Bone Mineralization

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Summary

- Introduction - Bone mineralization

  …*What, When, How ?*

- Bone mineralization

  …*How to assess it ?*

- The chronology of bone mineralization

  …*And so What ?*

- Mineralization and mechanical behaviour

  …*Scale matters !*

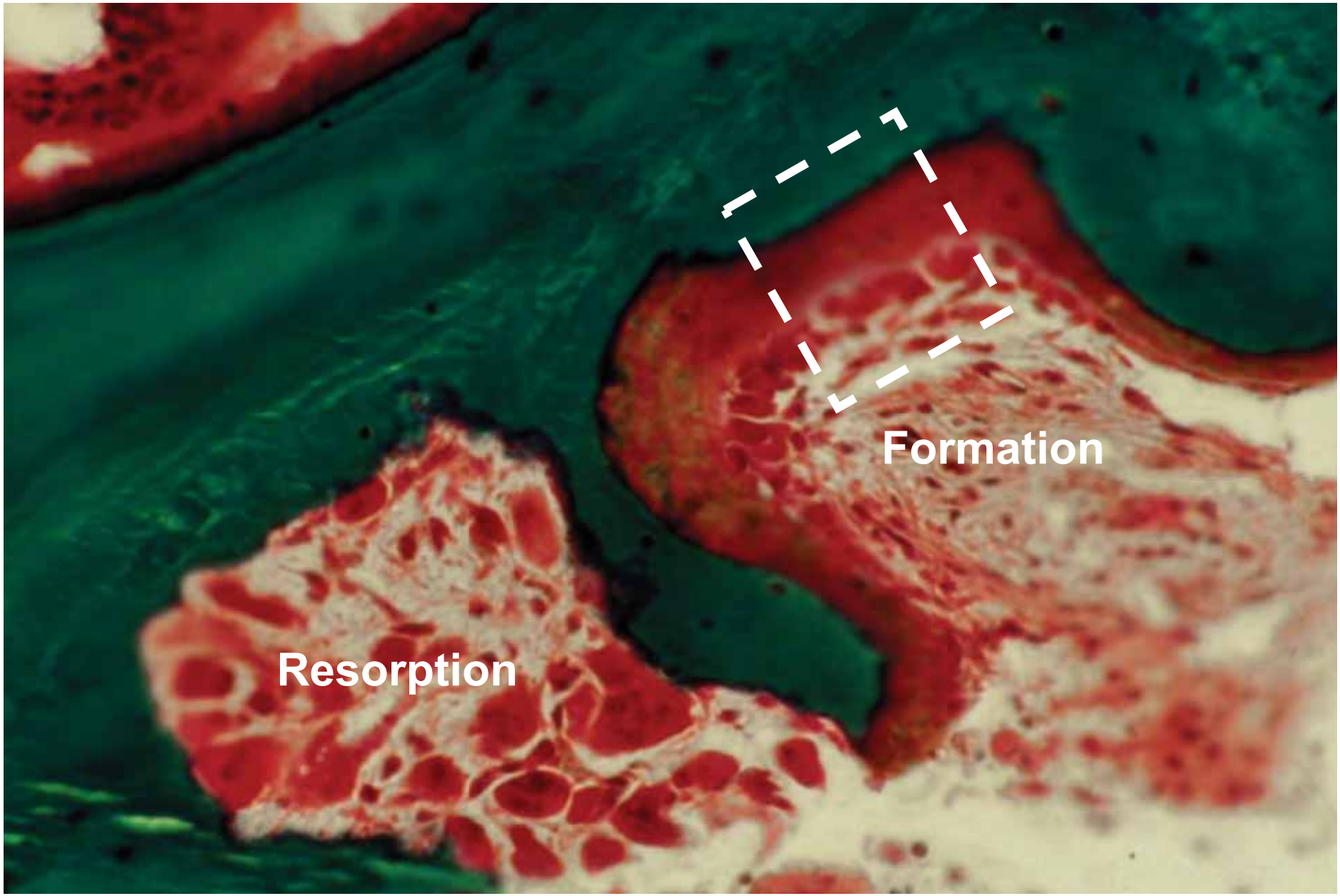
- Mineralization and bone remodelling

  …*a function of individual's age.*

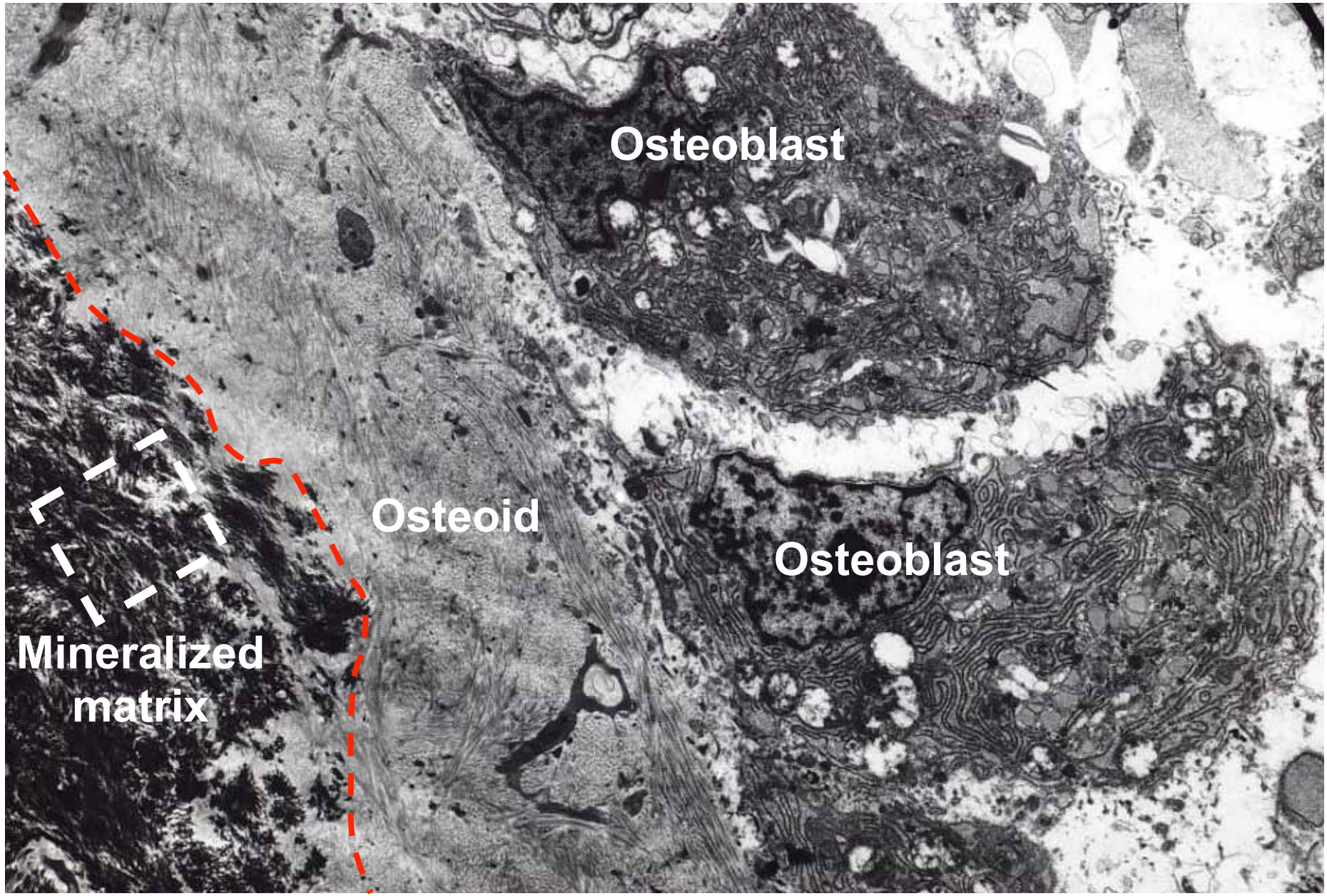
- Protracted use of bisphosphonate and mineralization

  ...a synthesis of all we have talked about.

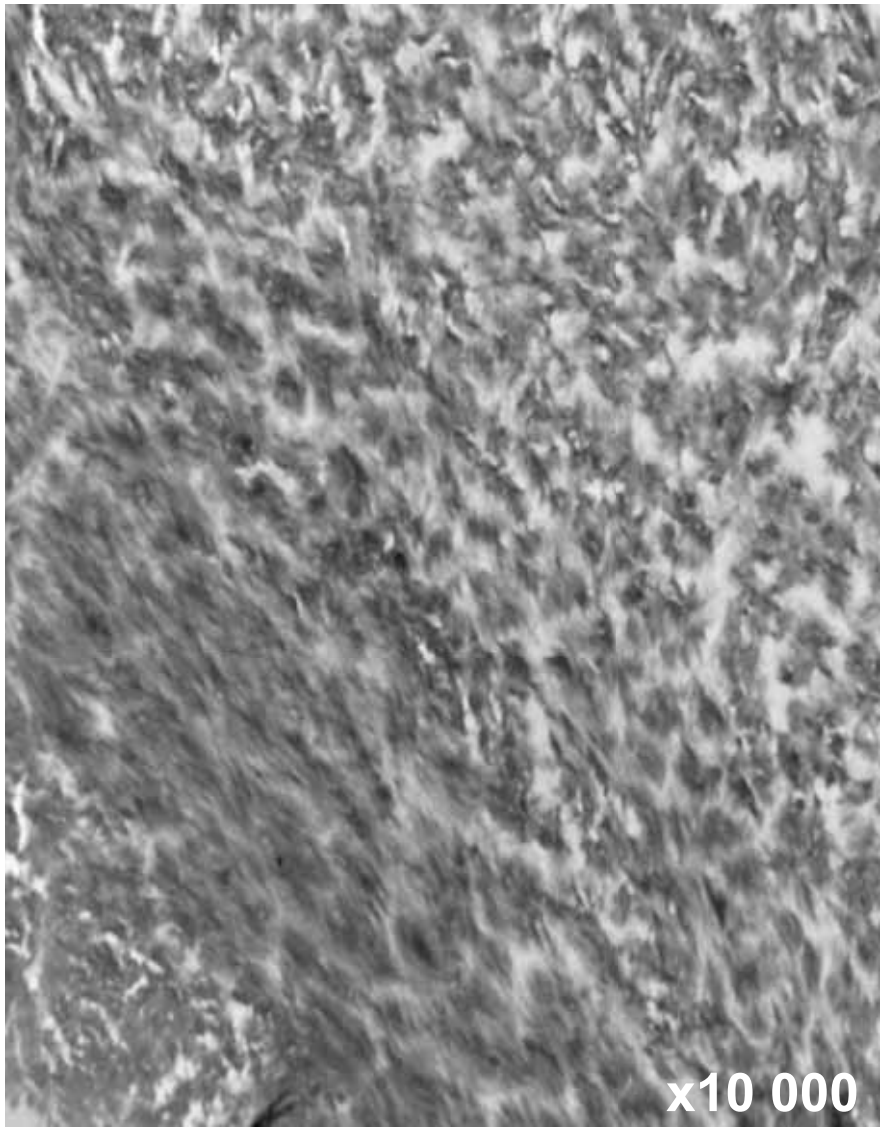
Introduction



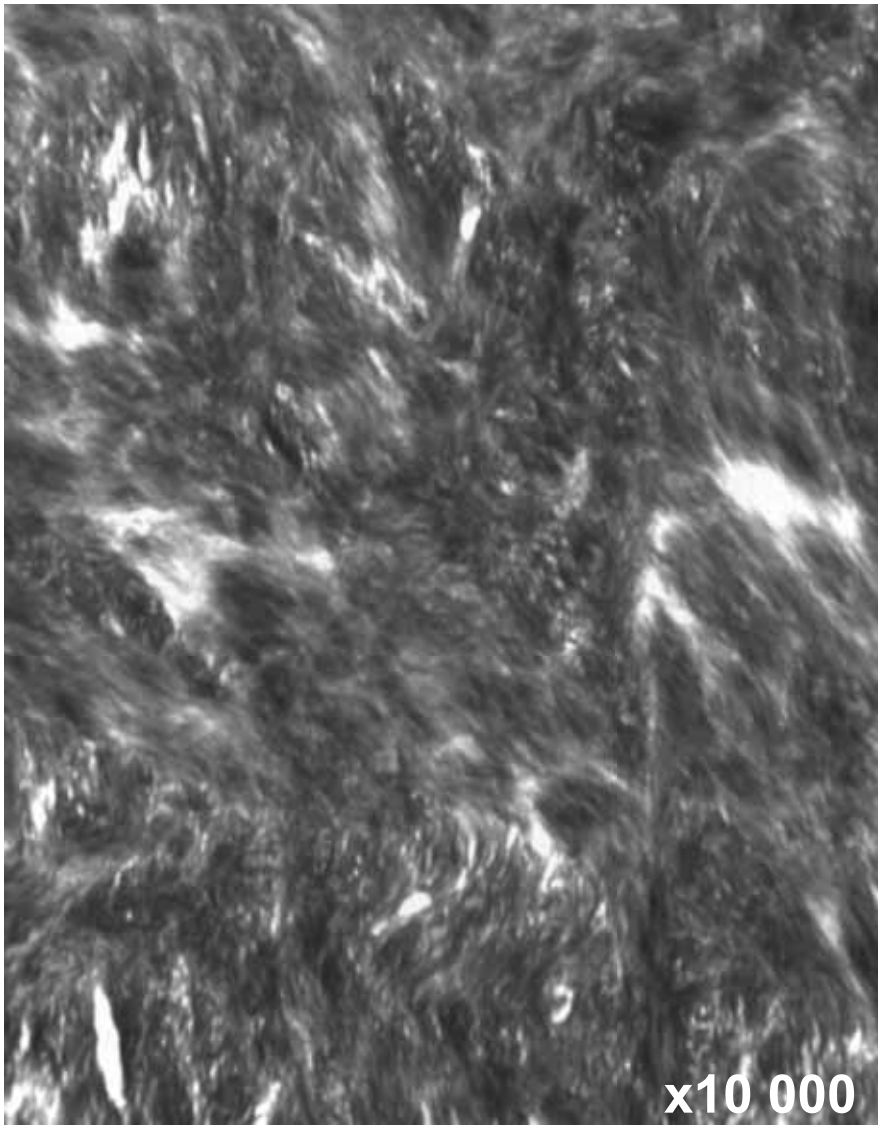
Introduction



Introduction



Primary mineralization



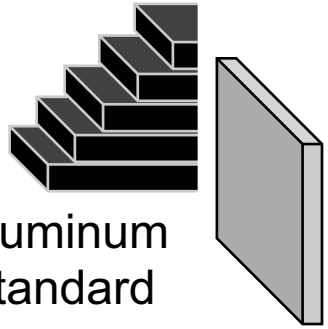
Secondary mineralization

Boivin *et al.* Osteoporos Int 2003

How to assess tissue mineral density (1/2)

Quantitative microradiography

X-Ray Beam
Voltage 40 kV
Intensity 50 µA
Exposure 7 sec

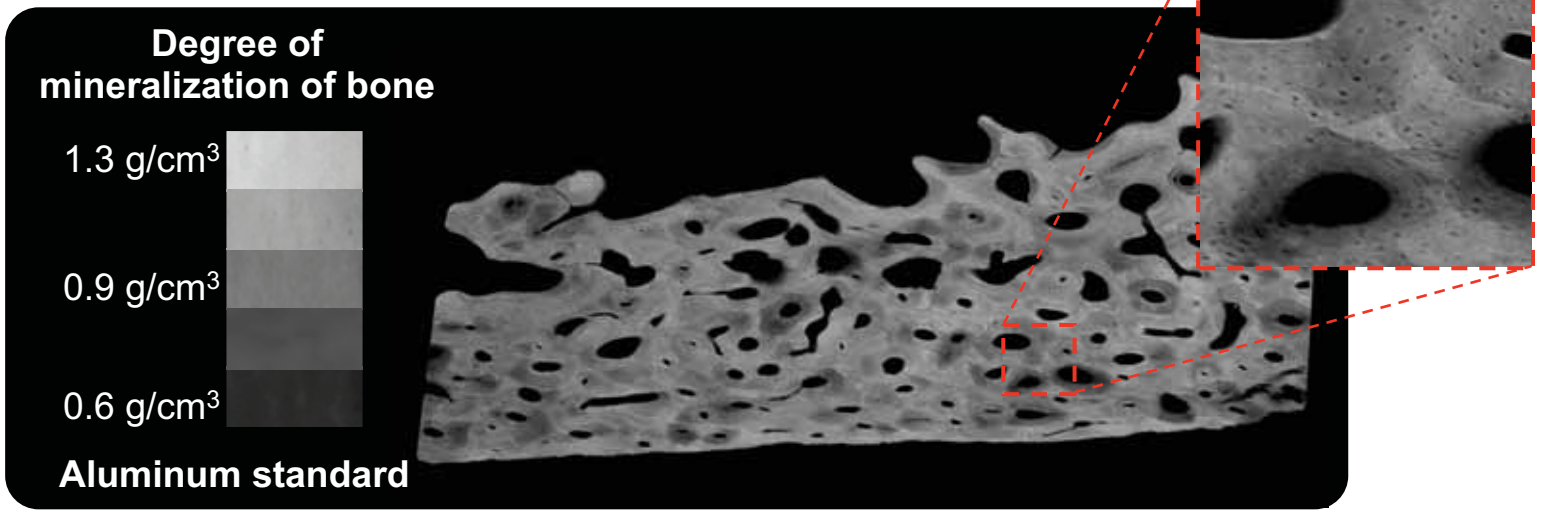


Aluminum standard

100 ± 1 µm
Bone section

CCD Camera

Spatial Res. 800 nm



Montagner *et al.* J X-Ray Science & Tech 2015 / Boivin *et al.* Bone 2008

How to assess tissue mineral density (2/2)

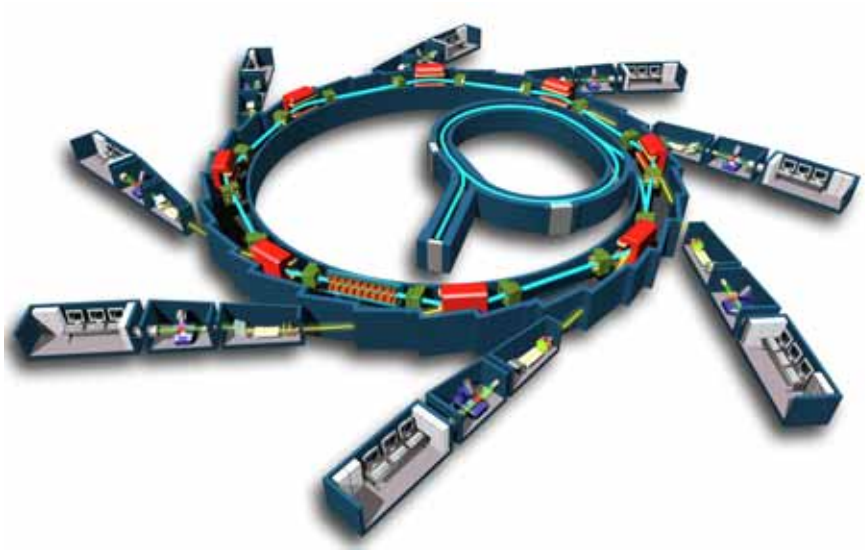
Quantitative backscattered electron imaging (qBEI)

Current: 20 kV, 110 pA
Calibration: C, MgF_2, Al, HA, FA
>1H scanning / sample
Pixel size: 4 µm

Output: Calcium concentration (Weight %) and its distribution

Roschger *et al.* Bone 1998

Synchrotron radiation based Micro-CT (SR-µCT)

