National Aeronautics and Space Administration

Exercise, Bisphosphonates & Bone Strength: Is the Bone problem solved?

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Disclosure Information

84th Annual AsMA Scientific Meeting

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I have no financial relationships to disclose.

I will discuss the off-label investigational use of bisphosphonates.

Four Identified “Bone” health risks for exploration missions.

1. Early Onset Osteoporosis

2. Bone Fracture

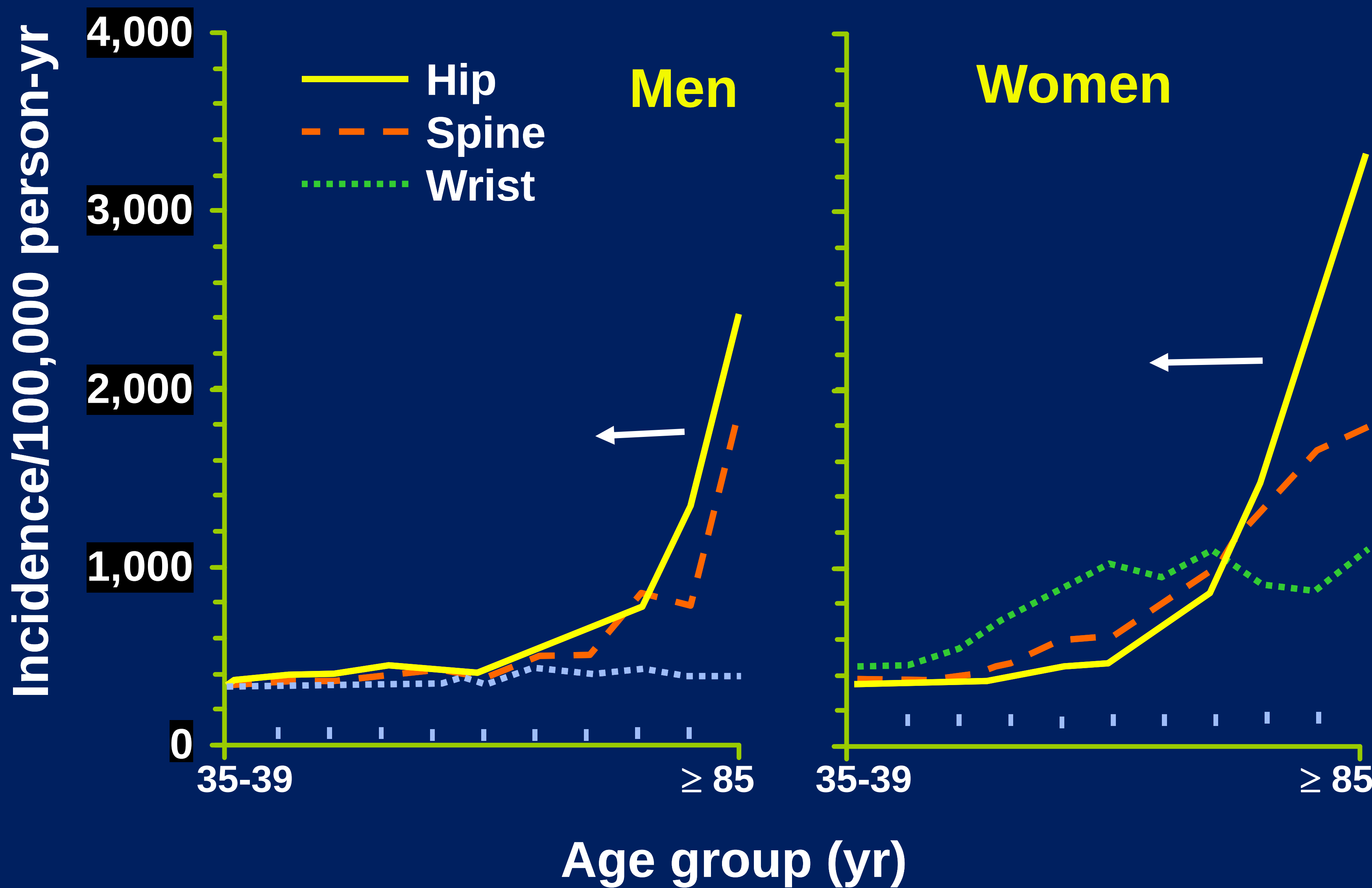
3. Formation of Renal Stones

4. Intervertebral Disc Injury *(or Damage)*

Four Identified “Bone” health risks for exploration missions.

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

Osteoporosis: Premature fractures in astronauts?

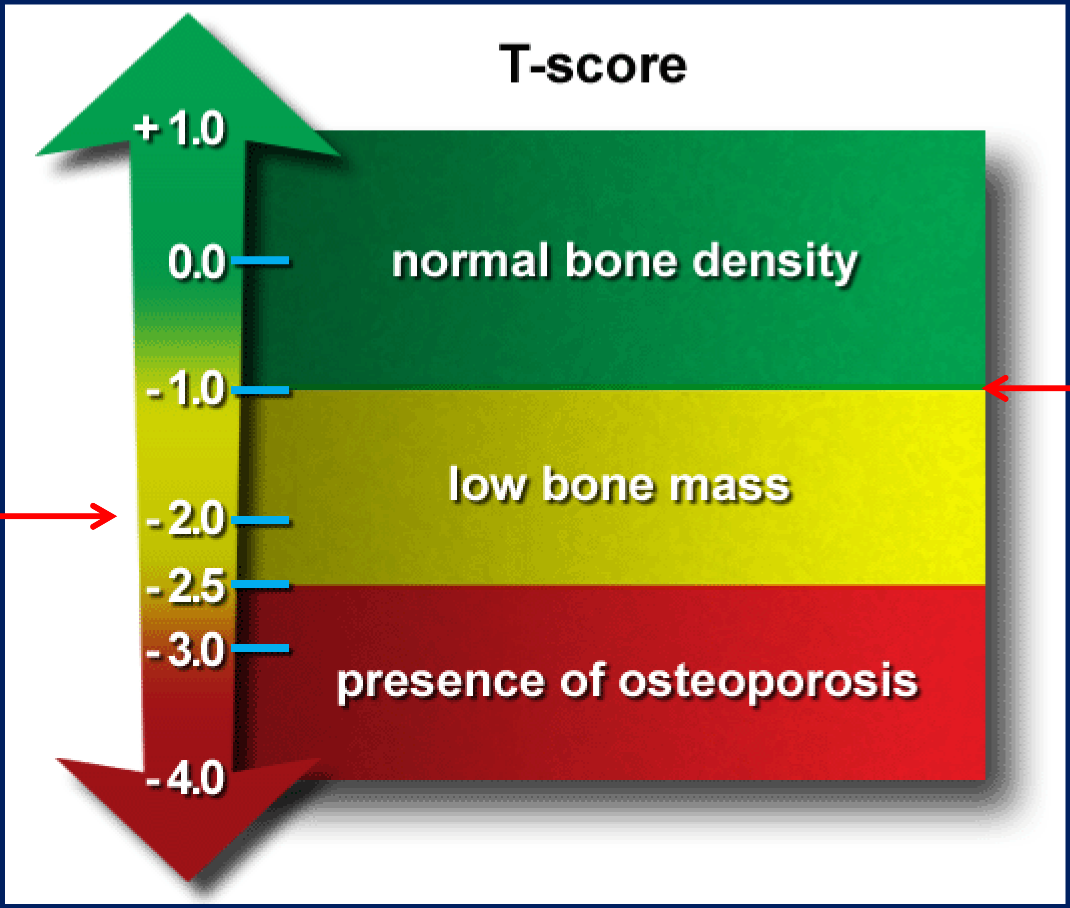


SLIDE COURTESY OF Dr. S. AMIN, Mayo Clinic

Cooper and Melton, 1992

NASA Standards for Crew Health Based on World Health Organization (WHO) –T-scores (Not BMD change).

Permissible Outcome Limit



Disconnects discovered In population studies.

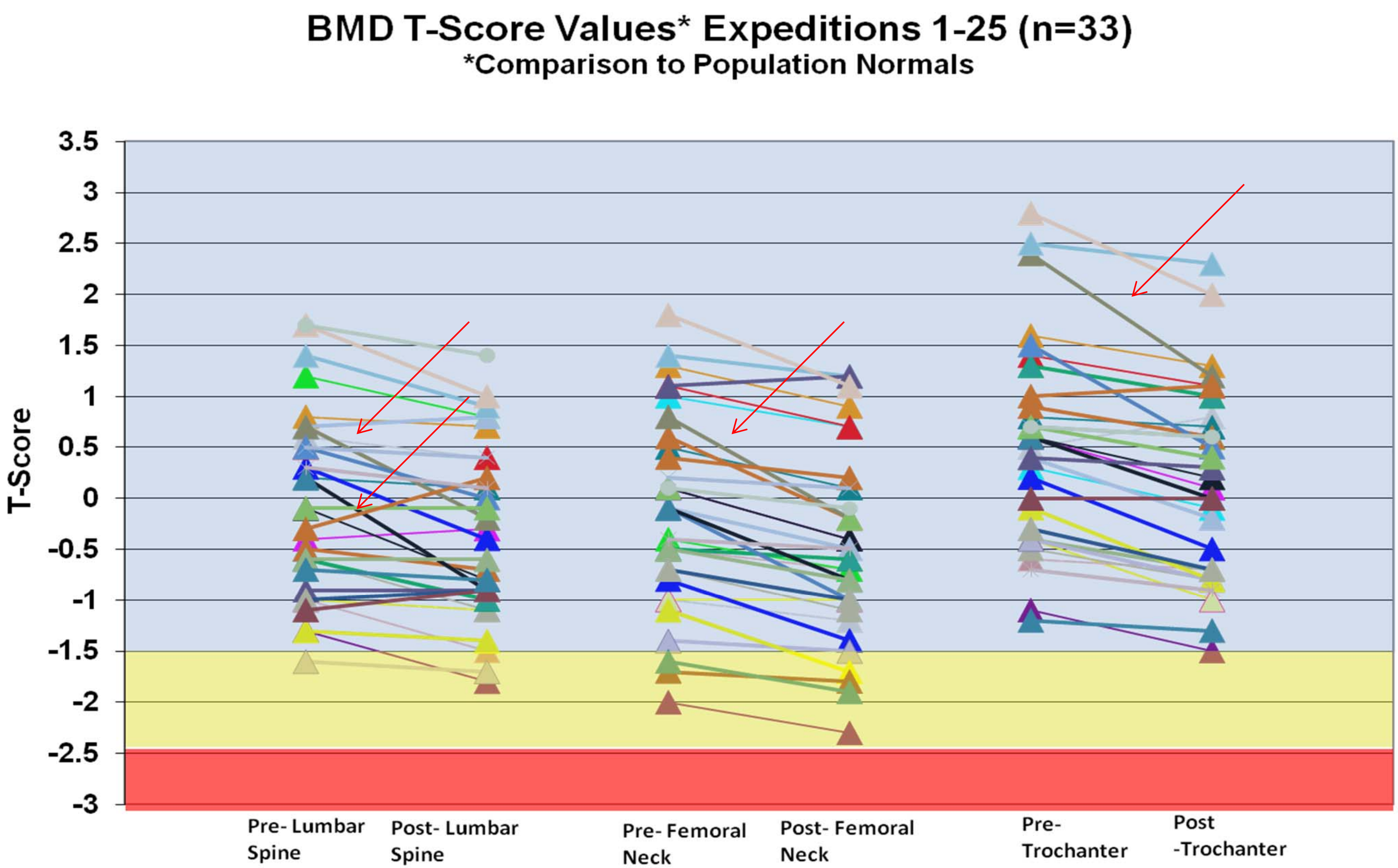
FRACTURE CASES

Fitness For Duty

NON FRACTURES

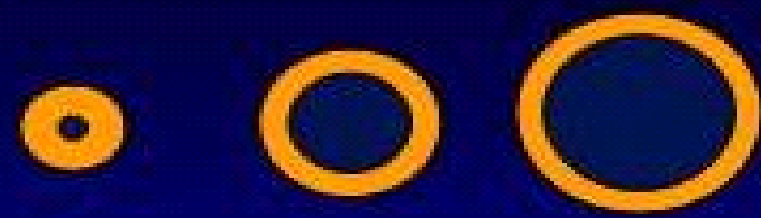
Diagnostic Guidelines Not for Astronauts

for peri- and postmenopausal women and men > 50 years.



