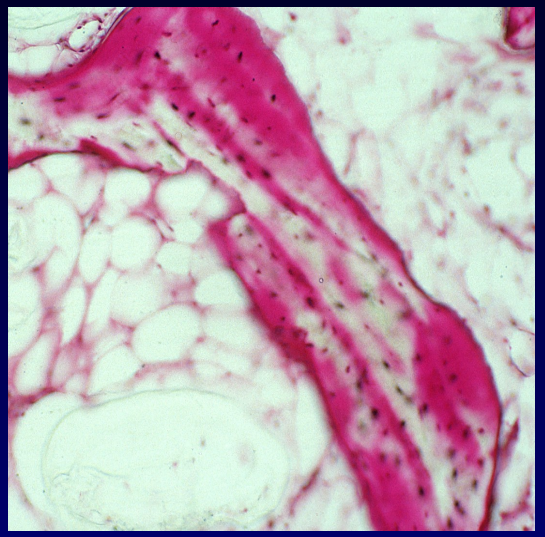


NL Fazzalari et al Bone 2002

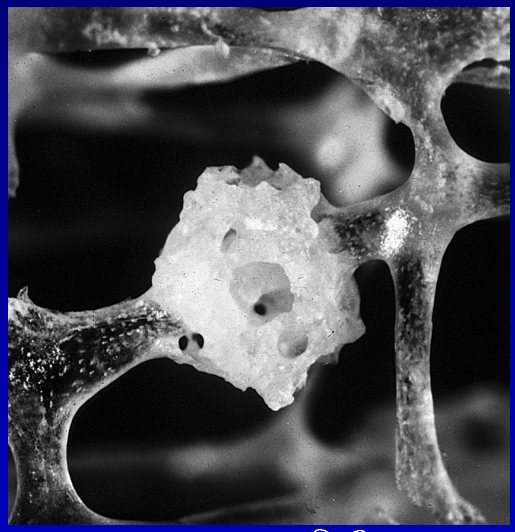
Bone & Jt Lab, IMVS



microdamage



microfracture



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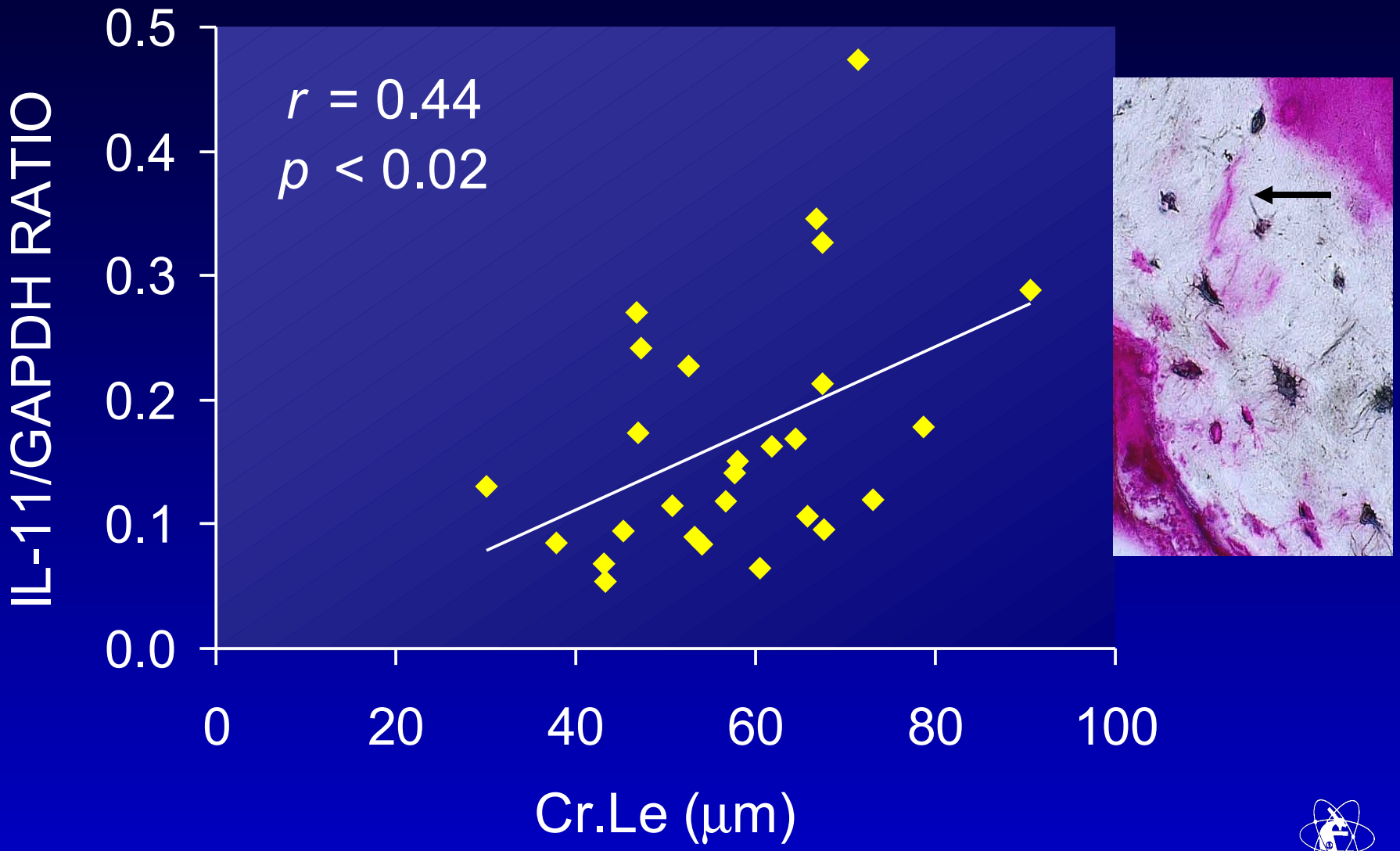
IL-11 mRNA vs Microcrack Length