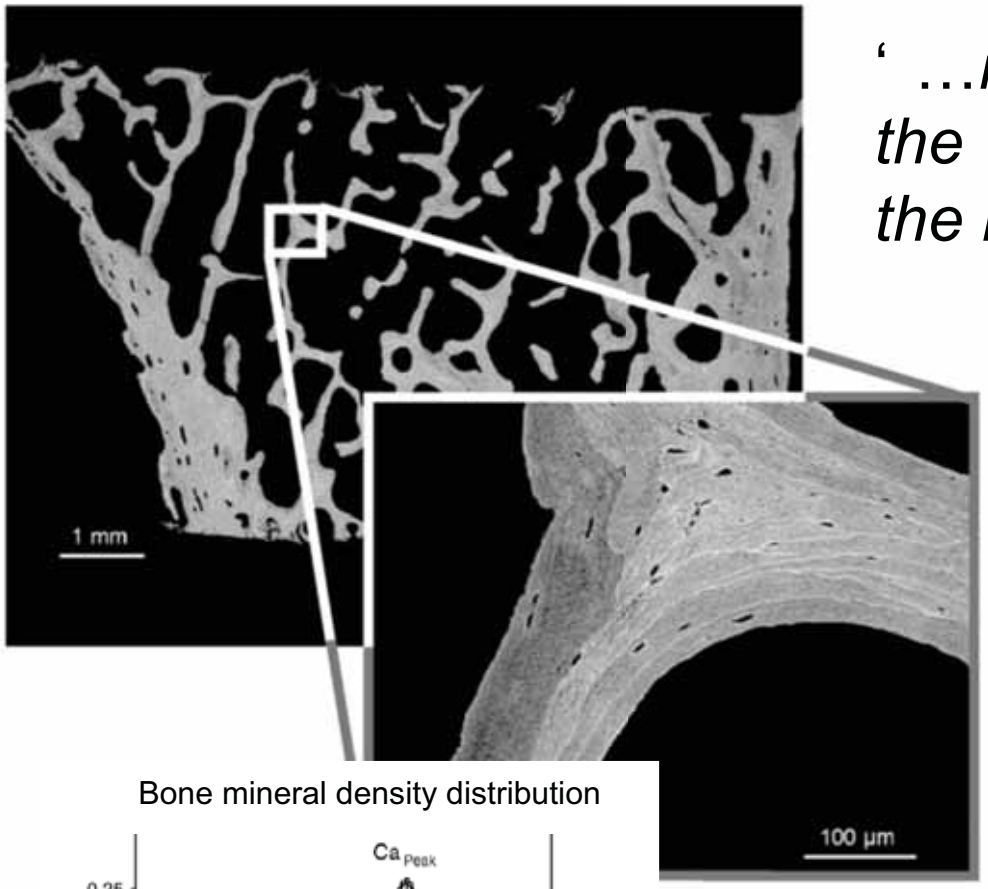


Monochromatic beam, Energy: 25 keV
Calibration: K_2HPO4 phantom
~ 20 min scanning / sample
Pixel size: 1-10 µm

Output: Degree of mineralization of bone (DMB, g/cm^3)

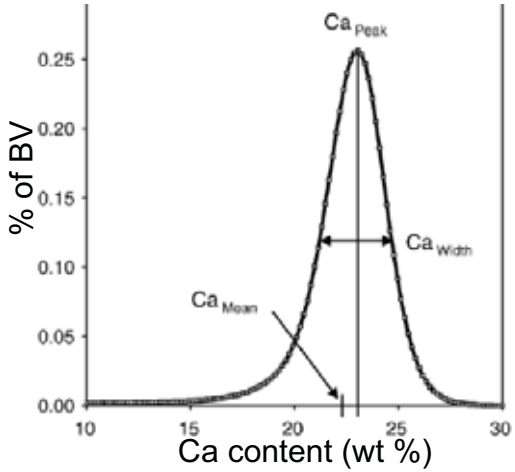
Nuzzo *et al.* Med. Phys 2002

Bone mineralization: a biphasic increase in mineral density

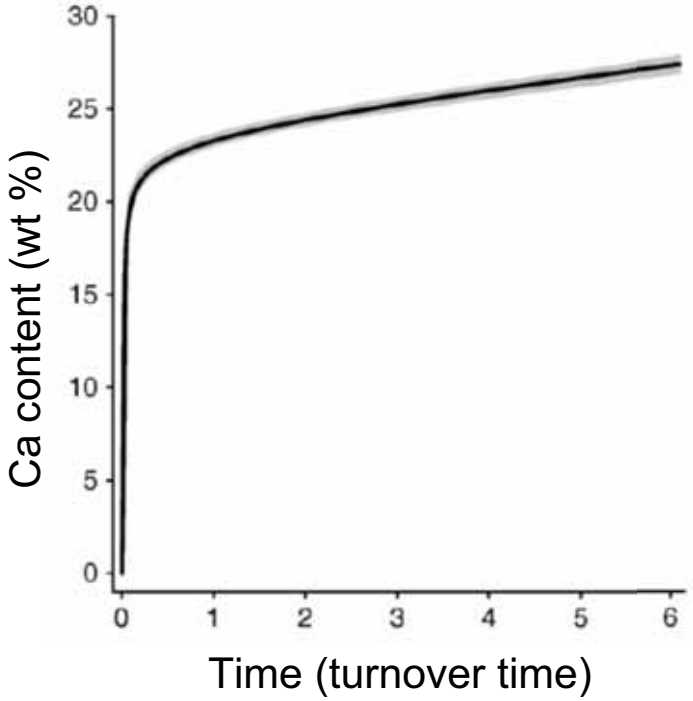


‘ …*mineral content is the result of the bone remodeling process and the kinetic of mineralization*… ’

Bone mineral density distribution

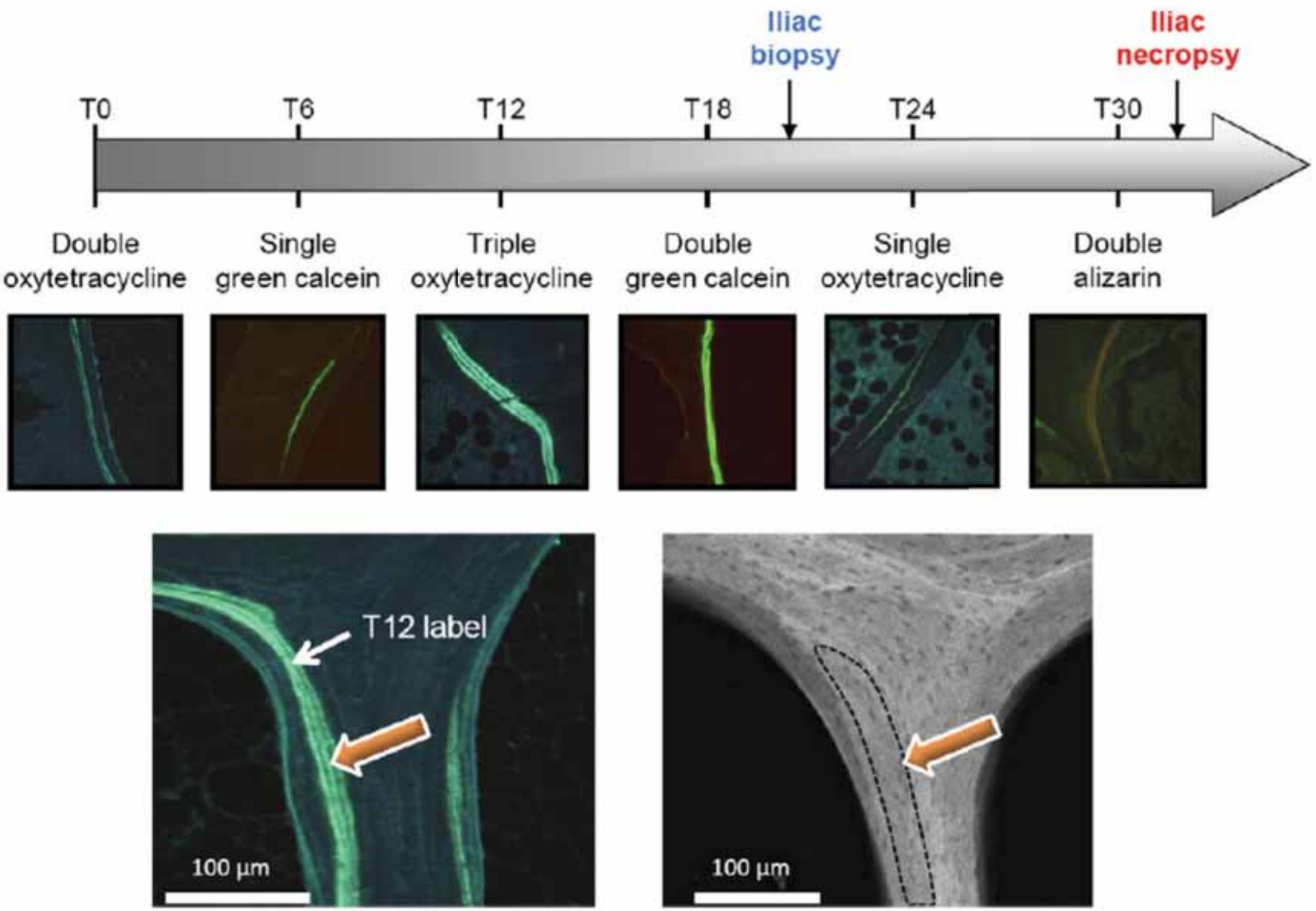


Mineralization law



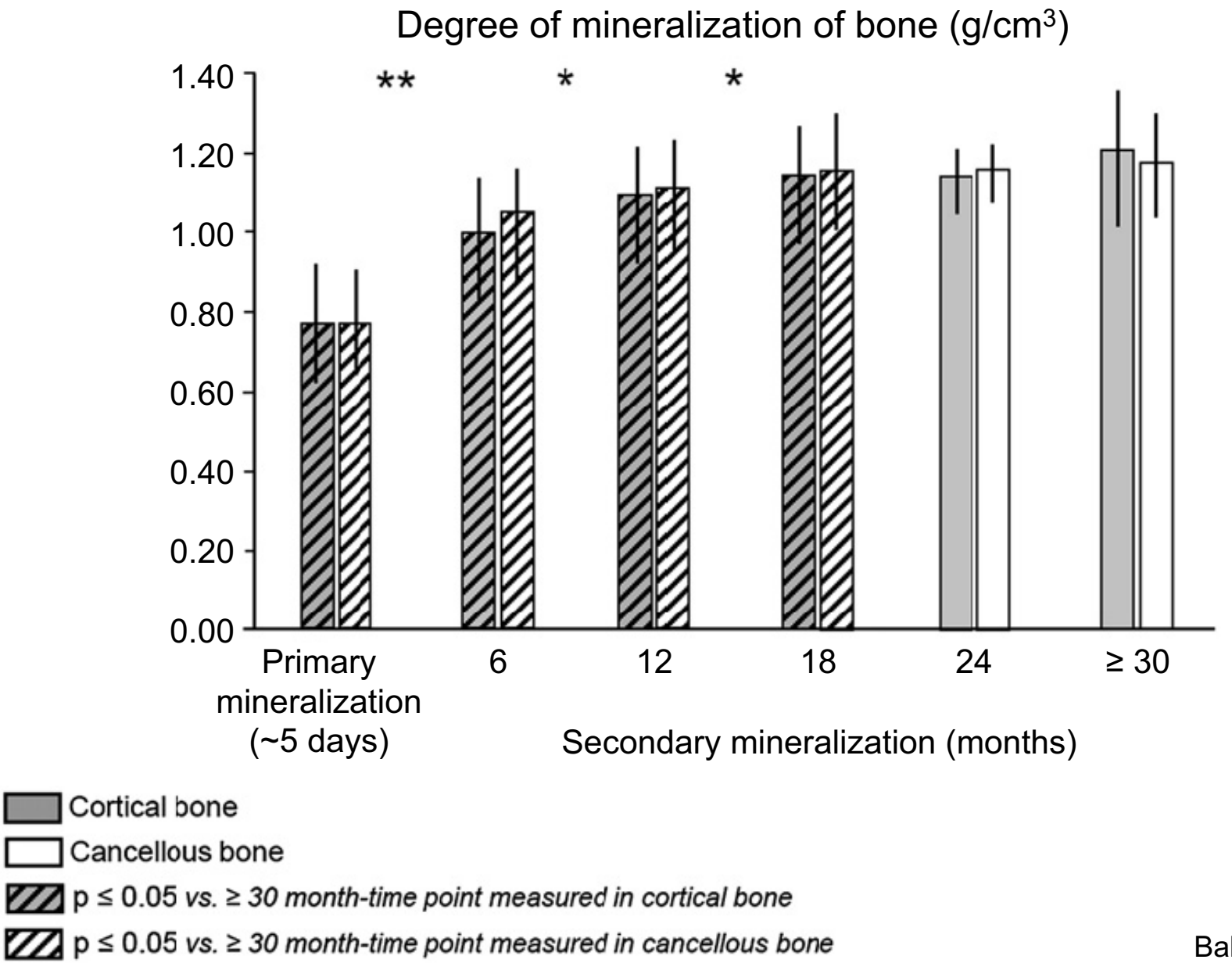
Ruffoni *et al.* JBMR 2008, Bone 2007 / Amprino *et al.* Acta Anat 1952

Chronology of bone mineralization in sheep (1/2)



Bala *et al.* Bone 2010

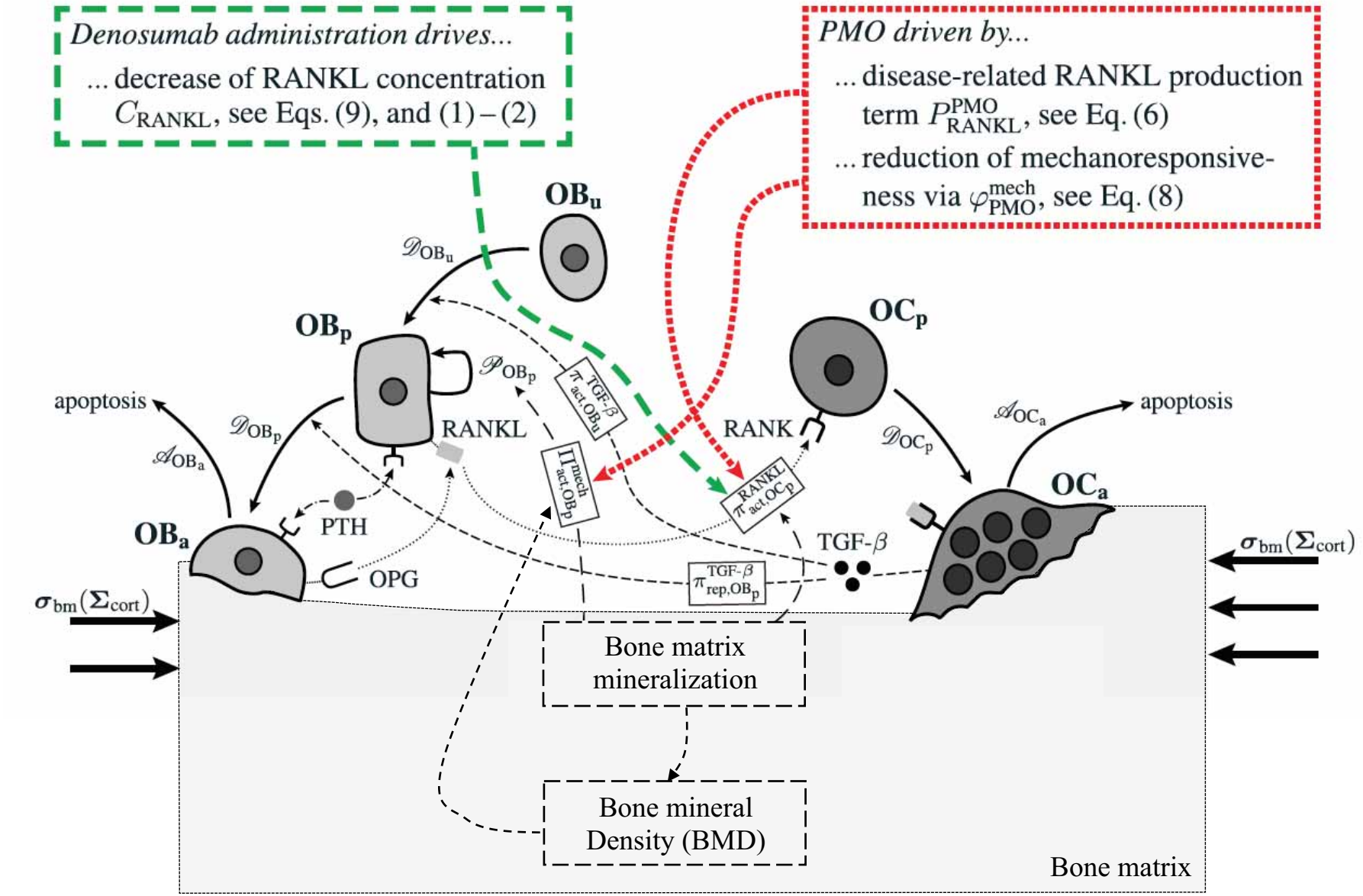
Chronology of bone mineralization in sheep (2/2)



Bala *et al.* Bone 2010

Chronology of bone mineralization…*and so what ?* (1/2)

Computational modeling of bone tissue-scale effects of DMAb in PMOP patients

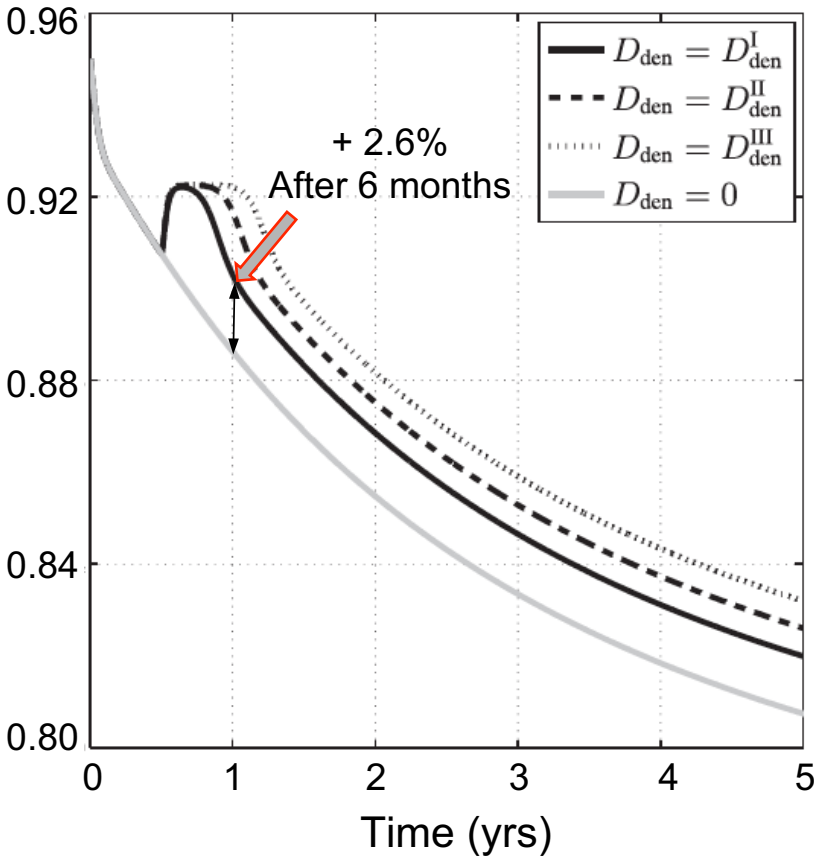


Courtesy of P. Pivonka, T.J. Martin & N. Sims (SVI, Melbourne, Australia)

