Effect of Microgravity on Bones:
Challenges to Addressing Risks to Human Health & Performance

Endocrine Grand Rounds McGuire Veterans Affairs Medical Center

Jean D. Sibonga, Ph.D.
Lead, Bone Discipline
Human Research Program [HRP]
Johnson Space Center, Houston, TX
May 14, 2014
Overview

• NASA’s challenges to addressing skeletal risks due to spaceflight: 3 C’s

• Unique Skeletal Adaptations to Spaceflight

• Recommended Forward Actions for Risk Assessment and Management
Overview

- NASA’s challenges to addressing skeletal risks due to spaceflight: 3 C’s
- Unique Skeletal Adaptations to Spaceflight
- Recommended Forward Actions for Risk Assessment and Management
Mitigating Risks for the Human System in HRP

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

Risks

Gaps

Inst of Medicine

Standing Review Panels

Exploration Missions & Architectures

NASA Spaceflight Human System Standards

Results and Deliverables

Customer Review

Solicitations & Directed Research

Peer Review

Integrated Research Plan

Prioritization & Implementation Approach

Constrained by
- Need dates
- Budgets
- Research platform availability
How should Space Medicine use Research Data in clinical care of astronauts?

1. Review of all Medical and Research Data.
2. What additional measure(s) for Op risk surveillance? “Bone Quality”

Bone Research @ NASA

Flight validation Research
Ground-Analog Research

Astronauts Clinical Care

BONE SUMMIT 2010, 2013
Skeletal Health in Long-Duration Astronauts: Nature, Assessment, and Management Recommendations from the NASA Bone Summit

Eric S Orwell,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
How do we manage here, to prevent condition here.

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

Cooper and Melton, 1992

SLIDE COURTESY OF Dr. S. AMIN, Mayo Clinic
Take Home Messages from Bone Summit

1. Bone is a complicated tissue.
2. NASA’s constraints – not likely to reach Level of Evidence.
3. Astronauts are understudied group.
4. Spaceflight effects on bone are unique.
5. Clinically-accepted tests have limitations (JAMA).
6. Bone medical standards (based upon terrestrial guidelines) are not applicable to long-duration astronauts and require modification.
7. NASA circumstances may require transition of research technologies to clinical decision-making.
Bone Discipline Lead Briefs NASA HQ Chief Health & Medical Office [OCHMO]

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

- Risks

- Gaps

- Exploration Missions & Architectures

- NASA Spaceflight Human System Standards

- Integrated Research Plan

- Results and Deliverables

- Solicitations & Directed Research

Bone Summit 2010

HRP slide courtesy C. Kundrot
Adapted Sibonga 2012
Use of the Research Clinical Advisory Panels [RCAP] to focus NASA’s Human Research for Bone Risks

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

Risks

Gaps

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Clinically-relevant Research Tasks

Closure Metrics
The long-duration astronaut – not typical subject to evaluate osteoporosis (4/2013).

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

T-score = # Standard Deviations from Normal bone mineral density [mean BMD] of young healthy persons.
WHO/ISCD* Guidelines developed for peri-, postmenopausal women and men > 50 yrs. DXA screening & surveillance unique to NASA

*Intl Society Clinical Densitometry
Fig. courtesy of S. Petak, MD

Adapted from: Kanis JA et al. Osteoporosis Int. 2001;12:989-995
Adapted from: Pathogenesis of Osteoporosis-Related Fractures (NOF) Cooper C, Melton LJ
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Diagnostic guidelines using areal BMD T-scores - not appropriate or predictive for fracture in astronaut population.

BMD T-Score Values* Expeditions 1-25 (n=33)
*Comparison to Population Normals
Paradigm Shift

- “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
Dual-energy X-ray Absorptiometry [DXA] BMD @ Johnson Space Center

- Monitor astronaut skeletal health
- Characterize skeletal effects of long-duration spaceflight
- Evaluate efficacy of bone loss countermeasures
- Verify restored health status
What are the risks for using inappropriate DXA-BMD based guidelines?

• Unnecessarily disqualifying applicants to Astronaut candidacy.

• Not fully understanding the effects of spaceflight on hip and spine integrity.

