Directed Research in Bone Discipline:

Refining previous research observations for space medicine.

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Human Research Program [HRP]
Johnson Space Center, Houston, TX
February 10, 2015

Directed Studies

- HRP Unique Processes, Criteria, and Guidelines (UCPG) – "Research tasks that are initiated without being competed … awarded directly to Principal Investigators (PIs) with the requisite skills to accomplish the work."
- Criteria: a) insufficient time for solicitation; b) highly constrained research.
- Choice by Bone Discipline Lead
- Building upon research data -- to meet aggressive schedule for Path to Risk Reduction [PRR]

Notably,

- Perceived refinements are <u>not</u> from SD - Space and Clinical Operations and <u>not</u> from SK investigators, per se.

- Translation of research data to SD previously attempted by team of SK investigators 2007 – 2009

- As Bone Risk Custodian convened a Bone Summit in 2010 – panel of osteoporosis experts – to address clinical risk management

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

"Bone Summit I – 2010"

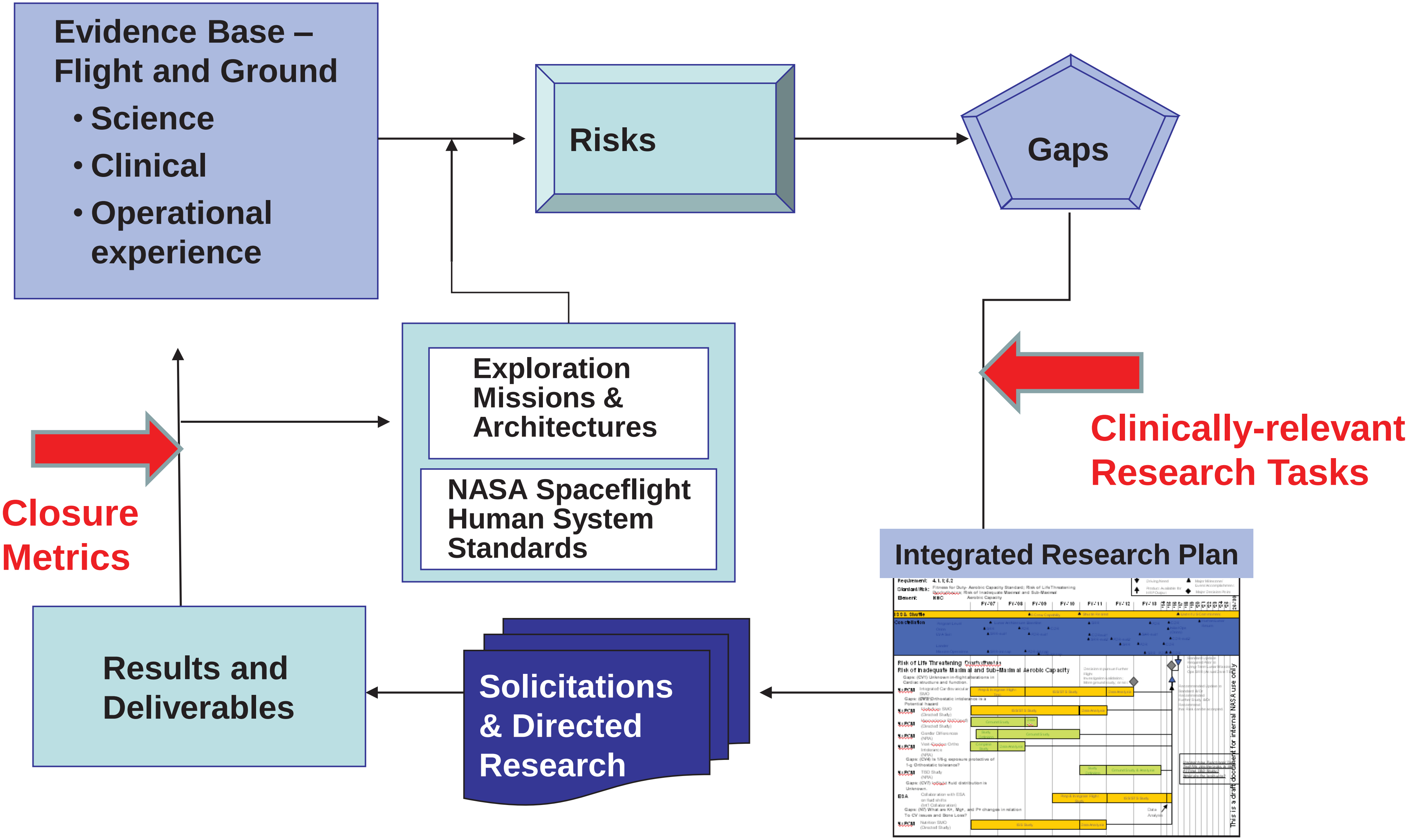
REVIEW

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]

Use of the *Research Clinical Advisory Panels* [RCAP] to prioritize NASA's Human Research for Bone Risks



HRP slide courtesy C. Kundrot
Adapted Sibonga 2012

Bone Summit II - Bottom Line

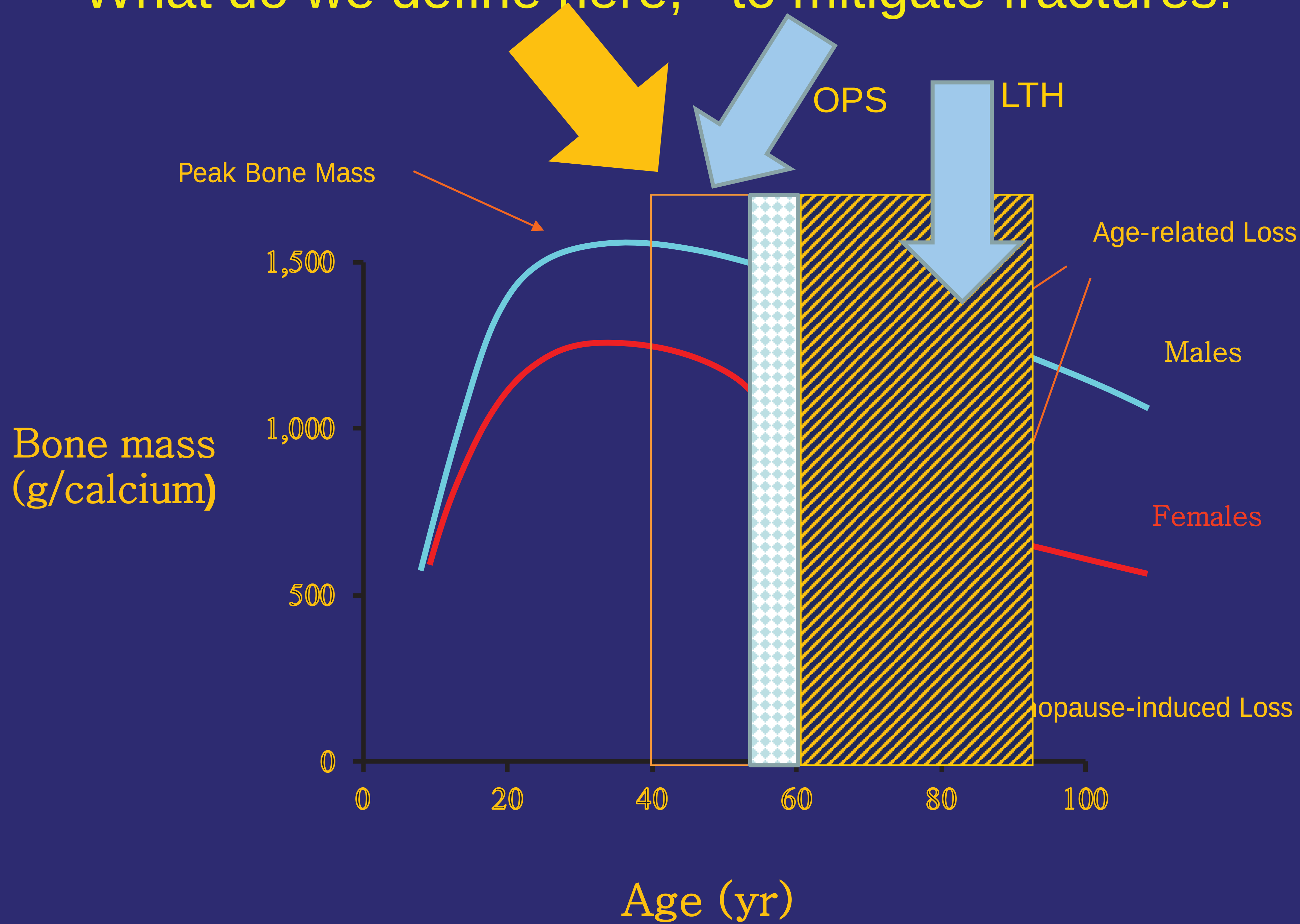
" Overall, NASA's strategy of assessing relative fracture risk in astronauts by T-score BMD-based guidelines alone needs to be refined. Accurately determining the absolute fracture risk in astronauts is an ambitious goal that may never be fully realized. A concerted effort however should be made to expand 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."

What do we define here, to mitigate fractures.

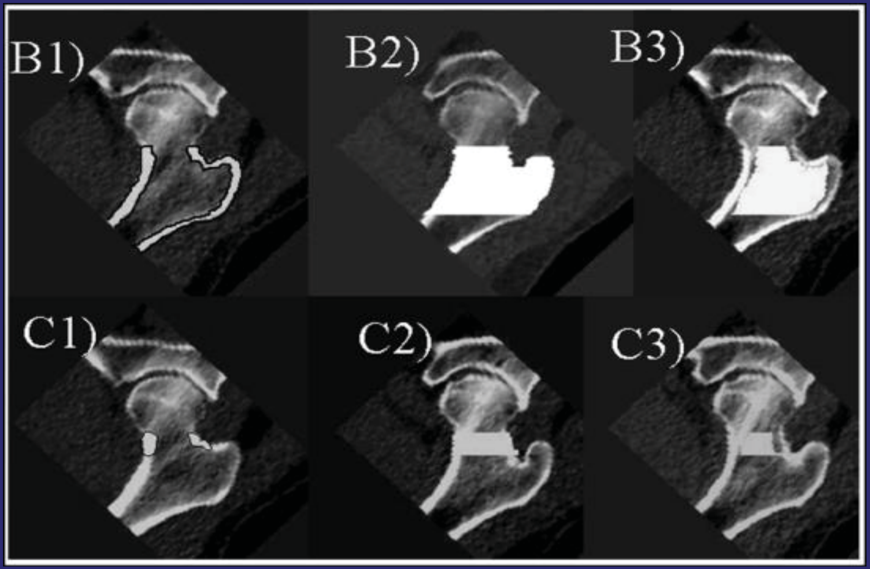


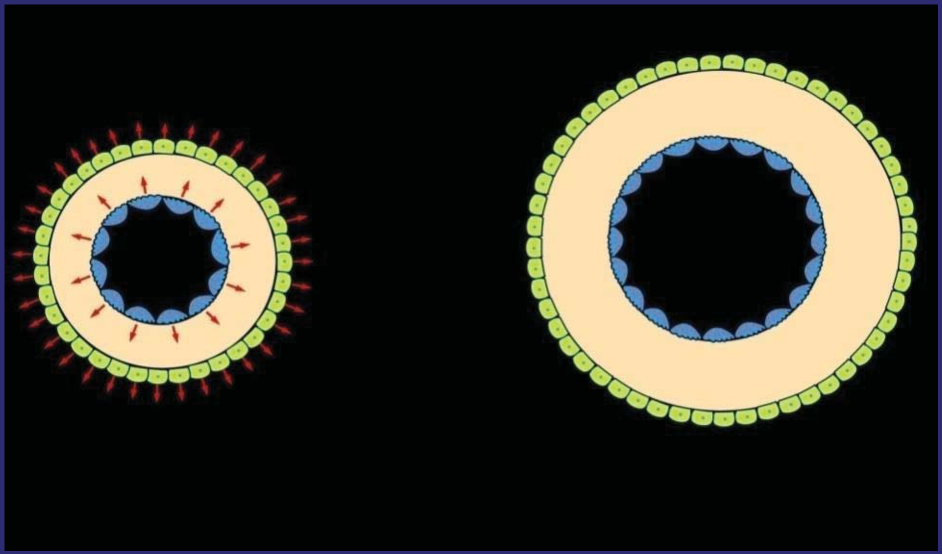
Riggs BL, Melton LJ: Adapted from Involutional osteoporosis
Oxford Textbook of Geriatric Medicine
ADAPTED SLIDE COURTESY OF Dr. S. AMIN, Mayo Clinic

Fracture probability dependent upon data being assessed.

1. What & when are surveillance measurements required for collection?
2. LTH: Bone Summit identified the lack of recovery as a critical trigger – and not just BMD.
3. OPS: probability of overloading of bones (task-related).
4. Early LTH – immediately after return (e.g., 1-3 years) related to activity level and limited test
5. NASA's Bone Fracture Module - not sensitive to changes in BMD due to ARED exercise or Bisphosphonates – *due to large variability*.
6. Proposed – using bone strength calculated by Finite element modeling to reduce the uncertainty.

Study on Risk Surveillance: Hip QCT

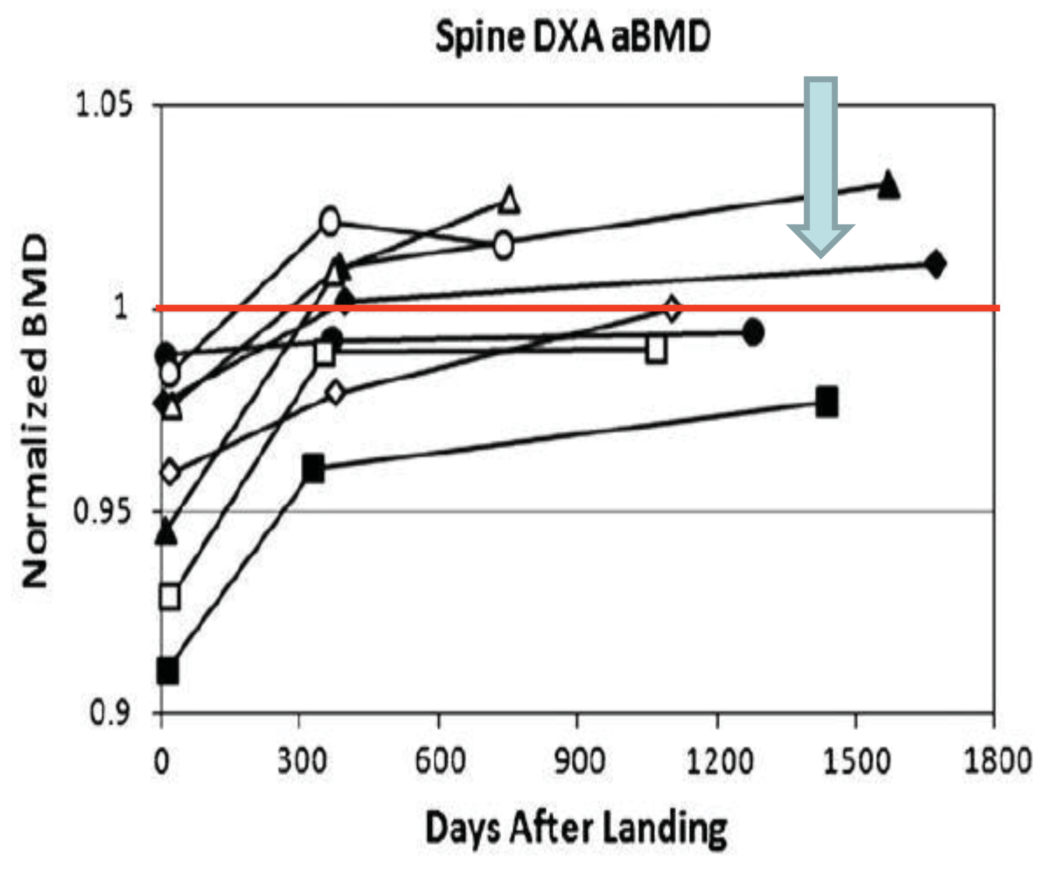


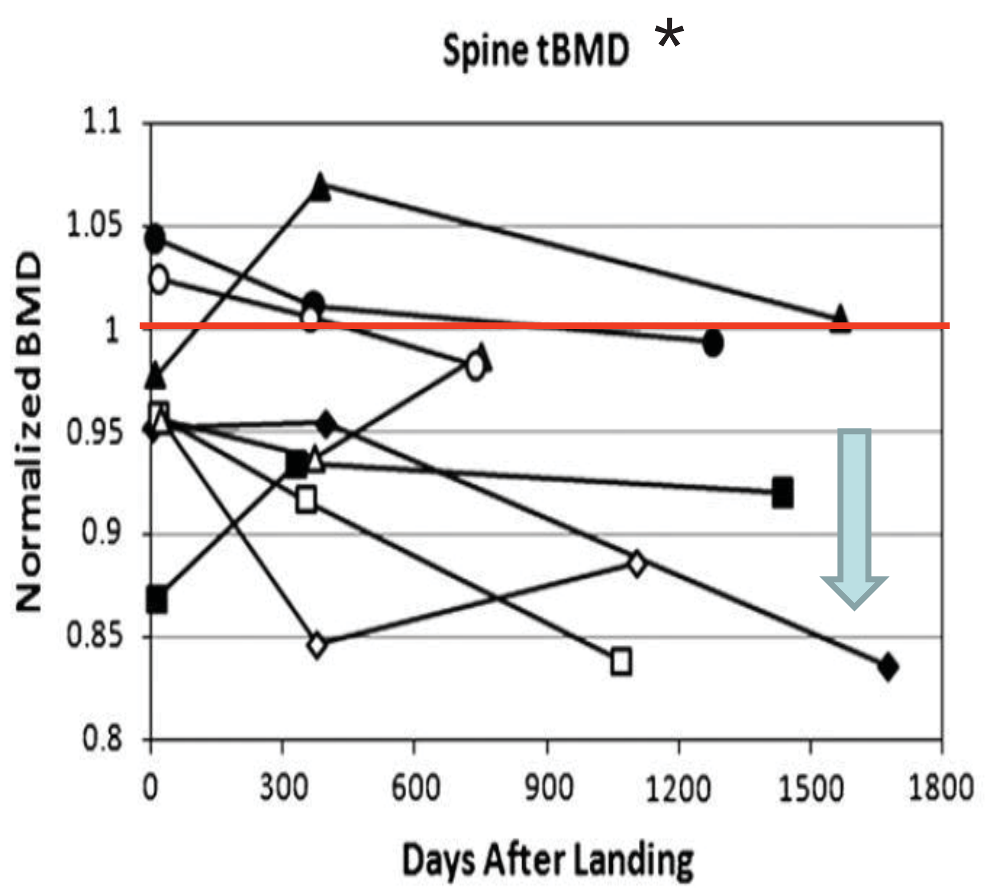


- Test feasibility of QCT protocol for surveillance of identified clinical trigger (later).
- Accumulate surveillance data for development of clinical practice /intervention guidelines (QCT and FEM)
- **Research**: Demonstrate how QCT can delineate biochemical from mechanical countermeasures. "Proof of Concept" Pilot Study