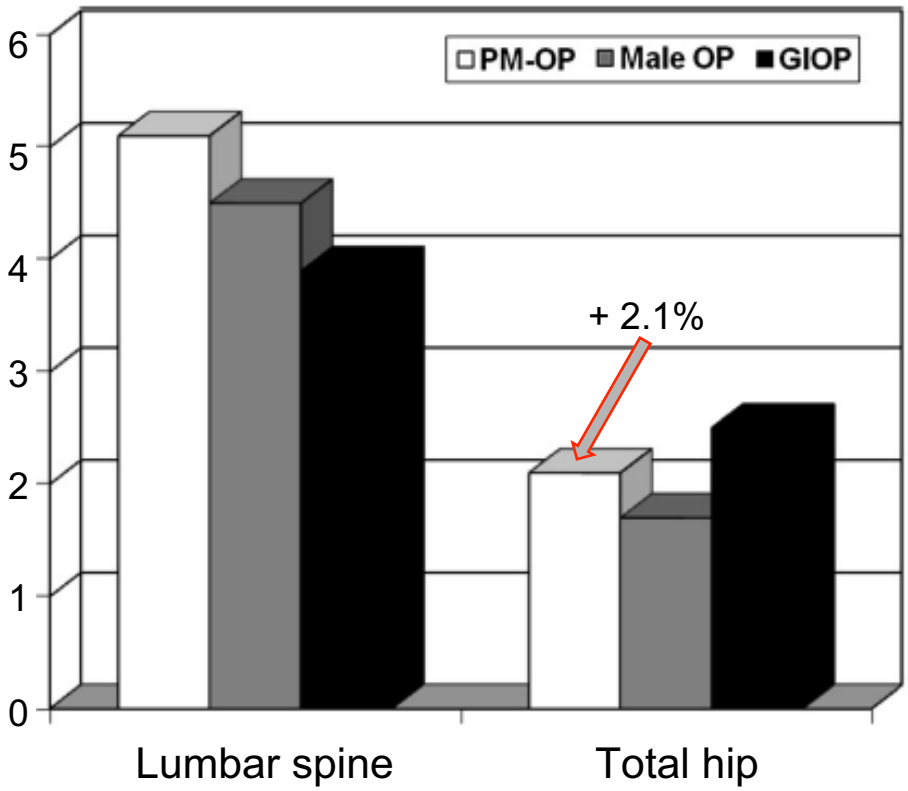
Chronology of bone mineralization…*and so what ?* (2/2)

Computational modeling of bone tissue-scale effects of DMAb in PMOP patients

Simulation of Total hip BMD (g/cm^3) changes in total hip after single injection of DMAb

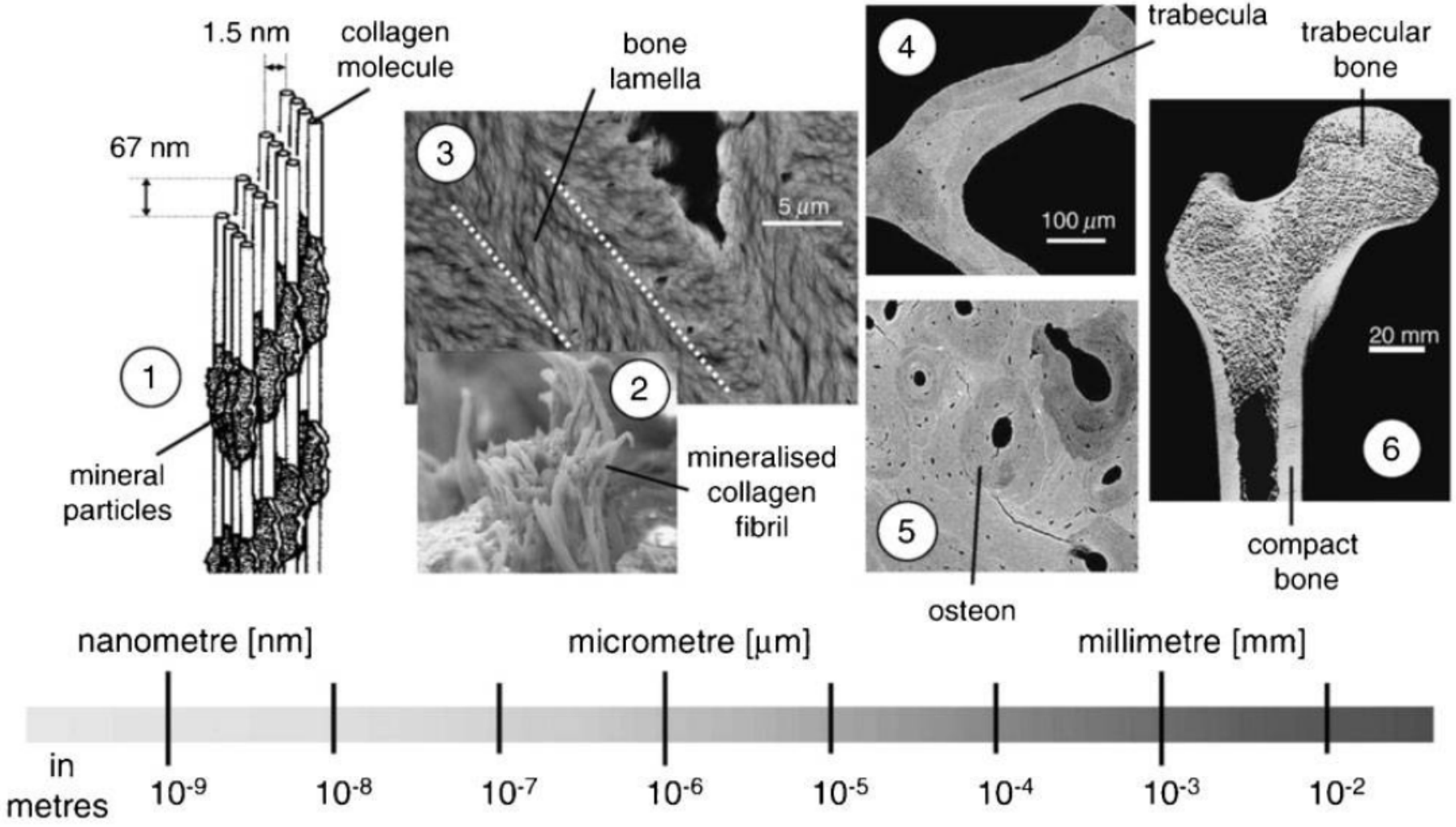


6-month BMD increase after DMAb injection (Mean % change vs. baseline)



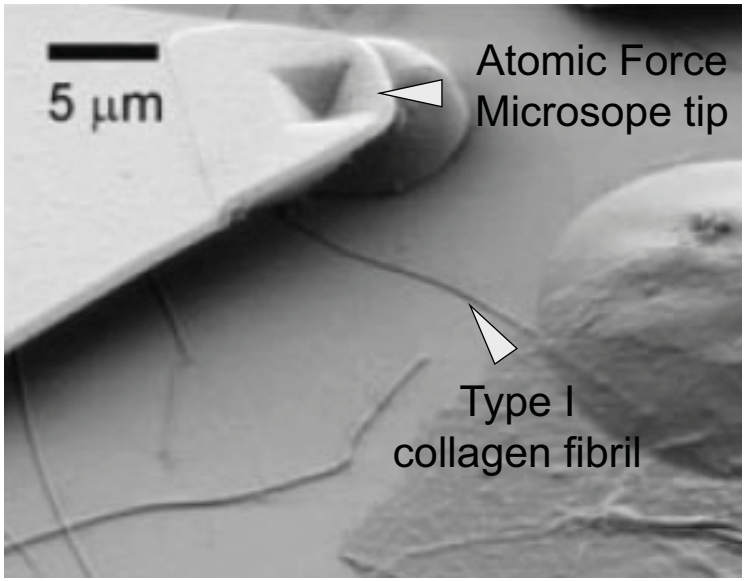
Scheiner *et al.* Int J Num Meth Biomed Engng 2014 / Ringe *et al.* Rheumatol Int 2014

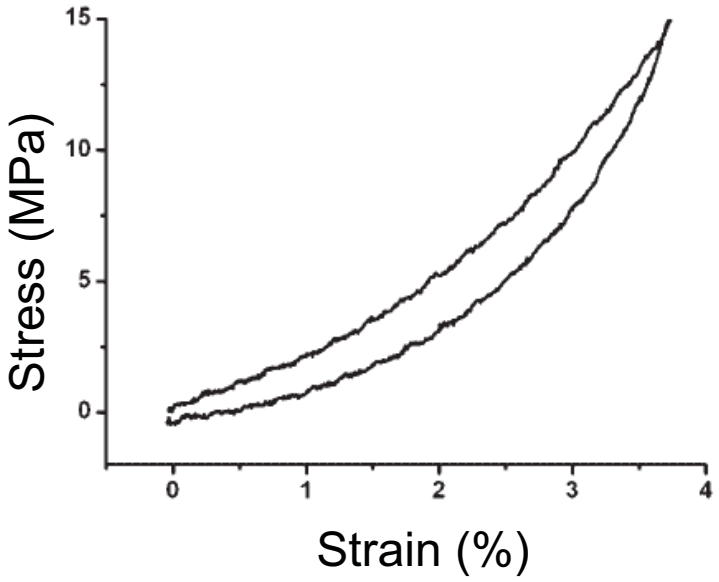
Mineralization and bone mechanical properties

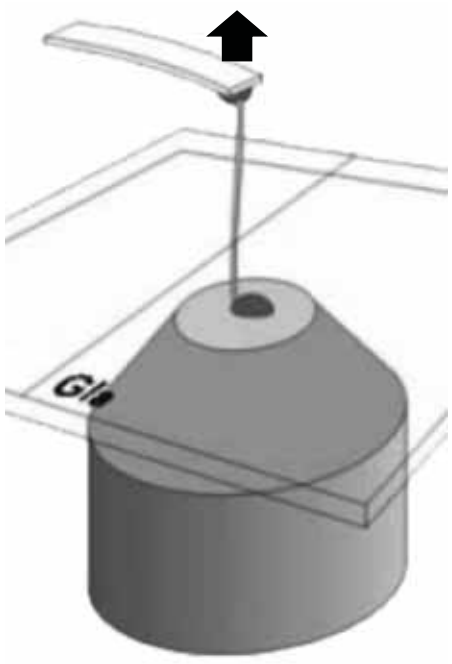


Weinkamer *et al.* Mat. Sci. Eng. 2011

Bone mechanics at the nanoscale level: Collagen



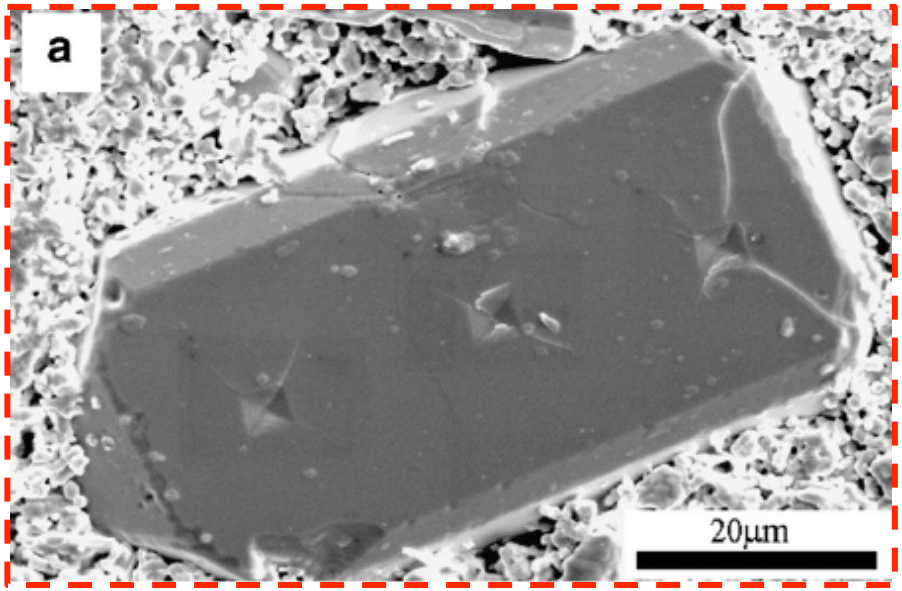


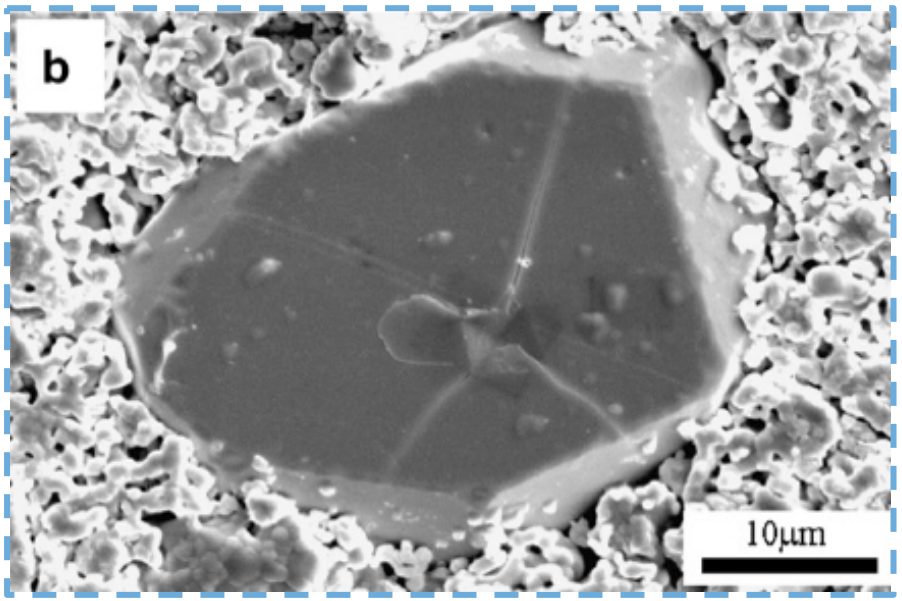


Type I collagen fibril has an elastic - viscous behaviour.

Van der Rijt *et al.* Macro mol Bioscience 2006

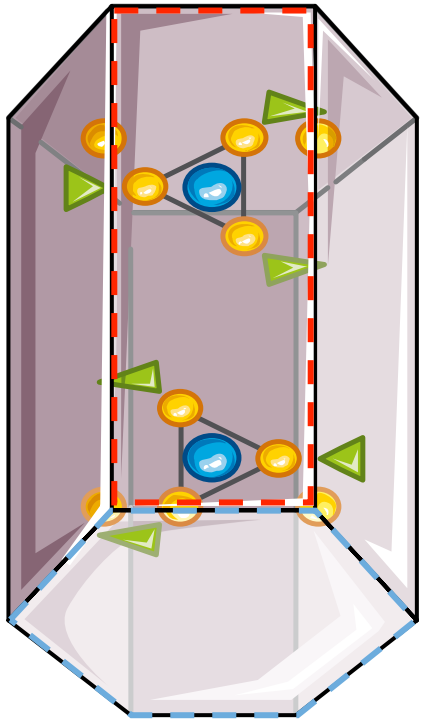
Bone mechanics at the nanoscale level: Mineral





Hydroxyapatite Crystal

$Ca_{10}(PO_4)_6OH_2$



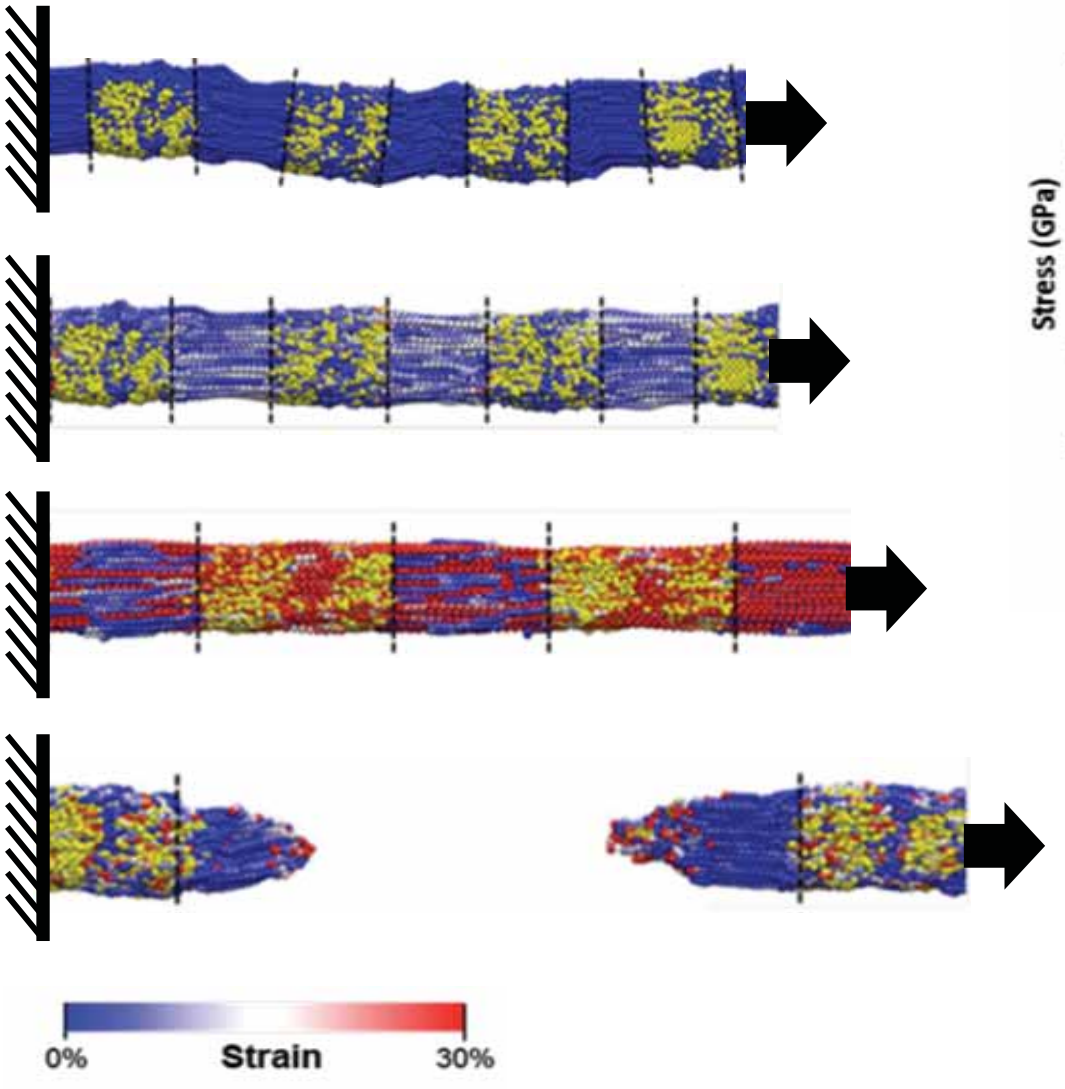
OH^- Ca^{++} PO_4^{++}

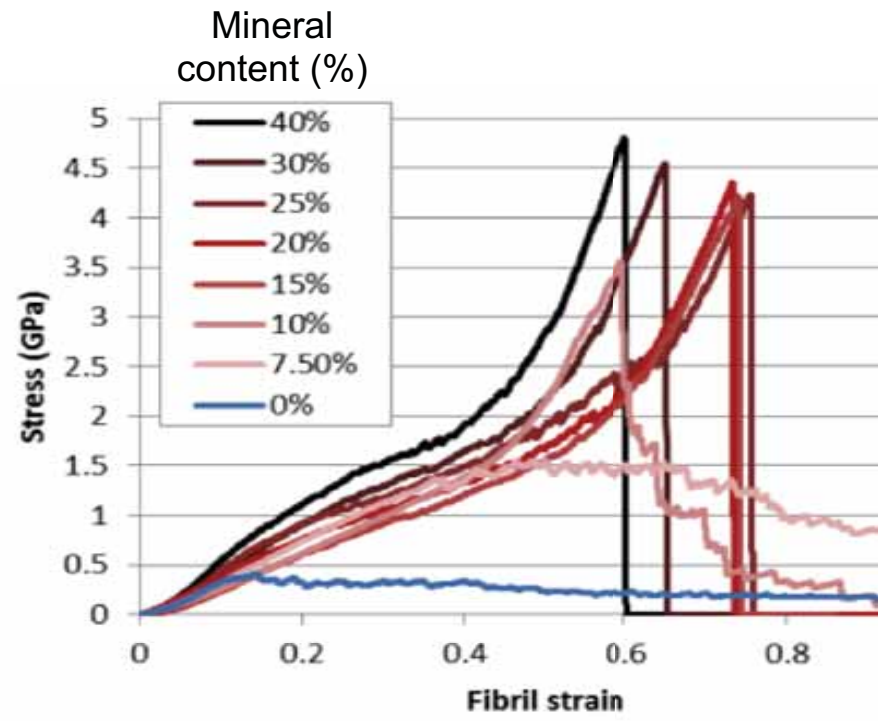
Hydroxyapatite crystals have a brittle behaviour.

