# Spaceflight-induced Bone Loss:

## Is there a risk for accelerated osteoporosis after return?

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HRP Bone Discipline Lead

# Recommendations of Institute of Medicine – Safe Passage: Astronaut Care for Exploration Missions

- Develop and use an occupational health model for the collection and analysis of astronaut health data, giving priority to the creation and maintenance of a safe work environment

- Incorporate an <u>evidence-based risk assessment</u> <u>and communication process into the risk identification and reduction approach</u>

# The IOM approach for Bone Discipline Evidence Base Reports

4 identified risks of an adverse outcome due to space exploration.

1. Accelerated Osteoporosis

   Long-term health

2. Formation of Renal Stones
3. Intervertebral Disc Injury *(or Damage)*
4. Bone Fracture

#2-4 Risk for mission but more evidence required.

# Overview

## Evidence Base for #1 Risk of Accelerated Osteoporosis

- **Involutional Osteoporosis**
- **Bone remodeling process**
- **Skeletal adaptation to space**
- **Skeletal changes: space vs. ageing**
  **- Circumstantial Evidence**
- **Gaps in our knowledge base**

# Two Risk Statements for Accelerated Osteoporosis

**Earlier: Bioastronautics Roadmap 2005**

"Osteoporosis associated with age-related bone loss may occur at an earlier age due to failure to recover bone lost during spaceflight."

**Current: Risk Statement in Human Research Program**

"…(If) mission-related bone loss cannot be corrected by post-mission rehabilitation; crew members could be at *greater risk* of osteoporosis-related fractures in later life."

Is there recovery? Are the changes irreversible?

→ Overlap with involutional changes in bone.

# “Involutional” Osteoporosis

The regressive alterations of a body or its parts characteristic of the ageing process

Age-related bone loss

# Osteoporosis Definitions

- OLD: "...a reduced amount of bone that is qualitatively normal."
  Albright F. Ann Intern Med. 1947

- MODERN:"…a systemic skeletal disease characterized by <u>low bone mass and microarchitectural deterioration</u> with a consequent increase in *bone fragility* with susceptibility to fracture …."
  Am. J. Med.1991

- NEWEST: "Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Bone strength reflects the <u>integration of two main features</u>: bone density and bone quality."
  JAMA. 2001

# Classifications of Osteoporosis

- Primary Osteoporosis - "Involutional Osteoporosis"

  Menopause-induced Bone Loss "Postmenopausal Osteoporosis"

  Age-related Bone Loss "Senile Osteoporosis"

- Secondary Osteoporosis – External causes

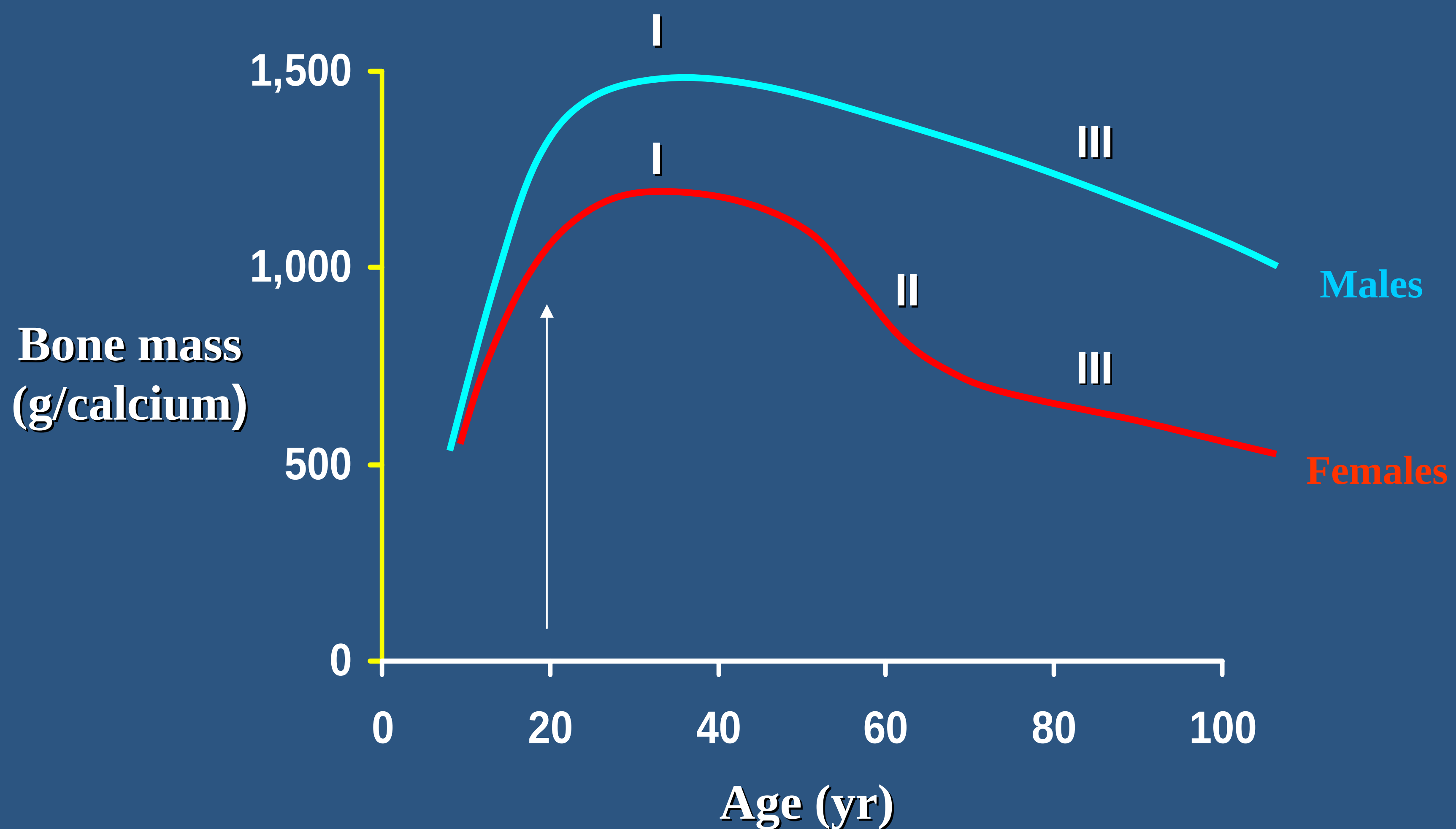
  Glucocorticoid Medication

  Alcohol-induced

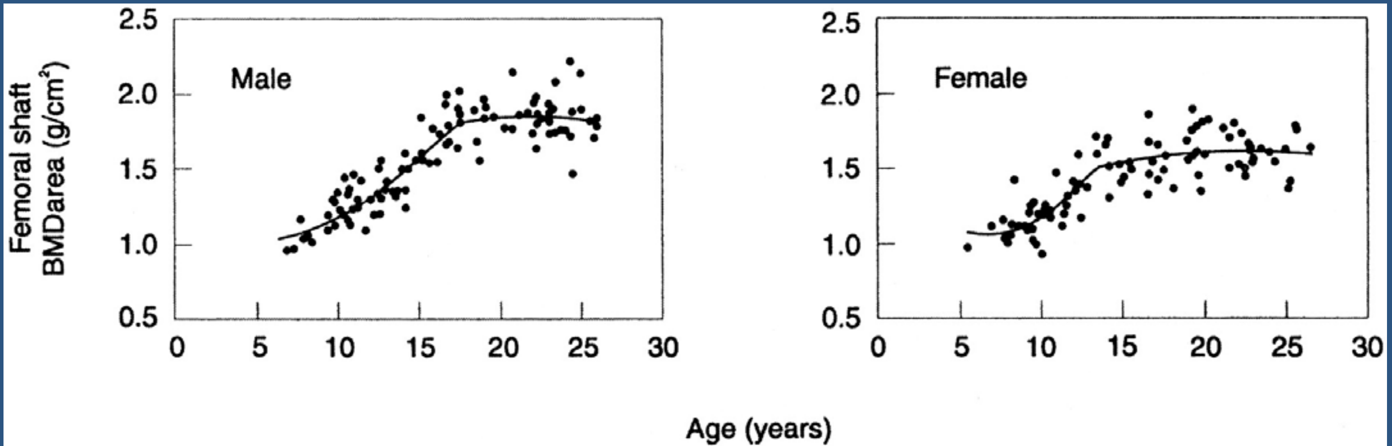
  Immobilization

  Anti-seizure drugs

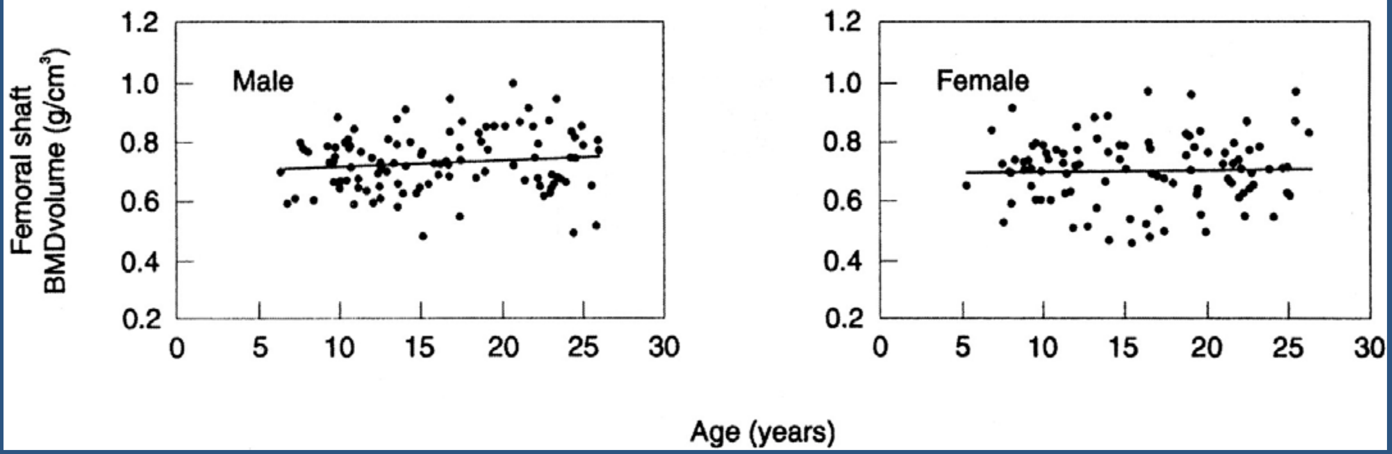
# Bone Gain and Loss with Age is Sex-specific




Riggs BL, Melton LJ: Involutional osteoporosis
Oxford Textbook of Geriatric Medicine




Dispelling a Fallacy:  NOT BMD, but Bone size increases in growing males.




**Phase I (Bone Gain): Femoral Shaft areal BMD increases with age, but volumetric BMD is independent of age in young males and females.**

**Seeman, E. J Clin Endocrinol Metab 2001;86:4576-4584**

The Journal of Clinical Endocrinology & Metabolism

# Being Female is a risk factor for osteoporosis.

- Smaller bones
- Undergo two phases of bone loss: an earlier rapid phase of loss (menopause induced) followed by a slower phase of loss (induced by ageing) equivalent to the rate of bone loss in men.

How does the "Risk for Accelerated Osteoporosis" in crew members fit in with Involutional Osteoporosis?

# Clarifying the "Risk for Accelerated Osteoporosis."

1. Accelerated: "to bring about at an earlier time"

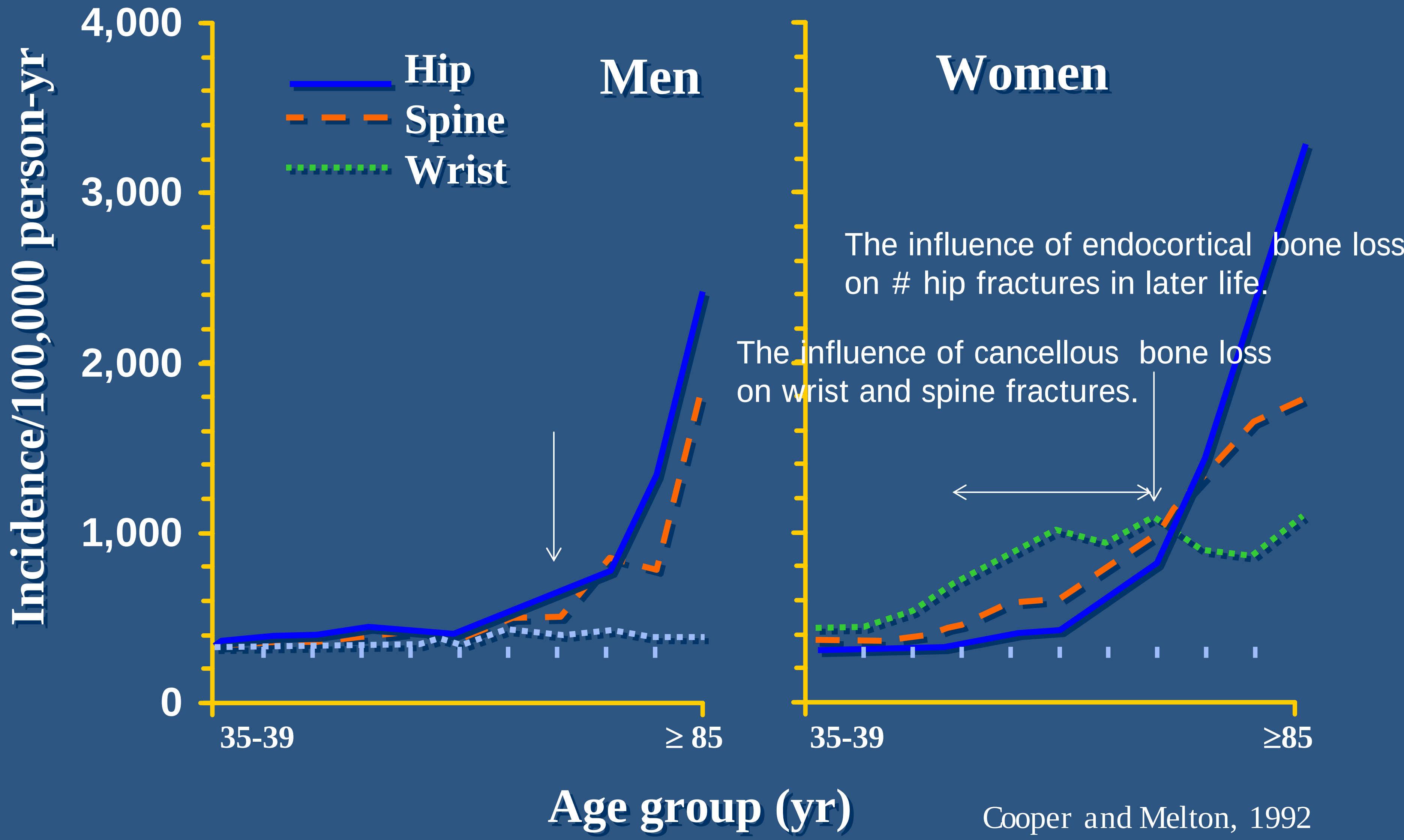
2. Osteoporosis: Occurrence of fractures under mechanical loading of normal activities "atraumatic"

3. Evidence: incidence of atraumatic fractures at an earlier age (relative to expected age of occurrence)

4. Evidence: Greater prevalence fractures in the former astronauts compared to peer group.

A STUDY EVALUATING FRACTURE AS THE OUTCOME IN ASTRONAUTS???

# Age-Related Fractures : when and how many?




Cooper and Melton, 1992

# Measuring surrogates to bone strength.

Supplementing DXA measures of areal BMD.

But, with which one?

