National Aeronautics and Space Administration

Spaceflight-Induced Changes to Bone

Jean D. Sibonga, Ph.D.
Lead, Bone Discipline
Human Research Program [HRP]
Johnson Space Center, Houston, TX

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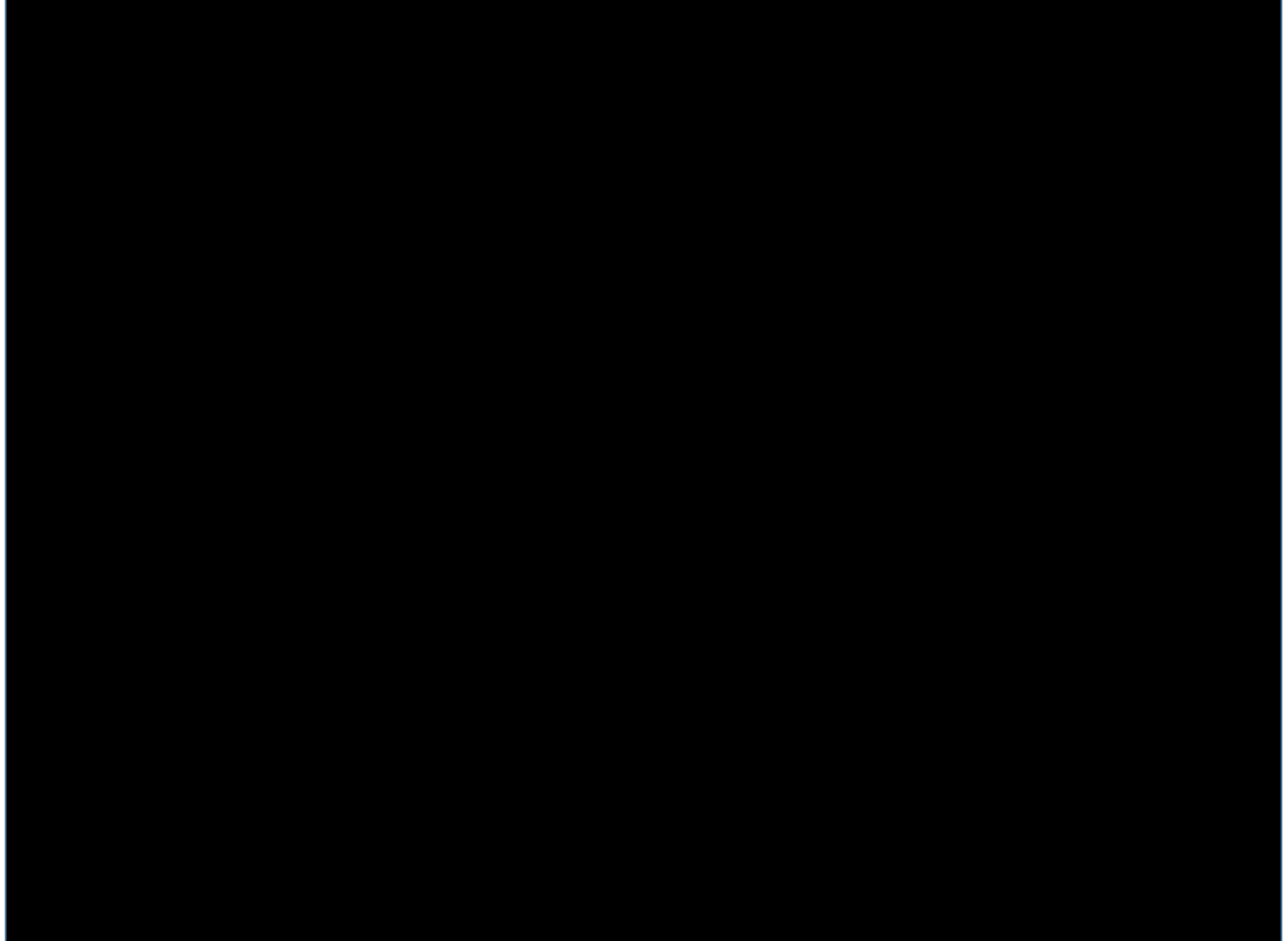
By the end of this lecture…

1. Bone is a complicated tissue.
2. NASA has constraints: low subject #'s; slow data acquisition.
3. Astronauts are understudied group.
4. Spaceflight effects on bone are unique.
5. Clinically-accepted guidelines not applicable.
6. Widely-applied imaging technology (for Bone Mineral Density – BMD) is insufficient fully understanding bone changes due to spaceflight exposure.

Given NASA's constraints for decision-making, Bone Discipline is investigating/advocating the transition of innovative research technologies to support decision-making (mission planning and risk management) and time-efficiency.



Whether the bone problem is "solved" depends upon the stakeholder's perspective.

1. Program Managers – Have we mitigated risks to astronaut health and performance to ensure mission objectives can be accomplished while minimizing impact on power/mass/volume/time/expense?
2. Human Risk Board – Does spaceflight increase the probability of fracture both during mission operations and long-term health [LTH]? Can we ensure that astronauts are *working* within the operating standards of bone health? Is current risk management considered CONTROLLED?
3. Space & Clinical Operations – Do/will the results of proven clinical tests substantiate that the bone health of astronauts is impaired and requires a clinical response? Do we know what should be the therapeutic response?

Whether the bone problem is "solved" depends upon uncertainties willing to accept.

5. Bone Biomedical Research: Are we collecting the right data to sufficiently assess the probability of fracture during missions (and after return)? To assess the causality of IVD/back injury to spaceflight? Do we know which risk factors for bone loss/for overloading bones we should target first for mitigation? Can we identify which astronauts are at greatest need for mitigation?
6. Human Systems Engineering: Can we sufficiently engineer-out hazards (e.g., mechanical loads) to the skeleton to prevent injury?

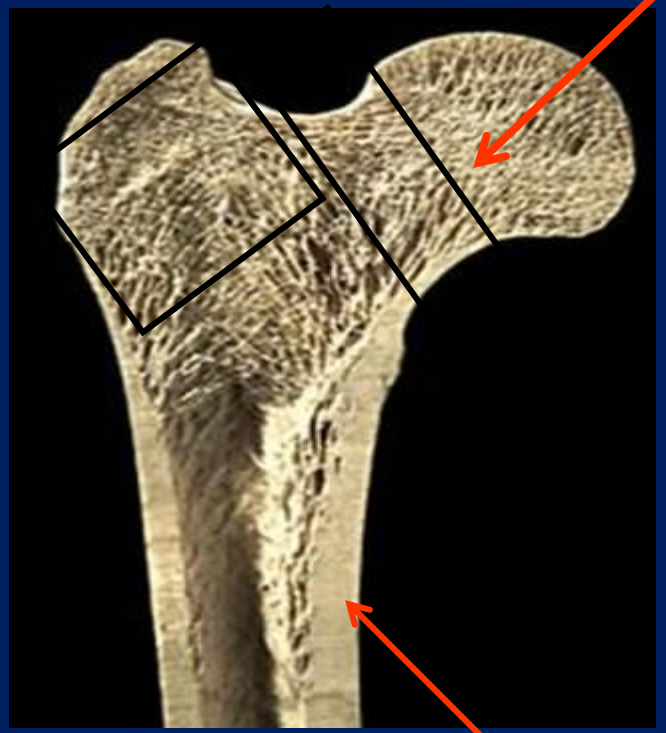
7. Challenge: Not all stake holders are on the same page regarding what is an acceptable and controlled risk. (Not understanding Bone physiology).

Skeletal Sites: Different composition of Bone Types with different contributions (a GAP) to Bone Integrity

PROXIMAL FEMUR

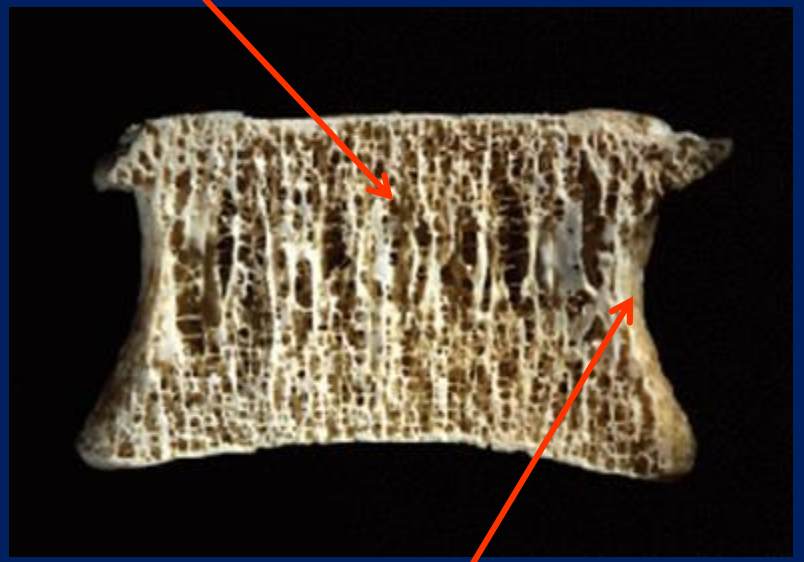
Trochanter
50% BMD

Femoral Neck
25% BMD



Cancellous "Spongy" Bone/Trabecular Bone

VERTEBRAL BODY – 66% BMD



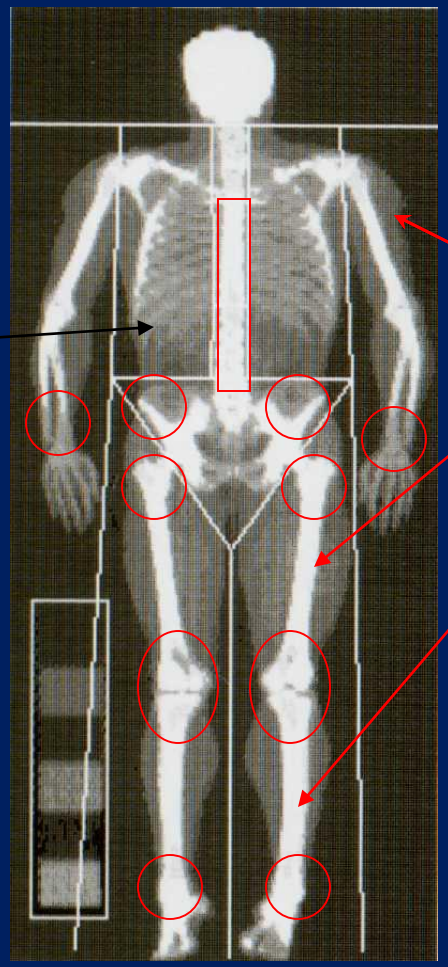
Cortical Bone/ "Compact Bone"

Sources: L. Mosekilde; SL Bonnick; P Crompton

Different Distribution and Turnover Rates for Bone Types to Support Skeletal Functions

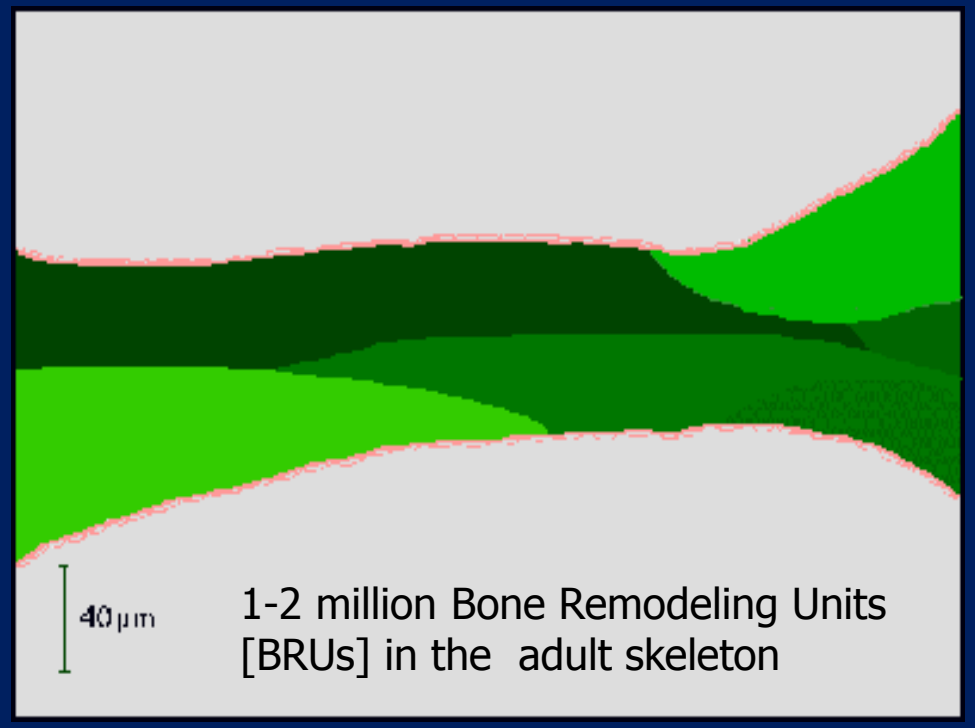
Entire skeleton turns-over 10%/year: 3% cortical bone but 25% of cancellous bone

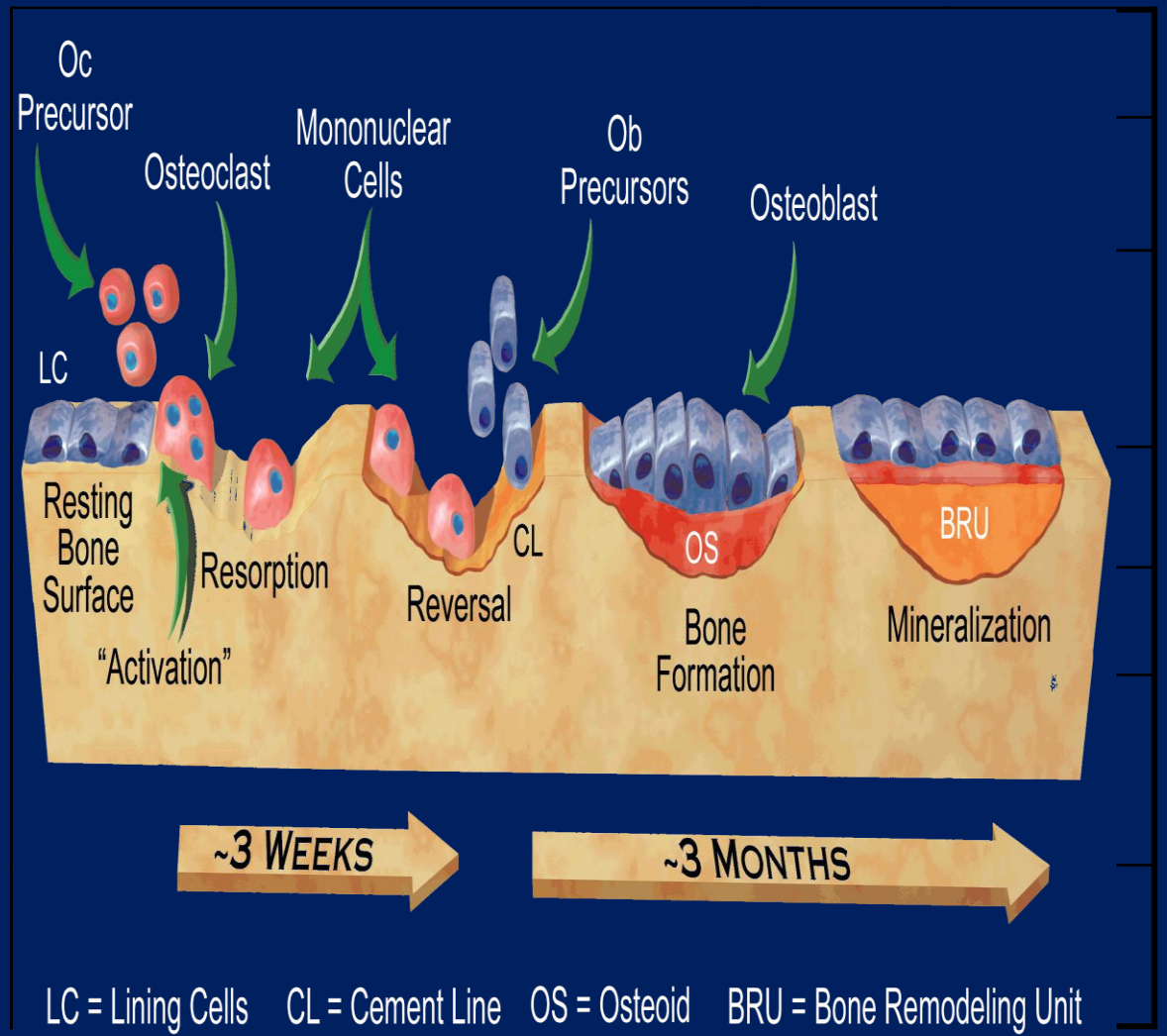
Cancellous Bone 20% of total skeleton (vertebrae, ribs, ends of long bones) **Contains 80% of bone surfaces**



Cortical Bone 80% of total skeleton (long bones)

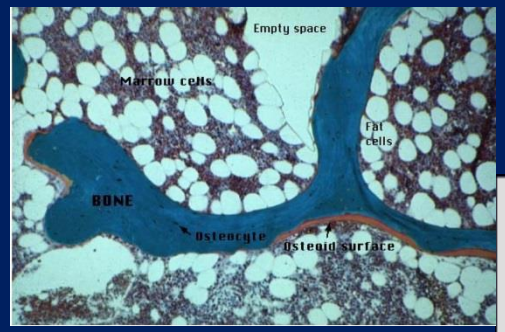
Remodeling of Bone Tissue in Adults is Highly Regulated* - Perturbations to Relative Rates can Influence Skeletal Integrity

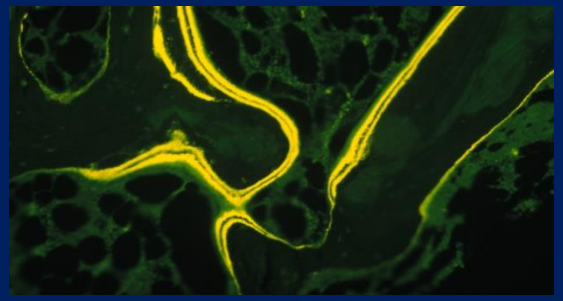


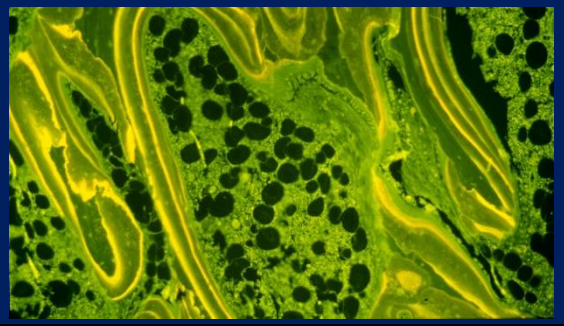


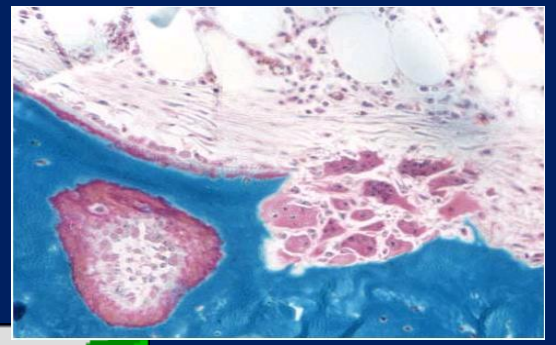
*Resorption occurs at faster rate, occurs first, relative to formation. Requires communication between cells.

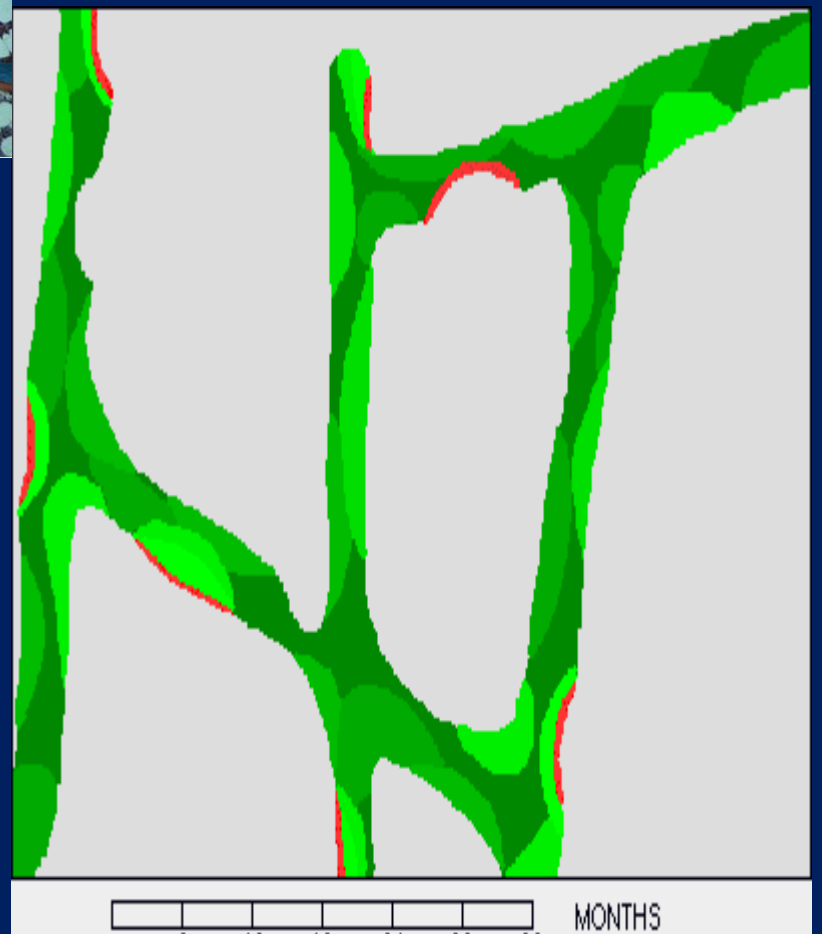
Some insight gained by comparison to Earth-based disorders of increased bone resorption.

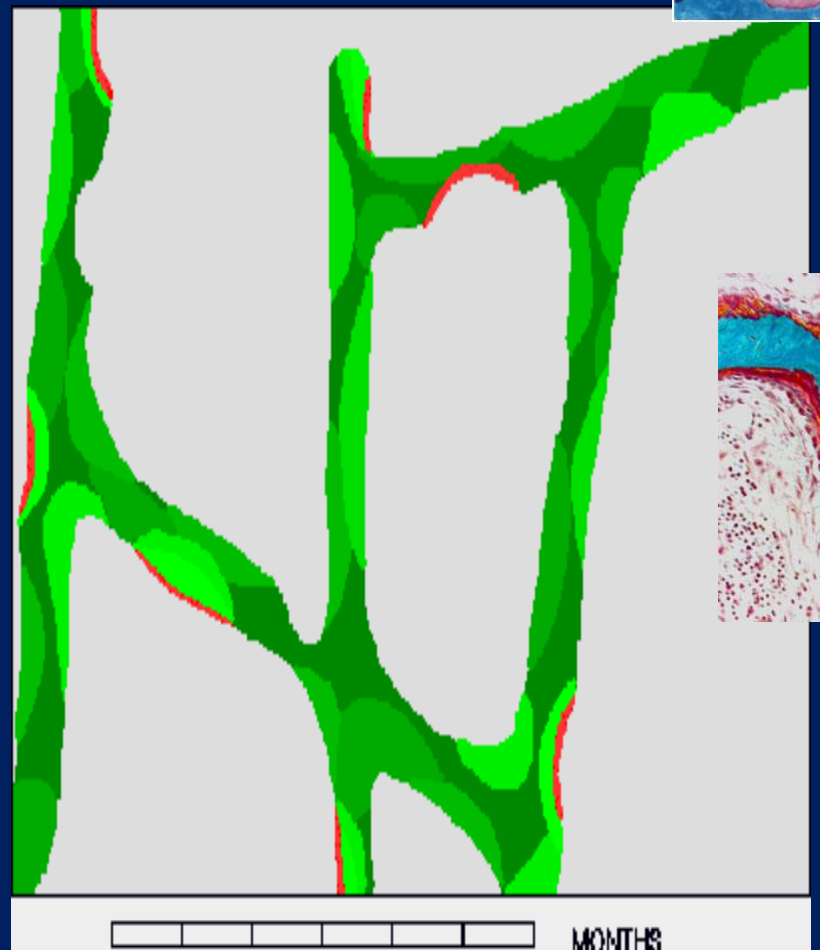


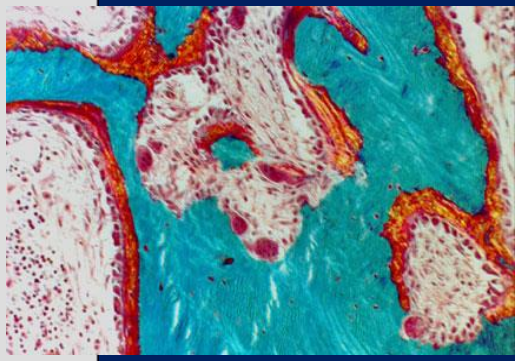












Research Specialties in Bone & Mineral Field

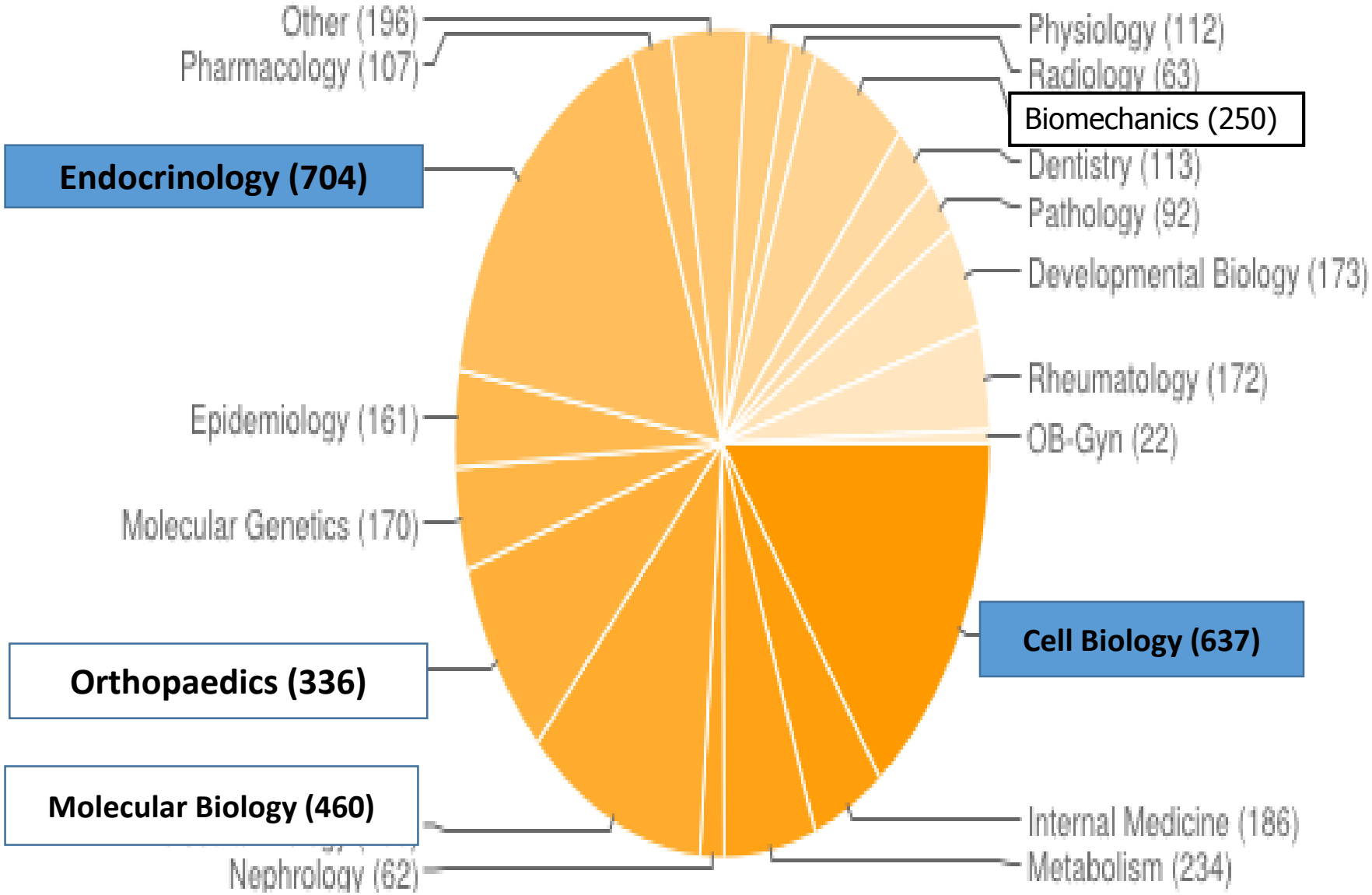


Figure Courtesy of the ASBMR 2014; adapted

Human Bone Risk: It's all about fracture.