• Inadequately evaluating efficacy of countermeasures.
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</th>
<th>%/Month Change ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar Spine</td>
<td>-1.06±0.63*</td>
</tr>
<tr>
<td>Femoral Neck</td>
<td>-1.15±0.84*</td>
</tr>
<tr>
<td>Trochanter</td>
<td>-1.56±0.99*</td>
</tr>
<tr>
<td>Total Body</td>
<td>-0.35±0.25*</td>
</tr>
<tr>
<td>Pelvis</td>
<td>-1.35±0.54*</td>
</tr>
<tr>
<td>Arm</td>
<td>-0.04±0.88</td>
</tr>
<tr>
<td>Leg</td>
<td>-0.34±0.33*</td>
</tr>
</tbody>
</table>

*p<0.01, n=16-18

LeBlanc et al, J Musculoskeletal 2000
DXA BMD increases in Postflight – but not sufficient to assess recovery of *bone strength*.

Sibonga et al. BONE 41:973-978, 2007
Changes in size, changes in bone strength.

Slide courtesy of M. Bouxsein, PhD – Bone Quality, 2005
Serum and urinary biomarkers reflect bone turnover and mineral metabolism.

Serum:
- Total and bone-specific alkaline phosphatase (formation)
- Osteocalcin (formation)
- Total serum Calcium (40% protein bound; calcium complexes)
- Ionized serum Calcium (physiologically active)

Urine:
- Pyridinium cross-links (resorption)
- Deoxypyridinoline cross-links (resorption)
- n-telopeptide (resorption)

Hormones: (regulation of calcium homeostasis)
- Parathyroid hormone – glands - main calcium sensing organ
- 1,25 Dihydroxyvitamin D -- stimulates Ca conservation
- 25 Hydroxyvitamin D – assayed vitamin D metabolite (substrate)
Bone Turnover Markers suggest a net loss in bone mass in the skeleton.

Slide Courtesy of Dr. SM Smith; Adapted by Sibonga
Calcium-regulating Hormones – Endocrine system is “normal” but perturbed.
% 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

* Updated data since 2010 Bone Summit
Bisphosphonates as a Countermeasure to Spaceflight Effects - mitigates of urinary calcium excretion

Urinary Calcium During and After Space Flight

- Mir n = 6; Bisphos + ARED n = 5 to 7; IRED n = 4 to 8; ARED n = 2 to 5

%Change in Mean Urinary Calcium vs. Pre Flight

- Pre-Flight
- In-Flight
- Post-Flight

* p<0.05, significant difference vs. Pre-Flight

Slide courtesy of Dr. A. LeBlanc
Densitometry & Reported Measurement

DXA reports areal BMD (aBMD)

QCT quantifies volumetric BMD

$\text{g/cm}^2$ averaged for cortical + trabecular bone

$\text{g/cm}^3$ for separate cortical & trabecular bones
DXA vs. QCT Spine: Discordant Recovery Patterns in Astronauts After Spaceflight


aBMD – areal bone mineral density g/cm²

tBMD – trabecular volumetric bone mineral density g/cm³
Why the clinical concern?

![Graph showing changes in normalized BMD over time for femoral neck DXA aBMD and tBMD.]

- aBMD – areal bone mineral density g/cm²
- tBMD – trabecular volumetric bone mineral density g/cm³

QCT measures are independent predictor of hip fracture.

Lower trabecular hip BMD is a predictor of hip fracture in aged men* (and in women, Bousson et al 2011)

SUMMIT RECOMMENDS AS THE CLINICAL TRIGGER FOR ASTRONAUTS.

This is the basis of Hip QCT flight study.
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Investigate a new medical standard for BONE Finite Element Modeling [FEM]: What is it and what can it tell NASA about hip fracture risk in the long-duration astronaut?
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%

Graph showing hip strength over time (months) with points indicating individual results.
Individual Results

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

![Graph showing hip strength over time with a max loss of 24%](image)
Two methods of monitoring space-induced changes in bone strength do not correlate.

Change in FE Strength

Change in areal BMD

Stance: \( R^2 = 0.23 \)
Fall: \( R^2 = 0.05 \)

Which is better?
Which is better?
Fracture risk by 1 measurement or by > 1 measurement?
It’s not complicated.

Finite Element Strength

Bone Strength Surrogate

Material Properties

Geometry

BMD

Loading

Finite Element Strength

Individualized Fracture Risk

Relative Fracture Risk

aBMD
Summit Recommendation

EXPLORE HOW FEM PREDICTS FRACTURE IN POPULATION STUDIES
Describing changes in hip bone strength with Finite Element Modeling/Analysis: Emerging data from population studies.