Figures courtesy of T. Lang (UCSF) and D. Carter (Stanford U)

DXA vs. QCT Spine: Discordant Recovery Patterns in Astronauts After Spaceflight



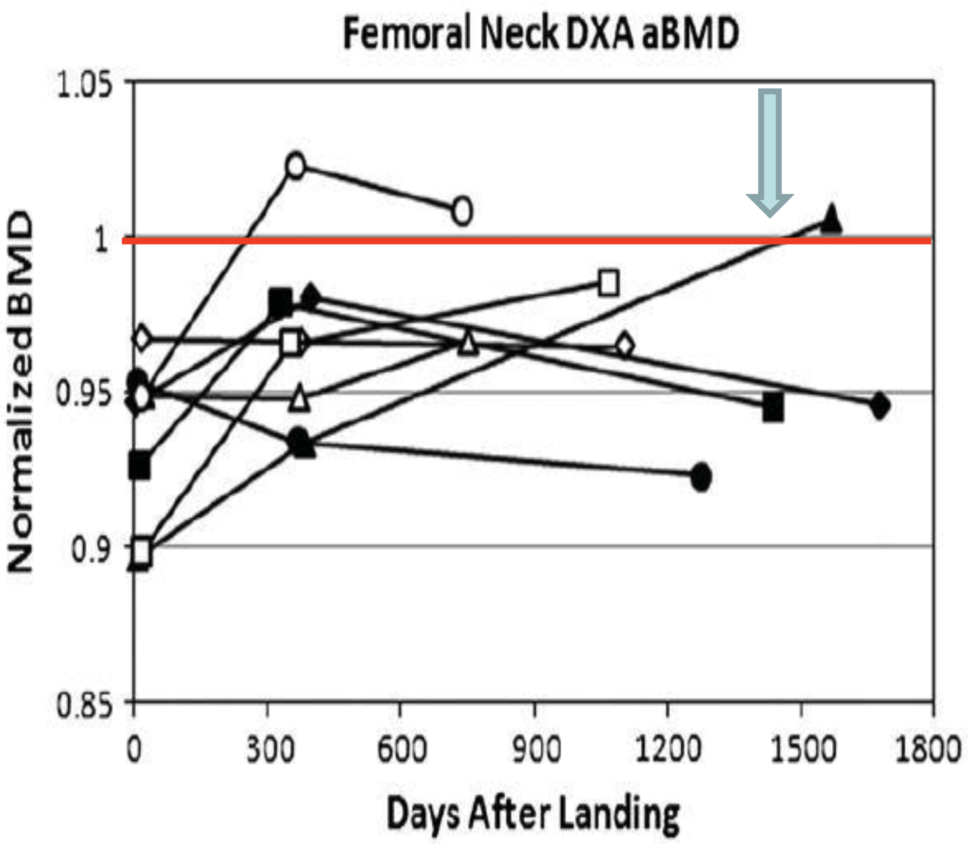


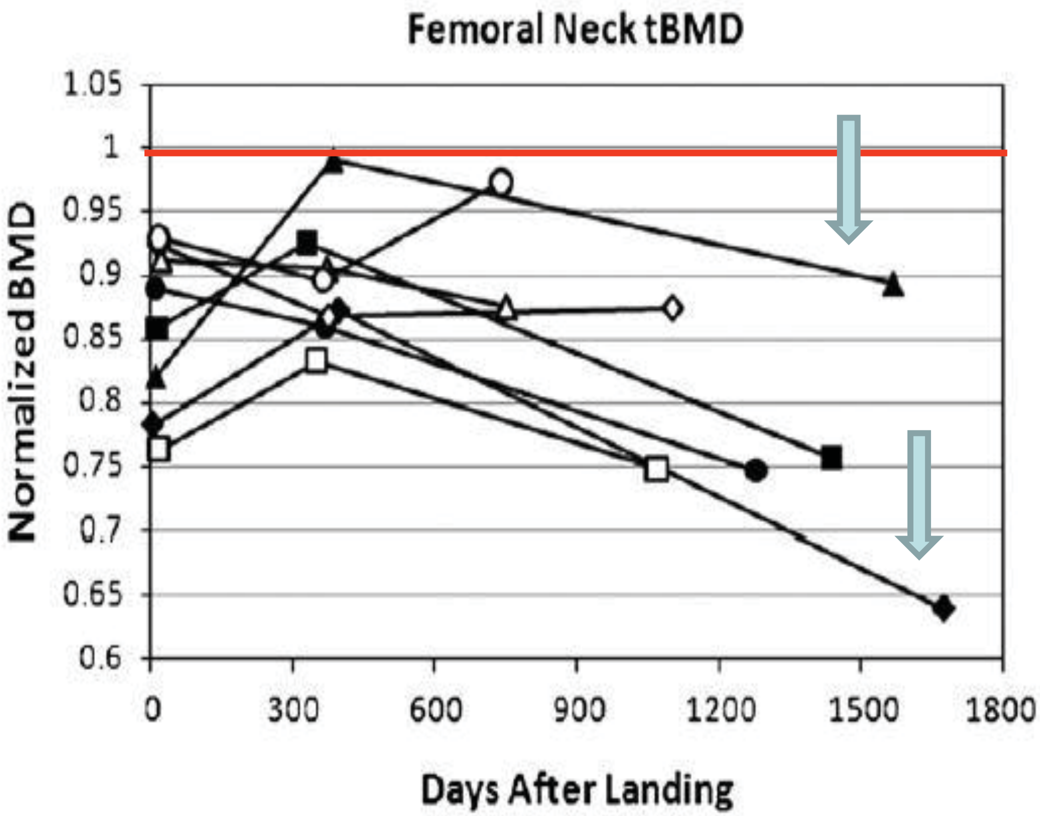
aBMD – areal bone mineral density g/cm^2

tBMD – trabecular volumetric bone mineral density g/cm^3

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

DXA vs. QCT Hip:
Why the clinical concern?





aBMD – areal bone mineral density g/cm^2

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

Lower trabecular BMD of hip is an independent predictor of hip fracture in elderly men. Surveillance of mitigation and recovery is warranted – hypothesis should not be required.

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

QCT measures -- useful information regarding etiology of hip fracture, evaluation of hip fracture risk and possible targets for intervention.

Flight Study– Reductions in Hip Strength with spaceflight.

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
Fall	2,580 N (560 N)	2,280 N (590 N)	0.003

Keyak et al Bone. 2009 Mar;44(3):449-53

QCT + FEM has superior capabilities for estimating fracture loads

BMD accounts for 50-70% bone strength

QCT estimates fracture loads better than DXA

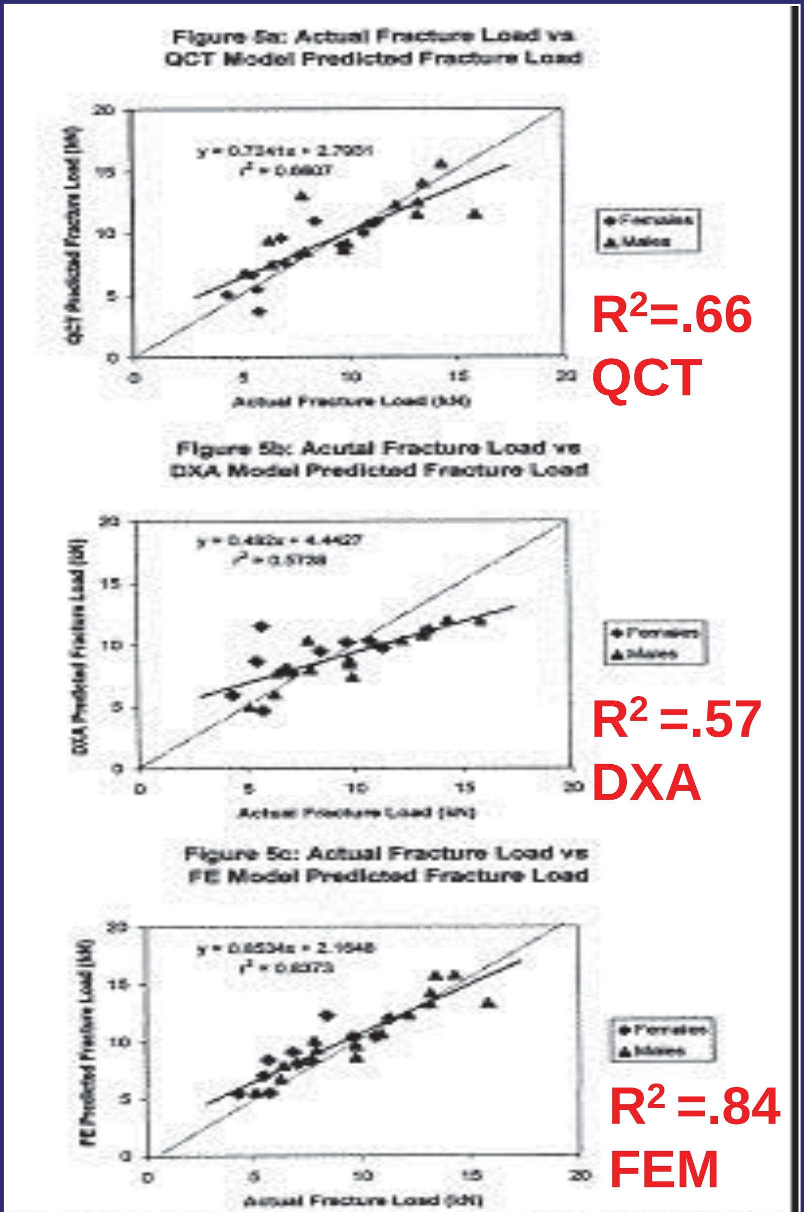
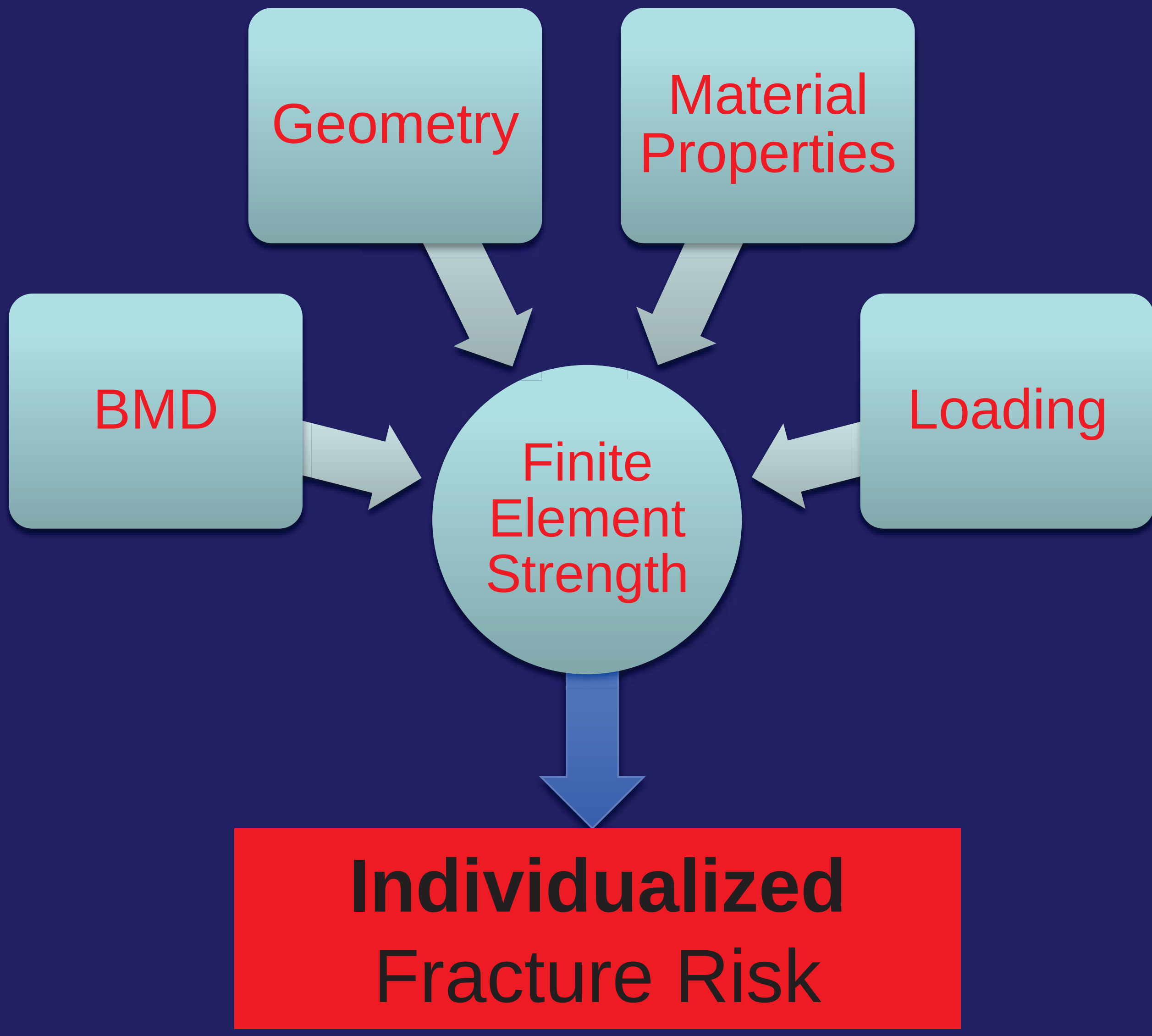


Fig. 5. The predicted strength of the specimens in the test set (developed from the models generated using the training set) plotted against their actual measured values for each of the three methods (a: QCT; b: DXA; c: FEM).

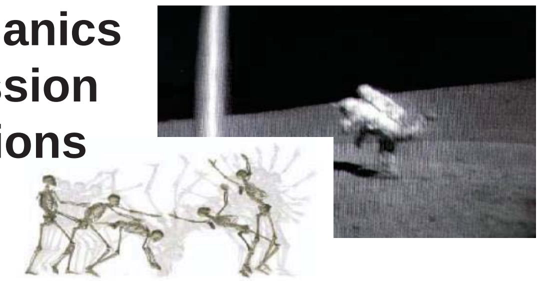
DD Cody: Femoral strength is better predicted by finite element models than QCT and DXA. J Biomechanics 32:1013 1999.

FEM of QCT data integrates multiple factors associated with fracture for single composite number to estimate bone strength.



NASA’s Probabilistic Risk Assessments for Model for Fracture – using QCT+ FEM

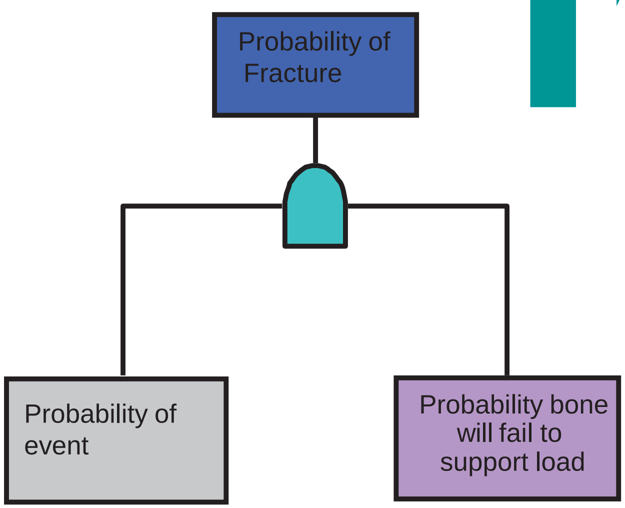
Biomechanics and Mission Operations



courses.washington
.edu/me598rc

Bone Loss in Space

Estimate of Fracture Probability



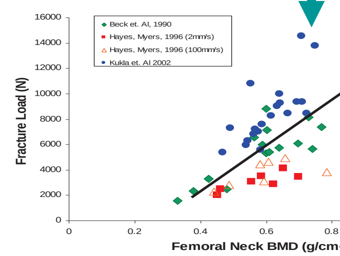


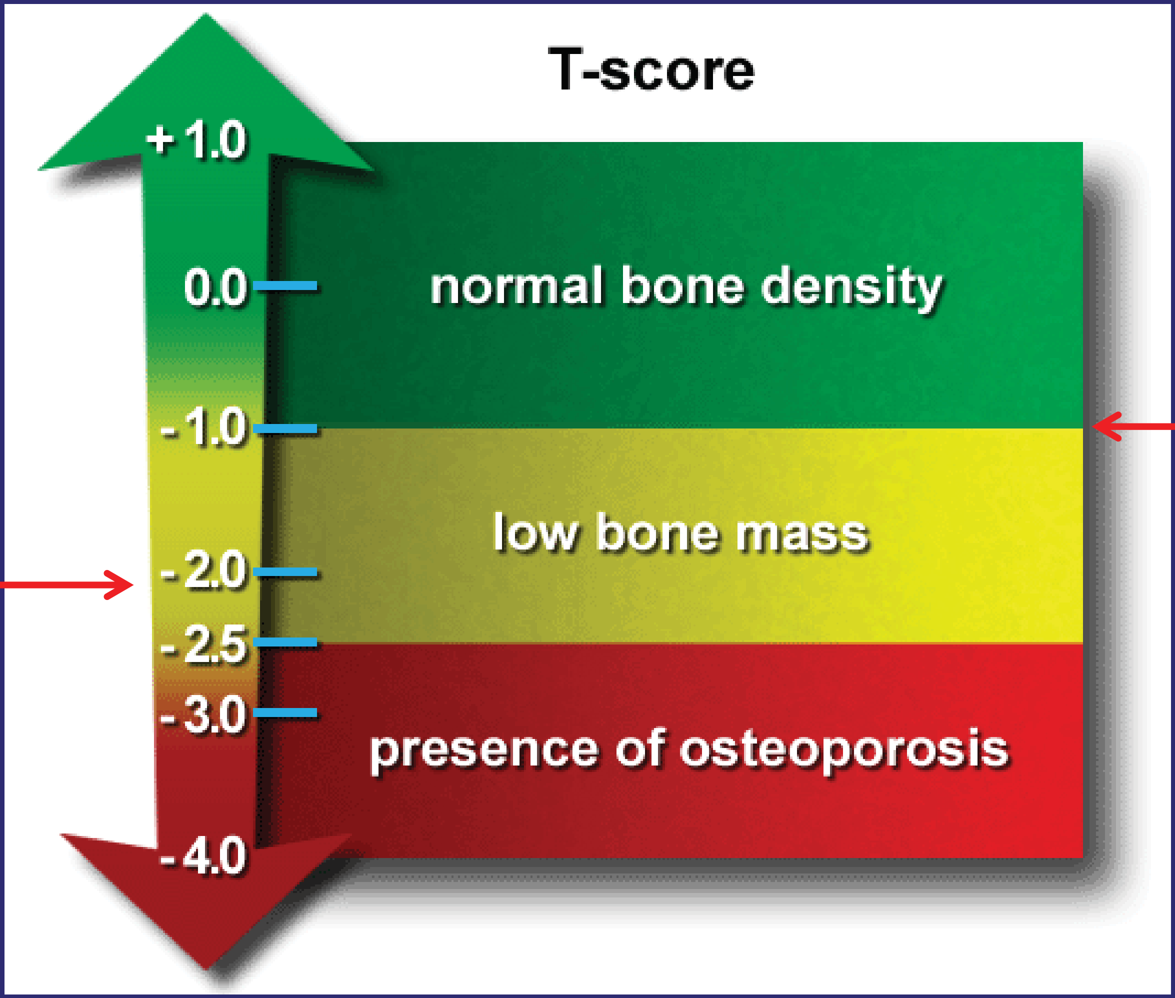
Figure 2. Summary of literature survey on fracture load as a
neck BMD

