Space: The Final Frontier of Bone Density

Jean D. Sibonga, Ph.D., Lead Bone Discipline, NASA Human Research Program at Johnson Space Center, Houston, TX

It is a medical requirement at NASA to evaluate the skeletal integrity of “long-duration” astronauts by measuring bone mineral density [BMD] with DXA technology. A long-duration mission is a spaceflight that is greater than 30 days but is typically the continuous 120-180 day missions aboard the International Space Station [ISS]. Not only does NASA use the BMD index to monitor fracture risk in this astronaut population, but these measures are also used to describe the effects of spaceflight, to certify skeletal health readiness for flight, to monitor the recovery of lost bone mass after return to earth, and to evaluate the efficacy of countermeasures to bone loss. However, despite the fact that DXA-based BMD is a widely-applied surrogate for bone strength that is grounded in an abundance of population-based fracture data, its applicability to the long-duration astronaut is limited. The cohort of long-duration astronauts is not the typical group for evaluating osteoporosis or determining age-related fracture risk. The cohort is young (< 55 years), predominantly male and exposed to novel risk factors for bone loss besides the weightlessness of space. NASA is concerned about early onset osteoporosis in the astronaut exposed to long-duration spaceflight, especially since any detectable symptoms are likely to manifest after return to earth and perhaps years after space travel. This risk raises the question: is NASA doing enough now to mitigate a fracture event that may manifest later? This presentation will discuss the limitations and constraints to understanding skeletal changes due to prolonged spaceflight and the recommendations, by clinical experts in osteoporosis and BMD, to transition research technologies for clinical decision-making by NASA.
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www.nasa.gov
Insert video

• editing of video
The Astronaut as the Human System

Systems Engineering & Integration

- Structure
- Electrical Power System
- Environ. Control Life Support
- Thermal
- I/T
- Human
Gain & Loss of Bone Mass with Aging

Peak Bone Mass

Age-related Loss

Menopause-induced Loss

Bone mass (g/calcium)

Age (yr)

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

Age Group (years)

Incidence/100,000 person –yr

Men

Women

Hip
Spine
Wrist

0
4,000
3,000
2,000
1,000
0
35-39
≥ 85
35-39
≥85

Cooper and Melton, 1992

SLIDE COURTESY OF Dr. S. AMIN, Mayo Clinic
History of Bone Imaging in Space

<table>
<thead>
<tr>
<th>Mercury</th>
<th>Apollo</th>
<th>Skylab</th>
<th>ISS</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray densitometry</td>
<td>SPA heel and wrist</td>
<td>SPA heel and wrist</td>
<td>DXA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Soyuz/Salyut</th>
<th>Mir</th>
</tr>
</thead>
<tbody>
<tr>
<td>1974-85</td>
<td>1974-85</td>
</tr>
<tr>
<td>SPA</td>
<td>DXA whole body</td>
</tr>
<tr>
<td>DPA</td>
<td>CT of lumbar spine BMD</td>
</tr>
</tbody>
</table>

Slide adapted from Dr. Jean Sibonga, NASA JSC
Overview

• Uniqueness of NASA

• Spaceflight Effects: *Out-of-this-World Data*

• *Bold* Approaches to Managing Bone Risk
The Long-duration Astronaut

- Typical mission duration – 163 ± 32d (range 90-215d)
- Average Age – 46.5 ± 4.5 y (range 36.8 – 55.3)
- T-score at first* DXA BMD –
- Male to Female Ratio – 3.8 : 1
- Current total number out of total # astronauts in Corps – TBD
- # repeat fliers – 4
- BMI etc– Males 25.9 ± 2.2; Females 22.6 ± 2.2 kg/m²
- Wt and Ht- Males: 179 ± 20 lbs, 5.8 ± 0.2 ft; Females: 143 ± 15 lbs, 5.6 ± 0.1 ft
Constraints to Understanding Skeletal Adaptation
BMD T-Score Values* Expeditions 1-25 (n=33)
*Comparison to Population Normals
Adapted from: Cooper C, Melton LJ.
Aging

Muscle Atrophy

Ca/Nutrition/Vit D

Increased and unbalanced bone resorption

Inadequate peak bone mass

Increased bone loss

Low bone density

Impaired bone quality

Skeletal fragility

Radiation on bone marrow cells
Fluid shifts and reduce regional blood flow

Postural instability

EVA Suit

Excess bone loading

Exercise Loads

Kinetic Energy of Mass

Fracture

PRA Models

Adapted from: Pathogenesis of Osteoporosis-Related Fractures (NOF) Cooper C, Melton LJ
Microgravity Effects on the Human Body

From Scientific American
Overview

• Uniqueness of NASA

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• Bold Approaches to Managing Bone Risk
DXA: BMD losses are regional and rapid

<table>
<thead>
<tr>
<th>Areal BMD</th>
<th>%/Month Change ± SD</th>
<th>LeBlanc et al, 2000</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>

*p<0.01, n=16-18

Whole Body 0.3% / month
Lumbar Spine 1% / month
Hip 1.5% / month
What about recovery?