Viswanath *et al.* Scripta Materialia 2007

Deformation mechanisms of mineralized fibrils

Coarse-grained model of finite size mineralized collagen fibril



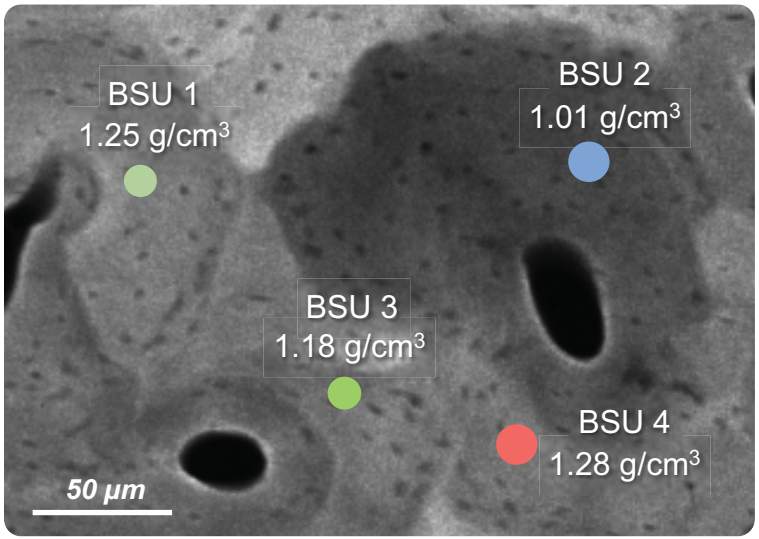


A ductile to brittle transition occurs when mineral content reaches 15%

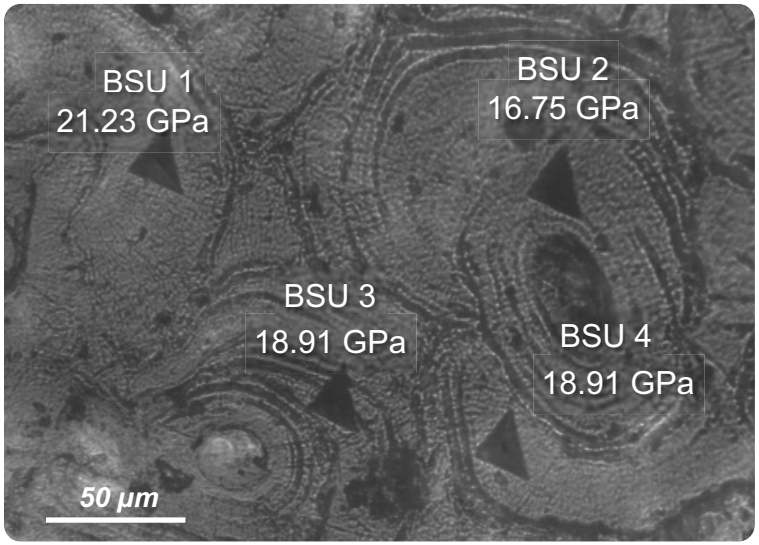
Dépalle *et al.* JBMR 2016

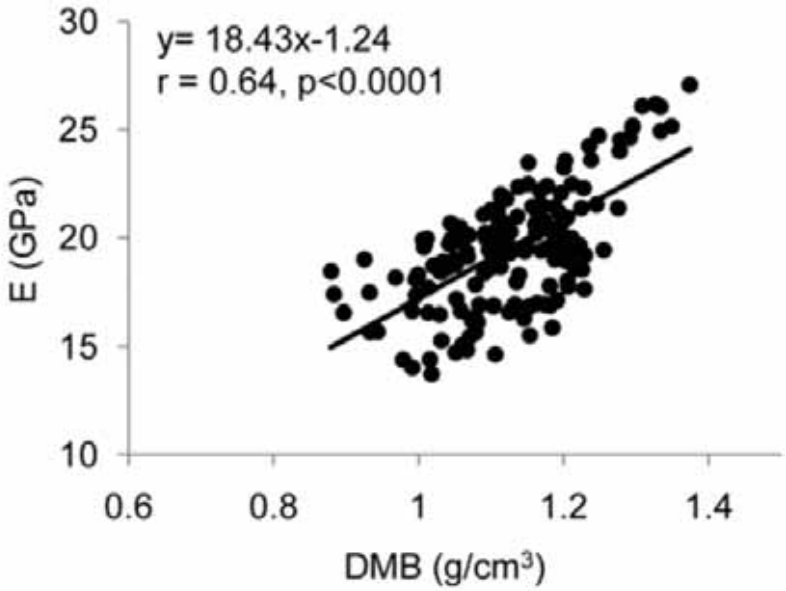
Mineralization and mechanical properties: BSU scale

Microradiography - DMB (g/cm^3)



Indentation – E (GPa)





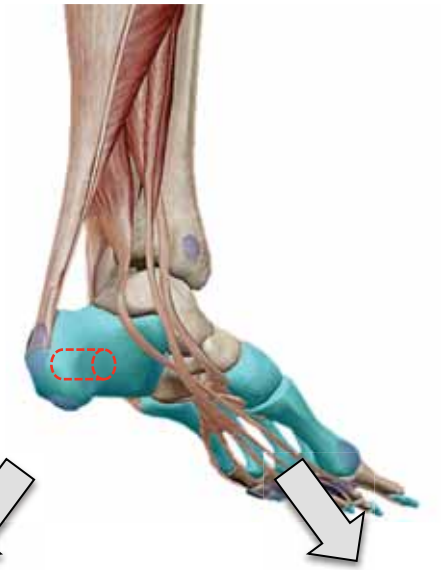
Multiple regression models

E (Gpa) =	DMB	+	Crystallinity Index	+	Collagen Maturity
R^2 = 0.68	1				
	0.68		*Out*		*Out*

Bala *et al.* J Mech Behav Biomed Mater 2011

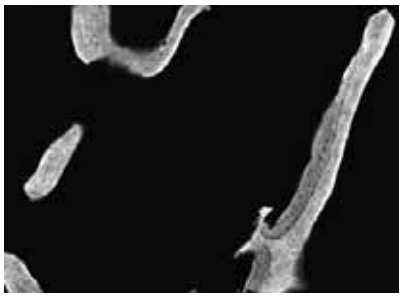
Mineralization and mechanical properties: The organ level (1/2)

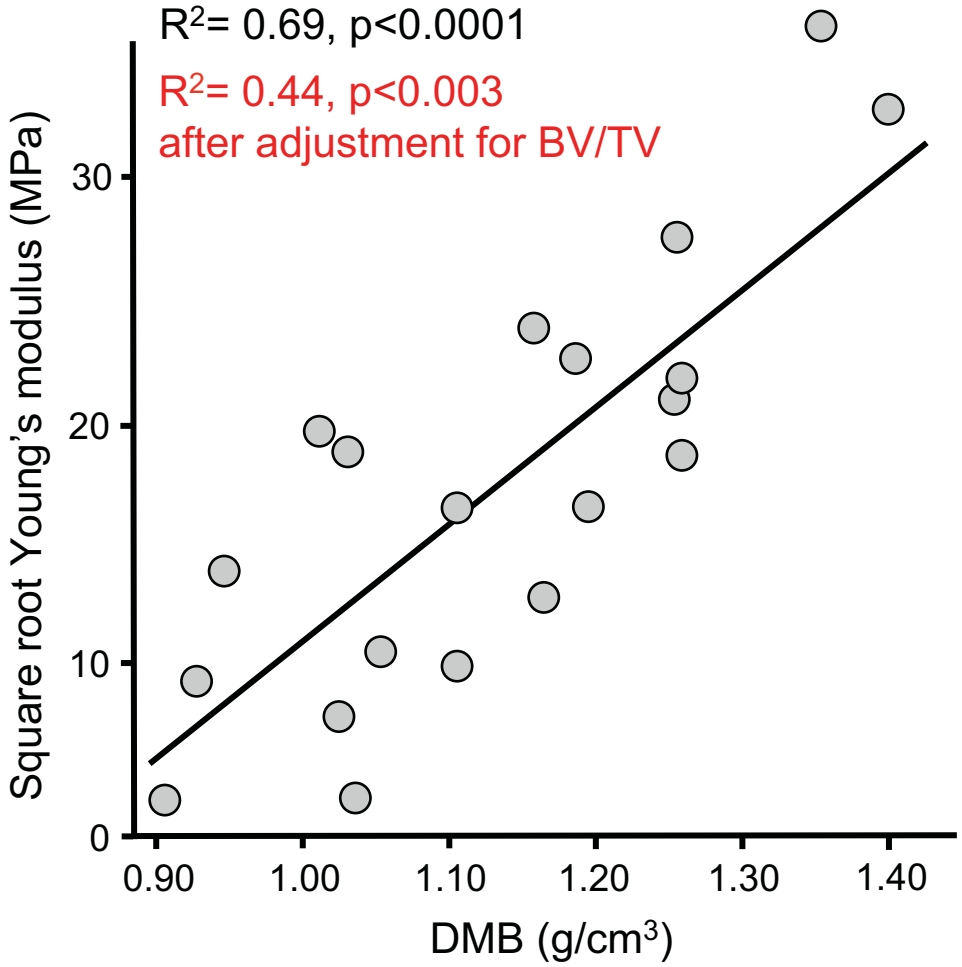
20 calcanei trabecular cores
Age 71 – 91 yrs



Compressive tests

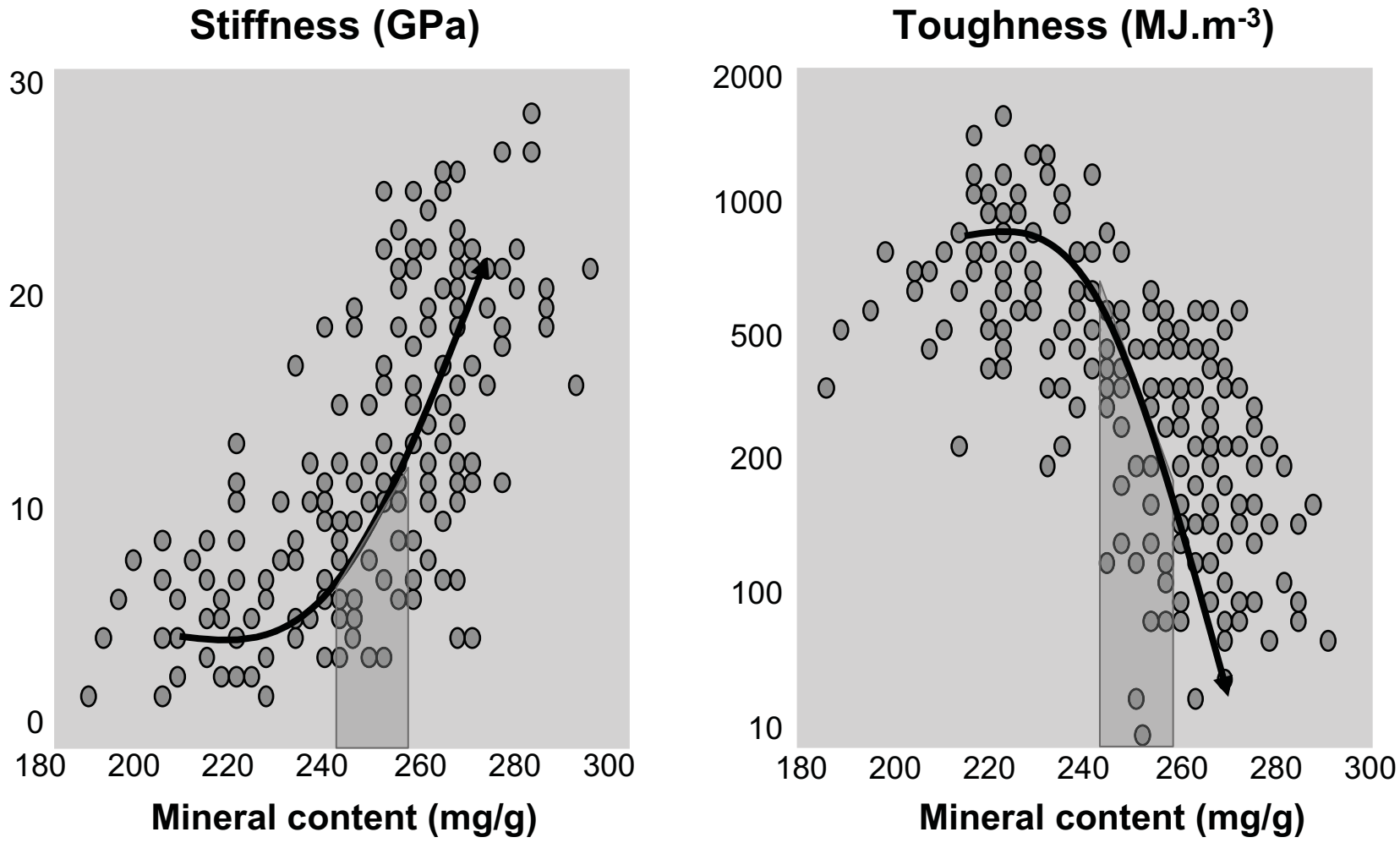
Microradiography





Follet *et al* Bone 2004

Mineralization and mechanical properties: The organ level (2/2)



Mineral brings stifness in tension and compression but dramatically reduces toughness.

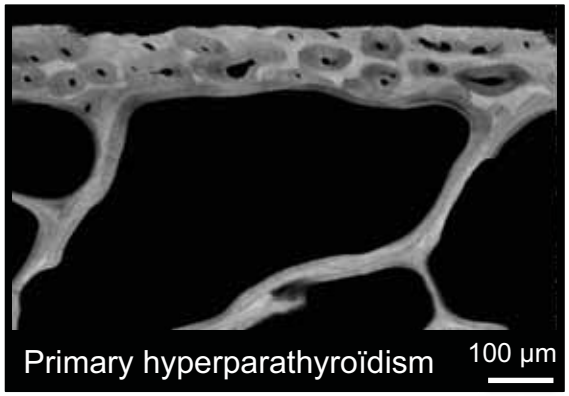
Bala & Seeman Calcif Tissue Int 2015 / Currey 2006 in Bones

Remodeling, mineralization & heterogeneity

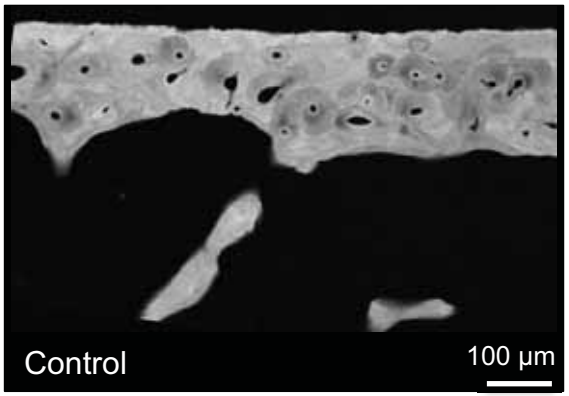
Increase in bone remodeling activity

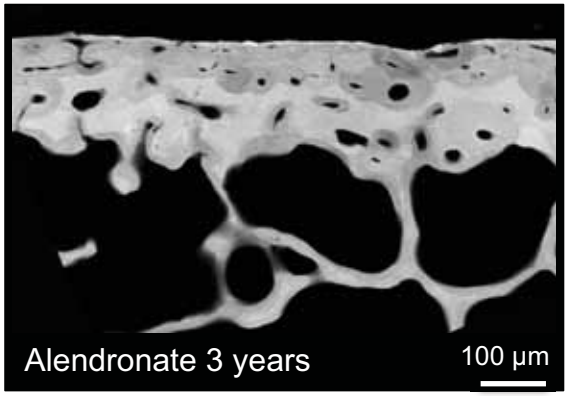
Decrease in bone remodeling activity

Birthrate of BMU	↓
Lifespan of BSU	↑
Duration of the secondary mineralization	↑
Degree of mineralization of bone	↑



Accumulation of immature hypomineralized matrix

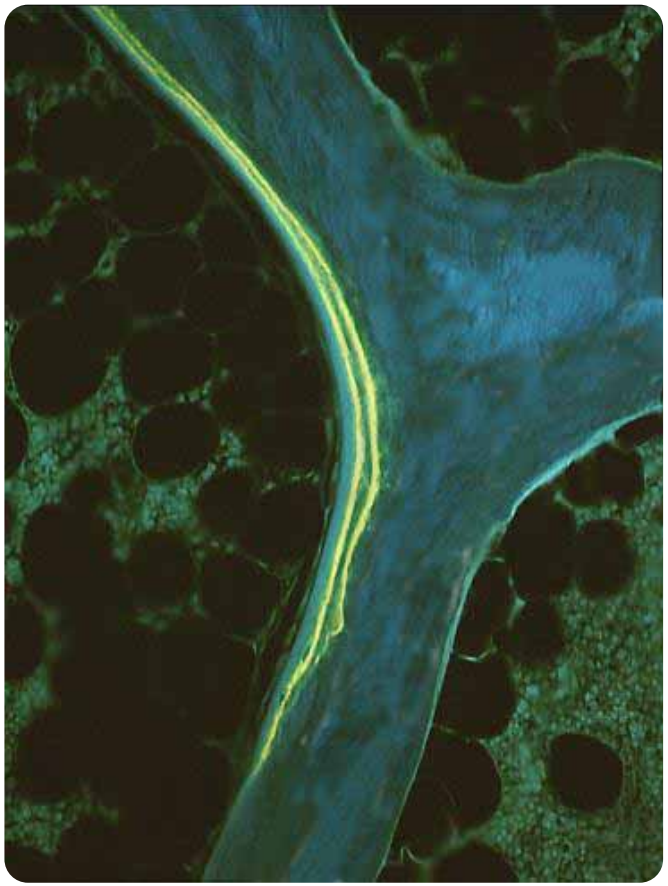


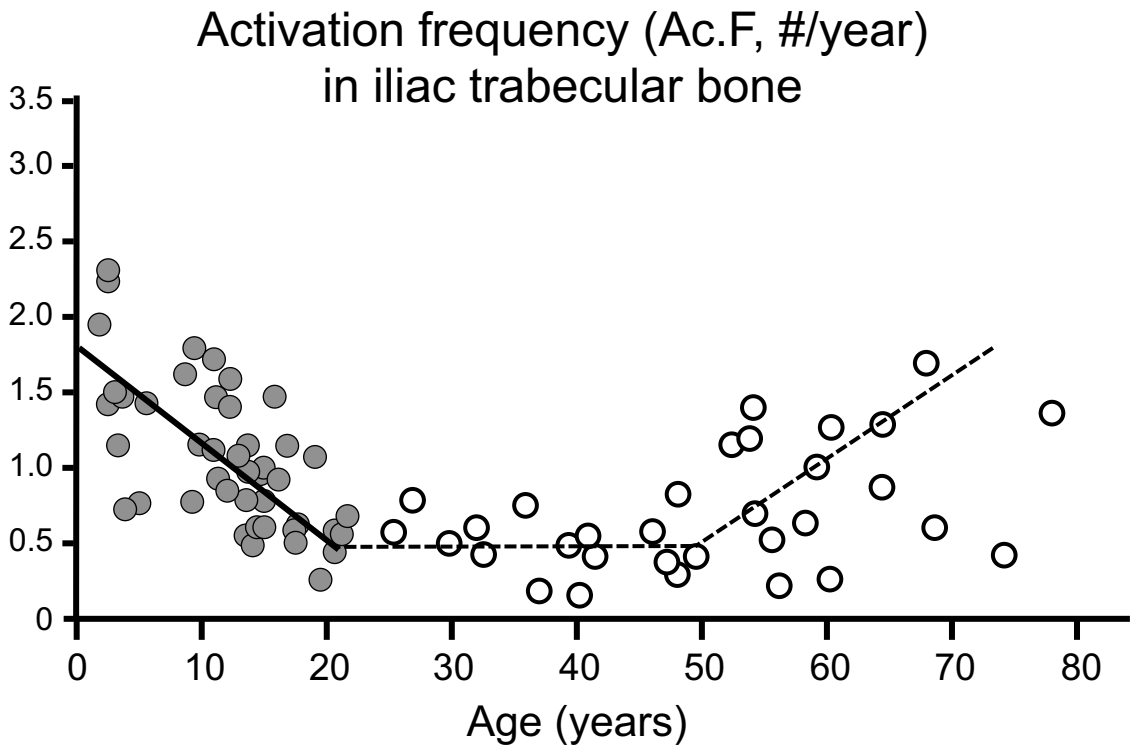


Accumulation of mature and more mineralized matrix

Bala *et al.* CTI 2015, Osteoporos Int 2013 / Boivin et al. Osteoporos Int 2009

Age-dependent fluctuation in bone turnover





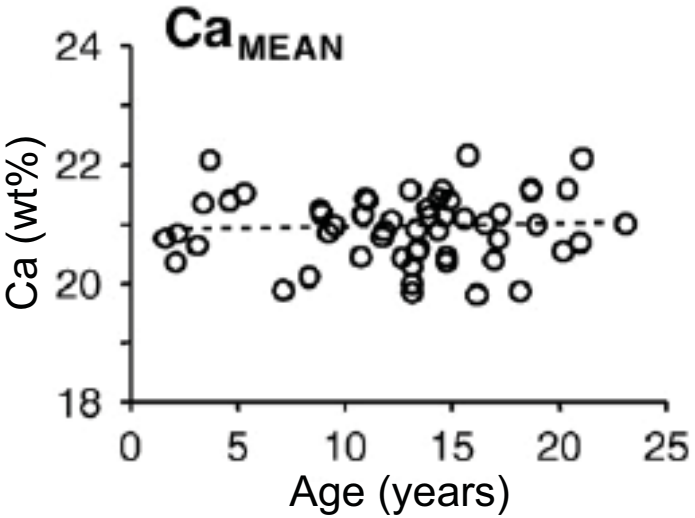
Ac.f = (BFR/BS) / W.Th

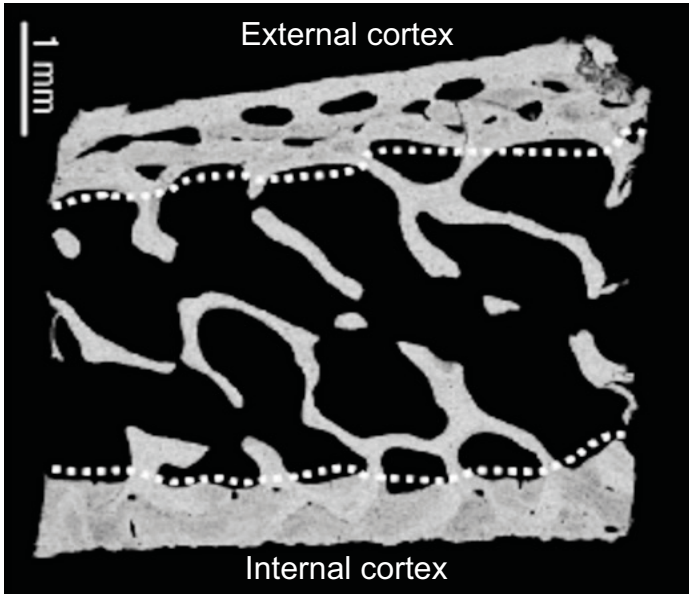
'*…annual probability of activation of a new remodeling site at any given locus on the trabecular surface…*'