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.

All Male Subjects
Stance Loading

AGE Controls
Pre-flight
AGES Fractures
Post-flight

*Red, Yellow and Green Operating Bands

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.
Similar approach proposed for terrestrial medicine.

Improving Bone Quality Assessment Biomarkers Consortium Project

Dennis Black, Ph.D.
Gayle Lester, Ph.D.
Federal Working Group on Bone Diseases
May 1, 2013
A new surrogate/patient management

**Estimating bone strength by QCT-based finite element analysis (FEA)**

- Standard engineering approach to evaluate mechanical behavior of complex structures
  - Integrates material & structural info from 3D QCT scans
  - Can provide multiple strength metrics
- Cadaver studies show that FEA predicts bone strength better than DXA-BMD
- Has been used *in vivo* to assess effect of treatments on bone strength and to predict fracture risk in untreated subjects
Summary

• DXA – may be underestimating fracture probability and poorly estimating countermeasure efficacy for the astronaut population.

• Bone Discipline Research in progress to test QCT as a surveillance technology and to derive new cut-points for baseline bone health based upon finite element modeling.

• Bone Summit Panel is trying to formulate a therapeutic course of action, and the optimal timing of intervention.

• Leveraging Level 4 Evidence (expert opinion) from Bone Summit Panel as a means of defining and managing skeletal risks in astronauts in the absence of fracture evidence.
NASA & EXTRAMURAL

- Shreyasee Amin, M.D. (Mayo Clinic)
- Adriana Babiak-Vasquez (NASA JSC)
- Craig Kundrot (NASA JSC)
- Harlan J. Evans, Ph.D. (NASA JSC)
- Joyce H. Keyak, Ph.D. (UC Irvine)
- Thomas F. Lang, PhD. (UC San Francisco)
- Adrian D. LeBlanc, Ph.D. (USRA)
- Jerry Myers, Ph.D. (NASA GRC)
- Robert Ploutz-Snyder, Ph.D (NASA JSC)
- Clarence Sams, Ph.D (NASA JSC)
- Richard Scheuring, M.D. (NASA JSC)
- Linda C. Shackelford, M.D. (NASA JSC)
- Scott A. Smith (NASA JSC)
- Scott M. Smith, Ph.D. (NASA JSC)
- Elisabeth R. Spector (NASA JSC)
- Robert Wermers, M.D. (Mayo Clinic)
Backup Slides
The bridge as a metaphor for bone.

I-35W Bridge Collapse in MN

• Probable cause - inadequate load capacity, due to a design error of the gusset plates (NTSB)

  “… the half-inch thick plates should have been an inch thick — double the size.”

• Contributing factors: underestimated loads to bridge, did not anticipate construction loads, did not integrate weather/salt temperature contribution to breakdown of material properties

• “Inadequate use of technologies for accurately assessing the condition of gusset plates on deck truss bridges.”
### Clinical Risk Factors for Osteoporosis-Related Fractures

<table>
<thead>
<tr>
<th>Fracture Probability</th>
<th>Aging</th>
<th>Hypogonadism and Menopause</th>
<th>Excessive Bone Loading</th>
</tr>
</thead>
</table>

### Skeletal Fragility

<table>
<thead>
<tr>
<th>Fracture Probability</th>
<th>Bone Quality</th>
<th>Propensity to Fall</th>
<th>Fall Mechanics</th>
<th>Certain Activities</th>
</tr>
</thead>
</table>

### Radiographic Evidence

- Low bone density
- Impaired bone quality
- Excessive bone loading

### Factors in Patients

#### Lifestyle factors
- Smoking
- Heavy alcohol consumption

#### Genetic factors
- Family history of osteoporosis

#### Medications and disorders
- Corticosteroids
- Thyroid disorders
- Hypogonadal disorder
- Renal disorders
- GI disorders
- Neurological disorders
- Endocrine disorders
- Rheumatic and autoimmune diseases
- Hematologic disorders
- Gastrointestinal disorders

#### Key: Adapted from Pathogenesis of Osteoporosis-Related Fractures (NOF) Cooper C
Bone fragility is influenced by factors that are not detected by DXA BMD.