# Bone Volume Changes in the Adult Skeleton :

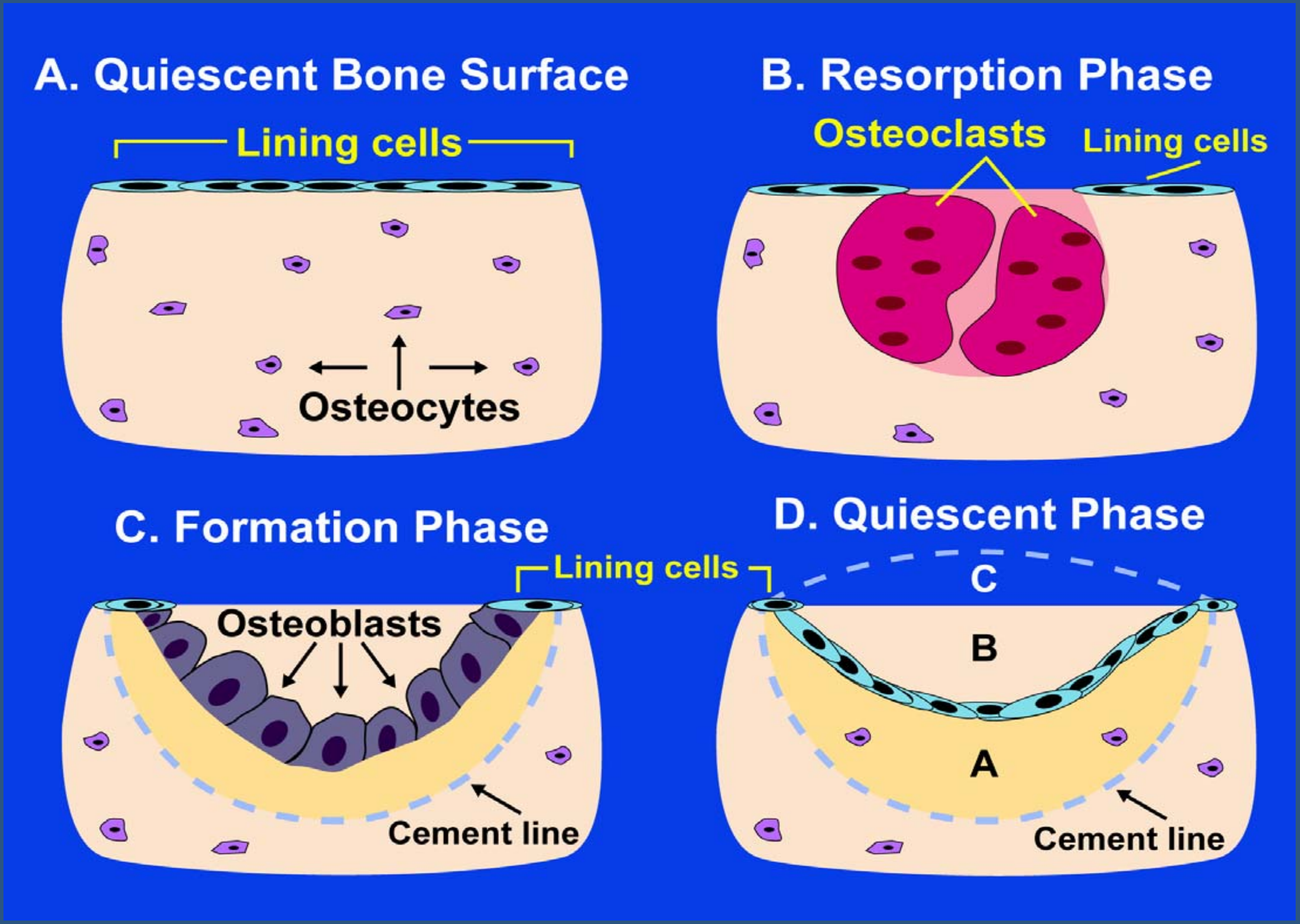
## The Bone Remodeling Process

# Changes in the skeletal tissue occur through 3 regulated processes

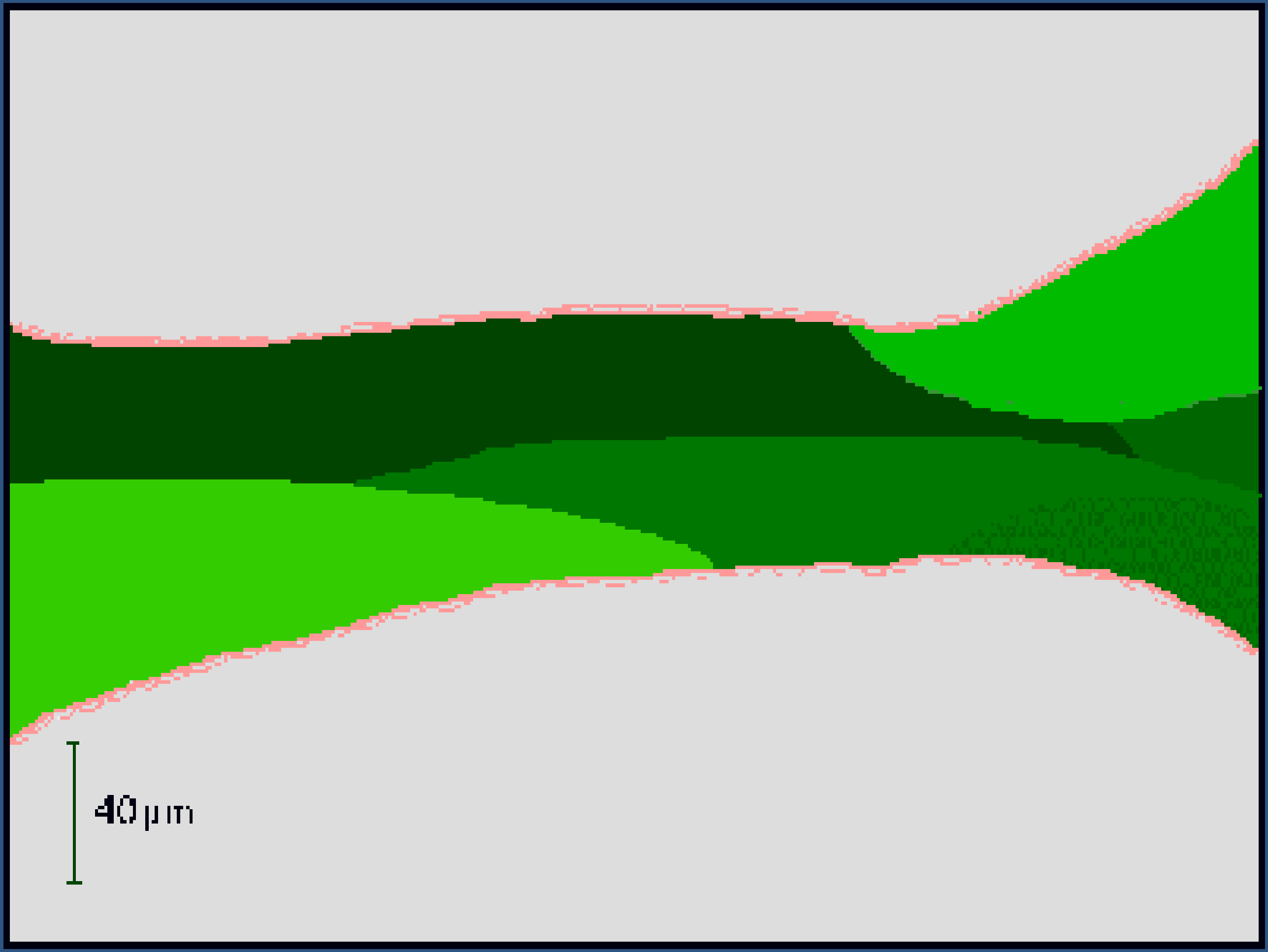
- Growth - **developing skeleton (BF>BR)**
- Modeling - **shaping of bone (e.g., elongation)**
- Remodeling – **repair, renewal, calcium homeostasis**
  - 10% of skeleton/year

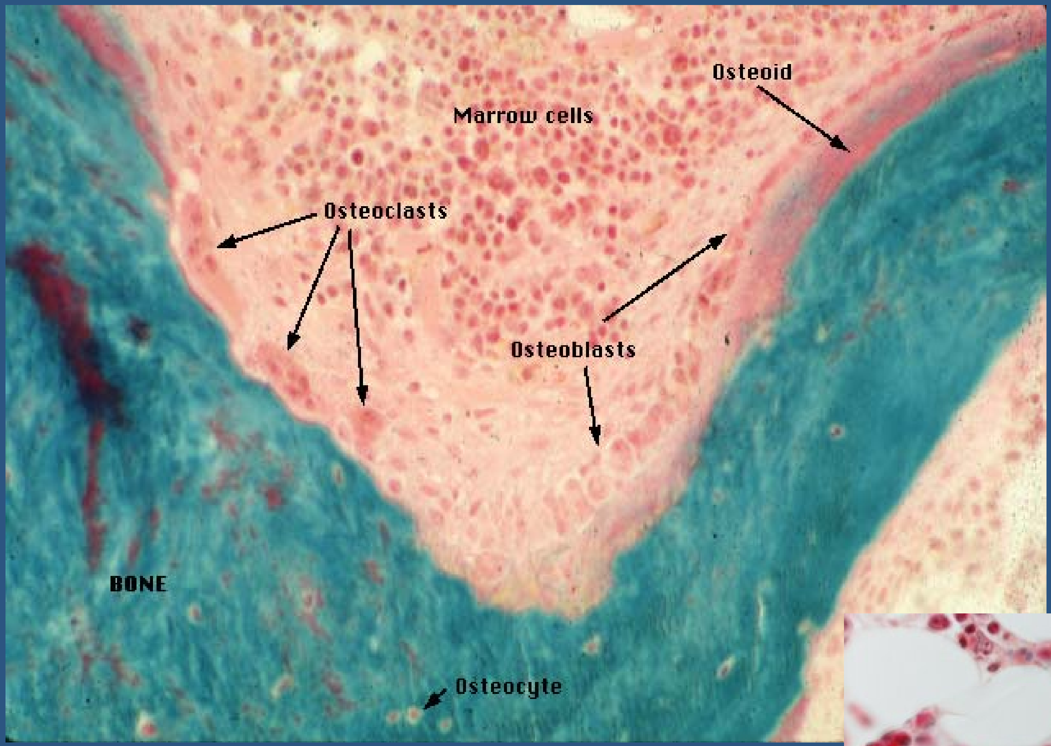
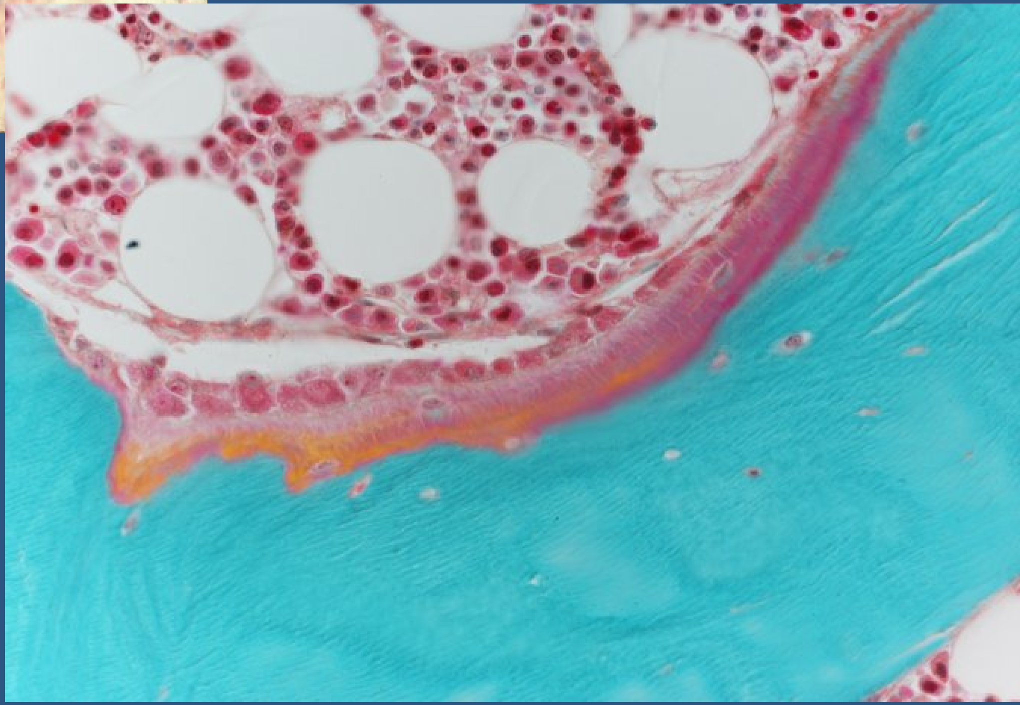
# Remodeling in Discrete Packets of Bone

(Bone Remodeling Unit BRU – Basic Multicellular Unit BMU)

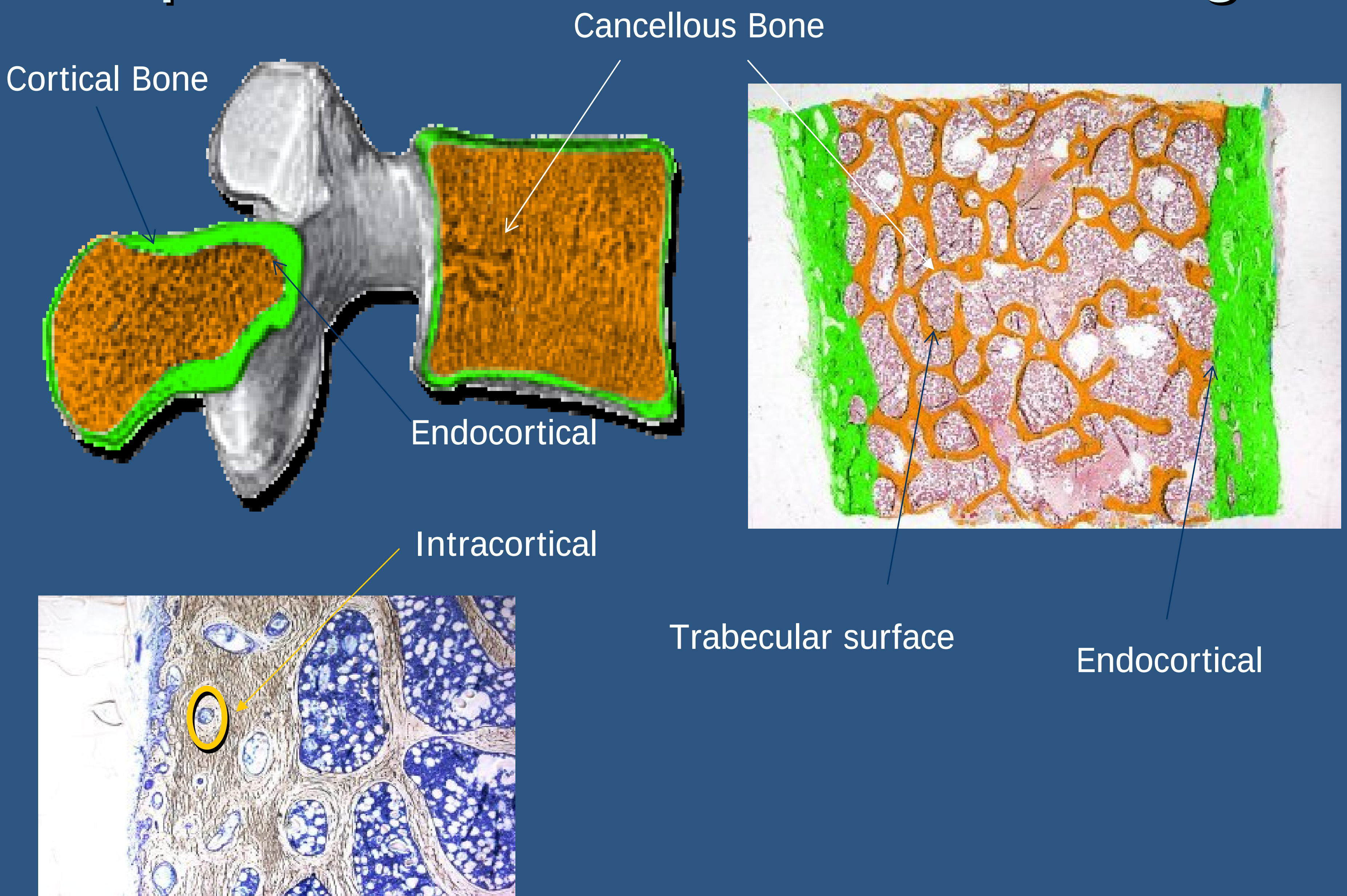


# Remodeling at the level of the BRU




Osteoid
Marrow cells
Osteoclasts
Osteoblasts
BONE
Osteocyte


# Specific sites of bone remodeling.



# Bone Remodeling of Cancellous Bone
## (aka Trabecular Bone)

- For normal turnover, bone repair & tissue renewal, mineral homeostasis
- Bone Resorption (BR) precedes Bone Formation (BF)
- Time for BR < Time for BF
- Two phases of BF: matrix production and mineralization
- 4-6 months
- Bone Balance vs. Bone Coupling

Osteoporosis in the adult likely results from a perturbation in the remodeling process.

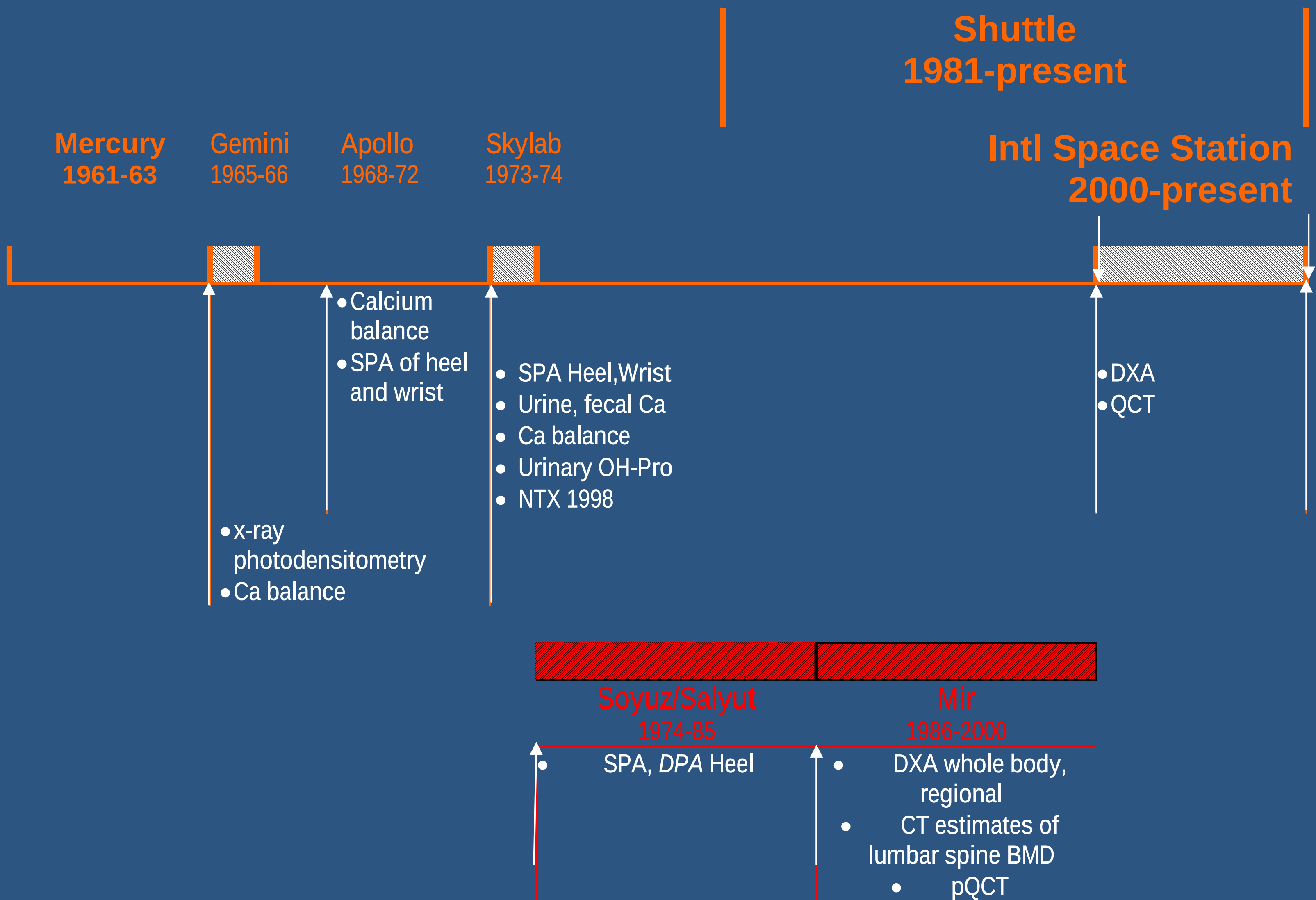
# Multiple Pathophysiologies for Osteoporosis: Perturbations to Remodeling

| Osteoporosis | BF | BR |
|---|---|---|
| Disuse* (“Skeletal unloading”) | | + |
| Aging | - | |
| Glucocorticoids | - | |
| Estrogen Deficiency | + | ++ |
| Alcohol | - | |
| Metabolic diseases of High Bone Turnover | + | ++ |