Dual-energy X-ray Absorptiometry [DXA]
Cannot distinguish changes in bone size

Effect of geometry on long bone strength



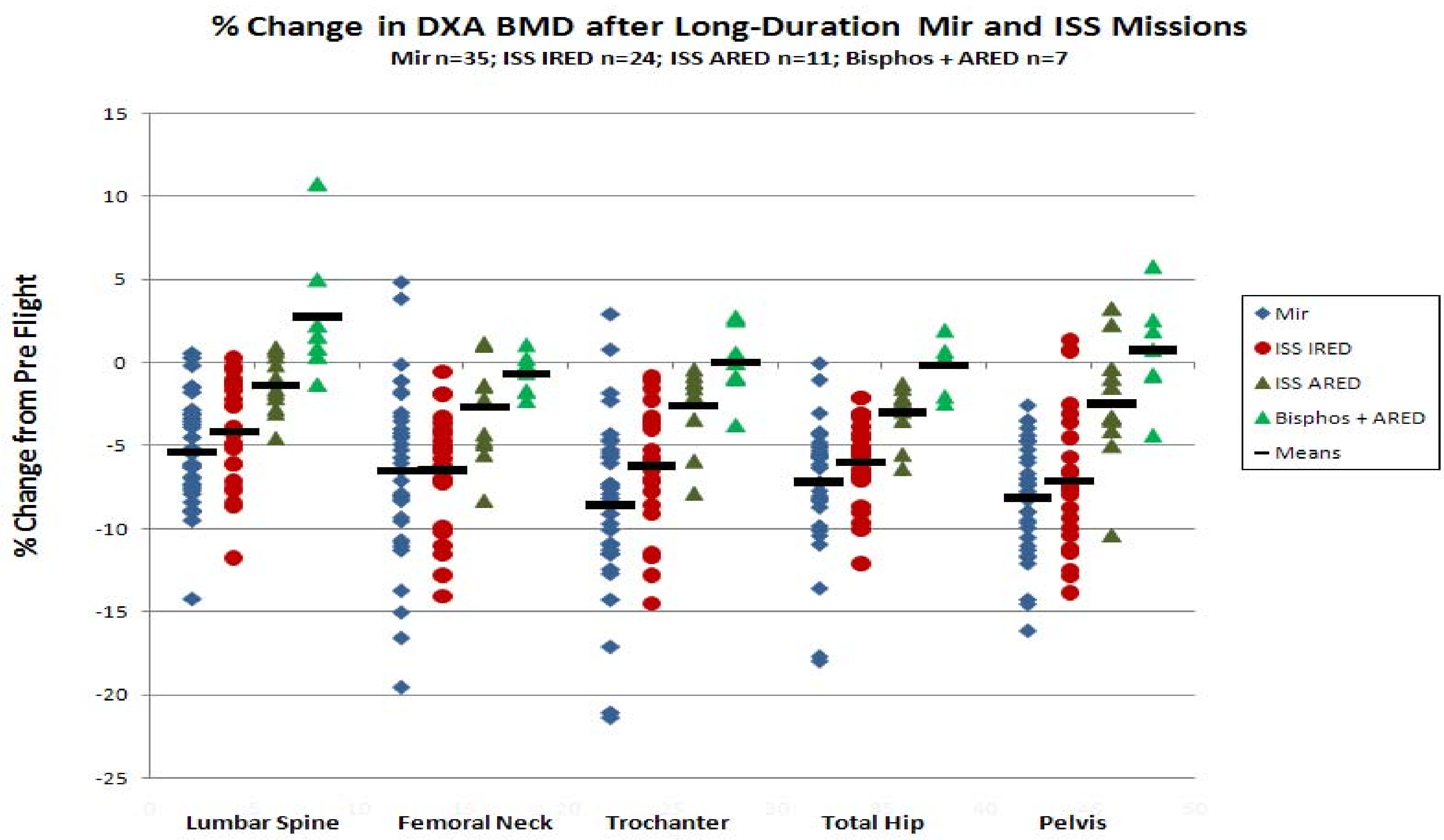
aBMD Areal (g/cm^2)	1	1	1
Compressive Strength	1	1.7	2.3
Bending Strength	1	4	8

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

Preparation for Exploration Missions

IS NASA USING THE RIGHT TEST FOR EVALUATING RISK?

DXA – BMD cannot address operational concern- Exercise vs. Pharmaceuticals?



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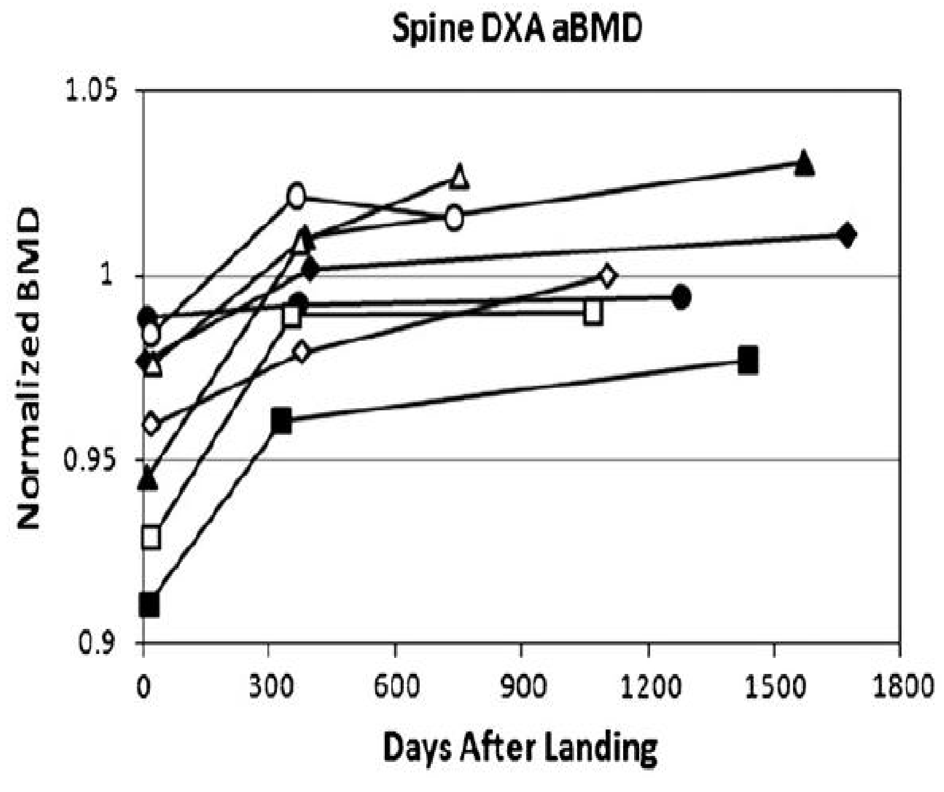
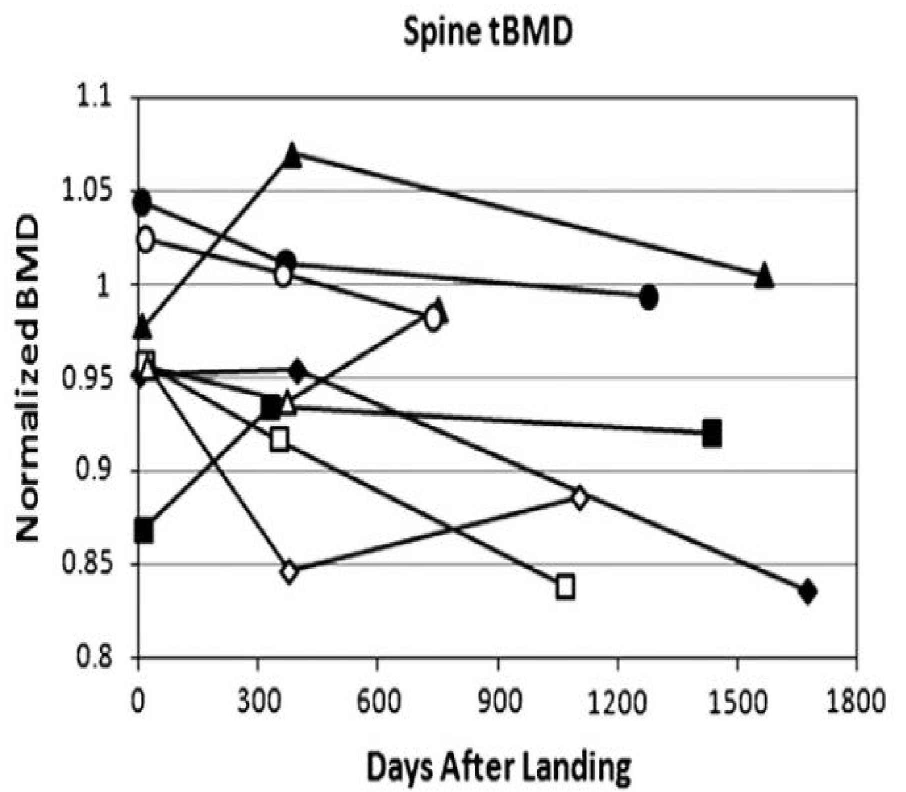
Quantitative Computed Tomography [QCT]

QCT MONITORING OF SPACEFLIGHT EFFECTS

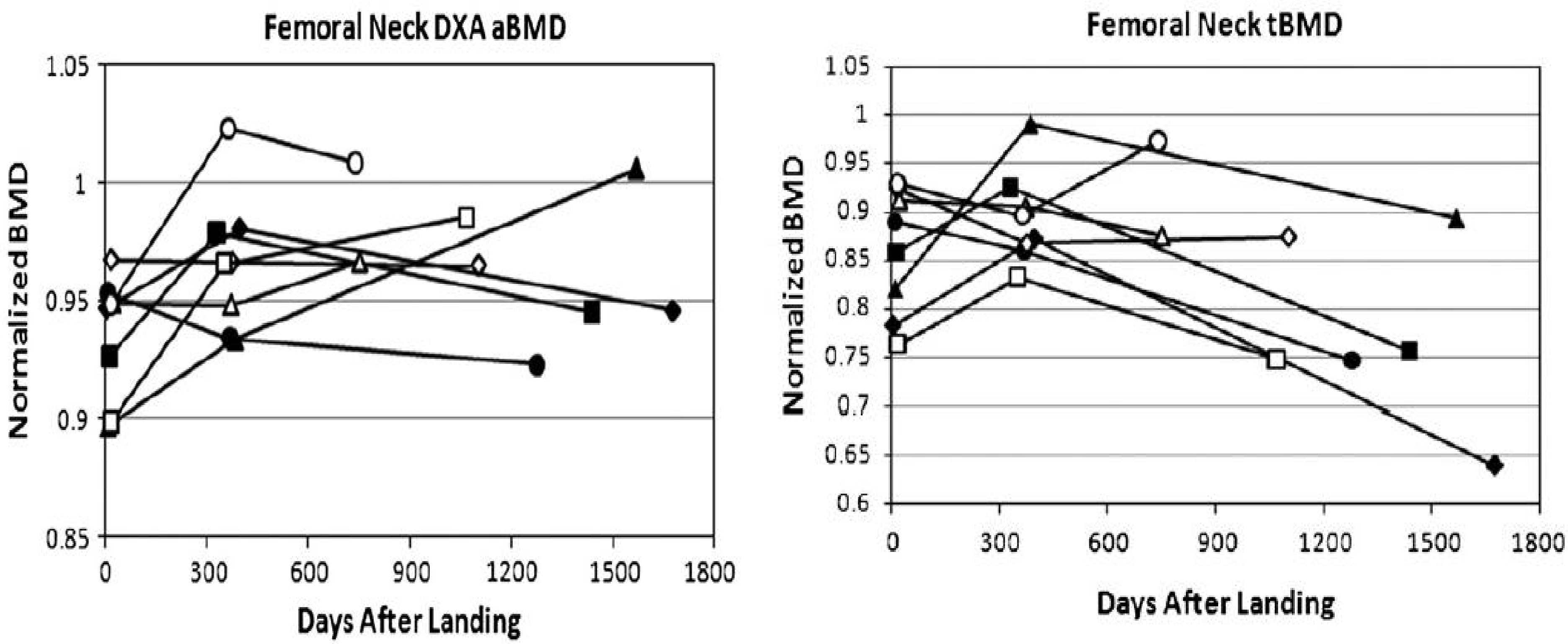
DXA vs. QCT Spine :
Discordant Recovery Patterns After Spaceflight





