National Aeronautics and Space Administration

Physiological Effect of Space on Bone Health

Aerospace Medicine
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Johnson Space Center, Houston, TX
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At the end of this lecture, you should understand:

- The *insufficiency* of DXA BMD as a surrogate for fracture risk in terrestrial medicine and as a research tool/clinical test for NASA.

- The flight data describing the unique effects of spaceflight on skeletal sites at risk for age-related osteoporosis.

- The bold approaches to translating *Research* to the *Clinical* arena to meet NASA's constraints and aggressive schedule for mission planning.

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.

Load > Bone Strength = FRACTURE

(Key Causality – BIOMECHANICS)

You don't have to have OSTEOPOROSIS.

Clinical Arena: Probability of Fractures Drives the Requirement for Intervention.

What do we need to monitor in order to assess if and when fractures might occur in *astronauts*?

Overview

- What makes Bone complicated?

- What makes space effects so unique?

- What steps are recommended to manage *fracture* risk in astronauts given NASA constraints?

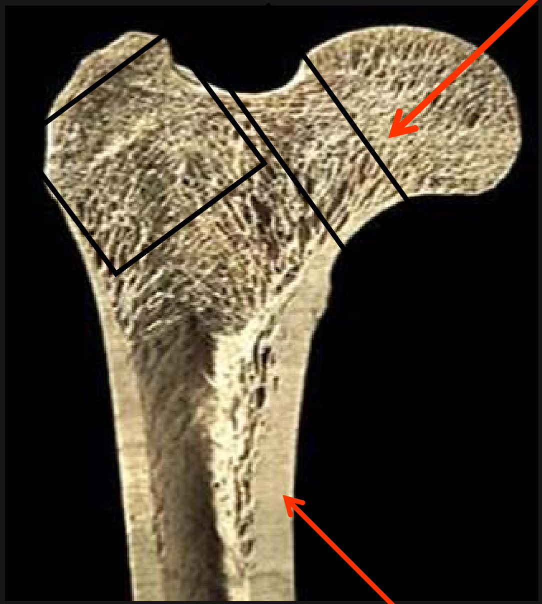
Skeletal Sites: Different composition of Bone Types with different contributions (a GAP) to Bone Integrity

PROXIMAL FEMUR

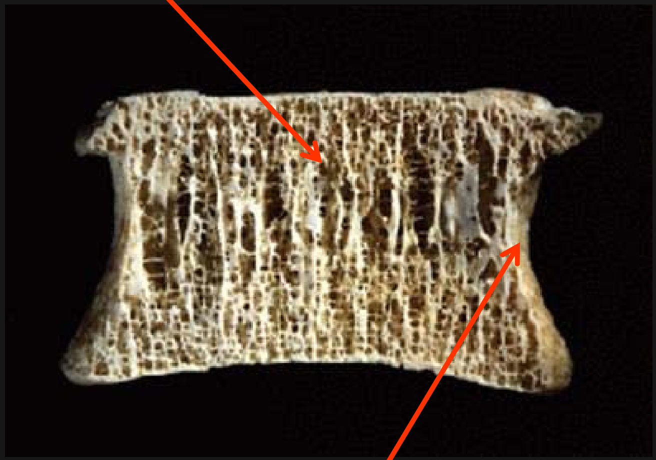
Cancellous "Spongy" Bone/Trabecular Bone

Trochanter
50% BMD

Femoral Neck
25% BMD



VERTEBRAL BODY – 66% BMD



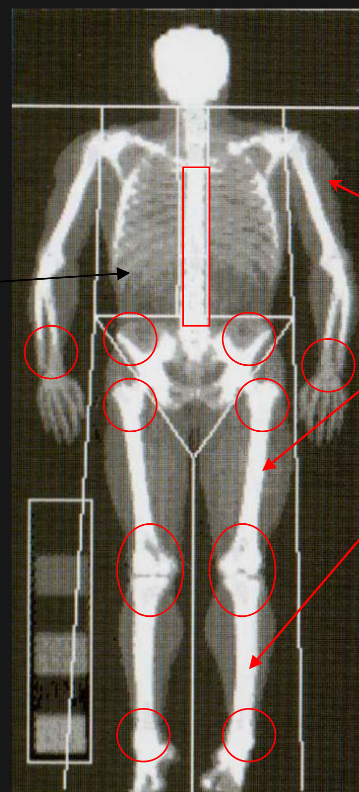
Cortical Bone/ "Compact Bone"

Sources: L. Mosekilde; SL Bonnick; P Crompton

Different Distribution and Turnover Rates for Bone Types to Support 2 functions of Skeleton

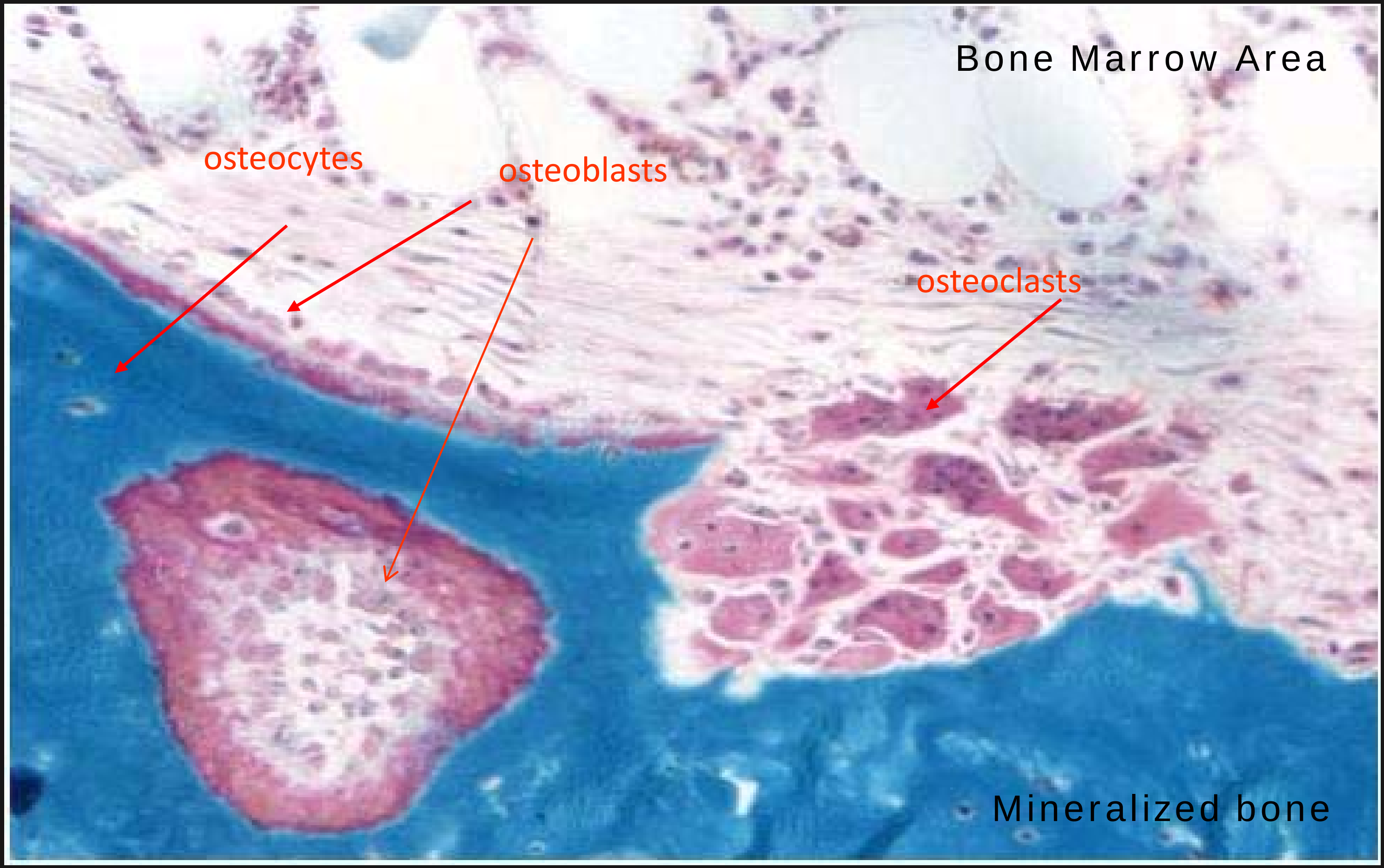
Entire skeleton turns-over 10%/year: 3% cortical bone but 25% of cancellous bone

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

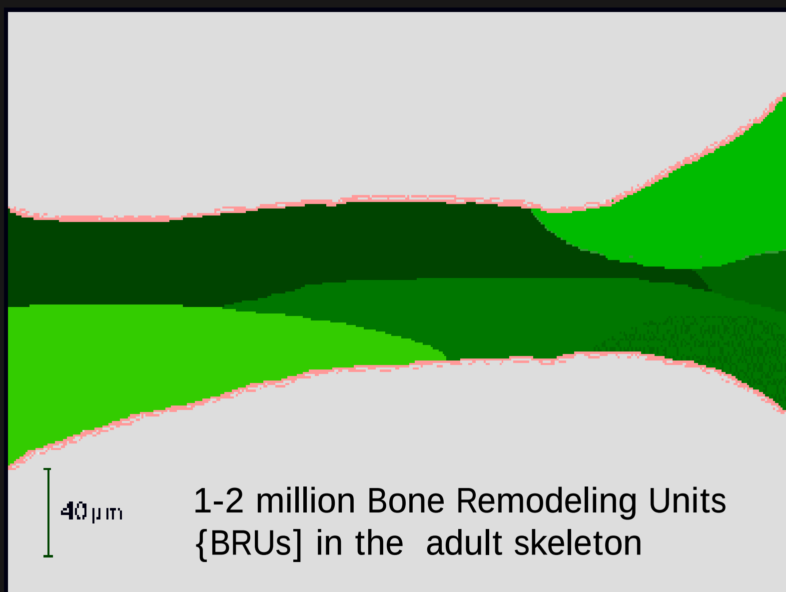


Cortical Bone 80% of total skeleton (long bones)

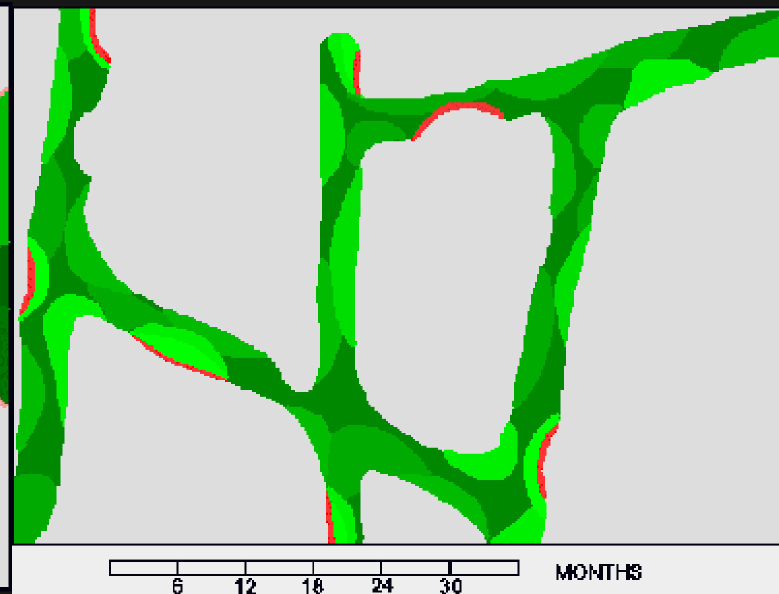
TYPES OF BONE CELLS: mediators of bone resorption, bone formation, mechanical sensing



Remodeling of Bone Tissue in Adults is Highly Regulated and Rates can Influence Integrity