"Osteoporotic/**Fragility** Fractures" – low to atraumatic Fractures due to Osteoporosis
(Causality - SKELETAL CONDITION)

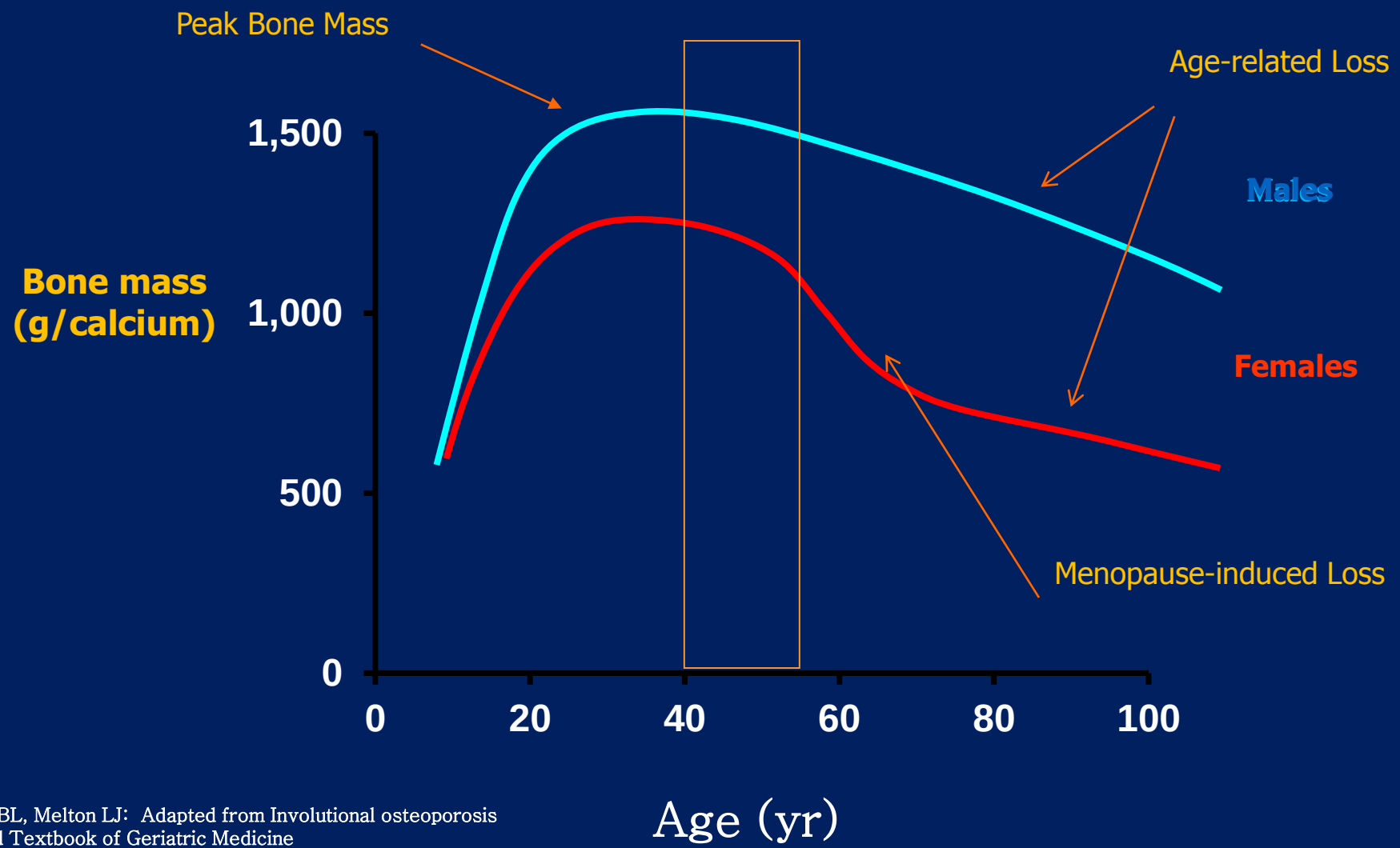
You don't have to be OLD.

Applied Load > Bone Strength = FRACTURE

(Key Causality – BIOMECHANICS)

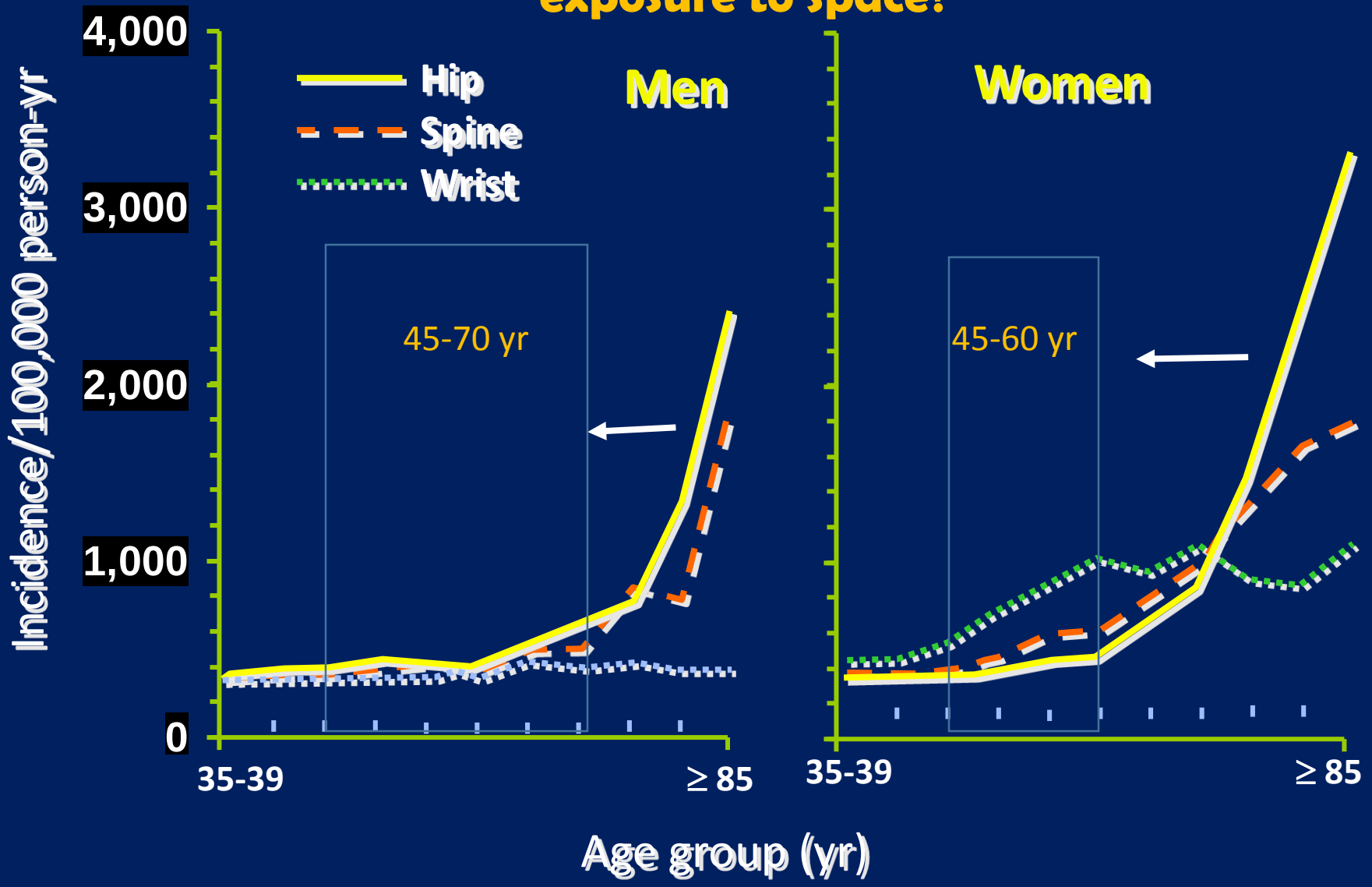
You don't have to have OSTEOPOROSIS.

Gain and Loss of Bone Mass in the Aging Human



Riggs BL, Melton LJ: Adapted from Involutional osteoporosis
Oxford Textbook of Geriatric Medicine
ADAPTED SLIDE COURTESY OF Dr. S. AMIN, Mayo Clinic

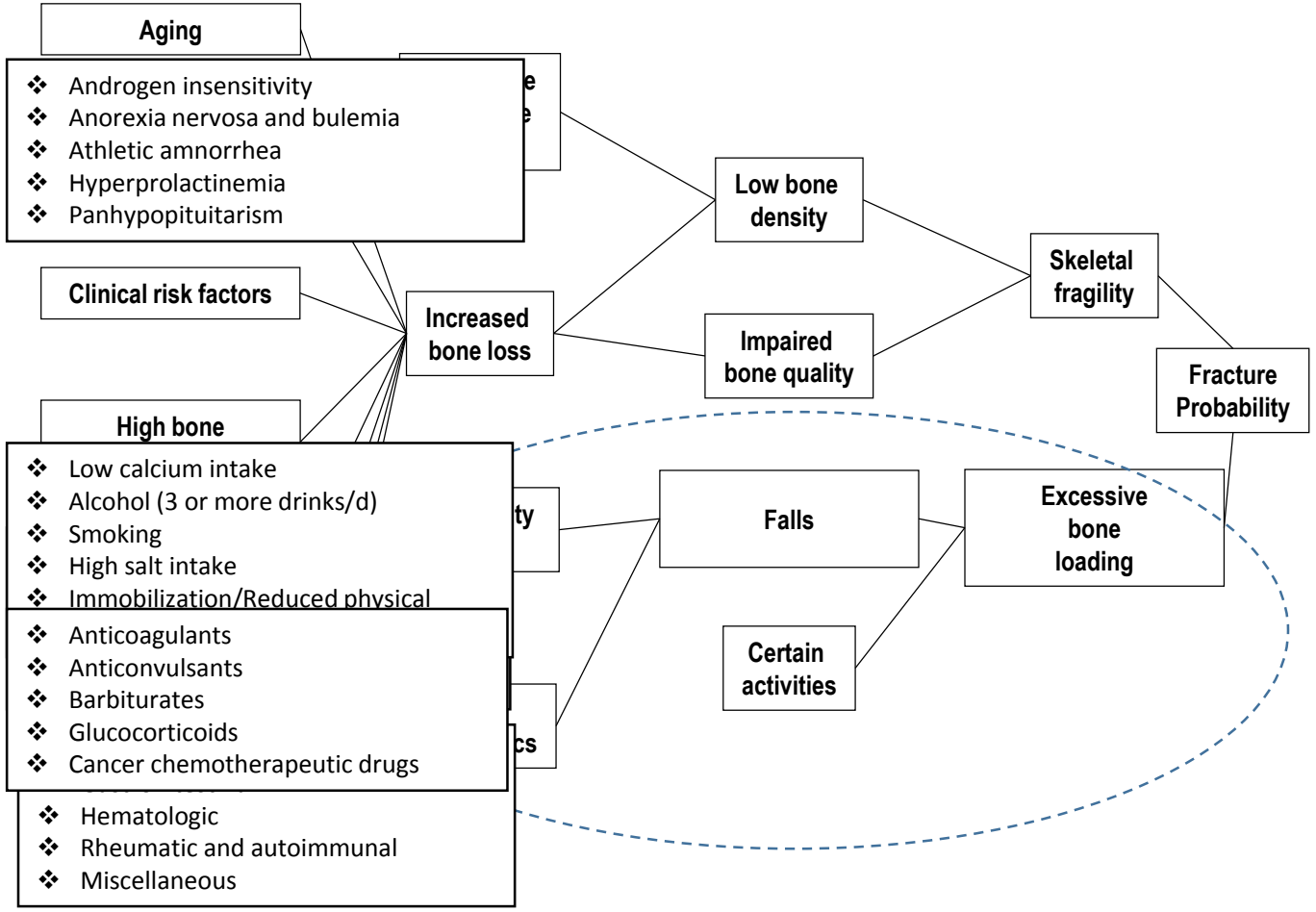
FRAGILITY FRACTURES in long-duration [LD] astronauts: Are they are risk for premature low trauma fractures due to prolonged exposure to space?



SLIDE COURTESY OF Dr. S. AMIN, Mayo Clinic

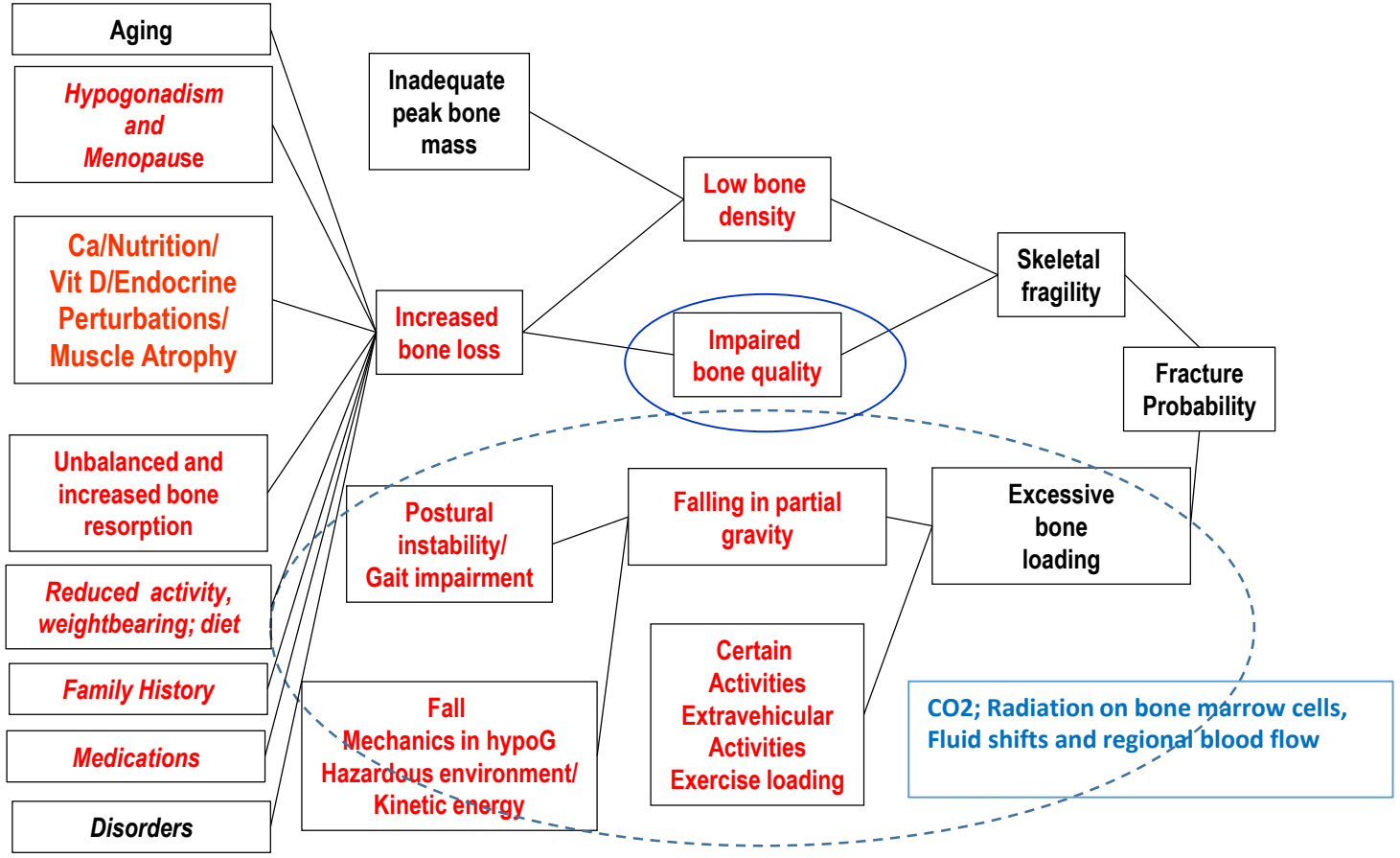
Cooper and Melton, 1992

Bone is a complicated tissue. Clinicians evaluate the multifactorial nature of bone loss and fracture risk for at risk patients here on Earth



Adapted from: Pathogenesis of Osteoporosis-Related Fractures (NOF) Cooper C, Melton LJ

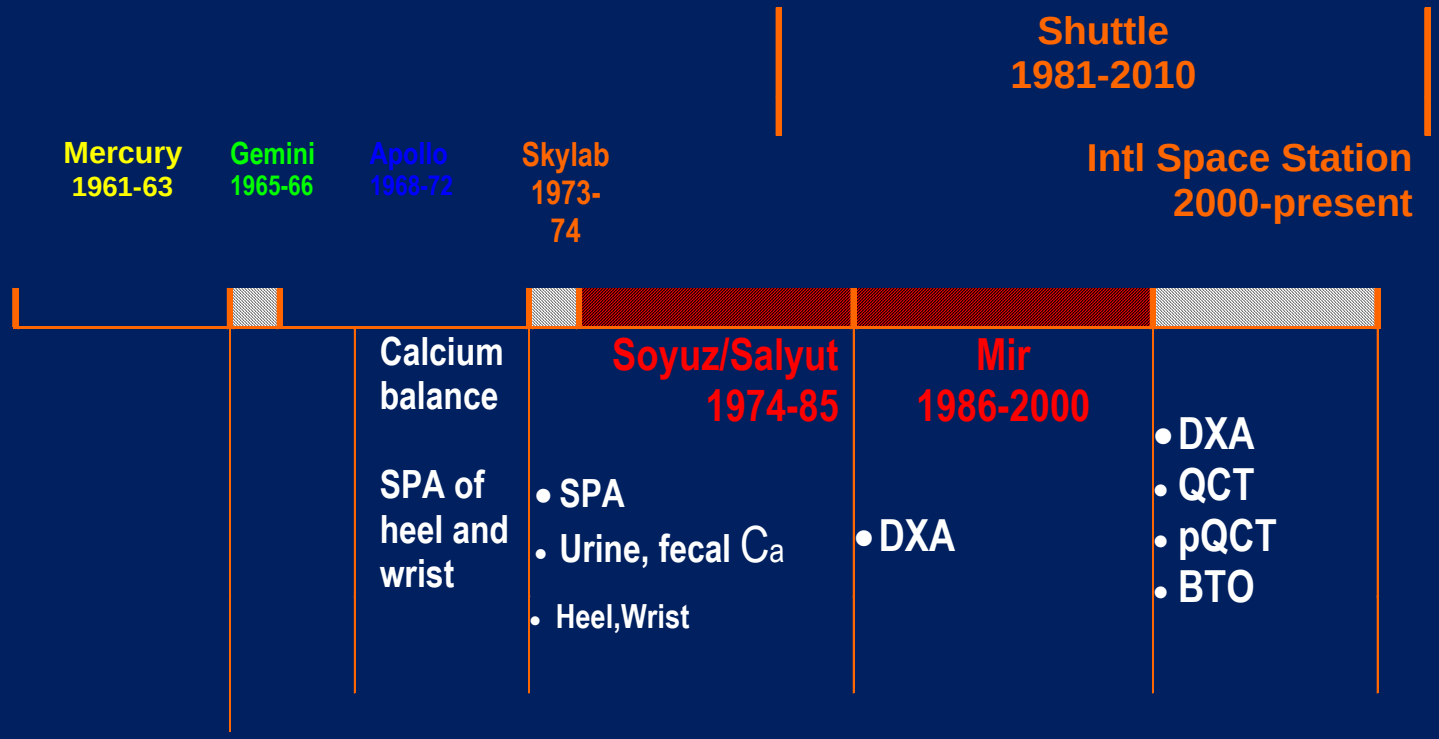
Bone loss in space is novel. While astronauts are not "patients" unique operationally-induced* factors in astronauts are possible contributors to fracture risk.



*exposure to space environment and mission operations

Adapted from: Pathogenesis of Osteoporosis-Related Fractures (NOF) Cooper C, Melton LJ

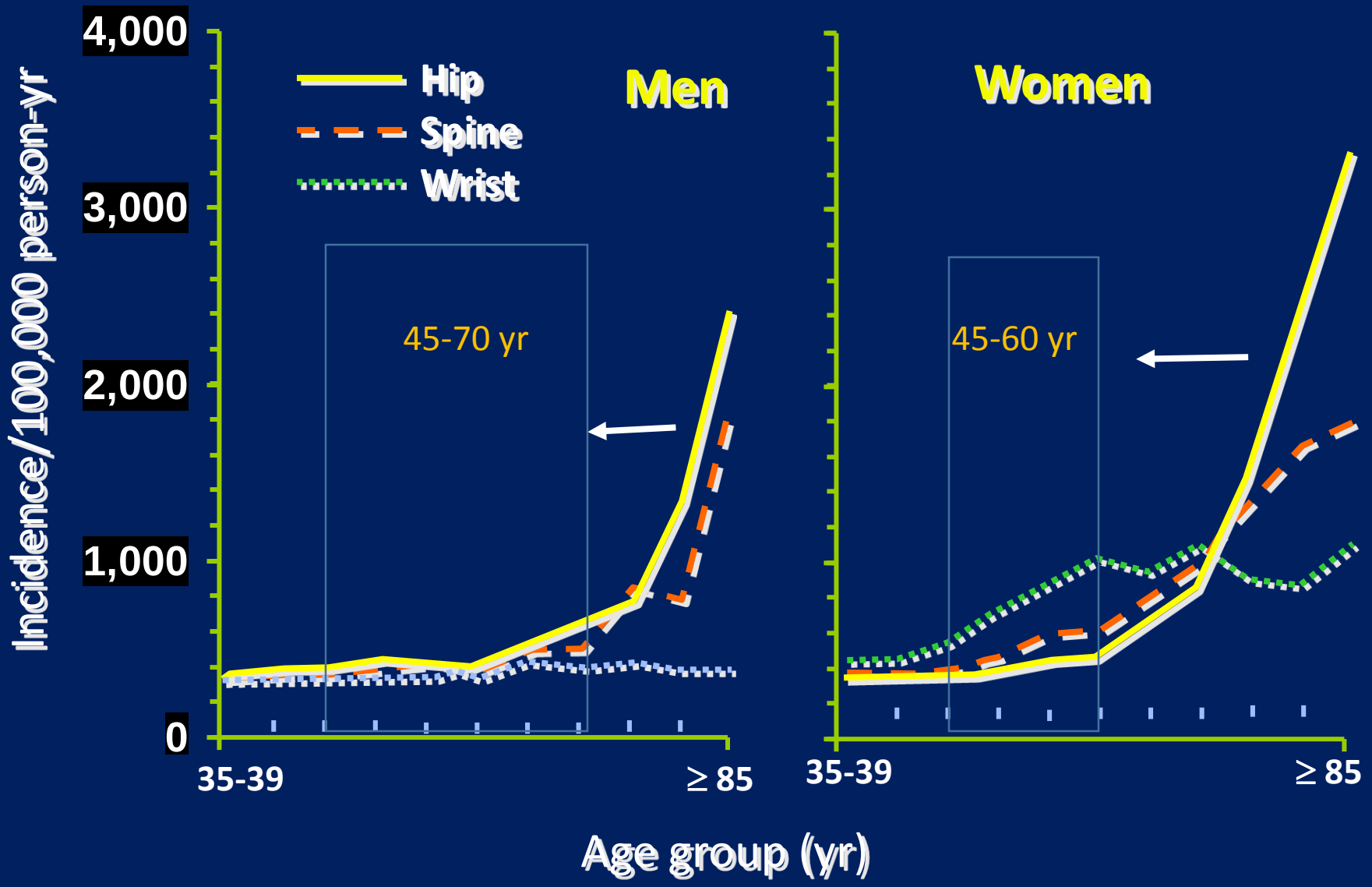
Characterizing Bone Changes* in Space



SPA=Single Photon Absorptiometry
DXA=Dual-energy X-ray Absorptiometry
QCT=Quantitative Computed Tomography
pQCT = peripheral QCT
BTO=biochemical markers of bone turnover

*Two functions of skeleton

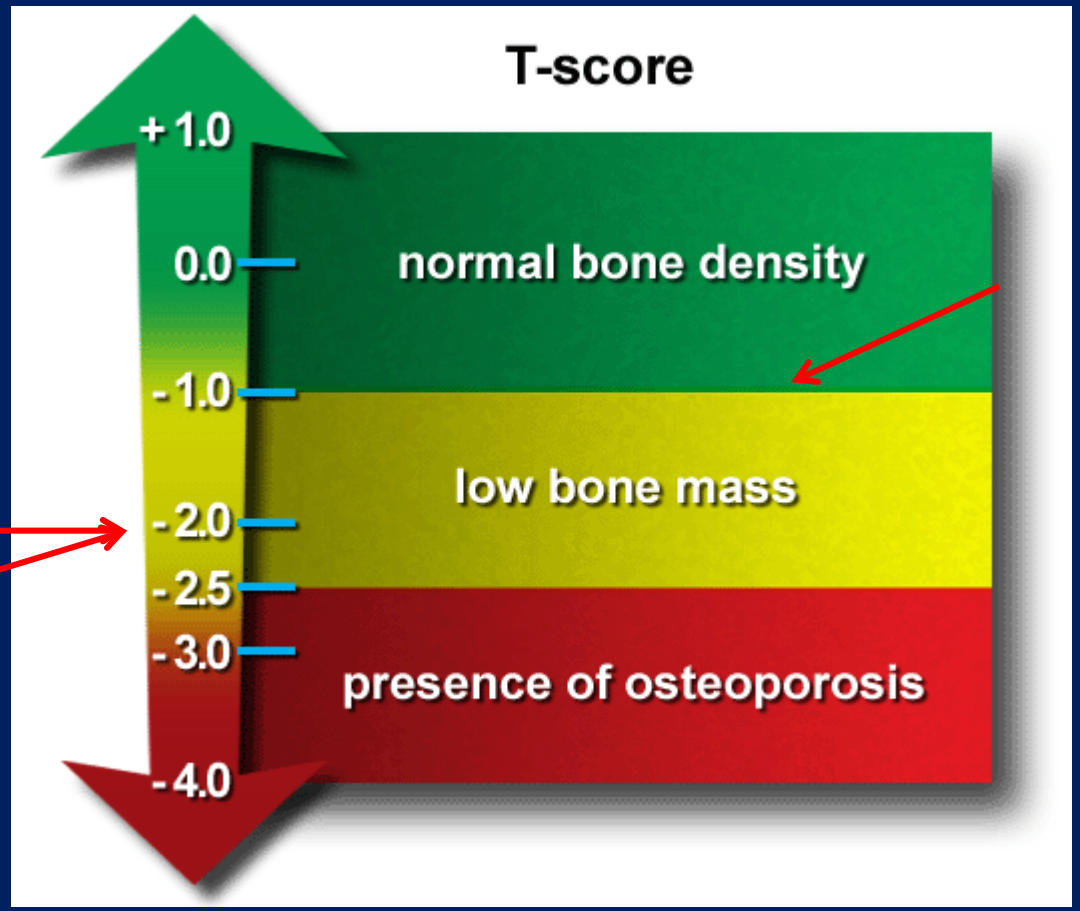
FRAGILITY FRACTURES during LTH: Quantifying # premature low trauma fractures in astronauts not practical.