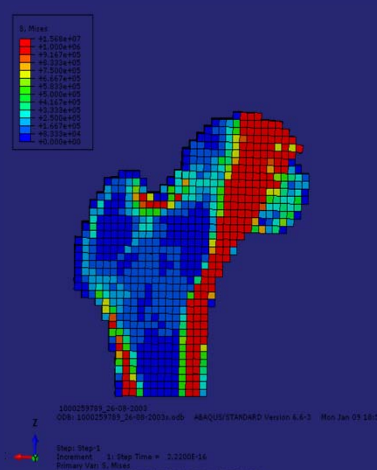
QCT Extension Study (n=8) Postflight Trabecular BMD in hip. Carpenter, D et al. Acta Astronautica, 2010.

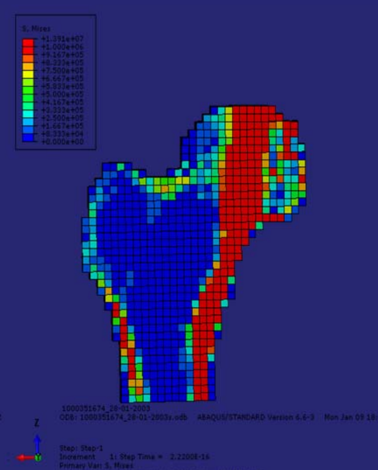
DXA vs. QCT Femoral Neck:
Discordant Recovery Patterns After Spaceflight



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

Finite Element Models of QCT data – “FE modeling” is a computational tool to estimate failure loads (“strength”) of complex structures.

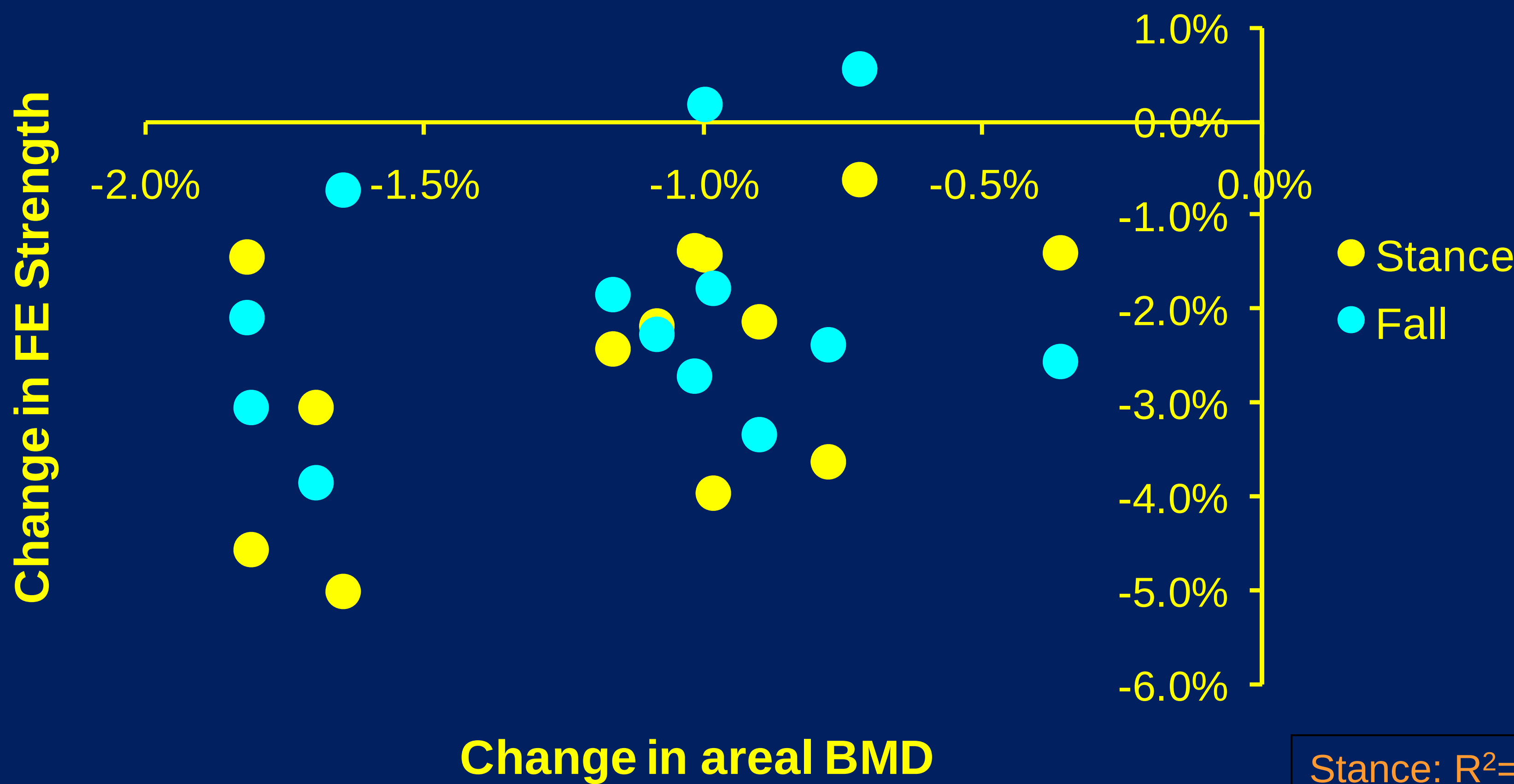




J. Keyak et al, 1998, 2001, 2005

Images courtesy of Dr. J Keyak

Astronaut Data (n=11): Space effects on surrogates of bone strength do not correlate.



Stance: R^2=0.23

Fall: R^2=0.05

Slides courtesy of J Keyak; Bone. 2009 Mar;44(3):449-53.

Summary

- DXA –widely-applied medical test for terrestrial medicine but may be too limiting for operational and decision-making for bone health of astronauts

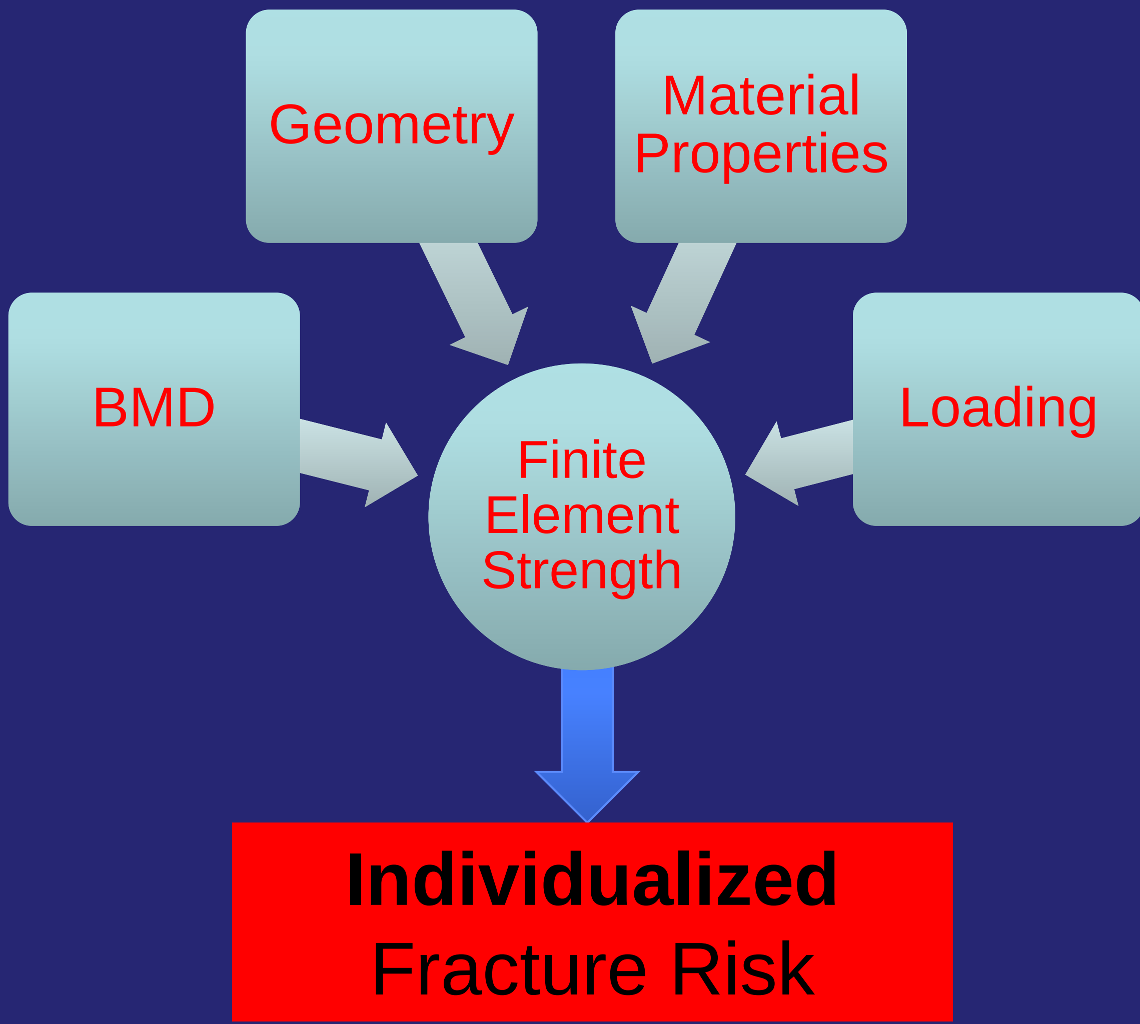
- As long as countermeasure efficacy is assessed by a <u>surrogate</u> measure of bone strength (DXA – BMD) vs. an <u>estimate</u> of bone strength (e.g., FE models), then there is a risk of underestimating fracture probability and countermeasure efficacy.

Thank you.

QUESTIONS? COMMENTS?