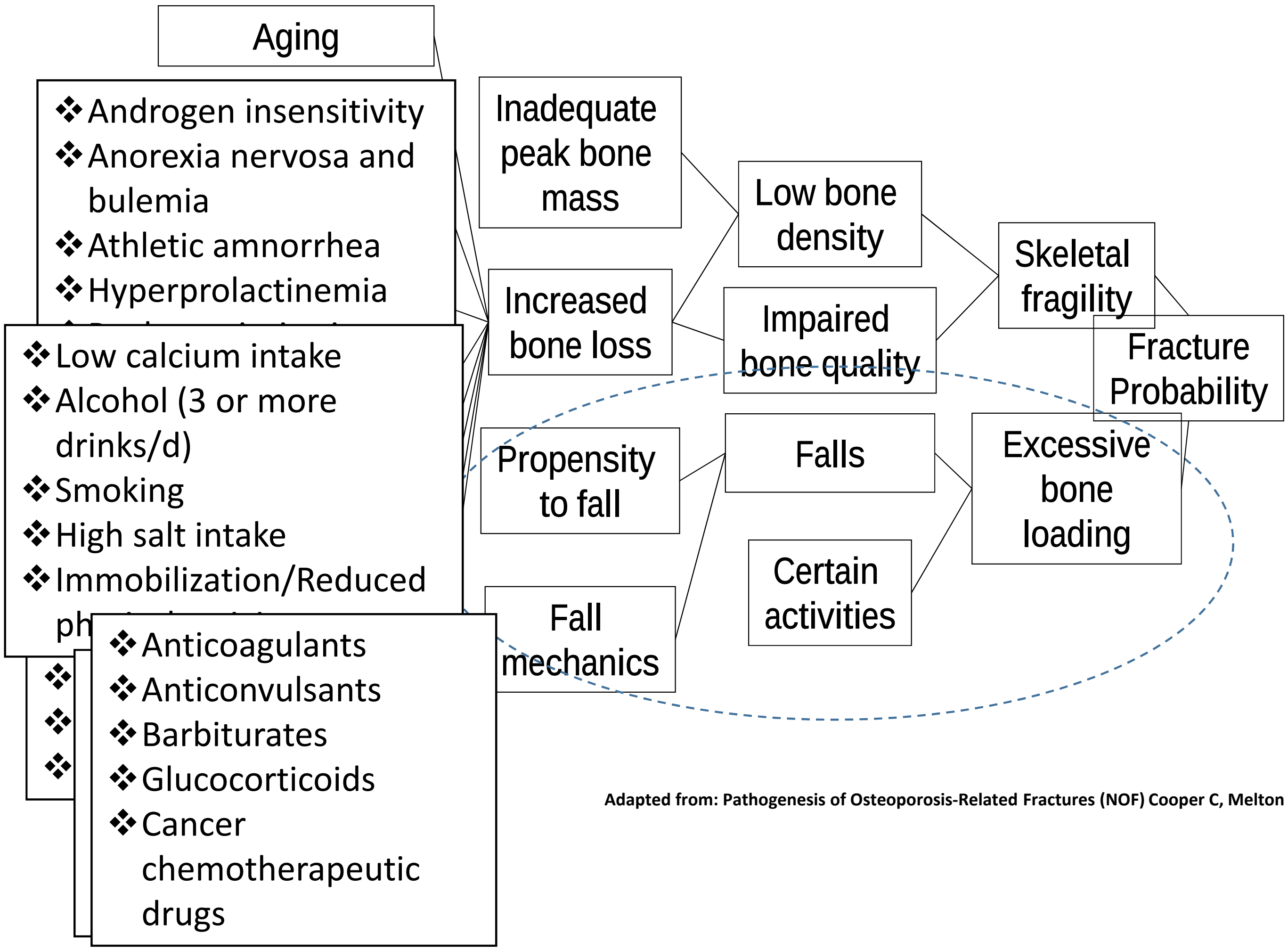


Normal Remodeling Rate at the Level of 1 Bone Remodeling Unit of Cancellous Bone



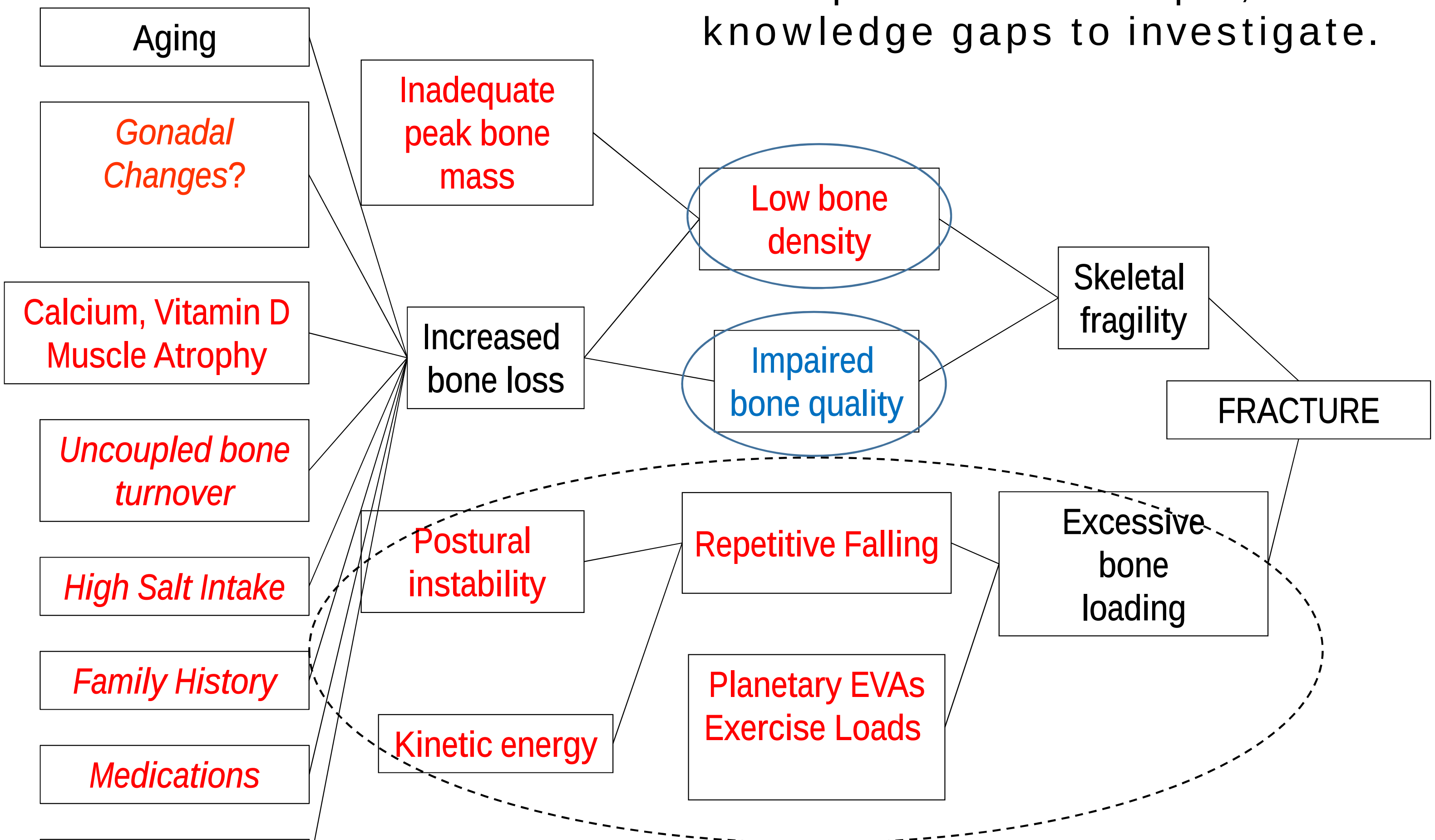
High Remodeling Rate at the Cancellous Bone Tissue Level

Fracture risk is *already* multifactorial in the Aged and At Risk populations.



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

Medical Operations: Multiple, *novel* knowledge gaps to investigate.



CO_2; Radiation on bone marrow cells
Fluid shifts and regional blood flow

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

Setting Priorities: It's not all about Bone.

Adaptations to Long-Duration Space Flight

Ocular
- ↑ intraocular pressure in flight
- ↑ retinal blood vessel constriction postflight
- ↓ visual motor task performance
- ↓ contrast discrimination
- ↓ visual field postflight
- ↓ intraocular pressure postflight

Cardiovascular
- ↑ resting heart rate
- ↑ stroke volume early in flight
- ↑ PACs & PVCs
- ↓ fluid volume
- ↓ orthostatic tolerance
- ↓ aerobic & anaerobic capacity
- ↓ resting blood pressure postflight
- ↓ central venous pressure (indirect)
- ↓ cardio/thoracic (CK) ratio postflight

Musculoskeletal/Bone
- ↓ muscle mass
- ↓ muscle endurance & strength
- ↓ bone mineral content
- ↓ bone integrity

Neurosensory
- ↑ vestibular disturbances
- ↑ space motion sickness
- ↓ postural stability
- ↓ sensorimotor function

Body Fluids
- ↑ hemoglobin & hematocrit postflight
- ↓ total body water
- ↓ plasma & urine volumes postflight

Electrolytes
- ↑ urinary Ca & PO_4 postflight
- ↓ plasma K & Mg postflight
- ↓ urinary Na, K, Cl, Mg

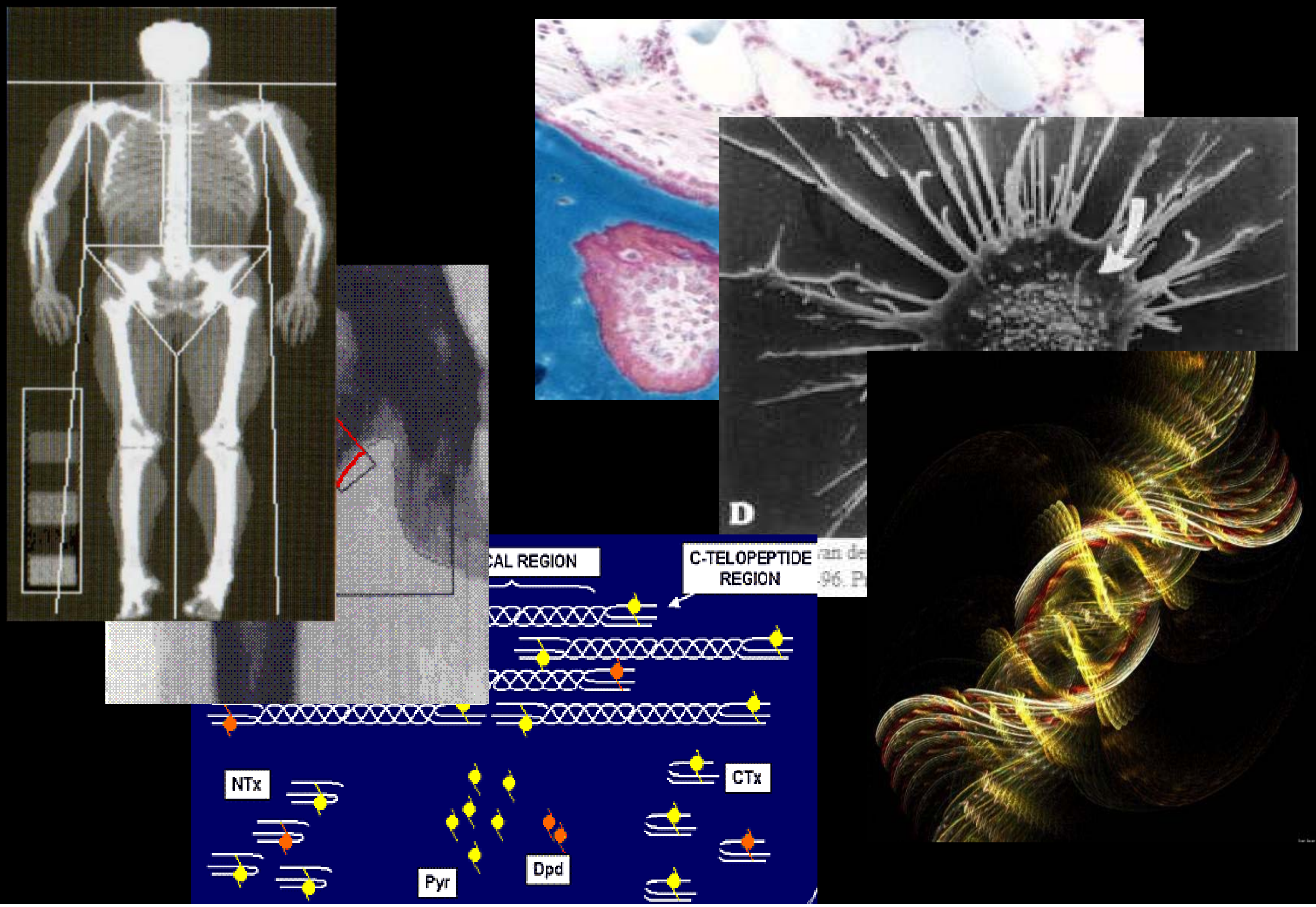
Hormones
- ↑ plasma ADH & ANF
- ↑ urinary aldosterone
- ↑ urinary ADH & cortisol postflight
- ↓ urinary epinephrine & androsterone postflight
- ↓ plasma ACTH, aldosterone, cortisol

Metabolites
- ↑ plasma glucose, creatinine, BUN postflight
- ↓ albumin, cholesterol, triglycerides, uric acid

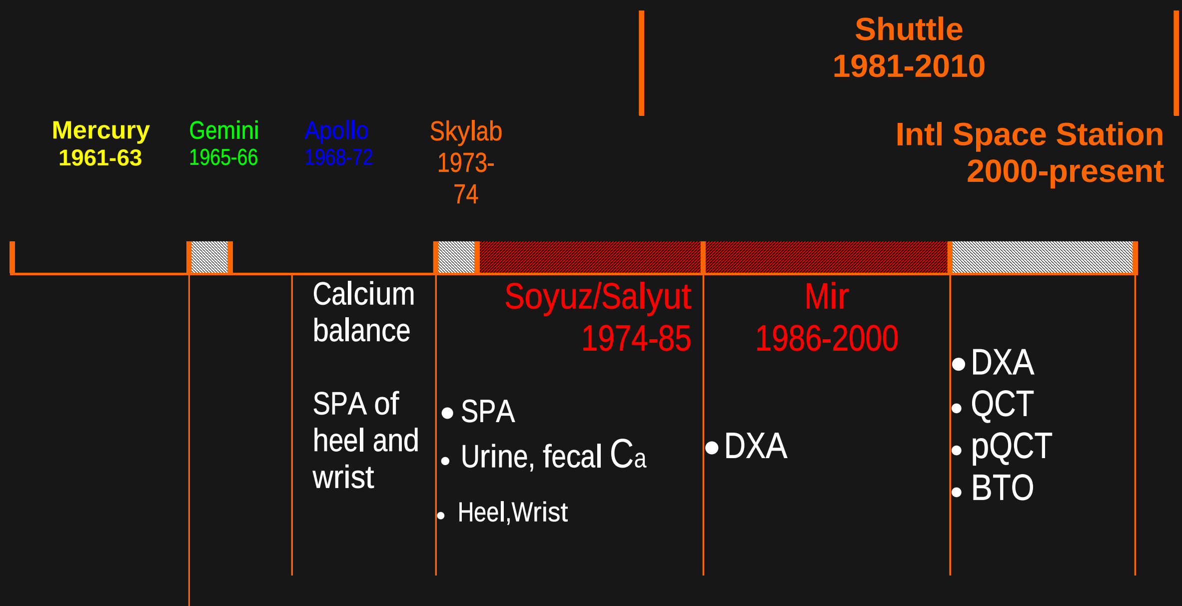
Overview

- What makes Bone complicated?
- What makes space effects so unique?
- What steps are recommended to manage fracture risk in astronauts given NASA constraints?

Constraints to Understanding Skeletal Adaptation



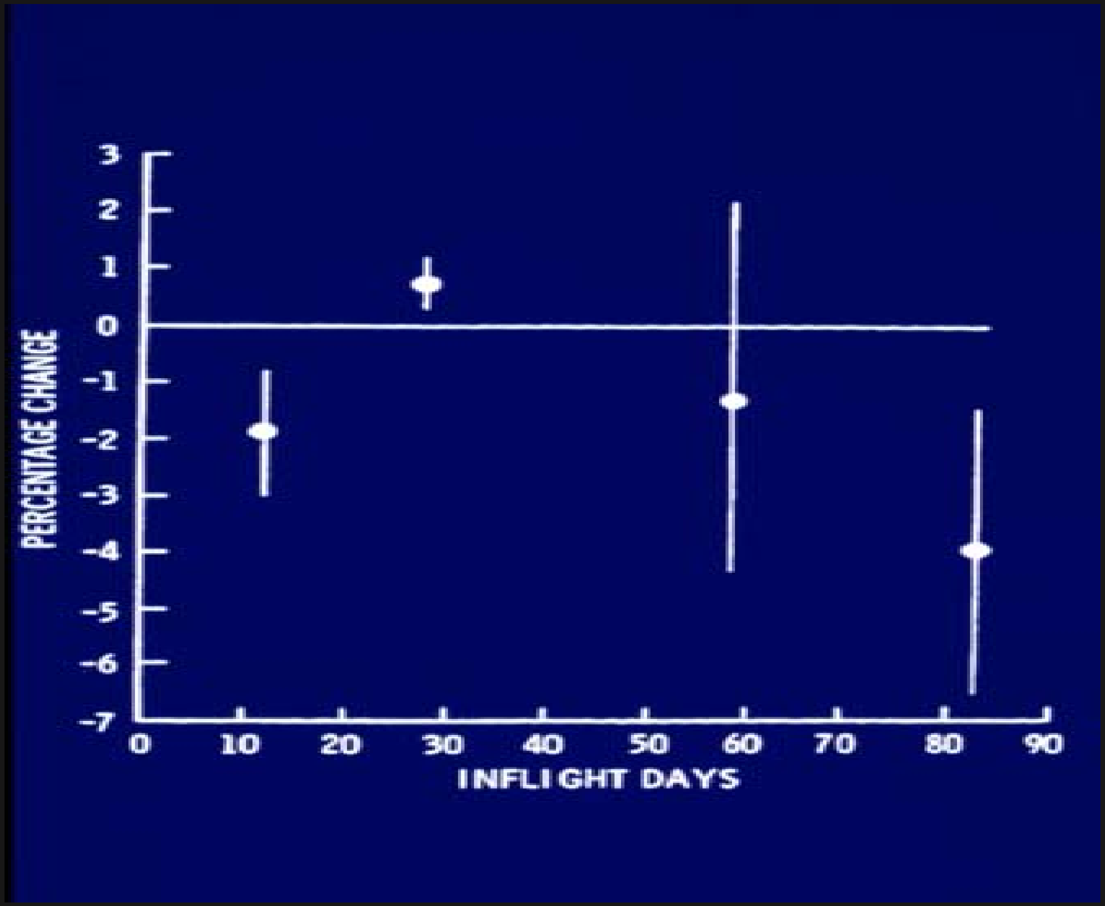
Characterizing Bone Changes* in Space



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

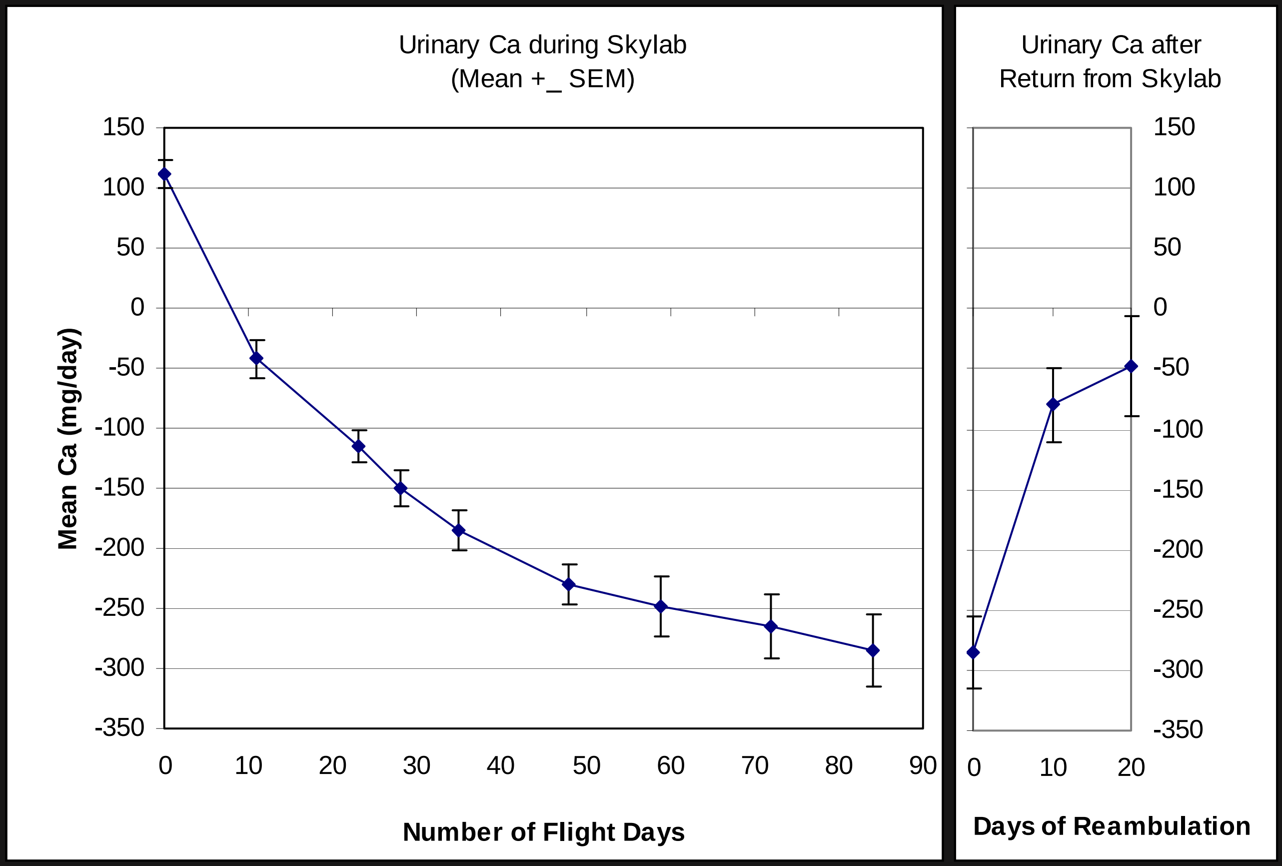
*Two functions of skeleton

Skylab-Bone Mineral Density of Calcaneus (vs. wrist)