SLIDE COURTESY OF Dr. S. AMIN, Mayo Clinic

Cooper and Melton, 1992

Thus, NASA adapted the clinical surrogate for fracture (BMD) and WHO guidelines for 1° Osteoporosis for bone health standards in long-duration astronauts (Circa 2000) T-scores* (Not BMD change).



Preflight
"Fit for Duty"

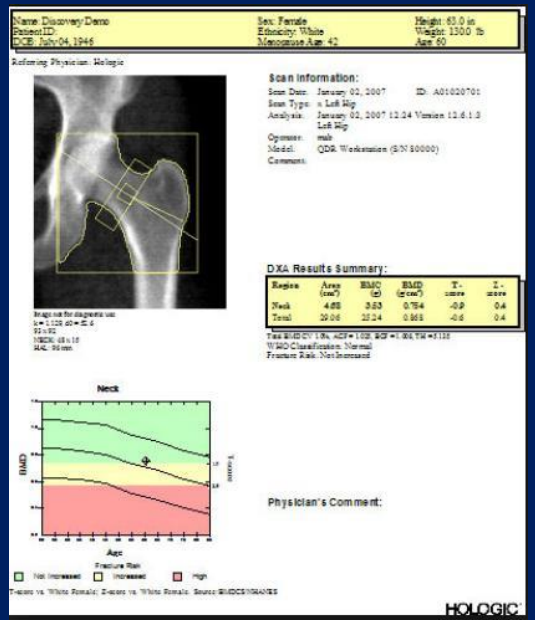
Permissible
Outcome
Limit

Mitigation
Efficacy

*T-score is # Standard Deviations from mean BMD of young normal "peak bone mass"

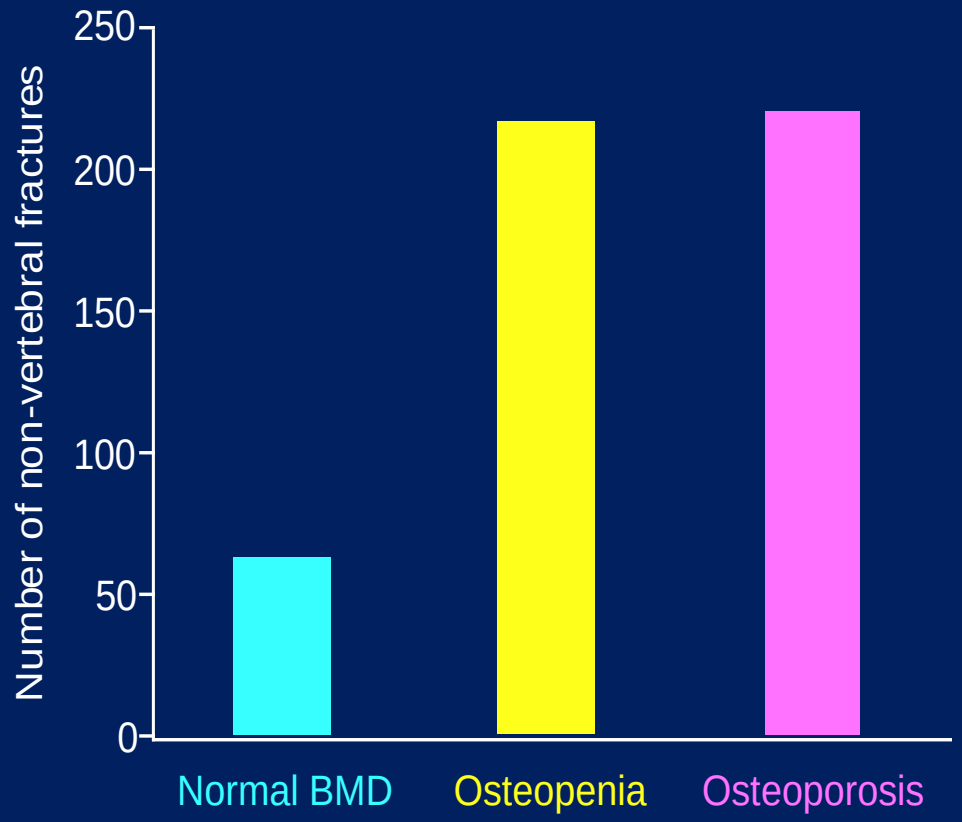
Bone Densitometry more than a fracture surrogate in ISS Astronauts (MedB 1.11)

- Describe skeletal effects of spaceflight
- Track individual bone loss and recovery after long-duration flights.
- Informs rehabilitation efforts
- Facilitates recertification for long-duration missions
- For evaluation of in-flight exercise countermeasures and postflight rehabilitation processes.



Meanwhile, Terrestrial Observation of Reduced Sensitivity of DXA Test: "T-score Osteoporosis" Misses Over 50% of Fragility Fractures"

Only 44% of women (21% of men) who sustain non-vertebral fractures have "osteoporosis" by BMD*



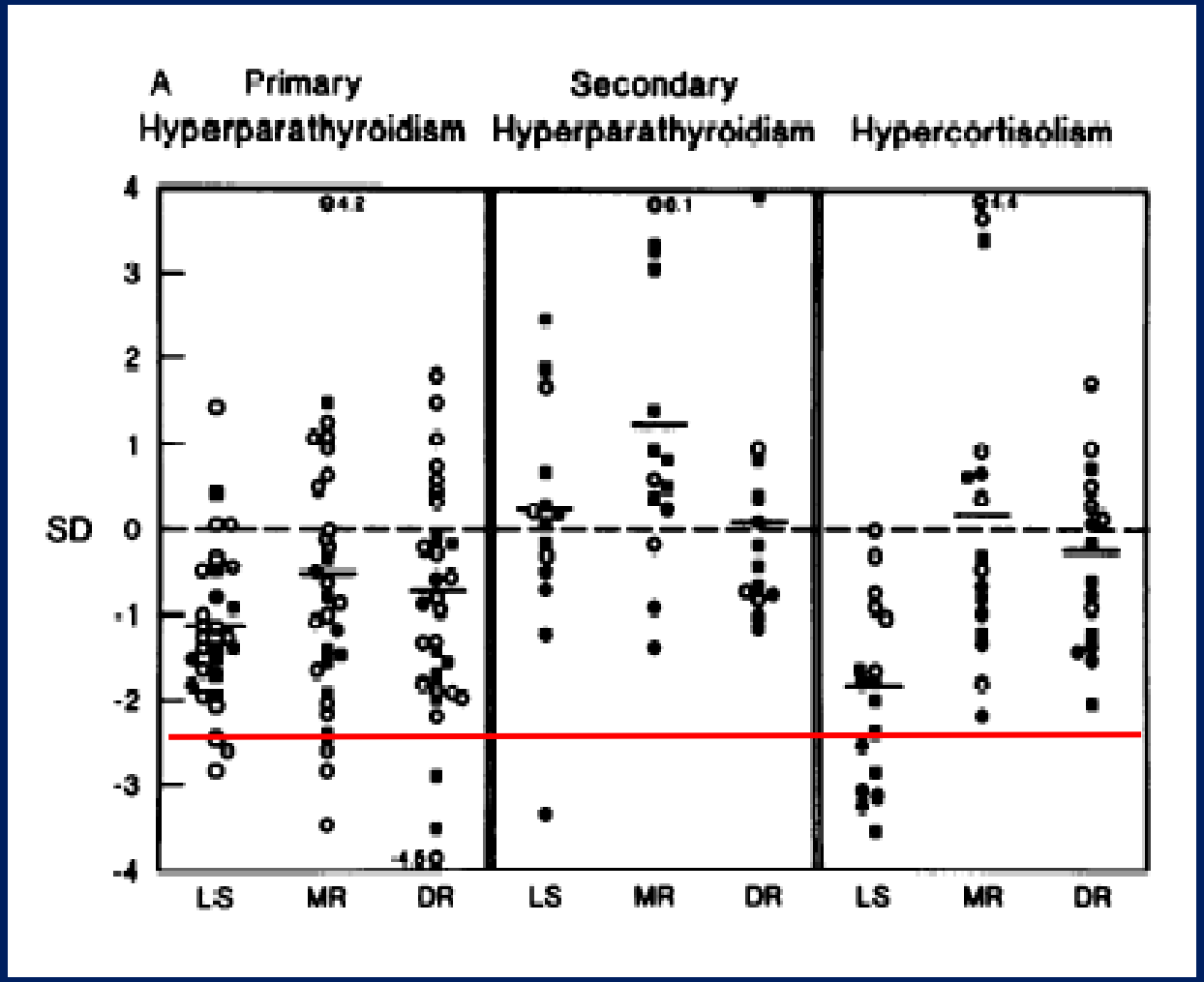
5794 participants in the Rotterdam study;
Mean follow-up 6.8 yrs
FN BMD at baseline

(Female data presented here)

Adapted from Schuit, Bone. 2004;34:195-202. Slide from J Shaker, MD; ISCD 2015 Annual Meeting

*Also disconnects evident with clinical trials– reduced ability to monitor therapeutic response to *pharm agents*.

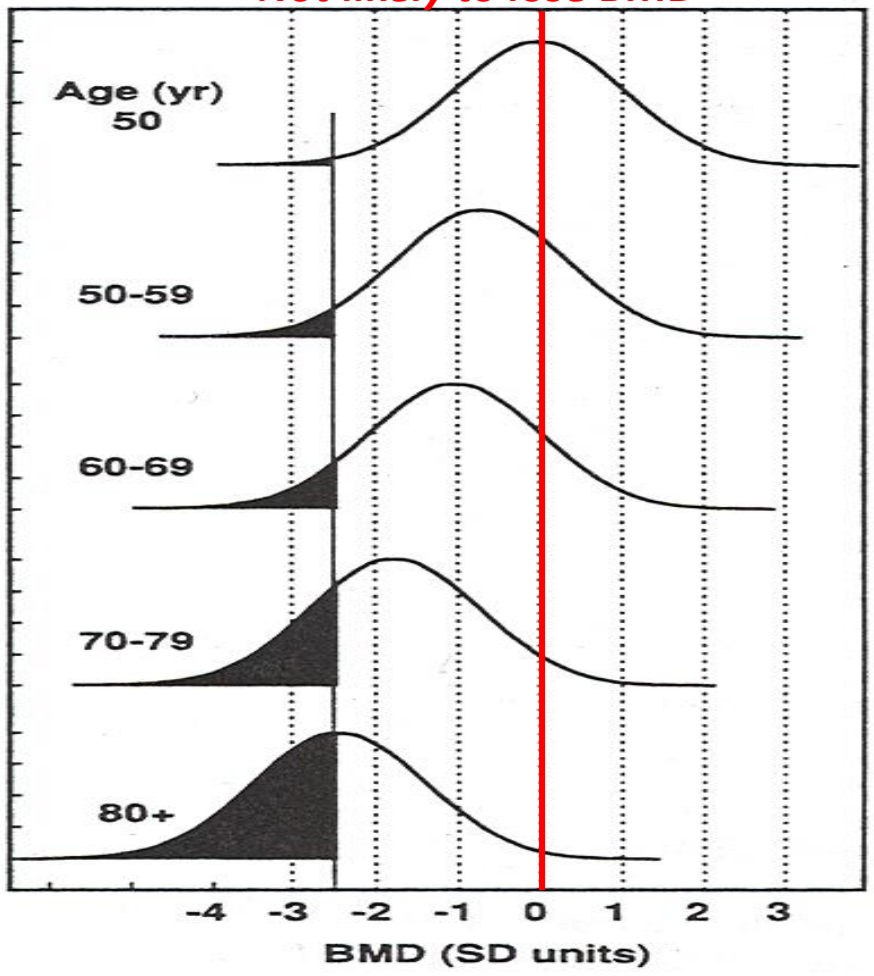
Addtl shortcoming with BMD Guidelines: Cannot identify high risk persons in patients with other patterns of sub-regional bone loss (i.e., distinct from bone loss with aging – relevance to spaceflight-induced changes).



Seeman, JCI 1992
DPA measure of BMD

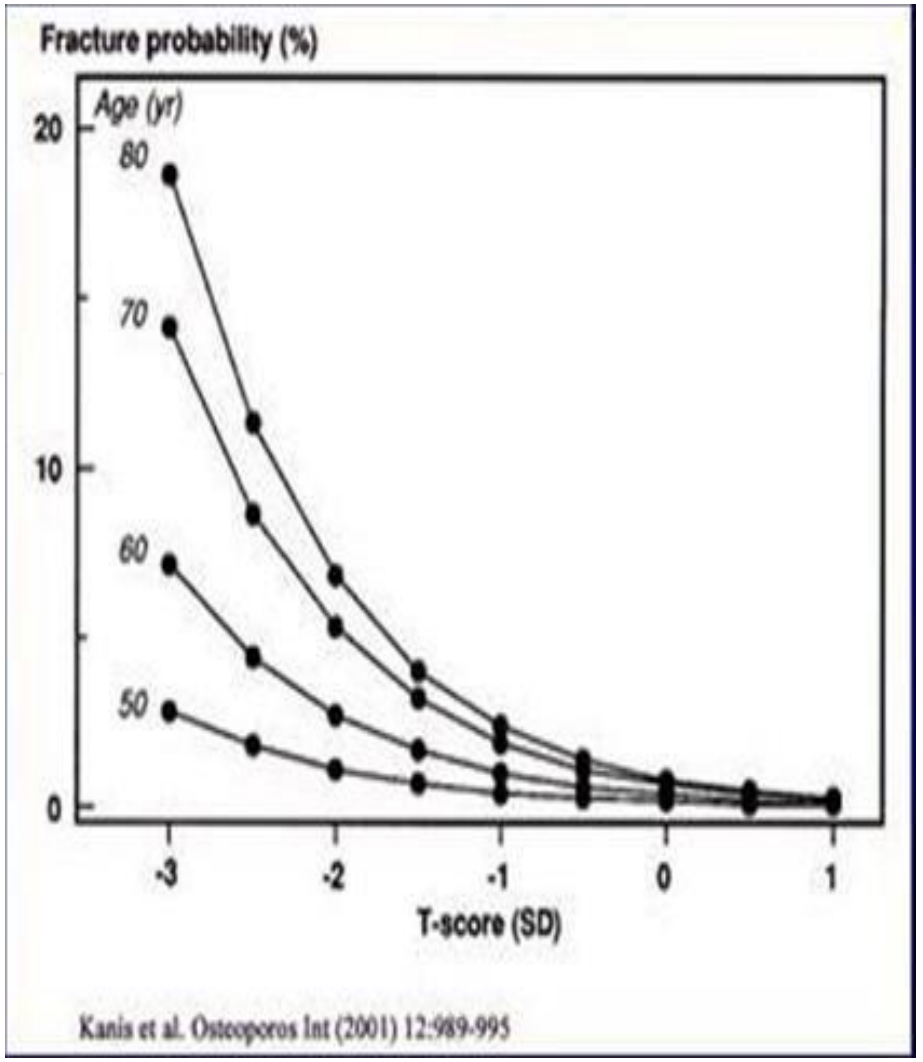
DXA BMD test/guidelines have limited clinical utility for younger-aged astronauts.

Not likely to lose BMD



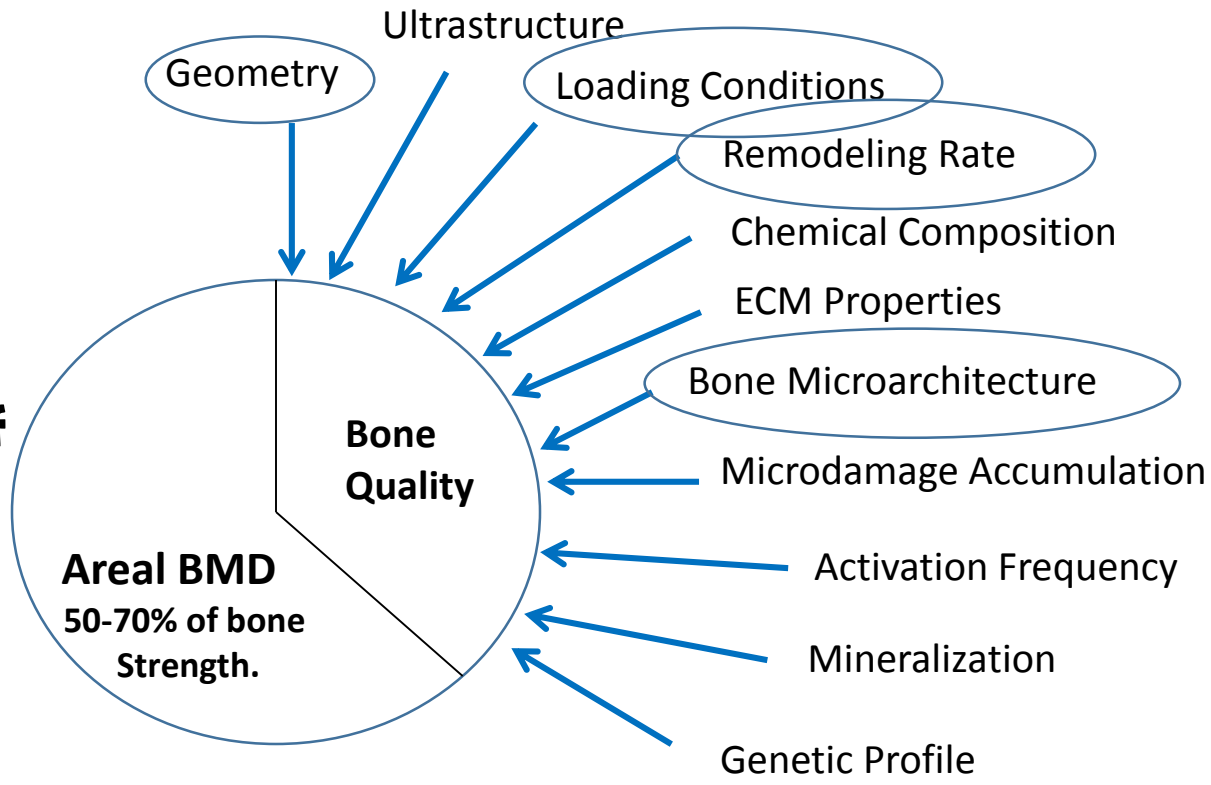
Kanis et al JBMR 9(8):1137, 1994

Not likely to fracture (hip data only) if they DID lose BMD*



** it is the probability of fracture that drives the requirement for interventions, not declines in BMD.*

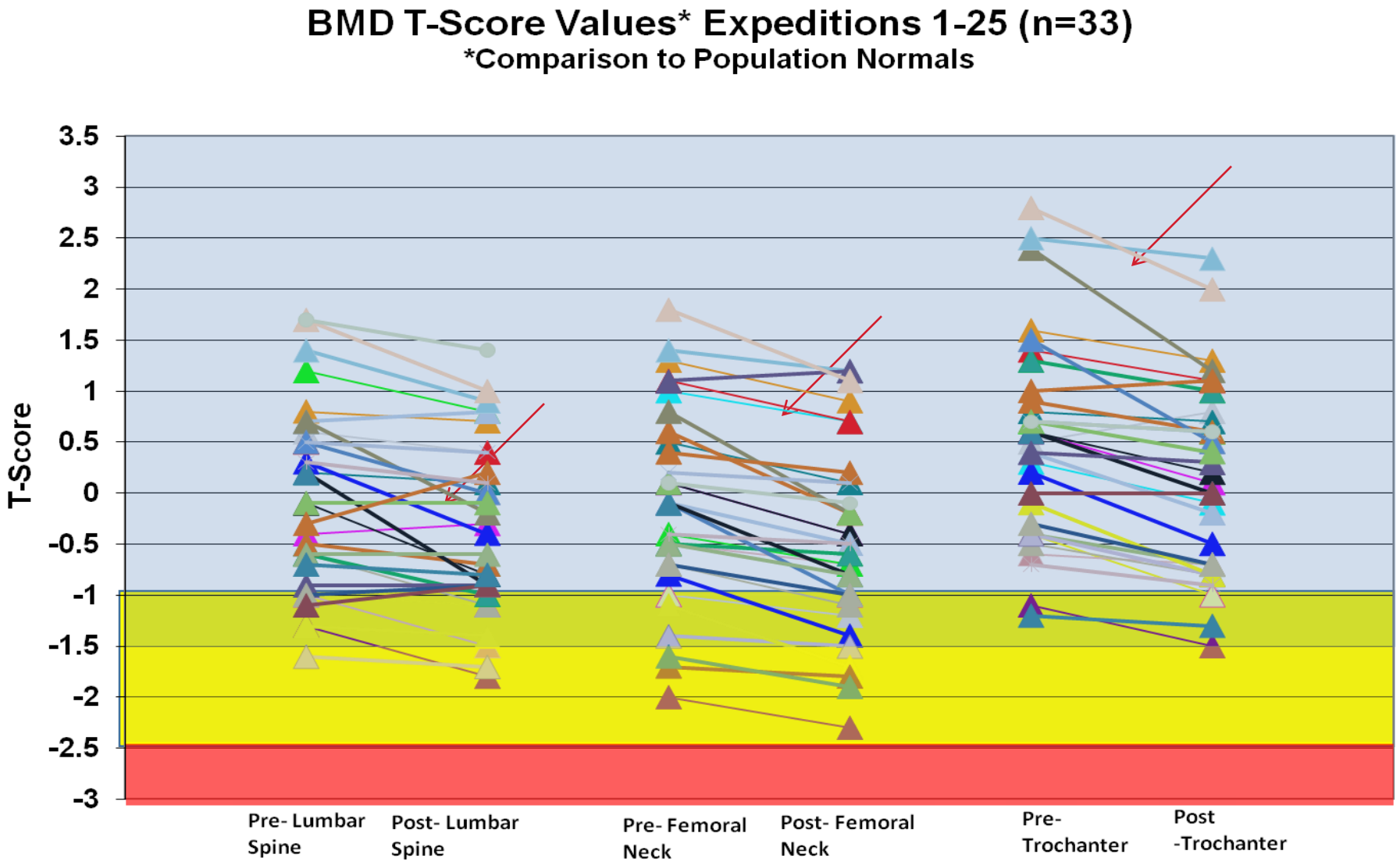
Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Bone strength reflects the integration of two main features: bone density and bone quality." JAMA 2001



"Bone Quality: What is it and Can we measure it?"

May 2005

SD Clinical Test: Not clinically applicable to younger-aged astronaut population (Bone Summit, 2010).



What about BMD as a metric for bone strength ?

The good, the bad, and the ugly.

Seminal DXA study of Mir Crew Members

Declines in bone mass are rapid and site-specific.

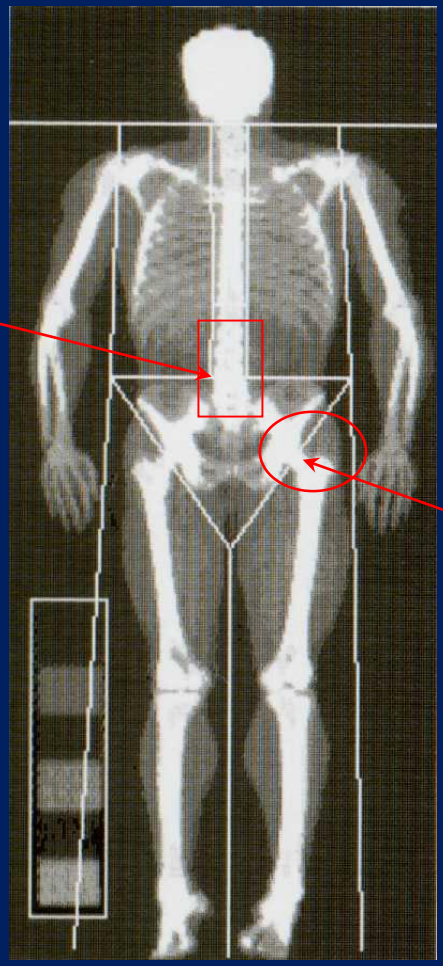
vs. 0.5 – 1.0 % BMD loss/yr in the aged

.

Areal BMD 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.