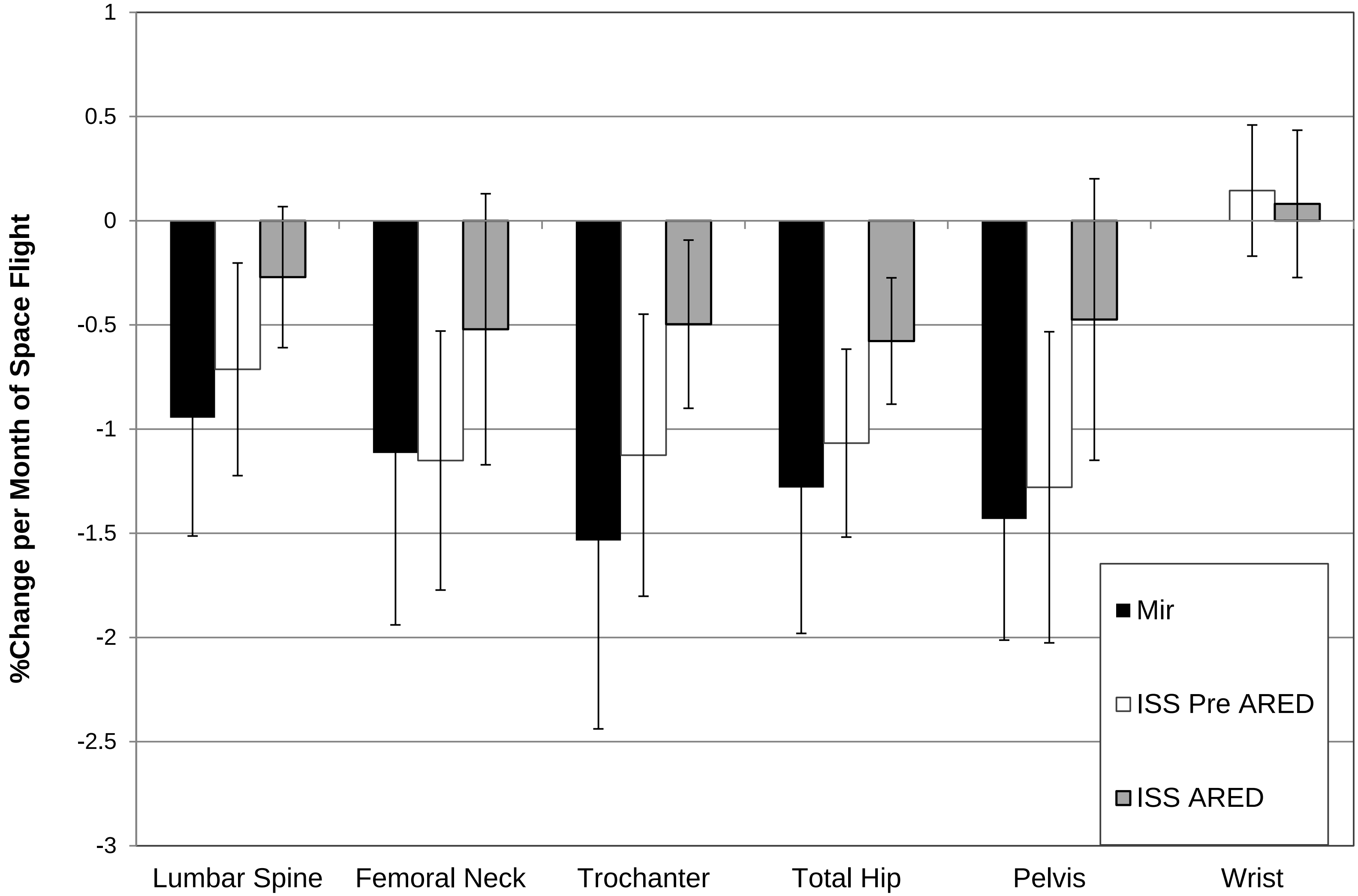
Backup Slides

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



ARED exercise appears to mitigate decline in areal BMD.

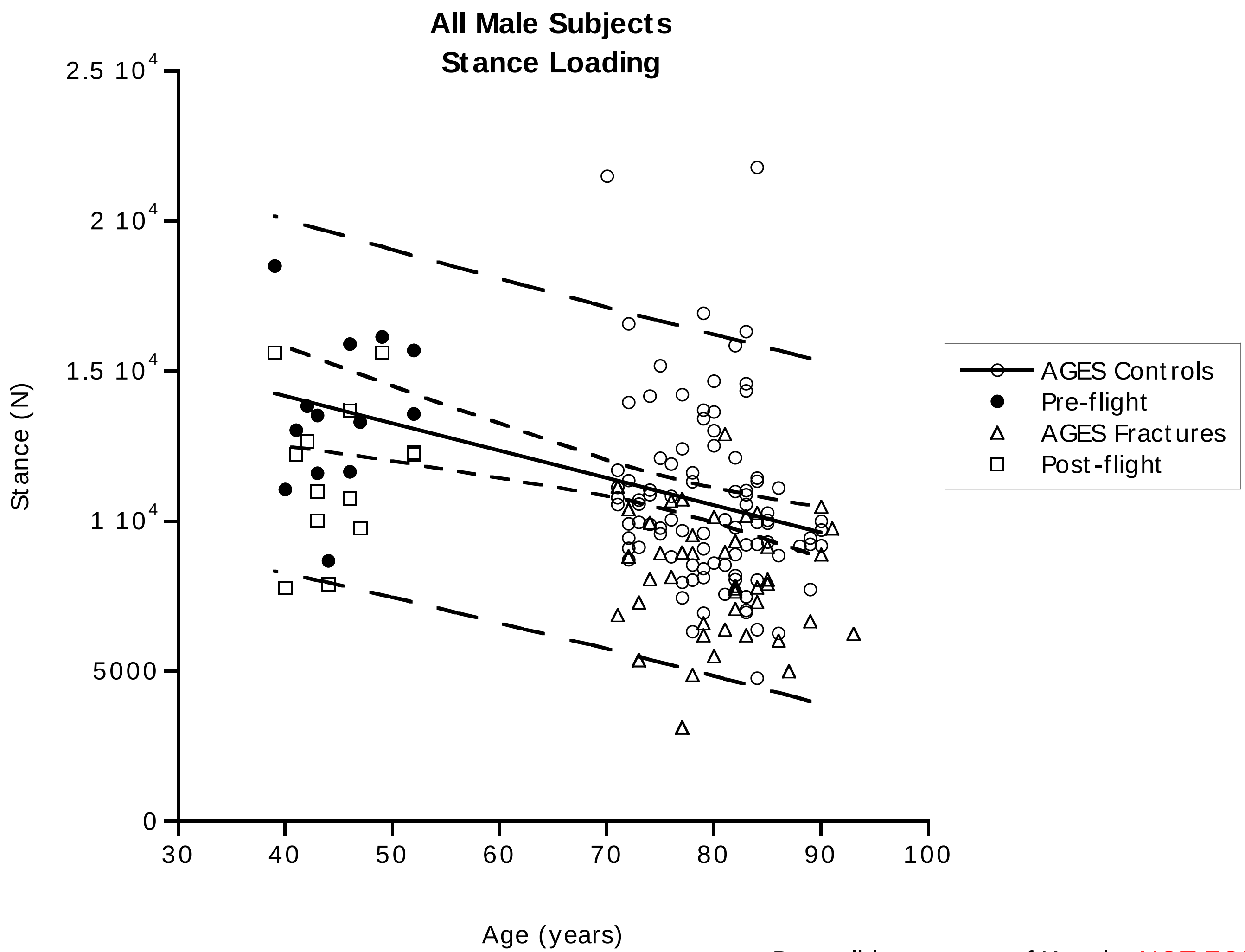
(J Bone Mineral Research. Smith et al 2012) * *this is not ref for figure*.



Exploring FEM of QCT Scans from Population Studies

FE Task Group:

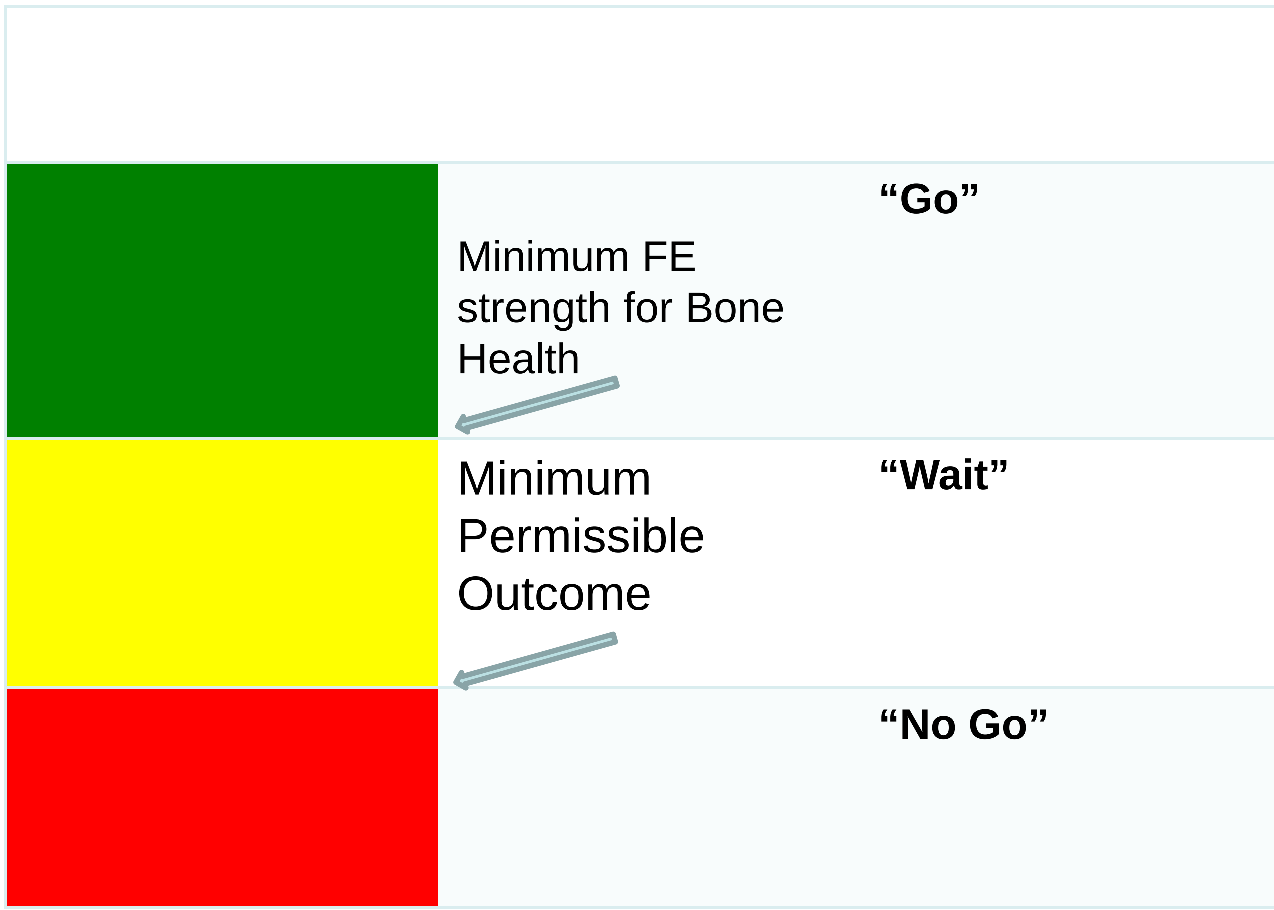
E. Orwoll MD, S Khosla MD, S Amin MD, T Lang PhD, J Keyak PhD, T Keaveny PhD, D Cody PhD, JD Sibonga, Ph.D.



REPRESENTATIVE POPULATION DATA

Data slide courtesy of Keyak. NOT FOR DISTRIBUTION

FE Standards Combine Aging and Spaceflight Changes to Hip Strength and used together with DXA BMD Standards.



Take Home Messages

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 complex.
5. Clinically-accepted tests have limitations.
6. Bone medical standards (based upon terrestrial guidelines) are not applicable to long-duration astronauts and require modification.

Clinical Trigger: Failure to Recover Hip Trabecular Bone Loss

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

Based upon: Lower trabecular BMD was an independent predictor of hip fracture in aged men in randomized controlled trial.