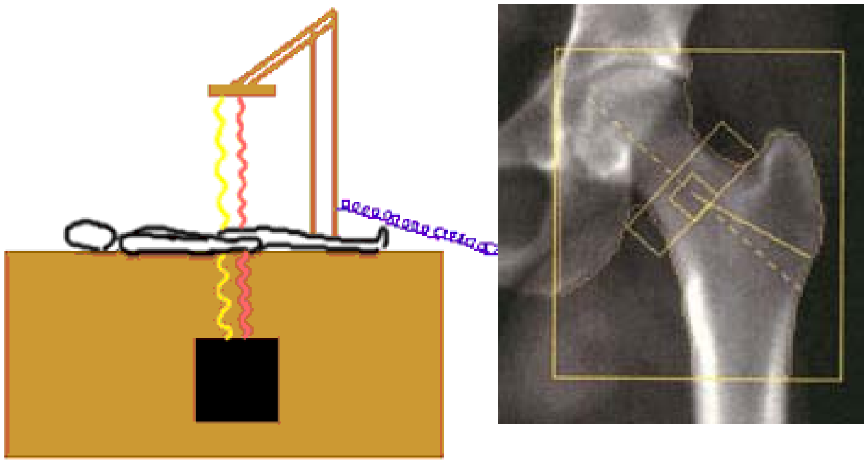


Rambaut P, Johnston R. Acta Astronaut. 1979;6:1113-22.

Skylab-Urinary Calcium Excretion



NASA JSC: Widely-Applied Technology for the Assessment of Bone Health- Dual-energy X-ray Absorptiometry [DXA]



DXA measurement of areal BMD [BMD_a] – a 3d measure in 2d units

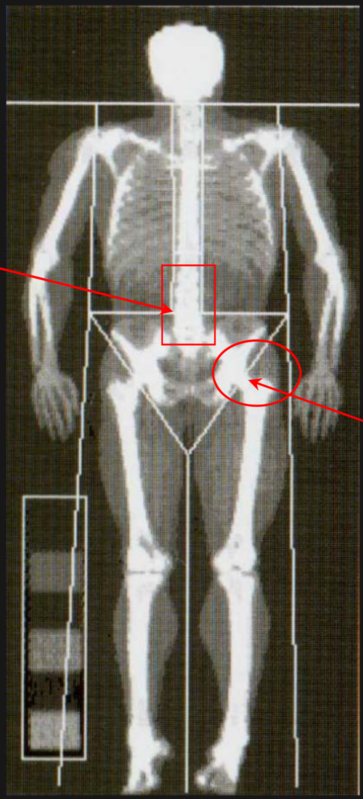
- Improved precision; low radiation; shorter scan times; BMD over multiple skeletal sites…
- Used in **large prospective studies for fracture prediction**

- Long established surrogate for bone strength
- Despite limitations, still considered best predictor of fracture

Regional BMD losses Mir Crew Members by DXA

Declines in bone mass are rapid and site-specific.

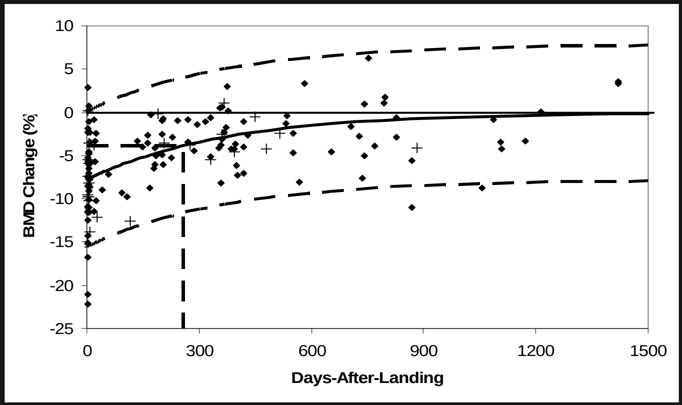
Areal BMD g/cm2	**%/Month Change ± SD**
Lumbar Spine	-1.06±0.63*
Femoral Neck	-1.15±0.84*
Trochanter	-1.56±0.99*
Total Body	-0.35±0.25*
Pelvis	-1.35±0.54*
Arm	-0.04±0.88
Leg	-0.34±0.33*
*p<0.01, n=16-18	Leblanc et al, 2000.



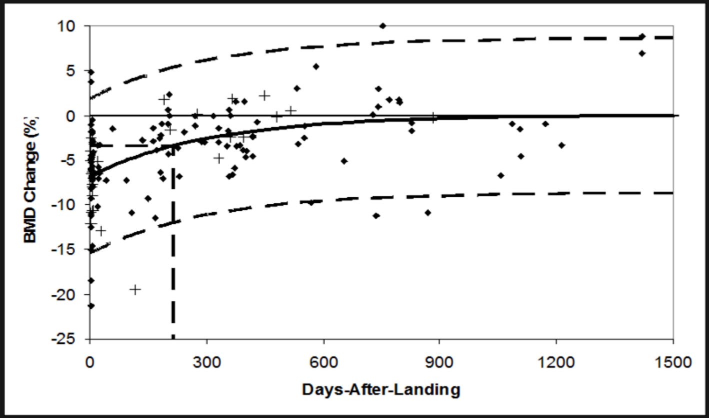
Subsequently, application of Dual-energy X-ray Absorptiometry [DXA] BMD @ Johnson Space Center to...

- monitor astronaut skeletal health,
- characterize skeletal effects of long-duration spaceflight,
- evaluate efficacy of bone loss countermeasures, and
- verify restored health status

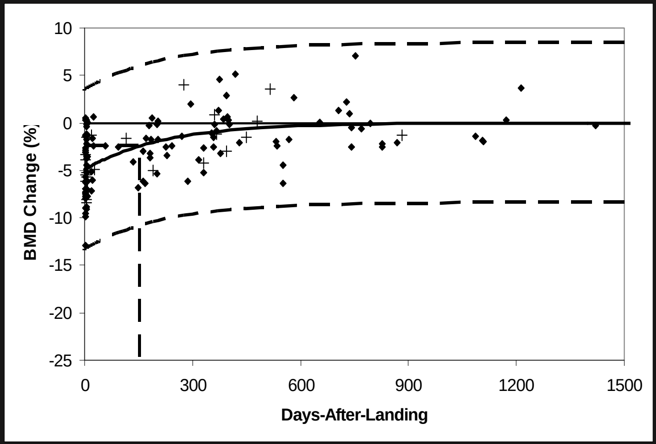
DXA BMD increases in Postflight –does that suggest a recovery of *bone strength*?



Trochanter



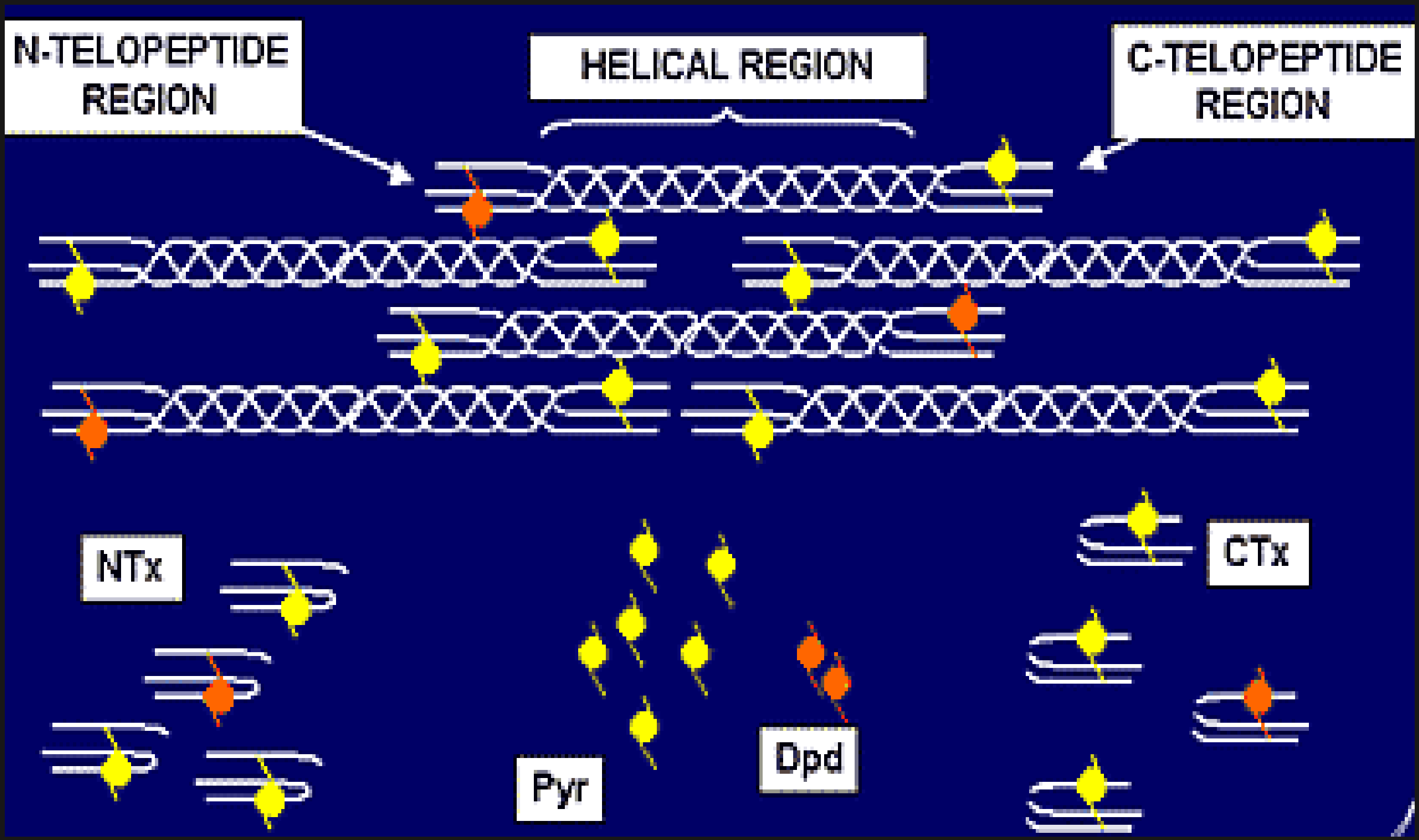
Femoral neck



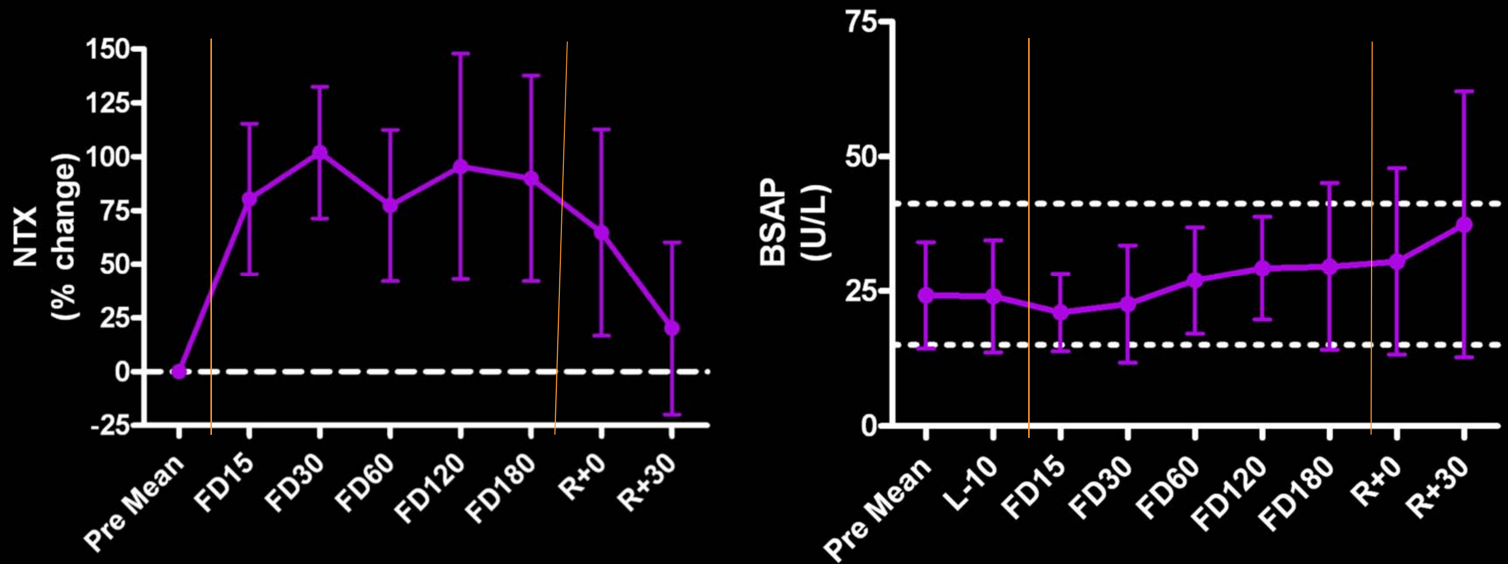
Lumbar Spine

Sibonga et al. BONE 41:973-978, 2007

Serum and urinary biomarkers reflect bone turnover and suggest changes in cellular activities