Clinical and Engineering Characteristics of Bone Strength

Slide courtesy of J Myers; Adapted by Sibonga

Rationale late 1990's: NASA develops standards for Crew Health Based on World Health Organization (WHO)

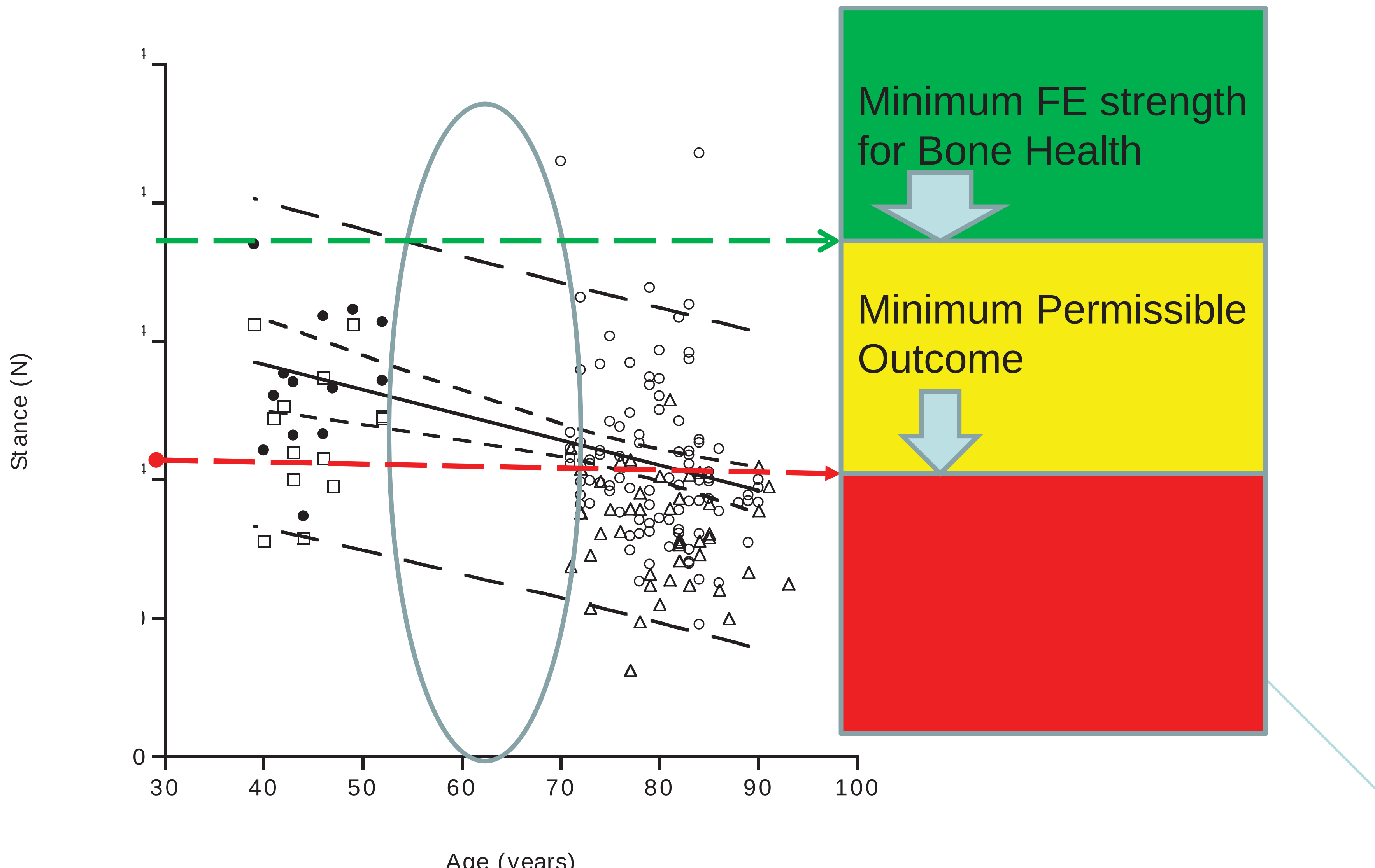
Permissible Outcome Limit



Fitness For Duty

T-score = # Standard Deviations from Normal bone mineral density [mean BMD] of young healthy persons.

RESEARCH: Hypothetical FE Cutoffs (N or kN) for “Operating Bands of Bone Health”- i.e., are hips strong enough to account for declines due to spaceflight and to aging- to be used together with DXA BMD Standards.



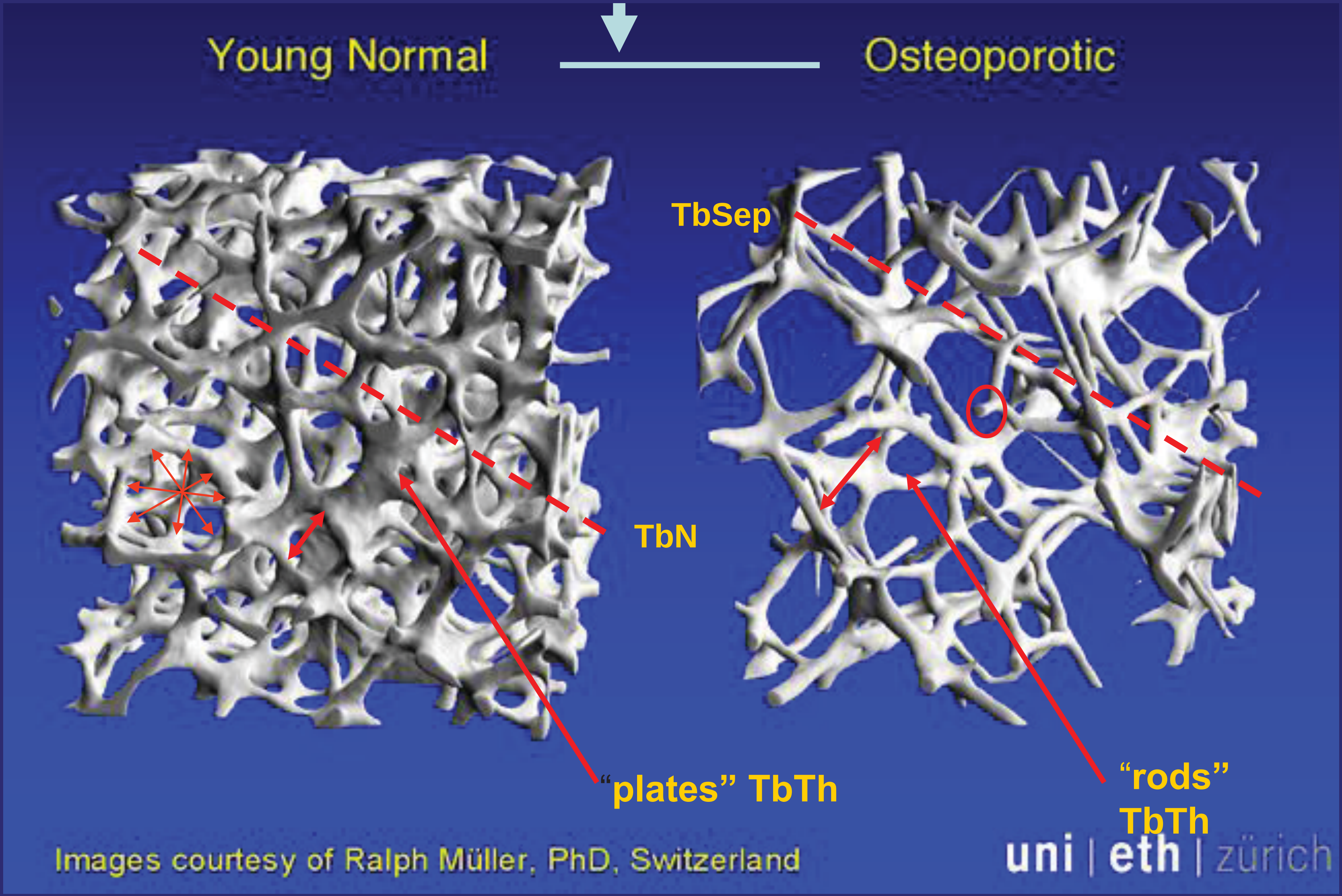
REPRESENTATIVE POPULATION DATA

Data slide courtesy of Keyak. [redacted]

Clinical Validation of Innovative Technologies: Bone Disruption in Microarchitecture

Male Astronauts?
Spaceflight Effect?
The Hip?

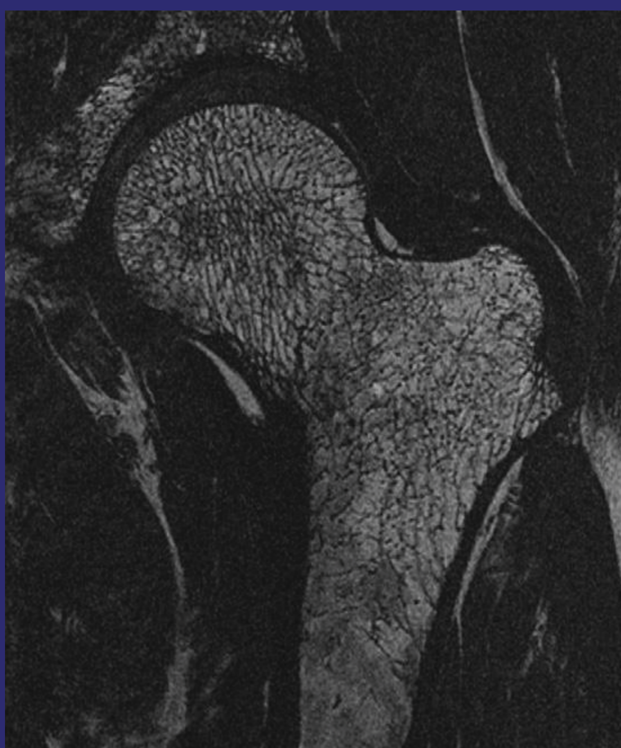
Microarchitectural Measures of Trabeculae and of Spatial Orientation

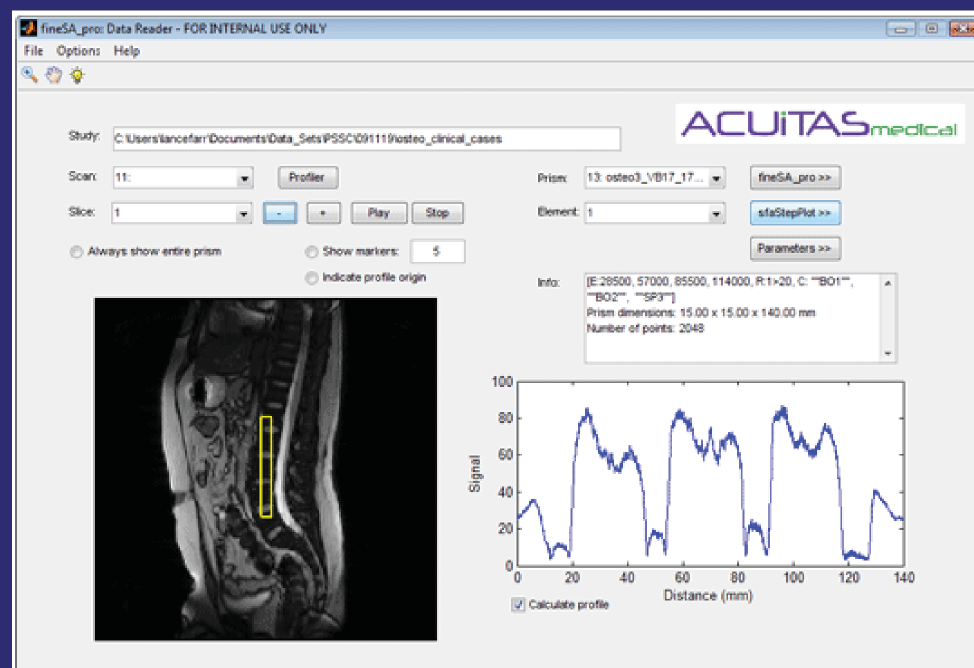


Adapted

Exploring Magnetic Resonance Technologies for Hip Bone Microarchitecture

- Virtual biopsy software (Acuitas: fineSA™)
- Easily translatable to any clinical or preclinical imaging system (No new hardware, No modifications)
- Innovative surface coils (and pulse sequences) show for MR-based assessments of trabecular structure in the proximal femur (Chang, NYUMC)





Source: www.acuitasmedical.com

To Sum, Directed Studies in Bone

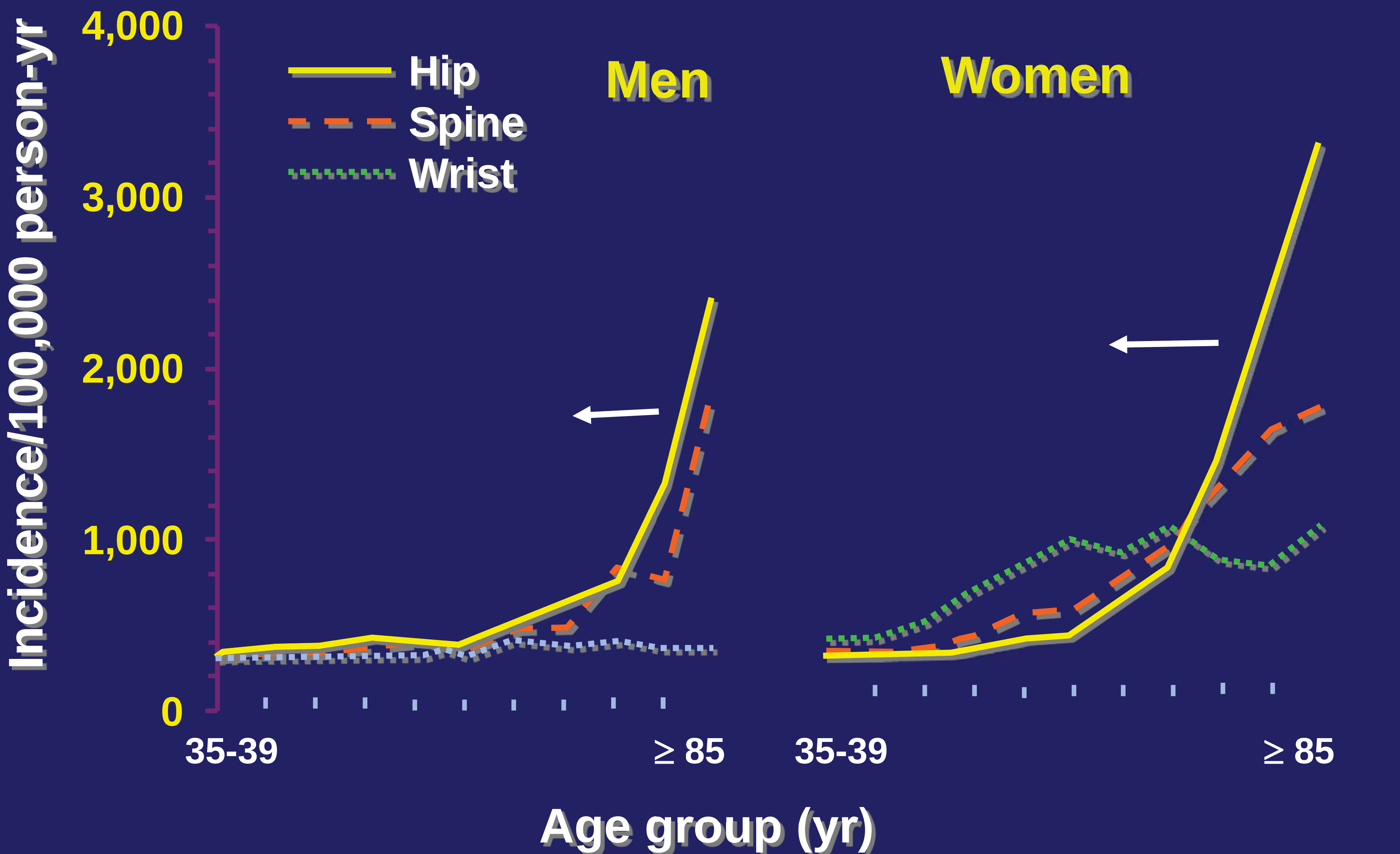
- Feasibility of using QCT for fracture risk surveillance – collects data that are BMD-independent predictors of hip fracture

- Developing a “decision-making tool” using FE modeling of hip bone strength derived from astronauts and from population studies with fracture outcome.

- Testing new technologies for bone microarchitecture that do not require ionizing radiation.