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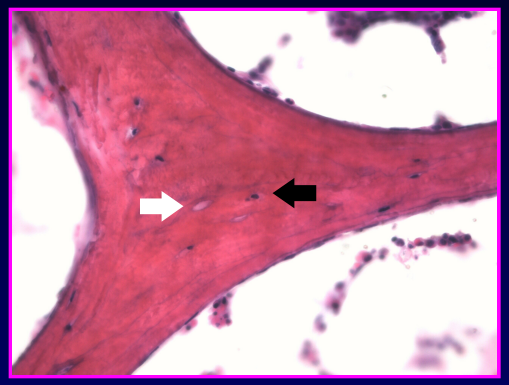
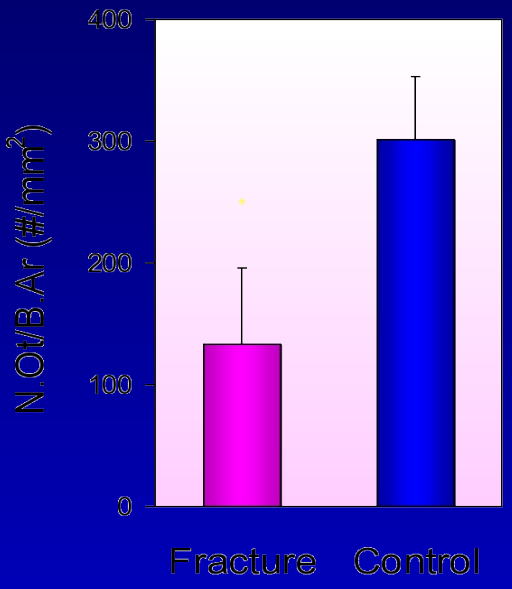
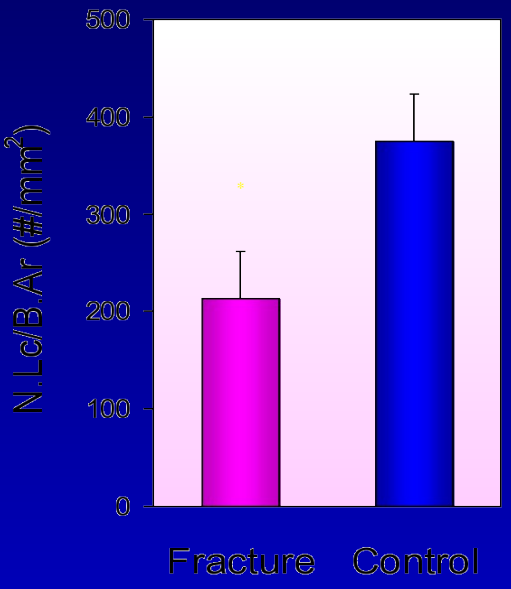