Whole Body
0.3% / month

Lumbar Spine
1% / month

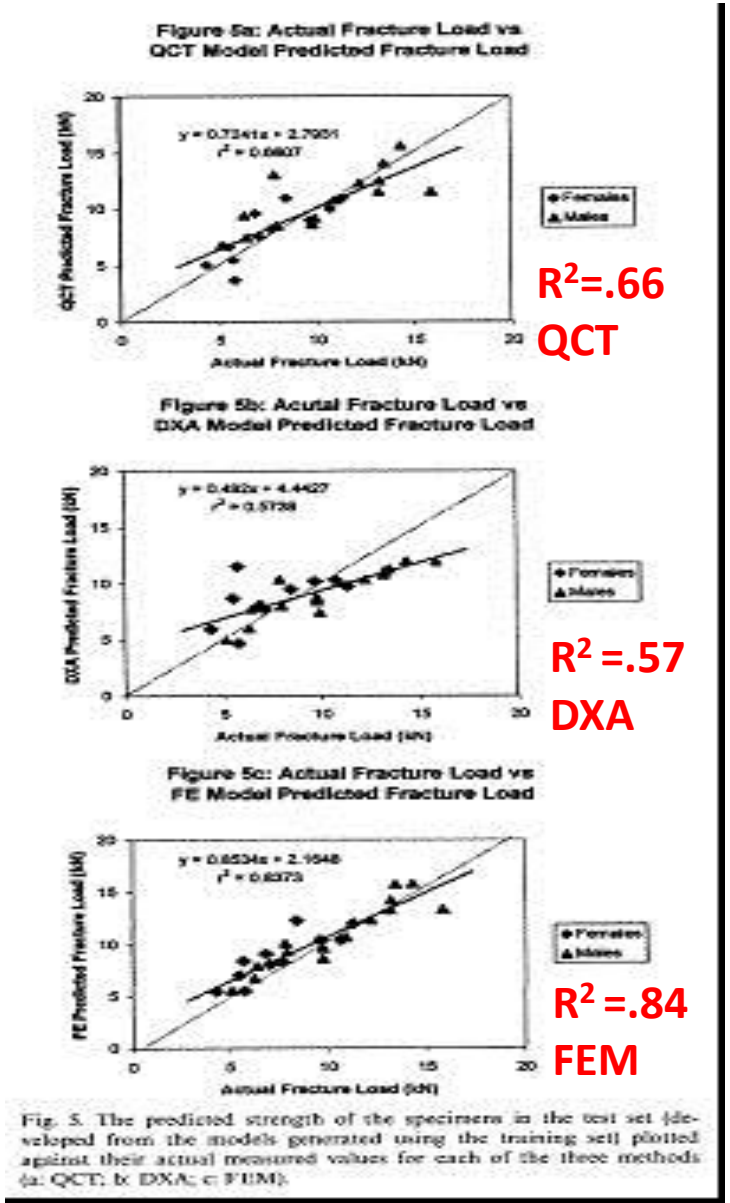


Hip
1.5% / month

In vitro studies : DXA BMD underestimates bone strength relative to QCT and QCT-FEM.

QCT estimates <u>fracture loads</u> better than DXA **R^2=.66 QCT**

QCT + FEM has superior <u>capabilities for estimating fracture loads</u> **R^2 =.84 FEM**



R^2=.66 QCT

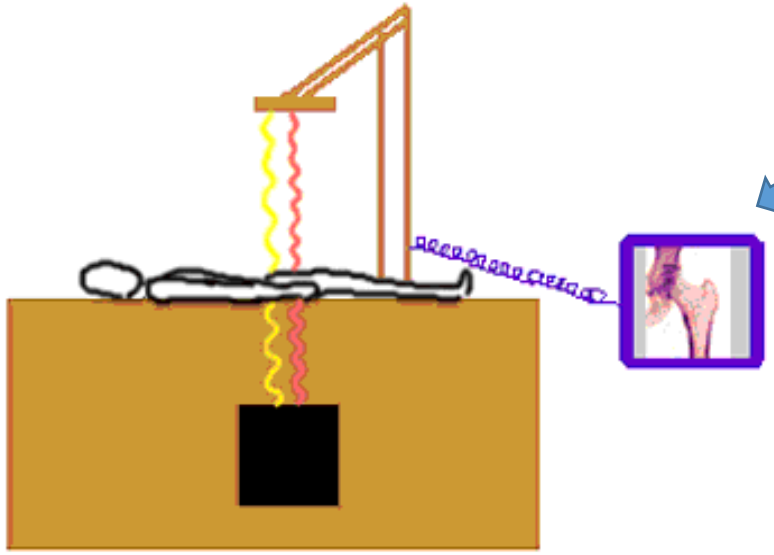
R^2 =.57 DXA

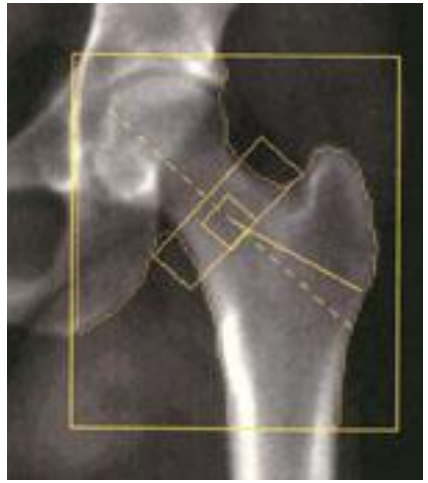
R^2 =.84 FEM

Fig. 5. The predicted strength of the specimens in the test set (developed from the models generated using the training set) plotted against their actual measured values for each of the three methods (a: QCT; b: DXA; c: FEM).

DD Cody: Femoral strength is better predicted by finite element models than QCT and DXA. J Biomechanics 32:1013 1999.

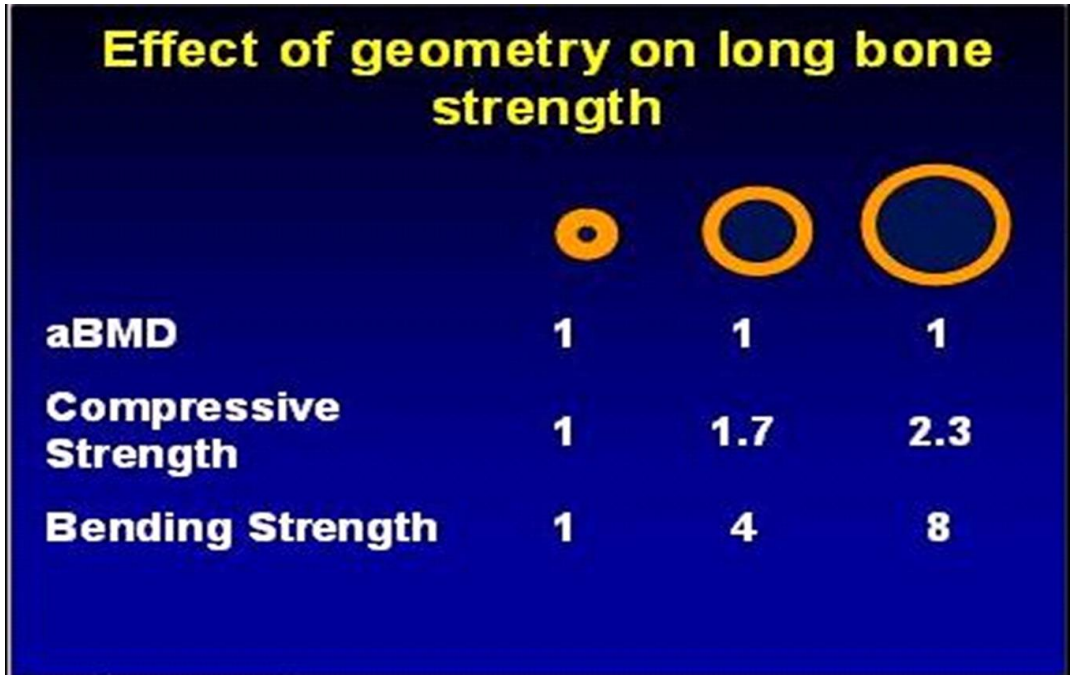
DXA 2-D Limitation for BMD as a surrogate for bone strength: BMD g/cm² cannot delineate different sizes (which influences bone strength).





2-d projected **areal** bone mineral density (BMD = g/cm ^{2})

Areal BMD is not a good measurement to monitor **restoration to** or **maintenance of preflight status**.



Adapted figure from M. Bouxsein, PhD
Presentation, Bone Quality May 2-3, 2005; Bethesda, MD

Literature: Exercise changes geometry/size of whole bone (adult skeleton)- Suggests DXA not good for monitoring exercise as countermeasure. (2011)

1. Haapasalo H, Sievanan H, Kannus P, Heinonen A, Oja P, Vuori I. 1996 **Dimensions and estimated mechanical characteristics of the humerus after long-term tennis loading**. J Bone Miner Res. 11:864-872.
2. Adami S, Gatto D, Braga V, Bianchini D, Rossini M. 1999 **Site-specific effects of strength training on bone structure and geometry of ultradistal radius in postmenopausal women.** J Bone Miner Res. 14(1):120-124.
3. Haapasalo H, Kontulainen S, Sievanen H, Kannus P, Jarvinen M, Vuori I. 2000 **Exercise-induced bone gain is due to enlargement in bone size without a change in volumetric bone density: a peripheral quantitative computed tomography study of the upper arms of male tennis players**. Bone 17(3):351-357.
4. Vainionpaa A, Korpelainan R, Sievanen H, Vihriaia E, Leppaluoto J, Jamasa T. 2007 **Effect of impact exercise and its intensity on bone geometry at weight-bearing tibia and femur**. Bone 40(3):604-611.
5. Hind K, Gannon L, Whatley, Cooke C, Truscott J. 2011 **Bone cross-sectional geometry in male runners, gymnasts, swimmers and non-athletic controls: a hip-structural analysis study**. Eur J Appl Physiol . e pub May 24

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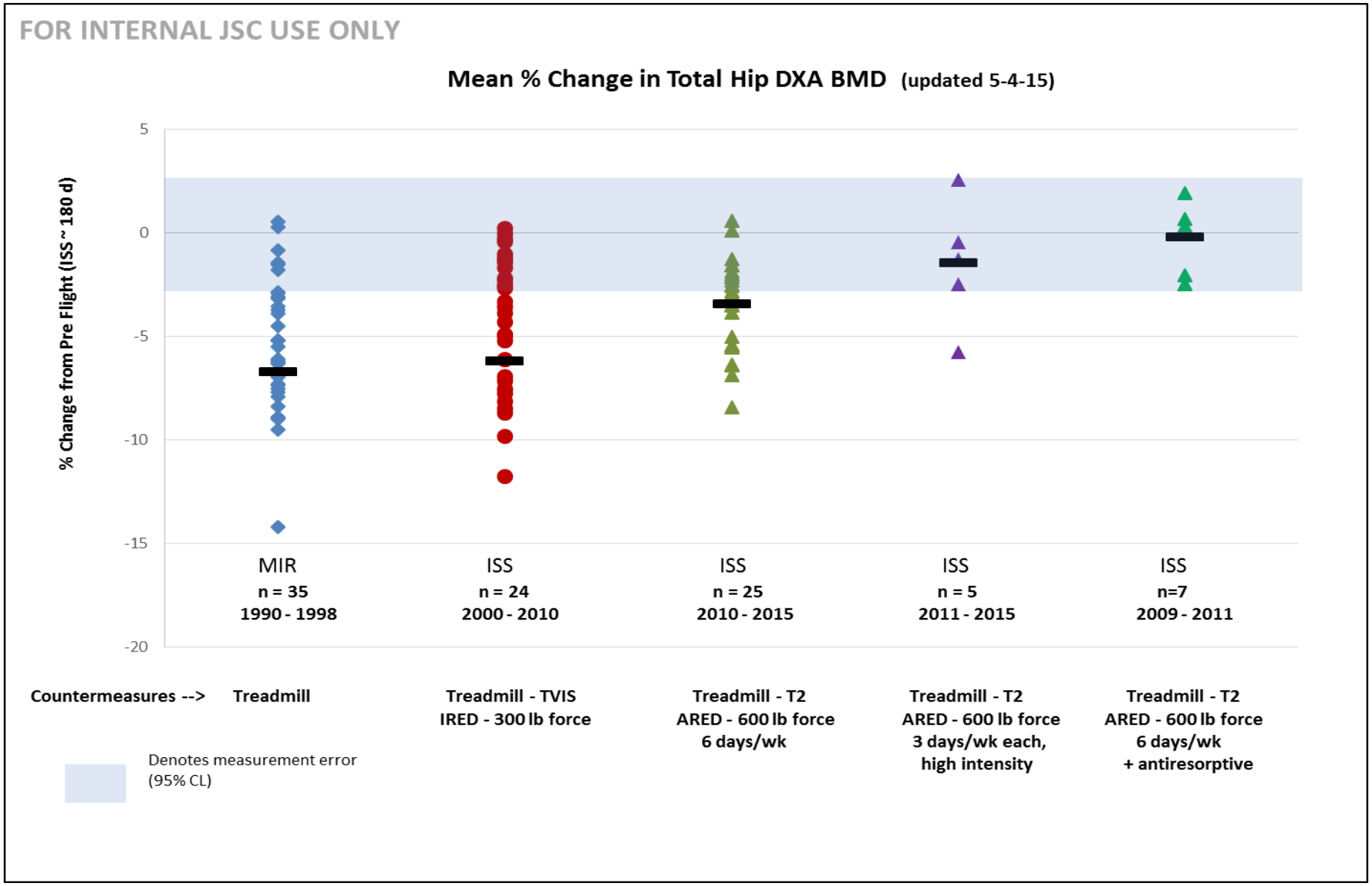
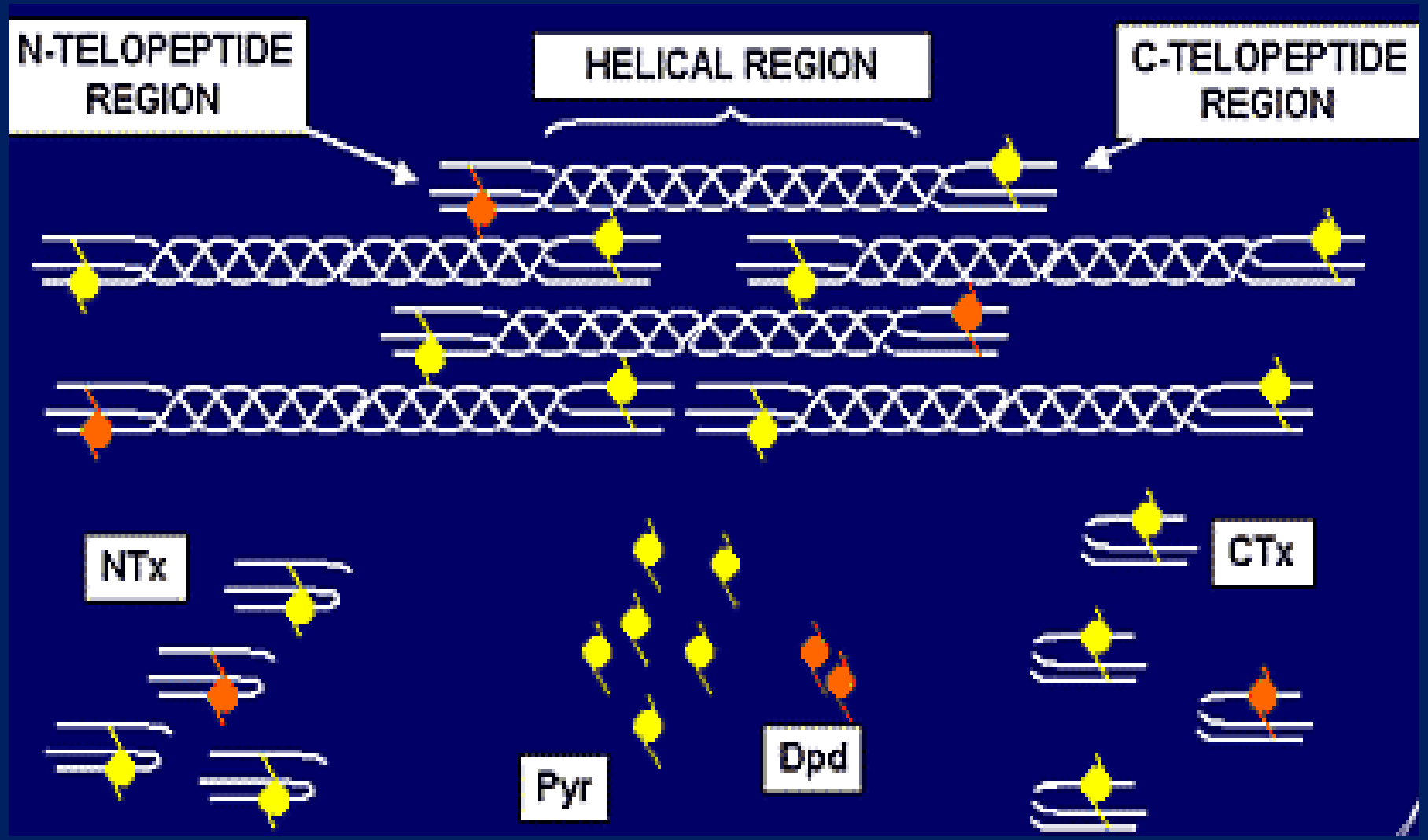
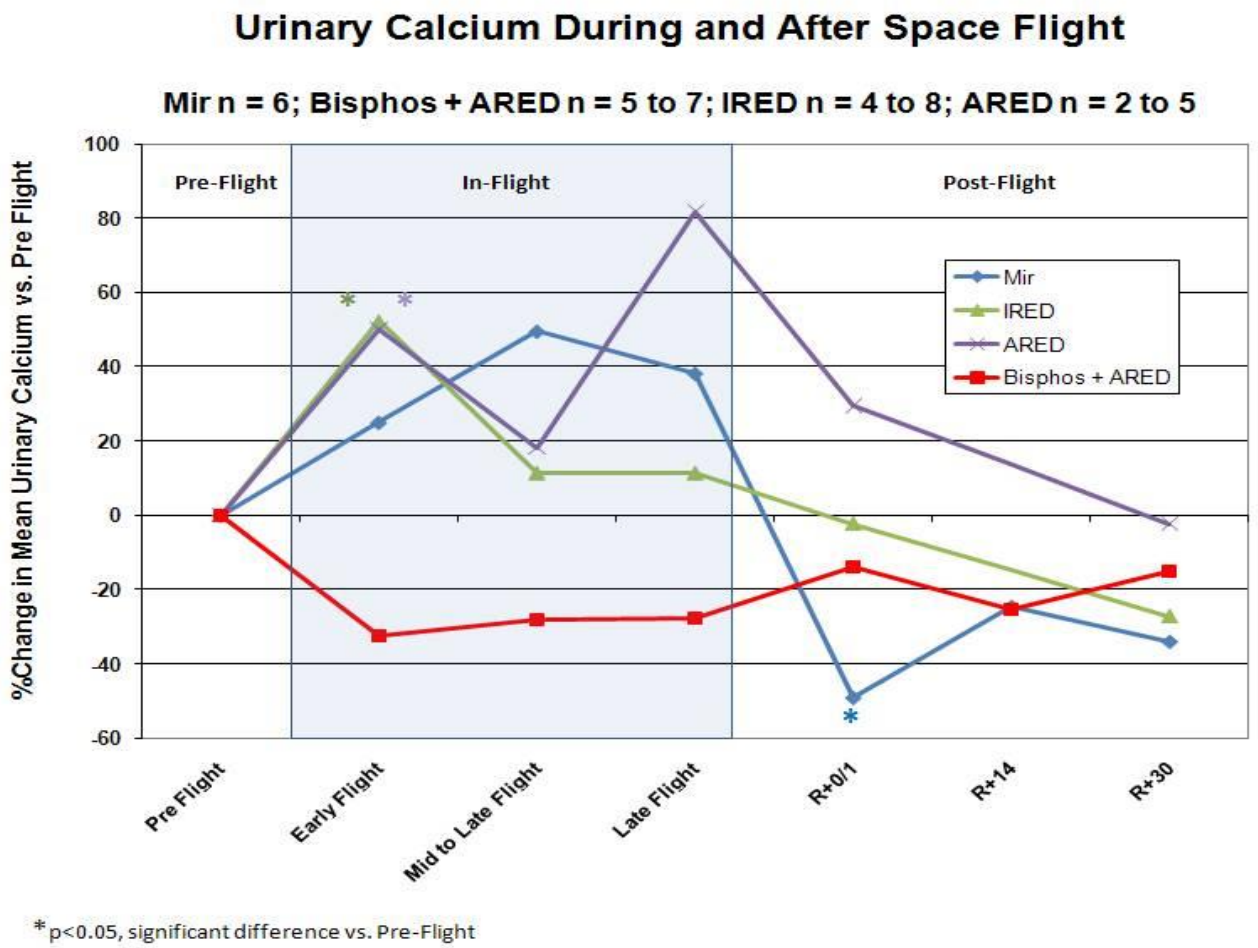
Bottom Line: Difficult to interpret % change in a DXA BMD over mission because cannot delineate bone gains or losses in different bone types.



Additionally, assays for biochemical markers in serum and urine suggest trends in cellular activities

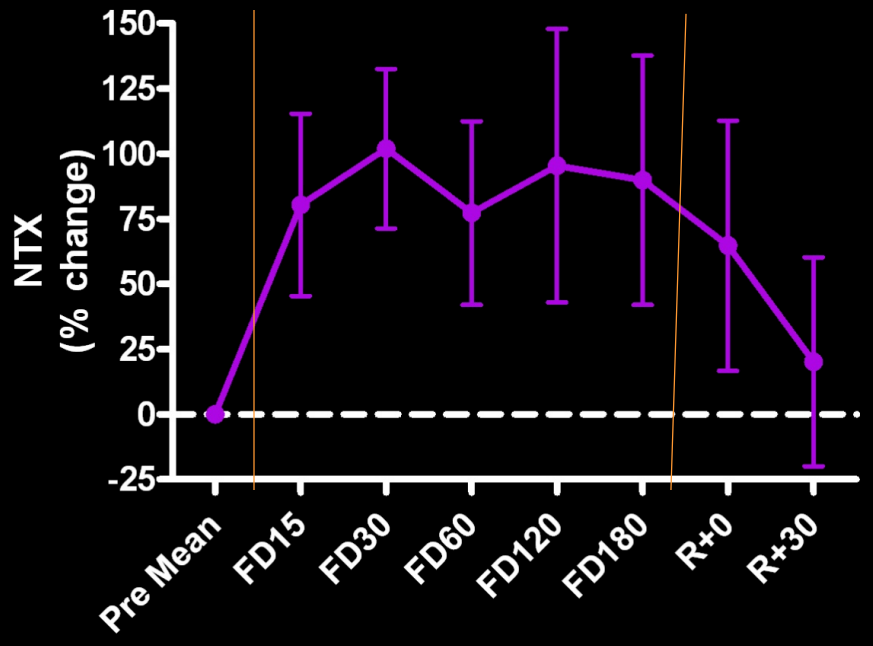


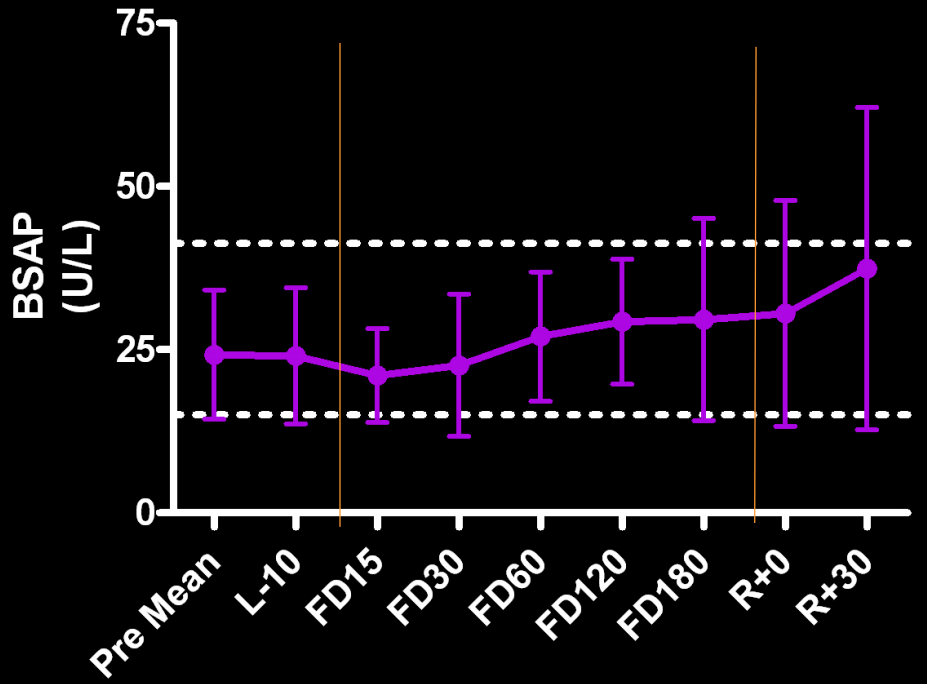
Urinary calcium excretion (trend **same** as bone resorption markers) help elucidate how countermeasures affect bone cell activities Suggests that Exercise does not suppress breakdown



* **Significantly different from pre-flight, p < 0.05**

Bone Turnover Markers: suggest uncoupling of remodeling -- may result in net loss in bone mass *from skeleton.*





Slide Courtesy of Dr. SM Smith; Adapted by Sibonga

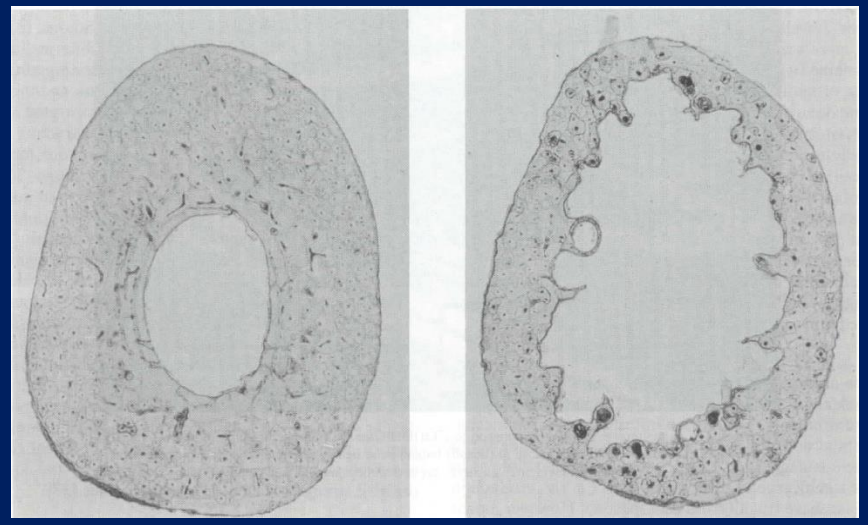
Subsequent Pilot Study: Hip QCT to monitor response to countermeasure.