NASA

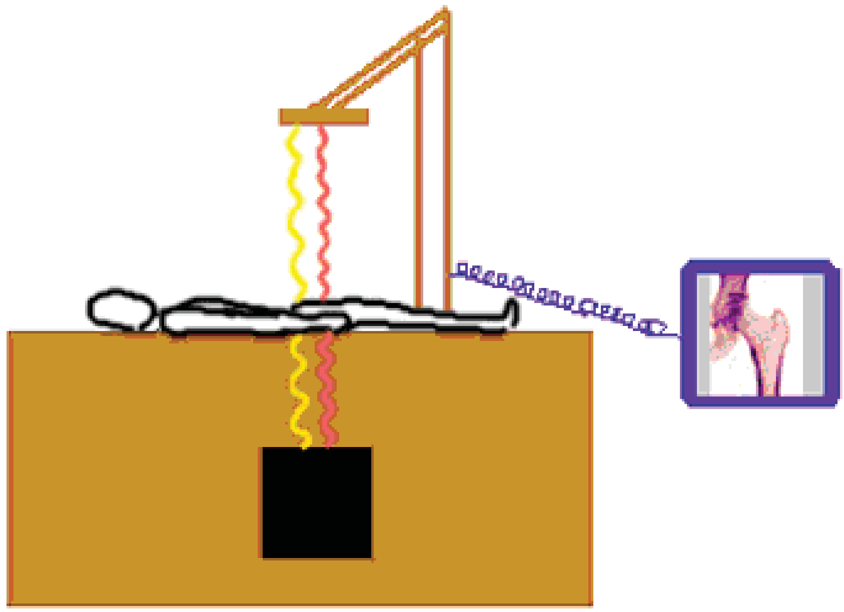
Consequence: Premature fragility fractures in astronauts due to previous exposure to spaceflight?



SLIDE COURTESY OF Dr. S. AMIN, Mayo Clinic

Cooper and Melton, 1992

Dual-energy X-ray Absorptiometry-DXA

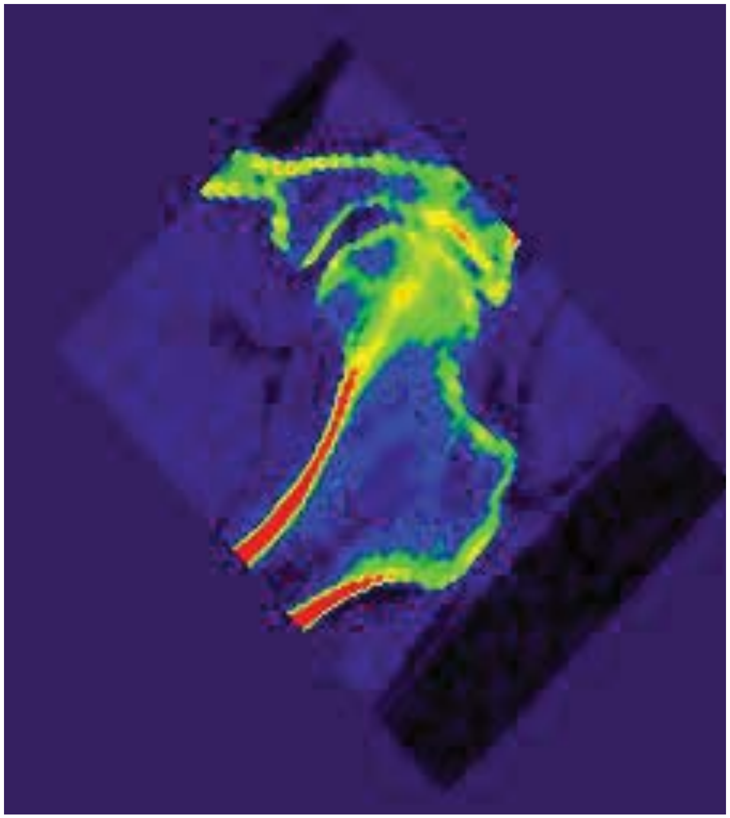


DXA measurement of areal BMD [BMD_a] – a inferred 3d measure from a 2d unit.

•Improved precision
• Low radiation
• Shorter scan times
• BMD measures over multiple skeletal sites
• Numerous studies: distribution of BMD in populations with fracture outcome
• Widely-applied surrogate for fracture – but for is it a good index for **bone strength?**

Hip QCT for surveillance: BMD changes in separate bone types, in response to countermeasures

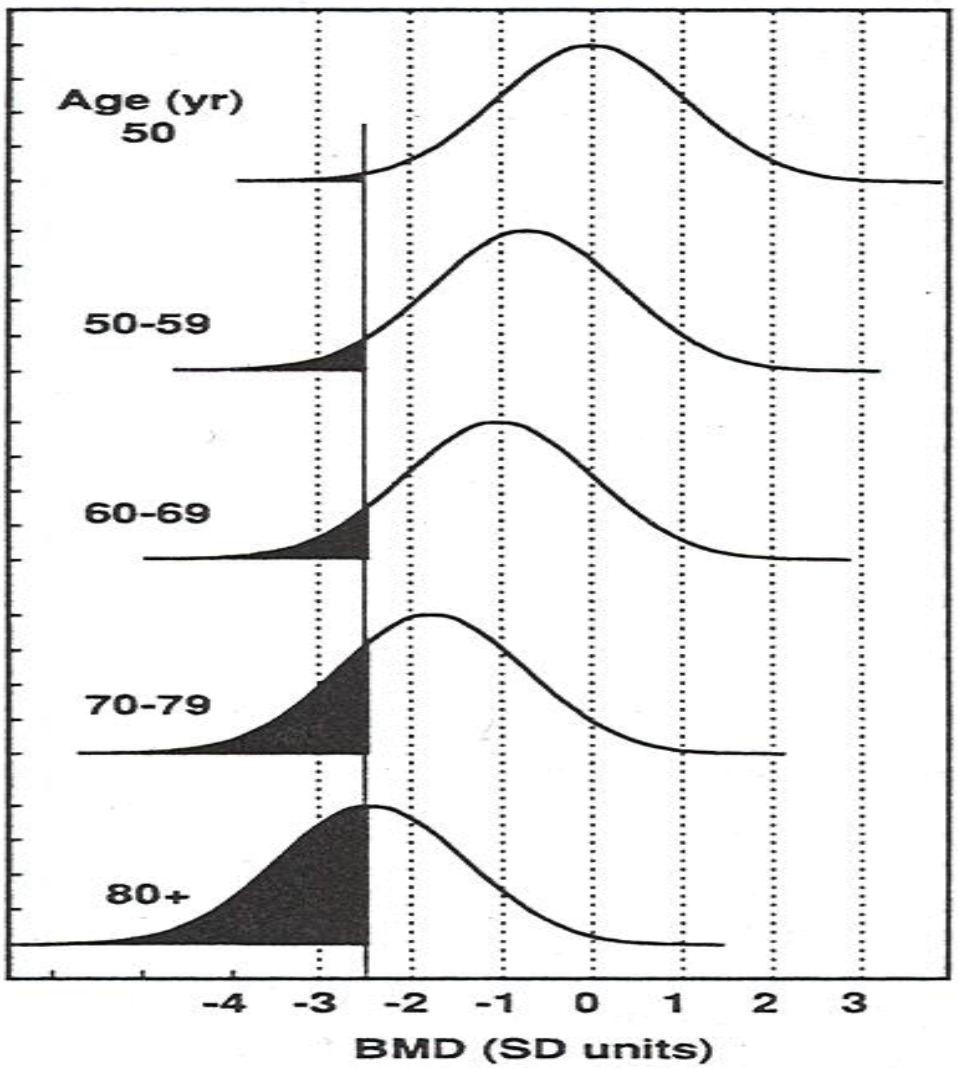
NOT detectable by DXA



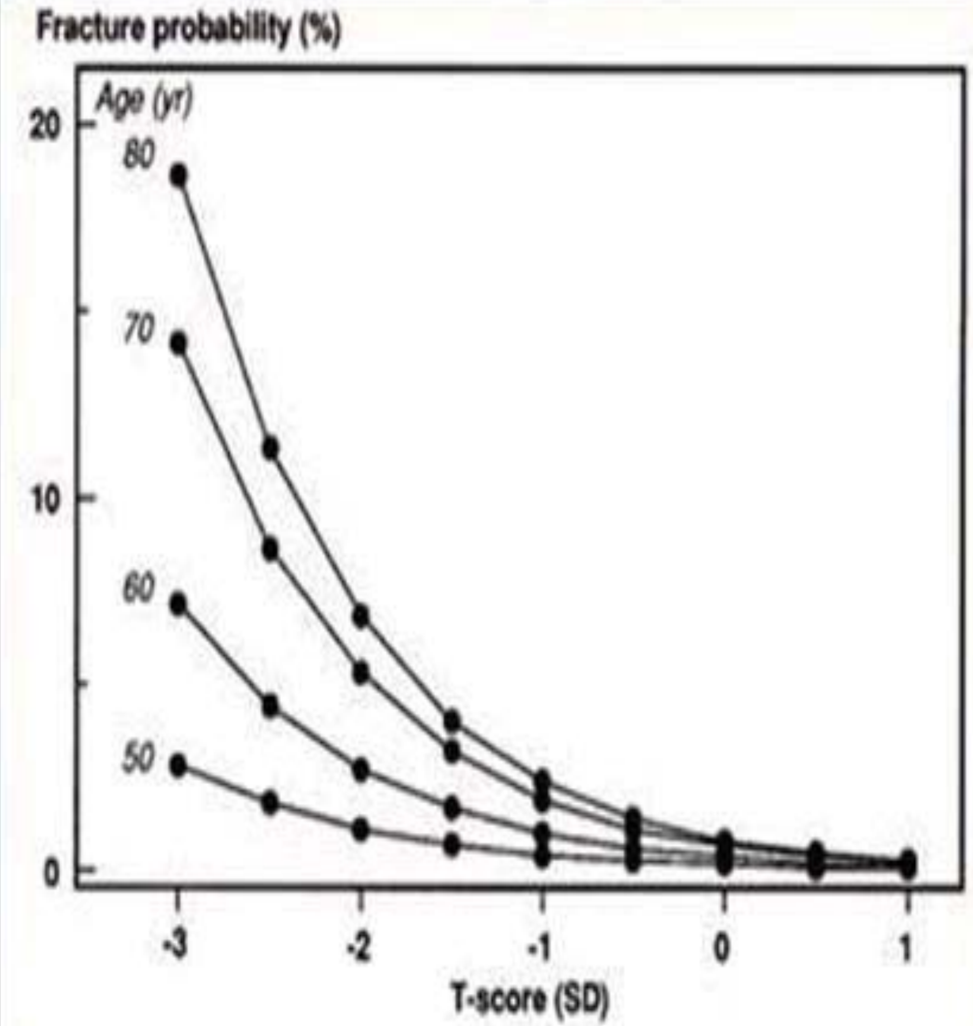
Index DXA	%/Month Change ± SD	Index QCT	%/Month Change ± SD
aBMD Lumbar Spine	1.06±0.63*	Integral vBMD Lumbar Spine	0.9±0.5
		Trabecular vBMD Lumbar Spine	0.7±0.6
aBMD Femoral Neck	1.15±0.84*	Integral vBMD Femoral Neck	1.2±0.7
		Trabecular vBMD Femoral Neck	2.7±1.9
aBMD Trochanter	1.56±0.99*	Integral 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; (n=16 ISS)
Vico, The Lancet 2000

Age: important risk factor for bone loss and fracture probability.



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



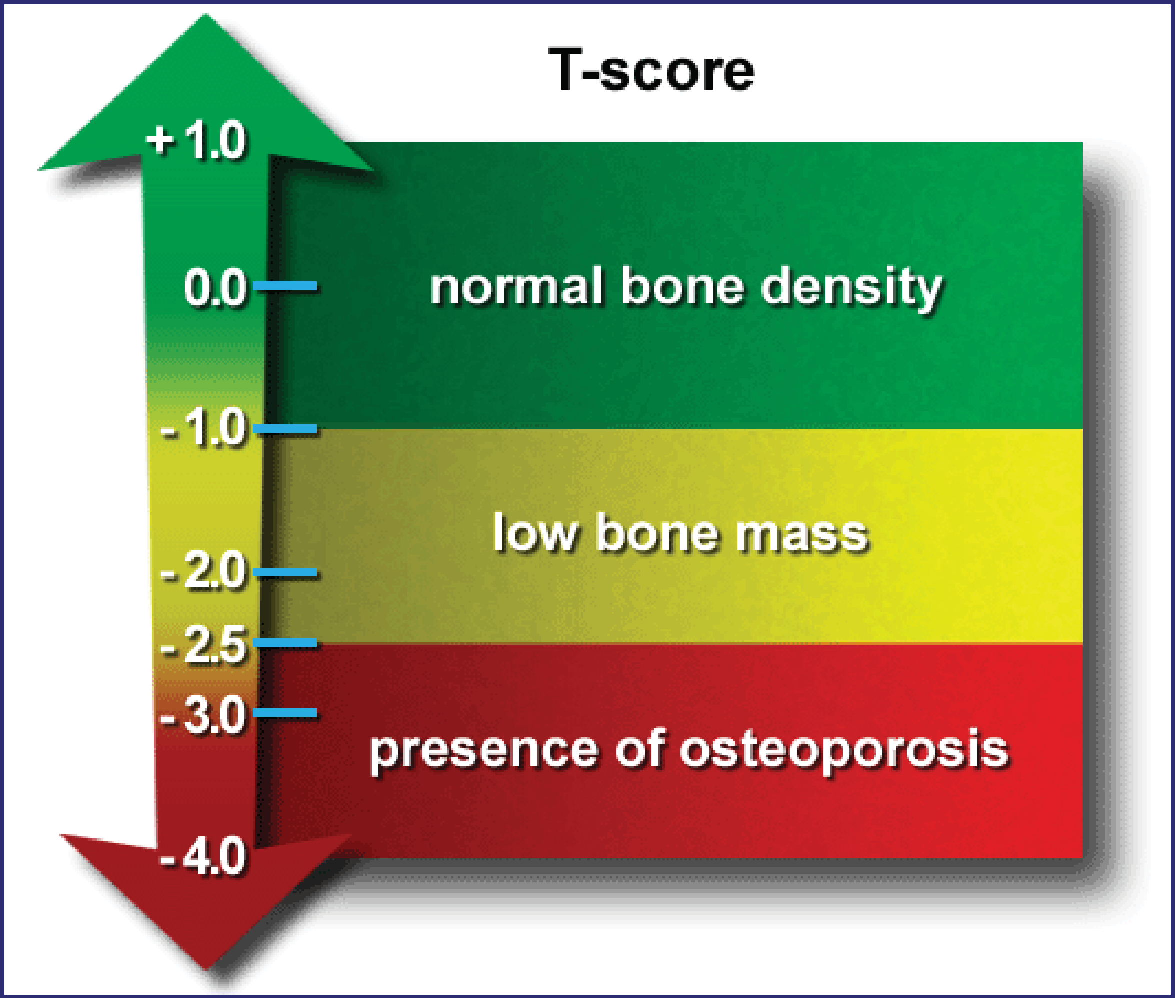
Kanis et al. Osteoporos Int (2001) 12:989-995

However, Paradigm Shift for assessing changes in Bone Strength as contributor to Fracture Risk.

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

- Why is this?

Bone fragility is influenced by factors that are not detected by DXA BMD.



Disconnects discovered In population studies – in response to countermeasures.

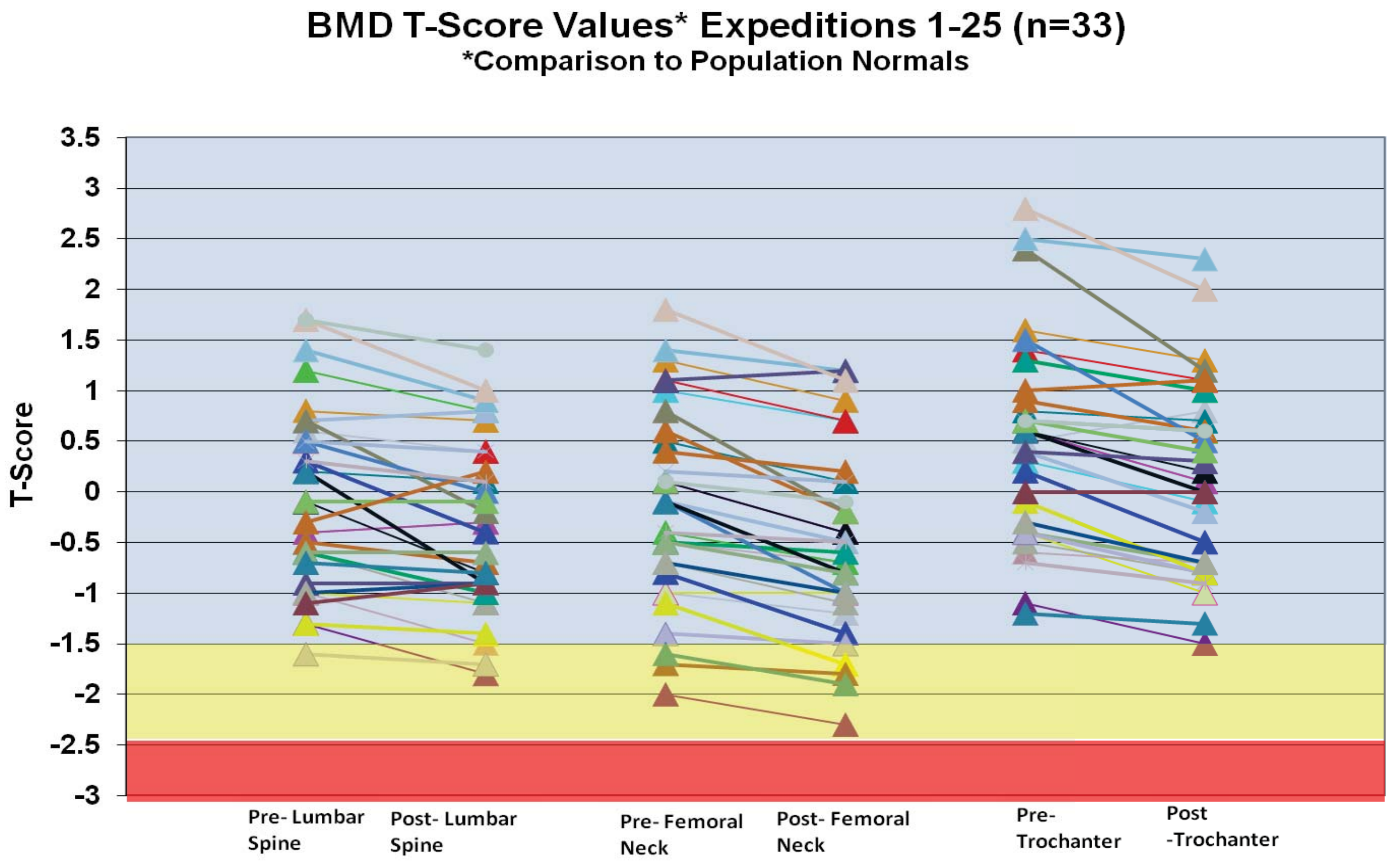
FRACTURE CASES

NON FRACTURES

How is DXA BMD used at JSC?