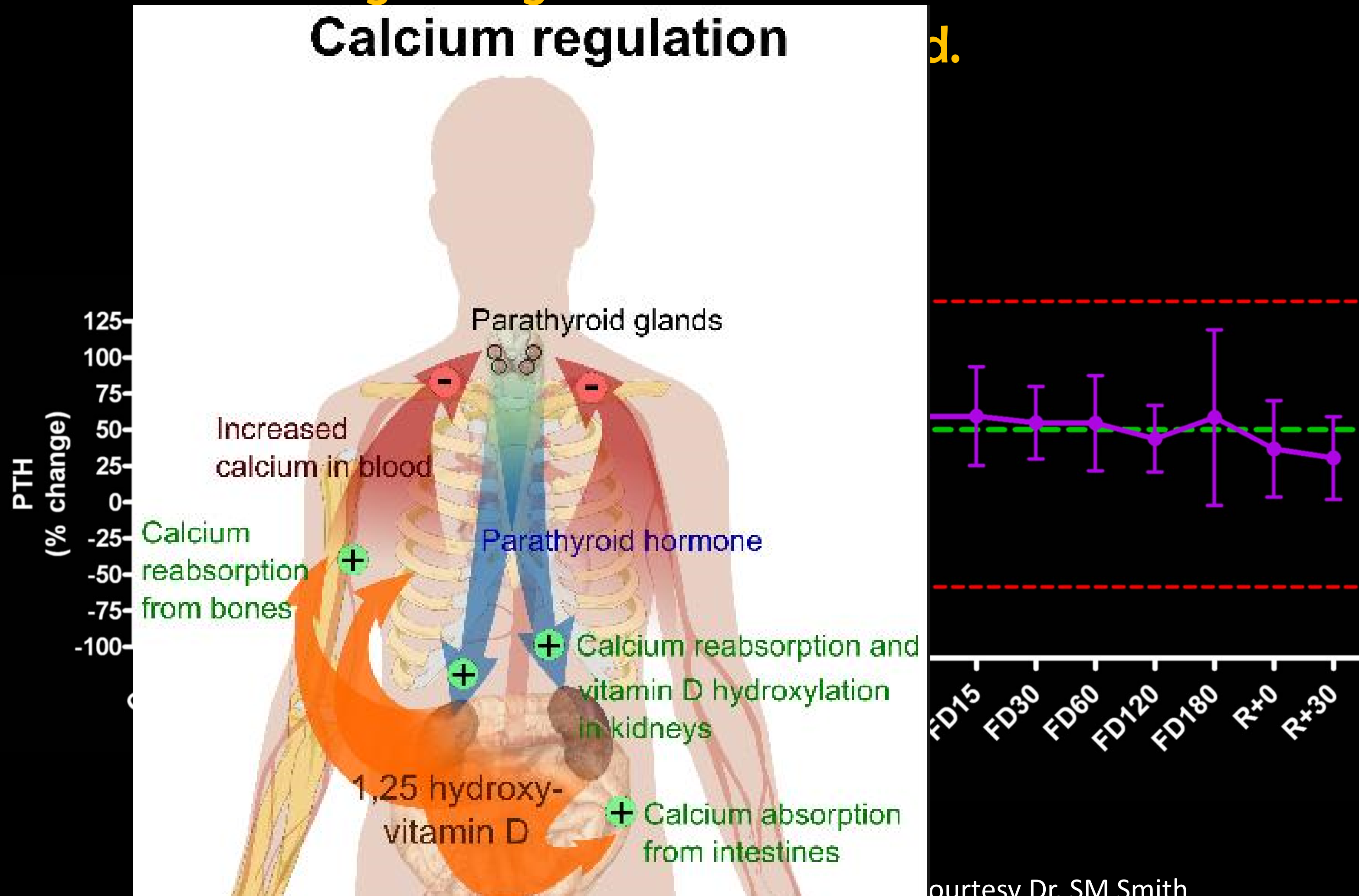
Bone Turnover Markers: suggest uncoupling of remodeling -- may result in net loss in bone mass *from skeleton.*



Slide Courtesy of Dr. SM Smith; Adapted by Sibonga

Calcium-regulating Hormones – Endocrine

d.



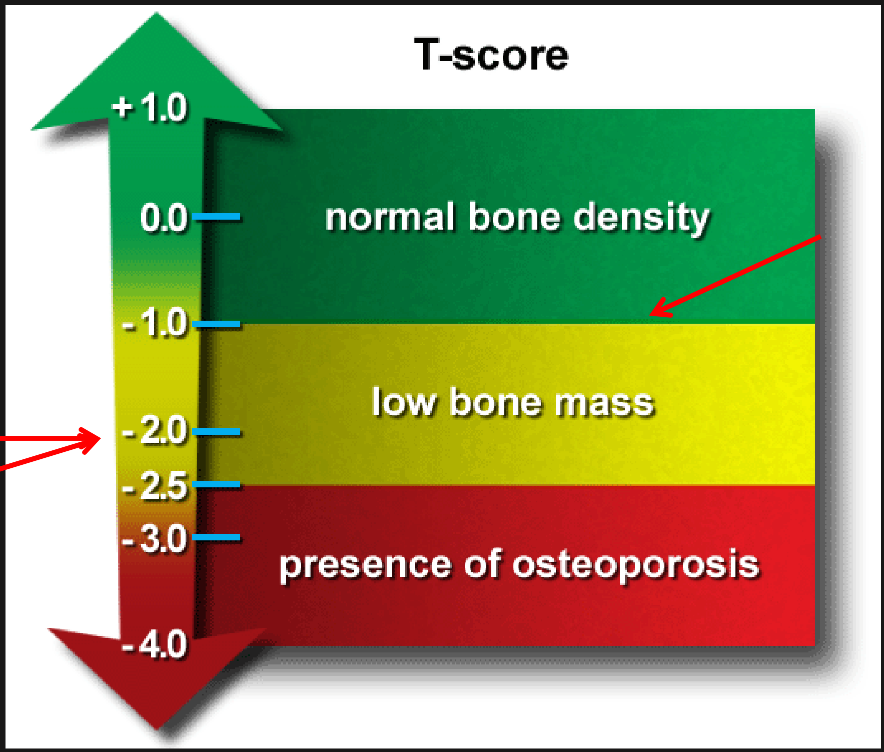
ourtesy Dr. SM Smith

Circa 2000, NASA adapts the only & best clinical guidelines available for Primary Osteoporosis as standards of bone health in astronauts.

T-scores* (Not BMD change).

Permissible Outcome Limit

Mitigation Efficacy

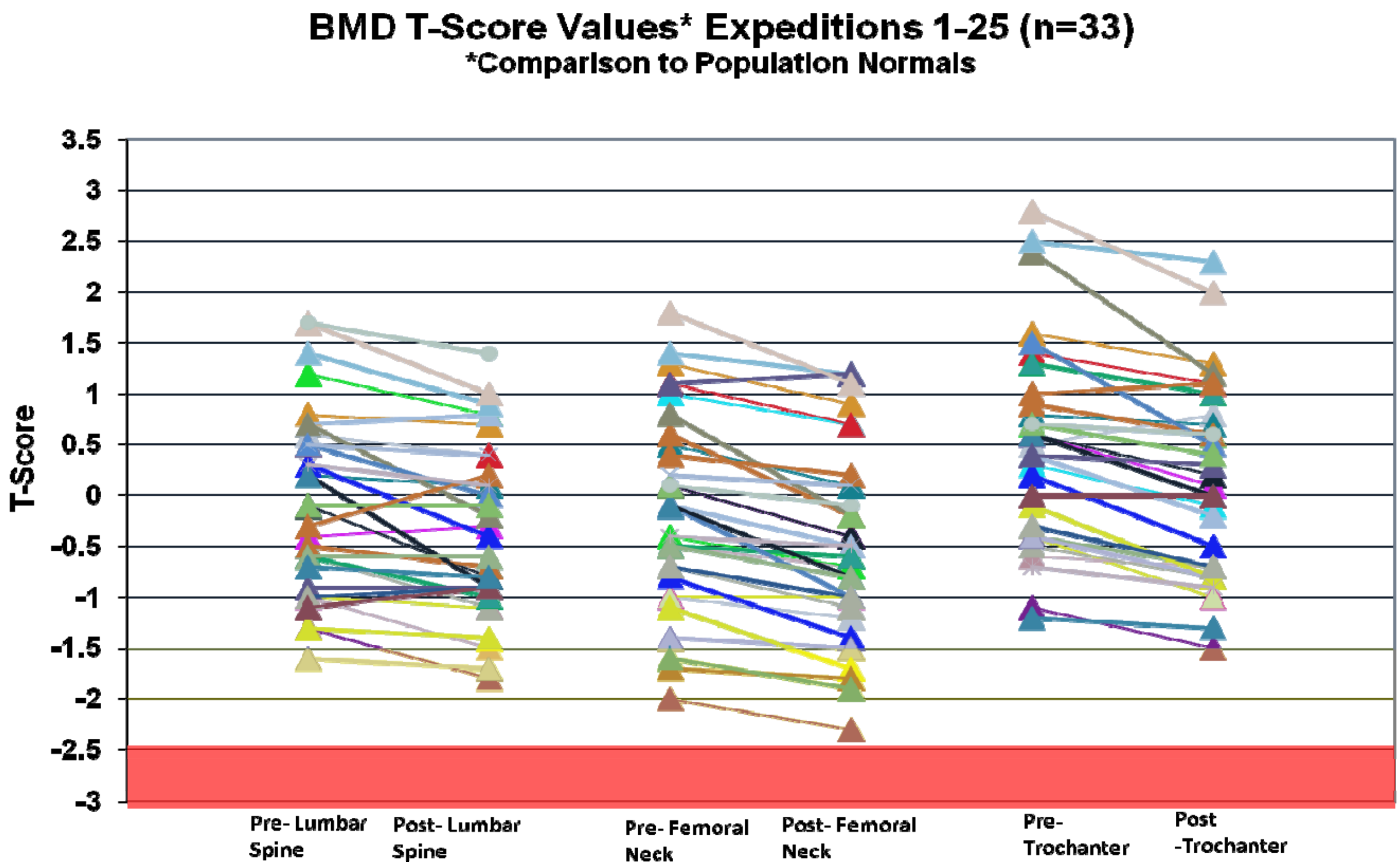


Preflight "Fit for Duty"

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

Clinical Guidelines used by NASA:

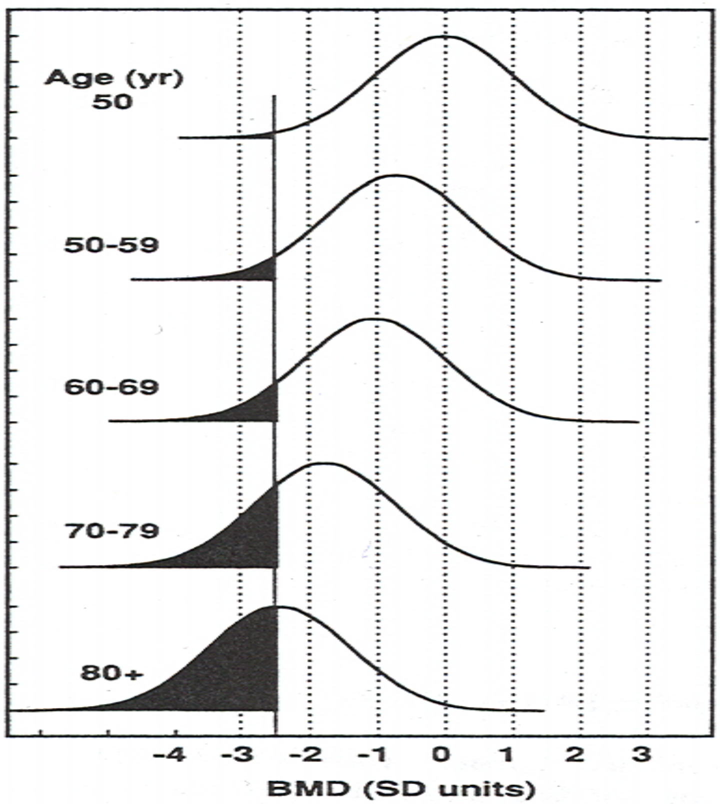
DXA-based T-scores not appropriate, informative or predictive for fracture in astronaut population.



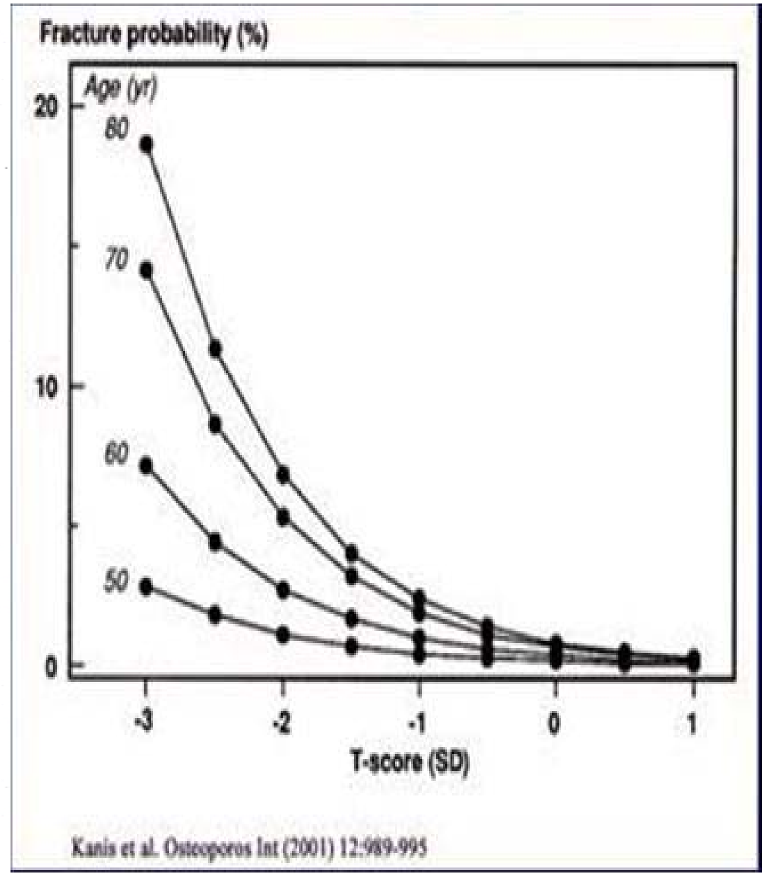
Limited Knowledge Base: The long-duration astronaut – not typical subject to screen for osteoporosis (1/2015).

- 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)
- ***YOUNGER PERSONS DO NOT FRACTURE.***

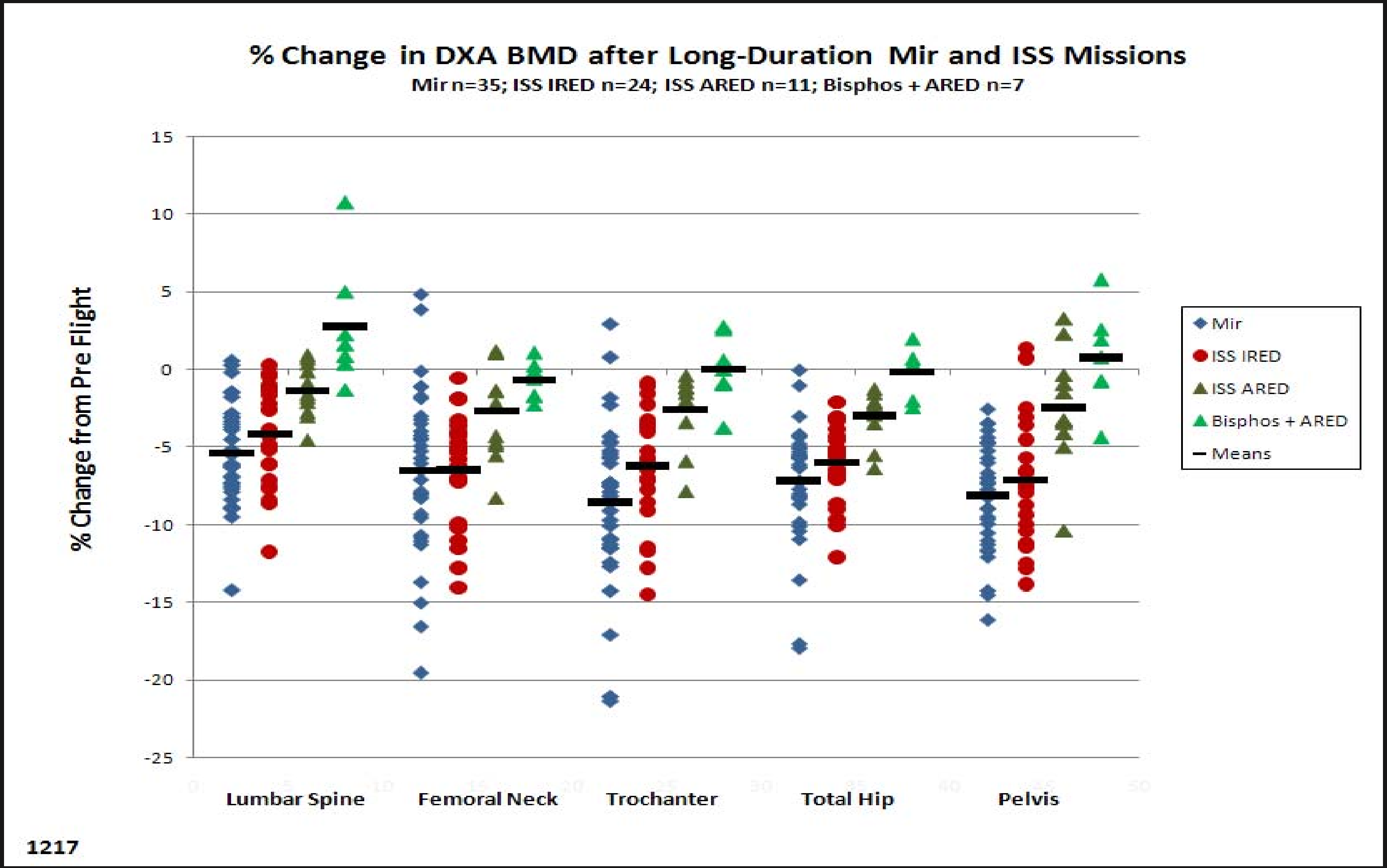
Age is important risk factor for bone loss and fracture probability. **The DXA as diagnostic clinical test is not for premenopausal females or males < 50 years.**