1. Utility: QCT will distinguish the effects of biochemical from mechanical countermeasures.

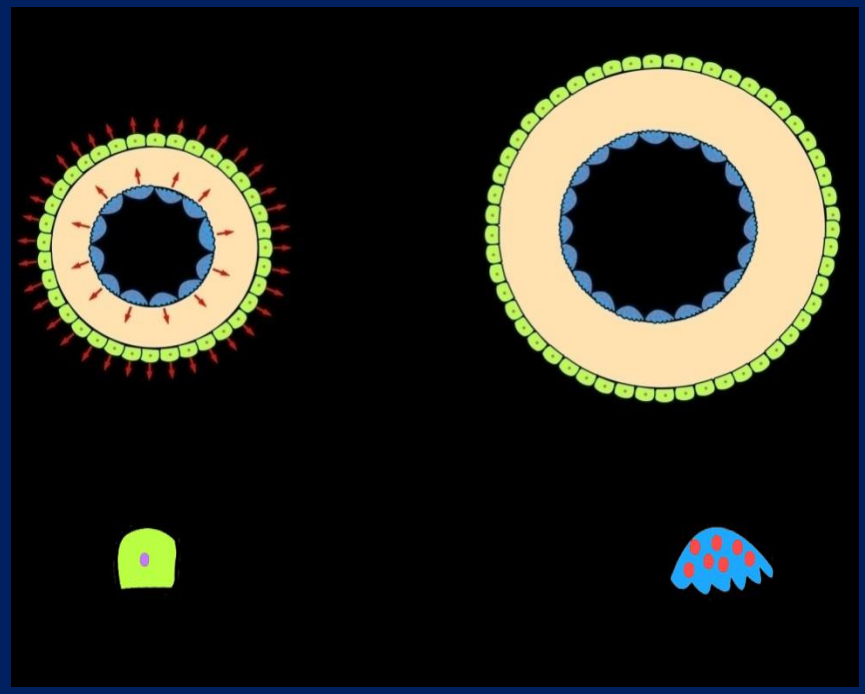
2. *Important to use QCT to evaluate Countermeasures that affect different bone types (anti-resorptives vs. anabolic drugs).*

3. Utility: QCT data to estimate *hip strength* to answer "so what?" question.

From J.W.Jaworski
Images Courtesy of D Carter, PhD



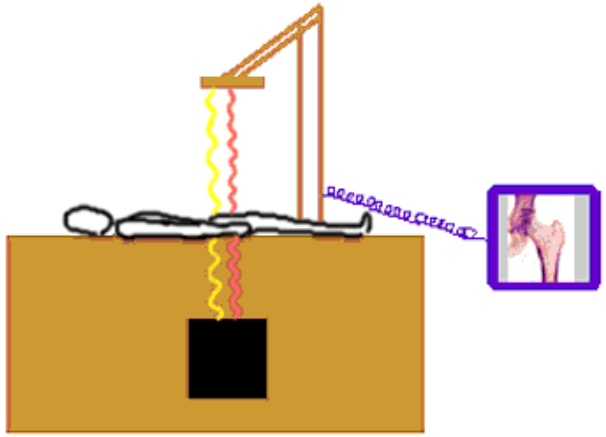
Endocortical bone resorption with disuse



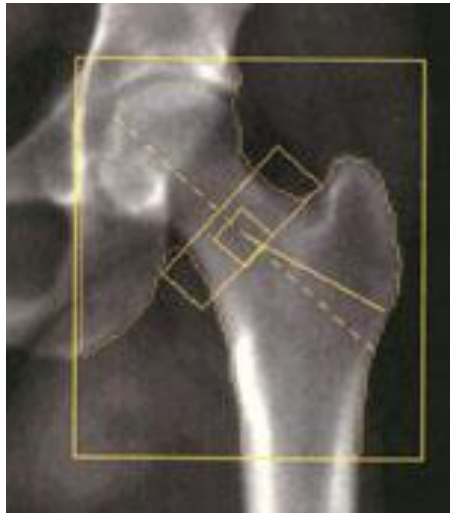
Fractures

Bone Research Plan

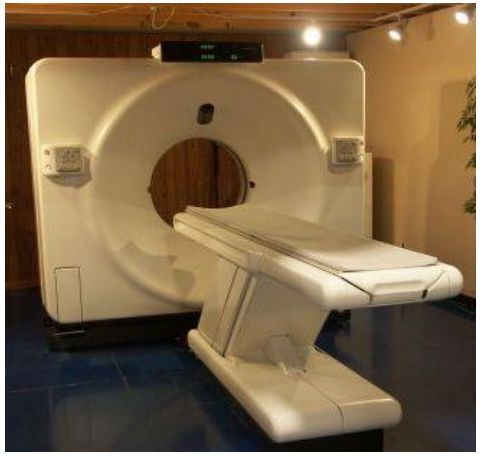
Densitometry for Bone Macroarchitecture



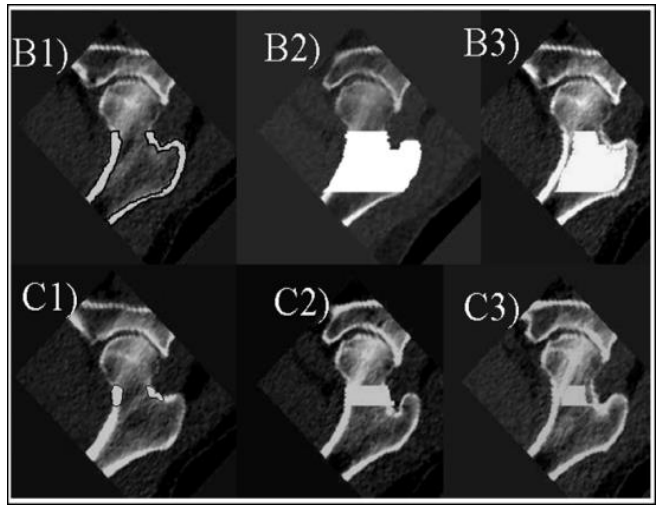
DXA reports areal BMD (aBMD)



g/cm² averaged for cortical + trabecular bone

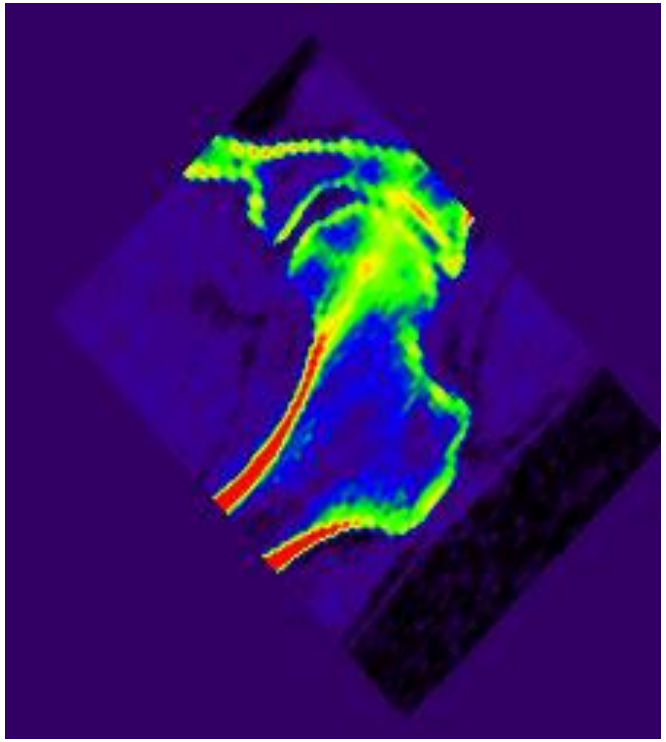


QCT quantifies volumetric BMD



g/cm³ for separate cortical & trabecular bones

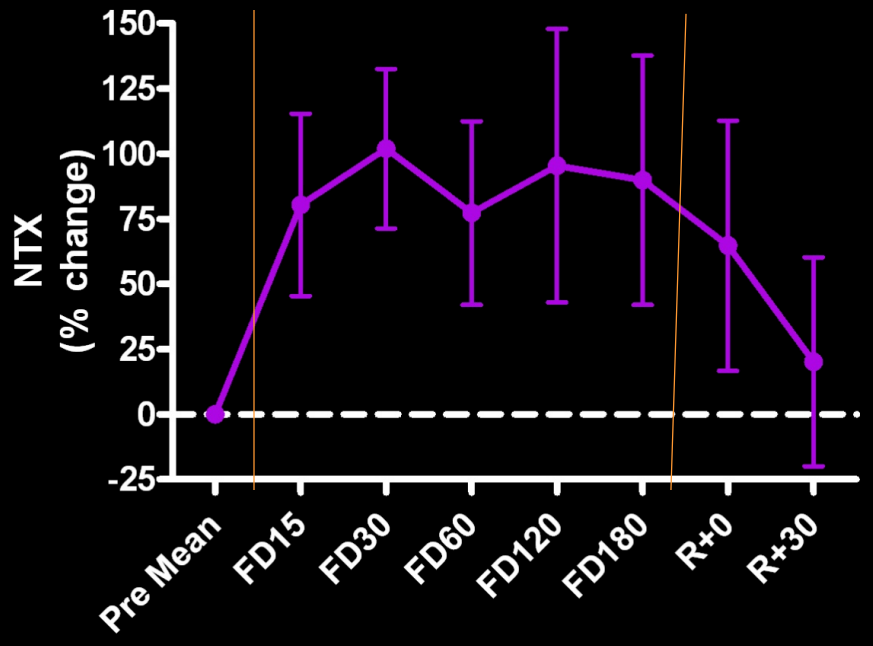
Flight Research: QCT detects different rate of vBMD loss in separate bone compartments of hip. (n=16 ISS volunteers)

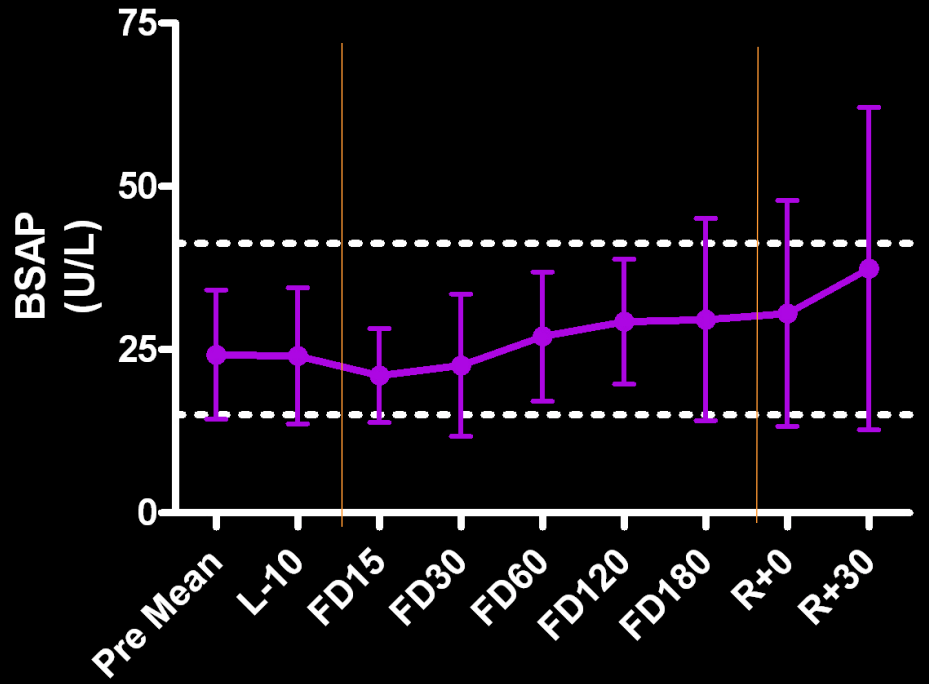


Index DXA	%/Month Change ± SD	Index QCT	%/Month Change ± SD
aBMD Lumbar Spine	1.06±0.63*	Integral vBMD Lumbar Spine	0.9±0.5
		Trabecular vBMD Lumbar Spine	0.7±0.6
aBMD Femoral Neck	1.15±0.84*	Integral vBMD Femoral Neck	1.2±0.7
		Trabecular vBMD Femoral Neck	2.7±1.9
aBMD Trochanter	1.56±0.99*	Integral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

LeBlanc, J Musculoskelet Neuronal Interact. 2000 ;
Lang , J Bone Miner Res, 2004;

Bone Turnover Markers: suggest uncoupling of remodeling -- may result in net loss in bone mass *from skeleton.*



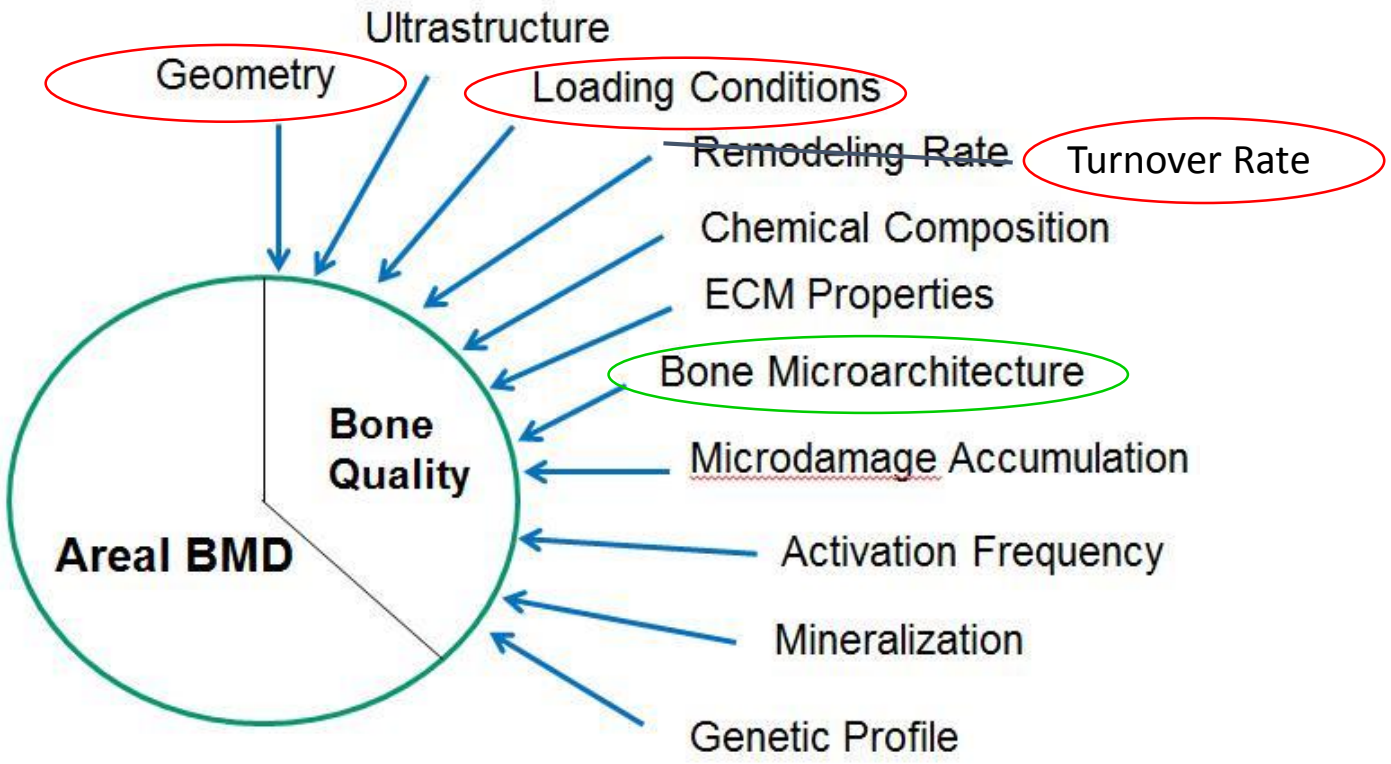


Slide Courtesy of Dr. SM Smith; Adapted by Sibonga

Bone Strength (a contributor to fracture risk) is affected by factors not detected by DXA BMD.

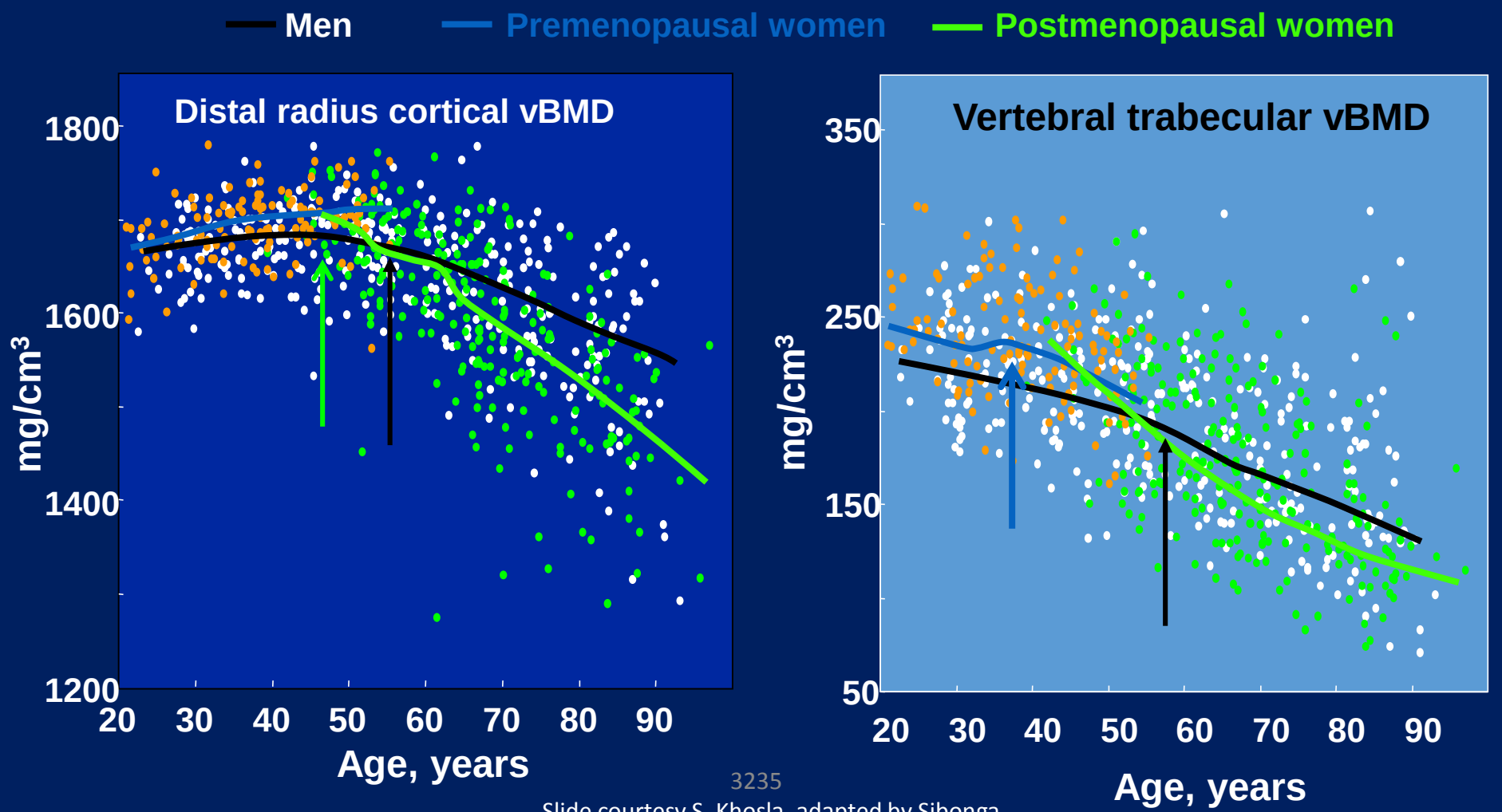
*Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Bone strength reflects the integration of two main features: bone density and bone quality." JAMA 285(6):785-95, 2001

"**Bone Quality: What is it and Can we measure it?**" Bethesda, MD, May 2005
"The other 30-50%"



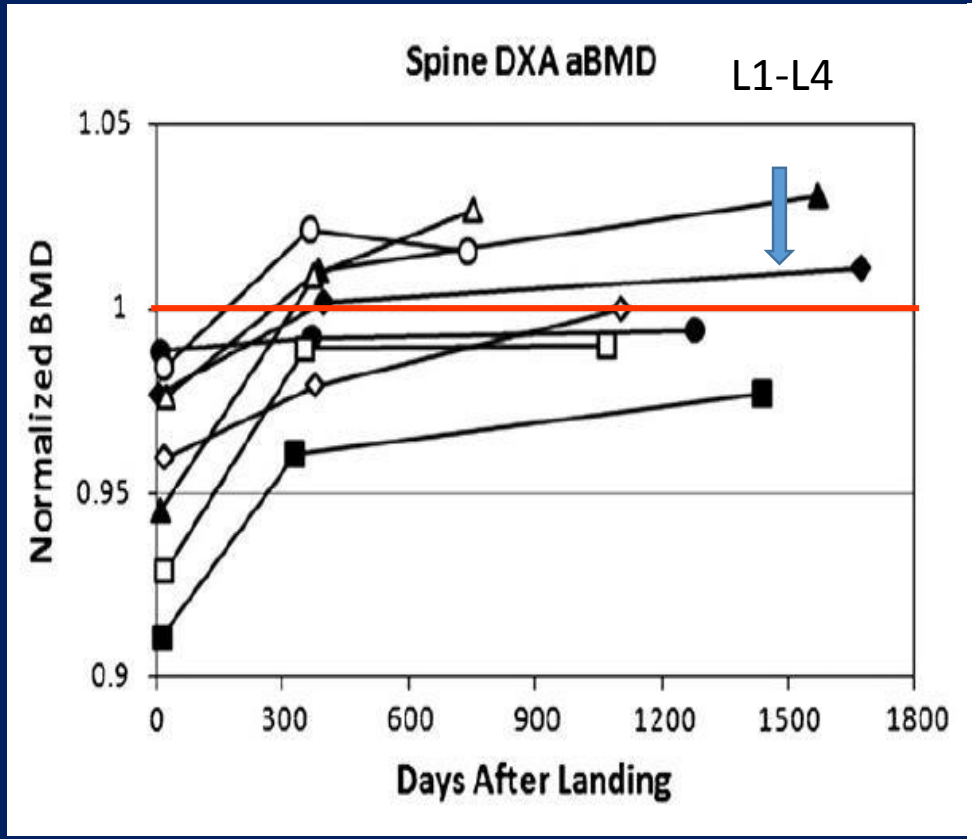
QCT in aging populations increases knowledge of macroarchitectural changes: Bone loss occurs at earlier age than expected. (Rec. from Bone Lead)

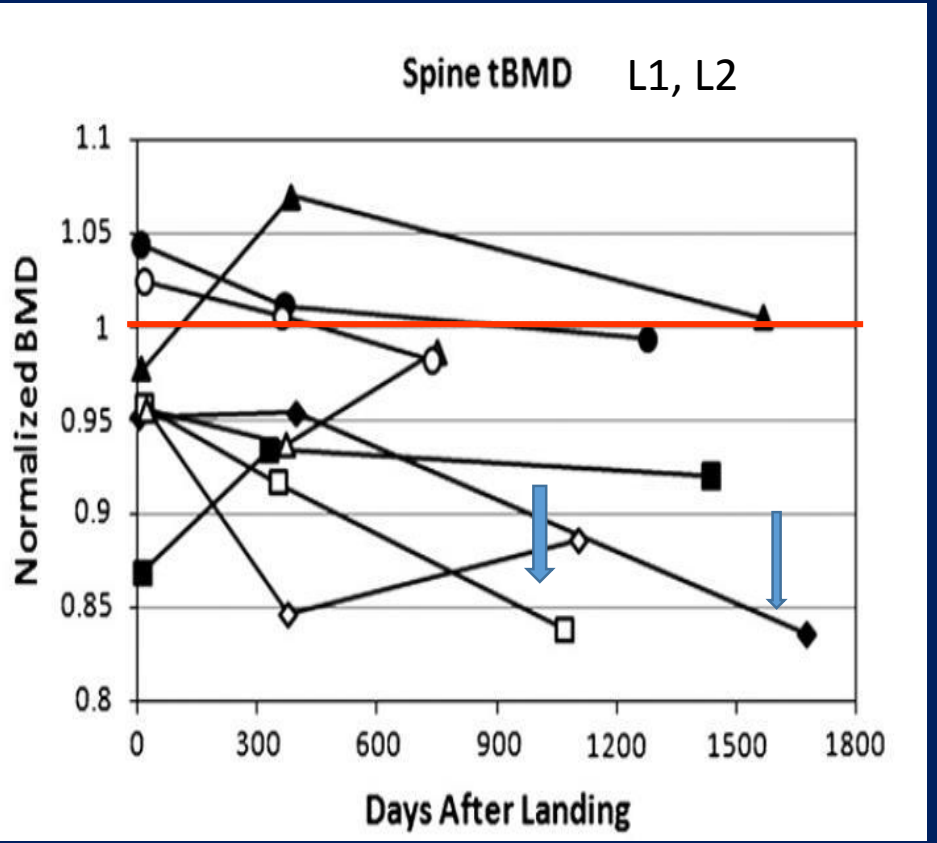
Riggs et al. JBMR19:1945, 2004.



Slide courtesy S. Khosla, adapted by Sibonga

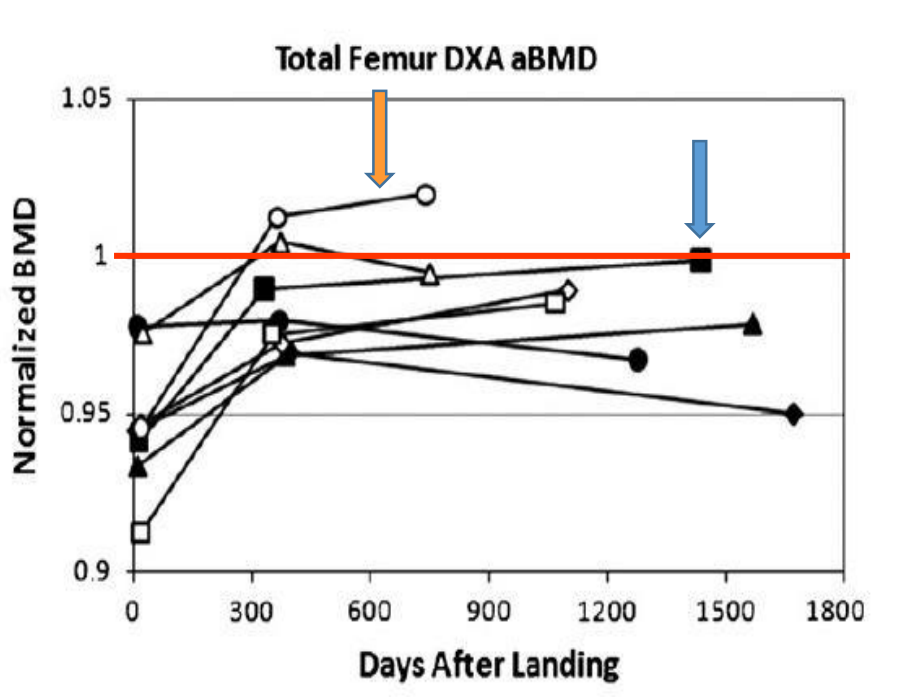
*Macro*architecture of Spine in 8 ISS astronauts of Extension Study : Discordant Recovery Patterns After Spaceflight

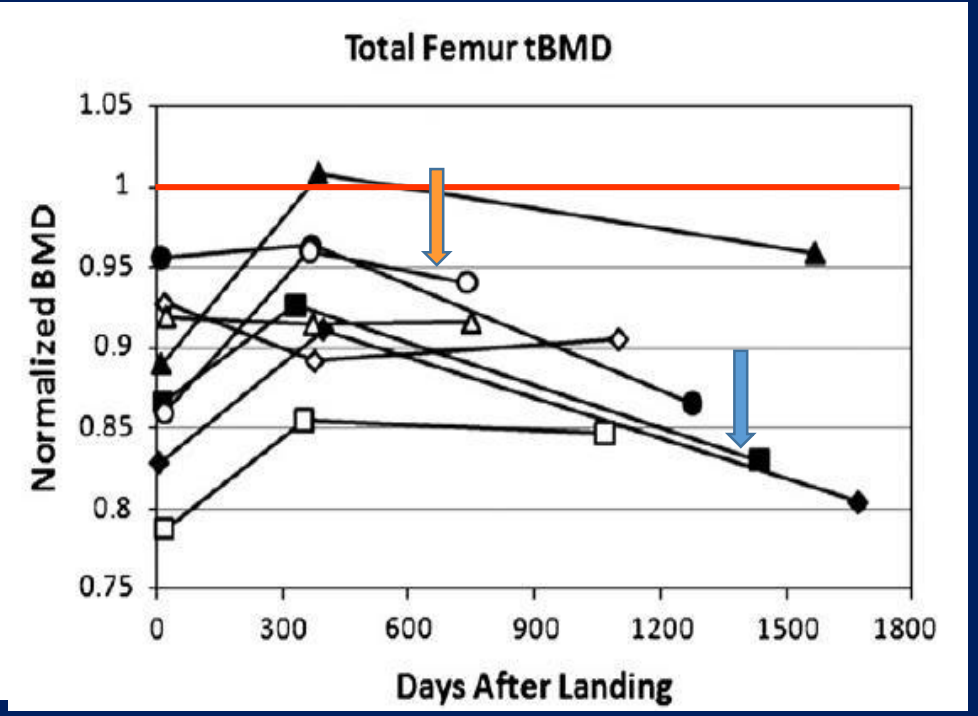




QCT Extension Study (n=8) Postflight Trabecular BMD in hip. Carpenter, D et al. Acta Astronautica, 2010.
Adapted by Sibonga

DXA vs. QCT Proximal Femur of Extension Study:
Clinical Advisory Panel identifies a clinical trigger for long-duration astronauts.
"Failure to recover in trabecular BMD by R + 2 years" *





*SD response – seek osteoporosis specialist for evaluation and possible intervention.