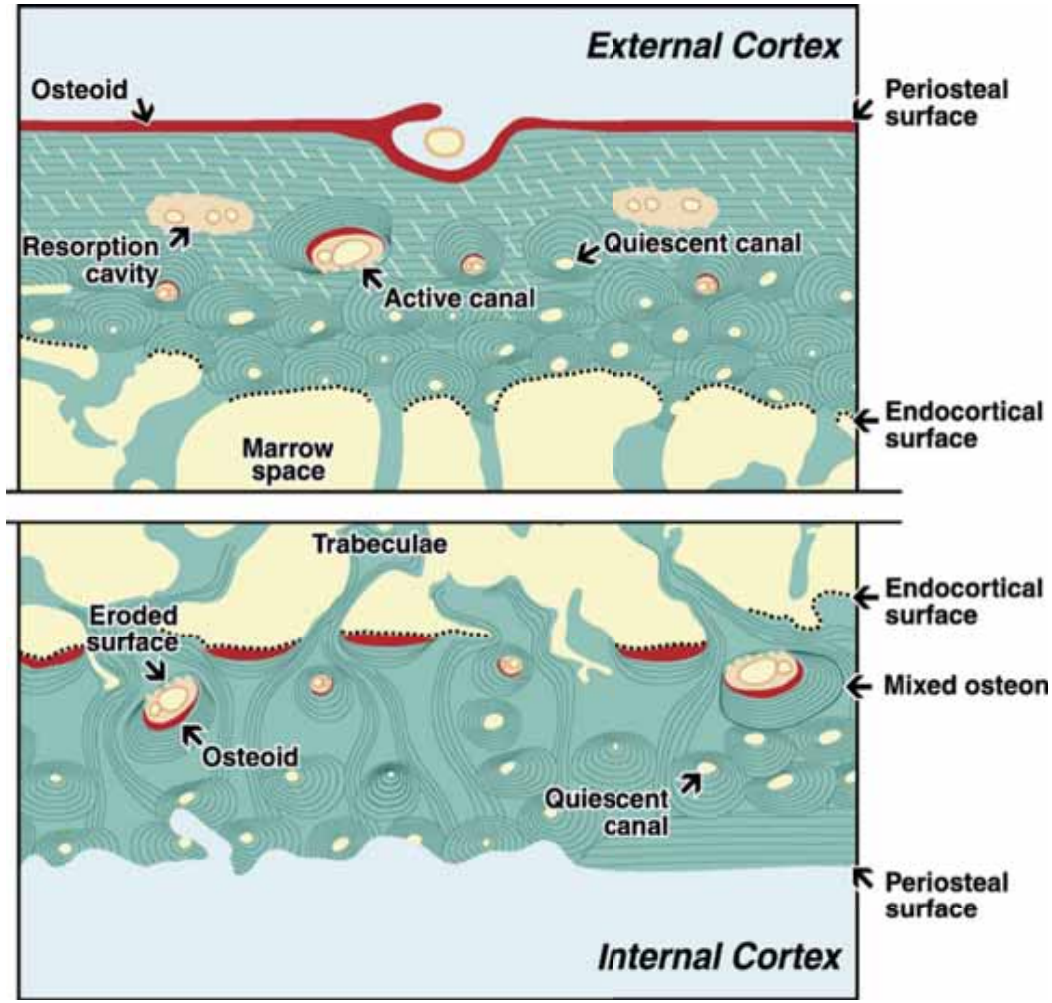
Parfitt *et al.* Bone 2000

Courtesy of J. Compston, University of Cambridge, UK.

Bone mineralization during growth (1/2)

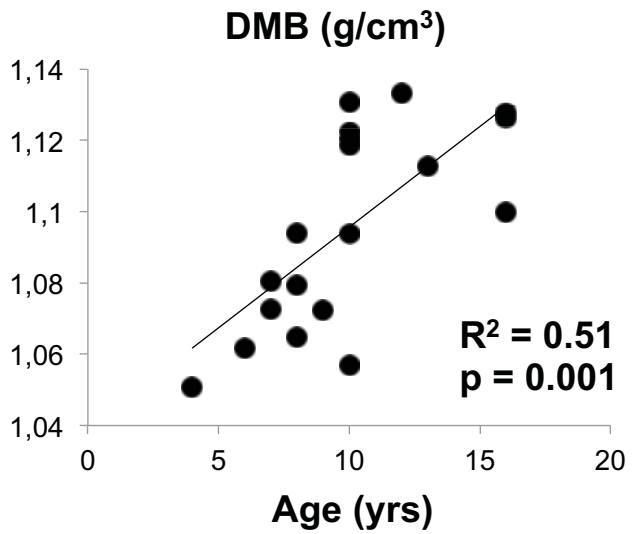


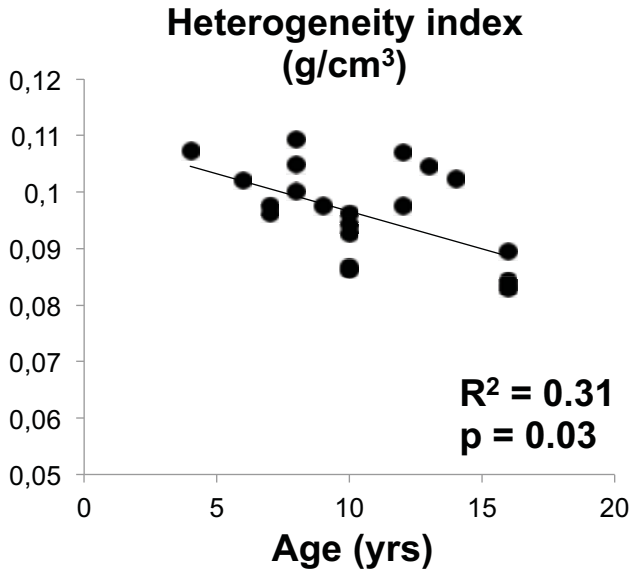




Fratzl-Zelman *et al.* Bone 2009 / Rauch *et al.* Bone 2000

Bone mineralization during growth (2/2)

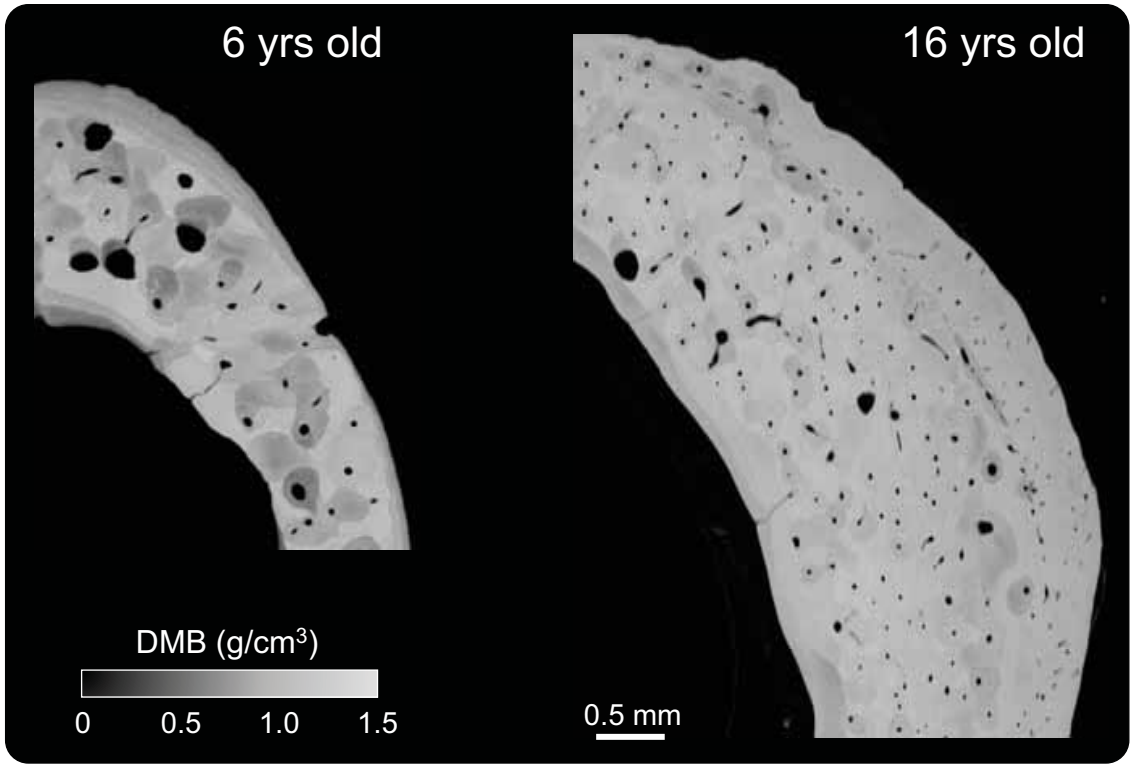




ANR Project MALICE
(**M**ultiscale **A**na**L**ys**I**s of **C**hildren's bon**E** growth)

n=16 (9M, 4F), 6 to 18 y.o. (12 ± 4 yrs)

Corrective surgeries for fracture at the growth plate or equinovarus of the foot

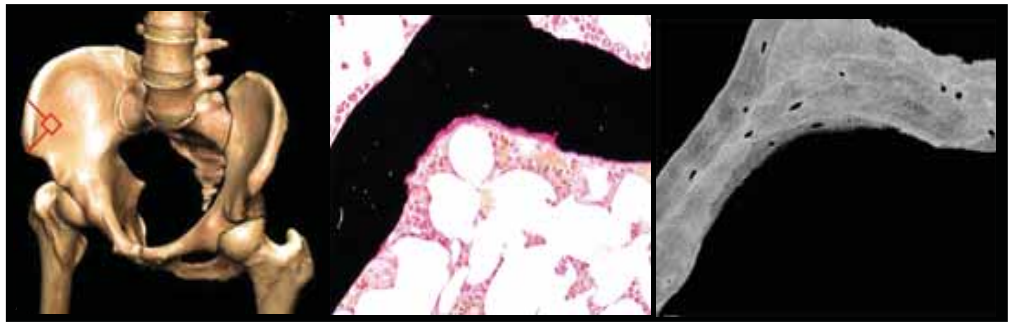


Bala *et al.* JMBBM 2016

Bone mineralization during ageing

Universitätsklinikum Hamburg-Eppendorf

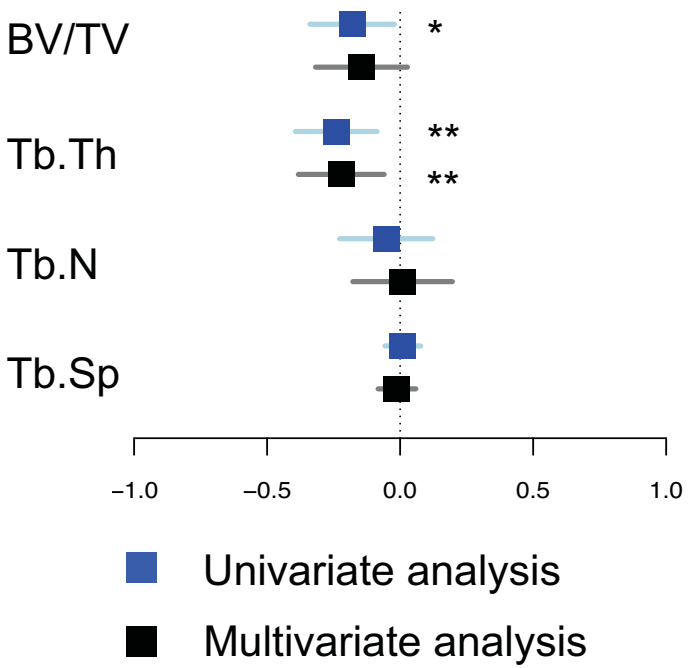
Bone structure *vs.* Mineralization: Trends in trabecular architecture and bone mineral density distribution in 152 individuals aged 30-90 years



- Bone structure indices were tested as predictors of hard tissue mineralization

- Age and bone loss are associated with higher trabecular bone mineralization
- Trabecular thinning and loss of low mineralized surfaces lifts mineral content

Ca_{Mean} (Wt%) – predicted effects



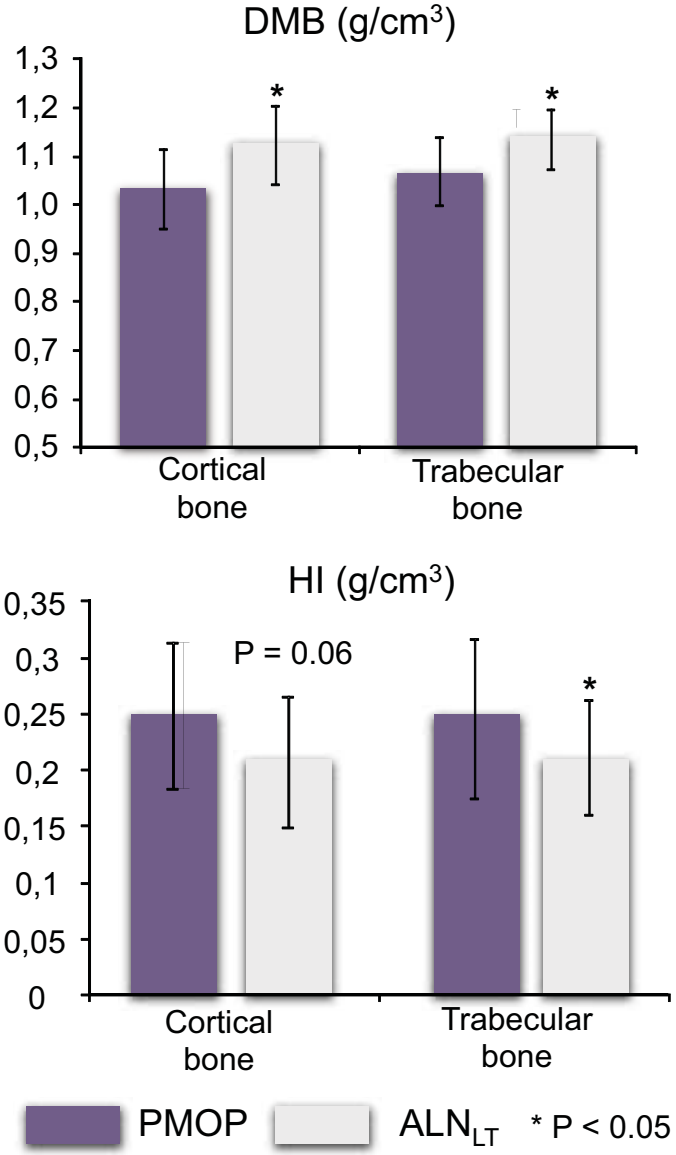
Busse B et al. Increased calcium content and inhomogeneity of mineralization render bone toughness in osteoporosis: mineralization, morphology and biomechanics of human single trabeculae. *Bone*. 2009 Dec;45(6):1034-43.

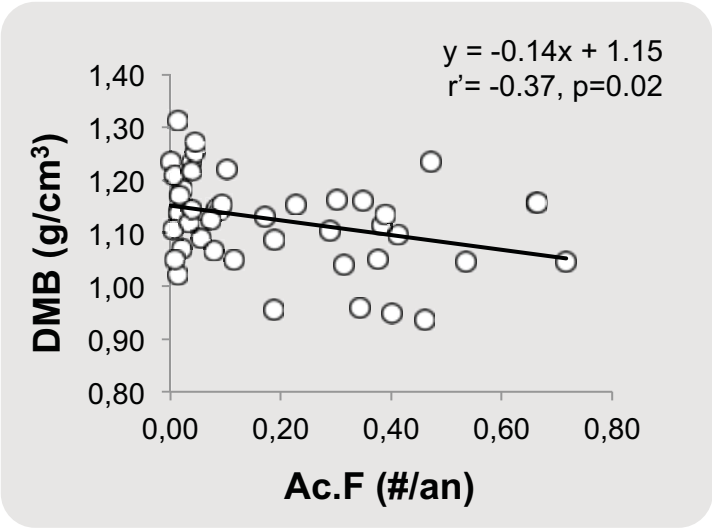
Köhne T, Busse B, et al. Trends in trabecular architecture and bone mineral density distribution in 152 individuals aged 30-90 years. *Bone* 2014

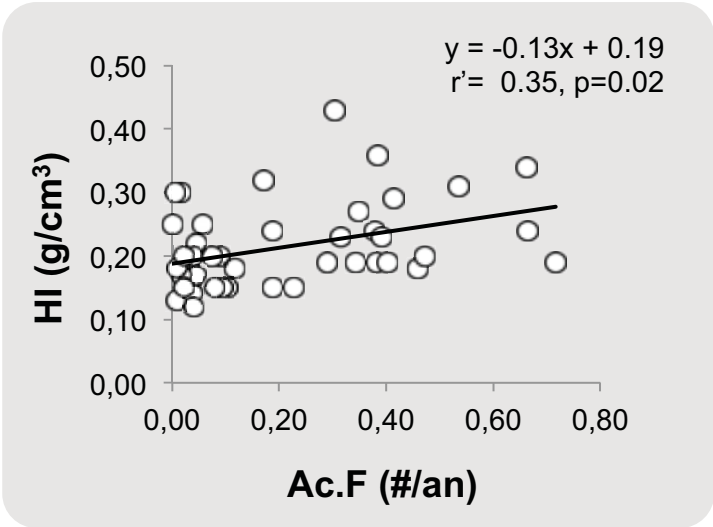
Courtesy of B. Busse (Hamburg, Germany)

Protracted use of bisphosphonate and mineralization (1/3)

Long-term effect of BPs in mineralization at the tissue level in 32 PMOP treated 6.4 ± 2.0 yrs with alendronate vs. 22 age-matched untreated PMOP.