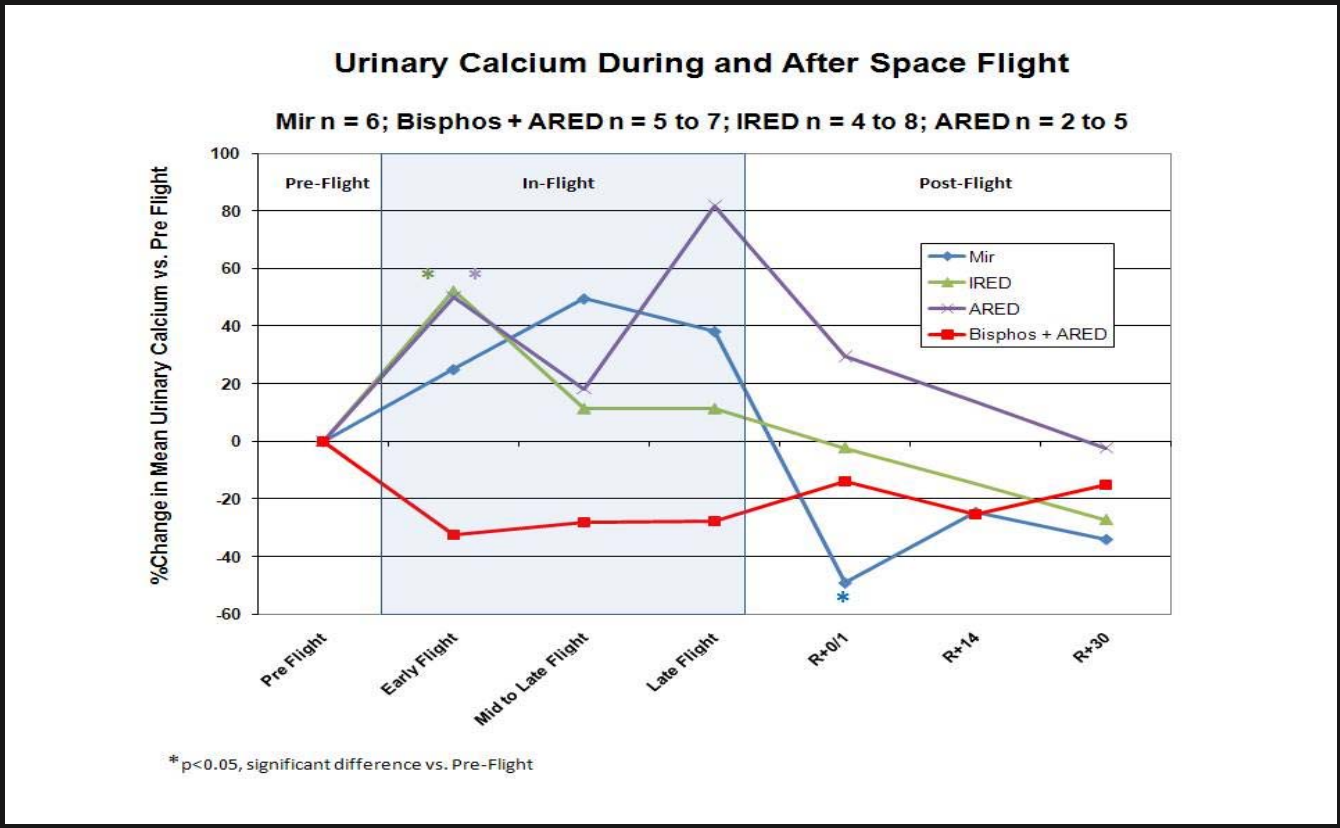
Kanis et al JBMR 9(8):1137, 1994



DXA as a Research Tool – Cannot distinguish effect of ARED exercise from bisphosphonates .

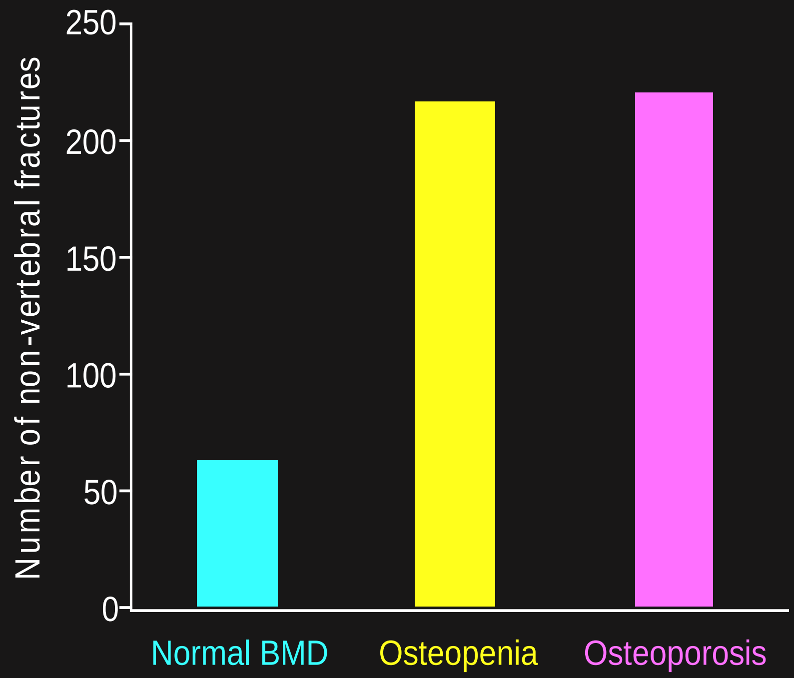


Bisphosphonates mitigate urinary calcium excretion by suppressing bone degradation.



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

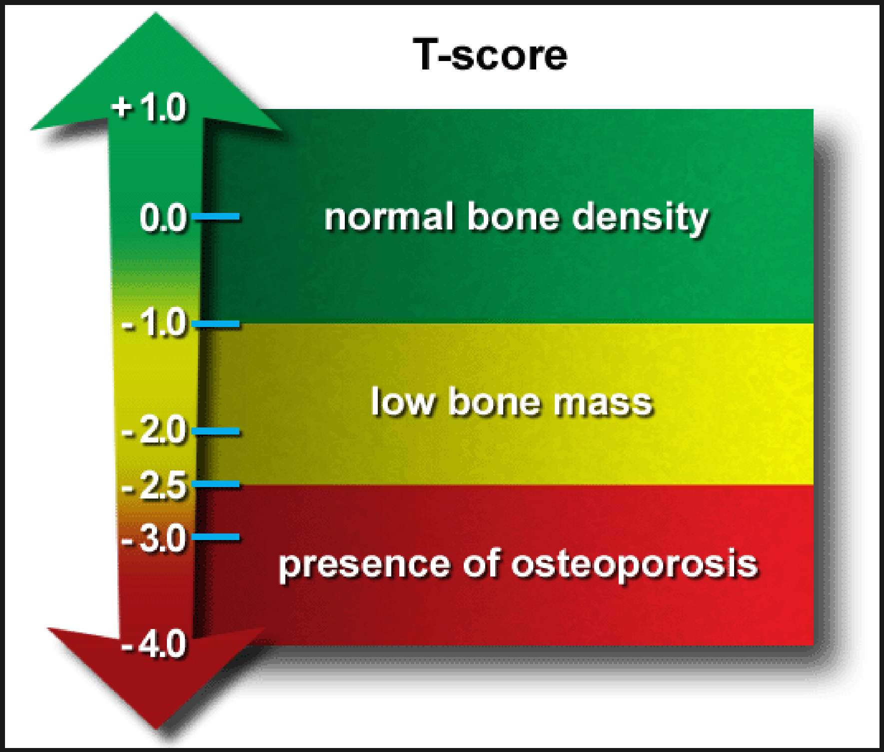
(Female data presented here)

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*.

Disconnects with BMD and Fracture risk in terrestrial medicine:

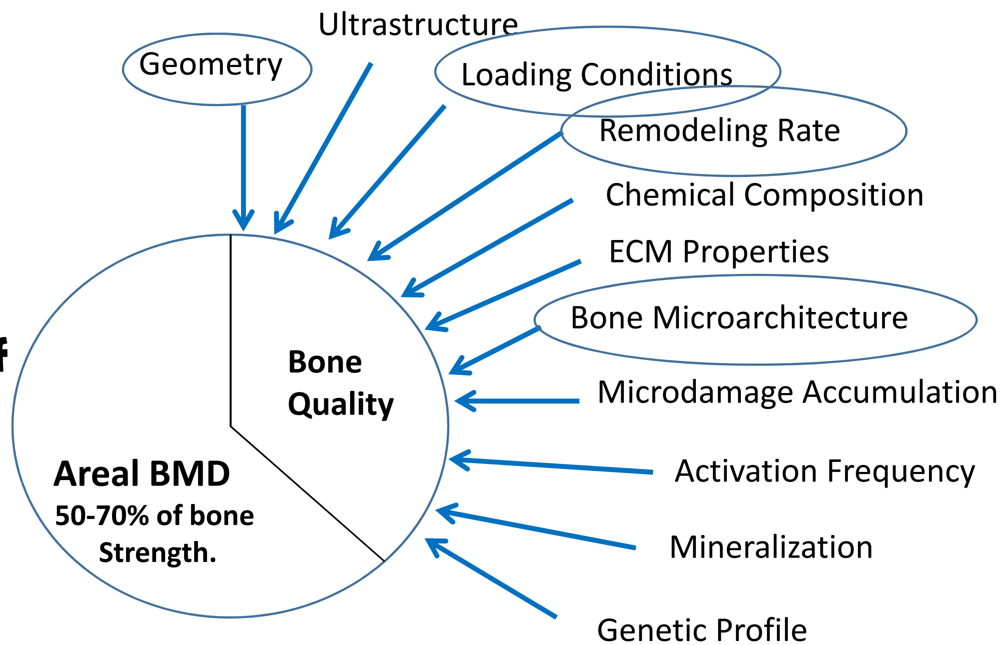
Fracture probability is influenced by additional factors that are not measured by DXA areal BMD



FRACTURE CASES

NON FRACTURES

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: bone density and bone quality.</u>" JAMA 2001



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

May 2005

Different QCT modalities to capture bone structure.

Example, GE QCT scanner

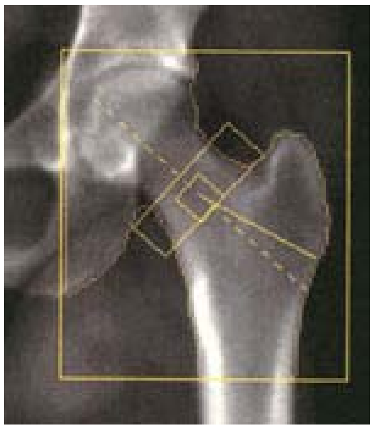
Lunar
Hip 1.2-1.5 mSv/ HIP
2-6 days ISS background

XtremeCT

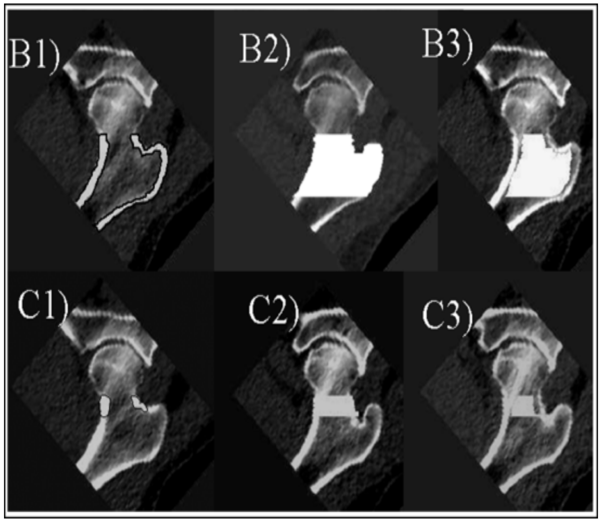
Stratec peripheral QCT
5 slices tibia 0.5 mRem

ScanCo
High Resolution “HR” peripheral QCT
< 0.5 mRem per site

QCT Research: Space induces compartment-specific losses in bone sub-regions (n=16)



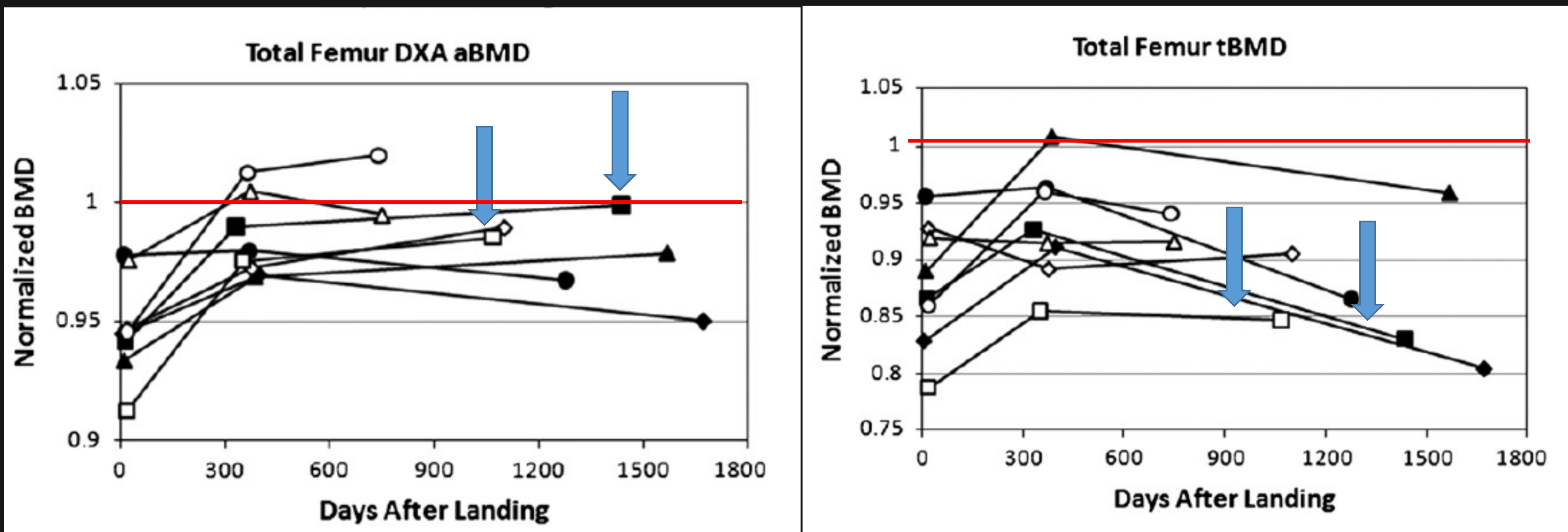
Index DXA	%/Month Change ± SD	Index QCT	%/Month Change ± SD
aBMD Lumbar Spine	1.06±0.63*	Integral vBMD Lumbar Spine	0.9±0.5
		Trabecular vBMD Lumbar Spine	0.7±0.6
aBMD Femoral Neck	1.15±0.84*	Integral vBMD Femoral Neck	1.2±0.7
		Trabecular vBMD Femoral Neck	2.7±1.9
aBMD Trochanter	1.56±0.99*	Integral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



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

DXA areal BMD and QCT trabecular volumetric BMD of Total Proximal Femur:

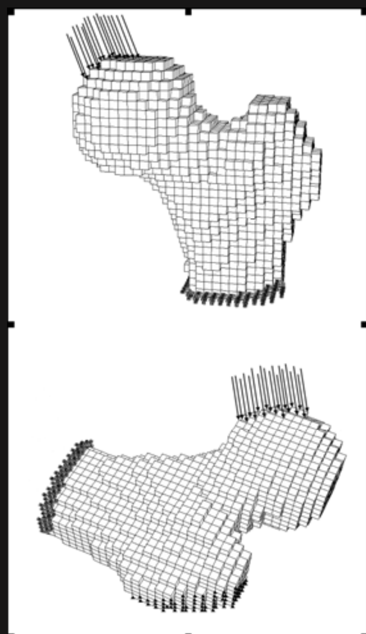
Discordant Recovery Patterns 2 -4 Years Post-flight

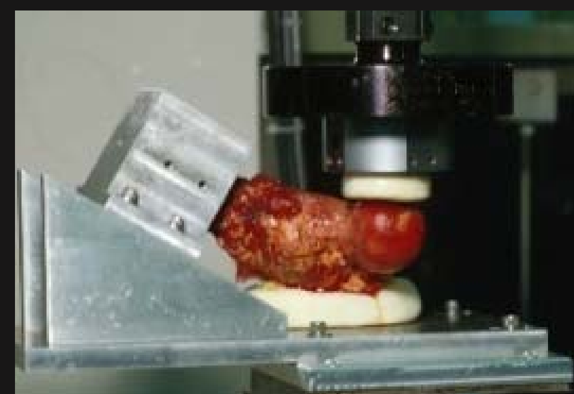


QCT Extension Study (n=8) Postflight Trabecular BMD in hip. Carpenter, D et al. Acta Astronautica, 2010.