QCT Extension Study (n=8) Postflight Trabecular BMD in hip. Carpenter, D et al. Acta Astronautica, 2010.
Adapted by Sibonga. * Orwoll JBMR, 2013

QCT measures are independent predictors of hip fracture in addition to aBMD. Persistent deficits may combine with age-related changes.

Clinical advisory panel recommends clinical trigger for possible intervention (monitor for recovery by two years after return).

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 23, Number 8, 2008
Published online on March 17, 2008; doi: 10.1359/JBMR.080316

Proximal Femoral Structure and the Prediction of Hip Fracture in Men: A Large Prospective Study Using QCT*

Dennis M Black,[1] Mary L Bouxsein,[2] Lynn M Marshall,[3] Steven R Cummings,[4] Thomas F Lang,[5] Jane A Cauley,[6] Kristine E Ensrud,[7] Carrie M Nielson[3] and Eric S Orwoll[3] for the Osteoporotic Fractures in Men (MrOS) Research Group

Journal of Bone and Mineral Research
Volume 26, Issue 4, Article first published online: 23 MAR 2011
Abstract | Full Article (HTML) | References | Supporting Information
Cited By

NASA Johnson Space Center

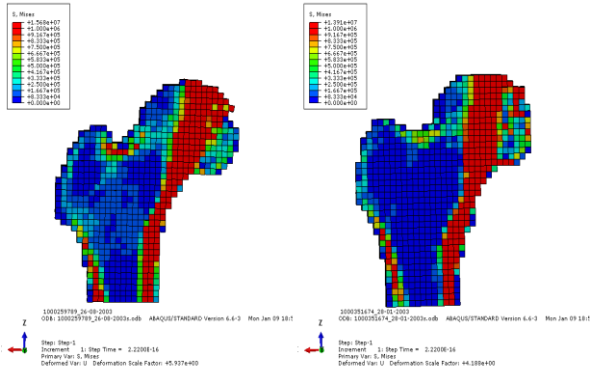
In Vivo Discrimination of Hip Fracture With Quantitative Computed Tomography: Results From the Prospective European Femur Fracture Study (EFFECT)

Valérie Danielle Bousson,[1,2] Judith Adams,[3] Klaus Engelke,[4] Mounir Aout,[5] Martine Cohen-Solal,[6] Catherine Bergot,[2] Didier Haguenauer,[7] Daniele Goldberg,[8] Karine Champion,[9] Redha Aksouh,[1] Eric Vicaut,[5] and Jean-Denis Laredo[1,2]

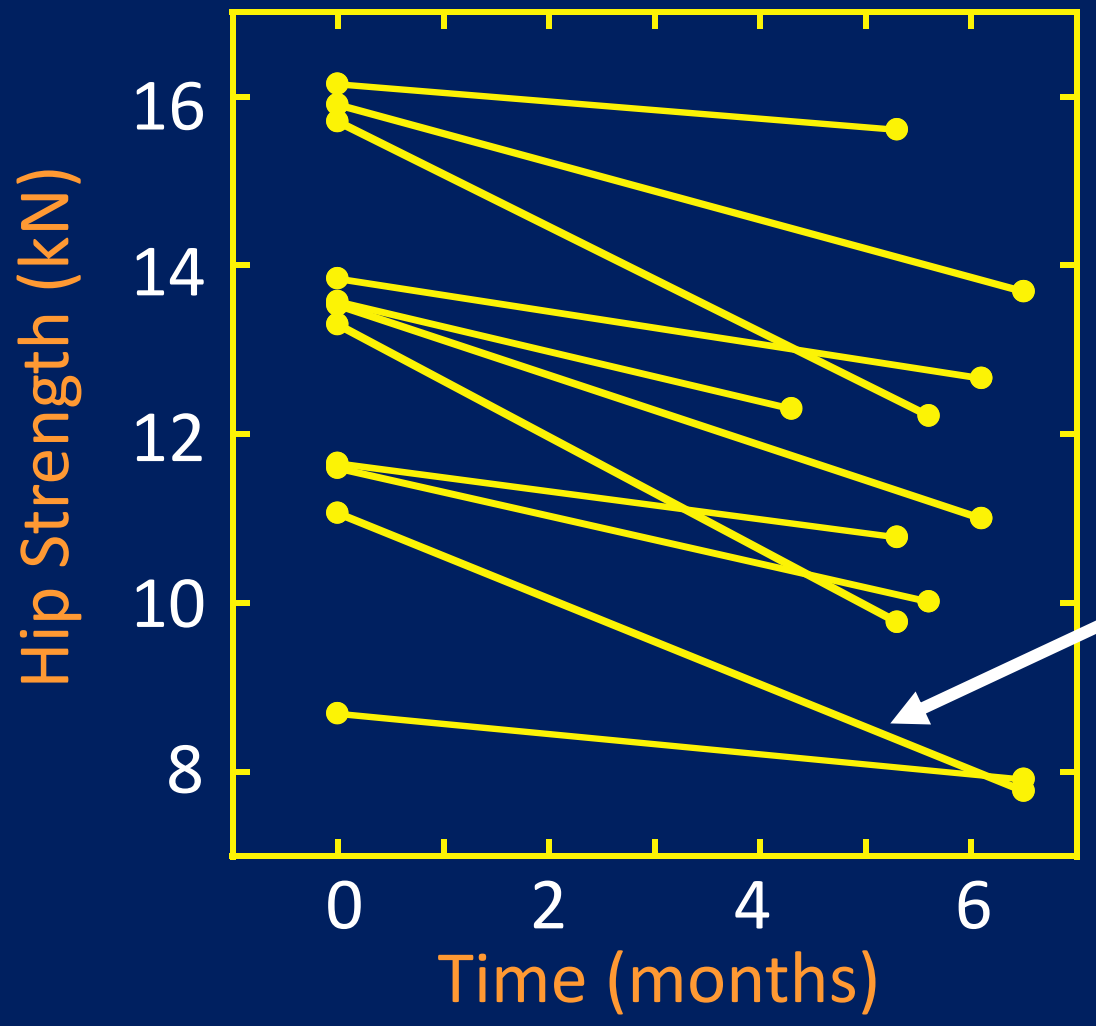
How can we assess fracture risk in astronauts from QCT data?

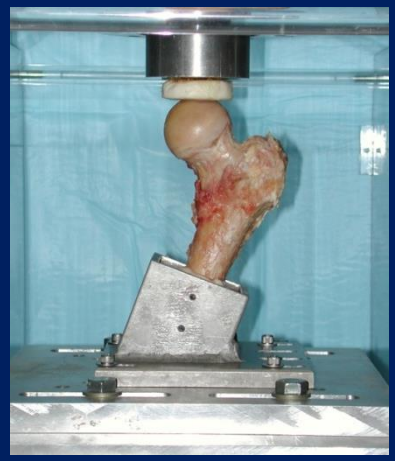
Clinical advisory panel: Explore the emerging data from population studies to propose how Finite Element Models of QCT data could be used to reflect fracture risk due to spaceflight. (Report back to the clinical advisory panel).

- **Male-female differences in prediction of hip fracture during finite element analysis.** Keyak JH, Sigurdsson S, Karlsdottir G, Oskarsdottir D, Sigmarsdottir A, Zhao S, Kornak J, Harris TB, Sigurdsson G, Jonsson BY, Siggeirsdottir K, Eiriksdottir G, Gudnason V, Lang TR. Bone. 2011;48(6):1239-1245.
- **Association of hip strength estimates by finite –element analysis with fractures in women and men**. Amin S,, Kopperdahl DL, Melton LJ 3rd, Achenbach SJ, Therneau TM, Riggs BL, Keaveny TM, Khosla S. J Bone Miner Res. 2011;26(7):1593-1600.
- **Age-dependence of femoral strength in white women and men**. Keaveny TM, Kopperdahl DL, Melton III LJ, Hoffmann PF, Amin S, Riggs BL, Khosla S. J Bone Miner Res. 2010;25(5):994-1001.
- **Osteoporotic Fractures in Med Study Group. Finite element analysis of the proximal femur and hip fracture risk in older men**. Orwoll ES, Marshall LM, Nielson CM, Cummings SR, Lapidus J, Cauley JA, Ensrud K, Lane N, Hoffmann PR, Kopperdahl DL, Keaveny TM J Bone Miner Res. 2009;24(3):475–483.
- More from the ISCD 2015 position development (22 total for QCT and FEM).



Individual Astronaut Results
Stance Loading (4 to 30% loss in strength)

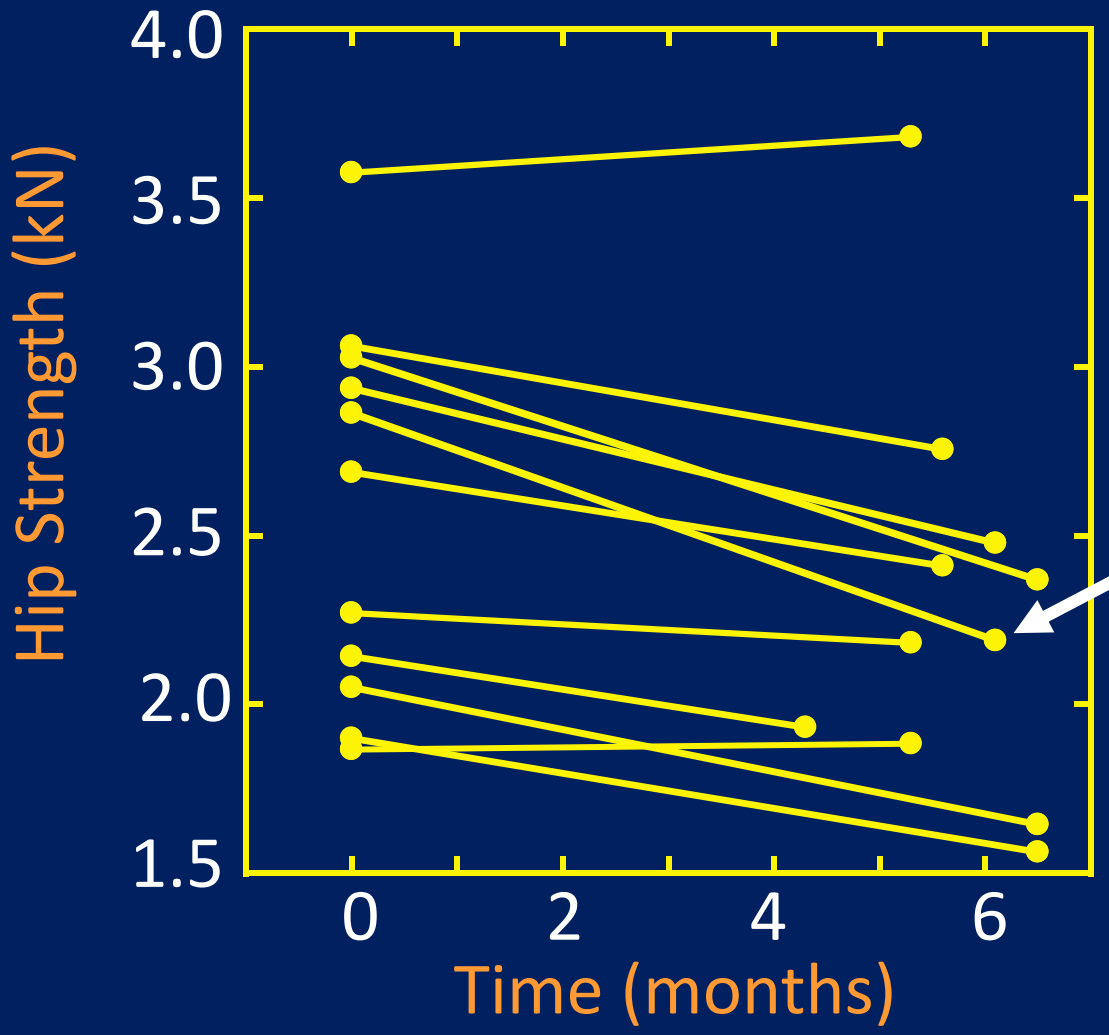


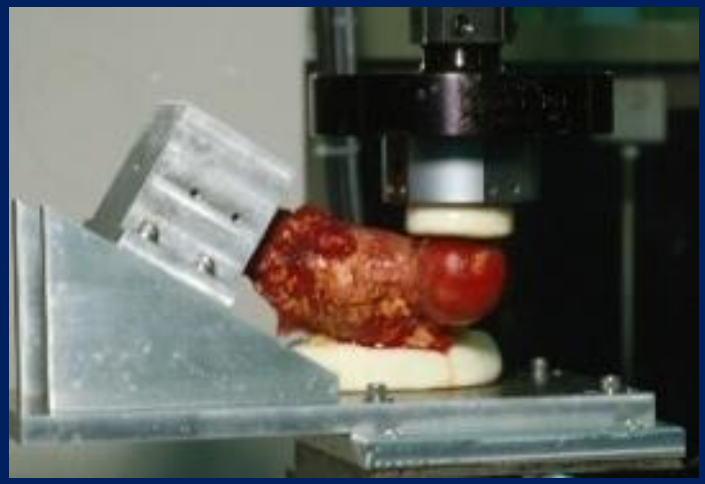


Max loss
30%

Keyak, et al. Bone 2009

Individual Astronaut Results
Fall Loading (3 gain to 24% loss in strength)



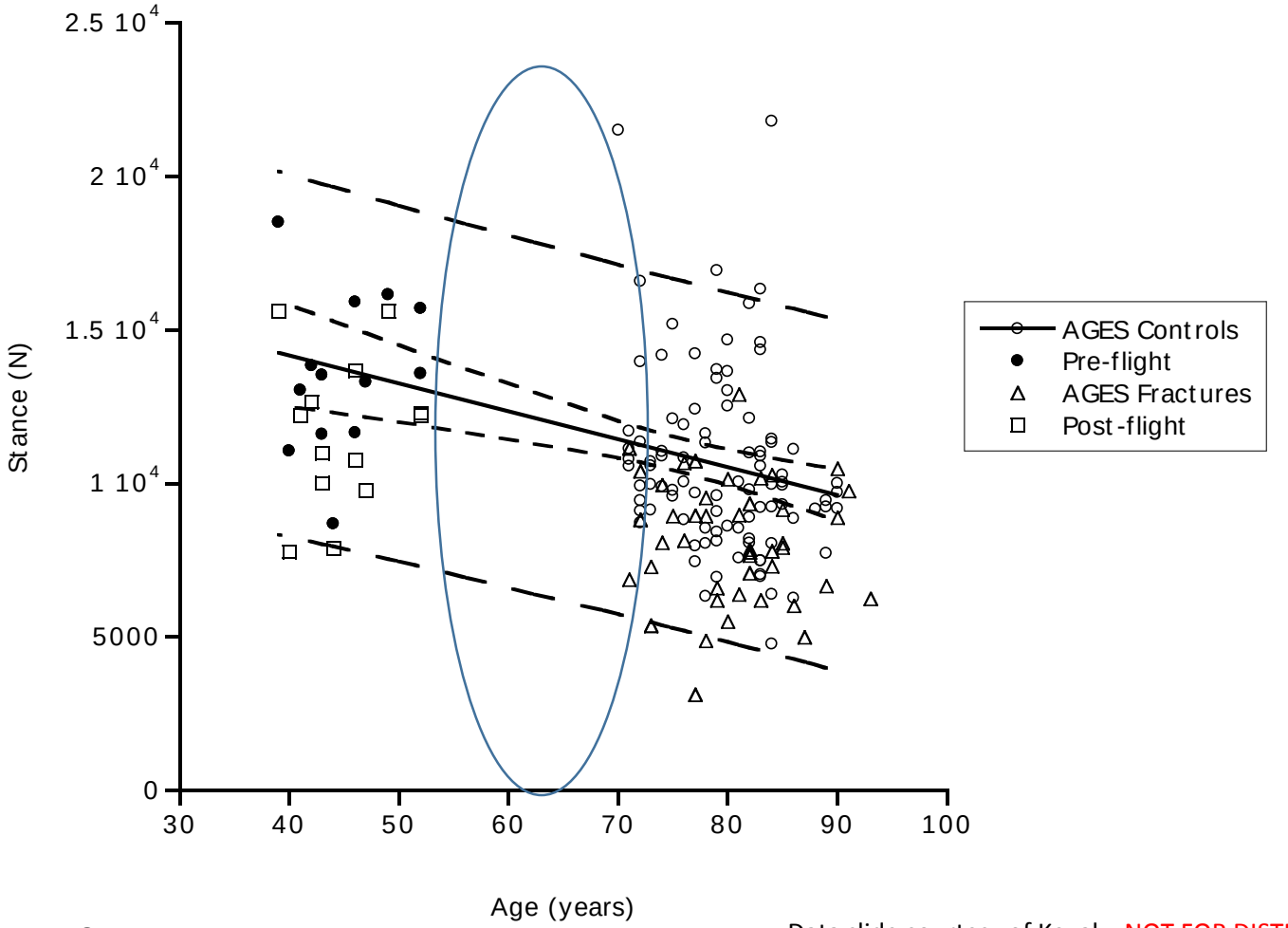


Max loss
24%

Keyak, et al. Bone 2009

The FEM knowledge, gained from population studies – how can it be used to support the monitoring of astronaut bone health?

E. Orwoll MD, S Khosla MD, S Amin MD, T Lang PhD, J Keyak PhD, T Keaveny PhD, D Cody PhD,
JD Sibonga, Ph.D.



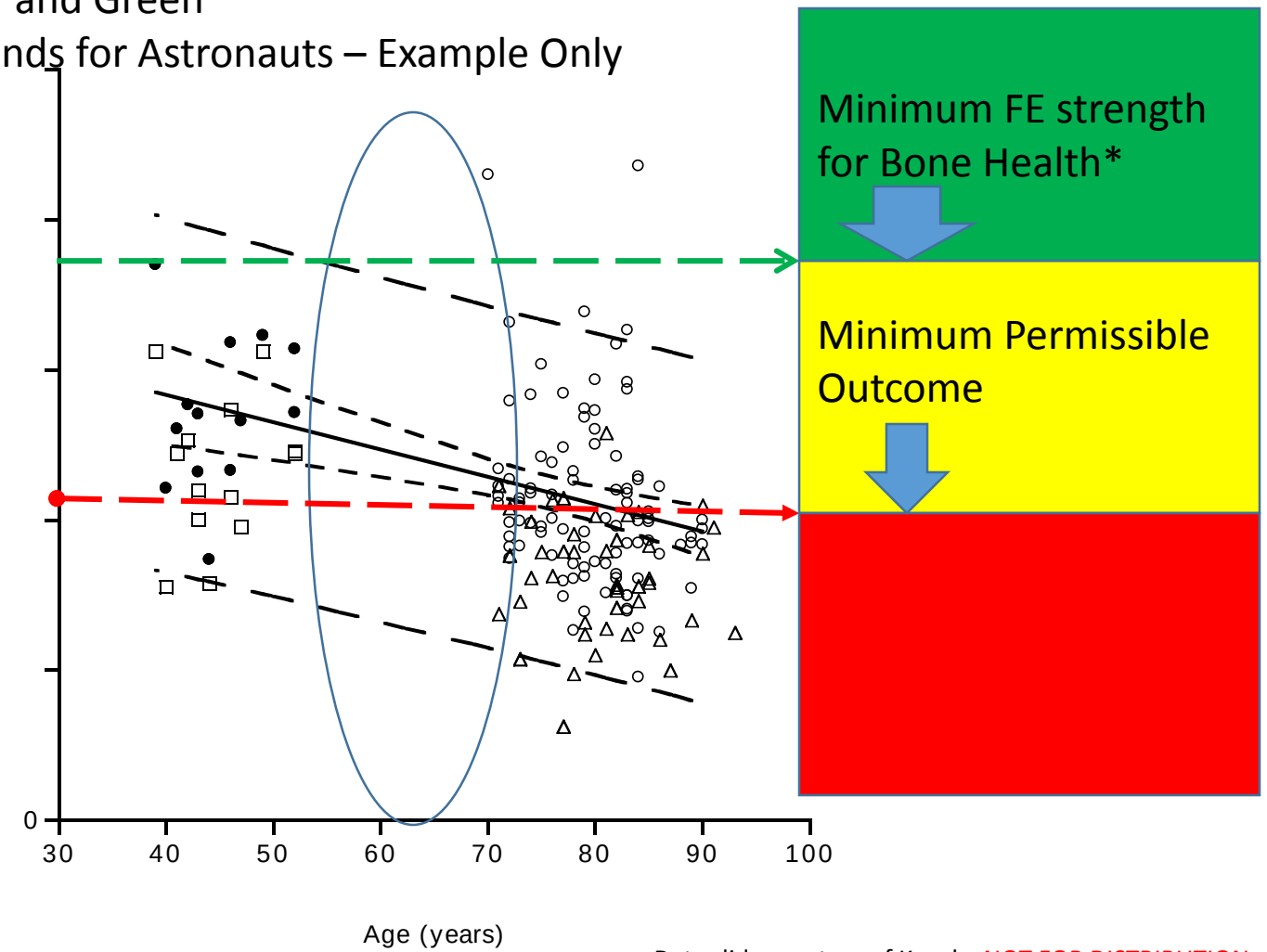
REPRESENTATIVE POPULATION DATA

Data slide courtesy of Keyak. NOT FOR DISTRIBUTION

RESEARCH MTL807: Recommendation of FE Operating Bands of "Bone Health"- by FE Task Group II - to be used together with DXA BMD Standards to inform clinical/operational decision-making.

E. Orwoll MD, ~~S Khosla MD~~, A Cheung, MD, S Amin MD, T Lang PhD, J Keyak PhD, D Nicolella PhD ~~T Keaveny PhD~~, D Cody PhD, and J Sibonga, PhD

*Red, Yellow and Green
Operating Bands for Astronauts – Example Only

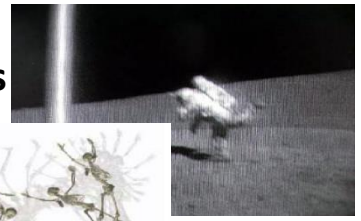


REPRESENTATIVE POPULATION DATA

Data slide courtesy of Keyak. NOT FOR DISTRIBUTION

Additional Goal is to integrate QCT and FEM hip strength* to assess probability of Bone Fracture -- NASA Glenn Research Center's Probabilistic Risk Assessment [PRA] Model for Fracture Likelihood

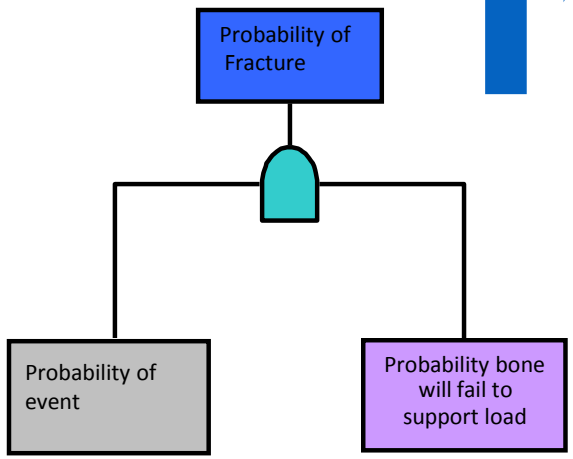
Biomechanics and Mission Operations



courses.washington.edu/me598rc

Bone Changes in Space

Estimate of Fracture Probability



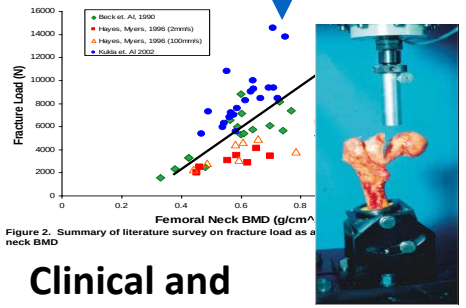


Figure 2. Summary of literature survey on fracture load as a neck BMD

Clinical and Engineering Characteristics of Bone Strength

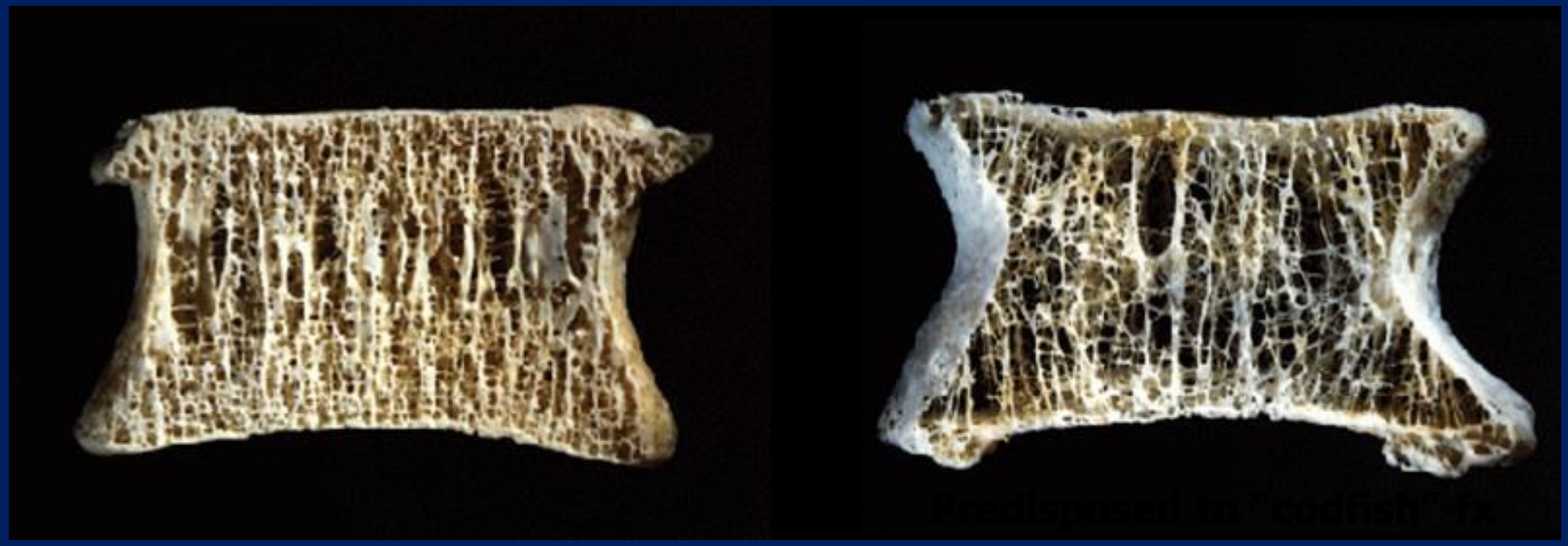
*Current PRA using DXA BMD for bone strength is insensitive to BMD changes due to ARED or Bisphosphonates. FE strength reduces uncertainty; can be used to individualize risk management.