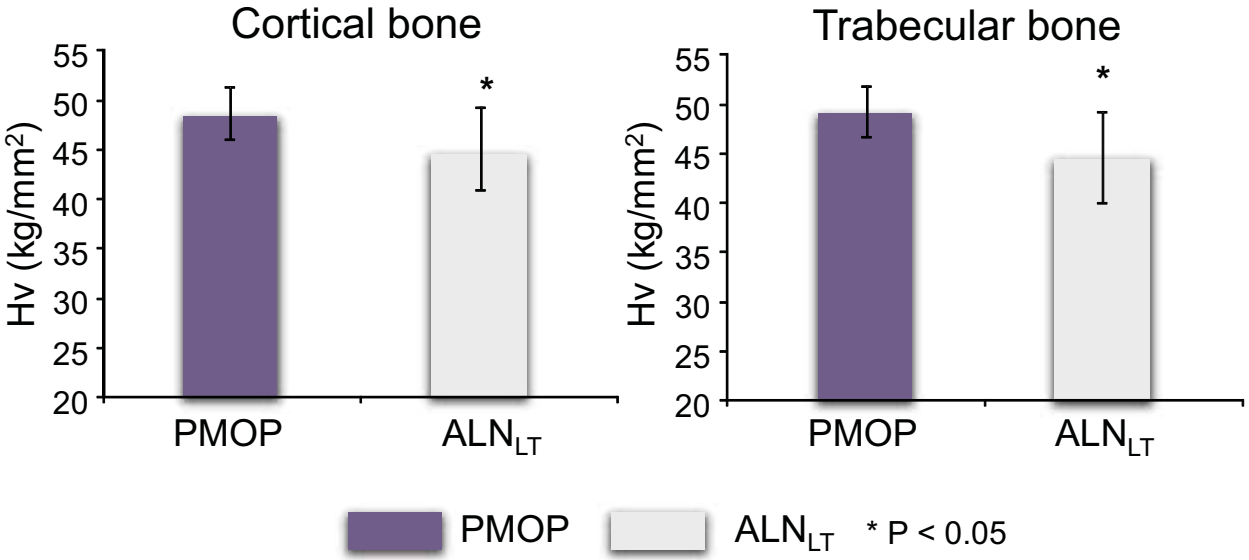


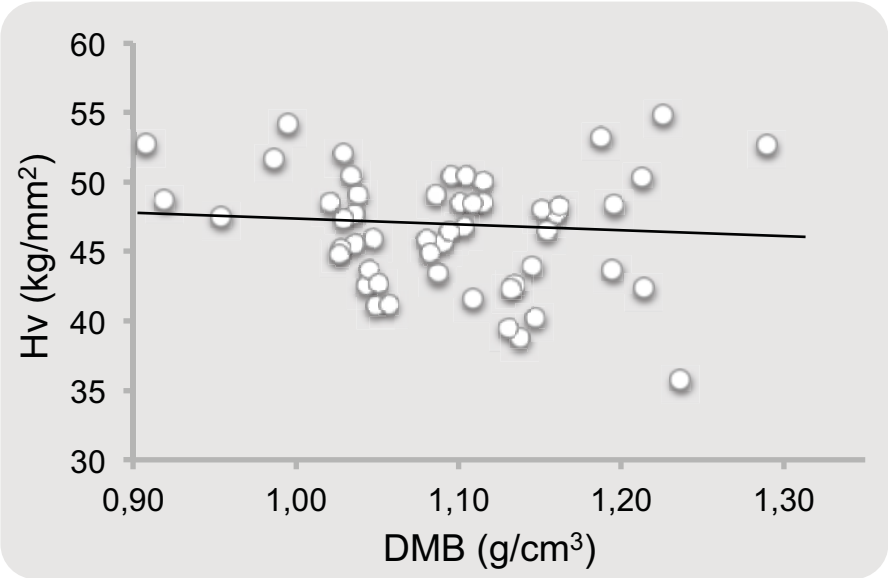




Bala *et al* EJE 2011

Protracted use of bisphosphonate and mineralization (2/3)



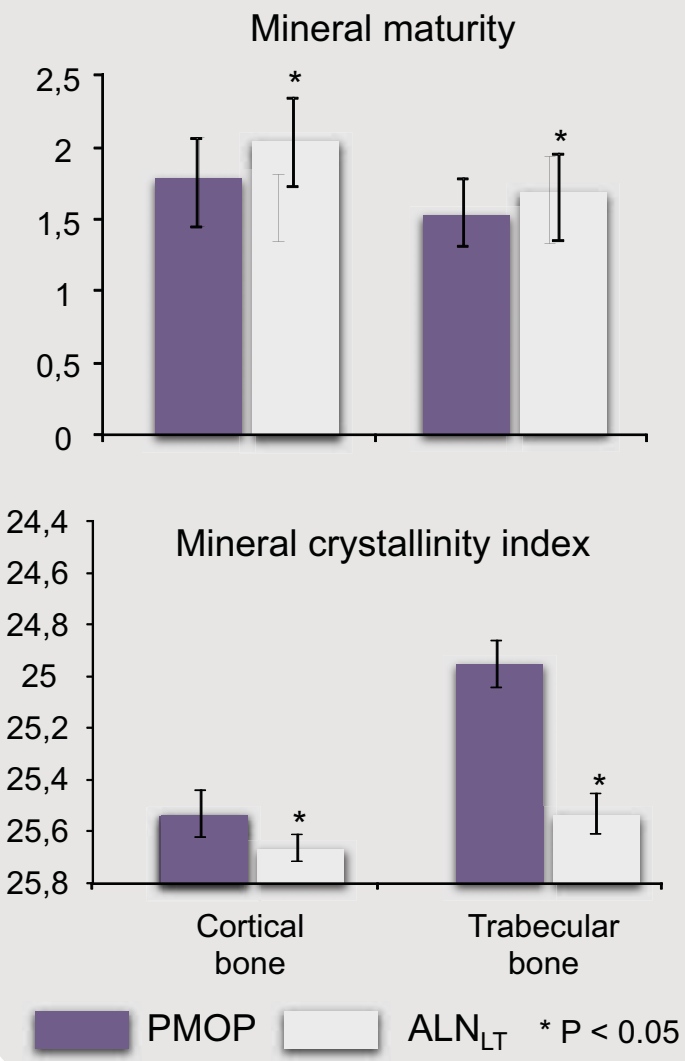


Protracted use of alendronate dissociates the relationship between hardness and DMB

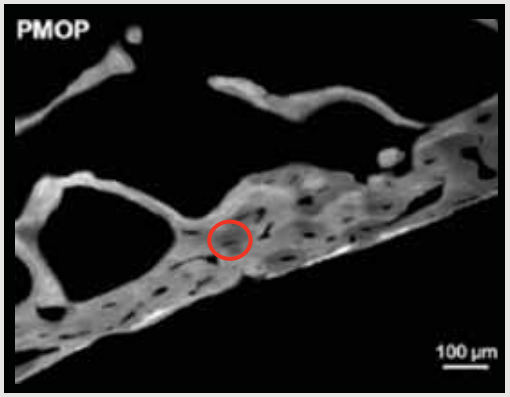
Bala *et al* EJE 2011

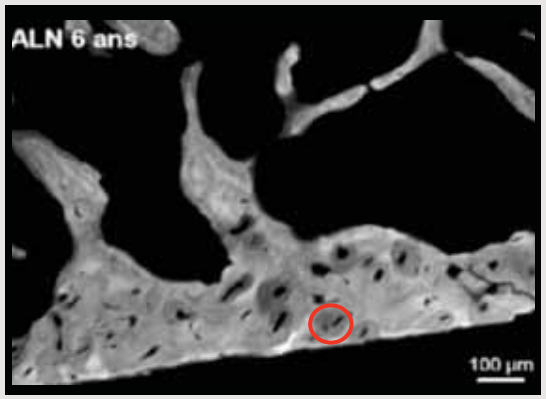
Protracted use of bisphosphonate and mineralization (3/3)

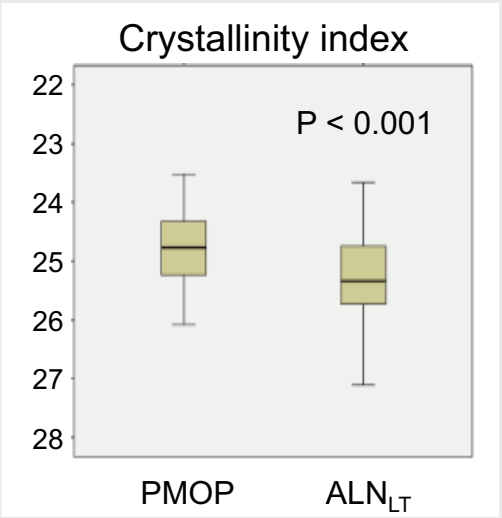
Mean ± SD obtained at the tissue level (a)

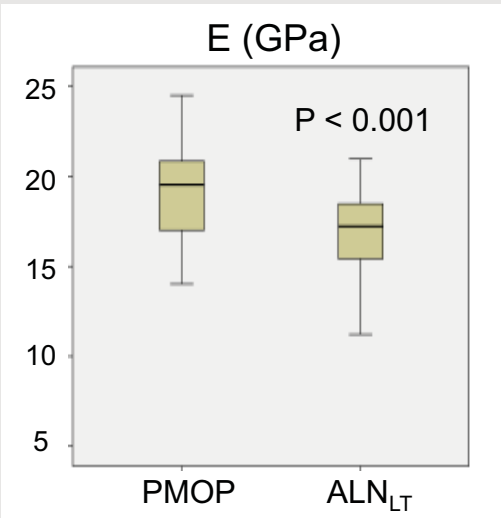


Results obtained in osteons matched for DMB and mineral maturity (80 ALN$_{LT}$, 80 PMOP) (b)









Protracted use of alendronate results in crystallinity alterations independent of mineral density decreasing the elastic modulus

(a) Bala *et al* EJE 2011 / (b) Bala *et al* JBMR 2012

Conclusions

- The degree of mineralization of bone is a key determinant of bone mechanical behaviour.

- Bone mineral characteristics impact mechanical properties independently of mineral density

- BE CRITICAL…! *Interpretation may vary according to the methodes, bone site, scale...*

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Emmanuelle Lefèvre
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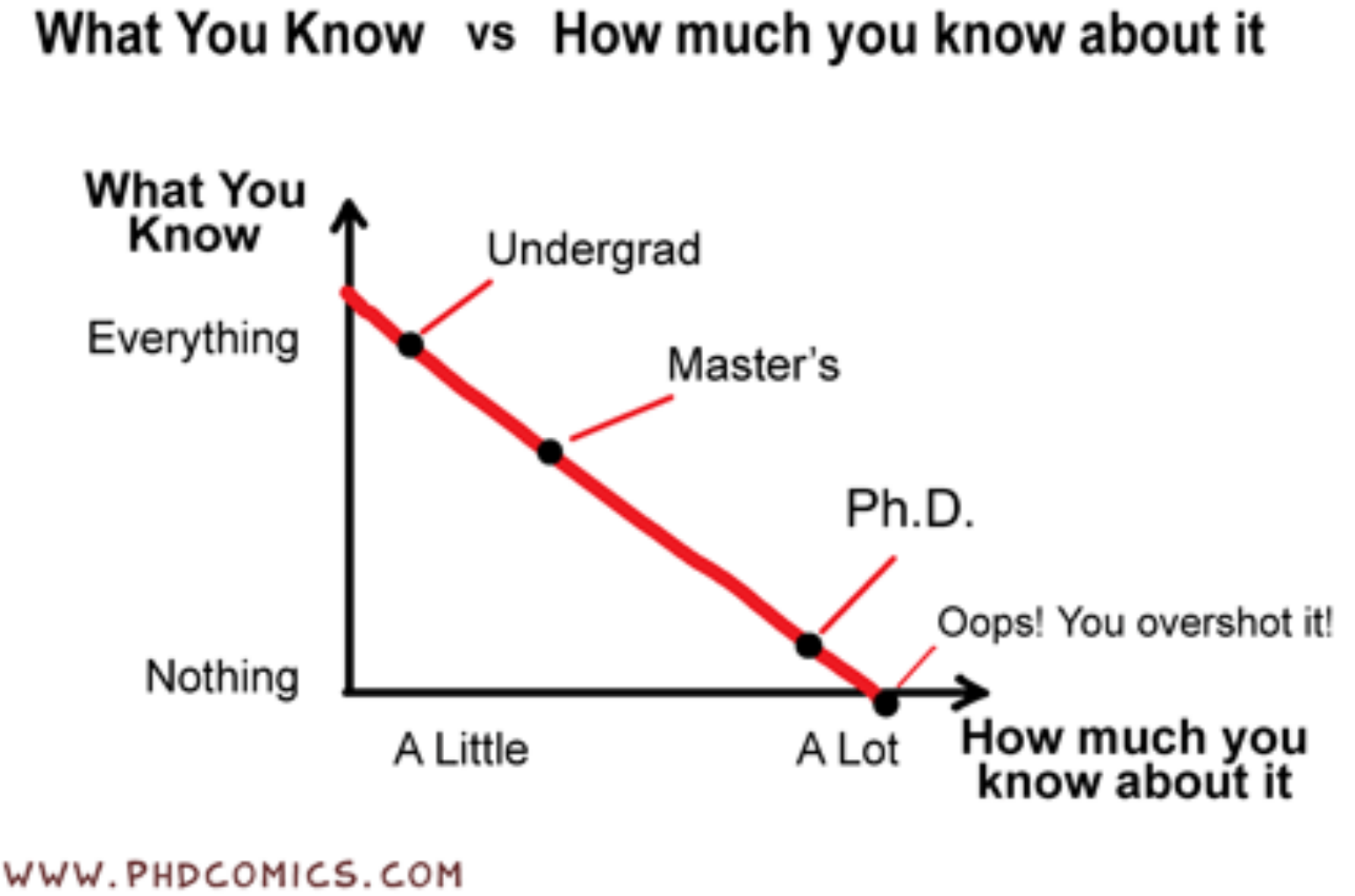
Ego Seeman
John G. Clement
David Thomas

Any question..?



Bone Mineralization

Yohann Bala, PhD.
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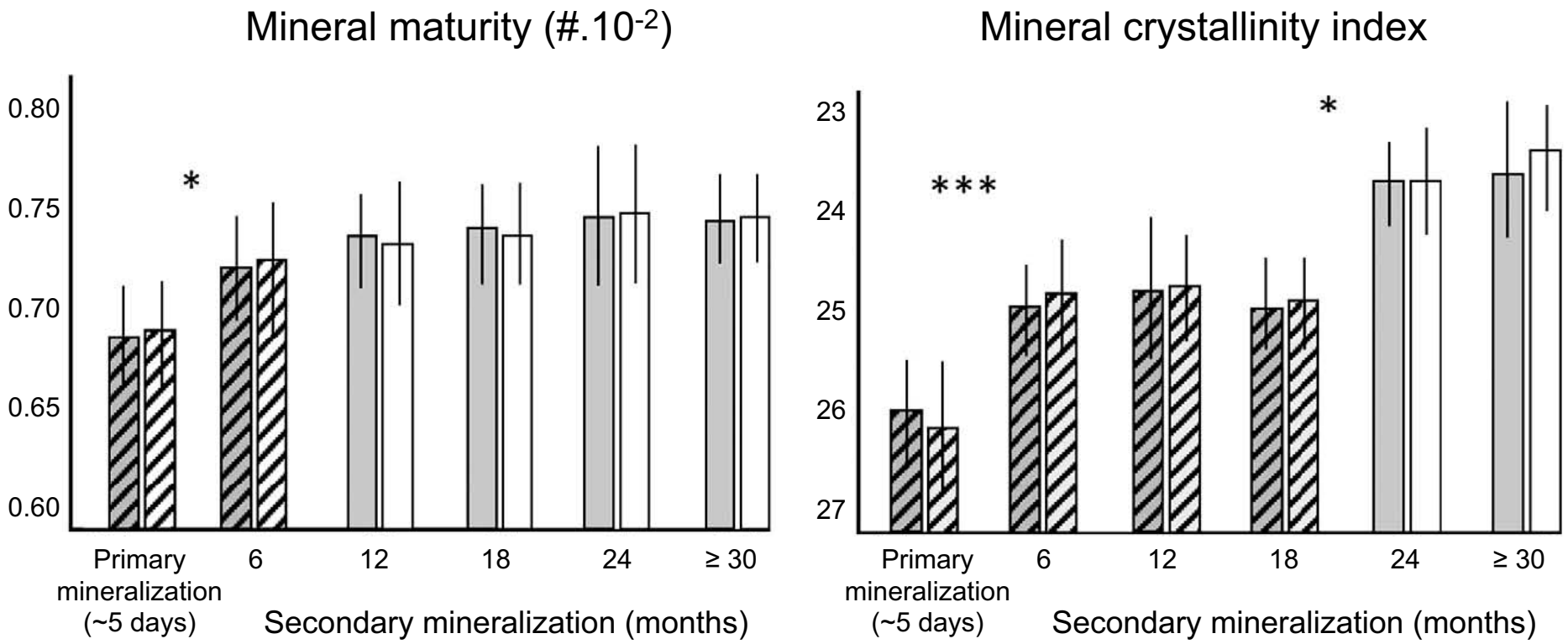
Back-Up slides

Chronology of bone mineralization in sheep (3/3)

Time-related improvement in mineral structure



Cortical bone

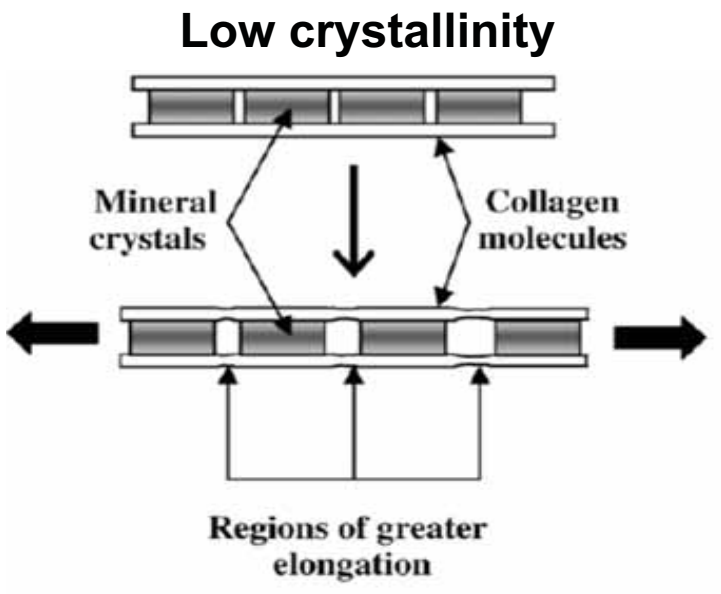
Cancellous bone

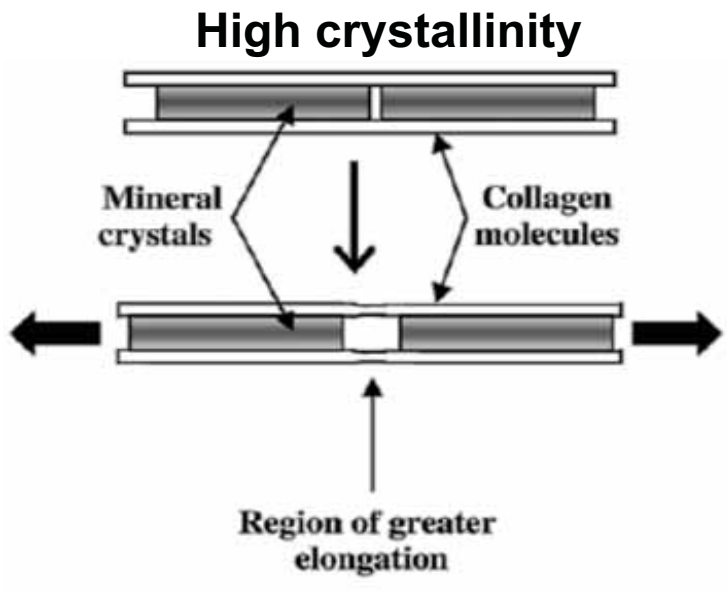
p ≤ 0.05 *vs.* ≥ *30 month-time point measured in cortical bone*