FEM – a computational tool to estimate failure loads ("strength") of complex structures.

i) Models generated from QCT data. ii) Applied to astronauts (n=11) in collaboration with QCT study.



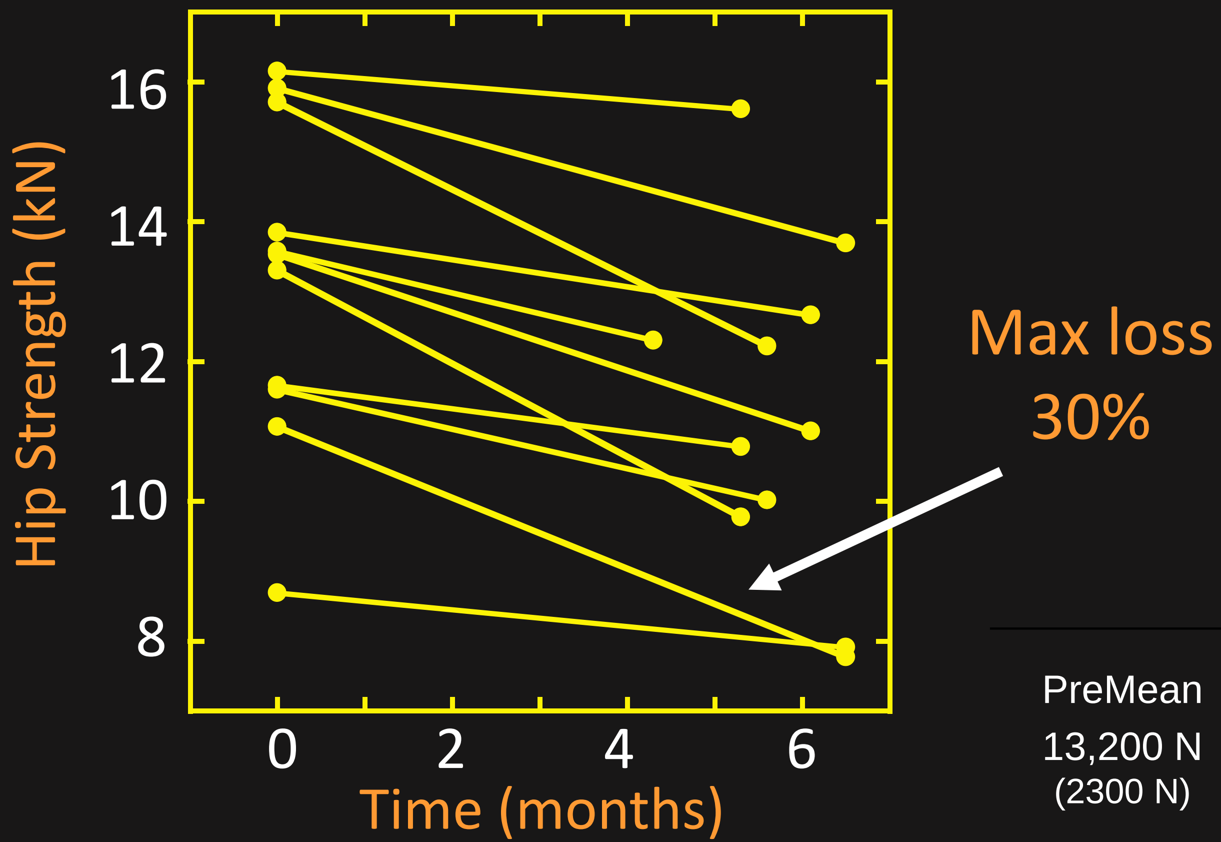


J. Keyak et al, 1998, 2001, 2005

Images courtesy of Dr. J Keyak

Individual Results

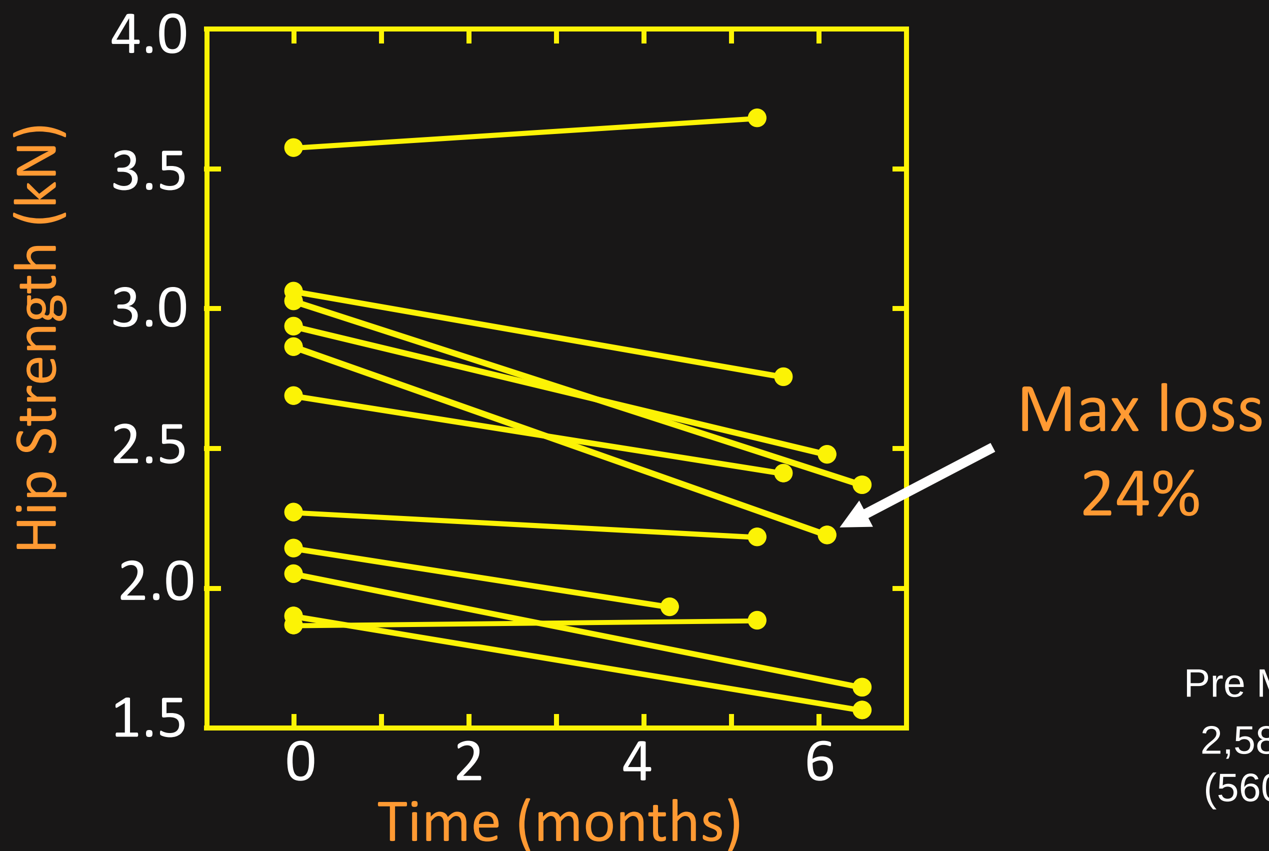
Stance Loading (4 to 30% loss in strength)



PreMean	Post Mean	P
13,200 N (2300 N)	11,200 N (2400 N)	<0.001

Individual Results

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

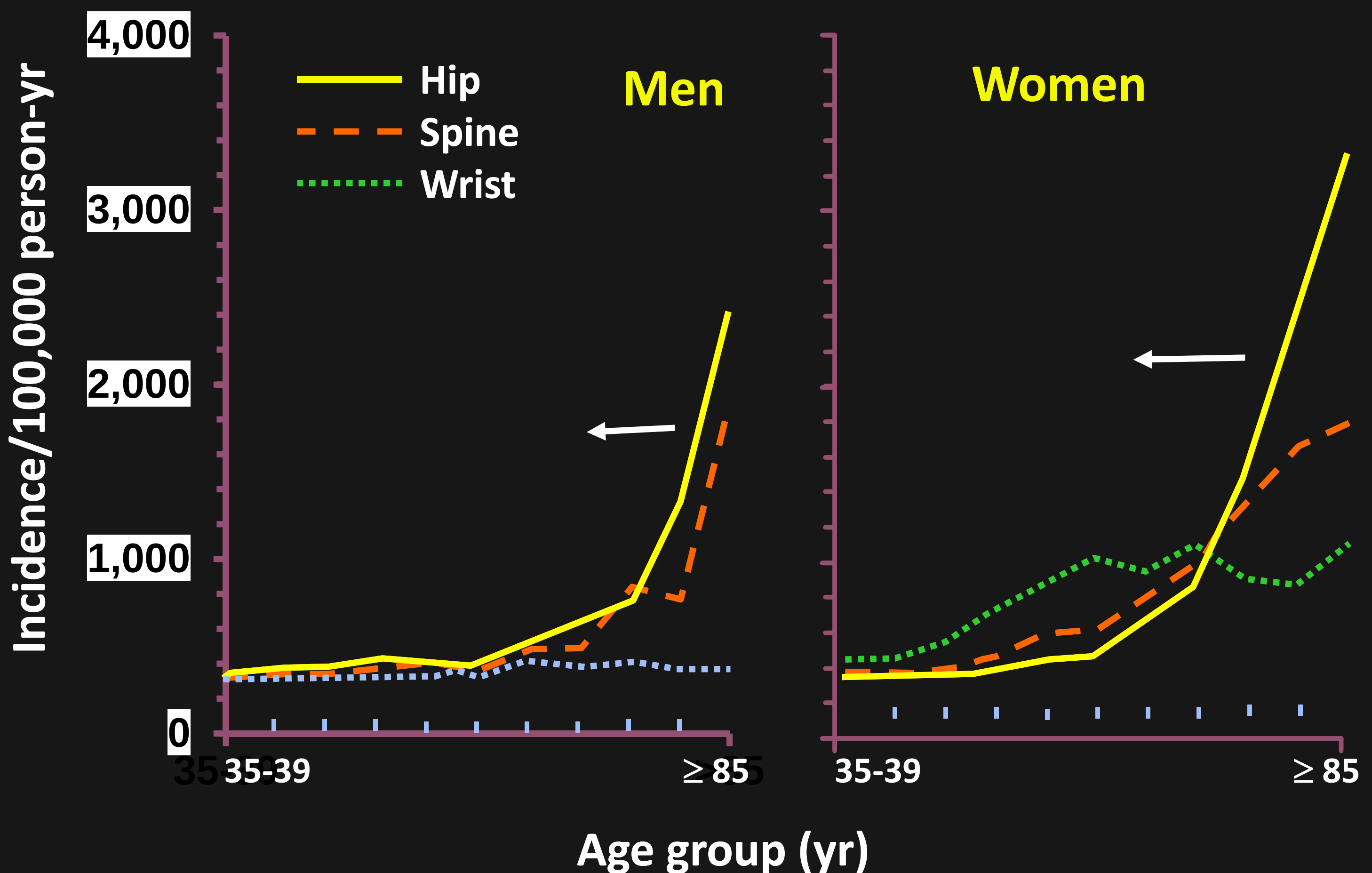


Pre Mean	Post mean	P <
2,580 N (560 N)	2,280 N (590 N)	0.003

Overview

- What makes Bone complicated?
- What makes space effects so unique?
- What steps are recommended to manage fracture risk in astronauts given NASA constraints?

If clinical test is insufficient, how can we predict *when* fragility premature fractures might occur in astronauts?



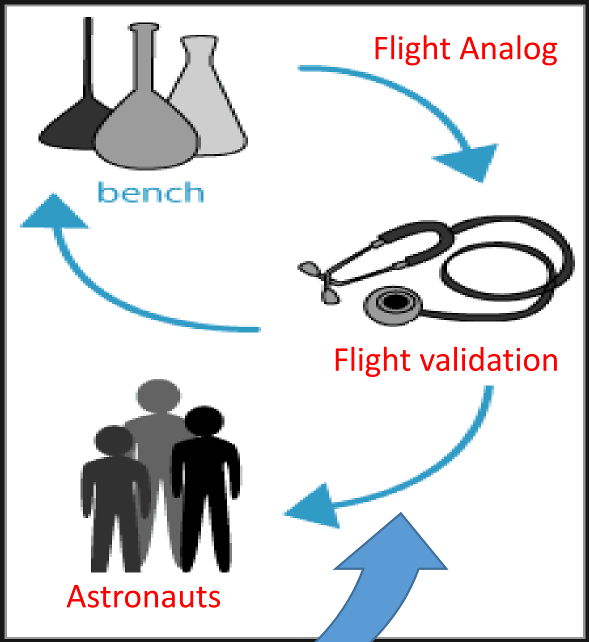
SLIDE COURTESY OF Dr. S. AMIN, Mayo Clinic

Cooper and Melton, 1992

Convening a panel of Policy Makers in BMD/Osteoporosis Field

BONE SUMMIT
Clinical Advisory Panel
2010, 2013

Translational Research @ NASA



Desired Deliverable: Clinical Practice Guidelines

1. What specific measure(s) do we need to monitor in lieu of incidence?
2. What's the clinical trigger?
3. What should be the clinical response?

