Physiological Effect of Space on Bone Health

Aerospace Medicine
University of Texas Medical Branch

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At the end of this lecture, you should understand:

• The *insufficiency* of DXA BMD as a surrogate for fracture risk in terrestrial medicine and as a research tool/clinical test for NASA.

• The flight data describing the unique effects of spaceflight on skeletal sites at risk for age-related osteoporosis.

• The bold approaches to translating *Research* to the *Clinical* arena to meet NASA’s constraints and aggressive schedule for mission planning.
It's all about fracture.

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

You don’t have to be OLD.

Load > Bone Strength = FRACTURE

(Key Causality – BIOMECHANICS)

You don’t have to have OSTEOPOROSIS.
Clinical Arena: Probability of Fractures Drives the Requirement for Intervention.

What do we need to monitor in order to assess if and when fractures might occur in astronauts?
Overview

• What makes Bone complicated?

• What makes space effects so unique?

• What steps are recommended to manage fracture risk in astronauts given NASA constraints?
Skeletal Sites: Different composition of Bone Types with different contributions (a GAP) to Bone Integrity

PROXIMAL FEMUR

Trochanter
50% BMD

Femoral Neck
25% BMD

Cortical Bone/ “Compact Bone”

VERTEBRAL BODY – 66% BMD

Cancellous “Spongy” Bone/Trabecular Bone

Sources: L. Mosekilde; SL Bonnick; P Crompton
Different Distribution and Turnover Rates for Bone Types to Support 2 functions of Skeleton

Entire skeleton turns-over 10%/year: 3% cortical bone 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
TYPES OF BONE CELLS: mediators of bone resorption, bone formation, mechanical sensing

Bone Marrow Area

Mineralized bone

osteocytes
osteoblasts
osteoclasts
Remodeling of Bone Tissue in Adults is Highly Regulated and Rates can Influence Integrity

1-2 million Bone Remodeling Units (BRUs) in the adult skeleton

Normal Remodeling Rate at the Level of 1 Bone Remodeling Unit of Cancellous Bone

High Remodeling Rate at the Cancellous Bone Tissue Level
Fracture risk is already multifactorial in the Aged and At Risk populations.

- **Aging**
  - Androgen insensitivity
  - Anorexia nervosa and bulimia
  - Athletic amenorrhea
  - Hyperprolactinemia
- **Low calcium intake**
- **Alcohol** (3 or more drinks/d)
- **Smoking**
- **High salt intake**
- **Immobilization/Reduced physical activity**
  - Anticoagulants
  - Anticonvulsants
  - Barbiturates
  - Glucocorticoids
  - Cancer chemotherapeutic drugs

- **Inadequate peak bone mass**
- **Increased bone loss**
- **Impaired bone quality**
- **Skeletal fragility**
- **Fracture Probability**
- **Falls**
- **Certain activities**
- **Excessive bone loading**

Adapted from: Pathogenesis of Osteoporosis-Related Fractures (NOF) Cooper C, Melton LJ
Medical Operations: Multiple, novel knowledge gaps to investigate.

- Aging
  - Gonadal Changes?
- Calcium, Vitamin D, Muscle Atrophy
- Uncoupled bone turnover
- High Salt Intake
- Family History
- Medications
- Disorders

- Inadequate peak bone mass
- Increased bone loss
- Low bone density
- Impaired bone quality
- Skeletal fragility
- FRACTURE
- Excessive bone loading
- Repetitive Falling
- Planetary EVAs
- Exercise Loads
- Kinetic energy

- Postural instability
- CO2; Radiation on bone marrow cells
- Fluid shifts and regional blood flow

Adapted from: Pathogenesis of Osteoporosis-Related Fractures (NOF) Cooper C, Melton LJ
Setting Priorities: It’s not all about Bone.