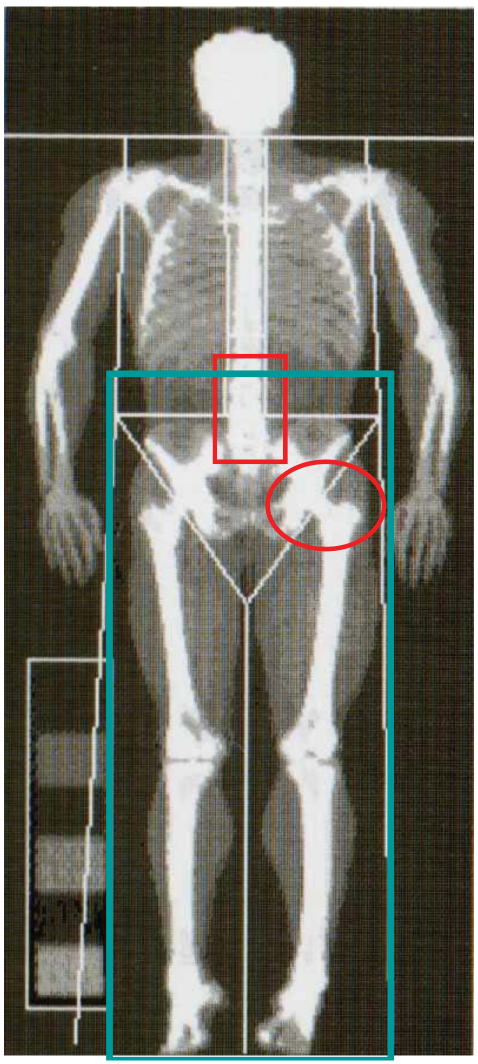
- Monitor skeletal health in all active and retired astronauts
- Characterize skeletal effects of *long-duration* spaceflight
- Evaluate efficacy of bone loss countermeasures
- Verify restored health status

However, diagnostic guidelines using areal BMD T-scores provide relative risk, but cannot predict who will fracture. Not useful when used alone.



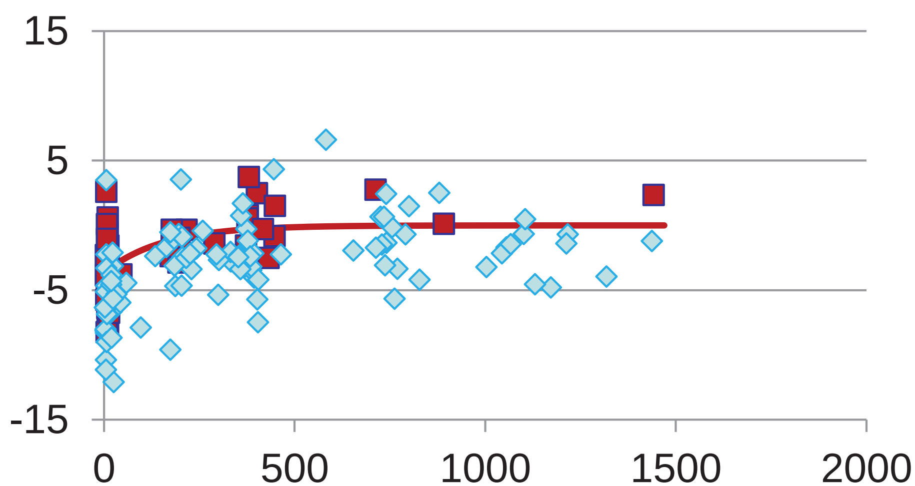
DXA BMD, not T-scores, reveals changes that are unique & complex. Drives requirement for research.

Rapid (1-1.5%/mo) and **site-specific** BMD loss (means local regulation occurring).



BMD Site	Mean Immediate Post Flight BMD (% change/month)			Mean Three Year Post Flight BMD (% change/month)		
	Predicted	Observed	p-value	Predicted	Observed	p-value
Total Hip	1.063 (0.05)	0.994 (-0.76)	<0.001	1.066 (0.02)	1.047 (-0.03)	<0.001
Lumbar Spine	1.081 (0.11)	1.016 (-0.58)	<0.001	1.085 (0.03)	1.069 (-0.00)	0.11
Ultra-Distal Radius	0.558 (-0.05)	0.550 (-0.20)	0.12	0.541 (-0.08)	0.551 (-0.04)	0.005
Mid-Shaft Radius	0.755 (0.19)	0.741 (-0.00)	0.04	0.749 (0.02)	0.741 (0.00)	0.28
Total Body	1.288 (-0.04)	1.262 (-0.26)	0.009	1.284 (-0.01)	1.261 (-0.05)	0.19

Total BMD **loss greater and persist** compared to BMD changes predicted from algorithms derived from earth-based population



Loss is variable due to multiple risk factors. Recovery is variable. Recovery is prolonged. But ARED can reduce BMD decline in hip.

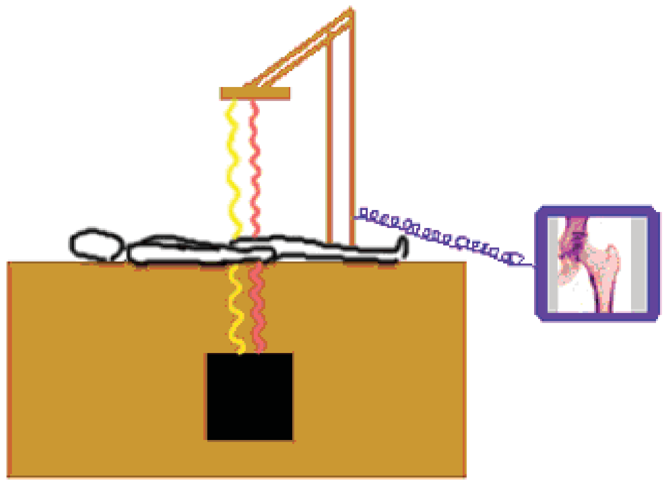
<u>However, DXA is limited as Research Tool</u>: Does not account for changes in bone size which impacts bone strength.

Effect of geometry on long bone strength

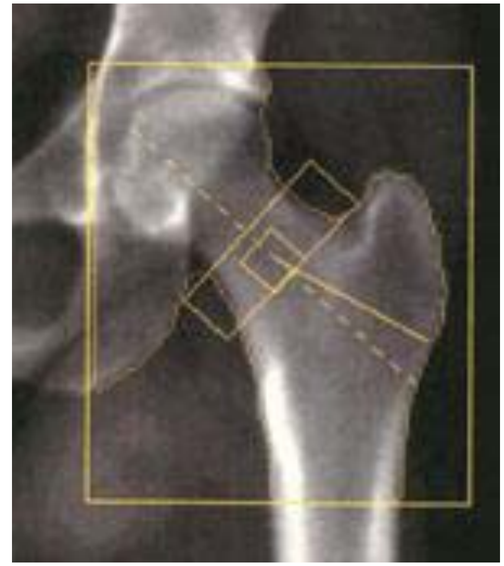
aBMD g/cm^{2}2	1	1	1
Compressive Strength	1	1.7	2.3
Bending Strength	1	4	8

Mary Bouxsein, Ph.D. Bone Geometry and Skeletal Fragility, May 2005

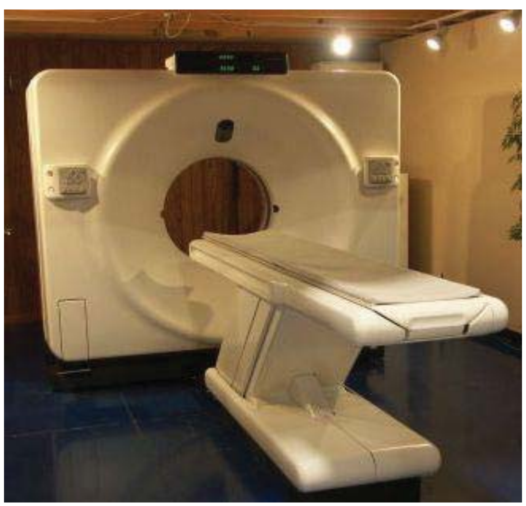
Densitometry & Reported Measurement



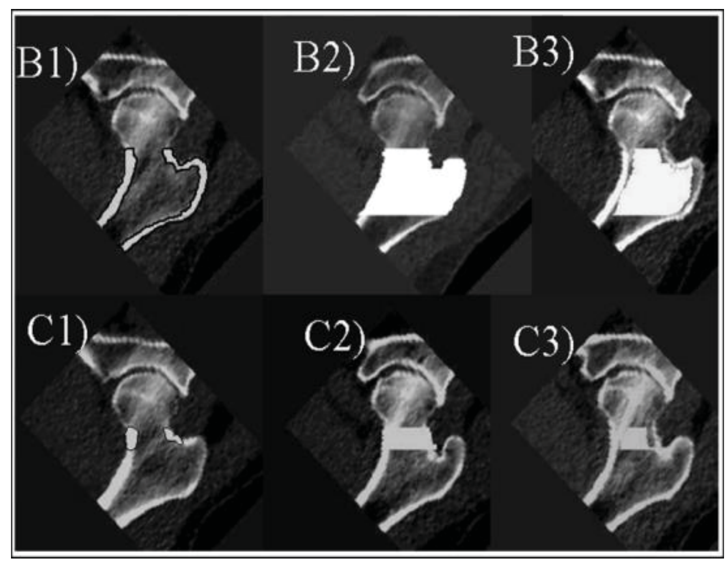
DXA reports areal BMD (aBMD)



g/cm² averaged for cortical + trabecular bone



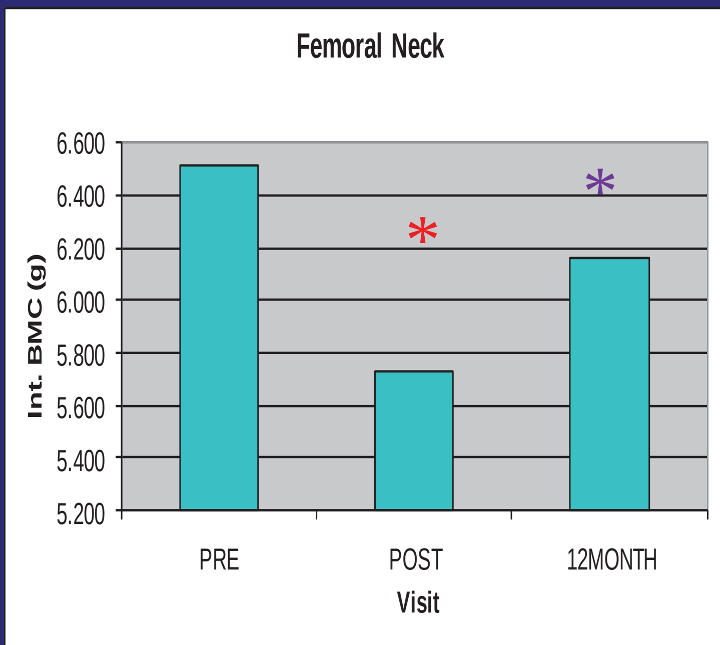
QCT quantifies volumetric BMD



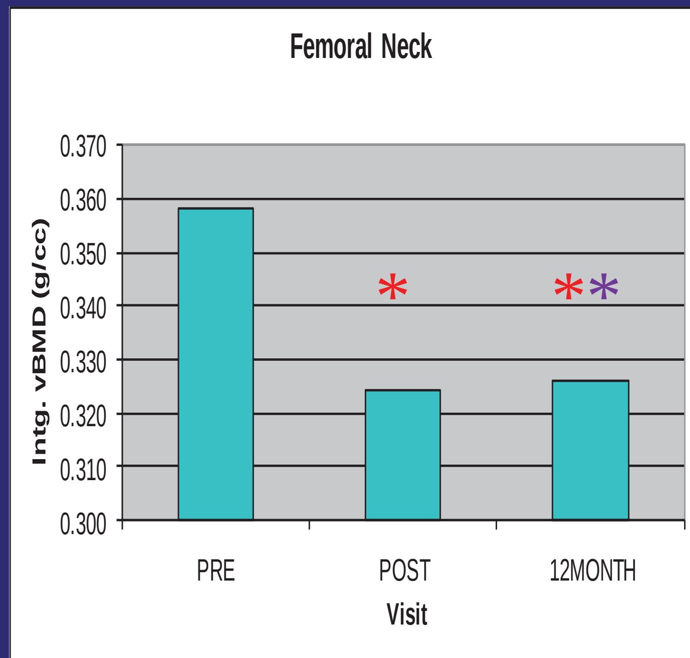
g/cm³ for separate cortical & trabecular bones

Surveillance by QCT– Changes in Femoral Neck structure detected 12 months postflight

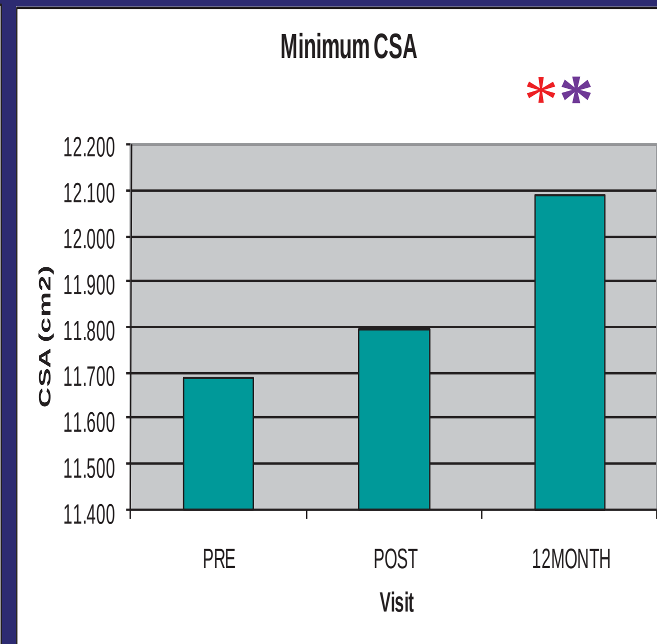
Bone Mineral Content
(g)



Volumetric Bone Mineral Density
g/cm³



Minimum Cross-sectional Area
cm²



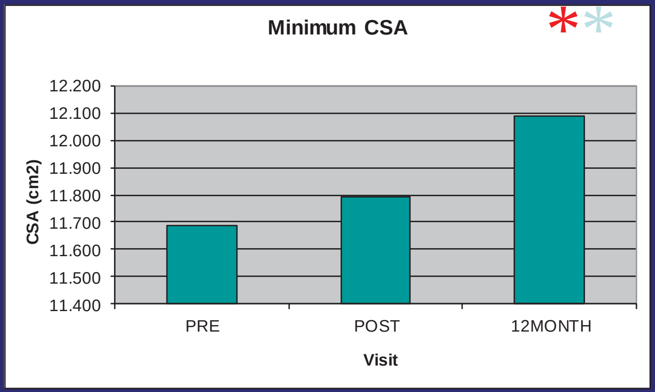
Pre Post 12 Pre Post 12 Pre Post 12

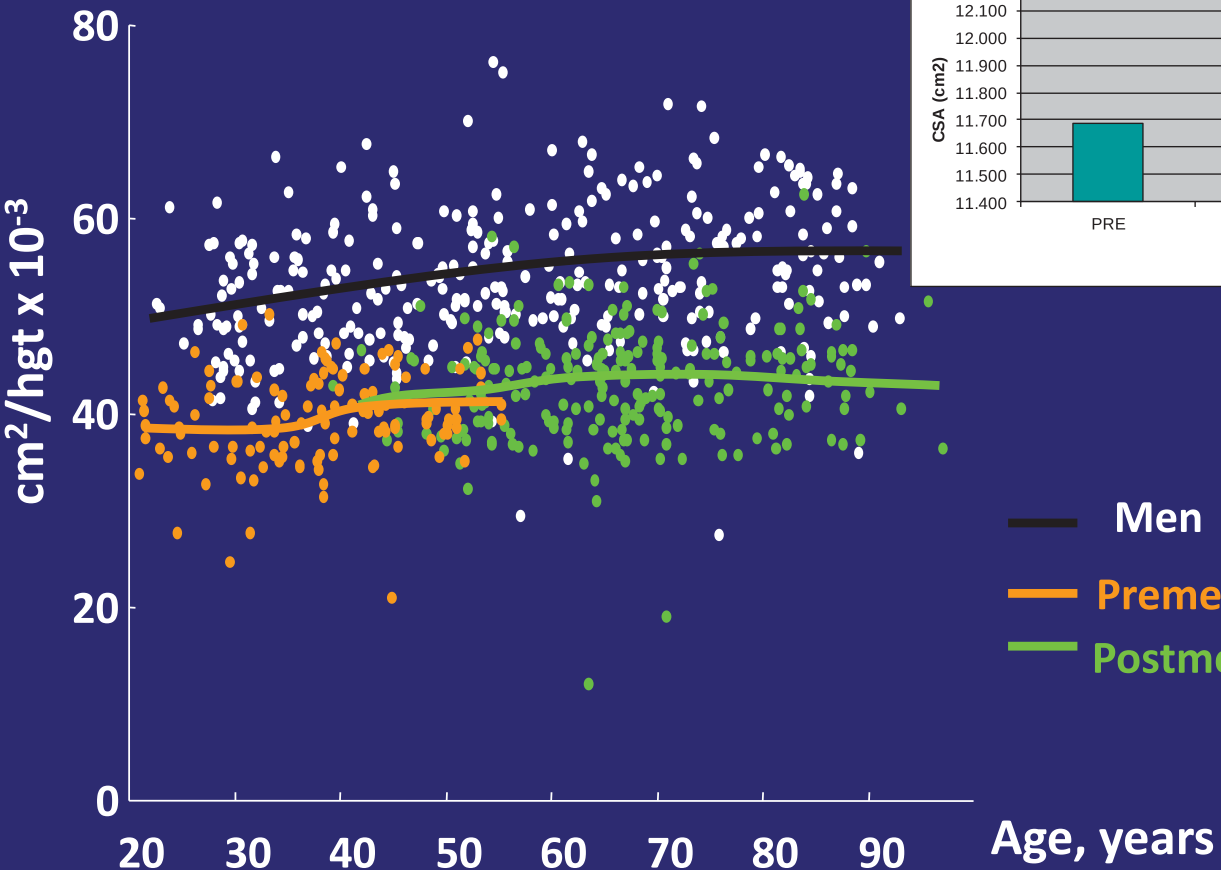
$P < 0.05$ with respect to preflight*, **postflight***

Slide adapted from T. Lang., JBMR 2006.

QCT in Population Study measures changes in bone size with aging.