Trochanter: $\text{Loss}_0 = 7.8\%$  \hspace{1cm} 50\% Recovery = 255d

DXA BMD increases in Postflight Period after long-duration flights.
Research Study: QCT measures loss hip vBMD due to spaceflight in trabecular bone compartment (n=16 ISS)

<table>
<thead>
<tr>
<th>Index</th>
<th>%/Month Change ± SD</th>
<th>Index</th>
<th>%/Month Change ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>DXA</td>
<td></td>
<td>QCT</td>
<td></td>
</tr>
<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></td>
<td></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></td>
<td></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></td>
<td></td>
<td>2.2±0.9</td>
</tr>
</tbody>
</table>

*p<0.01, n=16-18

QCT Postflight – Changes in bone mass and structure at Femoral Neck 12 months after return

Bone Mineral Content (g)

Volumetric Bone Mineral Density g/cm³

Minimum Cross-sectional Area cm²

$P < 0.05$ with respect to preflight*, postflight*
QCT: Trabecular BMD at hip does not appear to show a recovery 2 to 4 years postflight.

PRE: n = 16  POST: n = 16  1 YEAR: n = 16  EXT: n = 8

What is the impact of Trabecular Bone Loss on whole hip bone strength?

http://depts.washington.edu/bonebio/ASBMRed/structure.html

Photo by Paul Crompton
©University of Wales College of Medicine
And what has happened to bone microarchitecture of hip?

L Mosekilde
Overview

• Uniqueness of NASA

• Spaceflight Effects: *Out-of-this-World Data*

• *Bold* Approaches to Managing Bone Risk
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 that uses QCT data to estimate hip bone strength

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.
FEM to estimate changes to hip bone strength after spaceflight.

- Geometry
- Material Properties
- BMD
- Loading

Finite Element Strength

Individualized Fracture Risk
Individual Results

Stance Loading (4 to 30% loss in strength)

![Graph showing hip strength over time](image)

- Max loss: 30%
- Time (months): 0 to 6
- Hip Strength (kN): 16 to 8
Individual Results

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

Max loss 24%
Surrogates of bone strength do not correlate.

Slide courtesy of J Keyak
Summary

• Unique cohort, unique environment, unique changes in bone structure during long-duration missions in microgravity

• QCT – added measures of bone that increase our knowledge about how spaceflight affects bone structure – changes that may combine with aging effects

• FE estimates of strength – an improved surrogate for NASA by individualizing the estimates of hip bone strength per astronaut.
Final Comments

• Clinical goal: Prevention of fractures by identifying those at highest risk – risk factors to enhance DXA predictive capabilities

• NASA goal: To reduce the uncertainty of fracture risks (fragility and traumatic fractures) during a mission, after a mission and as the astronaut ages by employing the best technologies and analyses available.
Thank you!
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Backup Slides
QCT does not outperform DXA-BMD for fracture prediction but provides extra information that DXA does not.

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></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.

Bone Fracture Risk Module (BFxRM)

Biomechanics and Mission Operations

courses.washington.edu/me598rc

Estimate of Fracture Probability

Probability of Fracture

Probability of event

Probability bone will fail to support load

Bone Loss in Space

Clinical and Engineering Characteristics of Bone Strength

Bone Fracture Risk Module (BFxRM)

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

Beck et al., 1990
Hayes, Myers, 1996 (2mm/s)
Hayes, Myers, 1996 (100mm/s)
Kukla et al., 2002

0 0.2 0.4 0.6 0.8 1 1.2
Femoral Neck BMD (g/cm²)

0 2000 4000 6000 8000 10000 12000 14000 16000
Fracture Load (N)
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.
What is the impact of Trabecular Bone Loss on bone microarchitecture?

- Impact on HIPmicroarchitecture UNKNOWN*
- Knowledge base: Vertebral trabecular bone loss with menopause.
- Loss of horizontal trabecular struts and directionality, perforation of trabeculae*, reduction in mechanical strength, and increase in fracture risk (Mosekilde, 2000; Seeman, 2002, Silva 1997; Kleerekoper 1985)
## Results in Astronauts – Hip Strength

N=11 crewmembers

<table>
<thead>
<tr>
<th>Loading Condition</th>
<th>Mean (SD) Pre-flight</th>
<th>Mean (SD) Post-flight</th>
<th>p</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>

- **2.2% loss/month**
- **1.9% loss/month**
- **1.0-1.5% BMD loss /month**
QCT Postflight: Structural changes do not reflect a restoration of bone strength

Bone Strength Indices

*: p<0.05 with respect to preflight

*:

1.000
1.250
1.500
1.750
2.000
2.250
2.500
2.750
3.000
3.250
3.500

Strength Index

1 2 3
Pre Post 12

bending (cm³)
compressive (g²/cm⁴)

DXA: Losses at total hip and spine after ~6 months in space exceed 2-year losses on Earth in similar-aged population.
Aging
Triennials

Hypogonadism & Menopause
Sex Hormones

Clinical risk factors

High bone turnover
BTO markers

Inadequate peak bone mass
Selection Std

Increased bone loss
NTX/DPd

Low bone density
BMD Algorithm

Impaired bone quality

Skeletal fragility

Falls

Propensity to fall
Postural Sway

Fall mechanics

Excessive bone loading

Certain activities
RE Loads
Biomech Models

VFA/EMR/LSAH

Fracture
PRA Models

Reduced Activity
Endocrine Levels
Ca/Nutrition/Vit D
Muscle Atrophy

Adapted from: Pathogenesis of Osteoporosis-Related Fractures (NOF) Cooper C, Melton LJ
Percentage Reduction in Hip Strength

Stance

Fall

Number of Astronauts

% Reduction

% Reduction