Bone *Changes* During Spaceflight: How do we assess fracture probability in astronauts?

Navy and WSU Aerospace Medicine

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Human Research Program [HRP]
Johnson Space Center, Houston, TX
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At the end of this lecture, you should understand:

- The view of DXA BMD as a surrogate for fracture risk in terrestrial medicine. *Why DXA is not a good research technology to understand fracture risk in astronauts.*

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

- Bold research approaches to assessing the “biomechanical competence of bone” in the context of NASA’s constraints.
Getting on the same page.

BONE BIOLOGY
TWO TYPES OF BONE

PROXIMAL FEMUR

Trochanter
50% BMD

Femoral Neck
25% BMD

VERTEBRAL BODY – 66% BMD

Cortical Bone/ “Compact Bone”

Cancellous “Spongy” Bone/ Trabecular Bone

Sources: L. Mosekilde; SL Bonnick; P Crompton
Distribution of bone types in skeleton and turnover rates on earth

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

Cortical Bone 80% of total skeleton (long bones)

Cancellous Bone 20% of total skeleton (vertebrae, ribs, ends of long bones) Contains 80% of bone surfaces
BONE SURFACES – Sites of bone formation & removal – not random

- Trabecular Surface
- Endocortical “Endosteal” Surface
- Periosteal Surface
- Intracortical
Remodeling at the level of a single “Bone Remodeling Unit”

HIGHLY-REGULATED ACTIONS OF BONE CELLS on BONE TURNOVER.

1-2 million BRUs in the adult skeleton
TYPES OF BONE CELLS: mediators of bone resorption, bone formation, mechanical sensing

- Osteocytes
- Osteoblasts
- Osteoclasts

Bone Marrow Area

Mineralized bone
Characterizing Bone Changes* in Space

Shuttle 1981-2010
Intl Space Station 2000-present

Mercury 1961-63
Gemini 1965-66
Apollo 1968-72
Skylab 1973-74

Calcium balance
SPA of heel and wrist

Soyuz/Salyut 1974-85

Mir 1986-2000

SPA
Urine, fecal Ca
Heel, Wrist

DXA

DXA
QCT
pQCT
BTO

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)

Urinary Ca during Skylab
(Mean + SEM)

Urinary Ca after Return from Skylab

Skylab-Urinary Calcium Excretion
**Functions of the Skeleton**

- Internal support for the body
- Attachment for muscles / tendons for motion
- Protects vital organs
- Encloses blood-forming elements in marrow
- Mobilized store for Calcium ($Ca^{2+}$) homeostasis

*What potential risks to human health & performance? *During and after a mission.*
Four identified “Bone” health risks for exploration missions.

1. Early Onset Osteoporosis (fragility fractures)

2. Bone Fracture (trauma fractures)

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)
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 Sibonga10
1. What additional measure(s) do we need to monitor?
2. How frequently? For how long?
3. How should Med Ops use research data in its clinical practice?

Bone Research @ NASA

Ground-Analog Research

Flight validation Research

Astronauts Clinical Care

BONE SUMMIT 2010 and 2013
Take Home Messages from Bone Summit (2010)

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 tests have limitations.
6. NASA’s medical standards for bone health (based upon terrestrial guidelines) are not applicable to long-duration astronauts.
7. Recommended exploring the transition of research approaches to clinical arena.
Risk: Different types of fractures

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

You don’t have to be OLD.

Load > Bone Strength = FRACTURE
(Causality – BIOMECHANICS)

You don’t have to have OSTEOPOROSIS.
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
Increased risk in astronauts?
Limited time to count incidence of fractures.

Cooper and Melton, 1992
NASA measures Bone Mineral Density [BMD] by DXA as a surrogate for fracture just as clinical world. –T-scores (Not BMD change). circa 2000
“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 strength is influenced by additional factors that are not measured by DXA areal BMD.
Diagnostic Guidelines Not Meaningful for Astronauts
for peri- and postmenopausal women and men > 50 years.

BMD T-Score Values* Expeditions 1-25 (n=33)
*Comparison to Population Normals
Age is important risk factor for bone loss but the utility for < 50 years not clearly evident.*

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

* The use of DXA BMD for surveillance of active astronauts is a unique application.
Risk for osteoporotic fractures is lower at younger ages.

Given the probability of fracture drives the requirement for interventions, DXA testing for the younger aged is not considered necessary.

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

Adapted from:
Slide Courtesy of S. Petak, MD.
Uncertainty exists. Are the long-duration astronauts at risk?