# Skeletal Adaptation to Space

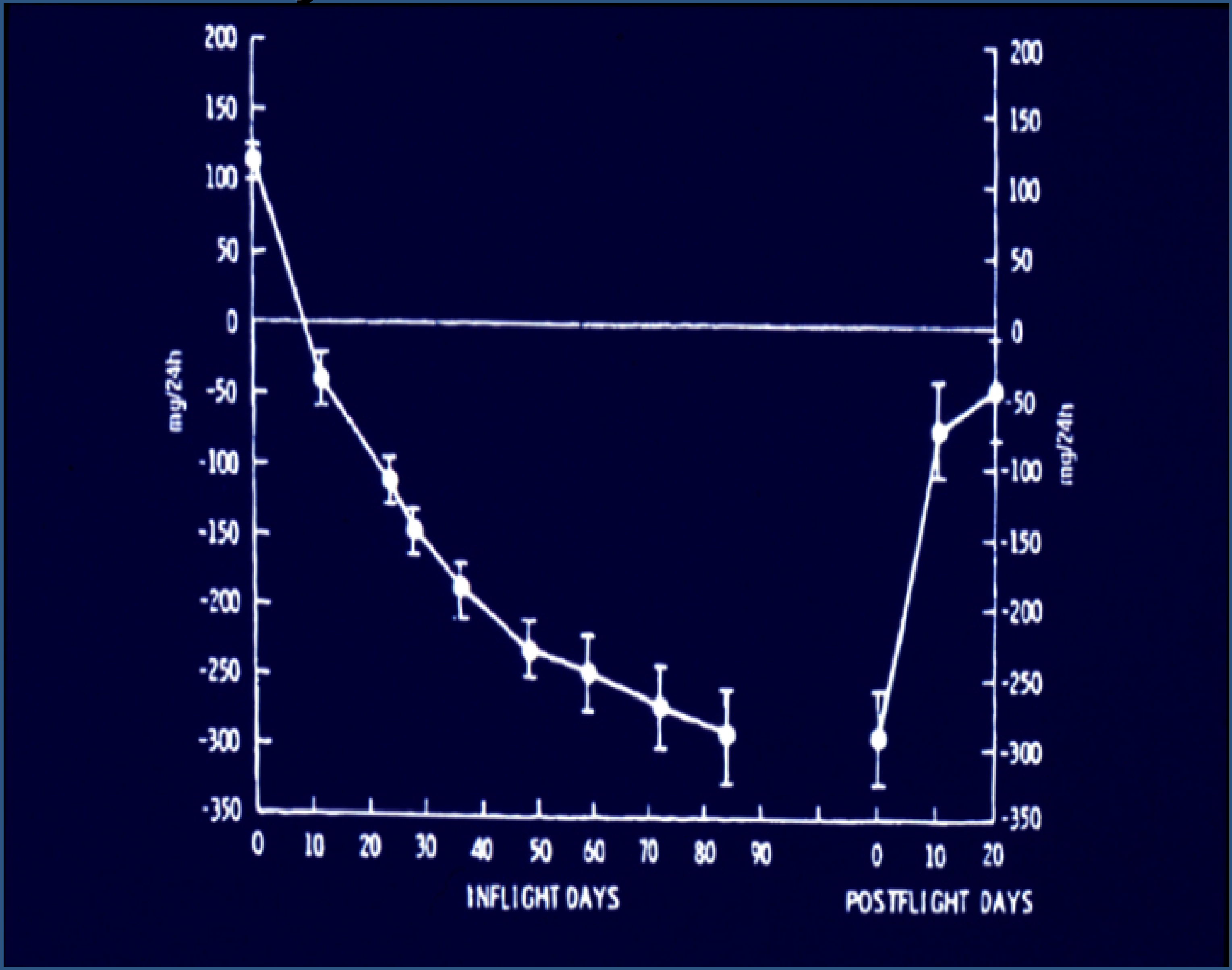
Evidence to Date

# Early Missions: Skeletal Measurements



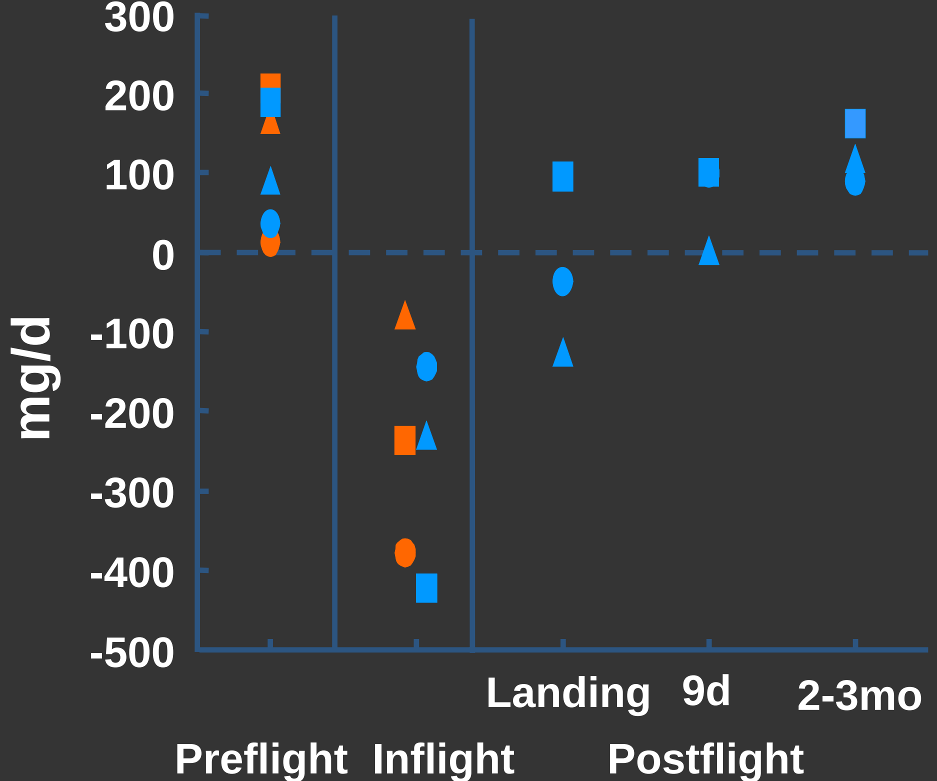
# Calcium Regulation

# Skylab-Calcium balance



Slide courtesy of Dr. Scott M. Smith

# Calcium Balance




**Bone Ca Loss ~ 250 mg/d**

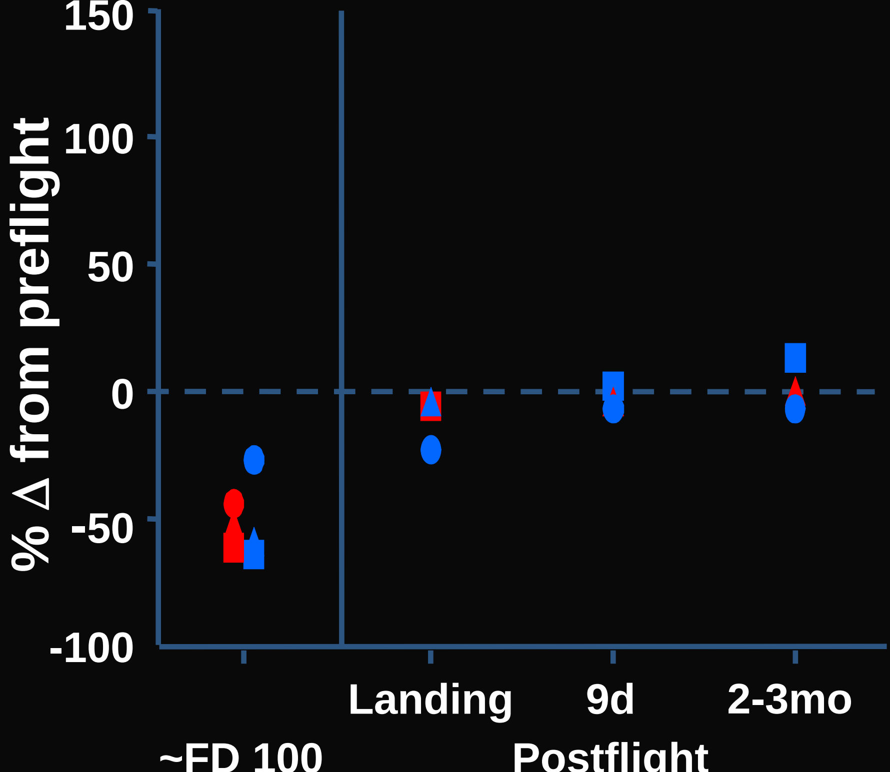
**Bone Ca Gain ~ 100 mg/d**

**Recovery: 2-3 x mission**

Smith et al., 1999
Smith et al., 2005

Slide courtesy of Dr. Scott M. Smith

# Calcium Absorption




**Spaceflight:**

↓ Vitamin D stores

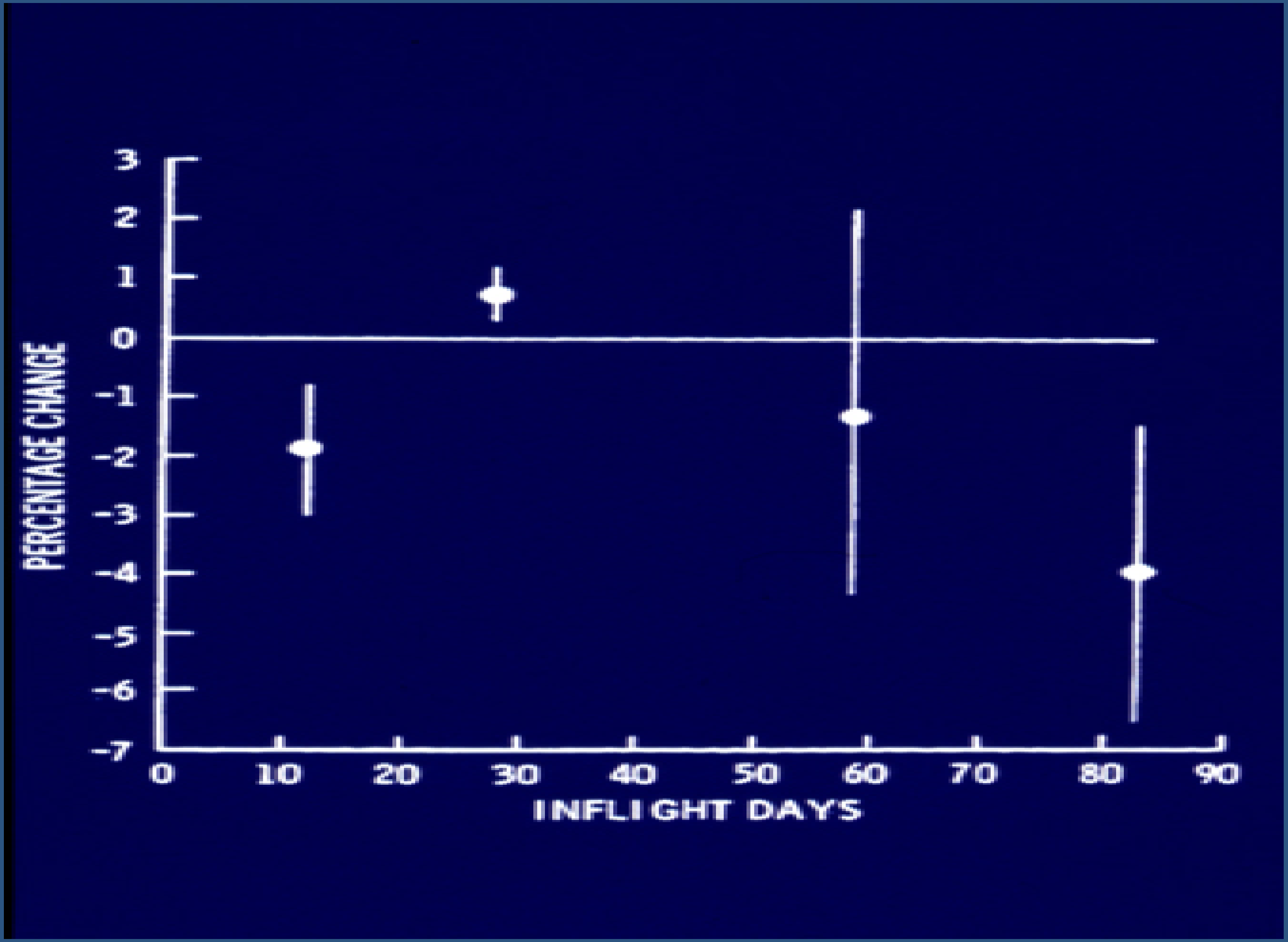
↓ PTH

↓ Active vitamin D

↓ Ca absorption

Smith et al., 1999
Smith et al., 2005

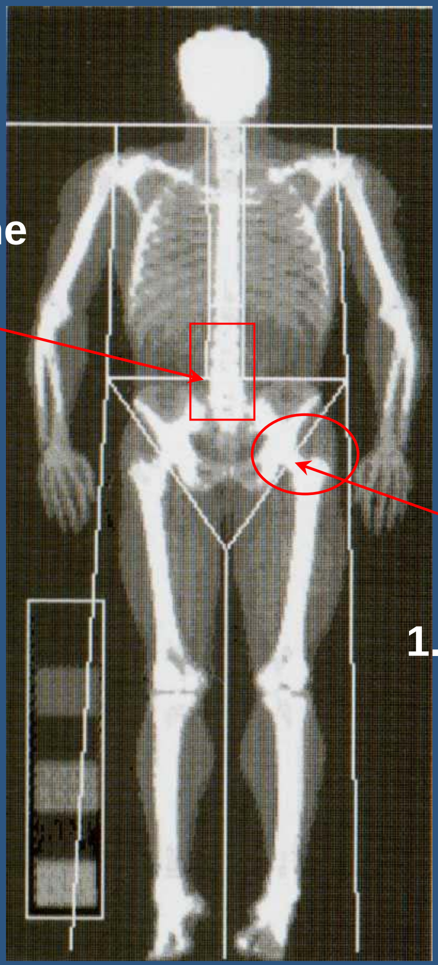
# Skylab-BMD of Calcaneus



# Bone Mineral Density

# Regional BMD losses Mir

| Index DXA aBMD g/cm2 | %/Month Change ± SD |
|---|---|
| Lumbar Spine | -1.06±0.63* |
| Femoral Neck | -1.15±0.84* |
| Trochanter | -1.56±0.99* |
| Total Body | -0.35±0.25* |
| Pelvis | -1.35±0.54* |
| Arm | -0.04±0.88 |
| Leg | -0.34±0.33* |
| | |
| *p<0.01, n=16-18 | LeBlanc et al, 2000 |



# DXA (Mir) and QCT (ISS)

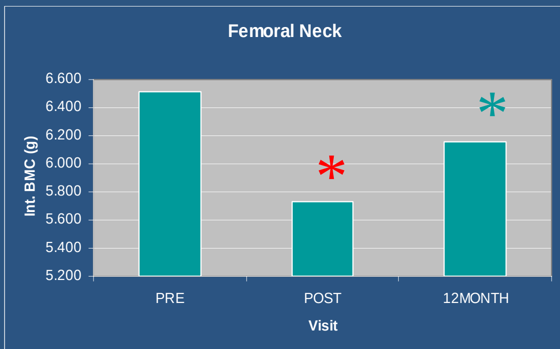
**LeBlanc, J Musculoskel Neuron Interact, 2000;**
**Lang , J Bone Miner Res, 2004; Vico, The Lancet 2000**

| Index DXA | %/Month Change ± SD | Index QCT | %/Month Change ± SD |
|---|---|---|---|
| aBMD Lumbar Spine | 1.06±0.63* | Integral vBMD Lumbar Spine | 0.9±0.5 |
| | | Trabecular vBMD Lumbar Spine | 0.7±0.6 |
| aBMD Femoral Neck | 1.15±0.84* | Integral vBMD Femoral Neck | 1.2±0.7 |
| | | Trabecular vBMD Femoral Neck | 2.7±1.9 |
| aBMD Trochanter | 1.56±0.99* | Integral vBMD Trochanter | 1.5+0.9 |
| *p<0.01, n=16-18 | | Trabecular vBMD Trochanter | 2.2+0.9 |

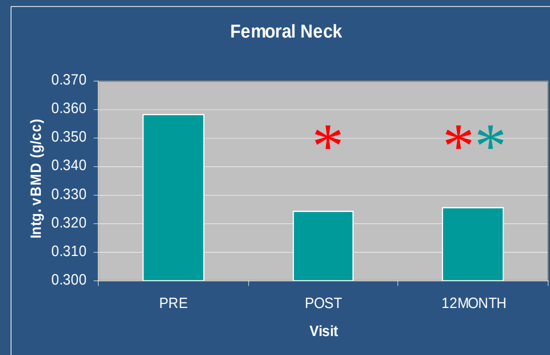
**T. Lang et al., JBMR 2006.**

bending (cm3)
compressive
(g2/cm4)

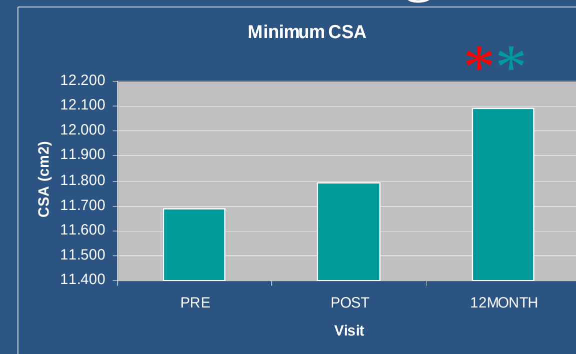
## BMC

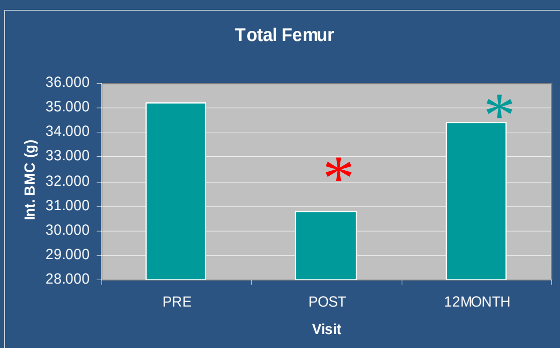


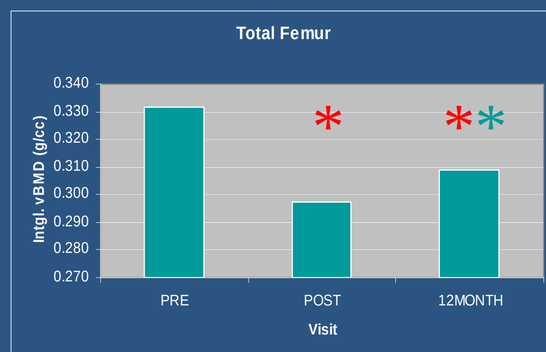

## vBMD

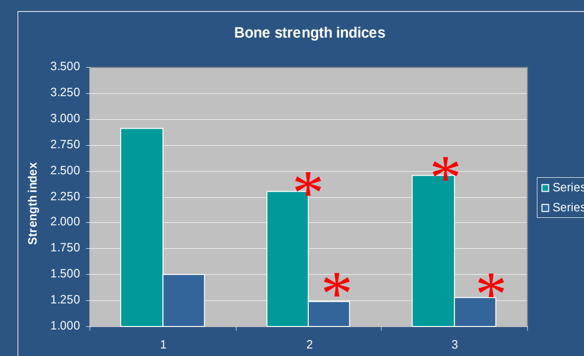



## Minimum FN CSA and strength



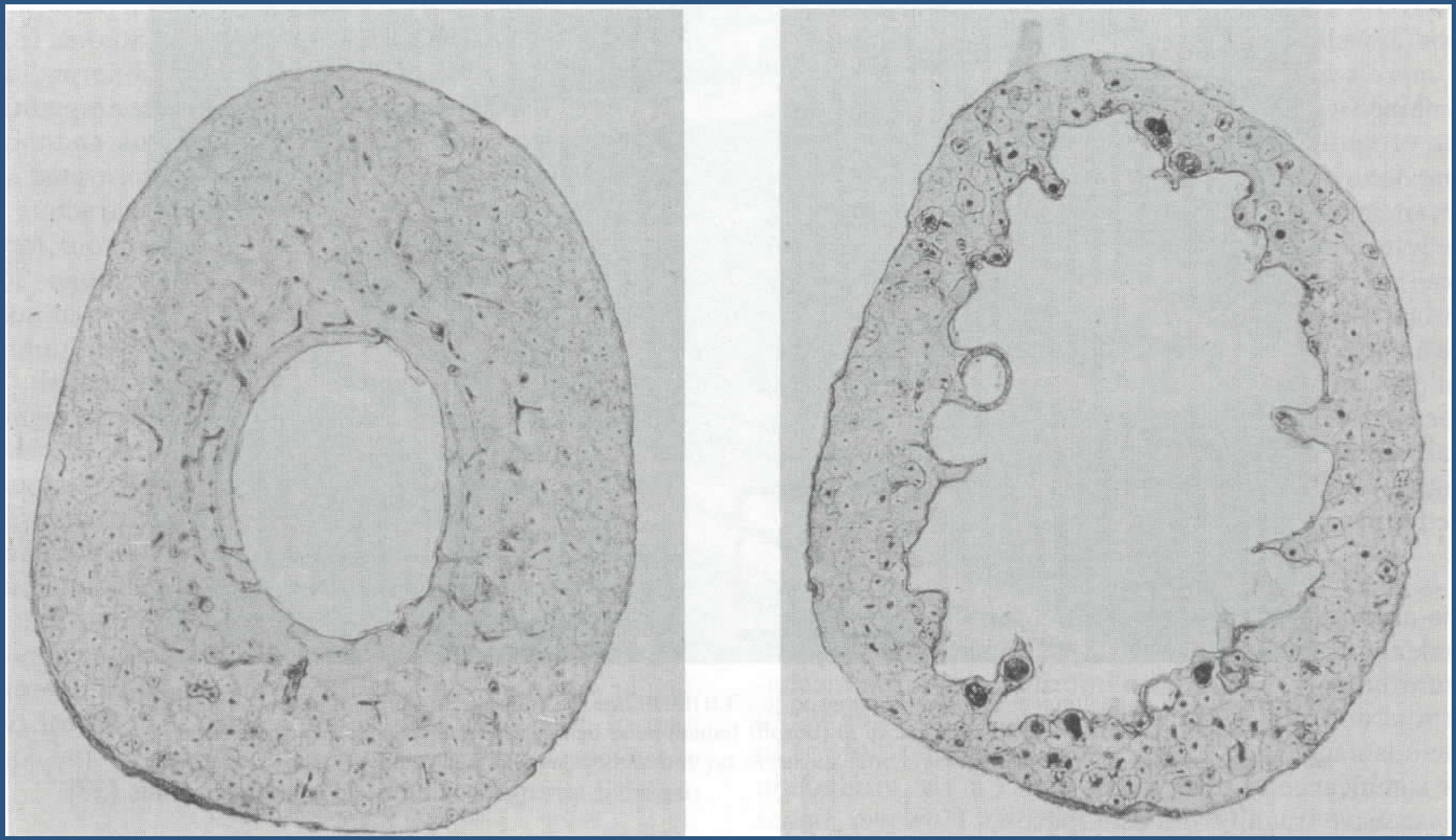

Pre Post 12 Pre Post 12 Pre Post 12

- *: $p<0.05$ with respect to preflight, postflight

Lang et al, JBMR 2004, 2006.