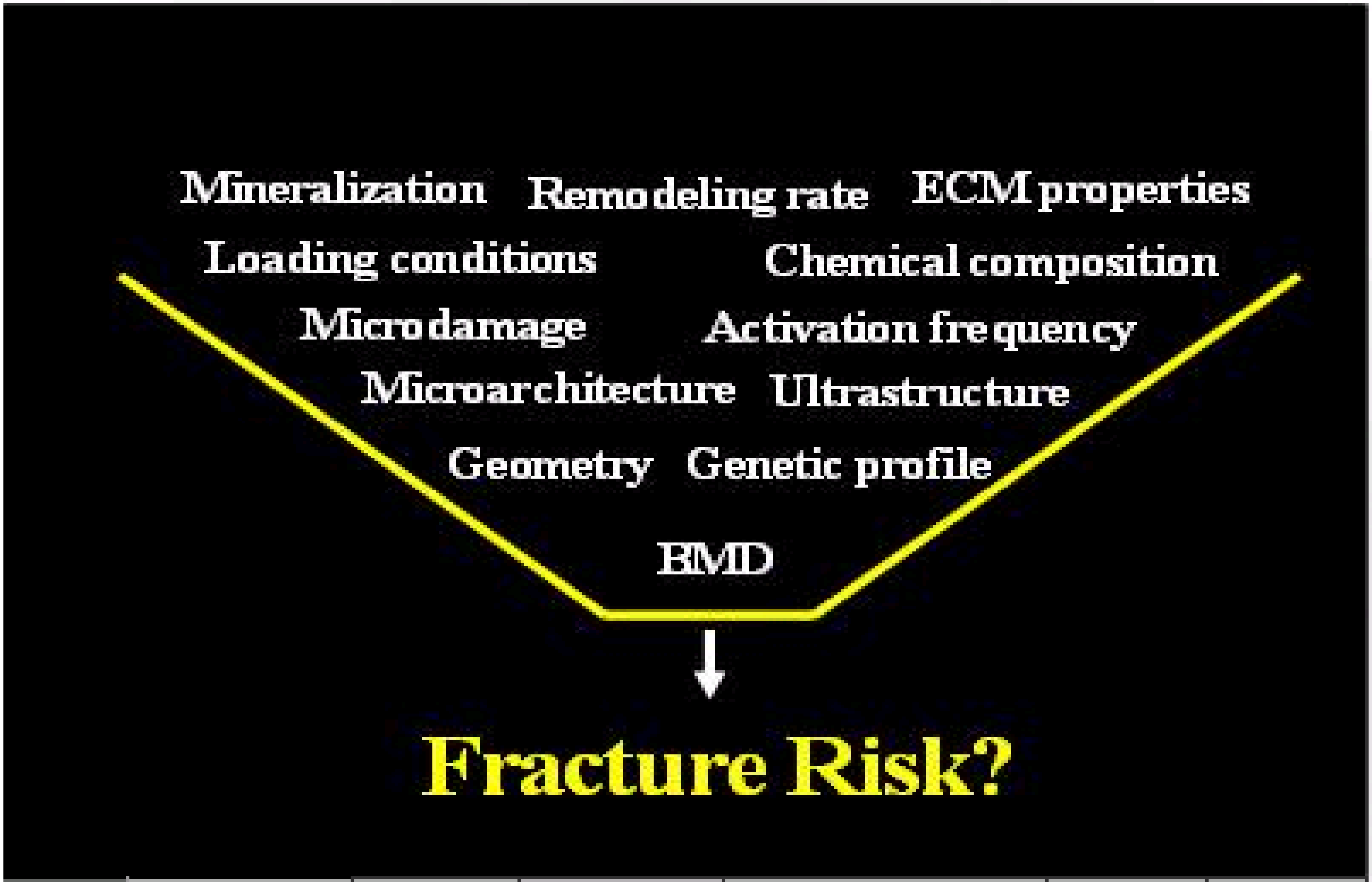
Note: QCT measures do not outperform BMD for fracture prediction…

QCT provides useful information re: causation of hip fracture, evaluation of hip fracture risk and possible targets for intervention.

TABLE 4. HRs OF MULTIVARIATE MODELS OF SKELETAL PARAMETERS AT THE FEMORAL NECK FOR HIP FRACTURE ADJUSTED FOR CLINIC SITE, AGE, AND BODY MASS INDEX

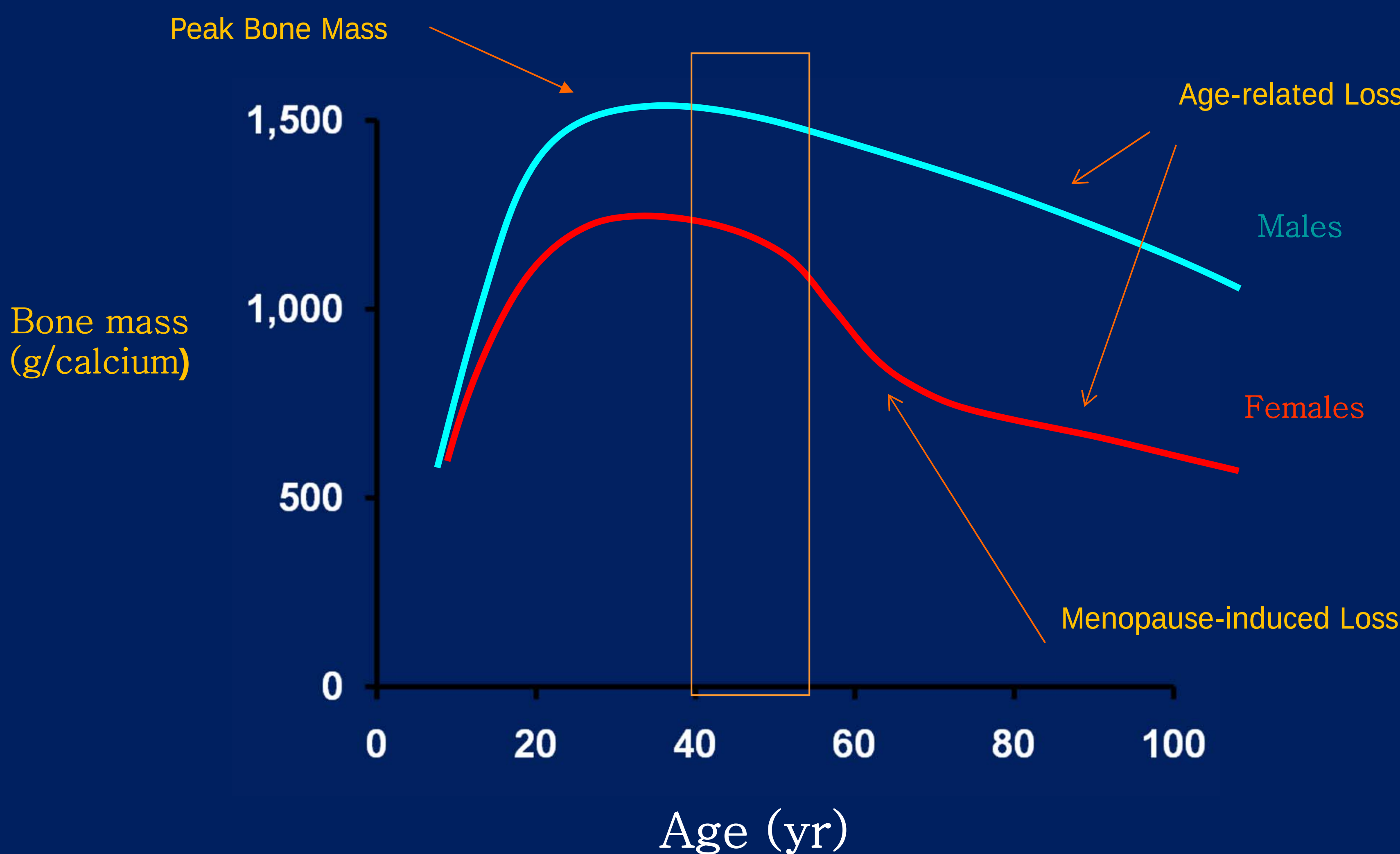
	Model A (HR per SD decrease)			*Model B (HR per SD decrease)*			*Model C (HR per SD decrease)*		
	HR	*95% CI*	*p*	*HR*	*95% CI*	*p*	*HR*	*95% CI*	*p*
Trabecular bone, volumetric BMD (g/cm^3)	—			1.65	1.15, 2.37	0.007	1.29	0.84, 1.98	0.250
Percent cortical volume	—			3.19	2.23, 4.57	<0.001	2.42	1.56, 3.76	<0.001
Minimum cross-sectional area (cm^2)	—			1.59	1.24, 2.05	<0.001	1.48	1.14, 1.94	0.004
Areal BMD from DXA (g/cm^2)	4.13	2.67, 6.38	<0.001	—			1.91	1.06, 3.46	0.033

Area under the ROC curve for Models A, B, and C were 0.853, 0.855, and 0.860, respectively.



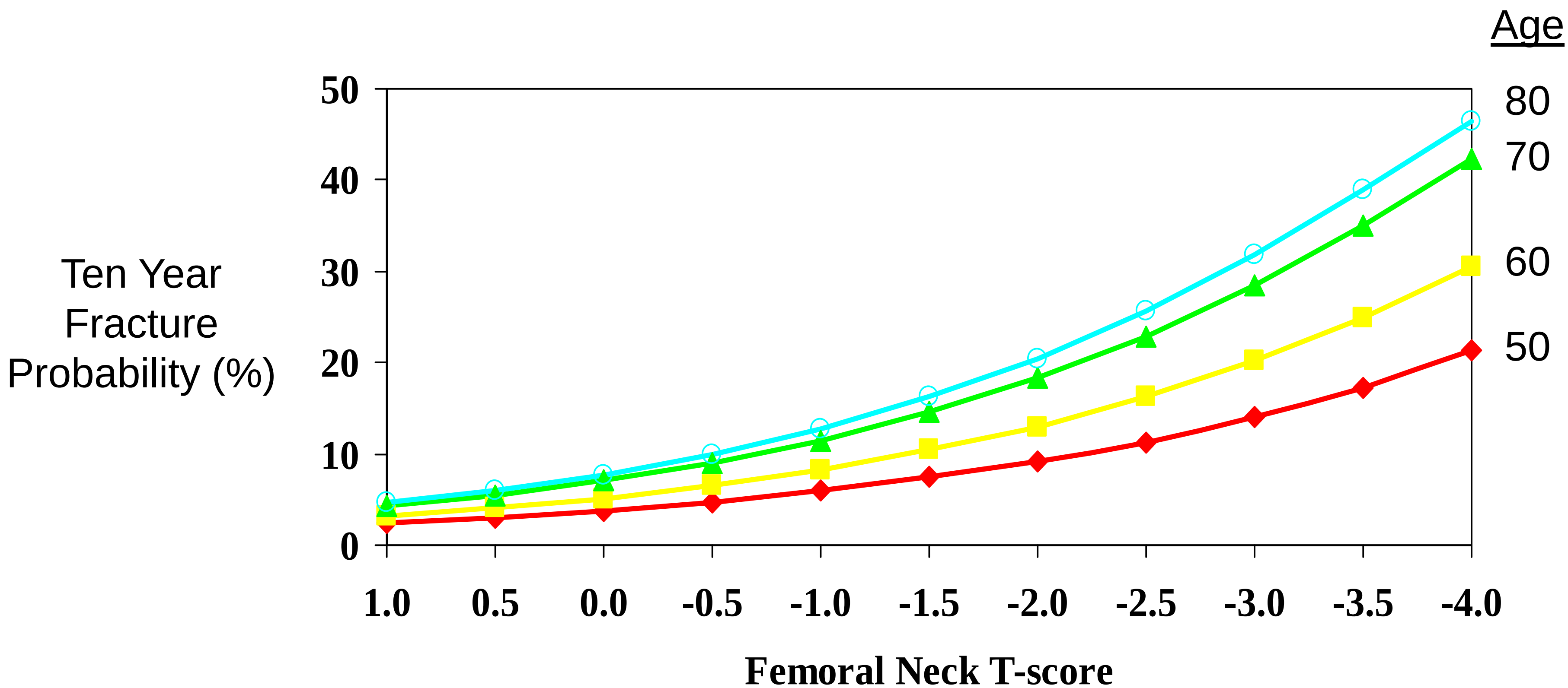
Steven Goldstein, Ph.D.
“Bone Quality: A Biomechanical Perspective”

Does spaceflight result in irreversible changes to bone that combine with age-related losses?