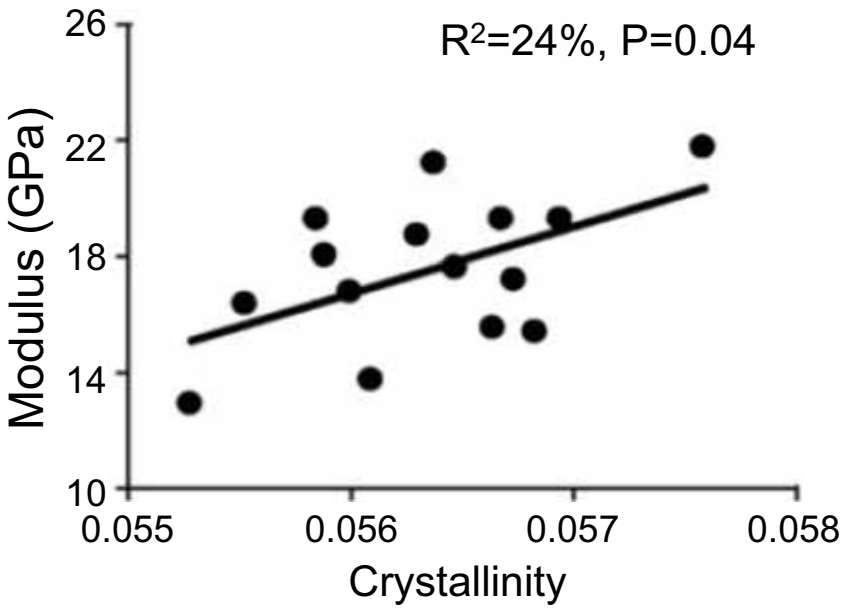
p ≤ 0.05 *vs.* ≥ *30 month-time point measured in cancellous bone*

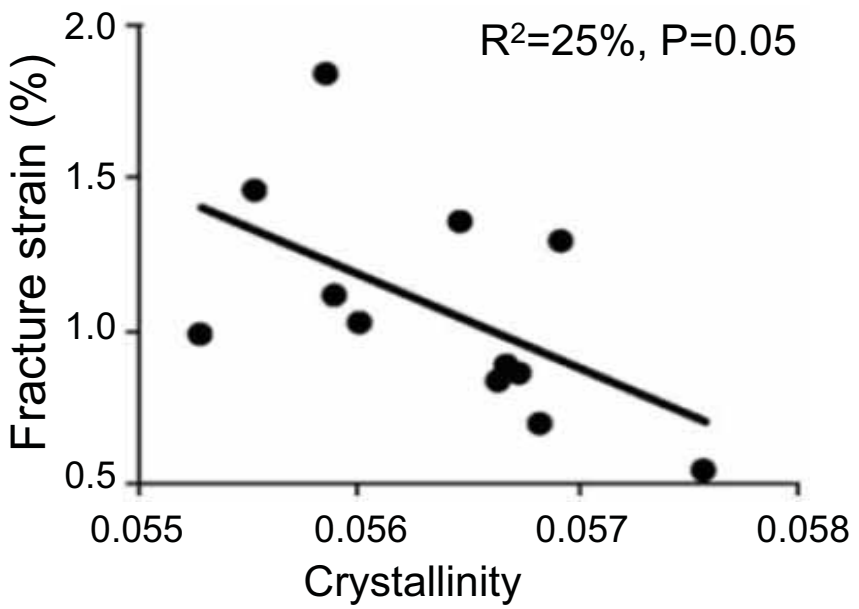
Bala *et al.* Bone 2010

Bone mechanics at the nanoscale level: Mineral-Collagen interface





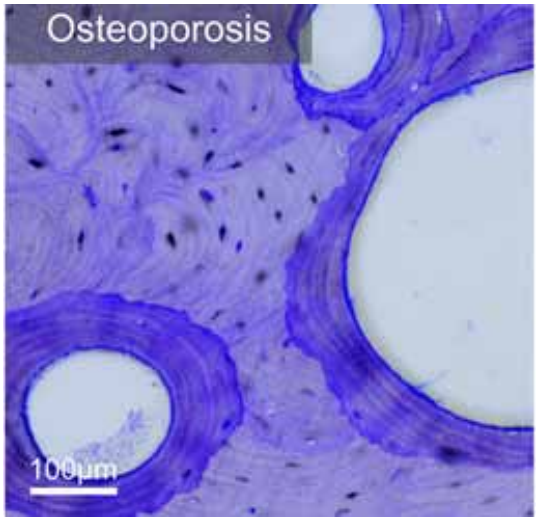


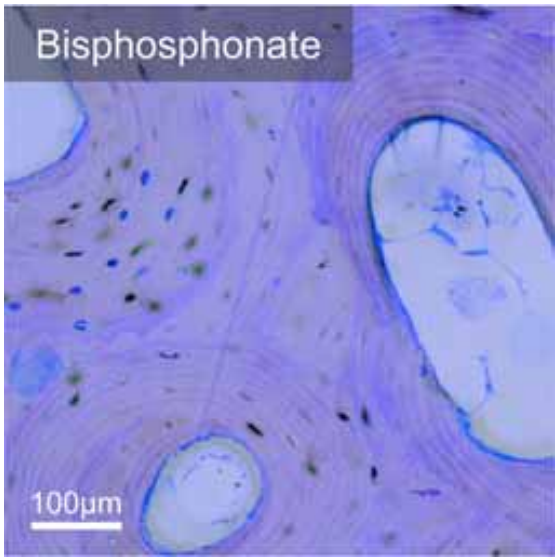


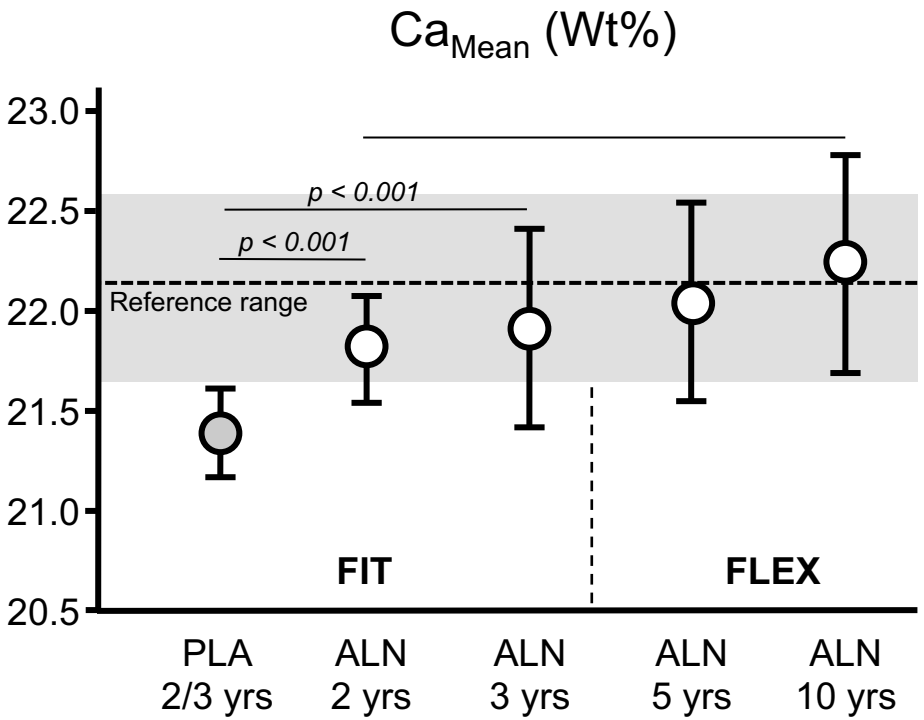
Yerramshetty *et al.* Bone 2008

Chronology of bone mineralization…*and so what ?*

Time course of BPs in postmenopausal osteoporosis treatments

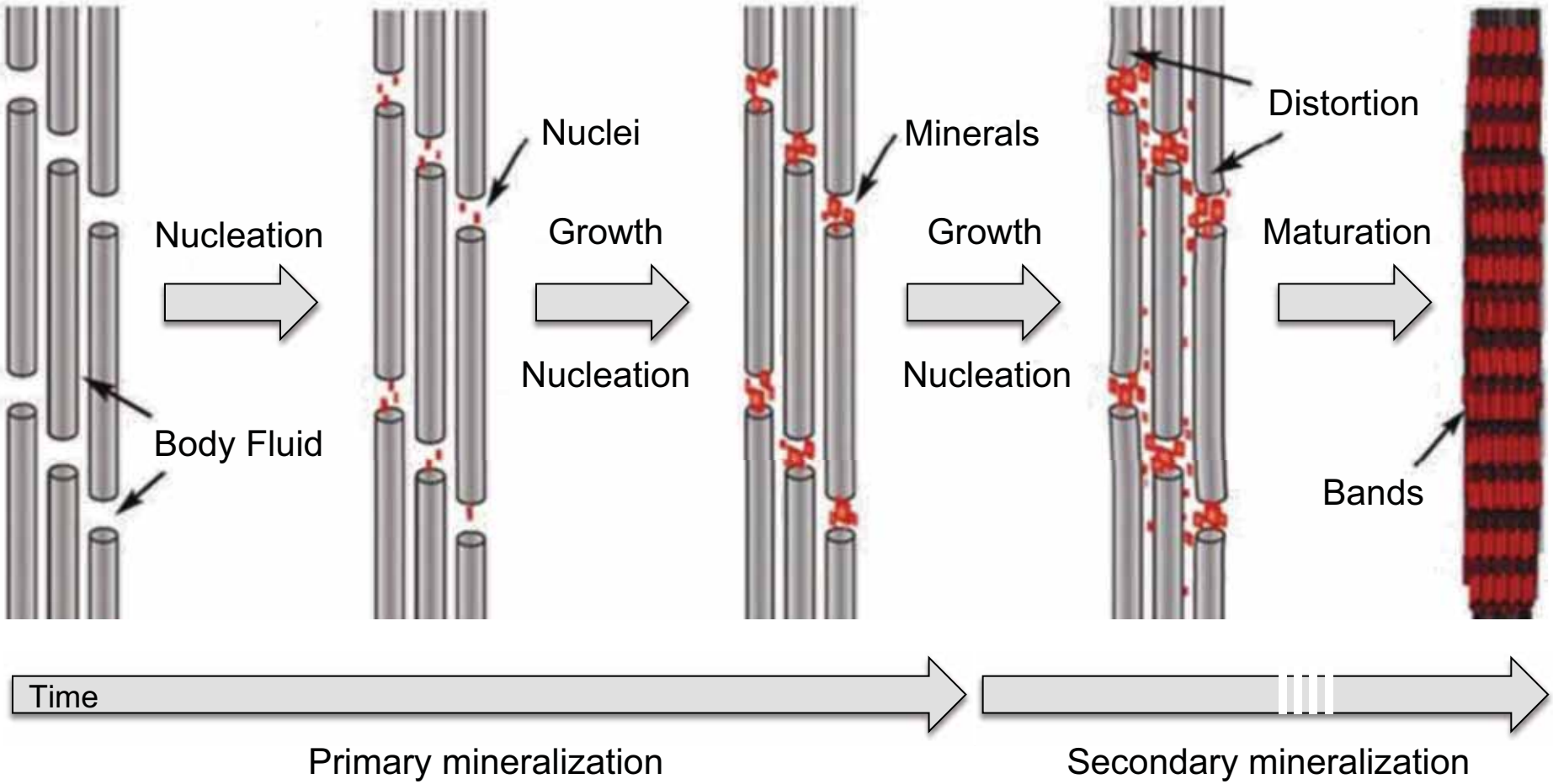






Bala *et al.* JBMR 2012 / Roschger *et al.* JBMR 2010 / Borah *et al.* Bone 2006 / Boivin *et al.* Bone 2000

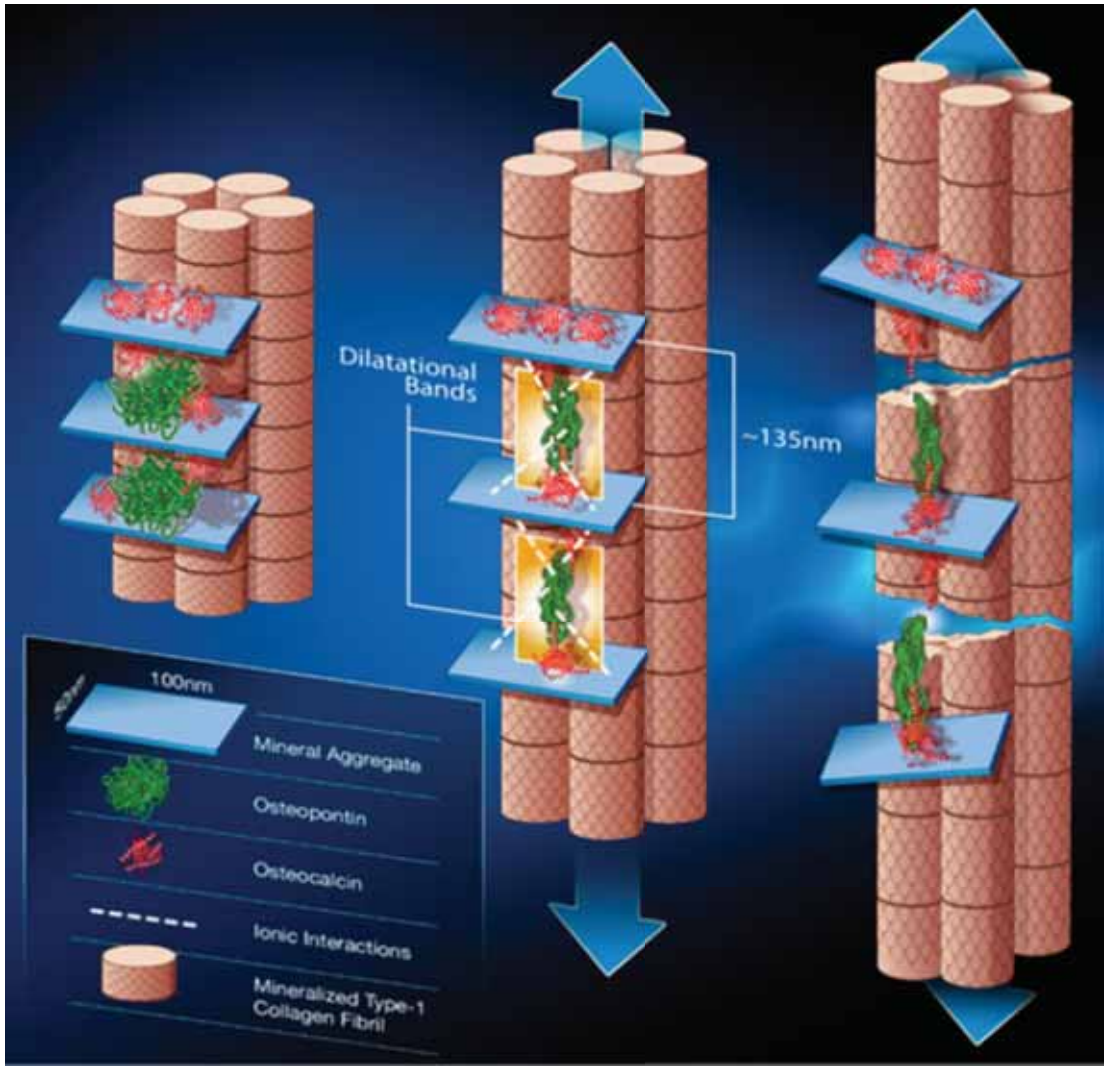
Introduction



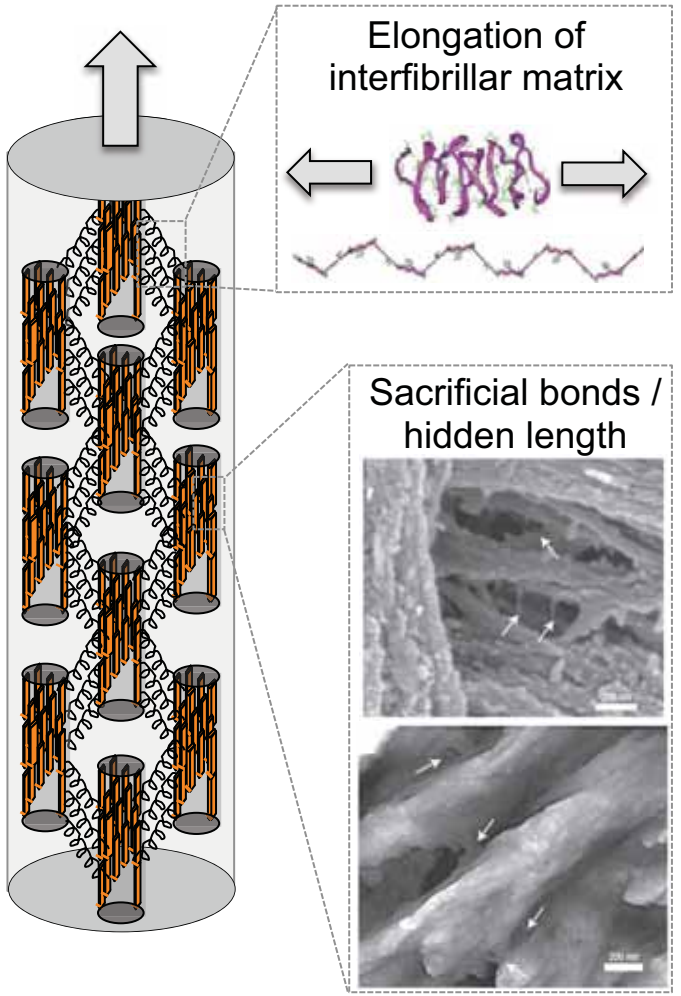
Alexander *et al.* J R Soc Interface 2012

Bone mechanics at the nanoscale level: Mineral-Collagen interface

Dilatational bands



Sacrificial bonds



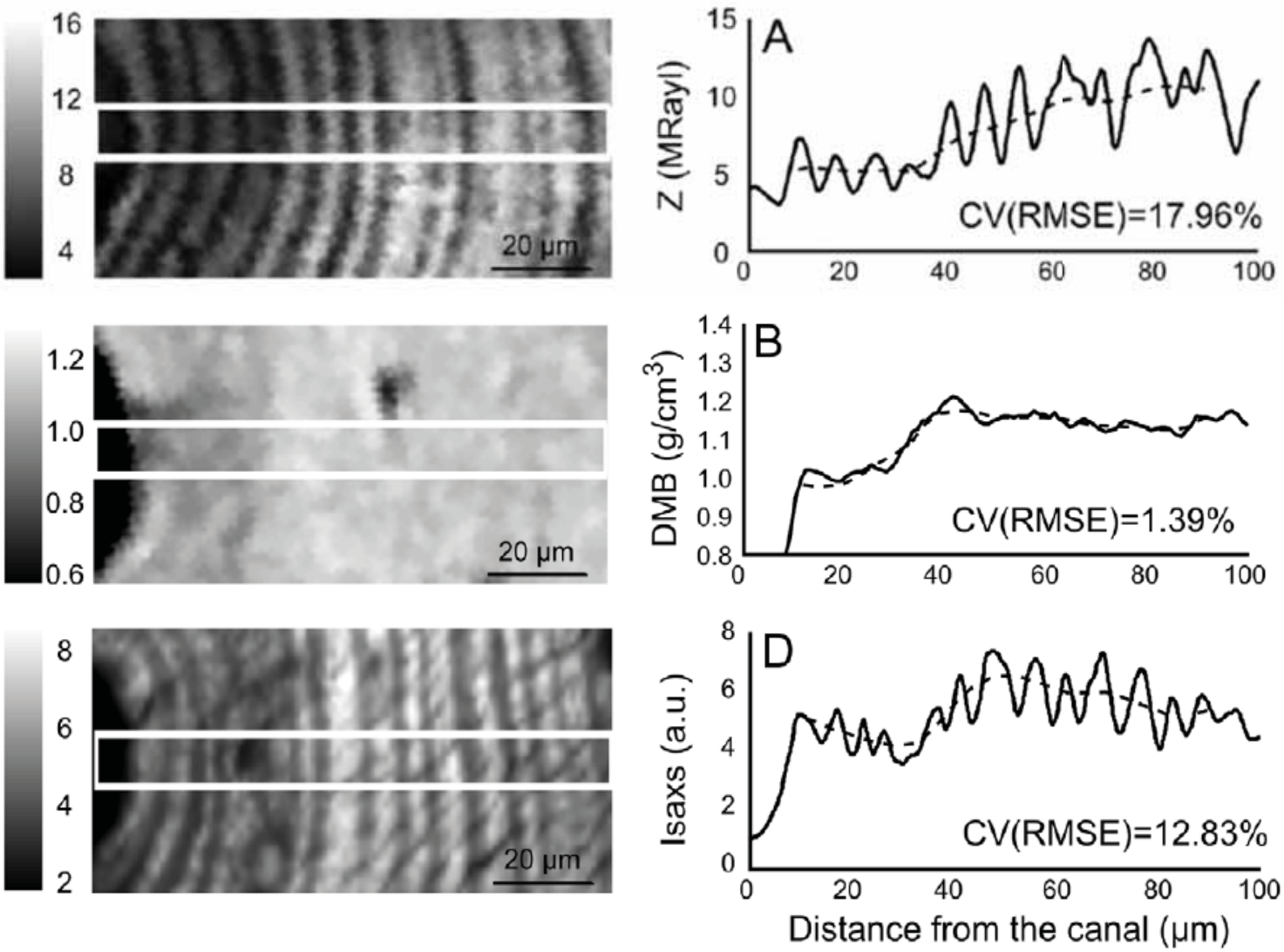
Poundarik *et al* PNAS 2012 / Fantner *et al* Nature Mater 2005

Mineralization and mechanical properties: lamellae scale

Scanning Acoustic Microscopy Z (MRayl)

SR-µCT DMB (g/cm^3)

Small-angle X-ray Scattering (a.u.)