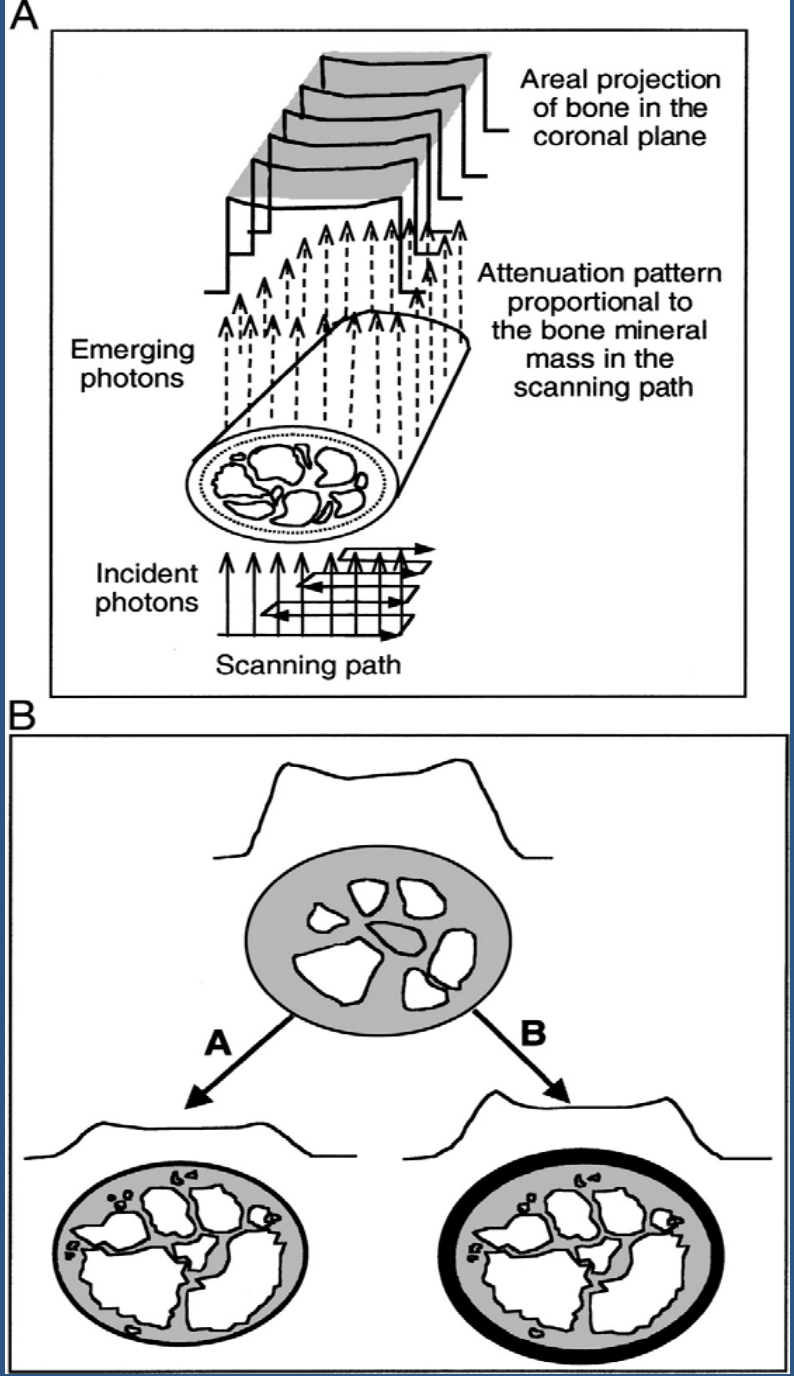
Losses in vBMD of integral femoral neck but <u>greater % losses In trabecular compartment</u>, <u>significant thinning of cortex</u> at the femoral neck during flight, and <u>periosteal expansion</u> during 12-month postflight period.

# Pattern of cortical bone thinning as seen in beagle after 40 wks of cast immobilization.



*From J.W.Jaworski*
*Slide Courtesy of D Carter*

Use of Imaging Technology to evaluate changes in bone mass



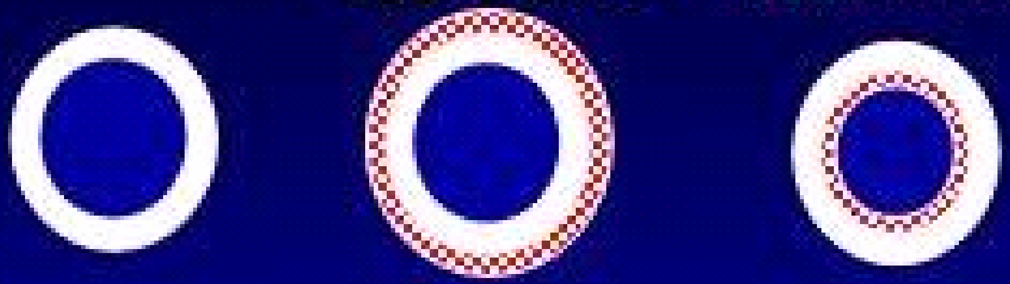

DXA Measurement

Skeletal Response

Seeman, E. J Clin Endocrinol Metab 2001;86:4576-4584

Mary Bouxsein, Ph.D.

# Physiological Changes in Bone Geometry



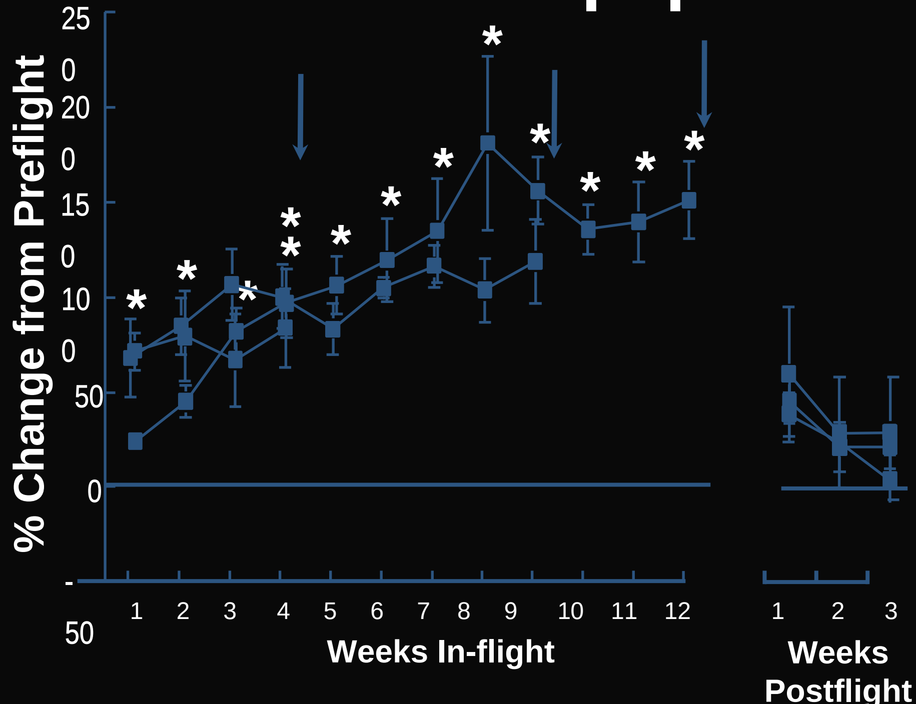
| | Baseline | Periosteal Apposition | Endosteal Apposition |
|---|---|---|---|
| Periosteal Diameter | 100 % | 110 % | 100 % |
| Endosteal Diameter | 100 % | 100 % | 90 % |
| Compressive Strength | 100 % | 148 % | 125 % |
| Bending Strength | 100 % | 168 % | 116 % |

# Bone Turnover Markers

Slide courtesy of Dr. Scott M. Smith

# Bone Resorption

## N-Telopeptide




**Space Flight:**

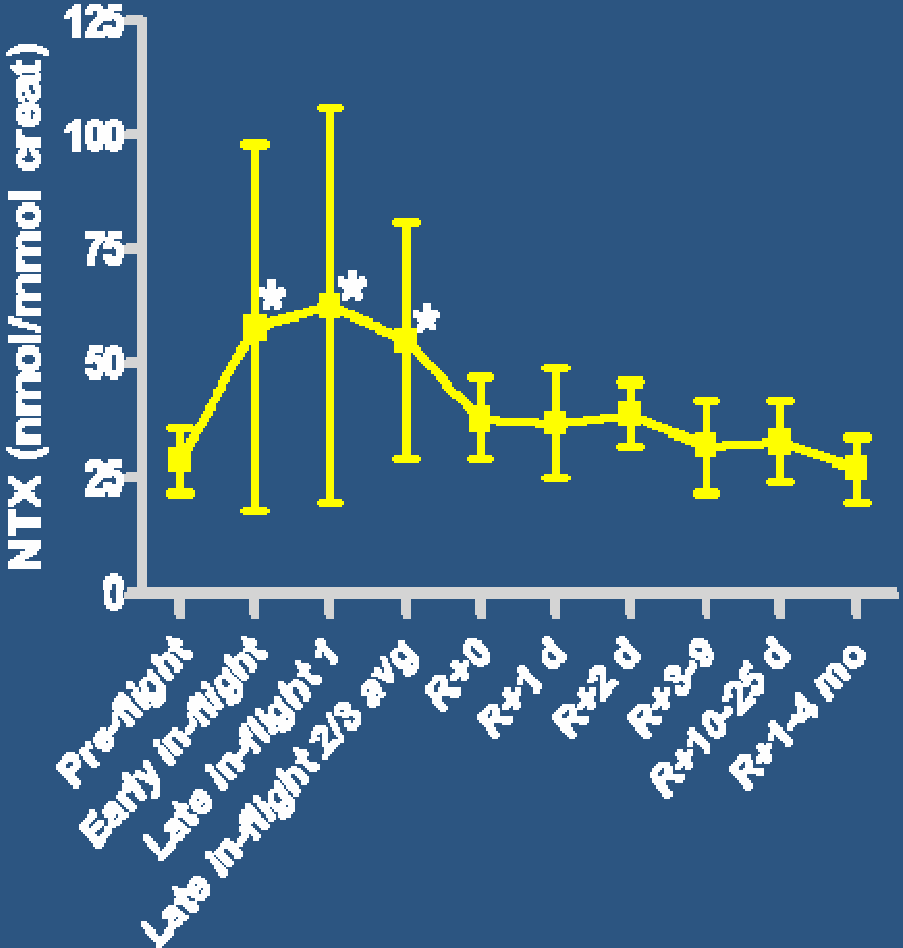
- ↑ **Urinary collagen xlinks**
- ↑ **Urinary Ca**
- ↑ **Urinary OH-Proline**

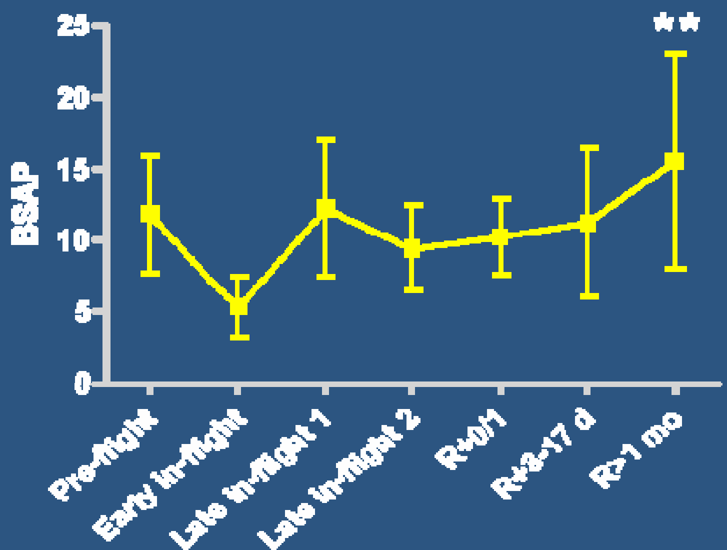
**Bone resorption is increased during flight**

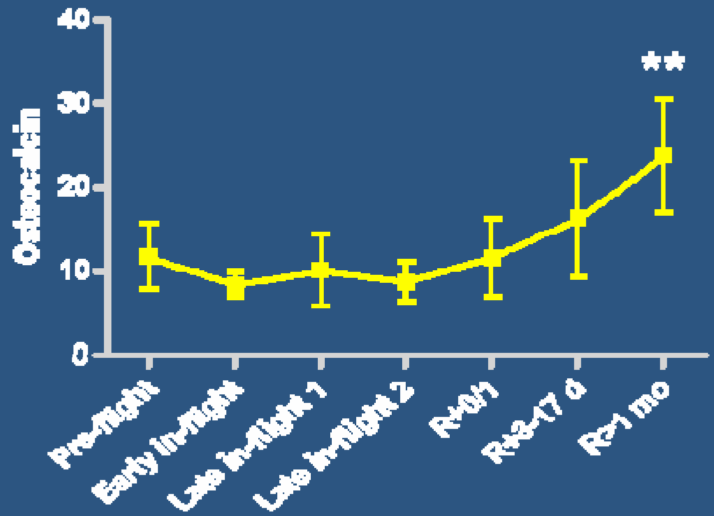
Smith et al., *JCEM*, 1998

# Response of Bone Biomarkers

(Smith et al, JBMR 2005)

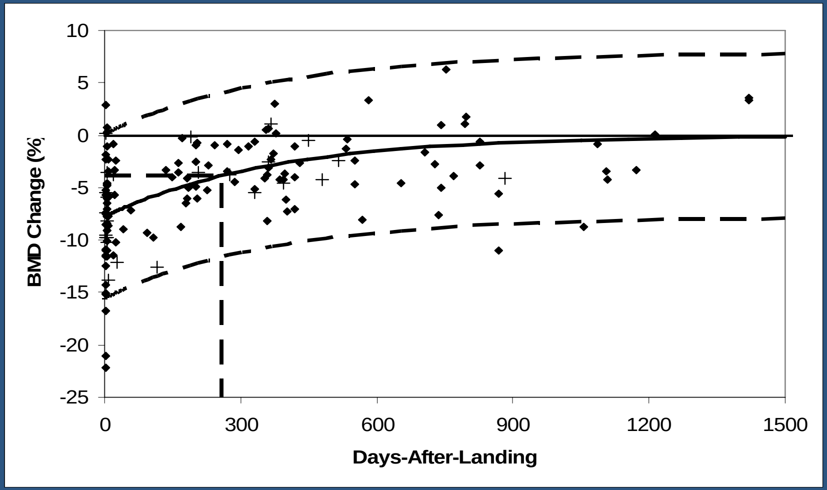


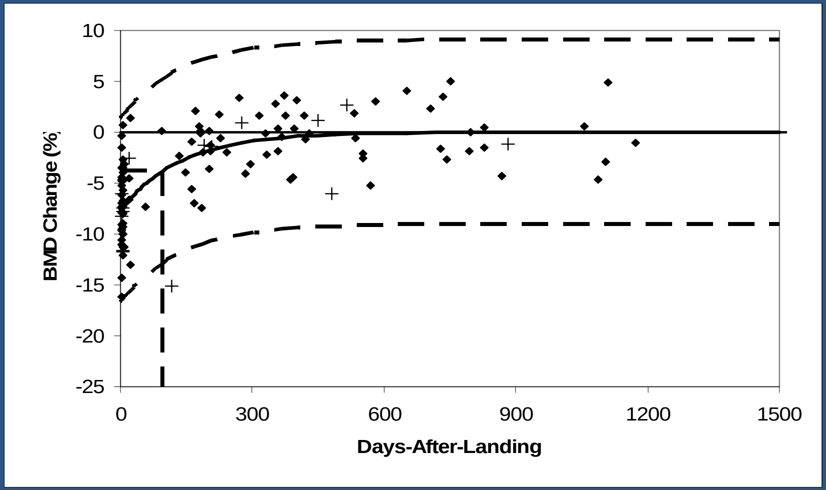



# Bone Recovery

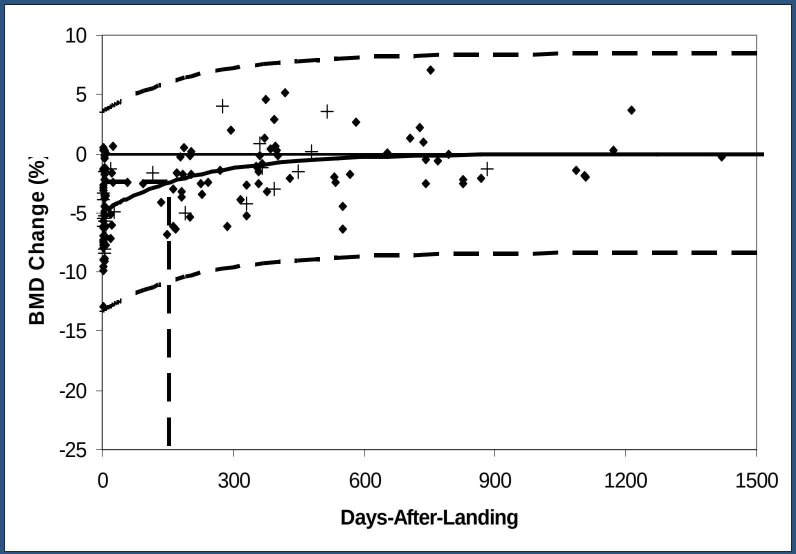
# Consistent increase in BMD in Postflight Period