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

Inappropriate: Probability for osteoporotic fractures is lower at younger ages.

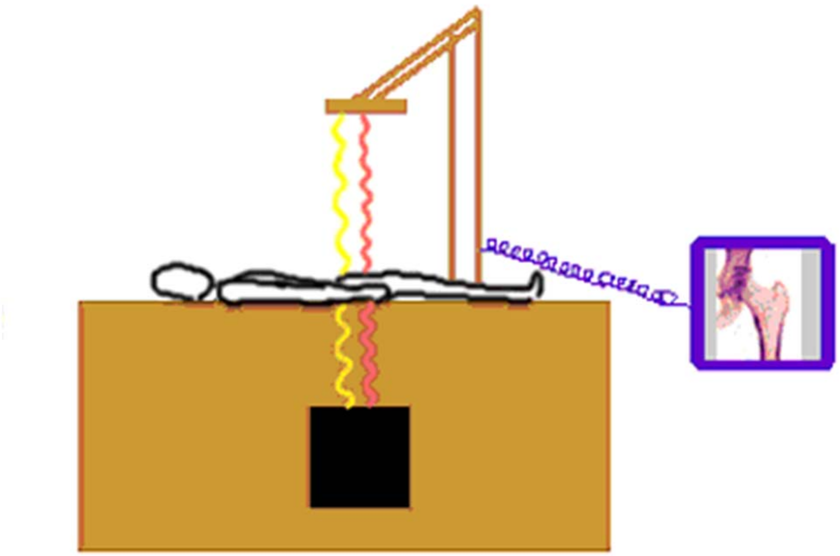


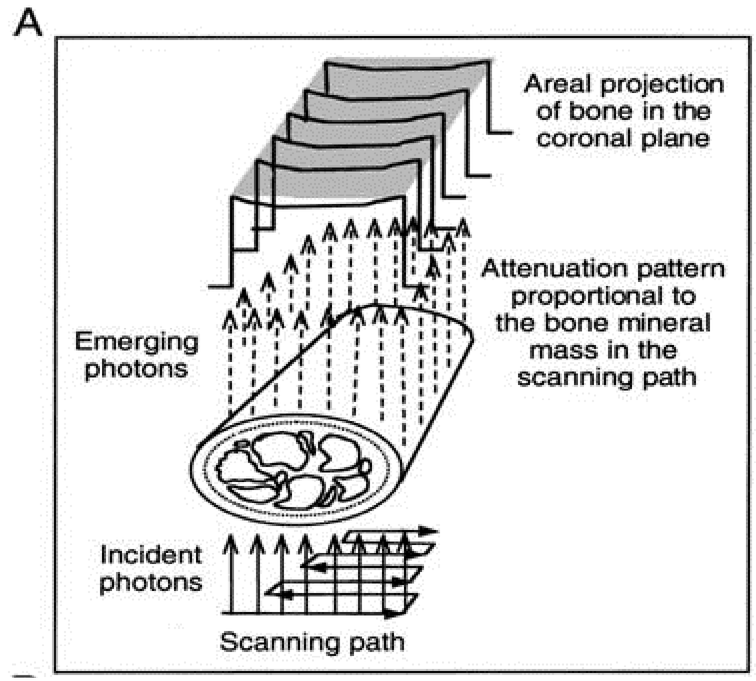
Probability of first fracture of hip, distal forearm, proximal humerus, and symptomatic vertebral fracture in women of Malmö, Sweden.

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

Slide Courtesy of S. Petak, MD.

Dual-energy X-ray Absorptiometry

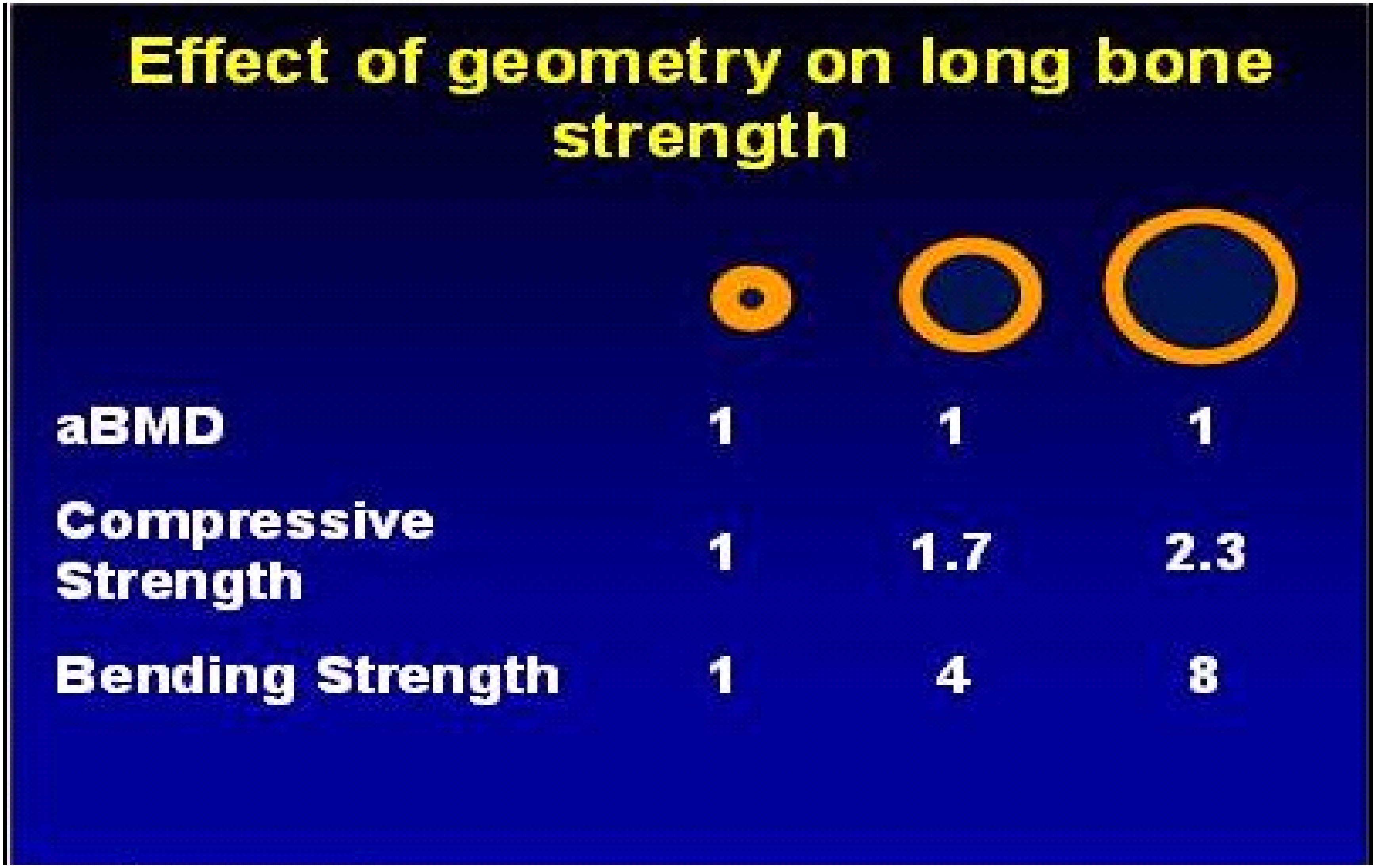




DXA measurement of areal BMD [BMD_a] – a 3d measure in 2d units

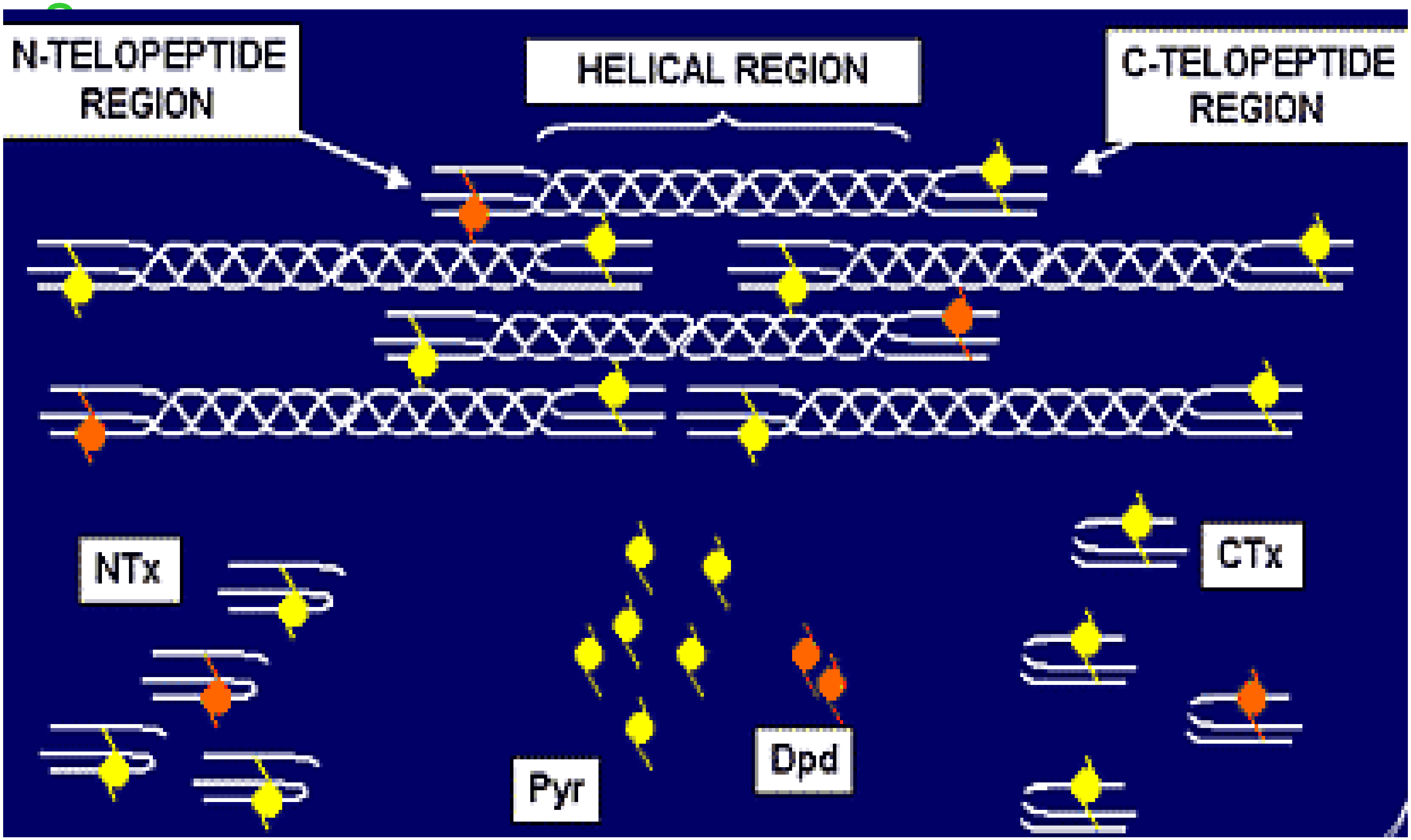
- Used in large prospective studies for fracture prediction
- Long established surrogate for bone strength
- Despite limitations, still considered best predictor of fracture

Limitation of DXA: cannot distinguish different geometries of bone and thus cannot reflect different levels of bone strength.