REVIEW

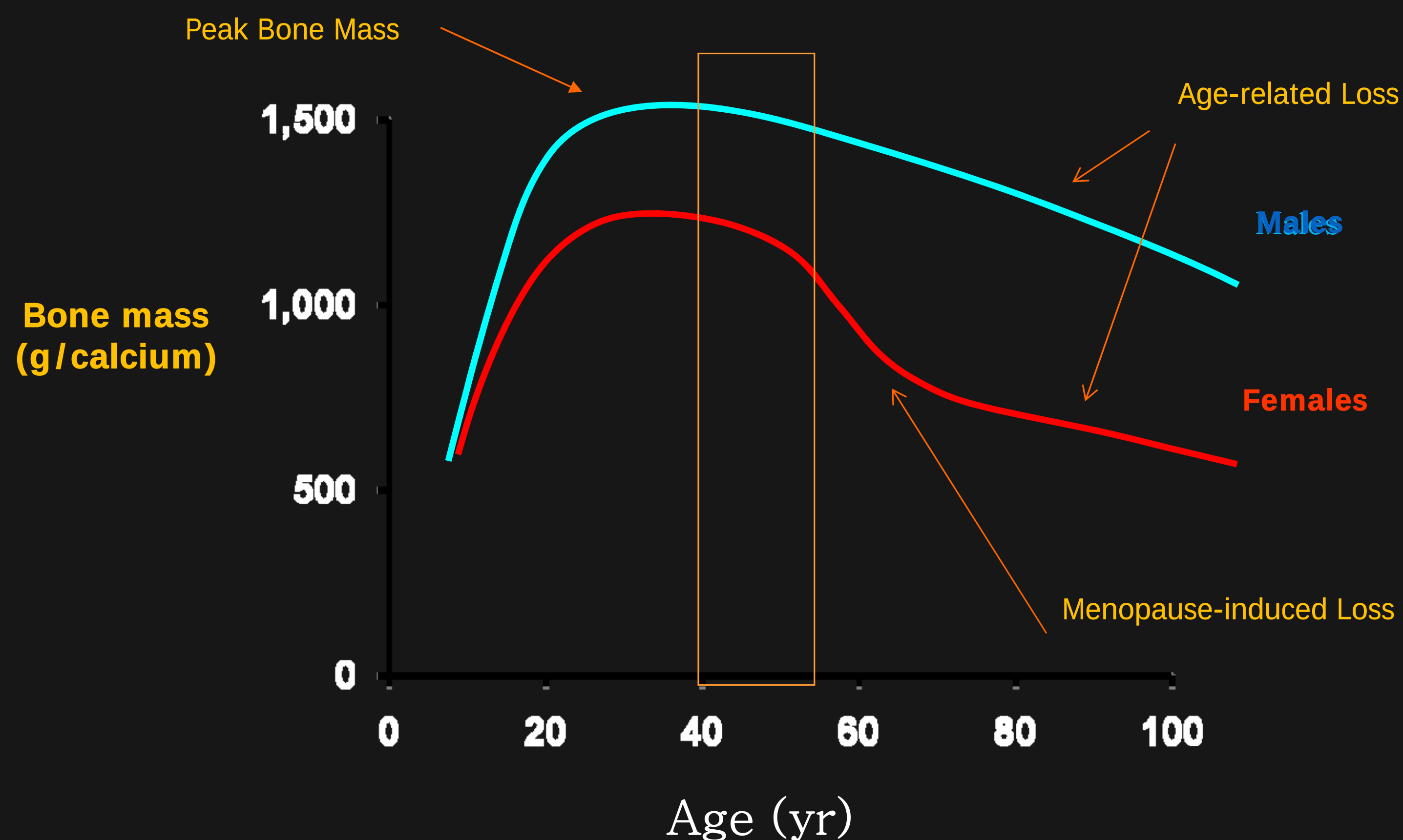
JBMR

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]

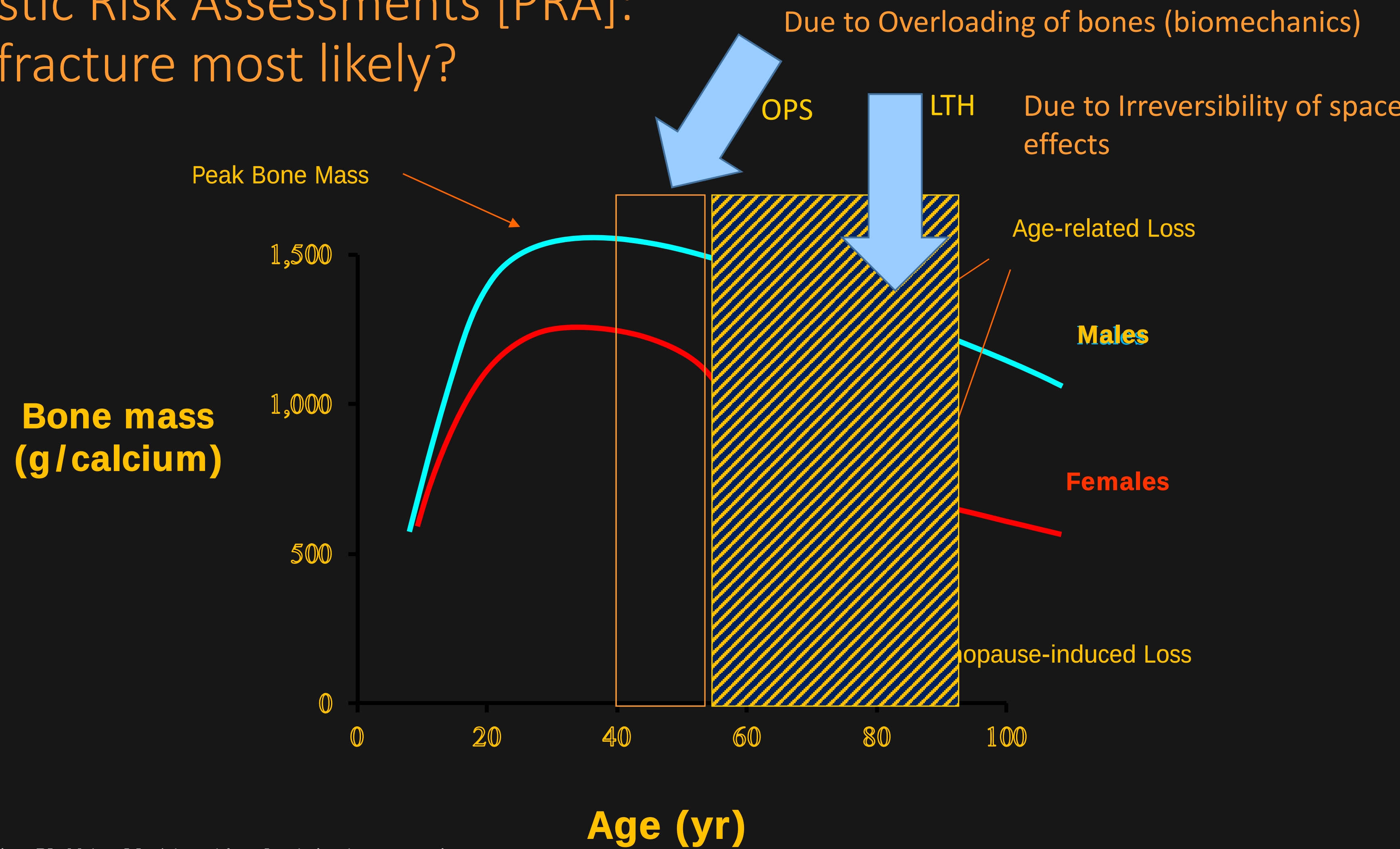
Journal of Bone and Mineral Research
Vol. 28, No. 6, June 2013, pp 1243–1255

What measurements should be performed to describe spaceflight changes?



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

Probabilistic Risk Assessments [PRA]: When is fracture most likely?



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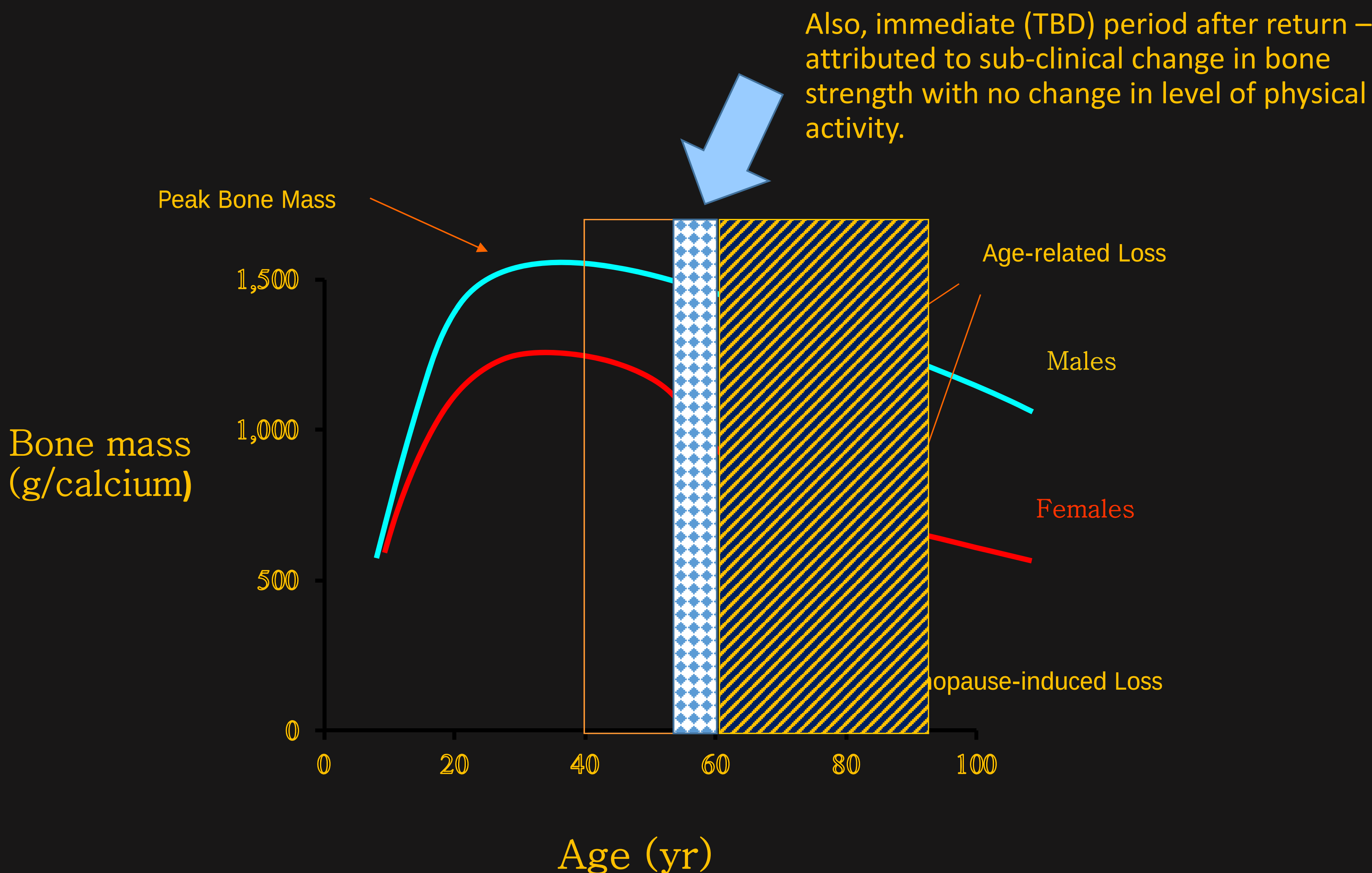


Riggs BL, Melton LJ: Adapted from Involutional osteoporosis
Oxford Textbook of Geriatric Medicine
ADAPTED SLIDE COURTESY OF Dr. S. AMIN, Mayo Clinic

Clinical Evidence: QCT measures are independent predictors of hip fracture to supplement aBMD in the aged.

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

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]

Subsequently, Clinical Advisory Panel recommends the following:

1. ClinicalTrigger: The failure to measure recovery of trabecular BMD of hip by two years after return in astronaut.
2. Clinical response: Seek an evaluation by an osteoporosis specialist. Correction of risk factor or possible intervention.
3. Overall, QCT measures provide useful information regarding causation of hip fracture, evaluation of hip fracture risk and possible targets for intervention. Good candidate for “Risk Surveillance.”

Science Rationale:

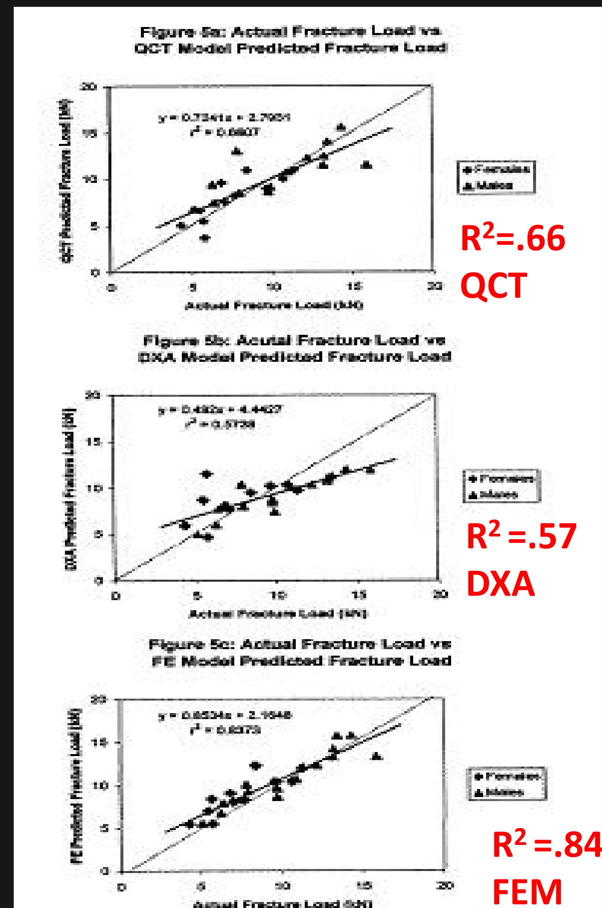
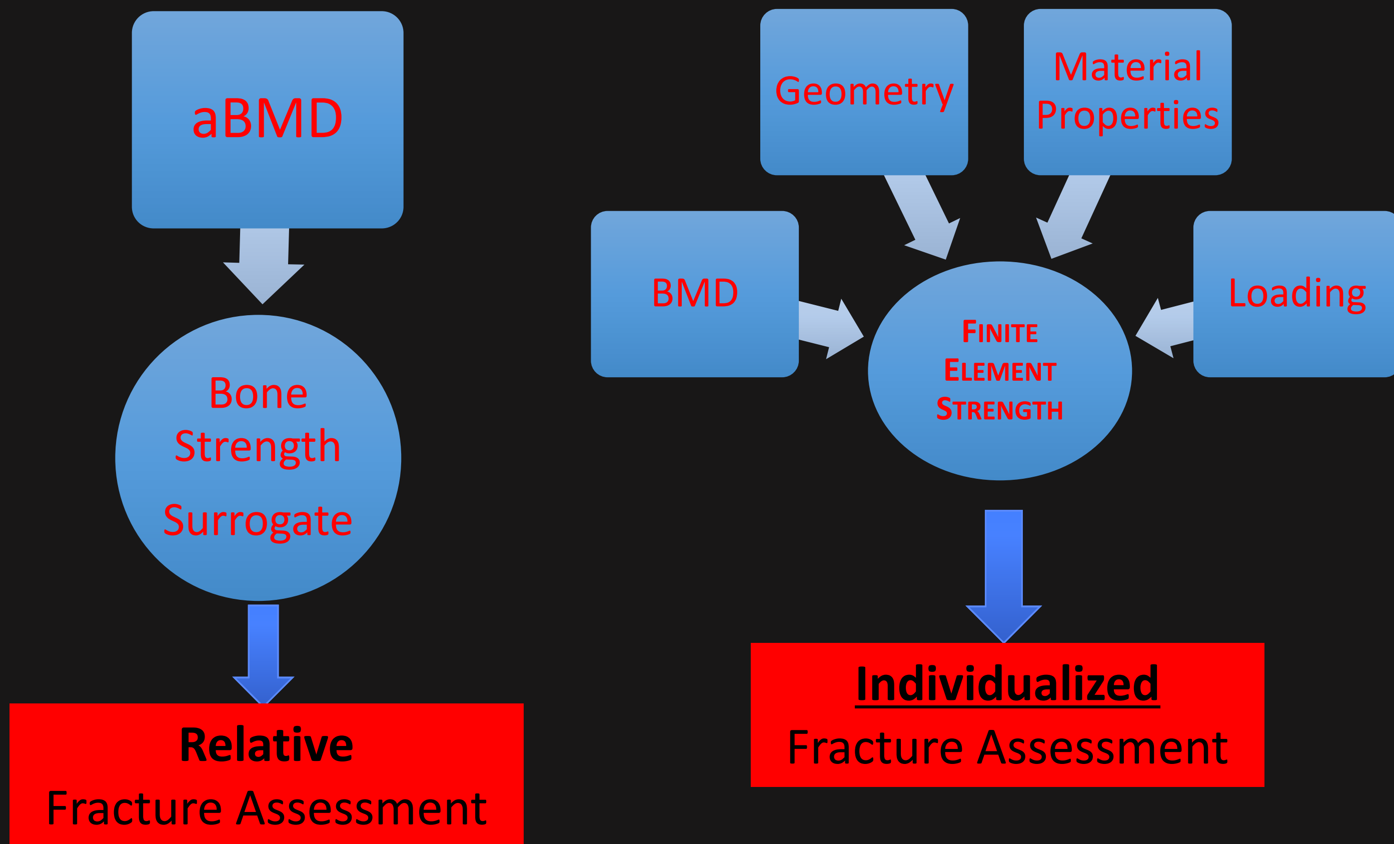


Fig. 5. The predicted strength of the specimens in the test set (developed from the models generated using the training set) plotted against their actual measured values for each of the three methods (a: QCT; b: DXA; c: FEM).