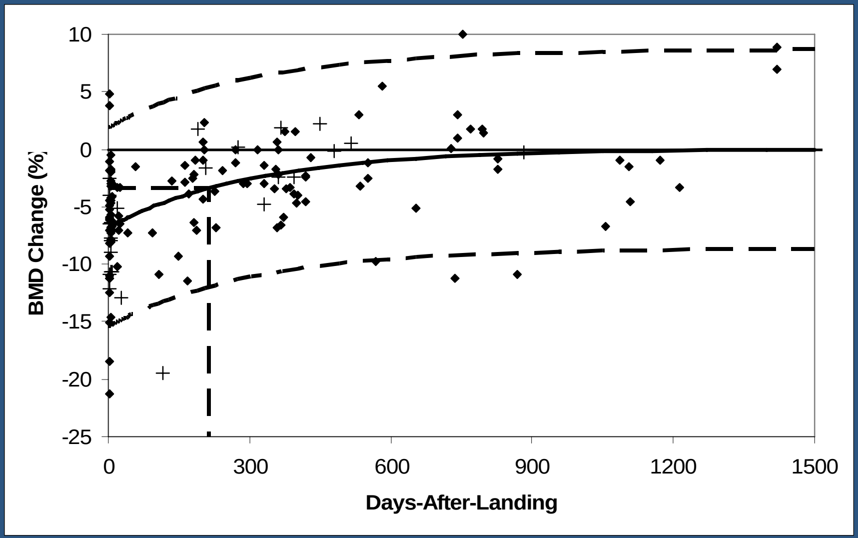

Trochanter




Pelvis




Lumbar Spine




Femoral neck

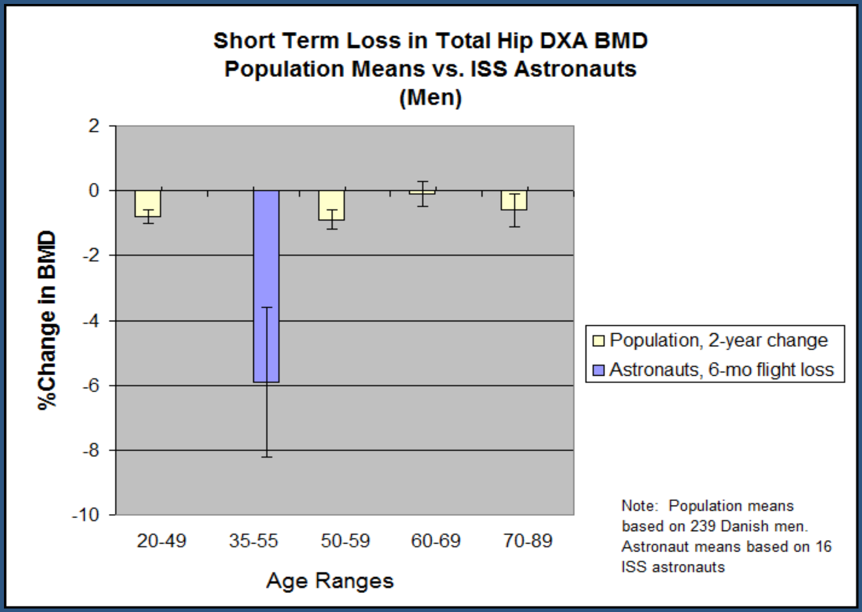
# Model for Skeletal Recovery

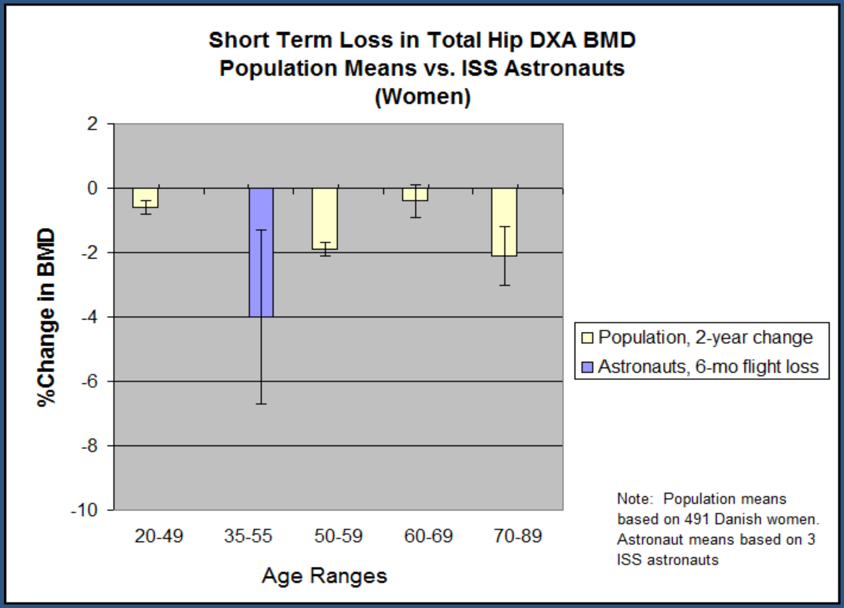
| Skeletal Site | Loss (L0) at landing % | 50% Recovery Time (days) |
|---|---|---|
| Femoral Neck | 6.8 *(5.7, 7.9)* | 211 *(129, 346)* |
| Trochanter | 7.8 *(6.8, 8.8)* | 255 *(173, 377)* |
| Pelvis | 7.7 *(6.5, 8.9)* | 97 *(56, 168)* |
| Lumbar Spine | 4.9 *(3.8, 6.0)* | 151 *(72, 315)* |
| Calcaneus | 2.9 *(2.0, 3.8)* | 163 *(67, 395)* |

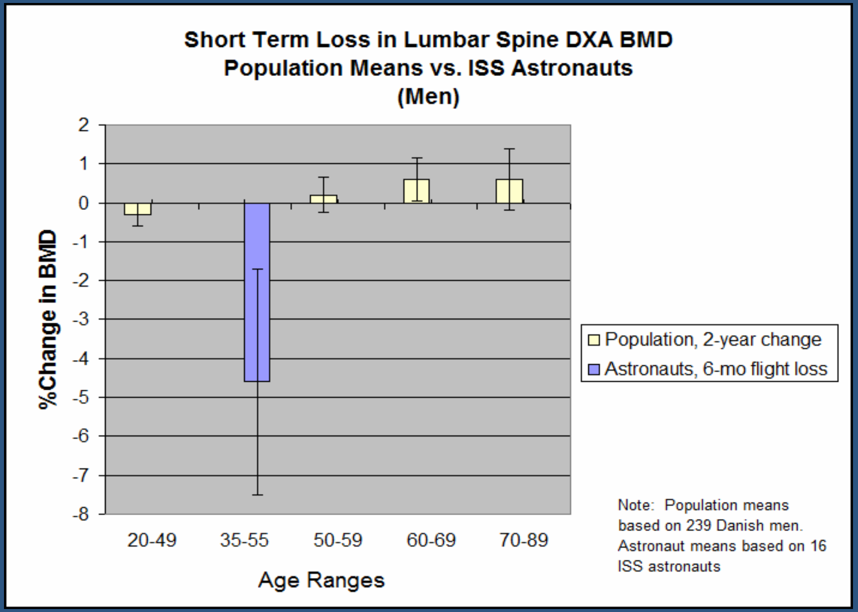
Sibonga et al BONE 2007

# Spaceflight Bone Loss vs. Age-related Bone Loss

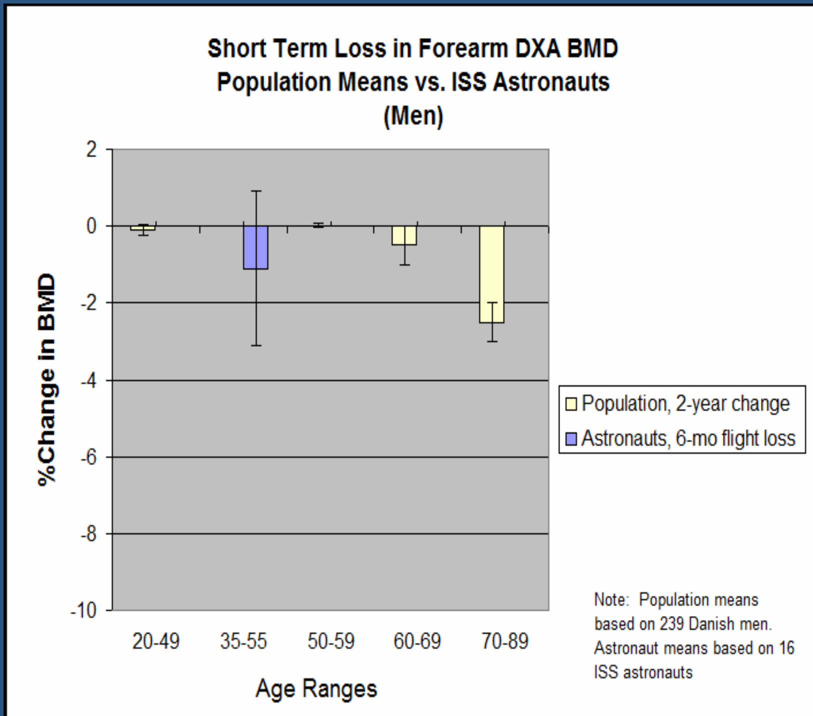
# BMD Loss vs. Age-matched Loss

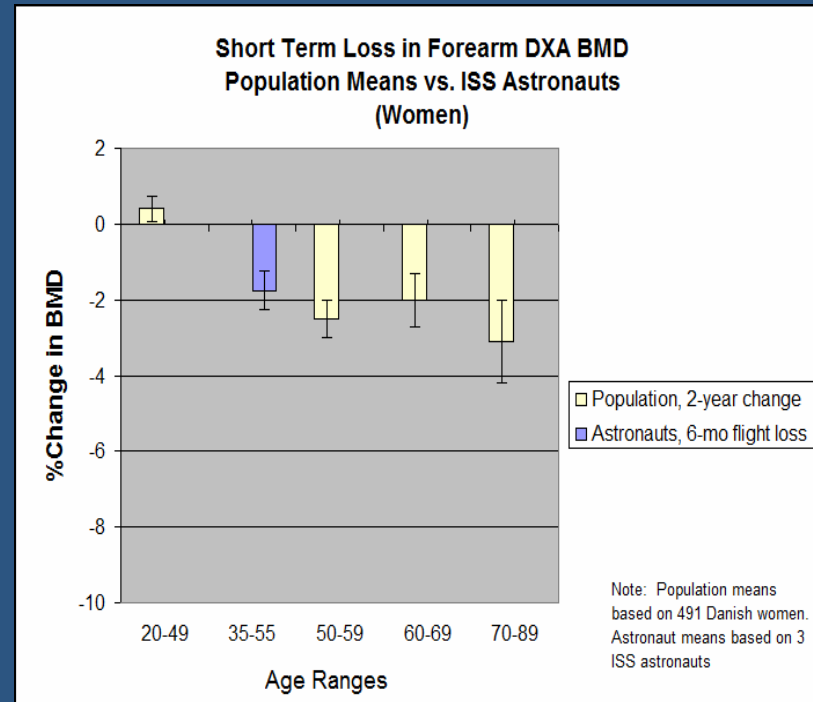


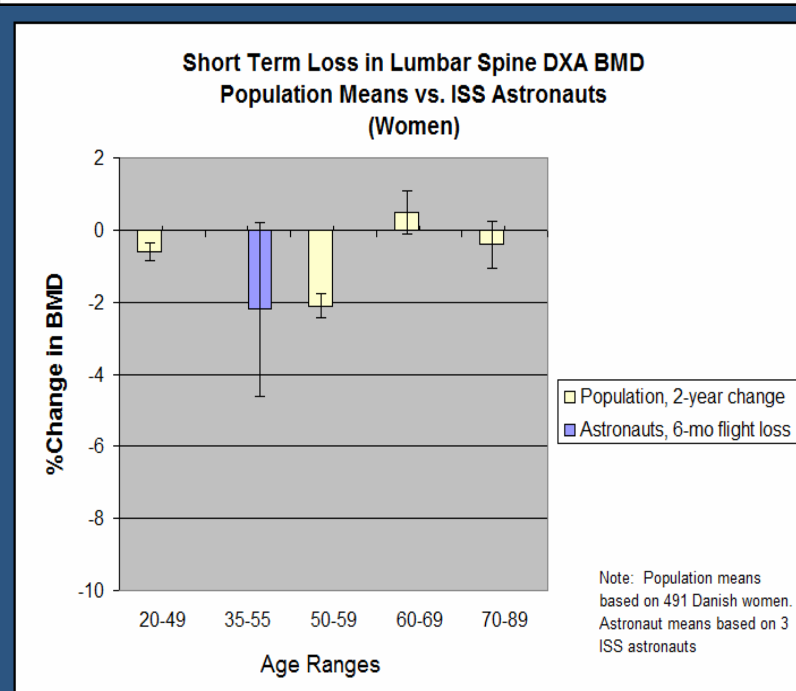




Losses in 6 months in space far exceed 2-year losses on Earth in similarly –age population.




Minimal BMD loss in forearms of males on earth.




Small n for females but <u>suggest</u> losses equivalent to postmenopausal losses on earth.

# Circumstantial Evidence: Parallels Menopause vs. SF

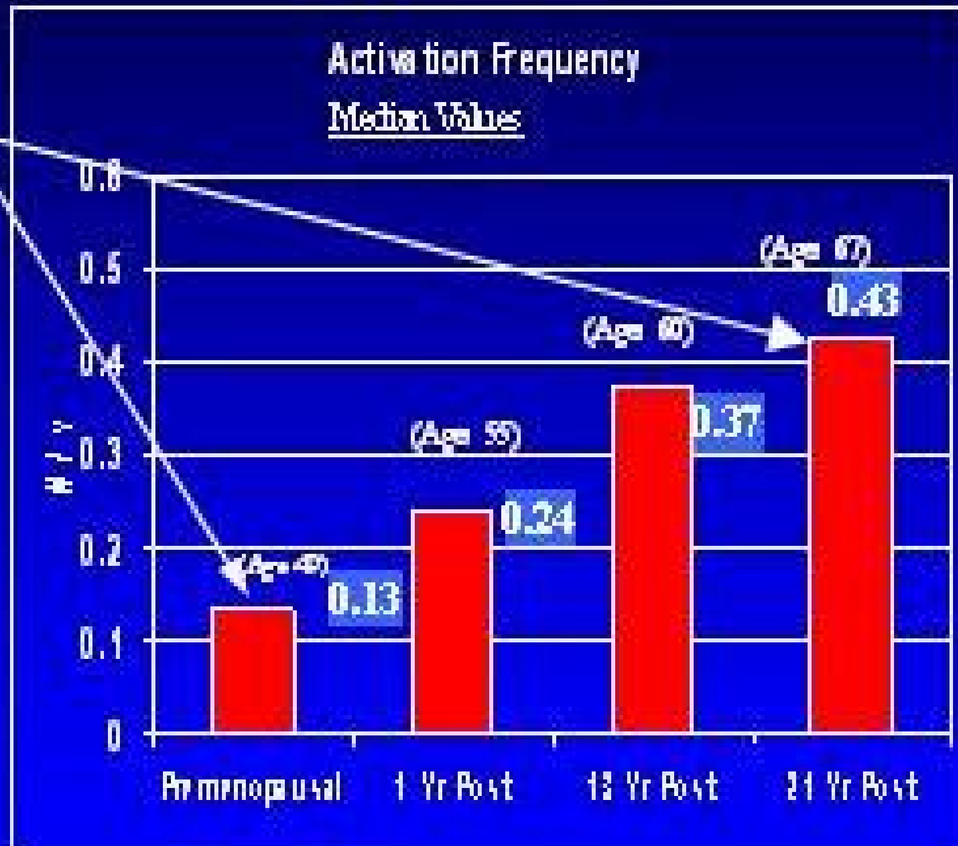
1. Reduction TbN, loss of connectivity in postmenopausal women (Kleerekoper, 1985)
2. Preferential cancellous bone loss (Riggs refs.)
3. BMD losses 2-3%/yr (Riggs refs)
4. Resorption on inside surface (endocortical) of cortex.
5. Activation Frequency <u>high</u> in postmenopausal women (Recker, 2004)

1. Biopsies after 120 days bed rest. TbN reduced (Thompsen, 2005)
2. Preferential cancellous bone loss in proximal femur (Lang, 2004)
3. Range BMD losses (3-9%) per ~6 months
4. Cortical thinning at femoral neck from endocortical surface.
5. Not quantified

Given the preferential loss in trabecular bone compartment and the rapid rate of loss in crew members, <u>suspect</u> that the impact on microarchitecture is at the very least equivalent to postmenopausal women.

# Bone Remodeling Rates: Histomorphometry

Seventy percent reduction in remodeling rate does not look so alarming given that it results in activation frequency about equal to healthy premenopausal women.

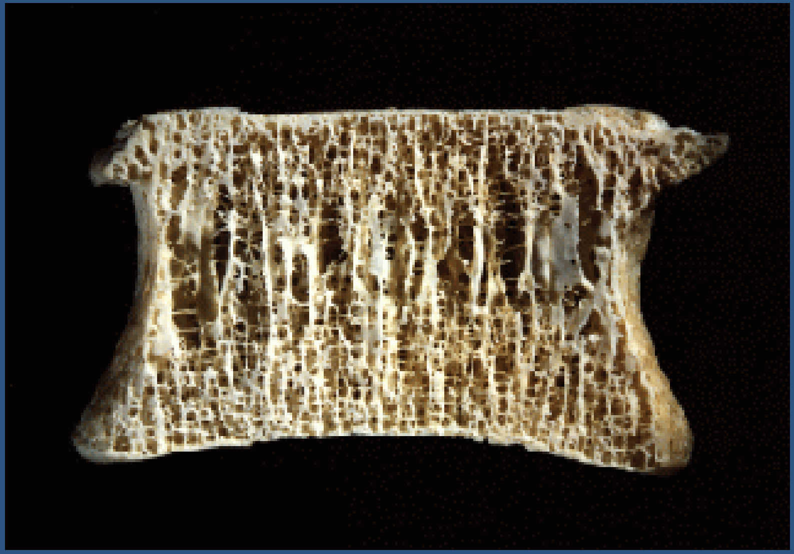


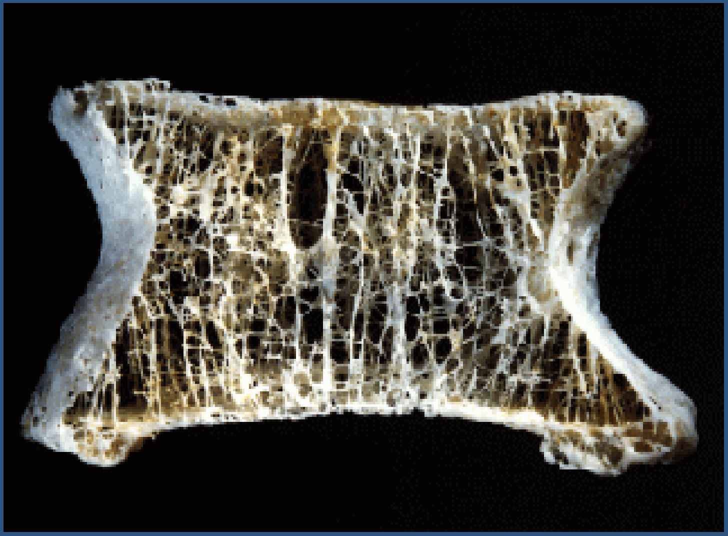

Osteoporosis Research Center

Recker, et. al, J Bone Miner Res 2004, 19:1628-1633.

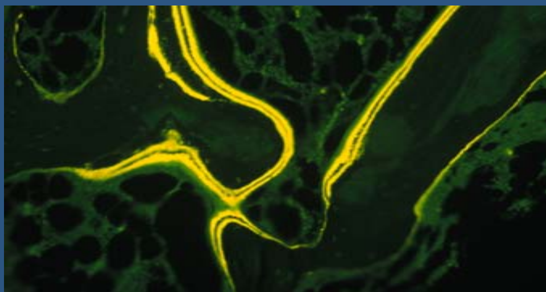
# Turnover in Crewmembers

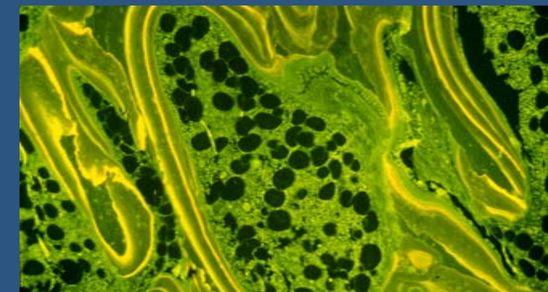
- Loss in crewmembers at faster rate than postmenopausal females (months vs. years)
- High turnover with menopause leads to perforations of trabecular struts.
- At what time point with SF does irreversible perforation occur?