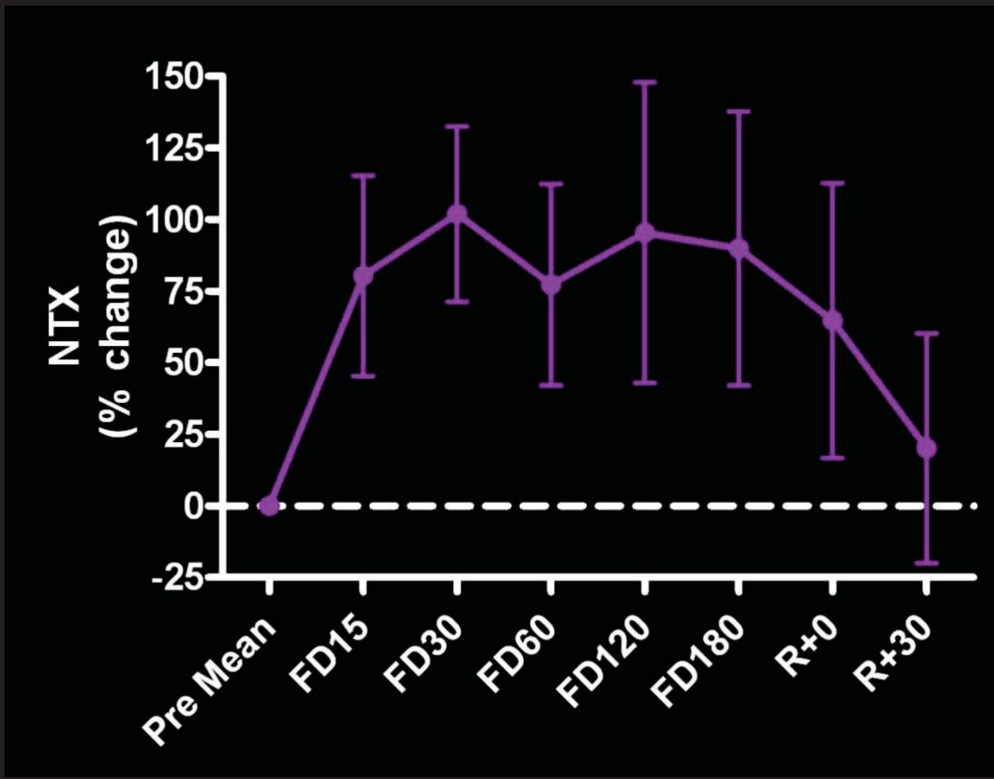
Suggests that outward displacement of femoral neck is response to cortex thinning with age

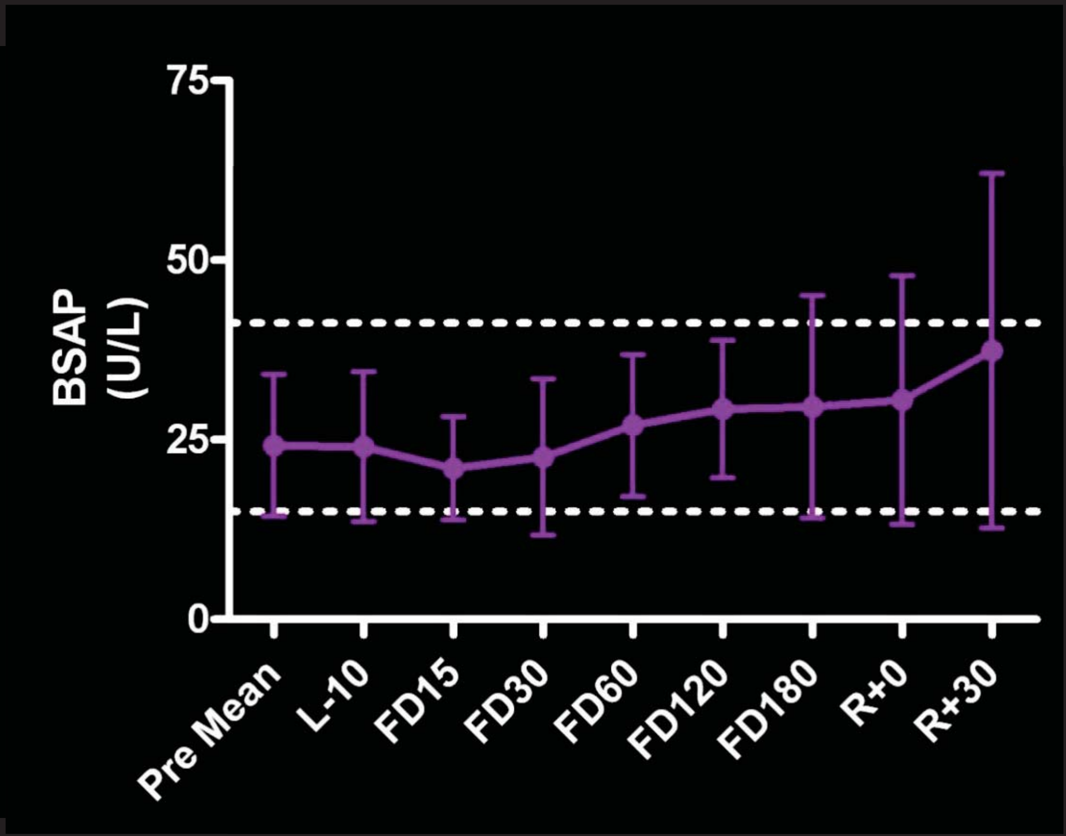




Riggs et al. JBMR19:1945, 2004.

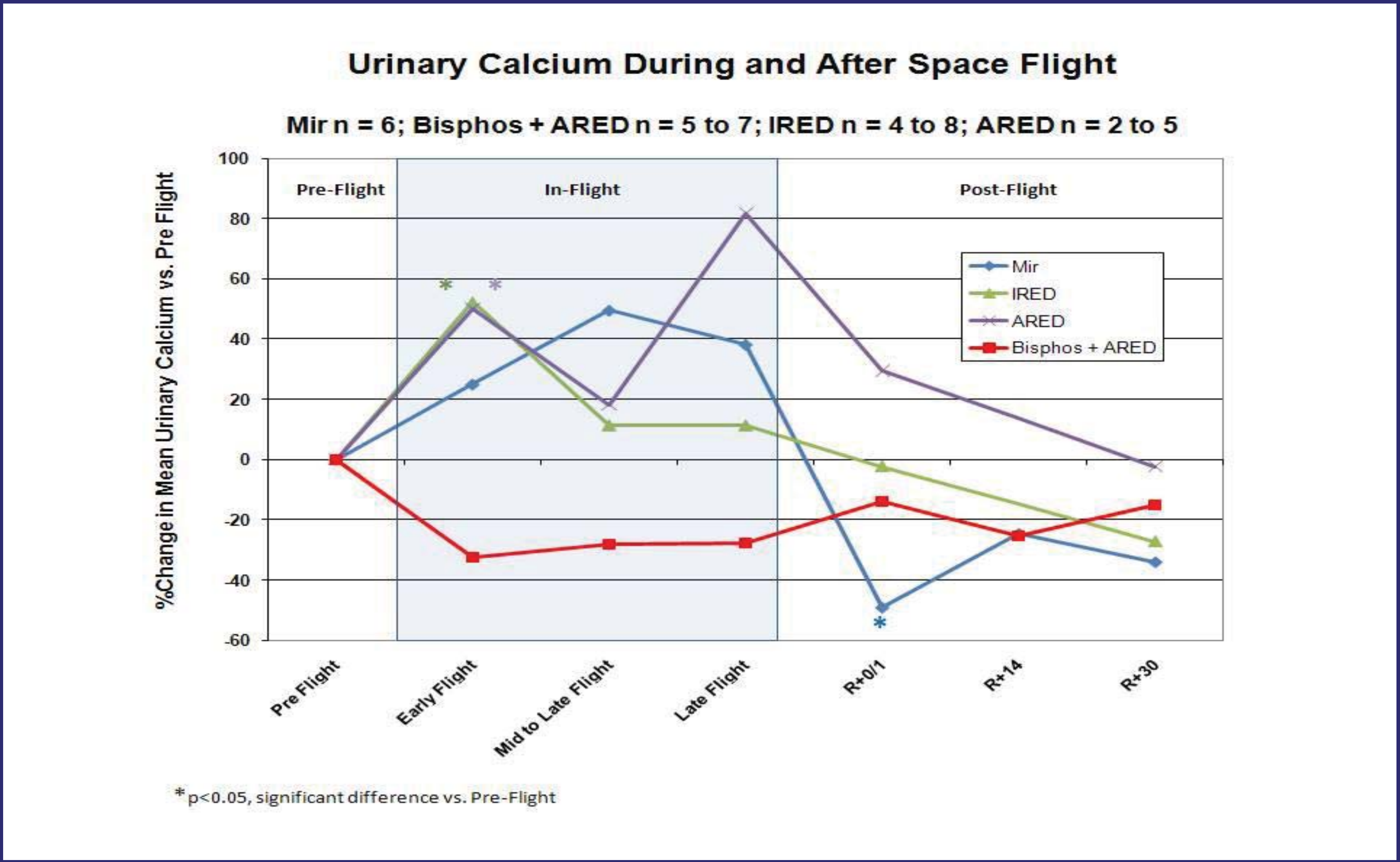
Bone Turnover Markers indirectly suggest a net loss in bone mass from the entire skeleton.





Slide Courtesy of Dr. SM Smith; Adapted by Sibonga

Exercise during Spaceflight does not mitigate urinary calcium excretion – as a biomarker for bone breakdown



Slide courtesy of Dr. A. LeBlanc

ORIGINAL ARTICLE

JBMR

Benefits for Bone From Resistance Exercise and Nutrition in Long-Duration Spaceflight: Evidence From Biochemistry and Densitometry

Scott M Smith,[1] Martina A Heer,[2,3] Linda C Shackelford,[1] Jean D Sibonga,[1] Lori Ploutz-Snyder,[4] and Sara R Zwart[4]

[1]Human Adaptation and Countermeasures Division, National Aeronautics and Space Administration (NASA) Lyndon B. Johnson Space Center, Houston, TX, USA

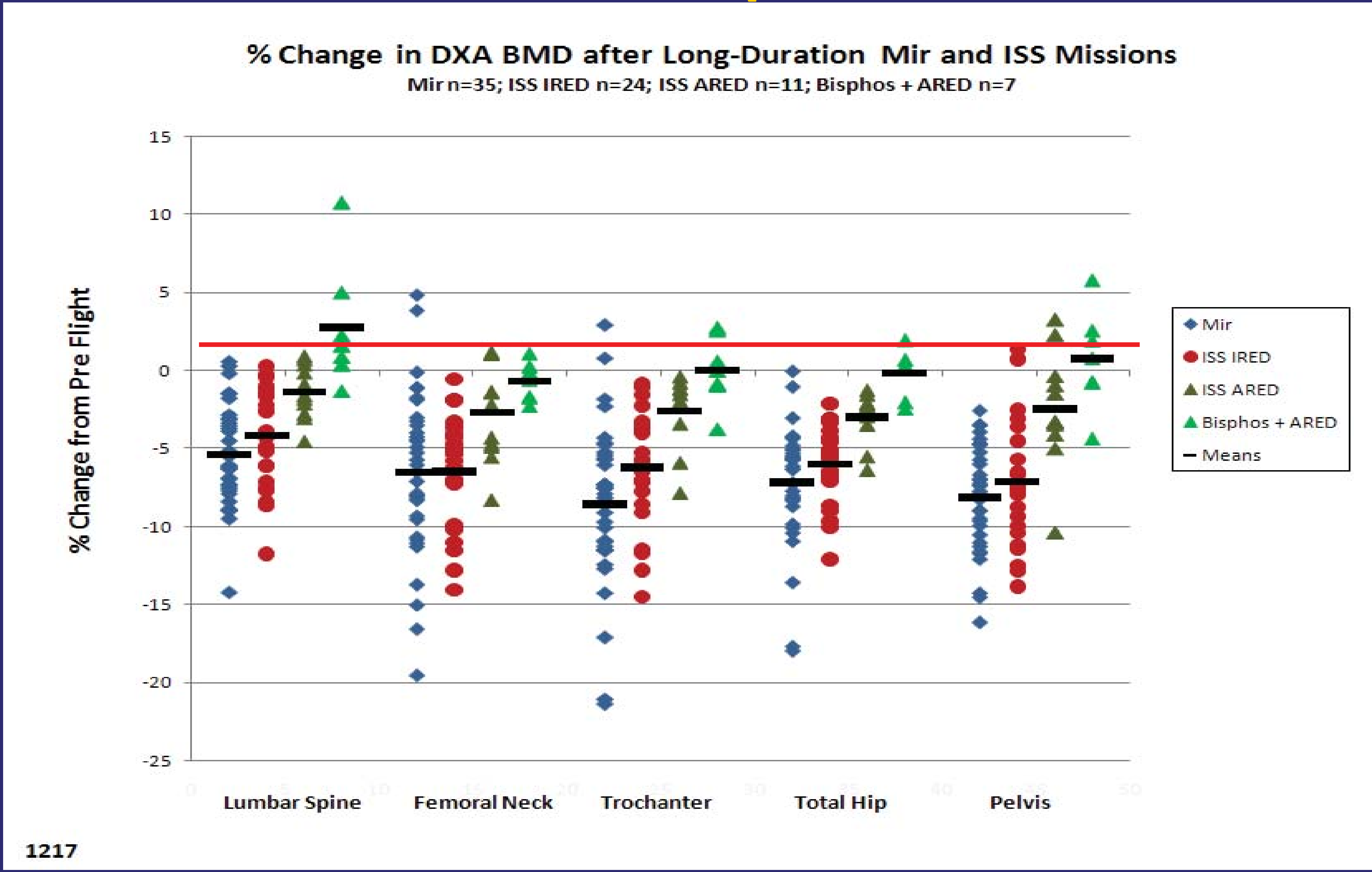
[2]Department of Nutrition and Food Science, Nutritional Physiology, University of Bonn, Bonn, Germany

[3]Profil Institute for Metabolic Research GmbH, Neuss, Germany

[4]Division of Space Life Sciences, Universities Space Research Association, Houston, TX, USA

JBMR 27(9):1896-1906.

Changes in areal BMD--useful information, but not a fracture predictor



* Updated data since 2010 Bone Summit

Bone RCAP Recommendations (2010)

1. Use QCT for risk surveillance data . To detect clinical trigger recovery in hip trabecular BMD. Conduct scans Pre- Post-, 1 year, 2 years (if recovery not established at 1 y)

2. QCT data required to formulate recommended clinical practice guidelines – which are driven by fracture probability.

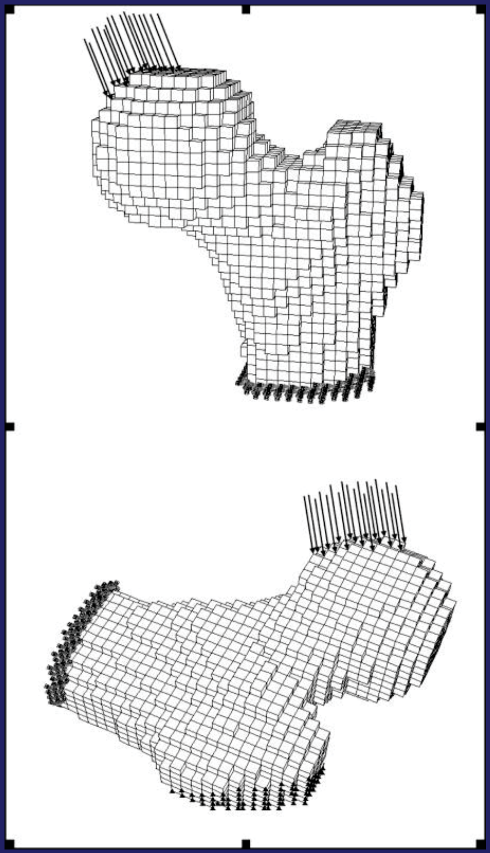
3. Individualize risk assessments – due to data constraints.

4. Modify Bone crew health standards to be more relevant to LD astronaut experience. Explore population studies with hip bone strength estimated by Finite Element analysis.

5. Search/validate new technologies to assess unique changes due to spaceflight, e.g., bone microarchitecture of central skeletal sites.

Investigate a new medical standard for BONE with Finite Element Modeling [FEM] : What is it and what can it tell NASA about hip fracture risk in the long-duration astronaut?

FEM – a computational tool to estimate failure loads ("strength") of complex structures - from models developed from QCT scans.



J. Keyak et al, 1998, 2001, 2005

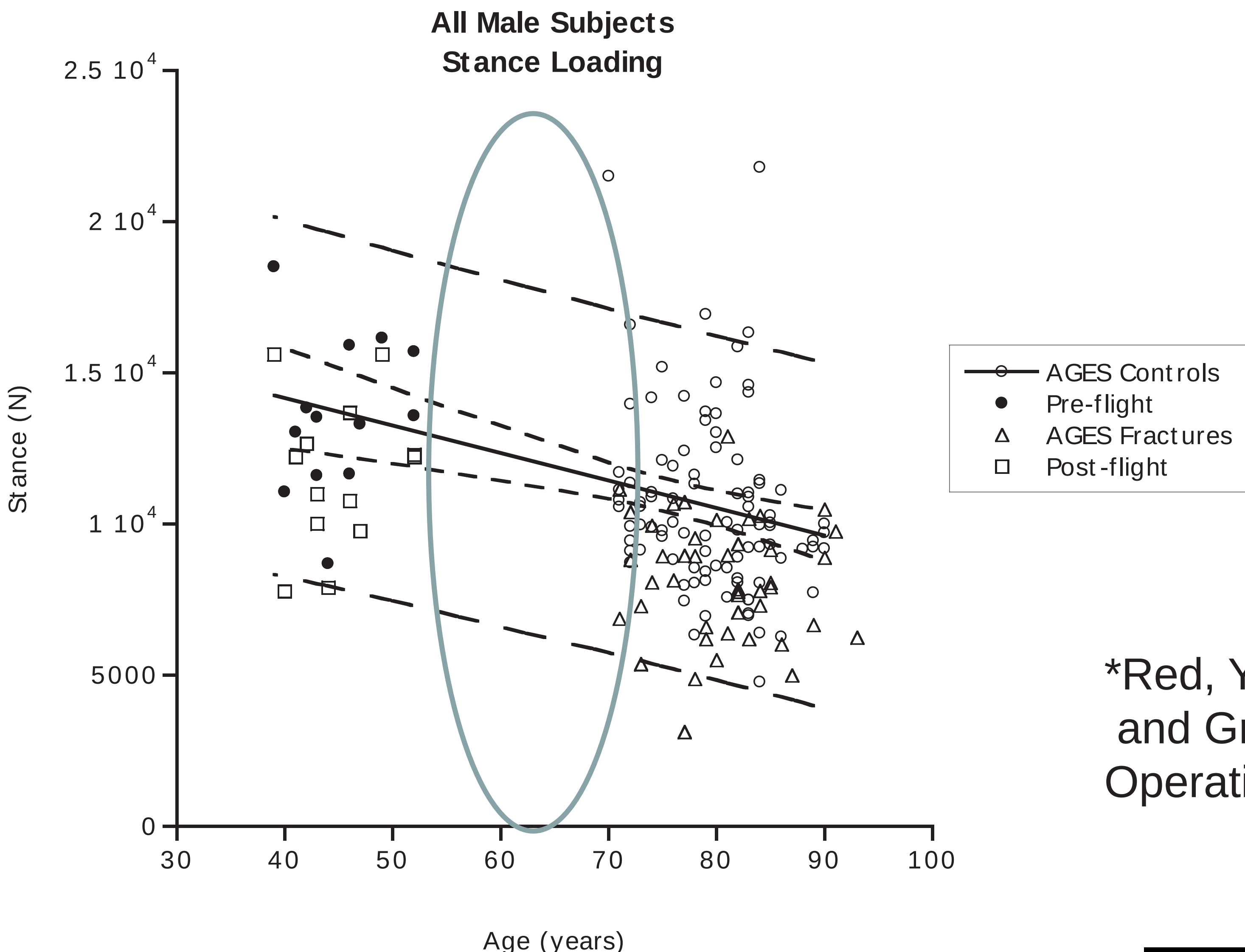
Images courtesy of Dr. J Keyak

Describing changes in hip bone strength with Finite Element Modeling/Analysis: Emerging data from population studies.