Slide courtesy of J Myers; Adapted by Sibonga

Bone *Micro*architecture

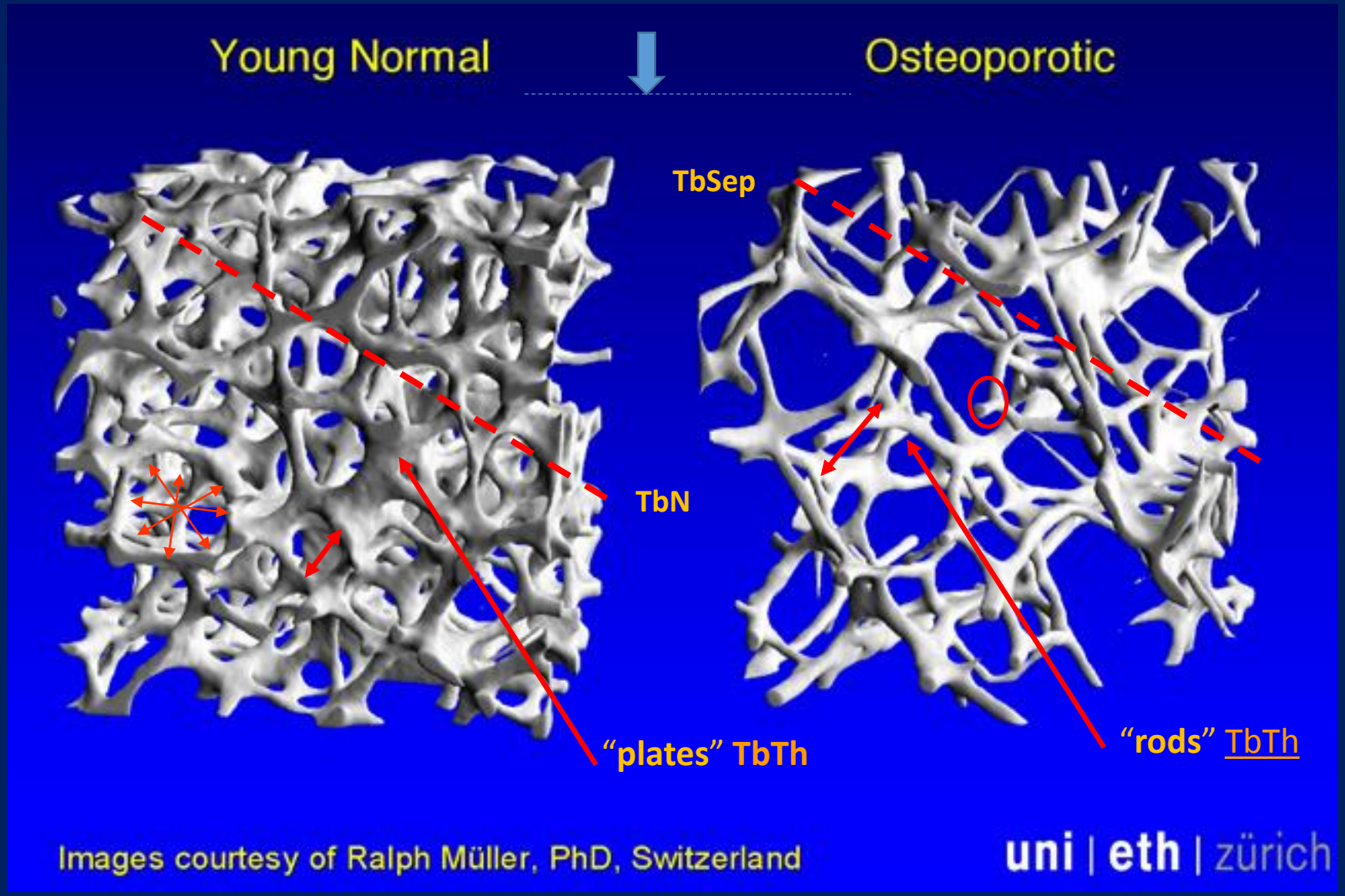
Knowledge and Technology Gap

High Resorption ➡Disrupts Microarchitecture ➡Fractures*
GAPS persist.



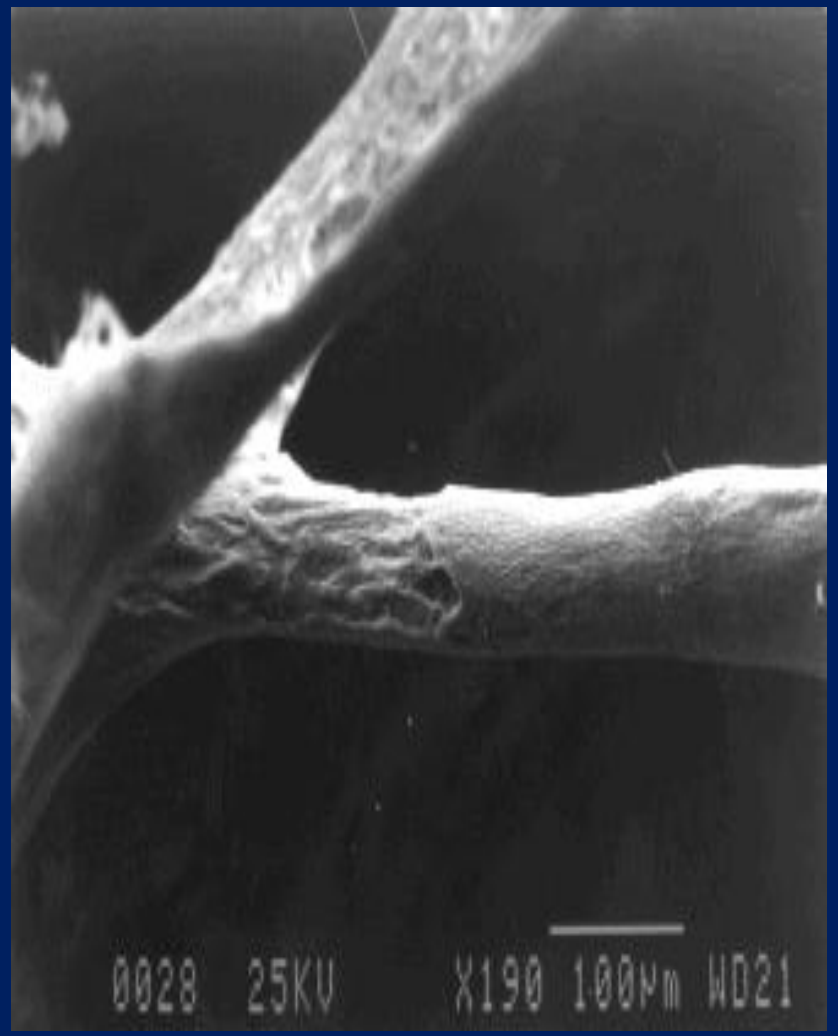
Male Astronauts?
Spaceflight Effect?
The Hip?

Indices of bone microarchitecture reflect changes in trabeculae size and spatial orientation – need to identify non-permissible outcome



Adapted by Sibonga

Monitoring microarchitectural changes: Establish when perforation may occur. Mechanism of disruption informs countermeasure (anti-resorptive or anabolic)



Electron Microscopic Images to demonstrate mechanism of disruption ONLY

Recap

It’s challenging.

Sole use of BMD data as a surrogate for fracture risk and skeletal integrity in astronauts may incur the following risks:

1. Restricting our understanding spaceflight effects on hip and spine integrity

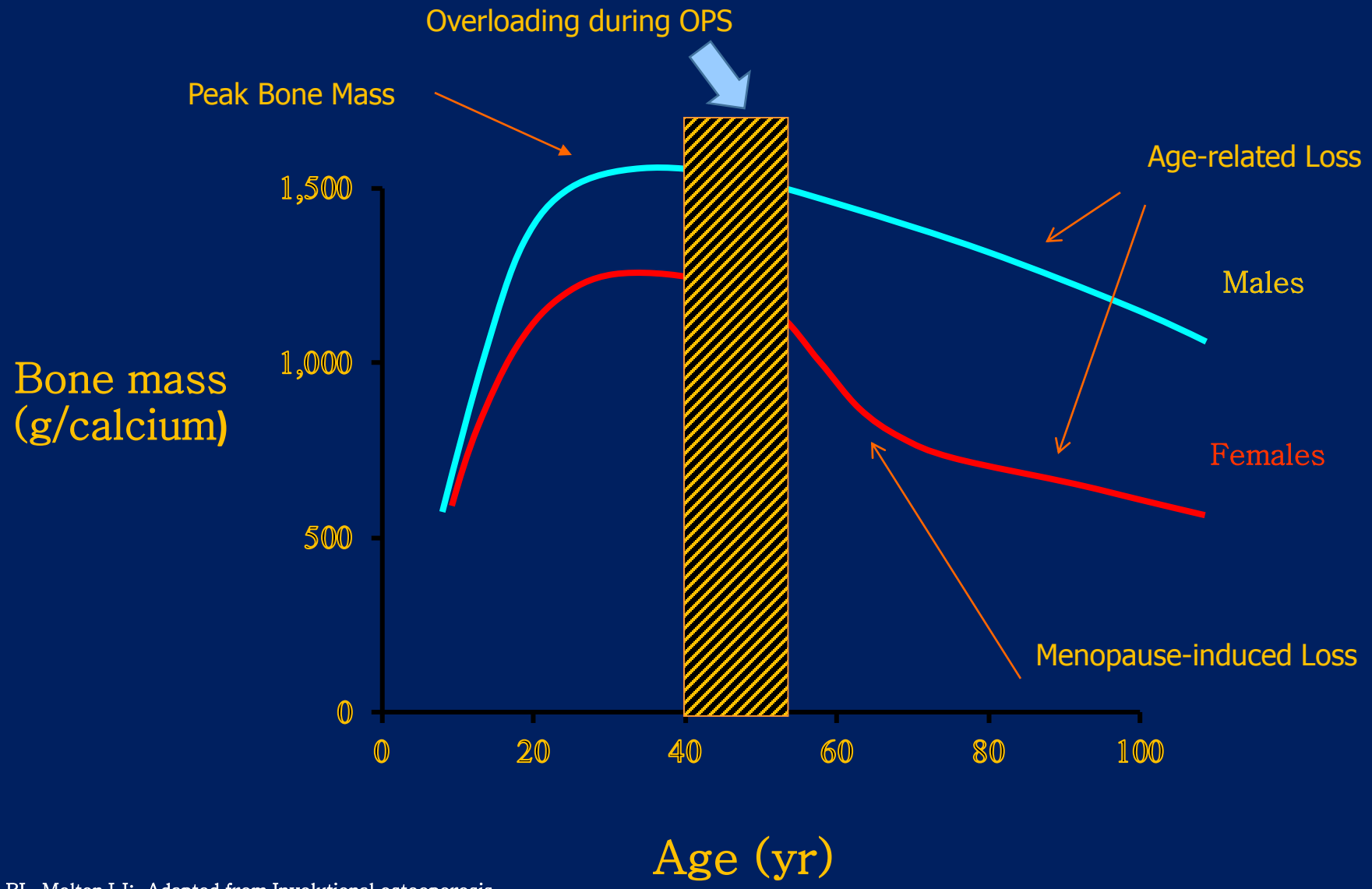
2. Inadequately evaluating efficacy of countermeasures

3. Failing to identify astronauts at greater risk (both during and after spaceflight)

4. Subsequently failing to provide greater protection against risk

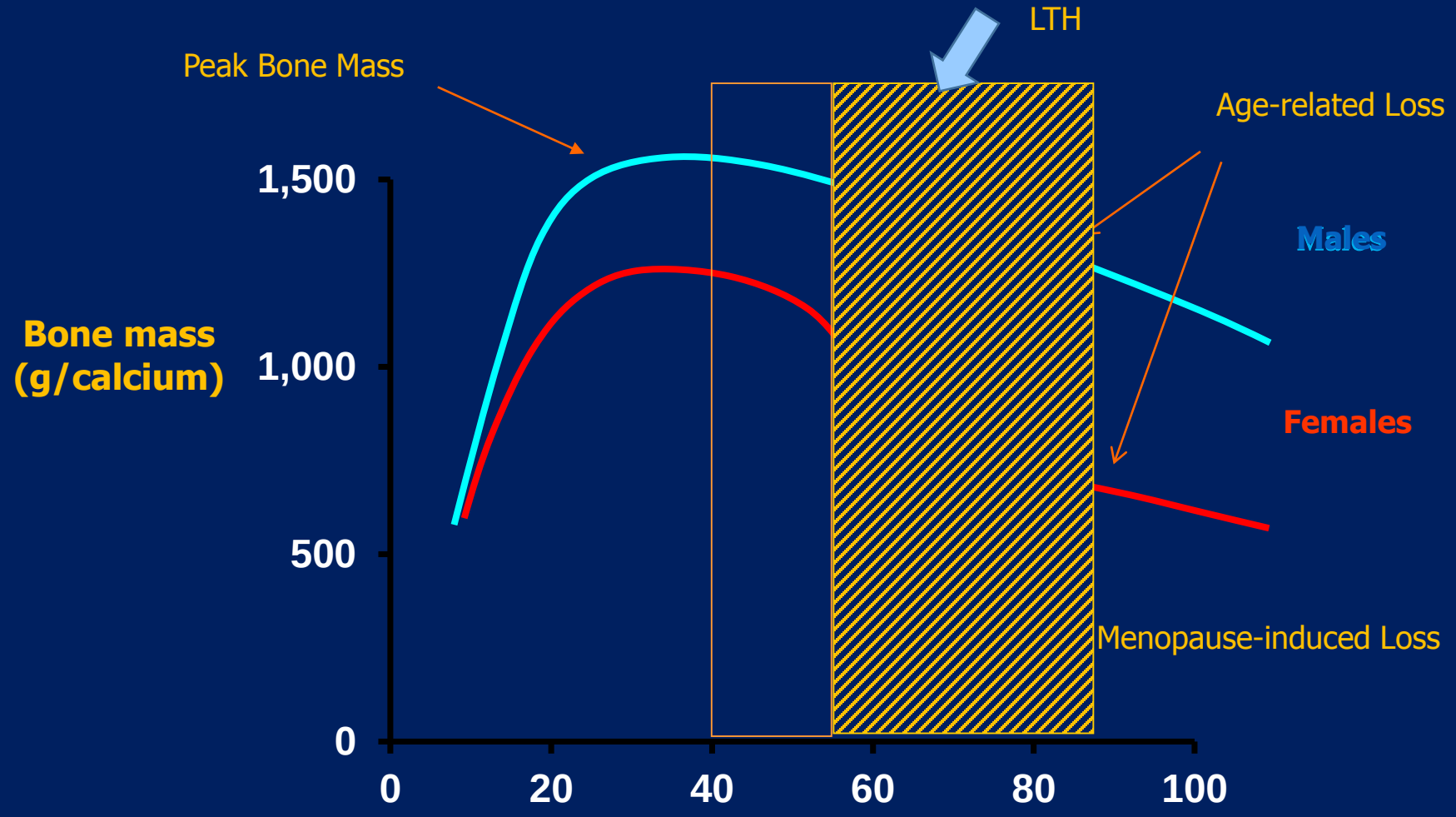
Hence, Bone Research is taking the following Path to Risk Reduction:

Fracture Risk during Mission Operations [OPS]: Collecting new bone data to estimate bone strength and inform NASA's PRA module for Applied Loads > Bone Strength



Riggs BL, Melton LJ: Adapted from Involutional osteoporosis
Oxford Textbook of Geriatric Medicine
ADAPTED SLIDE COURTESY OF Dr. S. AMIN, Mayo Clinic

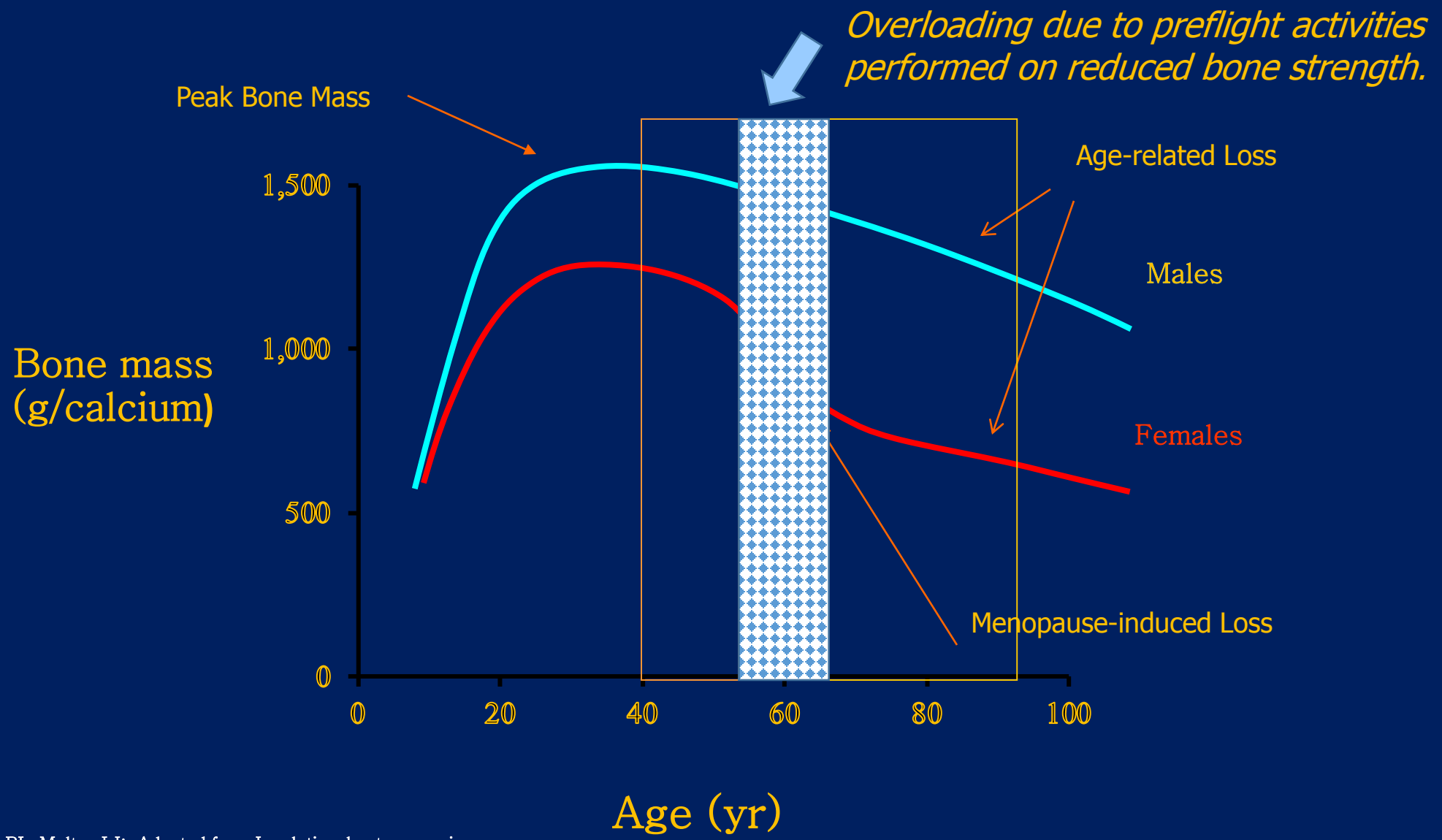
Fracture Risk during Long-term Health [LTH] : a) Monitor for persistent space-induced changes (*clinical trigger at R + 2 years)* and b) Develop new FE strength-based bands of bone health based upon predicted fractures for advanced ages.



Riggs BL, Melton LJ: Adapted from Involutional osteoporosis
Oxford Textbook of Geriatric Medicine
ADAPTED SLIDE COURTESY OF Dr. S. AMIN, Mayo Clinic

*Osteoporosis due to changes due to aging.

Fracture Risk soon after return to Earth: Explore a Factor of Risk (Applied load/bone strength) to inform astronauts about potential hazardous conditions?*



Riggs BL, Melton LJ: Adapted from Involutional osteoporosis
Oxford Textbook of Geriatric Medicine
ADAPTED SLIDE COURTESY OF Dr. S. AMIN, Mayo Clinic

*Counseling the "athlete vs. the office worker"?

Questions

Thanks for your attention.

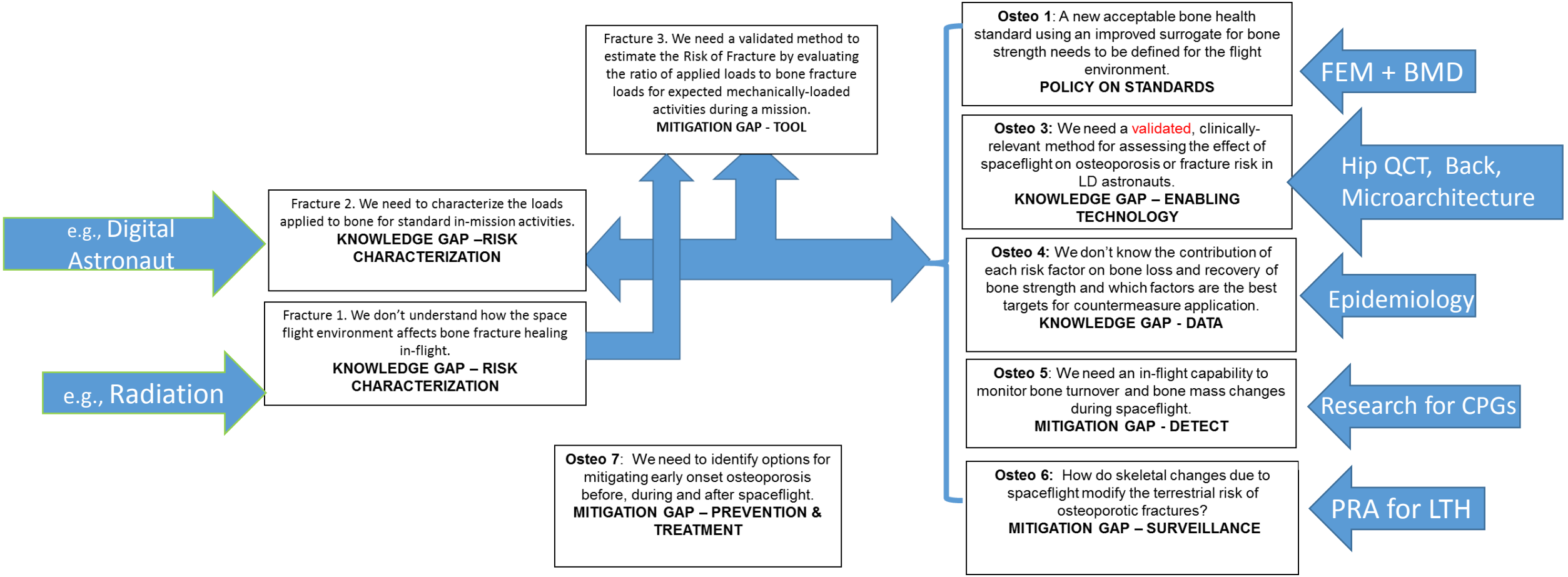
Backup Slides

(*) Risk Custodian: J. Sibonga

Path to Risk Reduction – what is Essential vs. Good-to-Know?

Optimize risk definition by end of ISS platform. (2020-2024)

Focus on risk factors that are modifiable.



CPGs – clinical practice guidelines
PRA=probabilistic Risk Assessment
LTH = Long term Health
FEM = Finite Element Models/Modeling
BMD=bone mineral density; QCT = quantitative computed tomography

Human System Risks – Proposed Likelihood vs Consequence

Consequence
Mission Health and Performance (OPS)

High	Death or permanently disabling injury to one or more crew (LOC) OR Severe reduction of performance that results in loss of most mission objectives (LOM)
Medium	Significant injury, illness, or incapacitation – may affect personal safety OR Significant reduction in performance results in the loss of some mission objectives
Low	Minor injury/illness that is self-limiting OR Minor impact to performance and operations- requires additional resources (time, consumables)
Very Low	Temporary discomfort OR Insignificant impact to performance and operations - no additional resources required

Consequence
Long Term Health (post mission) (LTH)

High	• Unknown and improbable return to baseline (requires drastic intervention surgery & therapy) • Major impact on quality of life (permanent reduced function, premature death)
Medium	• Return to near baseline requires extended medical intervention w/ known clinical methods/technologies (pharmaceuticals, etc.) • Moderate impact on quality of life
Low	• Return to baseline values within 1 year with nominal intervention (time, exercise, nutrition, lenses) • Negligible effect on quality of life
Very Low	• Return to baseline values within 3 months with limited intervention • No effect on the quality of life

Quality of Life is defined as impact on day to day physical and mental functional capability and/or lifetime loss of years

CM = Countermeasure
LOC = Loss of Crew
LOM = Loss of Mission

Do not delete this slide - may be needed for discussion at the HSRB

"Mega-analysis" for Fracture Prediction

Constraint: "Fracture Prediction" requires large # subjects.