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

Serum and urinary biomarkers reflect bone turnover and mineral metabolism.



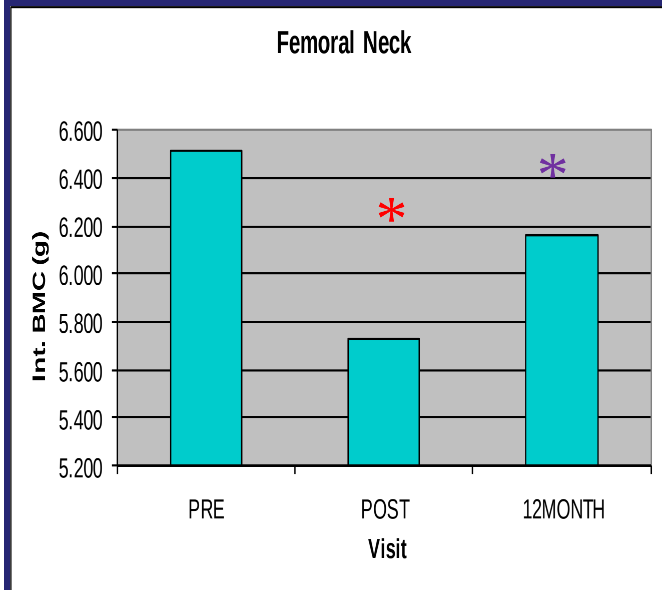
Research: QCT detects different rate of vBMD loss in separate bone compartments of hip. (n=16 ISS volunteers)

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

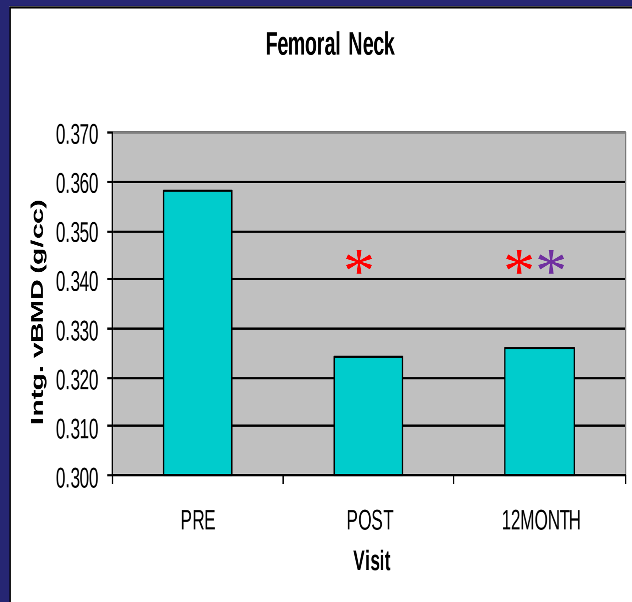
LeBlanc, J Musculoskelet Neuronal Interact. 2000 ;
Lang , J Bone Miner Res, 2004;

QCT Postflight – Changes in Femoral Neck structure detected 12 months after return

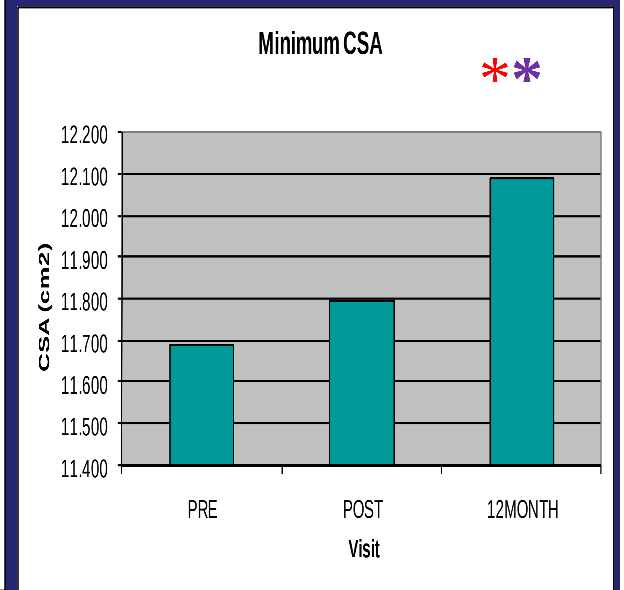
Bone Mineral Content
(g)



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.

Astronaut Data– Reductions in Hip Strength with spaceflight.

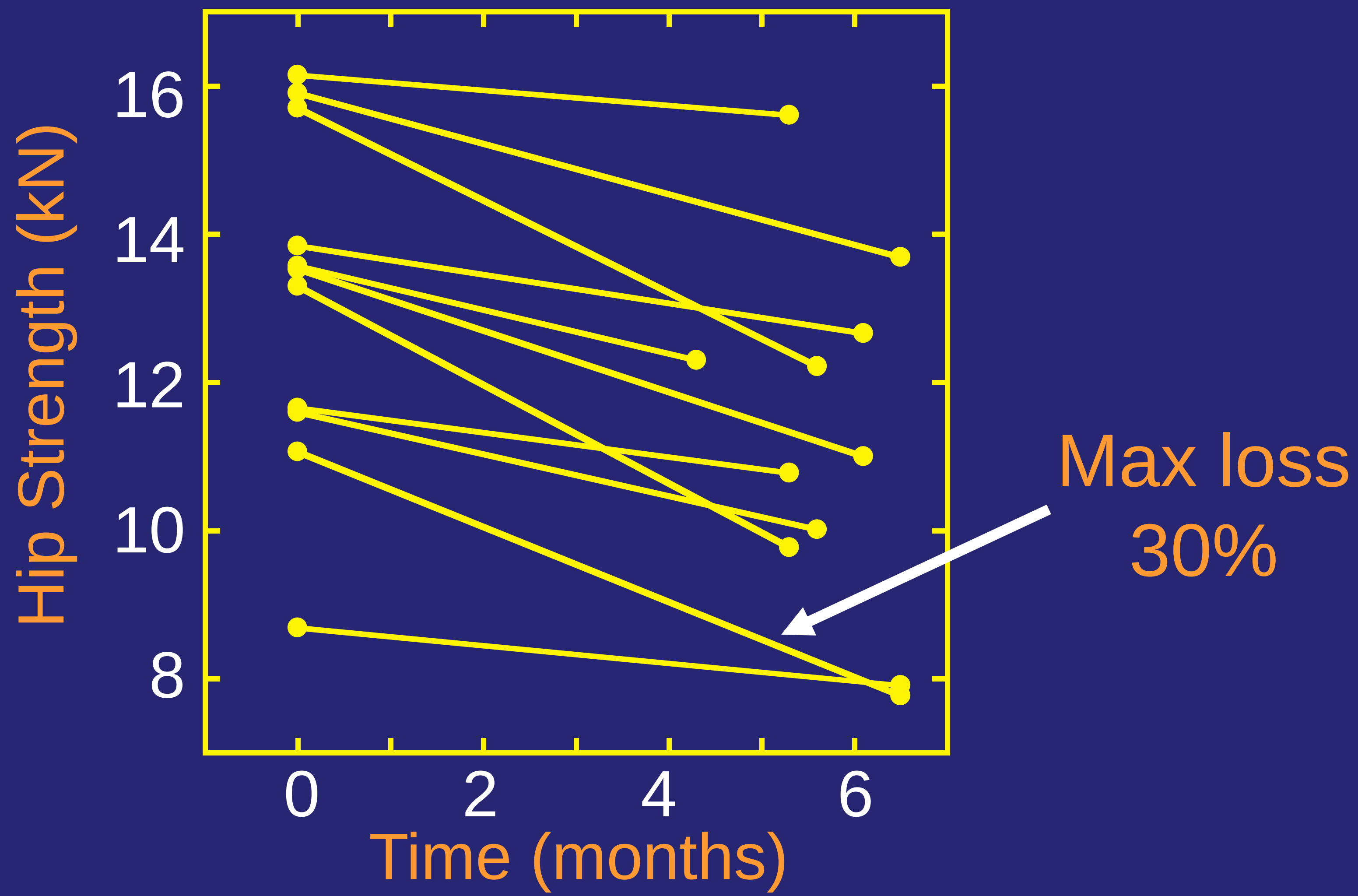
N=11 crewmembers

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

1.0-1.5% BMD loss /month

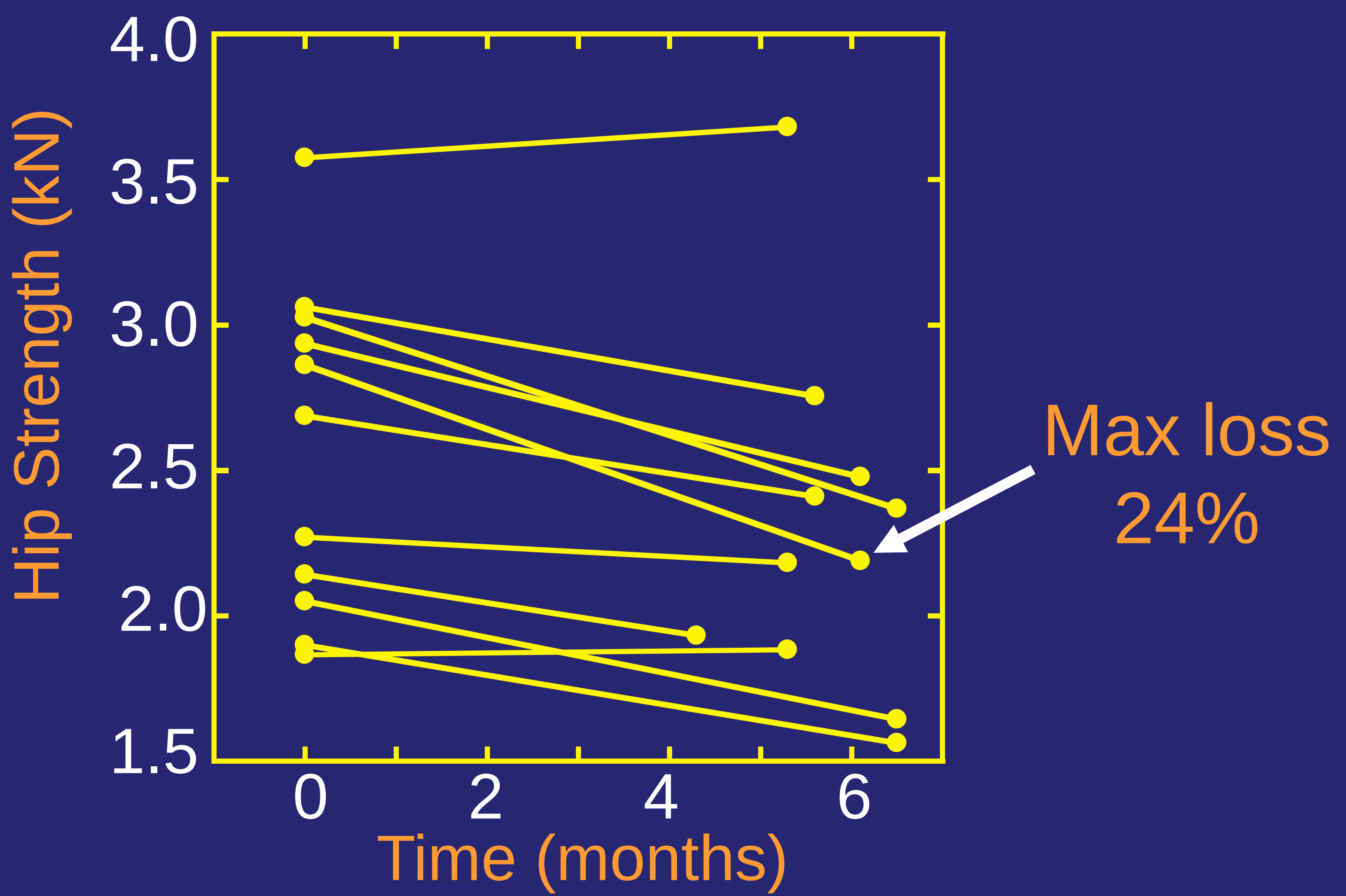
Individual Results

Stance Loading (4 to 30% loss in strength)