- **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.

FE Strength Cutoffs* 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.



*Red, Yellow and Green Operating Bands

REPRESENTATIVE POPULATION DATA

Data slide courtesy of Keyak. [redacted]

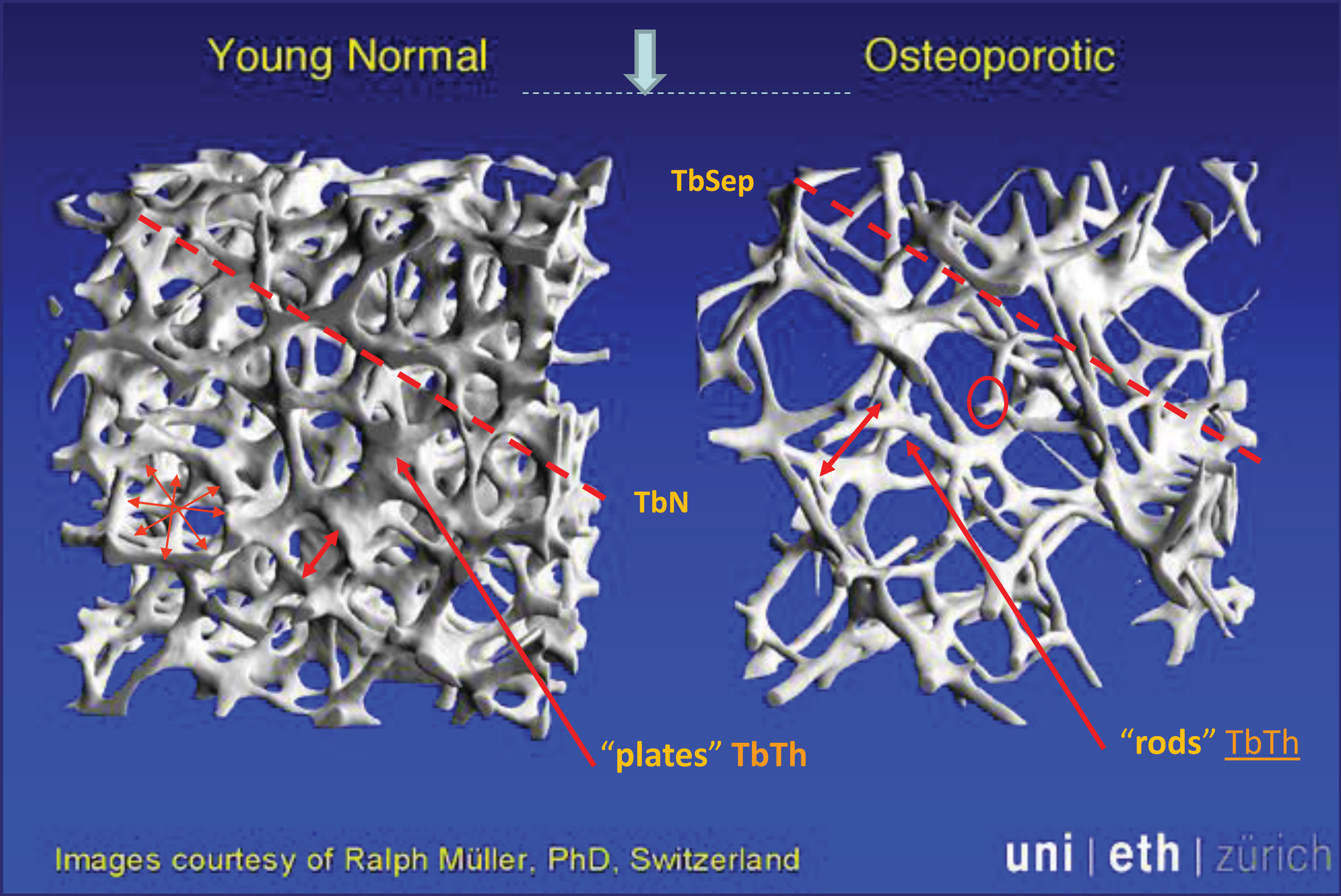
Why Bone Microarchitecture?

- "…low bone mass and microarchitectural deterioration with a consequent increase in bone fragility with susceptibility to fracture …." Am. J. Med.1991 *Defined Contribution*

- Disrupted microarchitecture is associated with vertebral compression fractures. *Validated Fracture Predictor*

- Bone Summit RCAP 2010: concern for rapid bone loss in astronauts and aggressive osteoclast activity disrupting bone microarchitecture --- which is not detectable by QCT. *Orwoll, 2013 JBMR review*

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

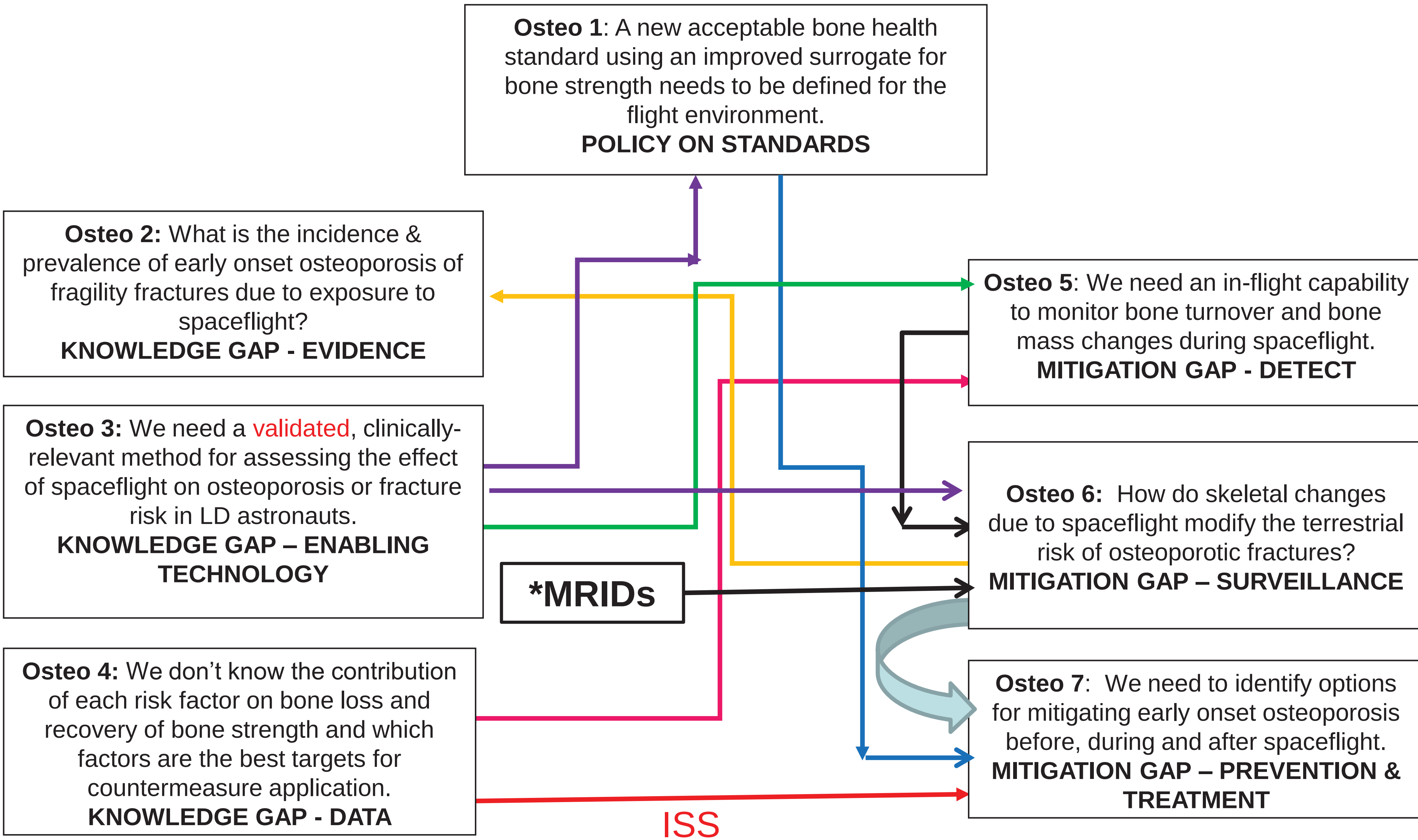


Adapted by Sibonga

Integrated Research Plan for Bone Portfolio

GAP MANAGEMENT FOR OSTEO & FRACTURE

Gaps to define the changes to bone and the contribution to fracture risk.



*MRIDs -*refer to data from medically-required tests* Medical Requirements Integrated Document

Gaps to understand the Risk for Bone Fracture=Applied Loads/Bone Failure Loads

B31: Need additional information regarding hard and soft tissue healing in-flight. If impaired healing exists, what countermeasures can enhance healing?

Fracture 1. We don't understand how the space flight environment affects bone fracture healing in-flight.

B30: What are the loads applied to bone in-flight and during EVA activities and do they increase fracture risk in light of expected bone loss?

Fracture 2. We need to characterize the loads applied to bone for standard in-mission activities.

Fracture 3. We need a validated method to estimate the Risk of Fracture by evaluating the ratio of applied loads to bone fracture loads for expected mechanically-loaded activities during a mission.

B2: What new technologies are available for in-flight fracture diagnosis?

Exploration Medical Capabilities

Summary

- DXA BMD, as a sole index, is an insufficient surrogate for fracture
- CPGs using BMD (both WHO and FRAX) are not specific for complicated subjects such as young, healthy persons following prolonged exposure to skeletal unloading (i.e. an attribute of spaceflight)
- Research data suggest that spaceflight induces changes to astronaut bones that could be profound, possibly irreversible and unlike age-related bone loss on Earth.
- There is a need to objectively assess factors across human physiology that are also influenced by spaceflight (e.g., muscle) that contribute to fracture risk.

Summary 2

- Some of these objective assessments may require innovative technologies, analyses and modeling.
- Astronauts are also exposed to novel situations that may overload their bones highlighting a need integrate biomechanics of physical activities into risk assessments.
- As we accumulate data, which reflects the biomechanical competence of bone under specific mechanically-loaded scenarios (even activities of daily living), BONE expects Bone Fracture Module to be more sensitive and/or have less uncertainty in its assessmentsof fracture probability.
- Fracture probability drives the requirement for countermeasures. Level of evidence will unlikely be obtained; hence, the Bone RCAP (like a Data Safety Monitoring Board) will provide the recommendations.

Bone Summit Panel Members

- Eric Orwoll, MD
  - Endocrinology and Male Osteoporosis
- E. Michael Lewiecki, MD, FACP, FACE
  - Endocrinology, ISCD
- Neil Binkley, MD, CCD
  - ISCD, Geriatrics and Vitamin D
- Shreyasee Amin, MD
  - Rheumatology, Male Osteoporosis and Epidemiology
- Sue Shapses, PhD
  - Nutritional Sciences and Weight-loss
- Robert A. Adler, MD
  - Male Osteoporosis and Epidemiology
- Steven Petak, MD, JD, FACE
  - Endocrinology, ISCD (
- Mehrsheed Sinaki, MD
  - Physical Medicine & Rehabilitation
- Nelson B. Watts, MD
  - Endocrinology, ISCD

Left to Right, Top Row down

Thank you.

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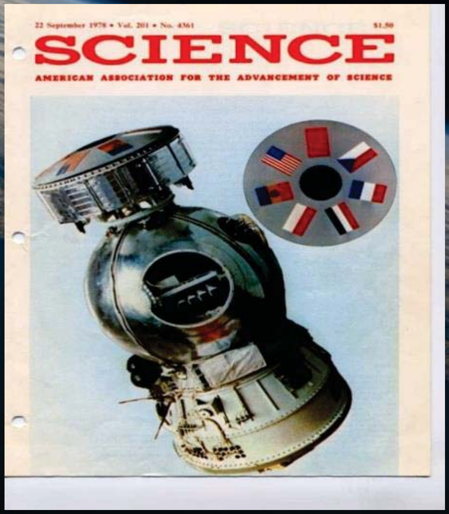


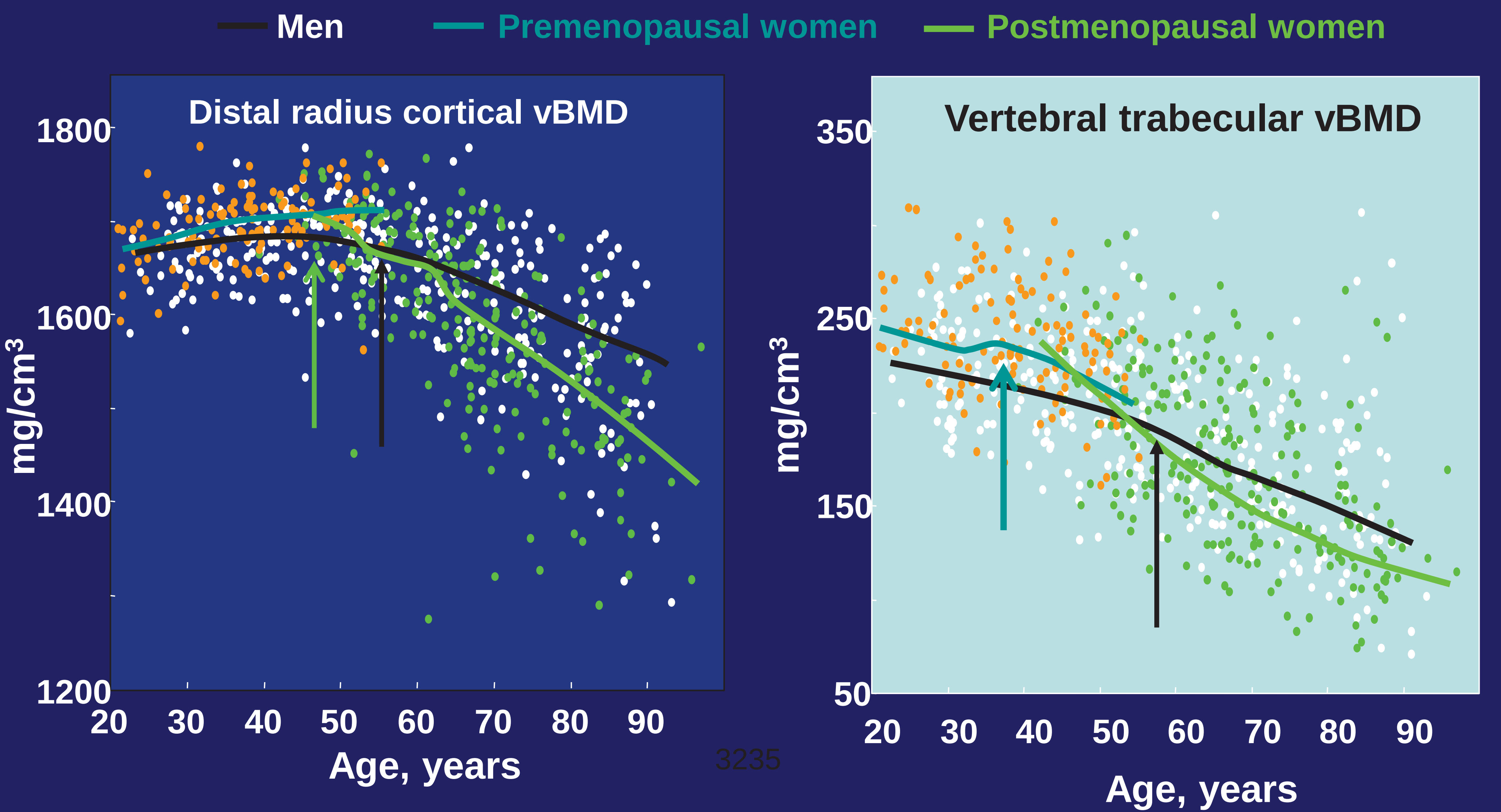
Backup Slides

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

AGE-REGRESSIONS: Bone loss occurs at earlier age than expected.

Riggs et al. JBMR19:1945, 2004.