~60,000 subjects ~250,000 person-years

~5,400 total fractures ~ 3,500 OP fractures

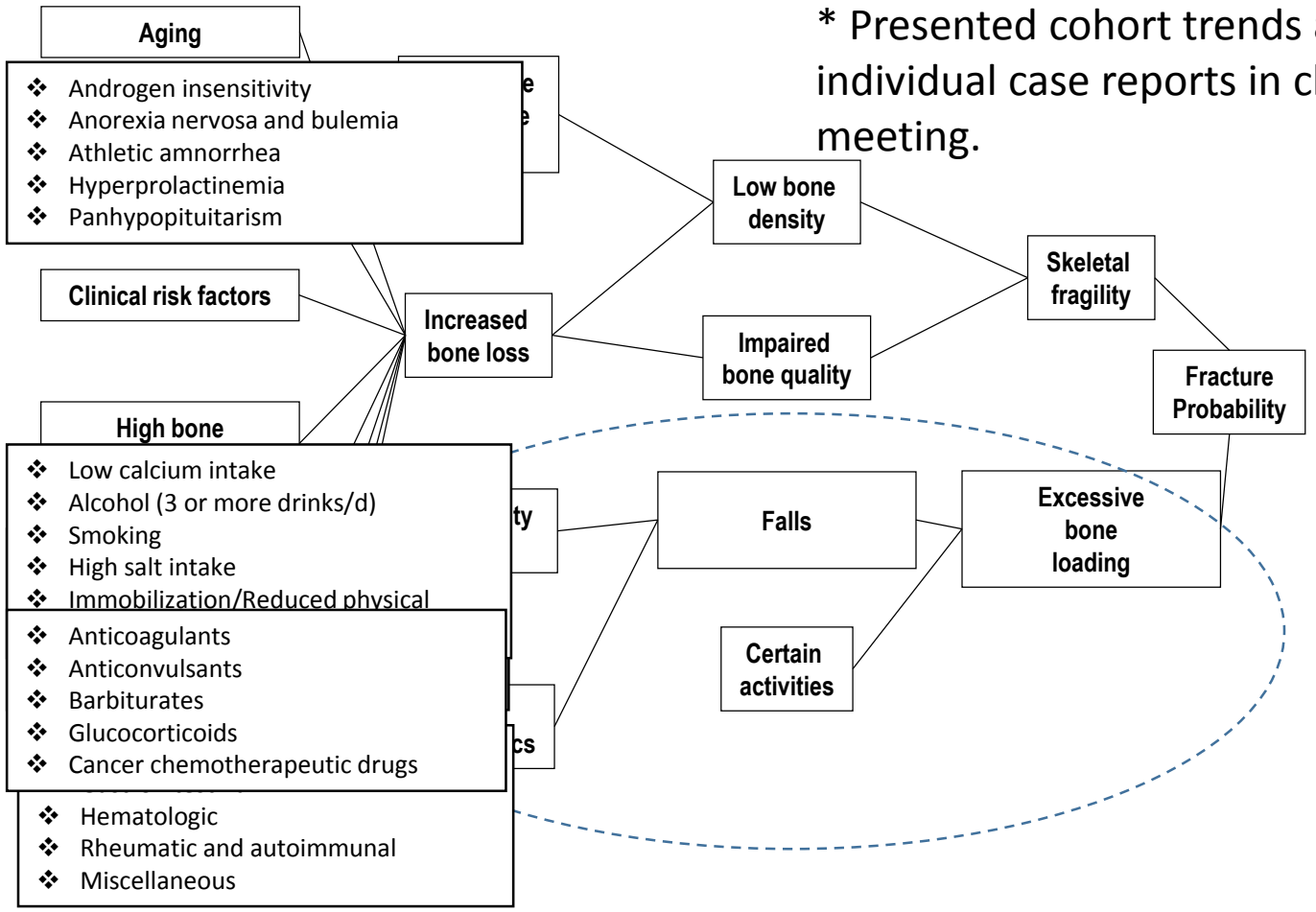
~1,000 hip fractures

- Rotterdam
- EVOS/EPOS
- CaMos
- Rochester
- Sheffield
- Dubbo
- EPIDOS
- OFELY
- Kuopio
- Hiroshima
- Gothenburg 1
- Gothenburg 2

Cohorts analyzed but not merged: MEDOS, NHANES, Asia
Possible future cohorts: OFELY extension, OPUS, SOF

Adapted, Slide courtesy of S. Petak, M.D.

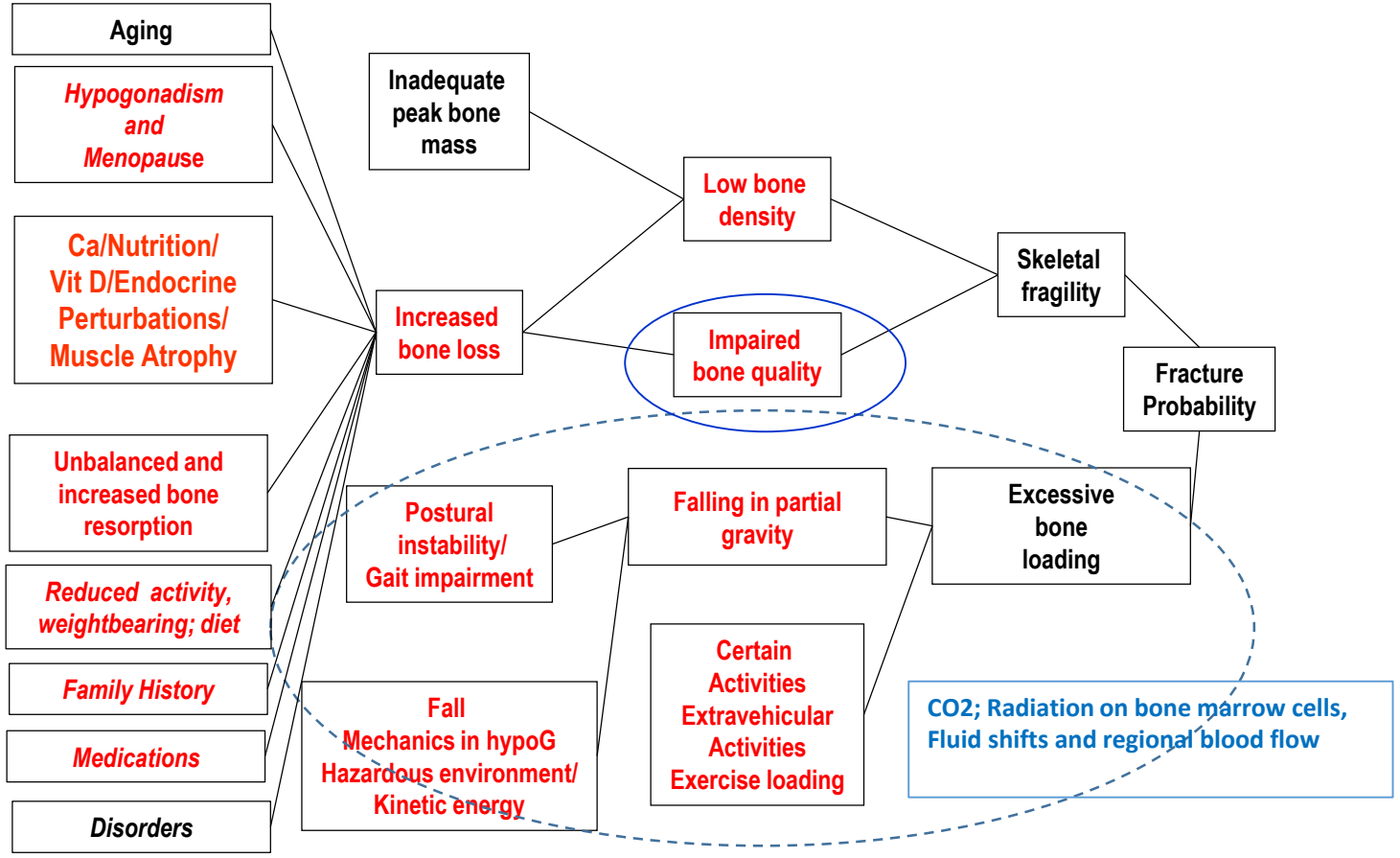
Background: Bone is a complicated tissue. Clinical assessment evaluates multifactorial nature of bone loss and fracture risk.*



* Presented cohort trends and individual case reports in closed meeting.

Adapted from: Pathogenesis of Osteoporosis-Related Fractures (NOF) Cooper C, Melton LJ

Bone loss in space is novel: Operationally-induced* factors in astronauts are possible contributors to fracture risk.



*exposure to space environment and mission operations

Adapted from: Pathogenesis of Osteoporosis-Related Fractures (NOF) Cooper C, Melton LJ

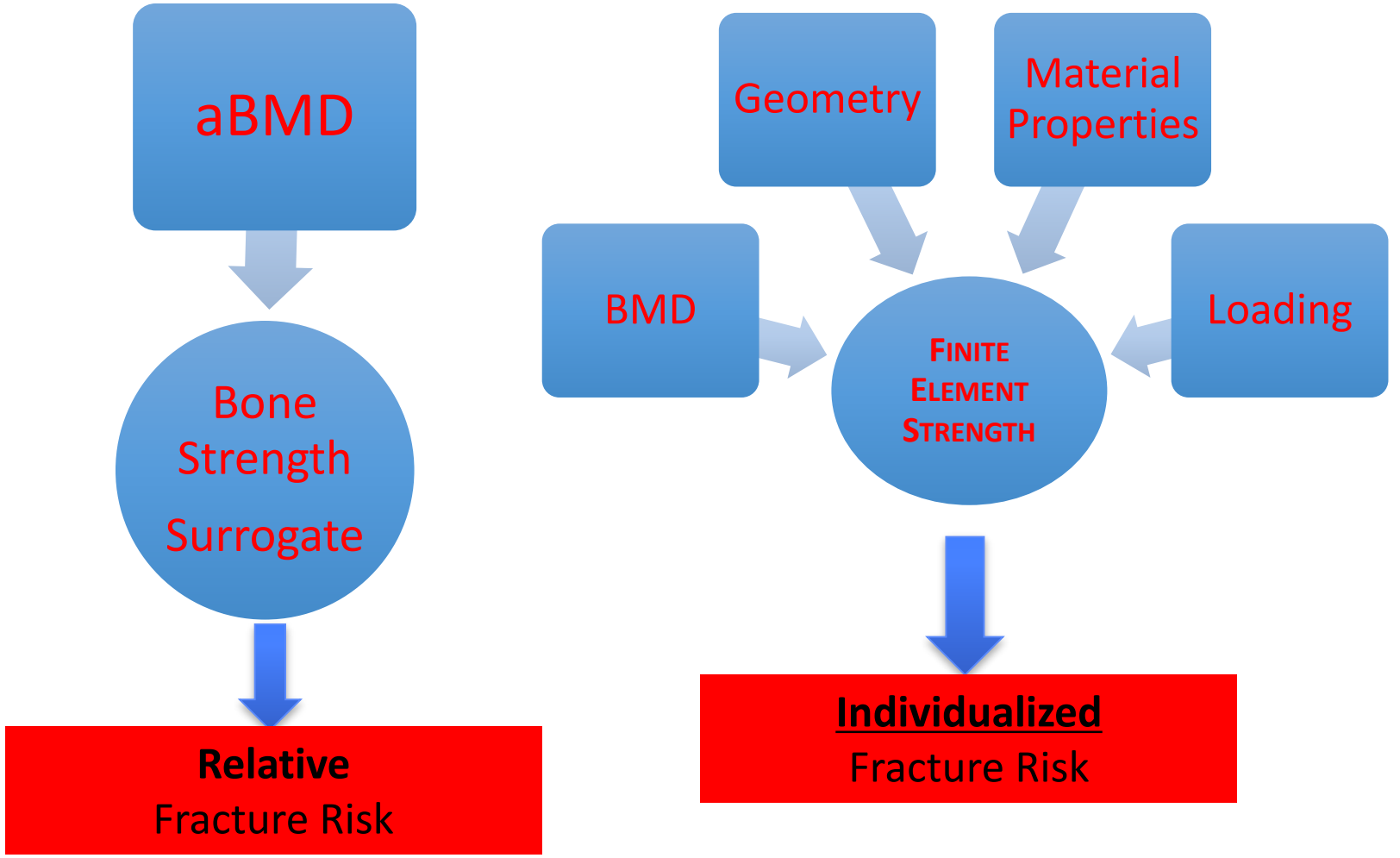
Constraint: Astronauts are understudied population- very limited baseline knowledge (1/2015).

- Typical space mission duration – 160 ± 32d (range 49-215d)
- Average Age – 47 ± 5 y (range 36 – 56)
- Male to Female Ratio – 4.7 : 1 (56:12)
- Current total # per astronauts in corps – 68 of 365
- # repeat fliers – 7
- BMI – Male BMI 25.7 ± 2.2 (range 21.2 to 30.7) Female BMI 22.3 ± 2.3 (range 20.1 to 25.9)
- Wt and Ht- Males: Males: 82 ± 9 (63 to 103); 177 ± 6 (163 to 188) Females : 65 ± 7 (54 to 81), 169 ± 4 (163 to 178)
- % Body Fat: Males: 23 ± 4 (14 to 31) Females: 29 ± 6 (22 to 44)

Which is better?

Fracture risk assessment by 1 measurement or by > 1 measurement?

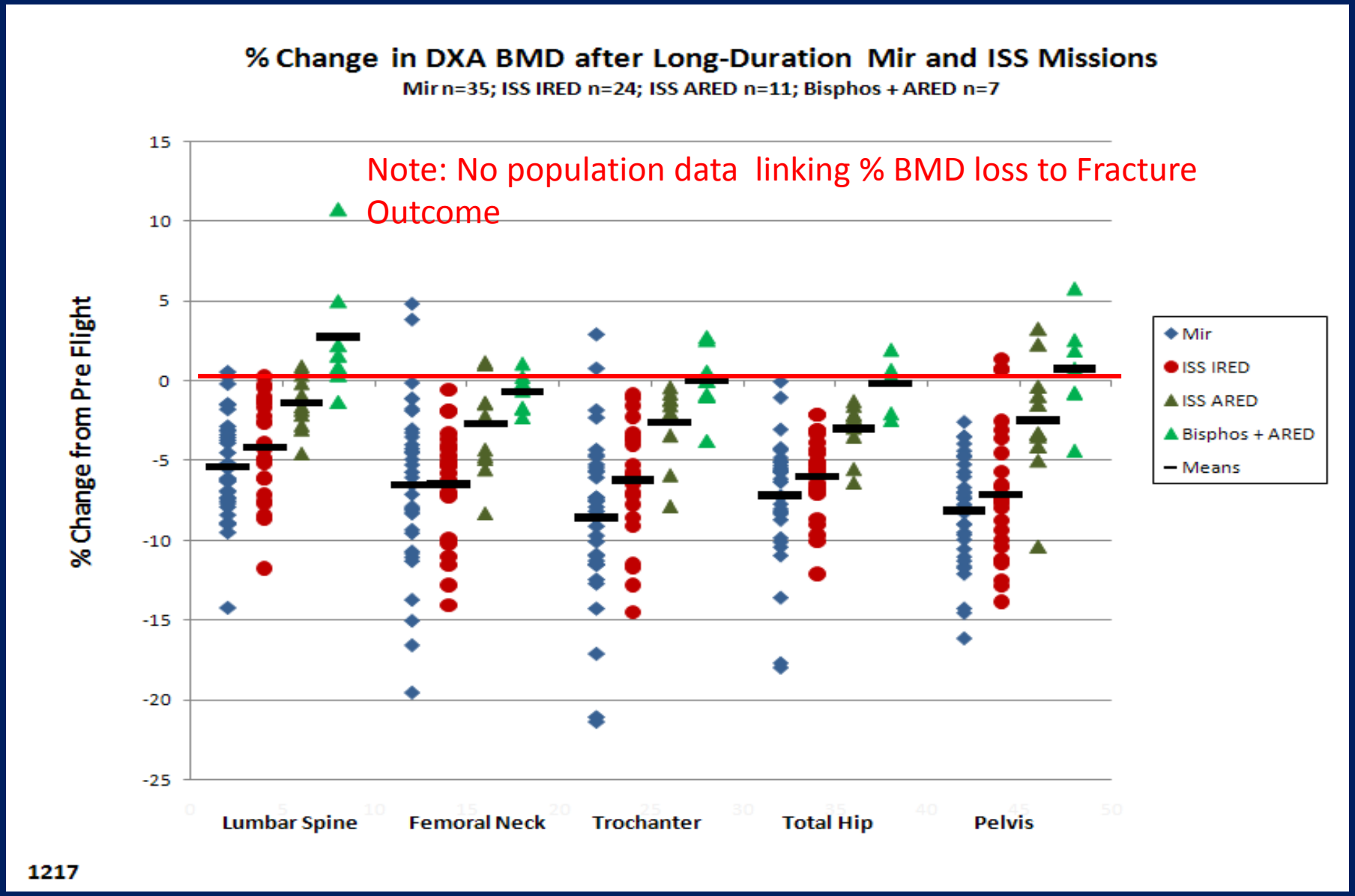
It's not complicated.



Reported “Disconnects” and Limitations of DXA BMD (Slide from 2007)

1. **Riggs BL** et al. Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis. N Engl J Med 322(12):802-809, 1990.
2. **Riggs BL** et al. Clinical trial of fluoride therapy in postmenopausal osteoporotic women: extended observations and additional analysis. J Bone Miner Res. 9(2):265-275, 1994.
3. **Cummings SR** et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998 280(24):2119-2120.
4. **Gutteridge DH** et al. A randomized trial of sodium fluoride (60 mg) +/- estrogen in postmenopausal osteoporotic vertebral fractures: increased vertebral fractures and peripheral bone loss with sodium fluoride; concurrent estrogen prevents peripheral loss, but not vertebral fractures. Osteoporosis Int 13(2):158-170, 2002.
5. **Black DM** et al. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. N Engl J Med 349(13):1207-1215, 2003. (DXA does not pick up significant impact of PTH detected by QCT.)
6. **Chesnut CH** et al. Effects of salmon calcitonin on trabecular microarchitecture as determined by magnetic resonance imaging: results from the QUEST study. J Bone Miner Res. 2005 Sep;20(9):1548-61.

Effects of exercise regimens described using DXA BMD



* Updated data since 2010 Bone Summit

Journal of Bone & Mineral
June 28(6):1243-1255, 2013

"Bone Summit I – 2010"

REVIEW

JBMR

Skeletal Health in Long-Duration Astronauts: Nature, Assessment, and Management Recommendations from the NASA Bone Summit

Eric S Orwoll,[1] Robert A Adler,[2] Shreyasee Amin,[3] Neil Binkley,[4] E Michael Lewiecki,[5] Steven M Petak,[6] Sue A Shapses,[7] Mehrsheed Sinaki,[8] Nelson B Watts,[9] and Jean D Sibonga[10]

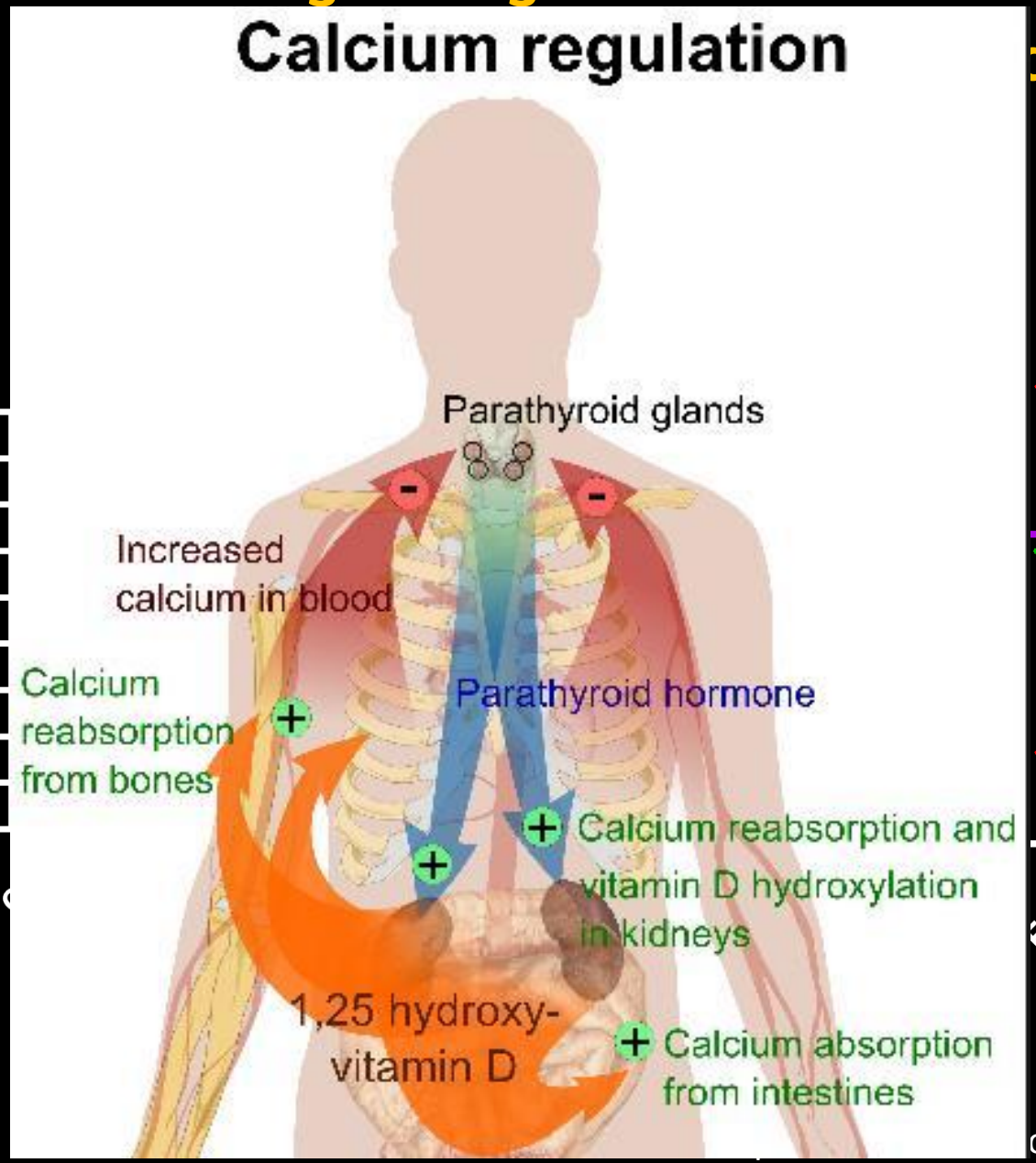
"Bottom Line" Bone Summit II (2013)

" Overall, NASA's strategy of assessing relative fracture risk in astronauts by T-score BMD-based guidelines alone needs to be refined. Accurately determining the absolute fracture risk in astronauts is an ambitious goal that may never be fully realized. A concerted effort however should be made to expand NASA's technical and scientific capabilities toward objectively assessing the factors contributing to the risk since long-duration space flight is expected to:

i) have profound and possibly irreversible bone changes that would not be adequately addressed by DXA BMD, ii) affect other physiological systems (e.g., muscle) that determine fracture likelihood and

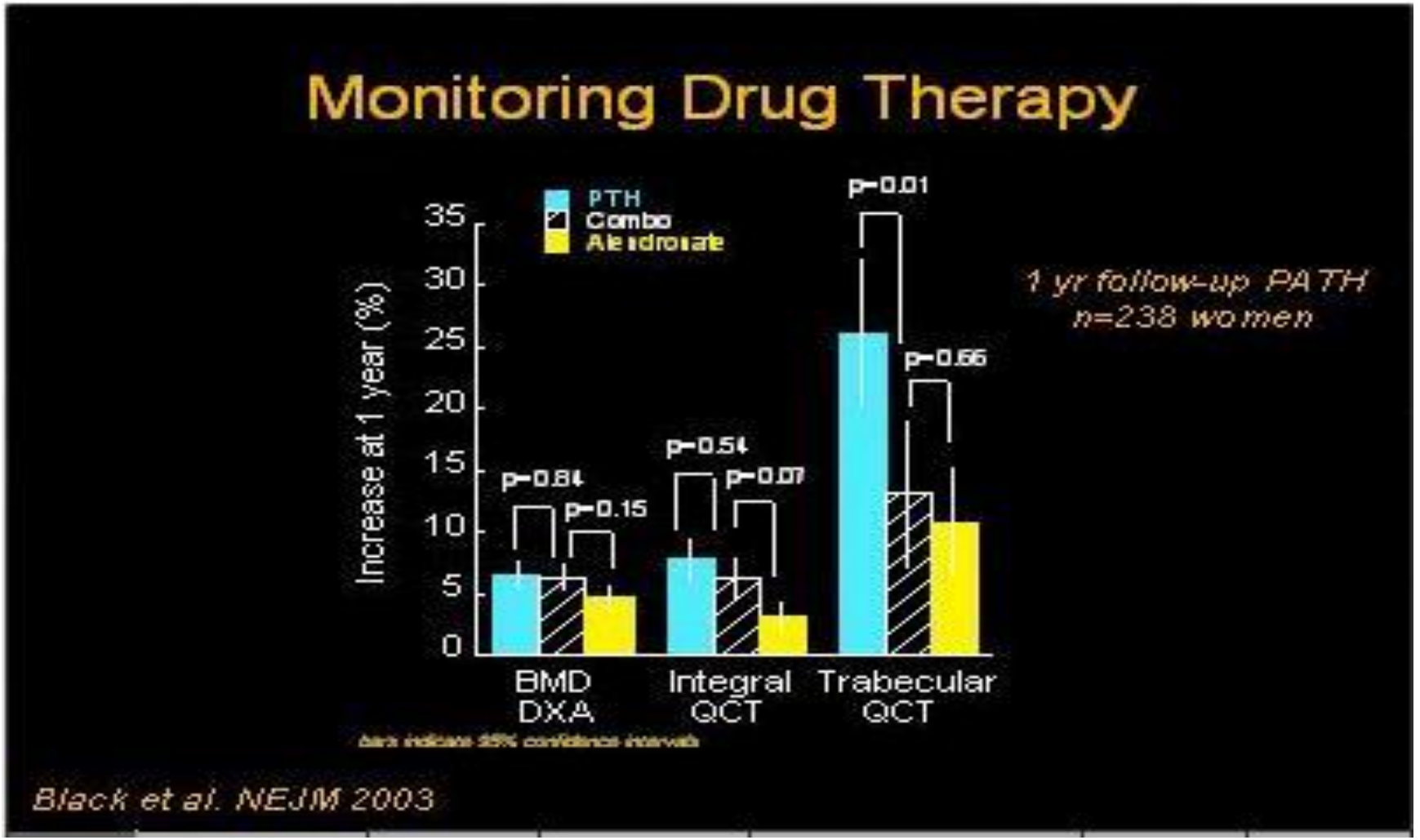
iii) expose astronauts to novel situations that involve a greater probability of overloading bones."

Calcium-regulating Hormones – Endocrine



Courtesy Dr. SM Smith

QCT critical for detecting countermeasure effects on different compartments of bone (cortical vs. trabecular BMDs)



NASA is an engineering agency in the business of space exploration –
i.e., extending human capabilities in space.
Human Research Program - an *R & D* for NASA - reducing risks to Human System.