WHAT COULD BE MEASURED TO DEFINE A RARE RISK IN YOUNGER PERSONS?
# History of Bone Imaging in Space

<table>
<thead>
<tr>
<th></th>
<th>Gemini</th>
<th>Space Shuttle</th>
<th>Soyuz/Salyut</th>
<th>Mir</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1968-72</strong></td>
<td>1968-72</td>
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<td>1973-74</td>
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<td><strong>1973-74</strong></td>
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<td>1974-85</td>
<td>1974-85</td>
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<tr>
<td><strong>2000-present</strong></td>
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<td>1974-85</td>
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</table>

- X-ray densitometry
- SPA heel and wrist
- SPA heel and wrist
- SPA
- DPA
- DXA whole body
- CT of lumbar spine BMD

*Slide courtesy of S. Amin, adapted from Dr. Jean Sibonga, NASA JSC*
Measurement of bone mineral in 2-d projection of bone [BMD$_a$] g/cm$^2$

• Improved precision; Low radiation; Shorter scan times; BMD measures over multiple skeletal sites

• Validated in numerous population studies for fracture prediction

• Long established, widely-applied surrogate for fracture outcome – become NASA standards, but T-scores give only Relative Risks
### DXA: BMD losses are site-specific and rapid vs. 0.5 – 1.0 % BMD loss/year in the aged

<table>
<thead>
<tr>
<th>Areal BMD g/cm²</th>
<th>%/Month Change ± SD</th>
<th>*p&lt;0.01, n=16-18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar Spine</td>
<td>-1.06±0.63*</td>
<td></td>
</tr>
<tr>
<td>Femoral Neck</td>
<td>-1.15±0.84*</td>
<td></td>
</tr>
<tr>
<td>Trochanter</td>
<td>-1.56±0.99*</td>
<td></td>
</tr>
<tr>
<td>Total Body</td>
<td>-0.35±0.25*</td>
<td></td>
</tr>
<tr>
<td>Pelvis</td>
<td>-1.35±0.54*</td>
<td></td>
</tr>
<tr>
<td>Arm</td>
<td>-0.04±0.88</td>
<td></td>
</tr>
<tr>
<td>Leg</td>
<td>-0.34±0.33*</td>
<td></td>
</tr>
</tbody>
</table>

*LeBlanc et al, J Musculoskeletal 2000*
Effects of exercise regimens described using DXA BMD

% Change in DXA BMD after Long-Duration Mir and ISS Missions
Mir n=35; ISS IRED n=24; ISS ARED n=11; Bisphos + ARED n=7

Note: No population data % BMD loss = Fracture Outcome

* Updated data since 2010 Bone Summit
A Limitation: DXA Cannot distinguish changes in bone geometry– a contributor to bone strength.

<table>
<thead>
<tr>
<th>aBMD</th>
<th>Areal (g/cm²)</th>
<th>Compressive Strength</th>
<th>Bending Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>1.7</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2.3</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Exercise changes geometry of whole bone (adult skeleton)- not detected by DXA.


The *location* of formed bone makes a difference.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Periosteal Apposition</th>
<th>Endosteal Apposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periosteal Diameter</td>
<td>100 %</td>
<td>110 %</td>
<td>100 %</td>
</tr>
<tr>
<td>Endosteal Diameter</td>
<td>100 %</td>
<td>100 %</td>
<td>90 %</td>
</tr>
<tr>
<td>Compressive Strength</td>
<td>100 %</td>
<td>148 %</td>
<td>125 %</td>
</tr>
<tr>
<td>Bending Strength</td>
<td>100 %</td>
<td>168 %</td>
<td>116 %</td>
</tr>
</tbody>
</table>

Slide courtesy of M. Bouxsein, PhD
Densitometry & Reported Measurement

DXA reports areal BMD (aBMD) $g/cm^2$ averaged for cortical + trabecular bone

QCT quantifies volumetric BMD $g/cm^3$ for separate cortical & trabecular bone
Research: QCT detects different rate of vBMD loss in separate bone compartments of hip. (n=16 ISS volunteers)