QCT + FEM outperforms DXA and QCT for estimating fracture loads

Investigate FE estimates of hip strength as new surrogate for bone health for individualized assessements- likely to capture more effects of spaceflight that affect bone integrity.



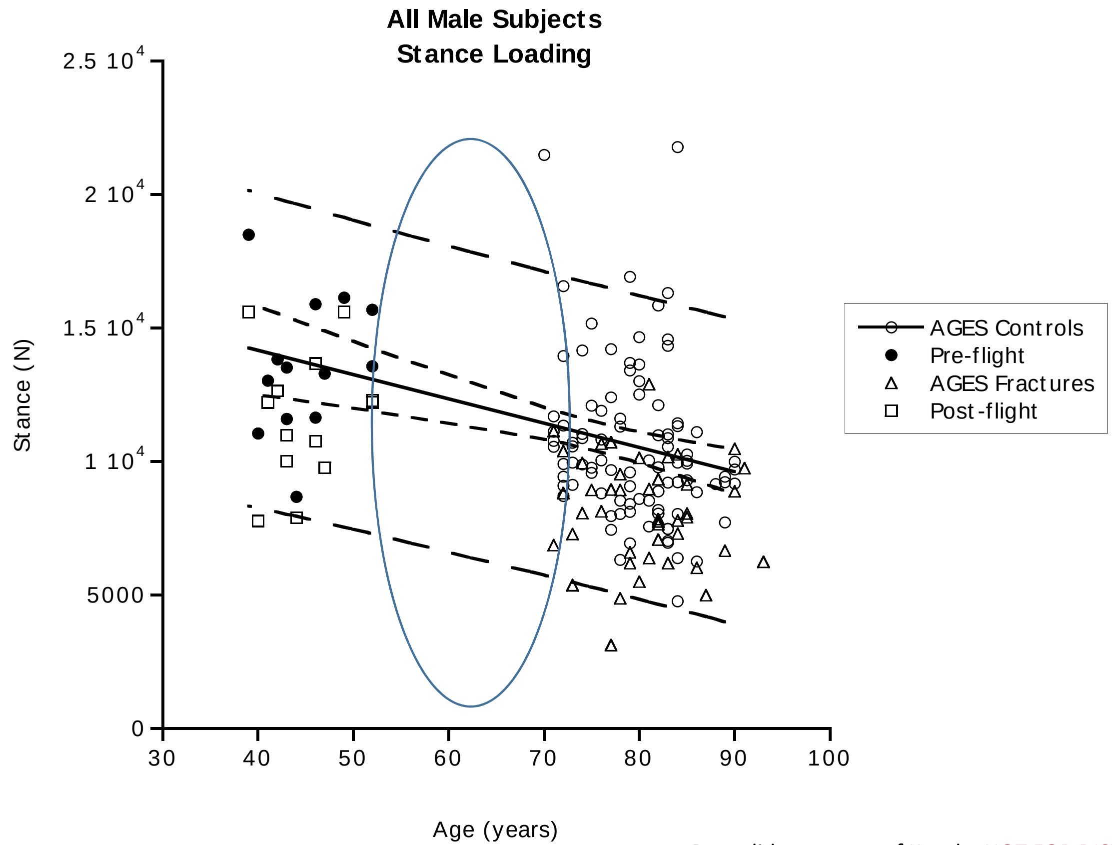
Recommendation: Explore emerging data from population studies using FE bone strength to predict fractures and return to panel with findings for clinical operating bands of astronaut health.

- **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.
- Position on the use of QCT for clinical decision making is being deliberated by International Society of Clinical Densitometry [ISCD] as of **Feb. 2015**. Data from clinical studies (n=22 reports of qCT and/or FEM) in this meta analysis.

Exploring Finite Element Models [FEM] of QCT Scans from Population Studies

FE Task Group:

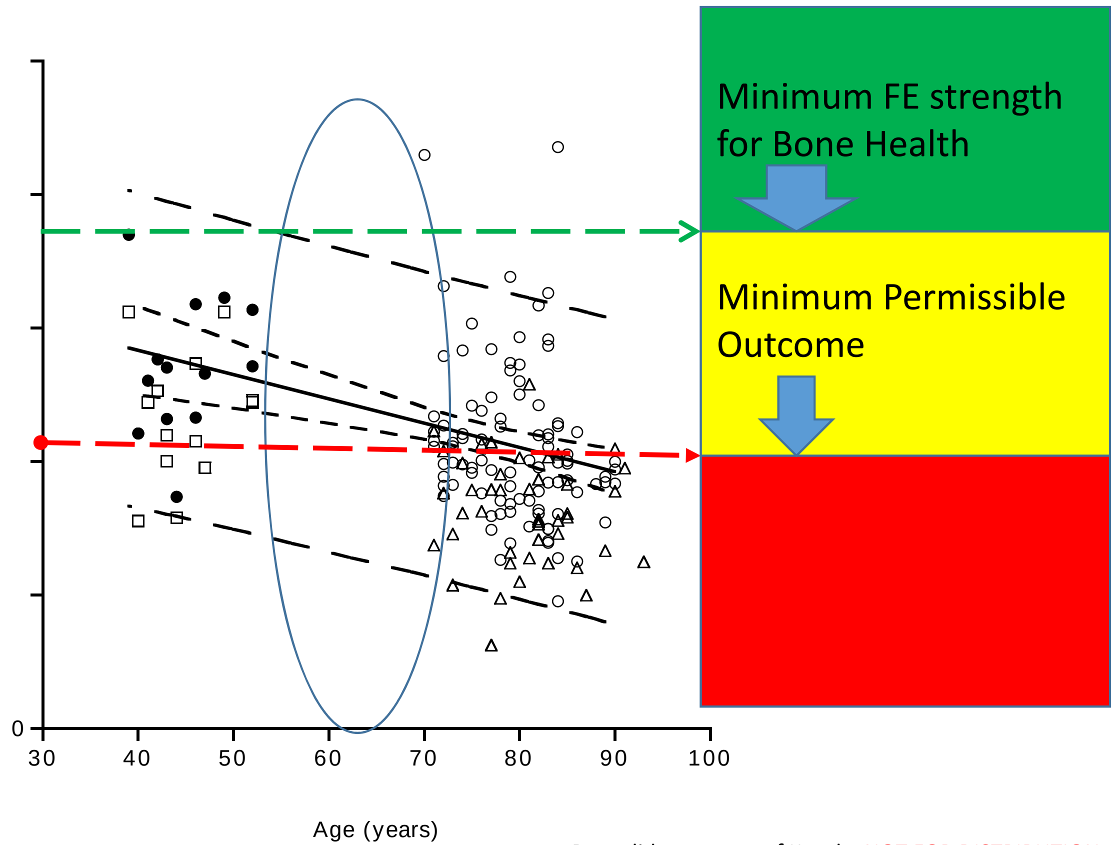
E. Orwoll MD, S Khosla MD, S Amin MD, T Lang PhD, J Keyak PhD, T Keaveny PhD, D Cody PhD, JD Sibonga, Ph.D.



ONE REPRESENTATIVE POPULATION DATA

Data slide courtesy of Keyak. NOT FOR DISTRIBUTION

RESEARCH: Selecting FE Cutoffs for "Bone Health"- i.e., hips strong enough to account for declines due to spaceflight and to aging- to be used together with DXA BMD Standards.



REPRESENTATIVE POPULATION DATA

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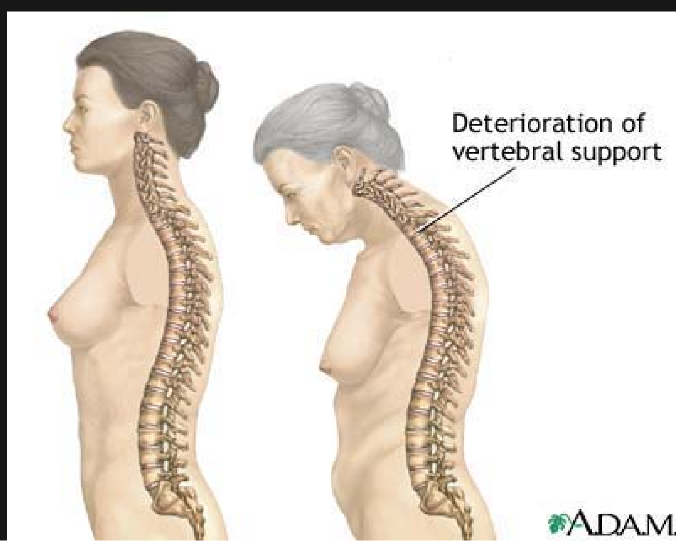
High Resorption ➡ Disrupts Microarchitecture ➡ Fractures*

GAPS persist.

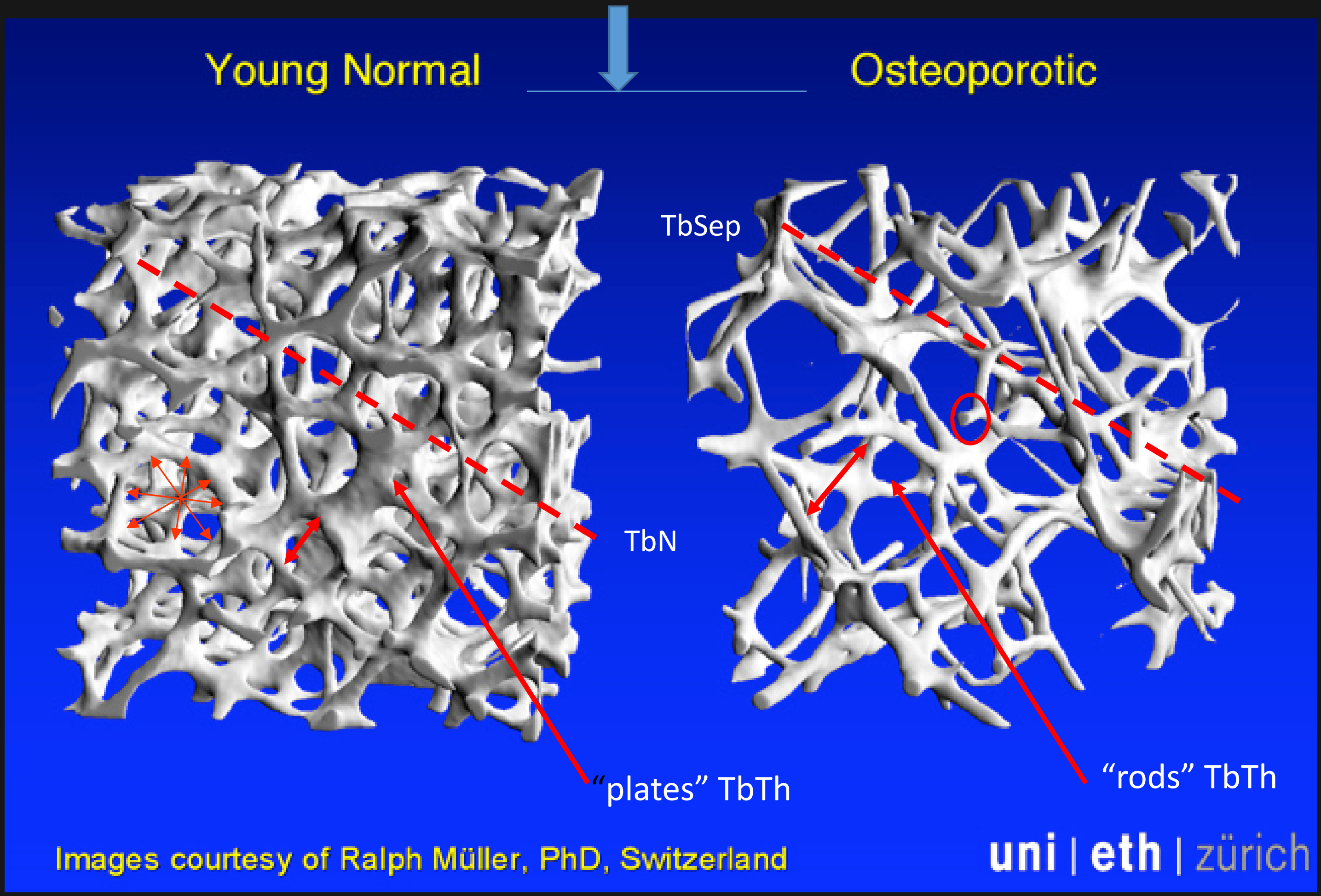


Male Astronauts?

Spaceflight Effect?

The Hip?

Bone Microarchitecture: Need to “discover” technology to monitor for a Non-permissible outcome because irreversible.



Adapted by Sibonga

Summary: Forward Actions for Bone Risk Management

1. Collect QCT data for risk surveillance – for operational and clinical decisions – based upon evidence from randomized controlled trials.

2. QCT provides opportunity for Finite Element Models, the analysis of which generates a "hip strength index" which could be used in a NASA-developed Probabilistic Fracture Assessment Module.

3. Explore FEM data from population studies to identify a possible hip strength cut-point as a modified astronaut standard for hip strength.

4. Search/validate new technologies for surveillance of unique bone measures (e.g., microarchitecture)

5. Note: Following a review of QCT data 9 additional astronauts (case reports), Bone Summit Panel maintained its recommendation to use QCT for surveillance.

Closing Remark

Bone Discipline Goal: To reduce the uncertainty of *spaceflight-induced* fracture risks in astronauts.

- Expand the definition of spaceflight effects on bone loss <u>and</u> recovery.
- Because of constraints, transition innovative technologies and analyses available to measure additional bone parameter and increase our ability to predict fractures

Thank you.

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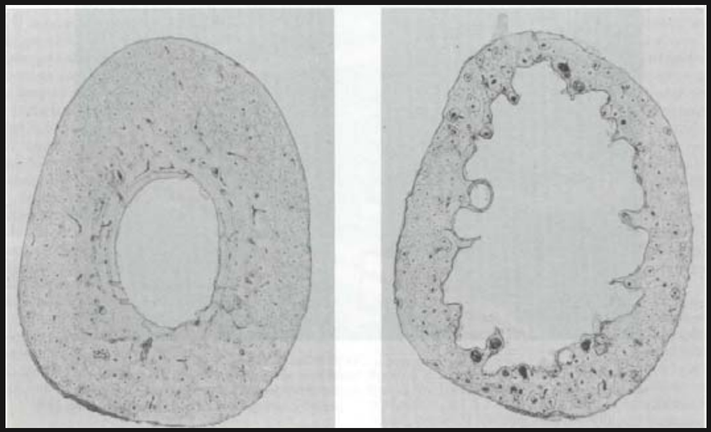
Pilot Study: Hip QCT

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

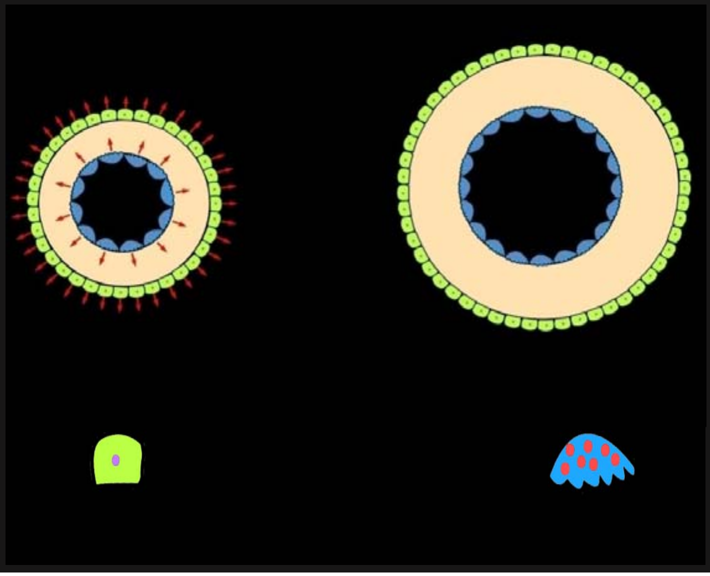
Important to use QCT to evaluate Countermeasures that affect different bone types.

2. Translate QCT data to *hip strength* with FEM.

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



Endocortical bone resorption with disuse



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