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History of Bone Imaging in Space

Gemini

Space Shuttle

Mercury

Apollo

Skylab

ISS

1961-63

1965-66
- **X-ray densitometry**

1968-72
- **SPA heel and wrist**

1973-74
- **SPA heel and wrist**

2000-present
- **DXA**
- **QCT**
- ***HR3DpQCT (ESA)***

Soyuz/Salyut

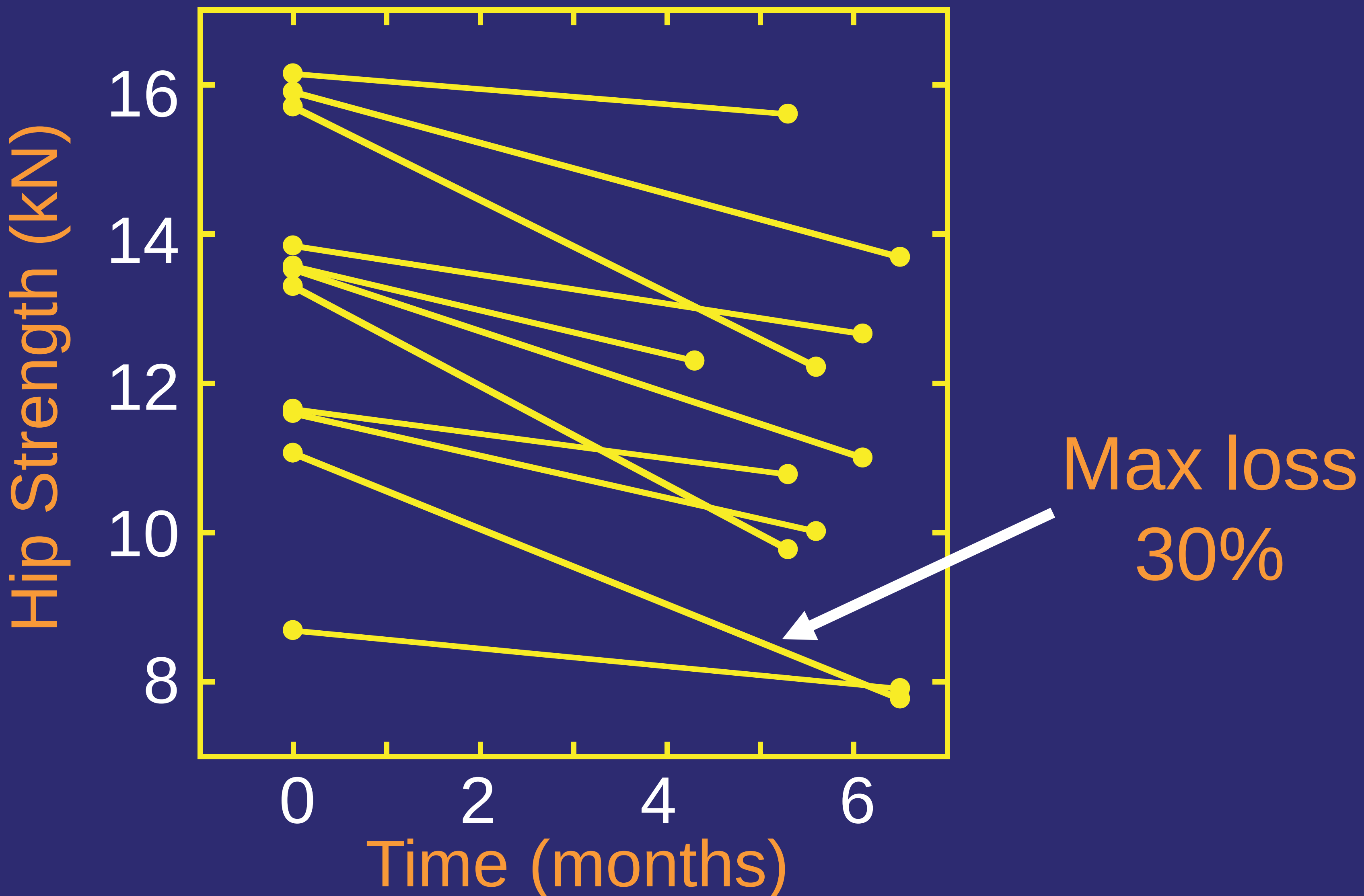
1974-85
- **SPA**
- **DPA**

Mir

1974-85
- **DXA whole body**
- **CT of lumbar spine BMD**

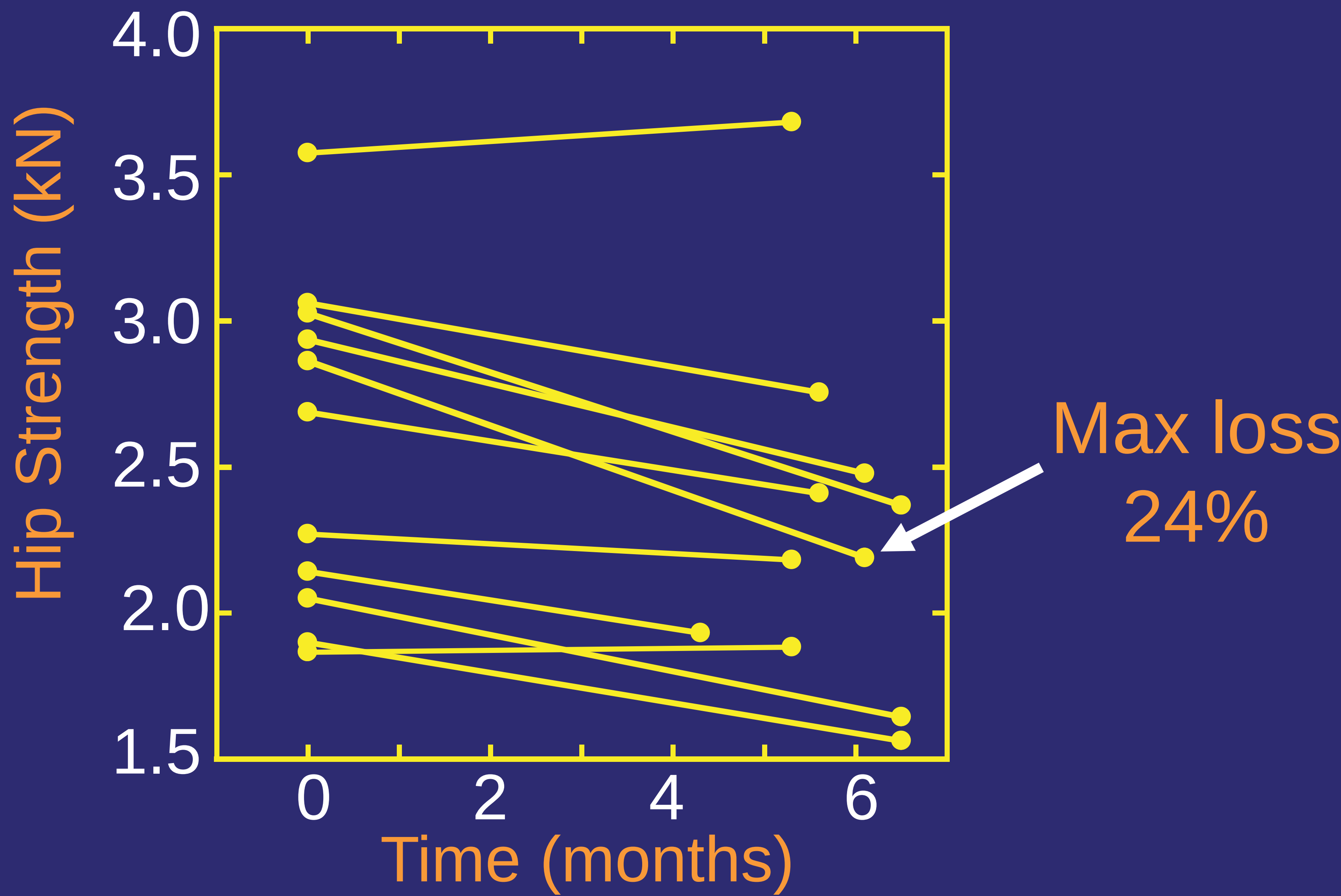
Slide adapted from by Amin, Mayo Clinic

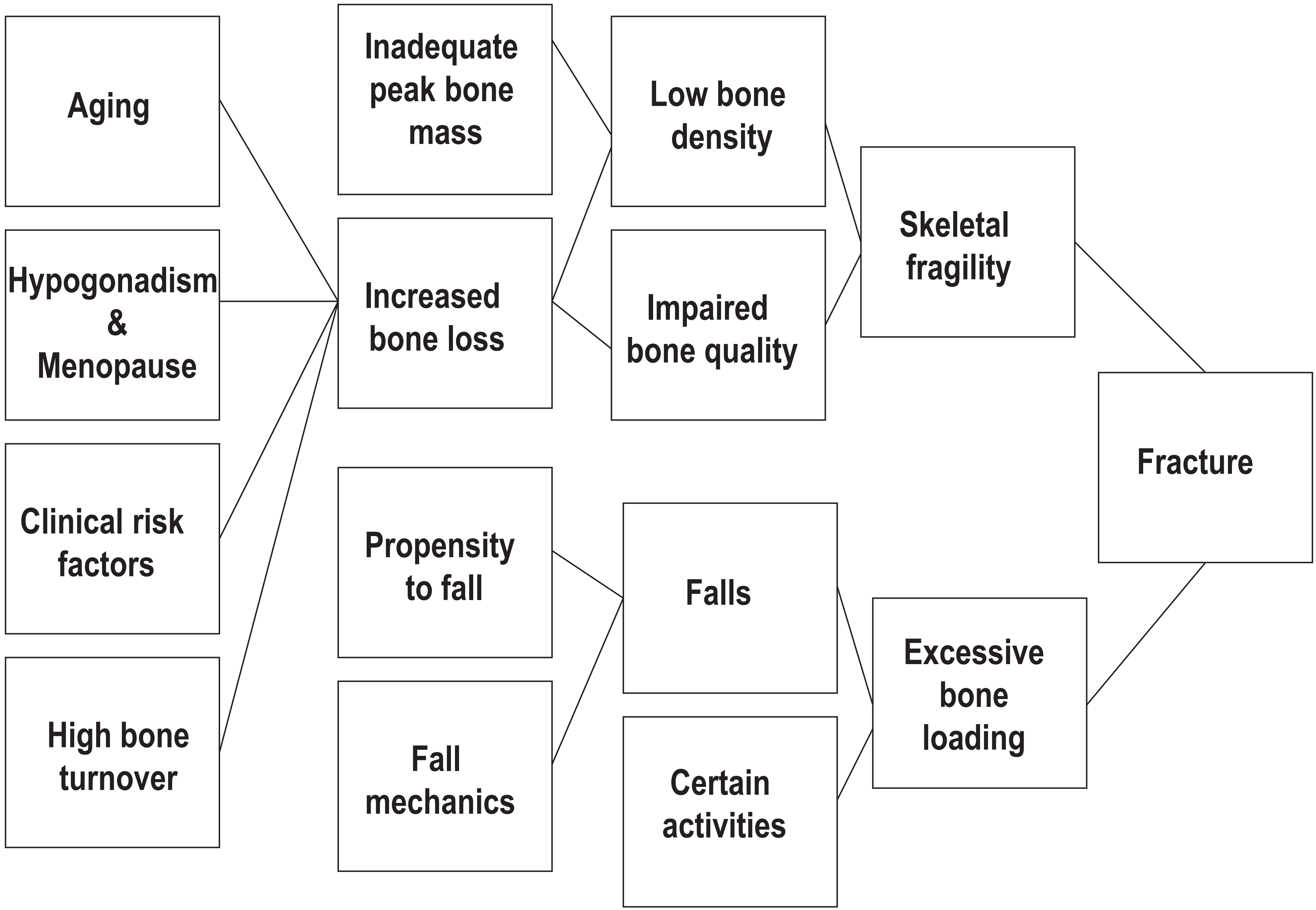
Individual Results
Stance Loading (4 to 30% loss in strength)



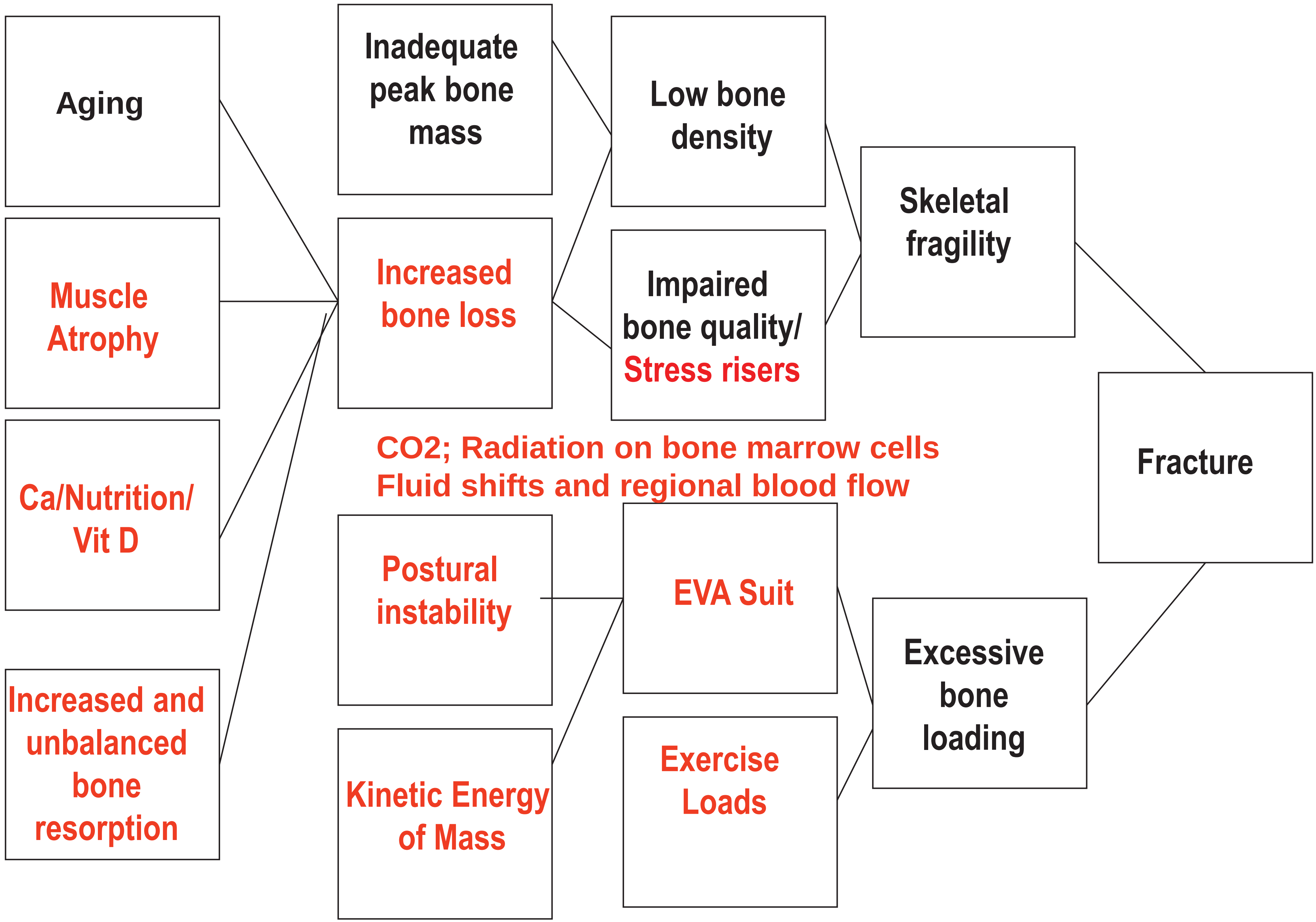
Individual Results

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





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



ASTRONAUTS EXPOSED TO UNIQUE SET OF POSSIBLE RISK FACTORS DURING SPACEFLIGHT

Risk Summary

Information

Risk Title: Risk of Bone Fracture due to Spaceflight-induced Changes to Bone*

Risk Statement: Given that space flight may induce adverse changes in bone ultimate strength with respect to mechanical loads during and post-mission, there is a possibility a fracture may occur for activities otherwise unlikely to induce fracture prior to initiating space flight.

Primary Hazard: μ-gravity

Secondary Hazard: Radiation, Closed Environment (spacecraft design),

Countermeasure: ***Prevention:*** selection standard, exercise, task design, diet, pharmaceuticals. ***Treatment:*** In-flight treatment/medical kit pharmaceuticals, post-mission rehab.

Contributing Factors: Physiological deconditioning (e.g., visual and gait impairments) and clinical factors (e.g., nutrition and neuro-muscular declines), radiation, insufficient accommodations for occupant safety and operational tasks, and detailed mission design (mission design will be closely monitored; when such details are made available, the team will ensure sub-optimal design choices are not implemented to the detriment of human health and performance).

State of Knowledge: Fracture probability is dependent upon loading and bone strength. BMD is widely used as a surrogate for bone strength but its sole use recognized to be insufficient for risk assessment. Extensive pre/post flight Bone Mineral Density data. ARED/T2 6 days/week exercise regimens have minimized declines in BMD, which are consistent with Permissible Outcome Limits (POL). It is important to point out that the standard POL was met before ARED/T2 were implemented on the ISS; however, this may reveal the possible inadequacy of the current standard metric, which is currently under evaluation. Changes to trabecular bone, whole bone … and without pharmaceuticals.

DRM Categories	Mission Duration	LxC OPS	Risk Disposition	LxC LTH	Risk Disposition
Low Earth Orbit	6 Months	1 x 4	Accepted Standard Refinement	2 x 3	Accepted Standard Refinement
	1 Year	1 x 4	Accepted Standard Refinement	2 x 3	Accepted Standard Refinement
Deep Space Sortie	1 Month	1 x 4	Accepted Low Probability	1 x 3	Accepted Low Probability
Lunar Visit/ Habitation	1 Year	1 x 4	Accepted/ Optimize	2 x 3	Accepted/ Optimize
Deep Space Journey/Hab	1 Year	1 x 4	Accepted/ Optimize	2 x 3	Accepted/ Optimize
Planetary	3 Years	2 x 4	Requires Mitigation	3 x 3	Accepted/ Optimize

… fracture in mission due to existing countermeasures (evaluated by BMD metric) effectiveness. **Planetary:** Increases due to mission duration and surface operations. **<u>Consequence</u> LEO, Sortie, Lunar:** Greater performance impacts due to LOM as bone fracture may be considered a significant injury with possible return to Earth for treatment. **<u>Consequence</u> Deep Space Journey and Planetary :** Based solely on health impacts - Injury may be disabling due to the inability to return to Earth for treatment. **LTH <u>Likelihood</u> LEO, Lunar, Journey**: Likelihood of fracture due to spaceflight > 0.1% and < 1%. Most crew could return to baseline BMD within 3 years. **Sortie:** Likelihood <0.1% due to limited mission duration. **Planetary:** > 1% due to mission duration. **LTH <u>Consequence</u>:** Bone fracture prevention may require extended medical interventions by known methods

Risk Disposition Rationale: Accepted for LEO/ISS missions, within standard limits. Additional data are highly desired to refine standard. Deep Space Sortie Accepted due to low probability of consequence. Lunar and Deep Space Habitation requires optimization of exercise equipment/protocol and/or use of pharmaceuticals. Planetary requires mitigation for potential operational impacts due to fracture from surface EVA and optimization for long term health due to long duration mission induced bone changes.

(*) Risk Custodian: J. Sibonga