<table>
<thead>
<tr>
<th>Index DXA</th>
<th>%/Month Change ± SD</th>
<th>Index QCT</th>
<th>%/Month Change ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>aBMD Lumbar Spine</td>
<td>1.06+0.63*</td>
<td>Integral vBMD Lumbar Spine</td>
<td>0.9+0.5</td>
</tr>
<tr>
<td>Trabecular vBMD Lumbar Spine</td>
<td>0.7+0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>aBMD Femoral Neck</td>
<td>1.15+0.84*</td>
<td>Integral vBMD Femoral Neck</td>
<td>1.2+0.7</td>
</tr>
<tr>
<td>Trabecular vBMD Femoral Neck</td>
<td>2.7+1.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>aBMD Trochanter</td>
<td>1.56+0.99*</td>
<td>Integral vBMD Trochanter</td>
<td>1.5+0.9</td>
</tr>
<tr>
<td>Trabecular vBMD Trochanter</td>
<td>2.2+0.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p<0.01, n=16-18

LeBlanc, J Musculoskeletal 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)

<table>
<thead>
<tr>
<th>Visit</th>
<th>Pre</th>
<th>Post</th>
<th>12MONTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral Neck</td>
<td>5.200</td>
<td>6.000</td>
<td>6.600</td>
</tr>
</tbody>
</table>

**Volumetric Bone Mineral Density** (g/cm³)

<table>
<thead>
<tr>
<th>Visit</th>
<th>Pre</th>
<th>Post</th>
<th>12MONTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral Neck</td>
<td>0.300</td>
<td>0.310</td>
<td>0.320</td>
</tr>
</tbody>
</table>

**Minimum Cross-sectional Area** (cm²)

<table>
<thead>
<tr>
<th>Visit</th>
<th>Pre</th>
<th>Post</th>
<th>12MONTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum CSA</td>
<td>11.400</td>
<td>11.600</td>
<td>12.000</td>
</tr>
</tbody>
</table>

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

Slide adapted from T. Lang., JBMR 2006.
Two Functions of the Skeleton—increasing understanding by biochemistry

Structural Framework

Mineral Reservoir

Osteoblasts

Bone Formation

Bone Resorption

Resorption Biochemical Markers

Formation Biochemical Markers

Osteoclasts

Bone Resorption
Serum and urinary biomarkers are by-products of bone turnover and bone cell activity.
Bone breakdown is increased, formation is **uncoupled** from resorption, and bone gain and loss are unbalanced*

Reflects changes in **bone cells** but not **where** bone mass is lost.

* Could lead to net bone loss in skeleton.
HIGHLY-REGULATED ACTIONS OF BONE CELLS on BONE TURNOVER.

Under-filling, over-filling, balanced filling of the bone remodeling unit [BRU]
Can impact overall structural strength of whole bone (skeletal region).

Remodeling of bone at the level of a single “BRU”
Some insight gained by comparison to Earth-based disorders of increased bone resorption.
Representative manifestation on bone microarchitecture. Clinical test not currently available for hip/spine.

(Mosekilde, 2000; Seeman, 2002; Silva, 1997; Kleerekoper, 1985)
How can research data be used for clinical care in the absence of fracture evidence?

Path to Risk Reduction
DXA BMD increases in Postflight – but not sufficient to assess recovery of *bone strength*.

Sibonga et al. BONE 41:973-978, 2007
DXA & QCT Spine in 8 ISS astronauts:
Expanding our Understanding of Recovery After Spaceflight

Clinical Evidence: QCT measures are independent predictors of hip fracture to supplement aBMD.
DXA BMD not as good of predictor of hip fractures for the “complicated patient” i.e., non-age-related bone loss

- Different patterns of bone “loss” (cortical vs. trabecular) with different metabolic disorders …analogous to spaceflight effects

Seeman, JCI 1992
Slide courtesy of Dr. Amin, MD
Dual Photon Absorptiometry (DPA)
Describing changes in hip bone strength with Finite Element Modeling/Analysis: Emerging data from population studies.


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


Images courtesy of Dr. J Keyak
Individual Results

Stance Loading (4 to 30% loss in strength)

Max loss 30%

Time (months)

Hip Strength (kN)
Individual Results

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

Time (months)

Hip Strength (kN)

Max loss 24%
QCT + FEM has superior capabilities for estimating mechanical strength of ex-vivo specimens.

QCT estimates fracture loads better than DXA

QCT + FEM has superior capabilities for estimating fracture loads

DD Cody: Femoral strength is better predicted by finite element models than QCT and DXA. J Biomechanics 32:1013 1999.
Assessing Fracture risk following spaceflight by 1 measure vs > 1 measure.