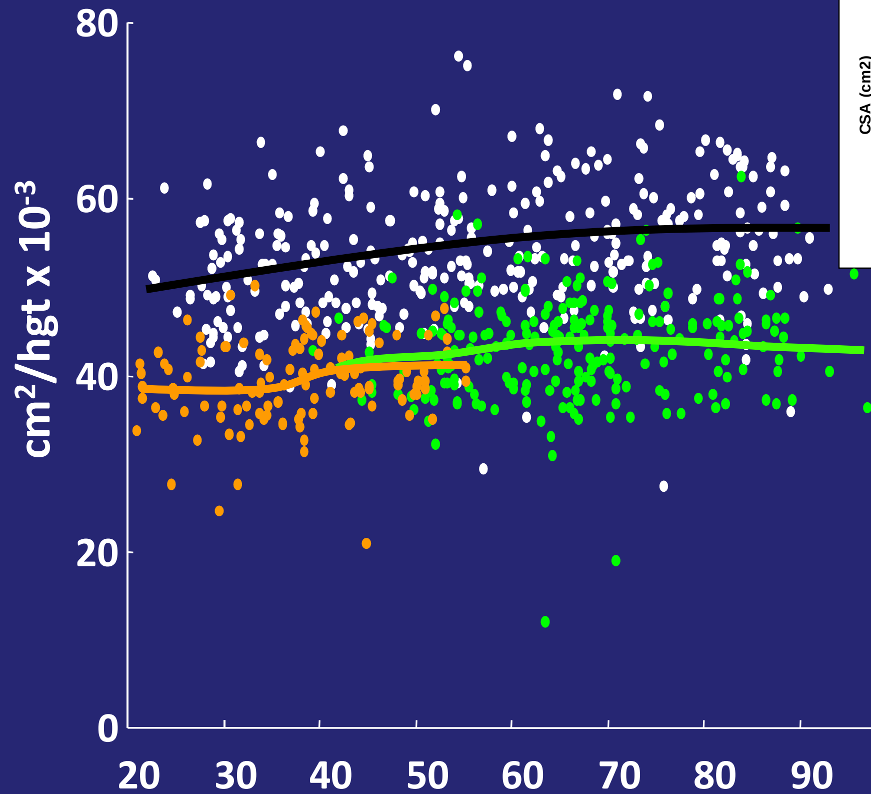
Individual Results

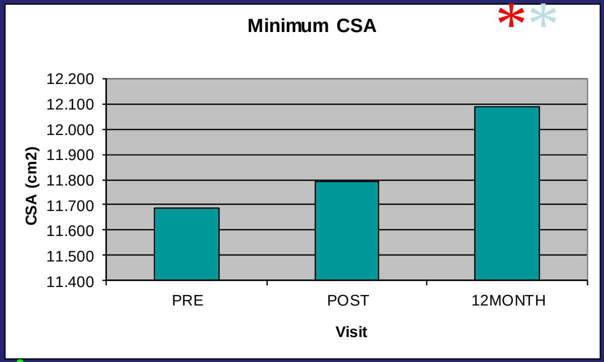
Fall Loading (3 gain to 24% loss in strength)



QCT in Population Study: Age-related Changes

Suggests that femoral neck total area increases by outward displacement when cortex thins with age

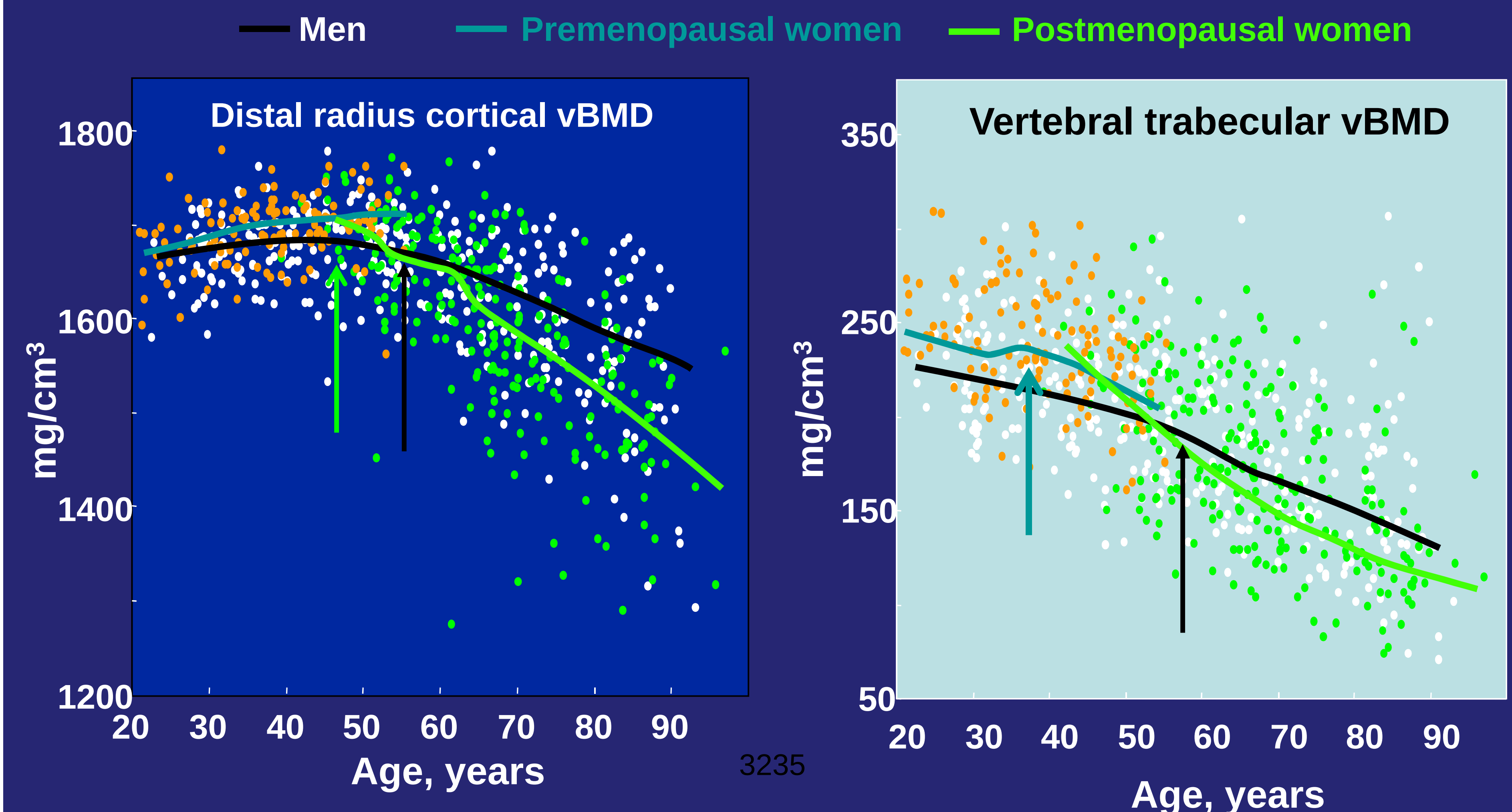




Riggs et al. JBMR19:1945, 2004.

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

Riggs et al. JBMR19:1945, 2004.



The long-duration astronaut - an atypical subject to evaluate osteoporosis risk.

- Typical space mission duration – 163 ± 32d (range 90-215d)
- Average Age – 46.5 ± 4.5 y (range 36.8 – 55.3)
- Male to Female Ratio – 3.8 : 1
- Current total # per astronauts in corps – 34 of 331
- # repeat fliers – 4
- BMI – Male BMI 25.9 ± 2.2 *(range 20.6 to 30.6);* Female BMI 22.6 ± 2.2 *(range 20.4 to 25.4)*
- Wt and Ht- Males: Males: 81 ± 9 kg *(range 62 to 101 kg),* 177 ± 6 cm *(range 163 to 185 cm)*;
- Females: 65 ± 7 kg *(57 to 80 kg),* 170 ± 4 cm *(range 165 to 178 cm)*
- *MEDICAL PRIVACY OF THE ASTRONAUT.*

QCT + FEM has superior capabilities for estimating mechanical strength of ex-vivo specimens.

QCT estimates <u>fracture loads</u> better than DXA

QCT + FEM has superior <u>capabilities for estimating fracture loads</u>

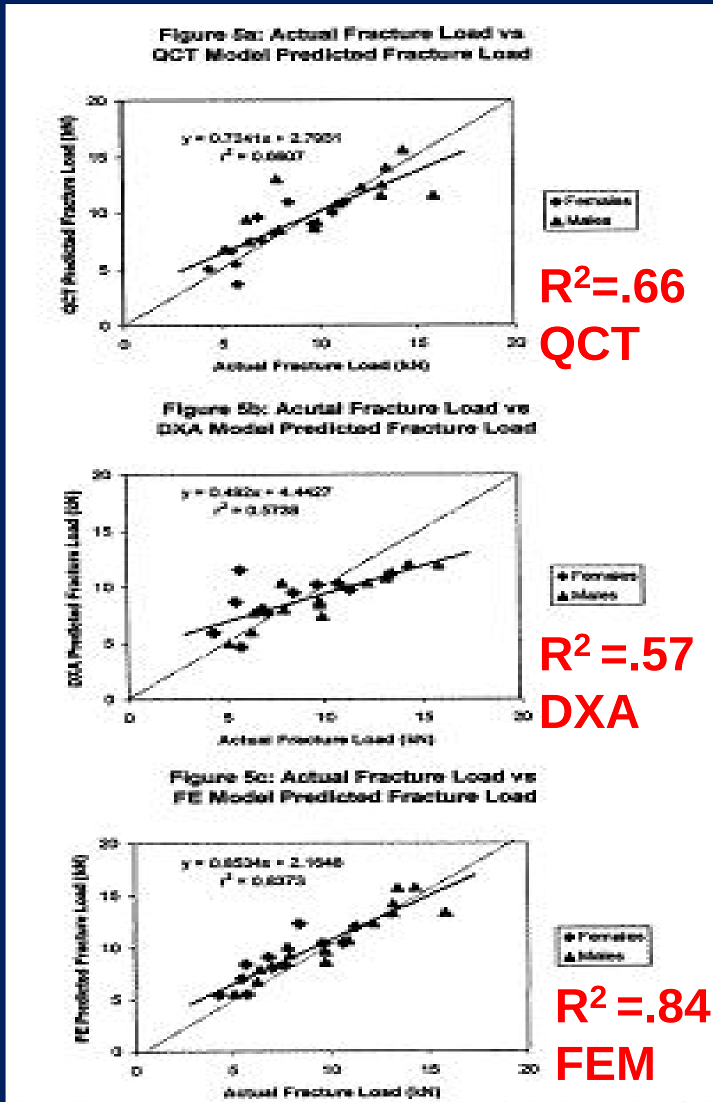


Fig. 5. The predicted strength of the specimens in the test set (developed from the models generated using the training set) plotted against their actual measured values for each of the three methods (a: QCT; b: DXA; c: FEM).

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