Osteocyte Density



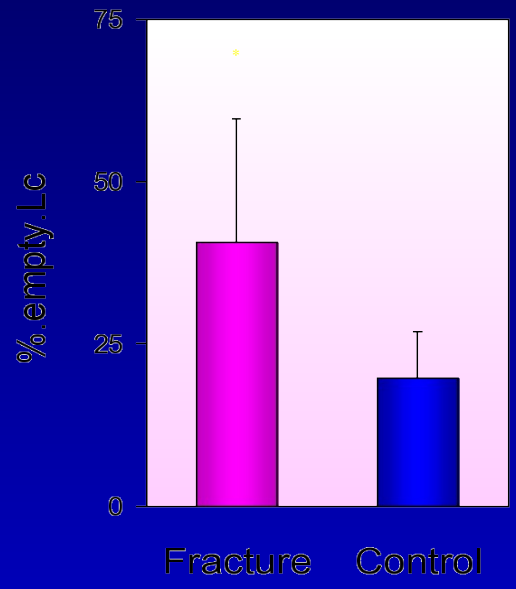
$p < 0.0001$

Total Lacunar Density



$p < 0.0001$

% Empty Lacunae



$p < 0.03$

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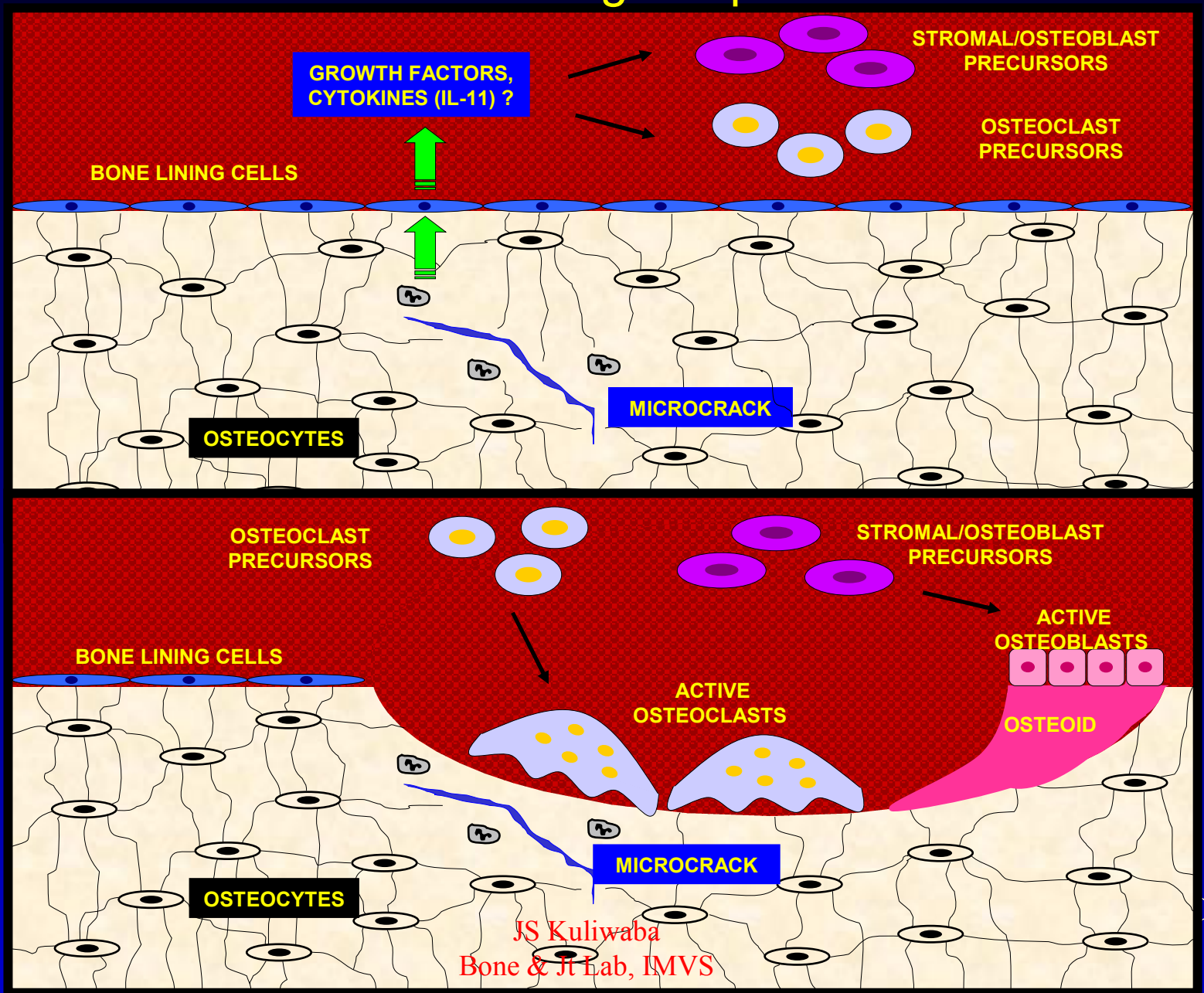
Microdamage is Repaired by Stimulating a Local Bone Remodelling Response



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Conclusions and Discussion

1. Trabecular bone spatial structure conforms to a design specification.
1. Structure of trabecular bone in OP and OA patients is linked to the original structure.
2. Load threshold to failure is critical – parameter distribution.
3. In vertebral bodies, AP elements may have a significant role in dissipation of energy acting as sacrificial elements, allowing dissipation of energy away from SI elements, minimising damage, analogous to the crumple zone in vehicles.
4. Due to the heterogeneity of human cancellous bone, there is microarchitecture where cancellous bone is more likely to fail.
5. Hardness and modulus are heterogeneous across the area of individual trabecular bone spicules

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