- Areal BMD
- Bone Strength 50-70% T-scores
- Relative Fracture Risk

- BMD
- Geometry & Size
- Material Properties
- Loading
- Finite Element Strength

- Individualized Fracture Risk
Additional cut-points for Bone Health: FE Modeling 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.
Probabilistic Risk Assessments for Bone Fracture: NASA’s Model for Fracture Likelihood

- Biomechanics and Mission Operations
- Bone Loss in Space
- Estimate of Fracture Probability
- Clinical and Engineering Characteristics of Bone Strength

Probability of Fracture

- Probability of event
- Probability bone will fail to support load

Slide courtesy of J Myers; Adapted by Sibonga
Summary

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

• If skeletal integrity is assessed solely by a surrogate measure of bone strength (DXA – BMD) vs. an estimate of bone strength (e.g., FE modeling), then there may be a risk of underestimating fracture probability and poorly estimating countermeasure efficacy.

• Bone Research in progress to test QCT as a risk surveillance technology and to derive new cut-points to supplement bone health standards.
Thank you.

QUESTIONS? COMMENTS?
Backup Slides
Study on Risk Surveillance: Hip QCT

- Test feasibility of QCT protocol for surveillance of clinical trigger.

- Accumulate surveillance data for development of clinical practice 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)
AGE-REGRESSIONS: Trabecular bone loss occurs at earlier age than expected.


Slide courtesy S. Khosla, adapted by Sibonga
Use of Osteoporosis Policy-makers help to translate research data to CPGs in absence of fracture data.

- Evidence Base – Flight and Ground
  - Science
  - Clinical
  - Operational experience

- Risks

- Gaps

- Exploration Missions & Architectures

- NASA Spaceflight Human System Standards

- Results and Deliverables

- Solicitations & Directed Research

- Integrated Research Plan

- Clinically-relevant Research Tasks

- Closure Metrics
Effects on Different Compartments of Bone (cortical vs. trabecular BMDs)
**ES Nelson et al.** *Development and validation of a predictive bone fracture risk model for astronauts* NASA Glenn Research Center, Cleveland, OH

*Ann Biomed Eng, 37(11), 2009, pg. 2337 - 2359.*
Different ways to **unbalance** remodeling at bone surface.

Different levels of cell number and cell activities ending in deficit of bone at the BRU.

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

<table>
<thead>
<tr>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model A (HR per SD decrease)</td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>Trabecular bone, volumetric BMD (g/cm³)</td>
</tr>
<tr>
<td>Percent cortical volume</td>
</tr>
<tr>
<td>Minimum cross-sectional area (cm²)</td>
</tr>
<tr>
<td>Areal BMD from DXA (g/cm²)</td>
</tr>
</tbody>
</table>

Area under the ROC curve for Models A, B, and C were 0.853, 0.855, and 0.860, respectively.
ARED exercise appears to mitigate decline in areal BMD.

*(J Bone Mineral Research. Smith et al 2012) * this is not ref for figure.*
FE Standards Combine Aging and Spaceflight Changes to Hip Strength and used together with DXA BMD Standards.

<table>
<thead>
<tr>
<th>Minimum FE strength for Bone Health</th>
<th>“Go”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum Permissible Outcome</td>
<td>“Wait”</td>
</tr>
<tr>
<td></td>
<td>“No Go”</td>
</tr>
</tbody>
</table>
Steven Goldstein, Ph.D.
“Bone Quality: A Biomechanical Perspective”
QCT in Population Study: Age-related Changes

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

The long-duration astronaut – not typical subject to evaluate osteoporosis (4/2014).

- Typical space mission duration – 159 ± 32d (range 49-215d)
- Average Age – 47 ± 5 y (range 36 – 56)
- Male to Female Ratio – 4.4 : 1
- Current total # per astronauts in corps – 59 of 365
- # repeat fliers – 6
- BMI – Male BMI 25.7 ± 2.2 (range 21.2 to 30.7); Female BMI 22.2 ± 2.3 (range 20.1 to 25.9)
- Wt and Ht- Males: Males: 81 ± 9 (64 to 101); 176 ± 6 (163 to 185)
- Females: 64 ± 7 (54 to 81), 169 ± 4 (163 to 178)
- % Body Fat: Males 20 ± 4 (9 to 27); Females 27 ± 8 (19 to 41)
- MEDICAL PRIVACY A MAJOR CONSTRAINT
Bone Remodeling Sequence

- Oc Precursor
- Osteoclast
- Mononuclear Cells
- Ob Precursors
- Osteoblast

Resting Bone Surface

Resorption

Reversal

Bone Formation

Mineralization

~3 WEEKS

~3 MONTHS

LC = Lining Cells

CL = Cement Line

OS = Osteoid

BRU = Bone Remodeling Unit

Slide courtesy of Dr. R. Wermers, Mayo Clinic