BMD accounts for 50-70% bone strength

Disconnection discovered in population studies.

FRACTURE CASES

NON FRACTURES
Dual Photon Absorptiometry DPA)

- Differences in patterns of bone “loss” (cortical vs. trabecular) for different diseases…

Seeman, JCI 1992
Slide courtesy of Dr. Amin, MD
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**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Model A (HR per SD decrease)</th>
<th>Model B (HR per SD decrease)</th>
<th>Model C (HR per SD decrease)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>p</td>
</tr>
<tr>
<td>Trabecular bone, volumetric BMD (g/cm³)</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Percent cortical volume</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Minimum cross-sectional area (cm²)</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Areal BMD from DXA (g/cm²)</td>
<td>4.13</td>
<td>2.67, 6.38</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Area under the ROC curve for Models A, B, and C were 0.853, 0.855, and 0.860, respectively.
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.
## Astronaut Data— Reductions in Hip Strength with spaceflight.

*N*=11 crewmembers

<table>
<thead>
<tr>
<th>Loading Condition</th>
<th>Mean (SD) Pre-flight</th>
<th>Mean (SD) Post-flight</th>
<th><em>p</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stance</td>
<td>13,200 N (2300 N)</td>
<td>11,200 N (2400 N)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fall</td>
<td>2,580 N (560 N)</td>
<td>2,280 N (590 N)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

### Calculations

- **Stance:** 2.2% loss/month
- **Fall:** 1.9% loss/month
Research: QCT detects different rate of vBMD loss in separate bone compartments of hip. (n=16 ISS volunteers)

<table>
<thead>
<tr>
<th>Index</th>
<th>%/Month Change ± SD</th>
<th>Index</th>
<th>%/Month Change ± SD</th>
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<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>Trabecular vBMD Lumbar Spine</td>
<td>0.7±0.6</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>Trabecular vBMD Femoral Neck</td>
<td>2.7±1.9</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>Trabecular vBMD Trochanter</td>
<td>2.2±0.9</td>
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*p<0.01, n=16-18

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)

<table>
<thead>
<tr>
<th>Visit</th>
<th>Femoral Neck</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>Int. BMC (g)</td>
</tr>
<tr>
<td>Post</td>
<td>5.200</td>
</tr>
<tr>
<td>12 MONTH</td>
<td>5.400</td>
</tr>
</tbody>
</table>

Volumetric Bone Mineral Density g/cm³

<table>
<thead>
<tr>
<th>Visit</th>
<th>Femoral Neck</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>Int. vBMD (g/cc)</td>
</tr>
<tr>
<td>Post</td>
<td>0.300</td>
</tr>
<tr>
<td>12 MONTH</td>
<td>0.310</td>
</tr>
</tbody>
</table>

Minimum Cross-sectional Area cm²

<table>
<thead>
<tr>
<th>Visit</th>
<th>Minimum CSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>11.400</td>
</tr>
<tr>
<td>Post</td>
<td>11.500</td>
</tr>
<tr>
<td>12</td>
<td>11.600</td>
</tr>
</tbody>
</table>

P < 0.05 with respect to preflight*, postflight*

Slide adapted from T. Lang., JBMR 2006.
QCT in Population Study: Age-related Changes

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

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

Microarchitectural Measures of Trabeculae and of Spatial Orientation

"plates" TbTh
"rods" TbTh
TbN
TbSep

Images courtesy of Ralph Müller, PhD, Switzerland

Adapted
1. Purpose of Hip QCT Surveillance is to implement recommendations of a clinical advisory panel of osteoporosis experts (Bone Summit 2010).

2. Collect specific QCT surveillance data to develop clinical practice guidelines to recommend to space medicine.

3. Evaluate recovery at R+1 y and, if required, R+2 y.

4. Research Study: Describe how in-flight countermeasures or how post-flight activities affect changes in bone strength and recovery.
Characterizing Bone Loss in Space

Mercury
1961-63

Gemini
1965-66

Apollo
1968-72

Skylab
1973-74

Shuttle
1981-2010

Intl Space Station
2000-present

- Calcium balance
- SPA of heel and wrist

Soyuz/Salyut
1974-85

- SPA
- Urine, fecal Ca
- Heel, Wrist

Mir
1986-2000

- DXA
- QCT
- pQCT
- BTO