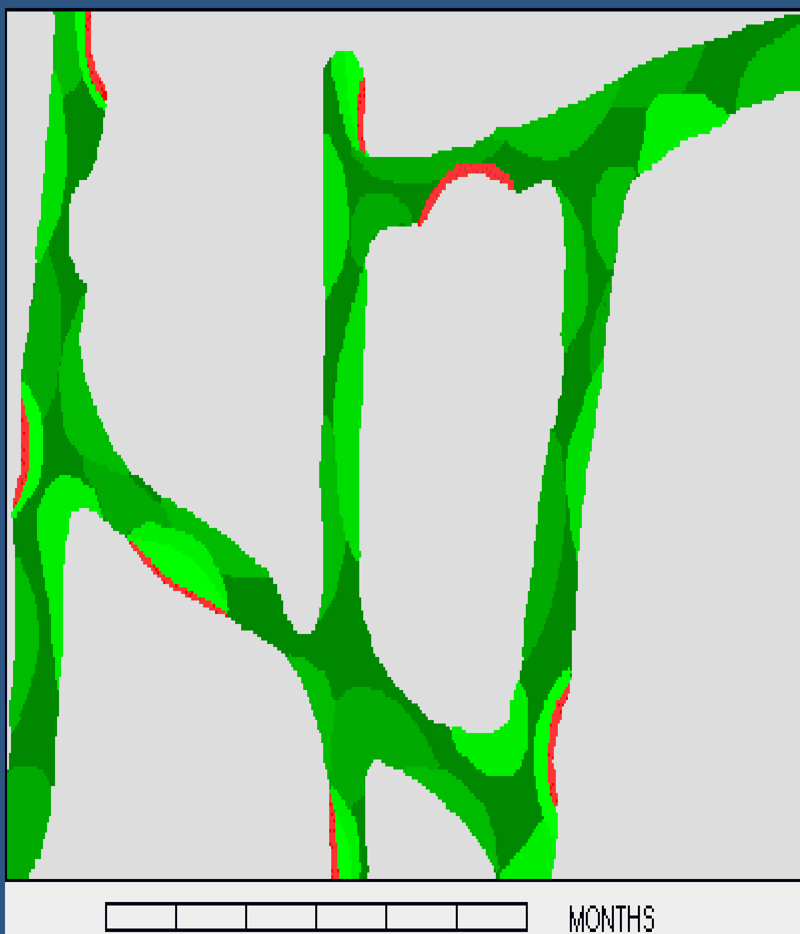


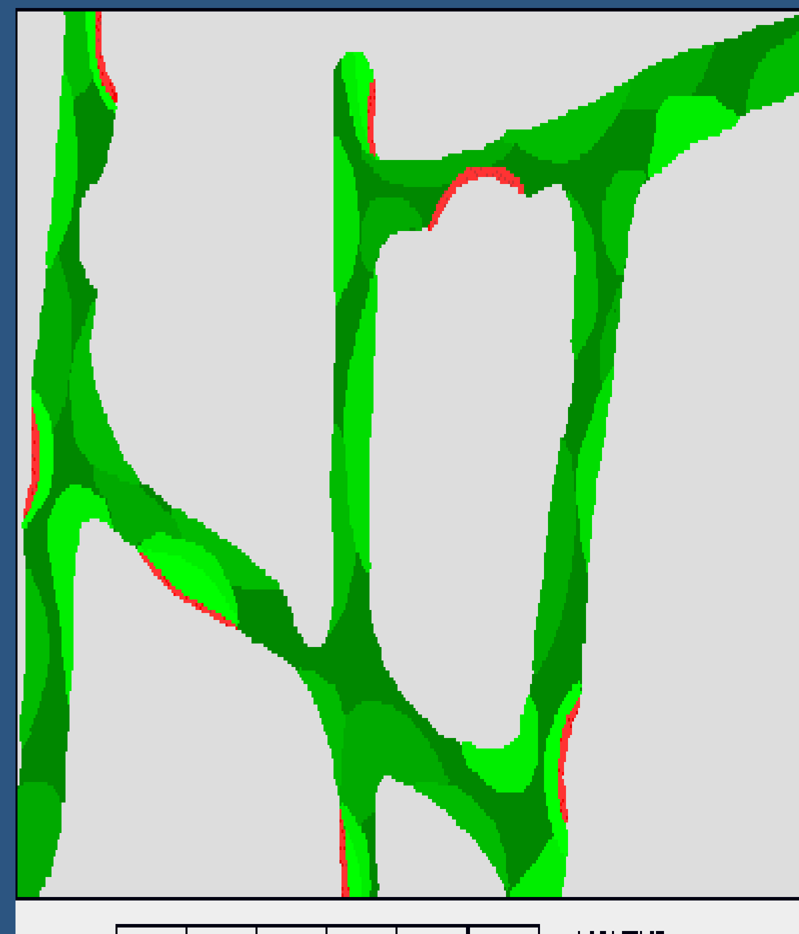


# Normal vs. High Bone Turnover







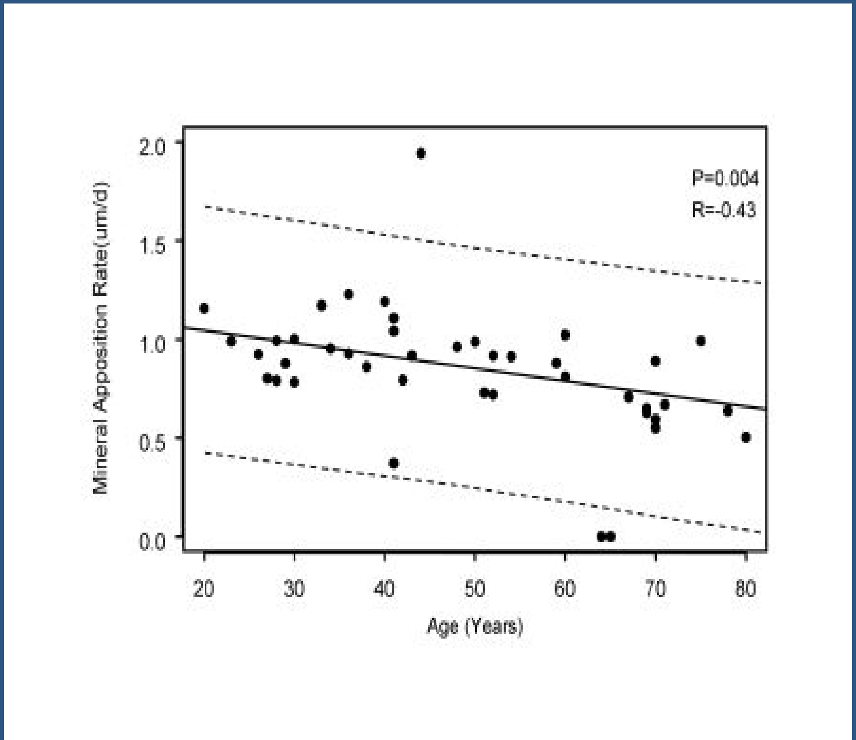
# Are crewmembers restored to preflight skeletal status? Recover bone that was lost in space?

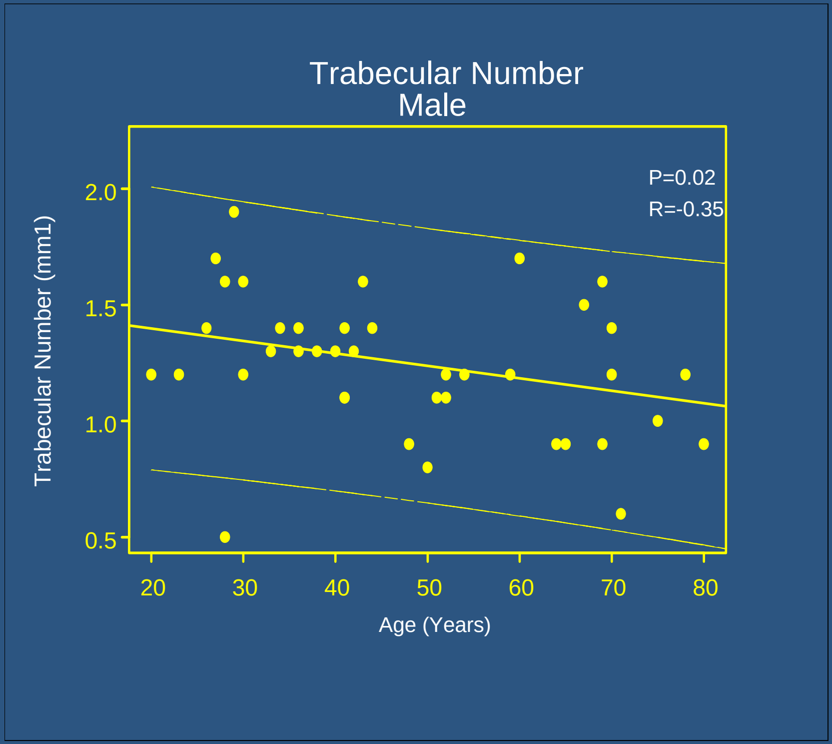
- DXA: Restoration of areal BMD within ~ 3 years but cannot assess structure.
- QCT: <u>Incomplete</u> recovery of vBMD at 12 months postflight
- Geometrical changes at femoral neck indicate early onset of age-related changes (Riggs, JBMR 2004; 2008)

# Histomorphometry of Bone Biopsies (Bed Rest Flight Analog)

- **Vico (1987) a <u>reduced mineralization</u>, no change in matrix formation and increased resorption of bone (osteoclast parameters)**
- **Arnaud (1992) <u>suppressed bone formation rate</u> and reduced osteoblast activity in as short as 7 d experiment**
- **Zerwekh (1998) mild <u>decrement in bone-forming osteoblasts</u> concurrent with <u>increased bone resorption</u> in 12 wk study**
- **Thomsen ( 2006) deterioration of trabecular microarchitecture 120 d suggestive of aggressive resorption**

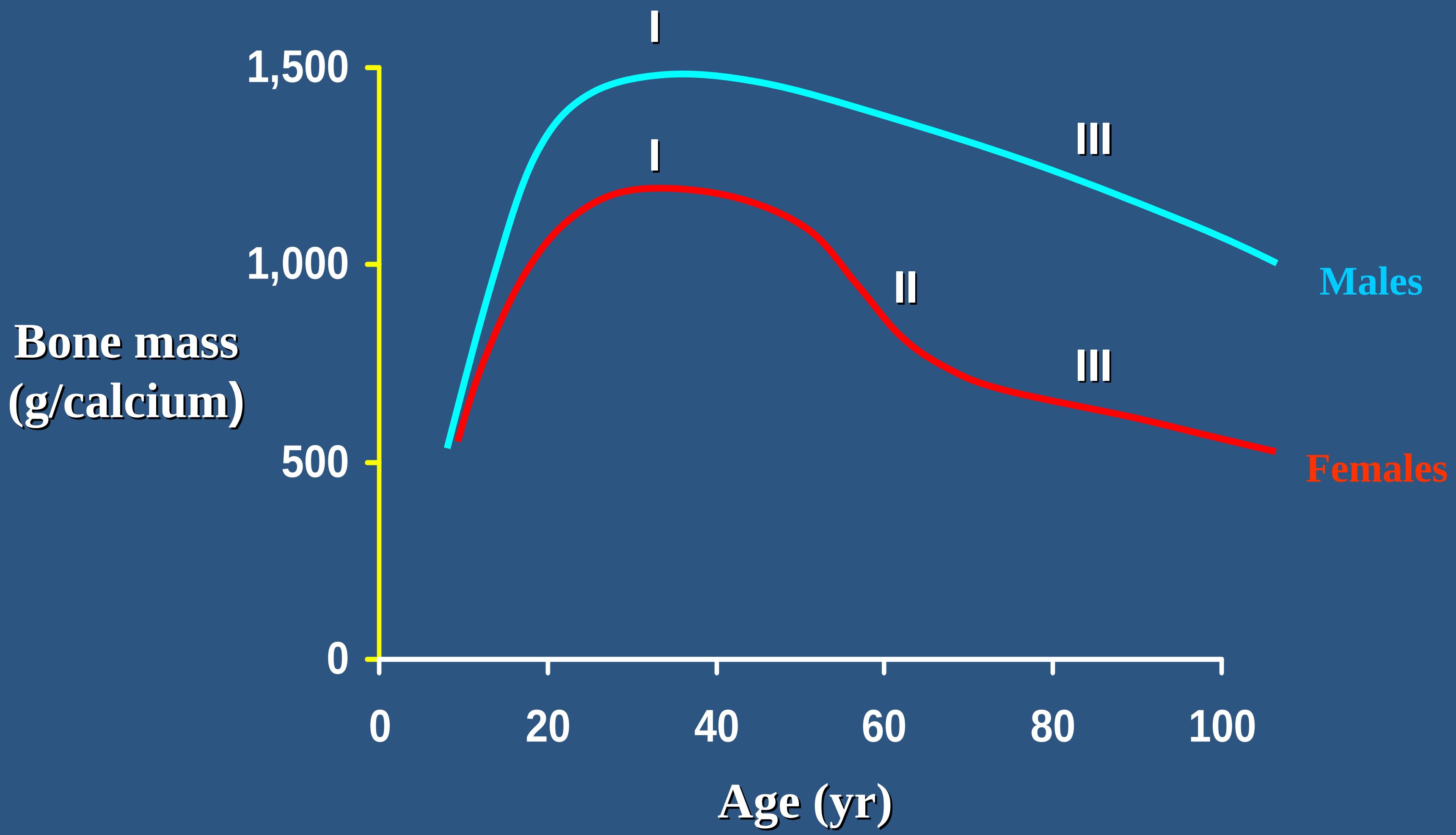
# Age-related Bone Loss




Sibonga et al, manuscript

# Bone Gain and Loss with Age is Sex-specific

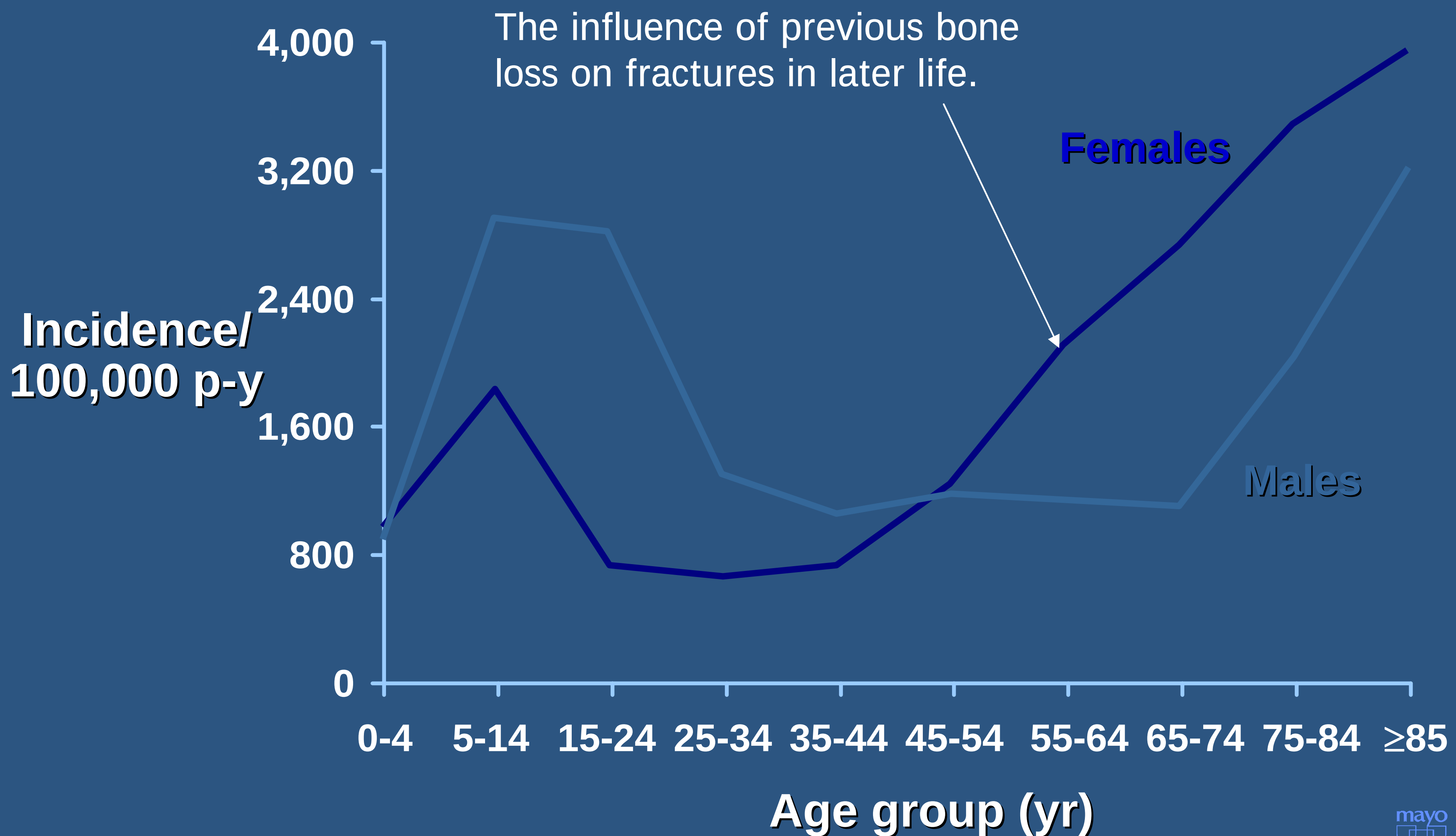



Riggs BL, Melton LJ: Involutional osteoporosis
Oxford Textbook of Geriatric Medicine

mayo

CP1014192-21

# Incidence of Limb Fractures




mayo

CP1014563-1

# Summary: Spaceflight Evidence

- **Negative calcium balance, reduced absorption and down-regulated calcitropic hormones**
- **Deficits in aBMD at weight-bearing sites, vBMD cancellous bone, thinning of cortical bone**
- **Increased bone resorption markers>formation markers**
- **Reductions in hip bone strength estimated by FEA, also in compressive and bending strengths at femoral neck after return**
- **Delayed and possibly incomplete restoration of preflight hip bone integrity.***

# Summary/Conclusions

- The evidence-to-date suggests that the rapid rate of site-specific bone loss in space, due to the unbalanced stimulation of bone resorption, may predispose crew members to irreversible changes in bone structure and microarchitecture.
- No analyses conducted in the postflight period to assess microarchitectural changes.
- There is no complete analysis of skeletal recovery in the postflight period to evaluate the structural changes that accompany increases in DXA aBMD.
- Postflight analyses based upon QCT scans performed on *limited* crew members indicate reductions in hip bone strength and incomplete recovery at 1 year.
- No recovery of trabecular vBMD after 1 year return (HRP IWG).
- Time course of bone loss in space unknown.

Thank you.

# Crew data


- Lang T, LeBlanc A, Evans H, Lu Y, Genant h, Yu A. 2004 Cortical and trabecular bone mineral loss from the spine and hip in long-duration spaceflight. J Bone Miner Res 19(6):1006-1012.LeBlanc A,
- Lang TF, LeBlanc AD, Evans HJ, Lu Y. The effect of long-duration spaceflight on the density, mass and geometry of the hip bone Submitted manuscript. 2006.
- Schneider V, Shackelford L, West S, Oganov V, Bakulin A, Voronin L. 2000 Bone mineral and lean tissue loss after long duration space flight. J Musculoskelet Neuronal Interact 1(2):157-160.
- Vico L, Collet P, Guignandon A, Lafage-Proust M, Thomas T, Rehailia M, Alexandre C 2000 Effects of long-term microgravity exposure on cancellous and cortical weight-bearing bones of cosmonauts. The Lancet 355:1607-1611.
- Vico L, Chappard D, Alexandre C, Palle S, Minaire P, Riffat G, et al. Effects of a 120 day period of bed-rest on bone mass and bone cell activities in man: attempts at countermeasure. Bone Miner. 1987;2(5):383-94.
- Sibonga JD, Evans HJ, Spector ER, Oganov, Bakulin, Shackelford LC, et al. Skeletal recovery following long-duration missions as predicted by preflight and postflight dual-energy x-ray absorptiometry (DXA) scans of 45 crewmembers BONE. 2007

# Bed rest citations


- Arnaud SA, Sherrard DJ, Maloney N, Whalen RT, Fung P. Effects of 1-week head-down tilt bed rest on bone formation and the calcium endocrine system. Aviation, Space and Environmental Med. 1992 64:14-20.
- Zerwekh JE, Ruml LA , Gottschalk F, Pak CY. The effects of twelve weeks of bed rest on bone histology, biochemical markers of bone turnover, and calcium homeostasis in eleven normal subjects JBMR. 1998;13 (10):1594-601.
- Thomsen JS, Morukov BV, Vico L, Alexandre C, Saparin PI, Gowin W. Cancellous bone structure of iliac crest biopsies following 370 days of head-down bed rest Aviation, Space, and Environmental Medicine 2005;76 (10):915-22.
- Minaire P, Meunier P, Edouard C, Bernard J, Courpron P, Bourret J Quantitative histological data on disuse osteoporosis. Calcif Tiss Res 1974;17:57-73.