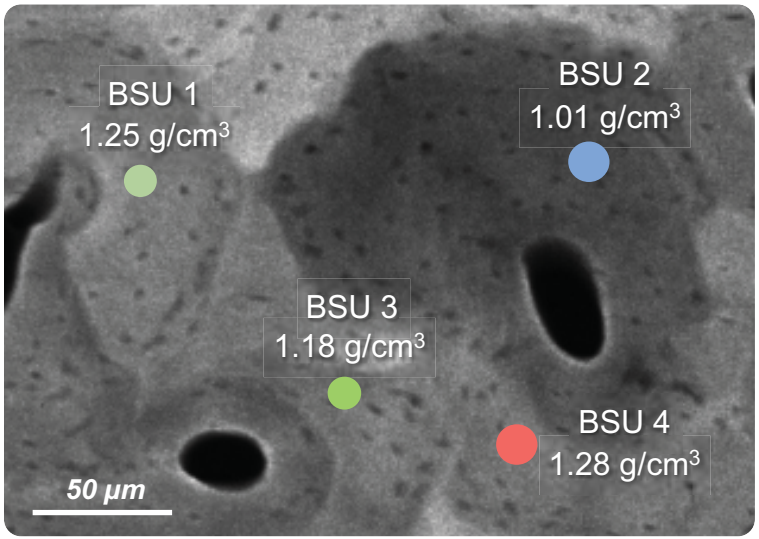


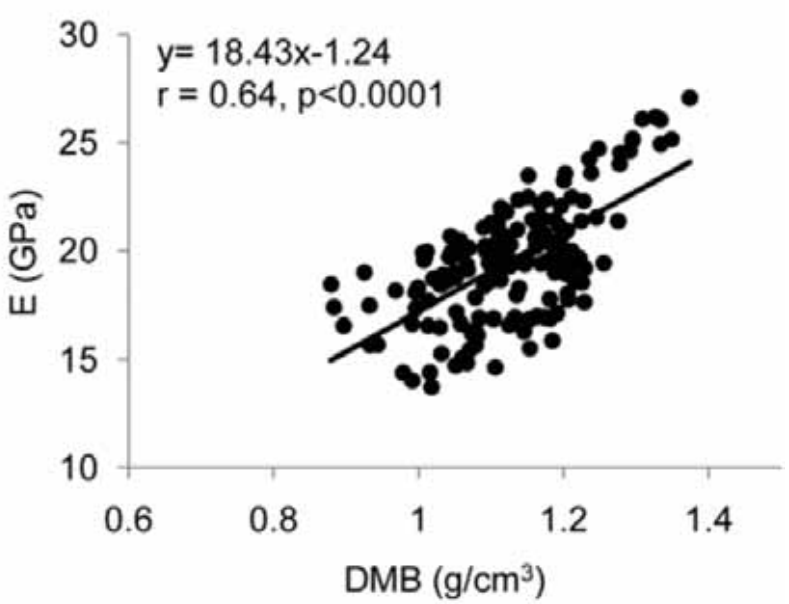
Mineralized fibrils orientation explains ~85% of lamellae elastic properties variability.

Granke *et al.* PlosOne 2011

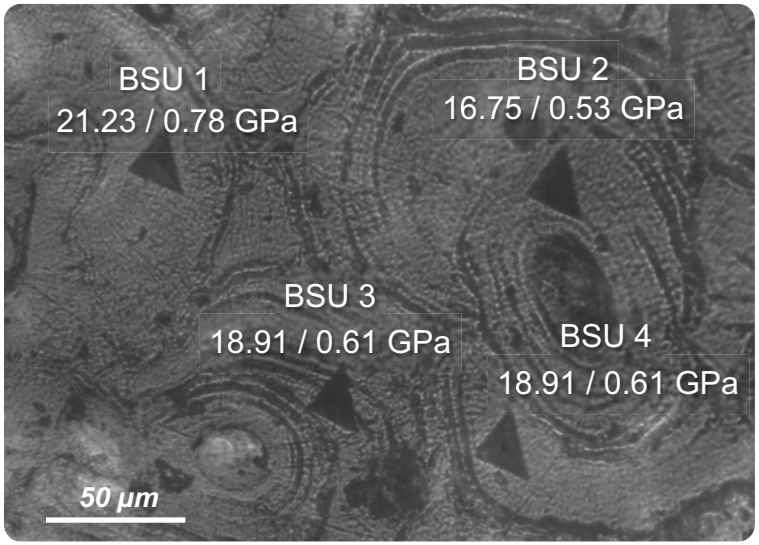
Mineralization and mechanical properties: BSU scale

Microradiography - DMB (g/cm^3)





Indentation – E / H_c (GPa)



Multiple regression models

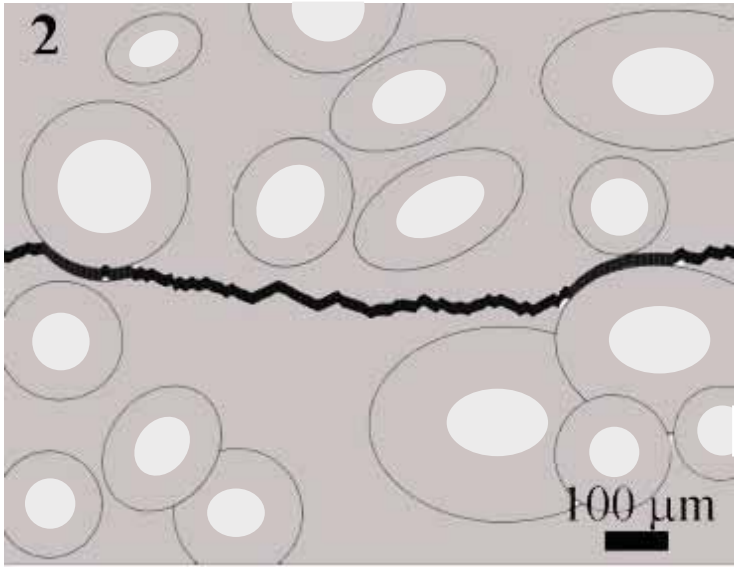
E (Gpa) =	DMB	+	Crystallinity Index	+	Collagen Maturity
R^2 = 0.68	1				
	0.68		*Out*		*Out*

Hc (Gpa) =	DMB	+	Crystallinity Index	+	Collagen Maturity
R^2 = 0.74	1				2
	0.46		*Out*		*0.33*

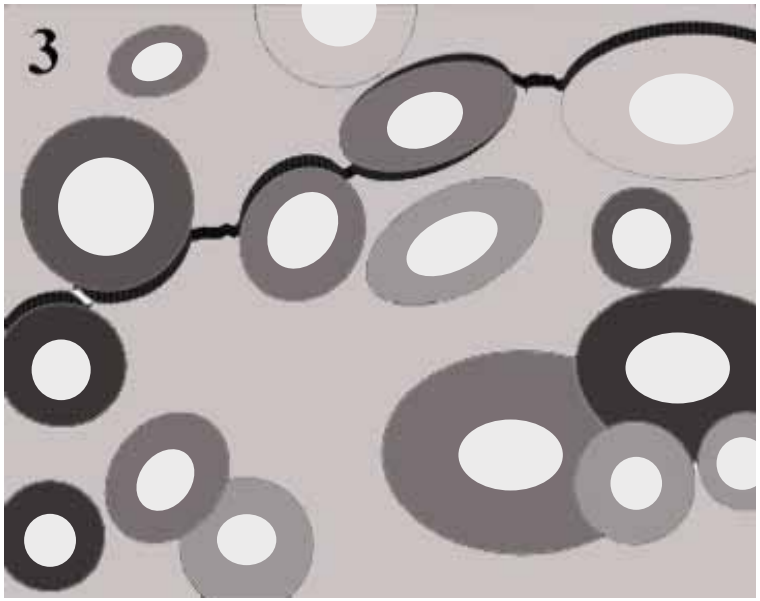
Bala *et al.* J Mech Behav Biomed Mater 2011

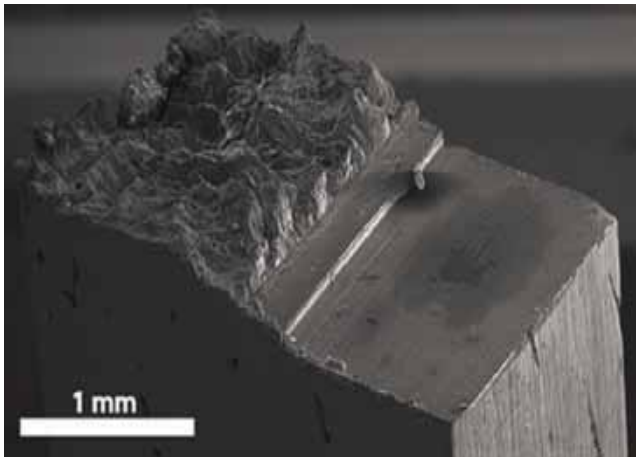
Mineralization and mechanical properties: Tissue level

Homogeneous tissue

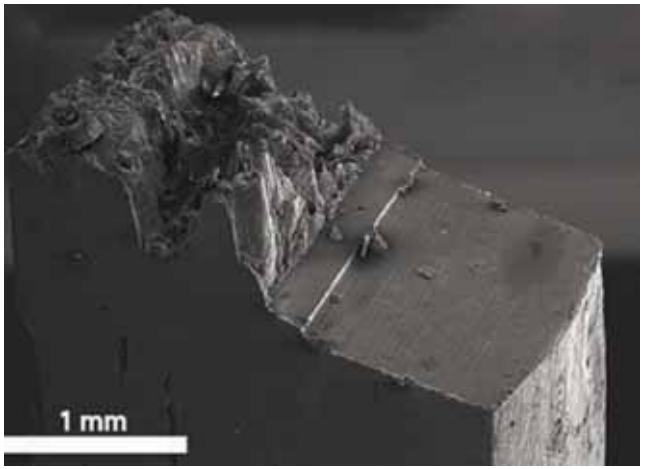


Heterogenous tissue





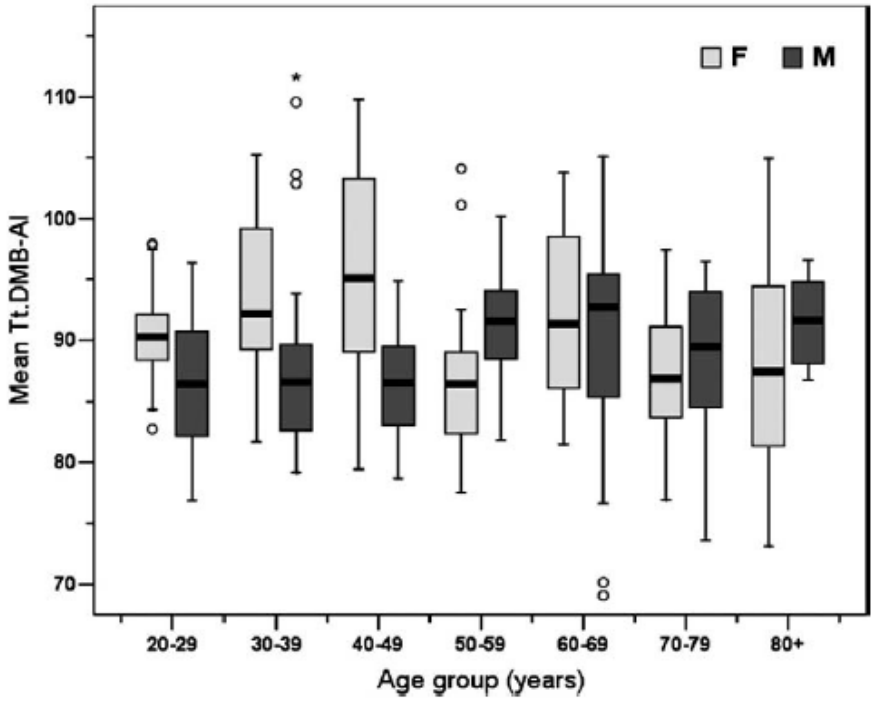
Toughness



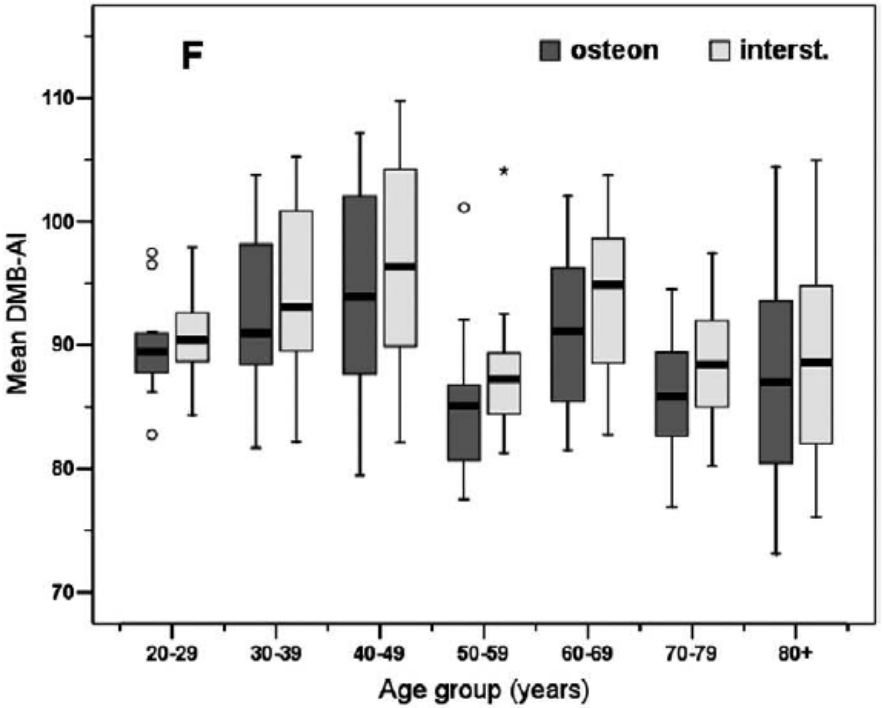
Mischinski *et al.* Comput Methods Biomech Engin 2013 / Courtesy of E. Zimmermann & B. Busse (Hamburg, Germany)

Bone mineralization during ageing (2/3)

DMB assessed in cadavers femoral shaft from 99 females (F) and 94 males (M)



DMB negatively correlated with age only in women (r=0.26, p=0.01).

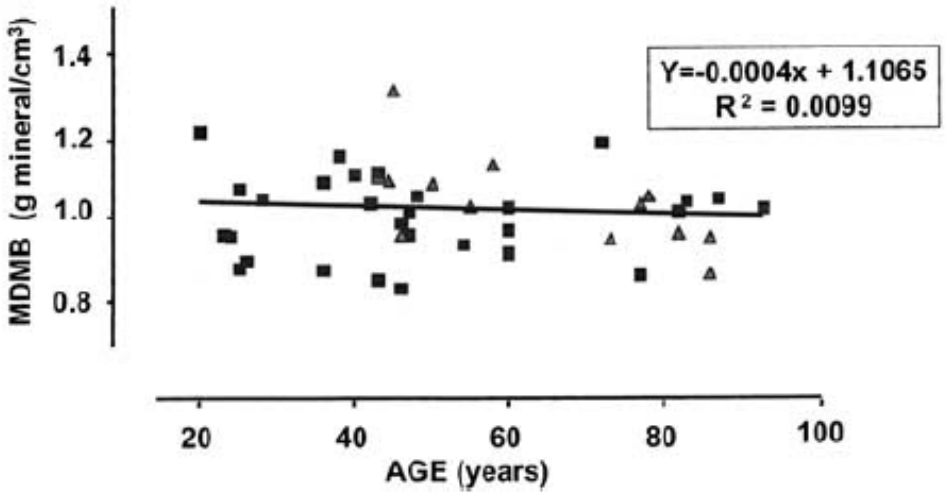


This apparent decrease was related to both lower DMB in both osteonal and interstitial bone.

Bergot *et al* Bone 2009

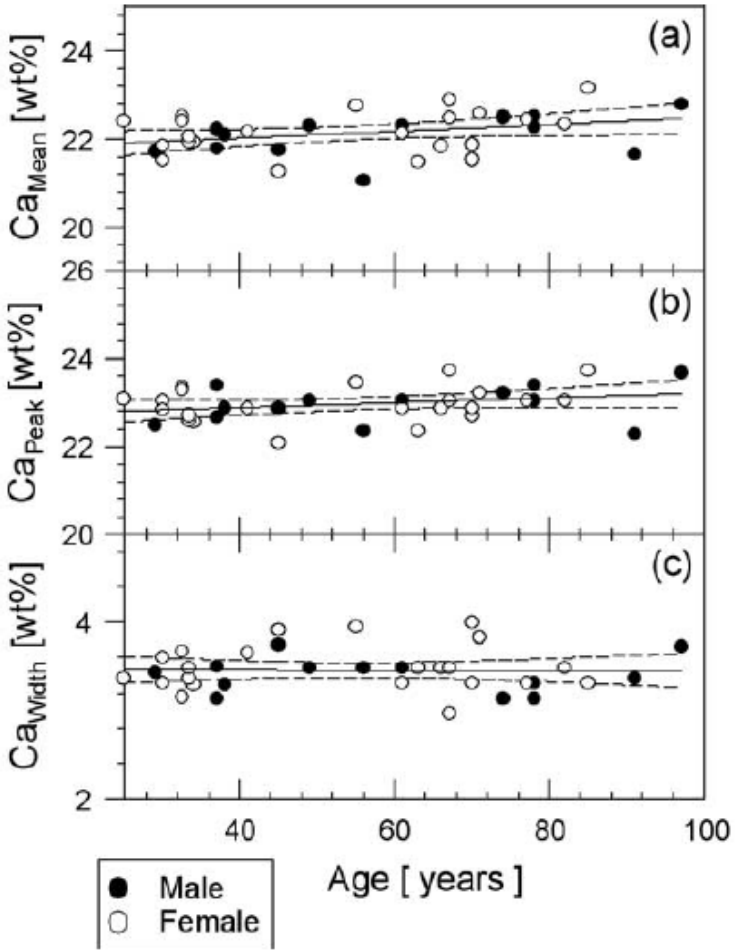
Bone mineralization during ageing (1/2)

Total DMB (Cortical + Trabecular) assessed in iliac crest samples from 30 females (square) and 13 males (triangle).



Boivin *et al* Calcified Tissue Res 2002

Trabecular Ca content assessed in iliac crest samples from 22 women and 13 men.



Roschger *et al* Bone 2003