# Backup slides

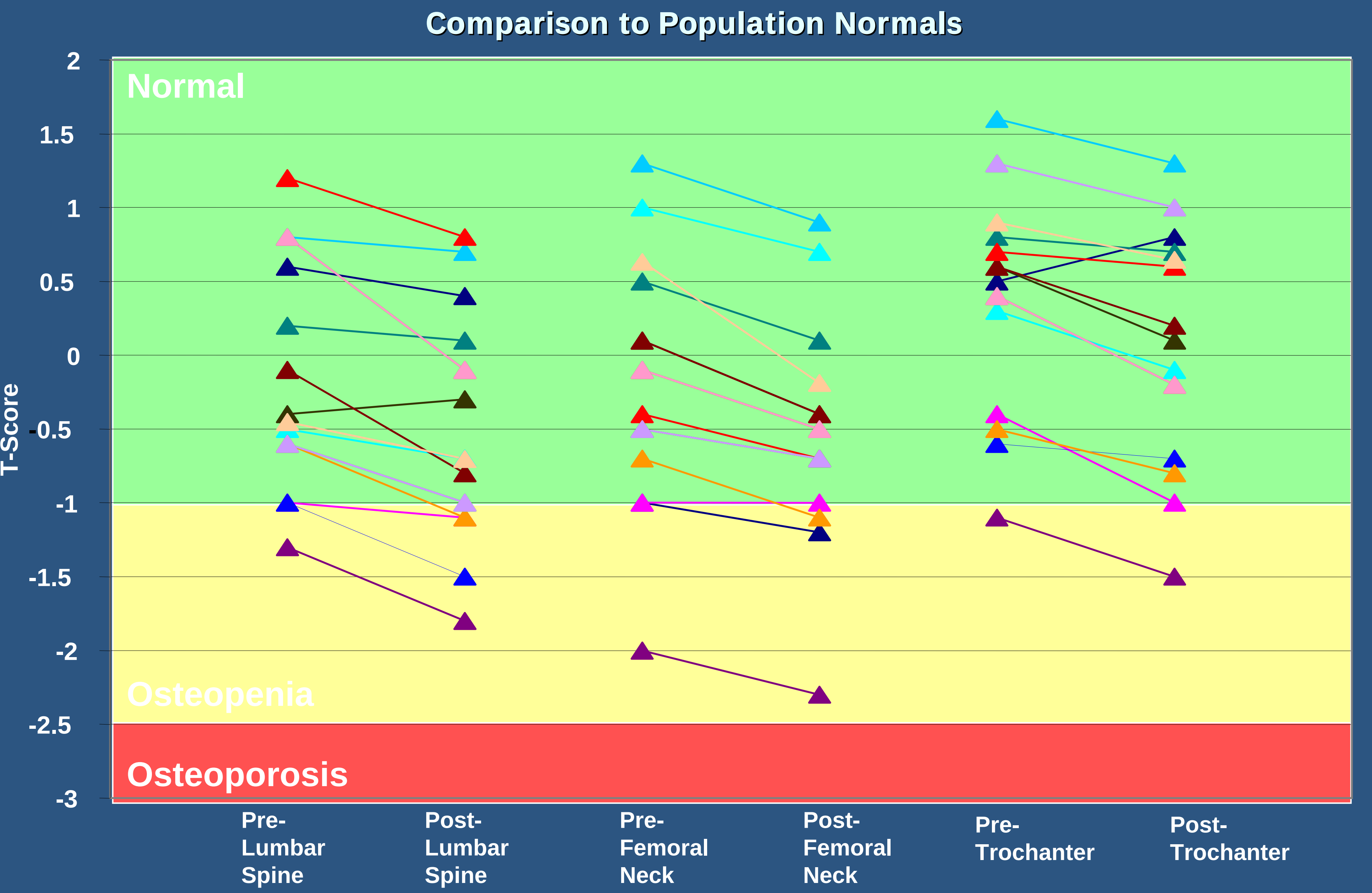
"Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture.  Bone strength reflects the <u>integration of two main features</u>:  bone density and bone quality."

*JAMA.  2001*

"….Bone quality, in turn, is stated to refer to architecture, turnover, damage accumulation, (e.g., microfractures) and mineralization…."

*Osteoporosis Int.  2002*

# BMD T-Score Values by Area Expeditions 1-13 (n=16)



# Russian Data

- 0.9-19.8% losses in calcaneus after 75-84d missions (Stupakov, 1984)
- CT scans Salyut-7 crew (5-7 months) (Oganov 1990) document vertebral BMD losses of 0.3, 2.3, 6.2 and 10.8%
- Highlighted the variability in losses between crew members (as with Apollo missions)
- Losses did not correlate with flight duration

# Correlations of Spaceflight-induced Changes (%) in DXA BMD to DXA Lean Muscle Mass

| Correlation BMD with Lean Muscle Mass | $R^2$ | p value |
|---|---|---|
| Pelvis vs. Leg Lean Mass | 0.295 | <0.05 |
| Total Hip vs. Leg Lean Mass | 0.053 | <0.05 |
| Trochanter vs. Leg Lean Mass | 0.210 | <0.05 |
| Femoral neck vs. Leg Lean Mass | 0.006 | NS |
| Leg BMD vs. Leg Lean Mass | 0.139 | <0.01 |
| Lumbar Spine vs. Trunk Lean | 0.248 | NS |
| Arm vs. Arm Lean Mass | 0.041 | NS |

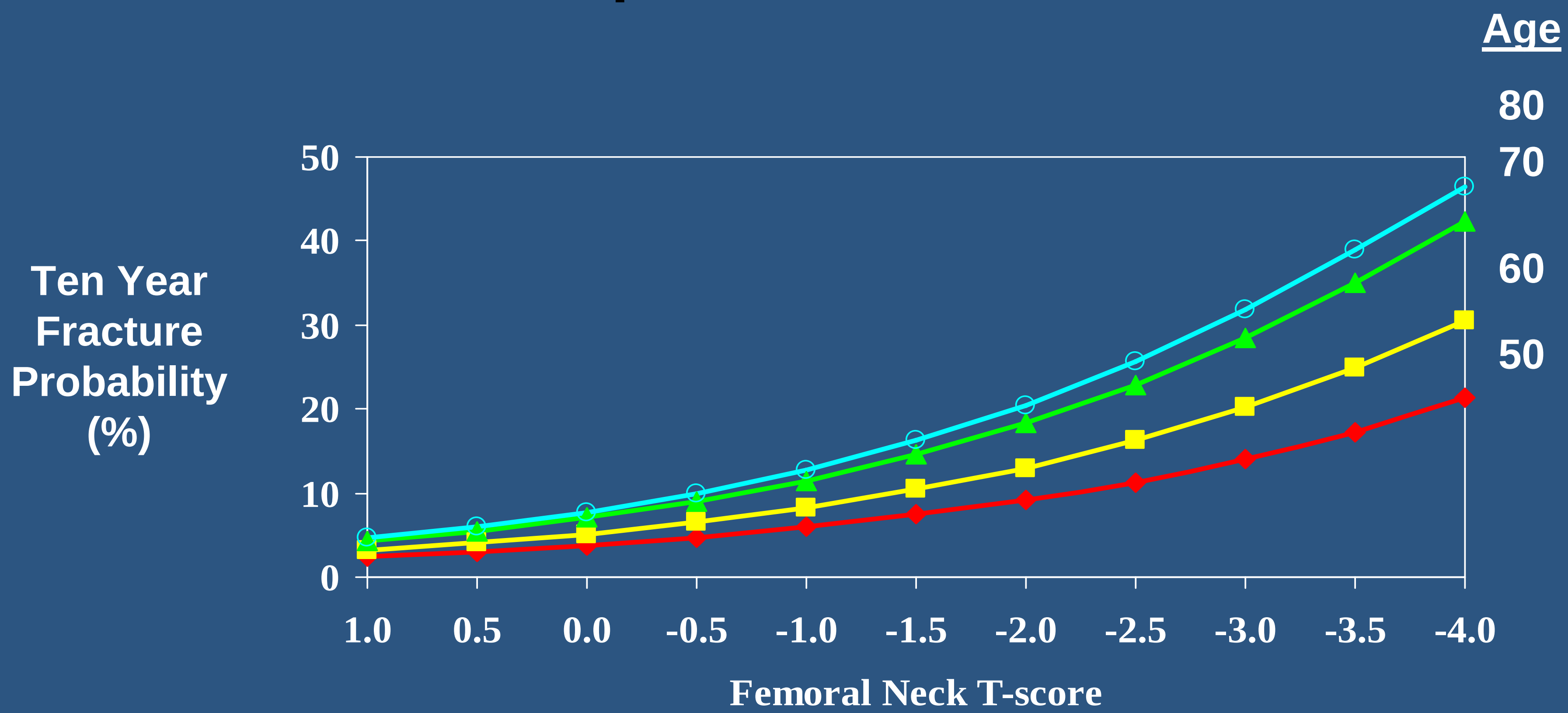
Note: A weak but significant correlation of hip BMD with area of muscle group attached to hip, as measured in CT scans in women without fracture compared to women with hip fracture. (Personal communication with T. Lang)

“Every change in the function of a bone is followed by certain definite changes in internal architecture and external conformation in accordance with mathematical principles"

J Wolff (1886)

The Law of Bone Remodelling. (1892) translated by Maquet P and Furlong R. New York, NY: Springer-Verlag; 1986.

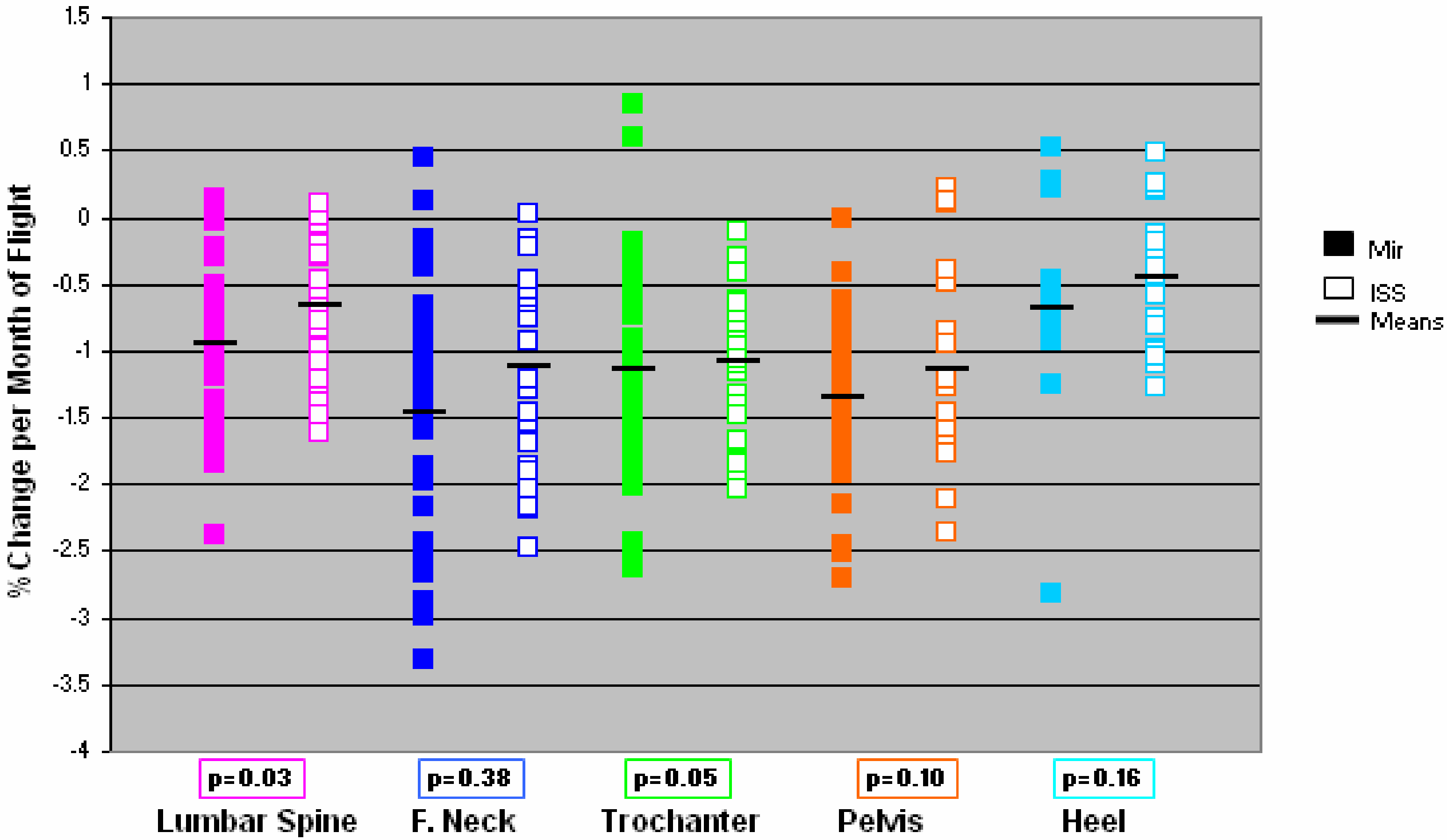
# Age is an Independent Risk Factor for Osteoporotic Fractures




**Probability of first fracture of hip, distal forearm, proximal humerus, and symptomatic vertebral fracture in women of Malmö, Sweden.**

Adapted from:
Kanis JA et al. *Osteoporosis Int*. 2001;12:989-995.

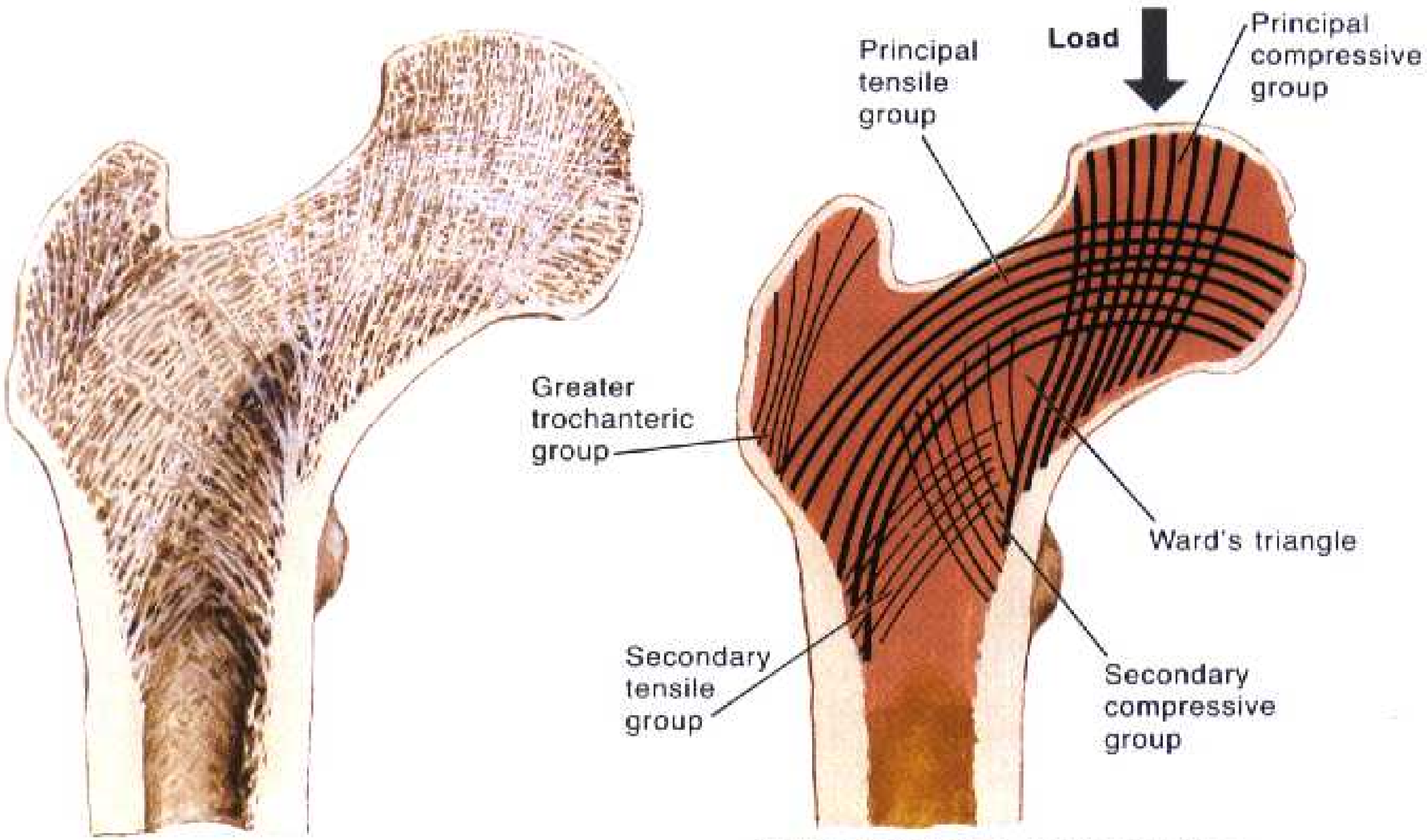
# Change in BMD after Space Flight (Mir and ISS)




p values based on one-tailed t-test assuming equal variances, ISS vs. Mir
For spine and hip, n = 16 ISS astronauts, 9 ISS cosmonauts, 7 Mir astronauts and 29 Mir cosmonauts (7 repeat flyers)
For pelvis, n = 16 ISS astronauts, 0 ISS cosmonauts, 7 Mir astronauts and 19 Mir cosmonauts
For heel, n = 16 ISS astronauts, 9 ISS cosmonauts, 7 Mir astronauts and 0 Mir cosmonauts

## Bone Architecture in Relation to Physical Stress

**Wolff's law.** Bony structures orient themselves in form and mass to best resist extrinsic forces (ie, form and mass follow function)

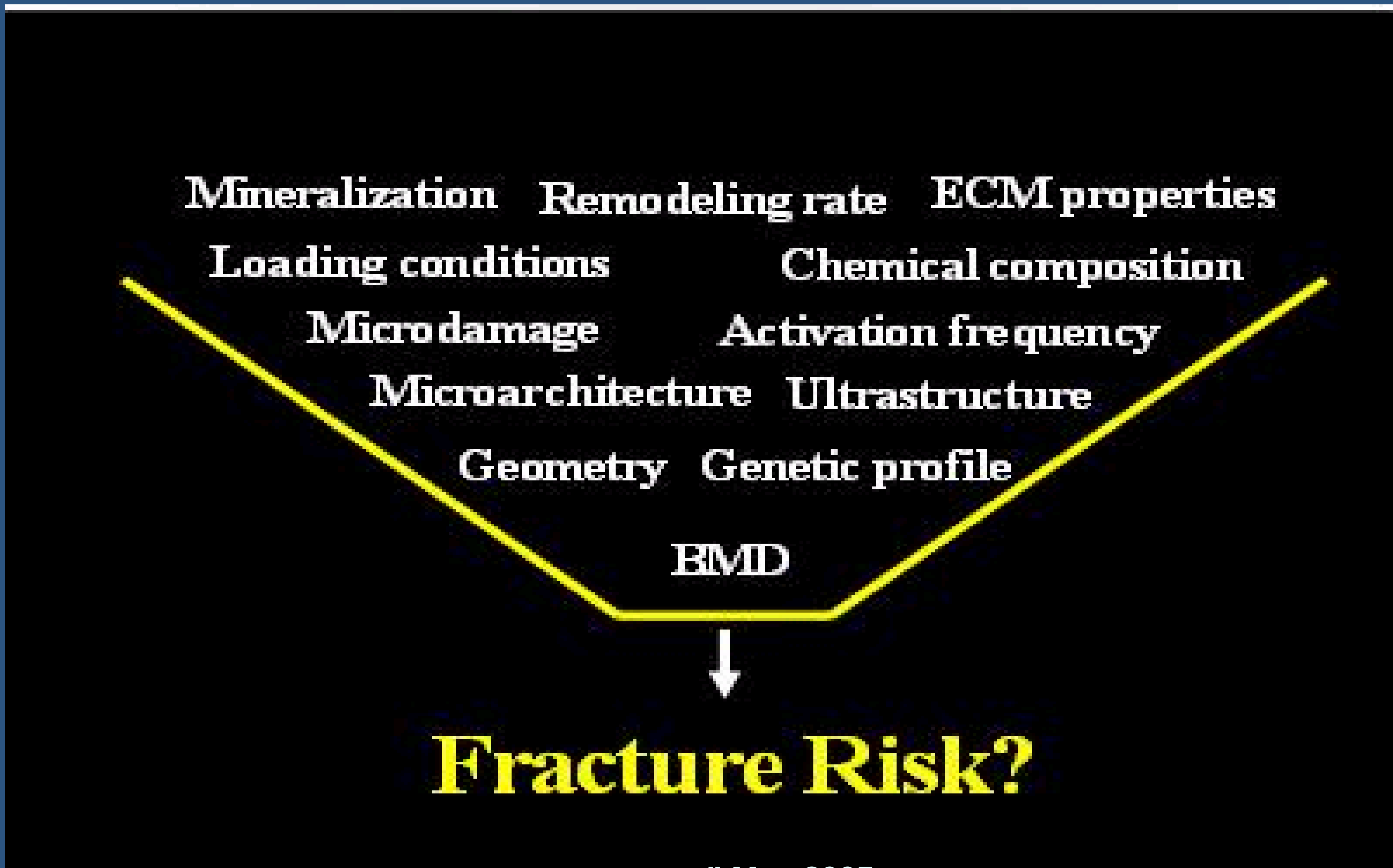



Trabecular configuration in proximal femur

Trabecular groups conform to lines of stress in weight bearing

| Feature | vivaCT 40 SCANCO MEDICAL | XtremeCT |
|---|---|---|
| |  |  |
| *Type* | in vivo (animal) | in vivo (human) |
| *Geometry* | Cone-Beam | Cone-Beam |
| *Peak/Mean Energy* | 30-70 kVp / 20-50 keV | 60 kVp / 40 keV |
| *Max. Scan Diameter* | 20-38 mm | 125 mm |
| *Max. Scan Length* | 145 mm | 150 mm |
| *Nominal Resolution* | 10 µm | 42 µm |
| *Resolution (10% MTF)* | 20 mm Ø: 16 µm | 125 mm Ø: 100 µm |
| *Slice Thickness* | 10-38 µm | 41-246 µm |

# Bone Qualities: Indices that influence bone strength.




Goldstein, "Bone Quality: A Biomechanical Perspective" May 2005

# Hip Bone Strength: Use of modeling

Finite Element Models of Left Proximal Femur

Keyak et al, 1998, 2001, 2005

Loading Conditions

# Results – Hip Strength

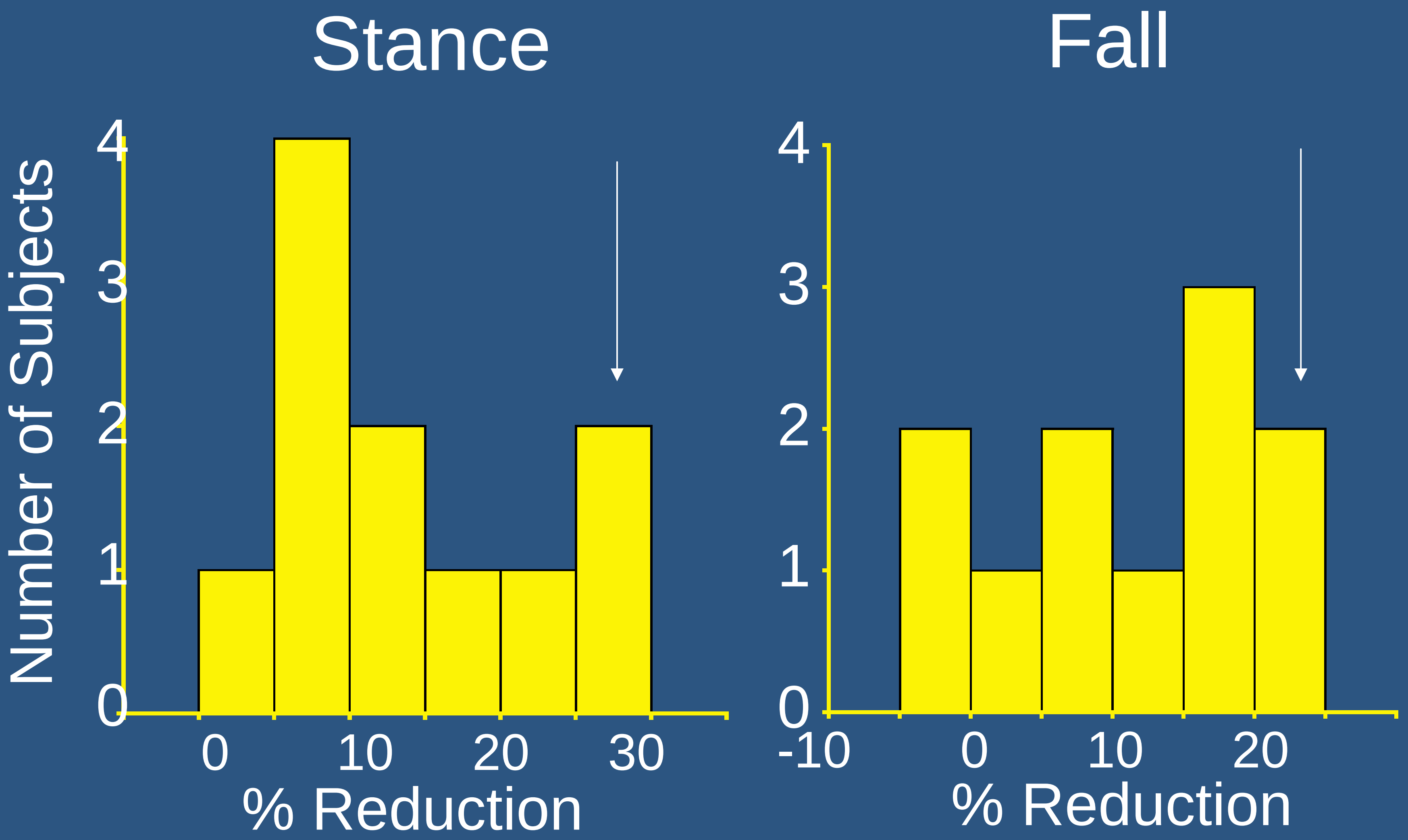
N=11 crewmembers

| Loading Condition | Mean (SD) Pre-flight | Mean (SD) Post-flight | *p* |
|---|---|---|---|
| Stance | 13,200 N (2300 N) | 11,200 N (2400 N) | <0.001 |
| | 2.2% loss/month | | |
| Fall | 2,580 N (560 N) | 2,280 N (590 N) | 0.003 |
| | 1.9% loss/month | | |

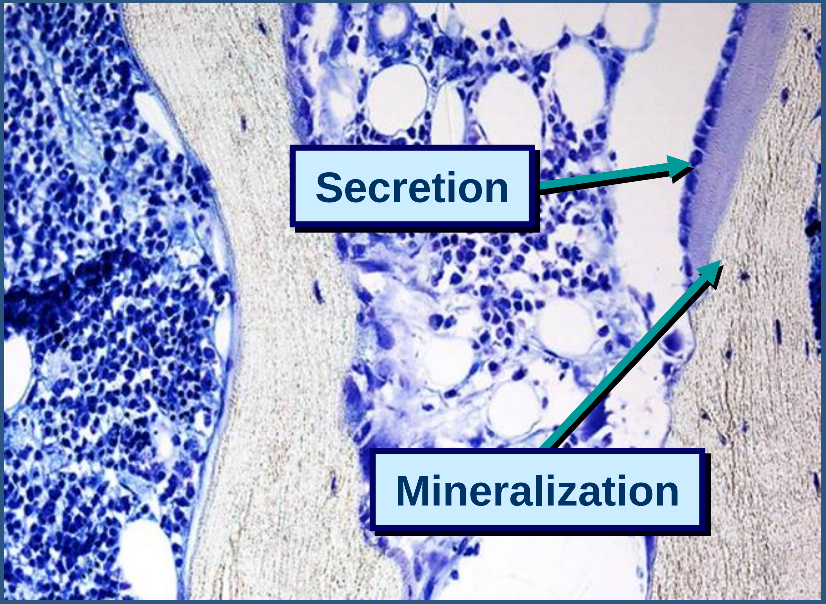
1.0-1.5% BMD loss /month

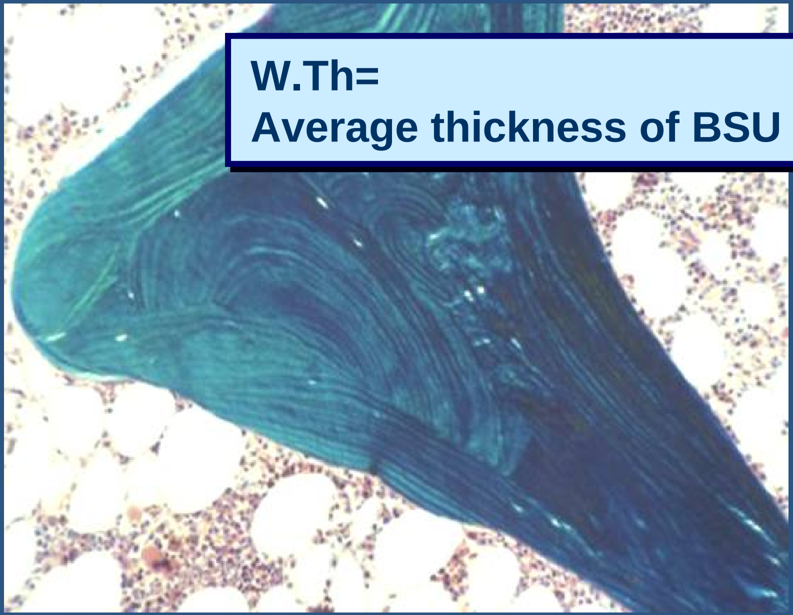
Slide Courtesy of J. Keyak

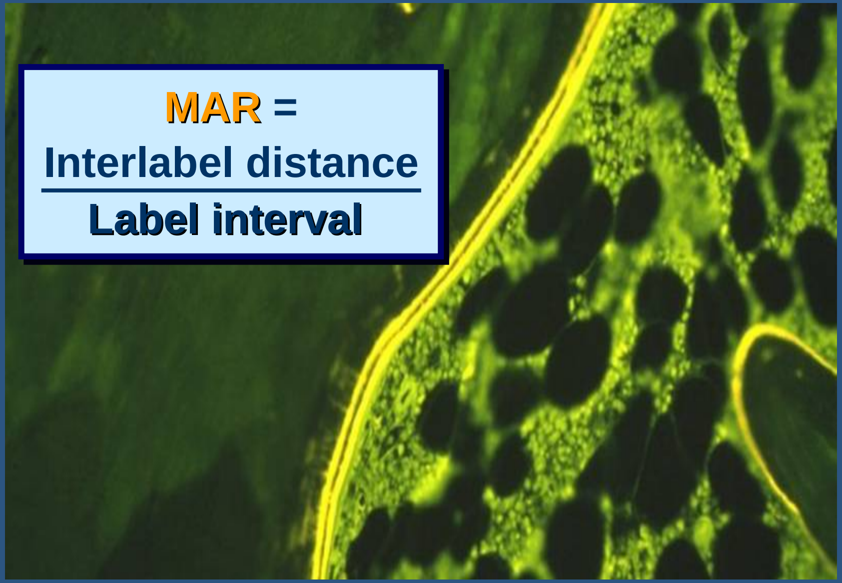
# Percentage Reduction in Hip Strength



# Activation Frequency requires Bone Histomorphometry



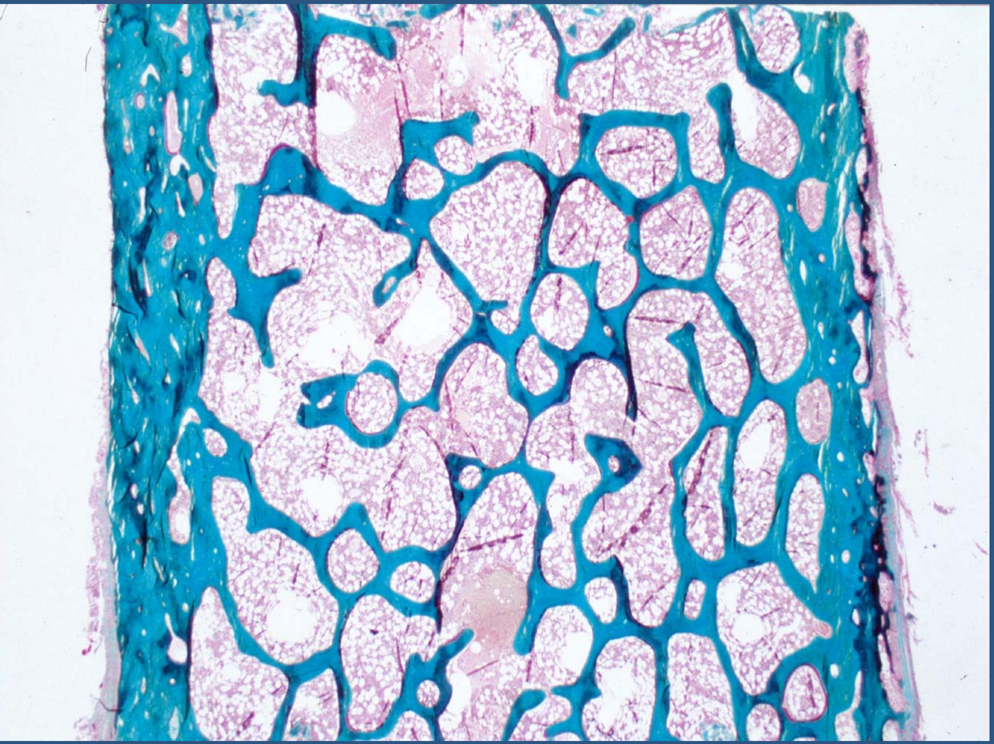



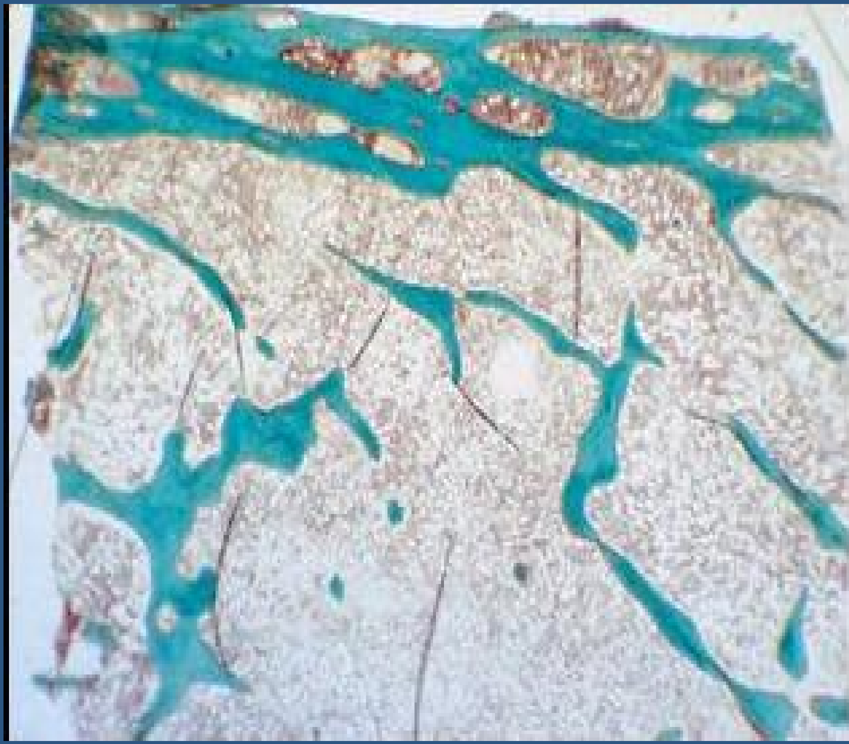




Average time that takes for a new remodeling cycle to begin on any point on a cancellous surface – an index for the rate of bone remodeling.

Not practical for site-specific bone remodeling see with mechanical unloading.

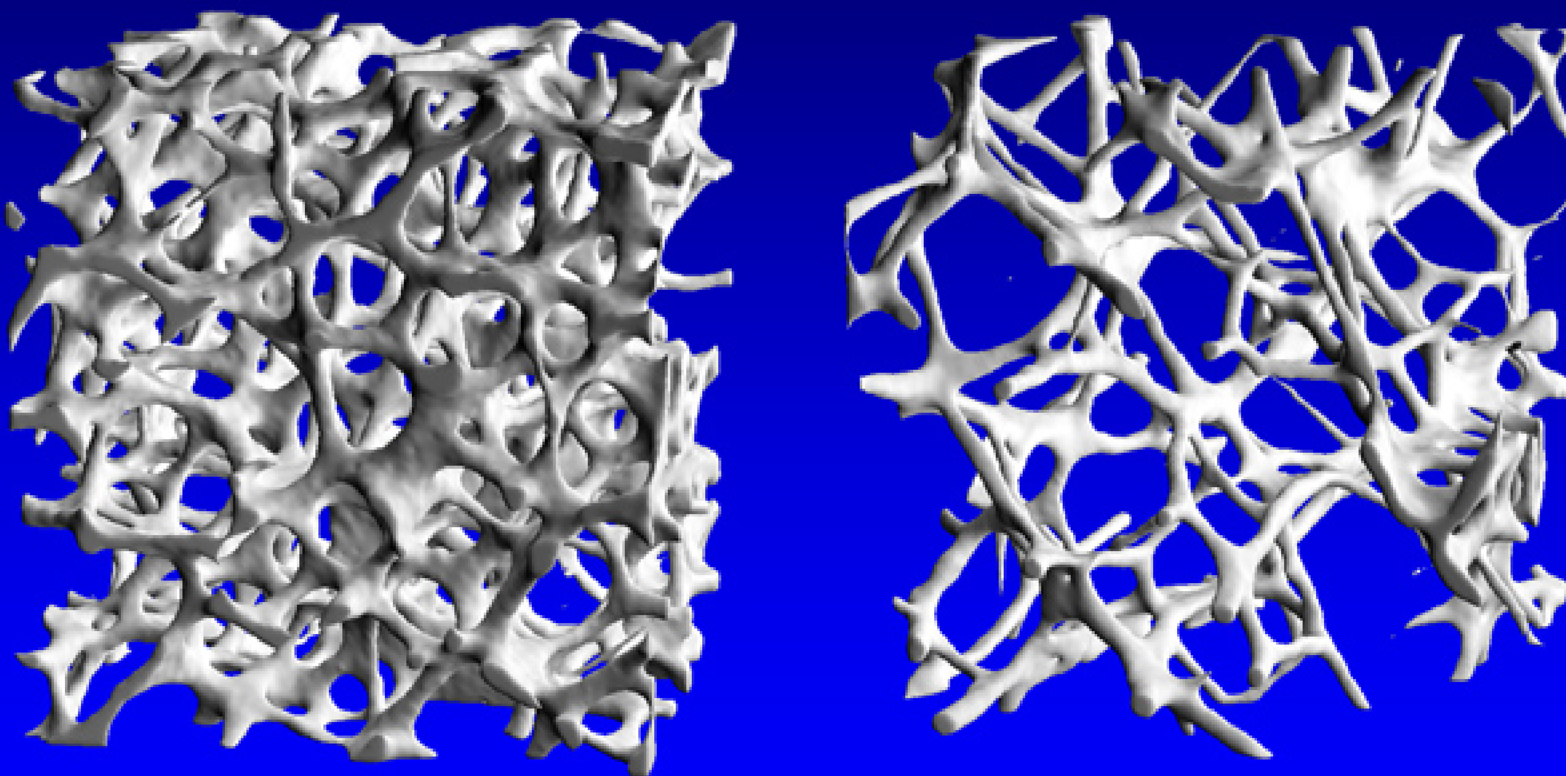
# Bone Histology





Young Normal

Osteoporotic



Images courtesy of Ralph Müller, PhD, Switzerland

uni | eth | zürich

# GAPS: Factors Related to Fracture Risk Besides Bone Mass

1. Energy released by fall or “injury”(need to identify tasks to be performed; perform modeling to predict*)
2. Neuromuscular protection of bone (need to preserve postural muscle mass and motor coordination)
3. Energy absorbed by soft tissue (need to provide adequate “protective padding,” evaluate putative osteoprotective effect of EVA suit and partial gravity)
4. Bone Strength:  Quantity & Quality (need supplement DXA bone mass measurements)

*Carpenter JBMR, 2005