### Adaptations to Long-Duration Space Flight

<table>
<thead>
<tr>
<th>Ocular</th>
<th></th>
<th>Body Fluids</th>
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<tbody>
<tr>
<td>↑ intraocular pressure in flight</td>
<td></td>
<td>↑ hemoglobin &amp; hematocrit postflight</td>
</tr>
<tr>
<td>↑ retinal blood vessel constriction postflight</td>
<td></td>
<td>↓ total body water</td>
</tr>
<tr>
<td>↓ visual motor task performance</td>
<td></td>
<td>↓ plasma &amp; urine volumes postflight</td>
</tr>
<tr>
<td>↓ contrast discrimination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ visual field postflight</td>
<td></td>
<td>Electrolytes</td>
</tr>
<tr>
<td>↓ intraocular pressure postflight</td>
<td></td>
<td>↑ urinary Ca &amp; PO₄ postflight</td>
</tr>
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<table>
<thead>
<tr>
<th>Cardiovascular</th>
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<th>Hormones</th>
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<tbody>
<tr>
<td>↑ resting heart rate</td>
<td></td>
<td>↑ plasma ADH &amp; ANF</td>
</tr>
<tr>
<td>↑ stroke volume early in flight</td>
<td></td>
<td>↑ urinary aldosterone</td>
</tr>
<tr>
<td>↑ PACs &amp; PVCs</td>
<td></td>
<td>↑ urinary ADH &amp; cortisol postflight</td>
</tr>
<tr>
<td>↓ fluid volume</td>
<td></td>
<td>↓ urinary epinephrine &amp; androsterone postflight</td>
</tr>
<tr>
<td>↓ orthostatic tolerance</td>
<td></td>
<td>↓ plasma ACTH, aldosterone, cortisol</td>
</tr>
<tr>
<td>↓ aerobic &amp; anaerobic capacity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ resting blood pressure postflight</td>
<td></td>
<td>Metabolites</td>
</tr>
<tr>
<td>↓ central venous pressure (indirect)</td>
<td></td>
<td>↑ plasma glucose, creatinine, BUN postflight</td>
</tr>
<tr>
<td>↓ cardio/thoracic (CK) ratio postflight</td>
<td></td>
<td>↓ albumin, cholesterol, triglycerides, uric acid</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Musculoskeletal/Bone</th>
<th></th>
<th>Neurosensory</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ muscle mass</td>
<td></td>
<td>↑ vestibular disturbances</td>
</tr>
<tr>
<td>↓ muscle endurance &amp; strength</td>
<td></td>
<td>↑ space motion sickness</td>
</tr>
<tr>
<td>↓ bone mineral content</td>
<td></td>
<td>↓ postural stability</td>
</tr>
<tr>
<td>↓ bone integrity</td>
<td></td>
<td>↓ sensorimotor function</td>
</tr>
</tbody>
</table>
Overview

• What makes Bone complicated?

• What makes space effects so unique?

• What steps are recommended to manage fracture risk in astronauts given NASA constraints?
Characterizing Bone Changes* in Space

Mercury 1961-63
Gemini 1965-66
Apollo 1968-72
Skylab 1973-74
Soyuz/Salyut 1974-85
Mir 1986-2000
Shuttle 1981-2010
Intl Space Station 2000-present

Calcium balance
SPA of heel and wrist
SPA
Urine, fecal Ca
Heel, Wrist
Soyuz/Salyut 1974-85
DXA
Mir 1986-2000
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)

Skylab-Urinary Calcium Excretion

Urinary Ca during Skylab
(Mean + _ SEM)

Urinary Ca after
Return from Skylab

Number of Flight Days

Days of Reambulation
DXA measurement of areal BMD $[\text{BMD}_a]$ – a 3d measure in 2d units
• Improved precision; low radiation; shorter scan times; BMD over multiple skeletal sites…
• Used in large prospective studies for fracture prediction

• Long established surrogate for bone strength
• Despite limitations, still considered best predictor of fracture
Regional BMD losses Mir Crew Members by DXA

Declines in bone mass are rapid and site-specific.

<table>
<thead>
<tr>
<th>Areal BMD g/cm²</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>

Whole Body 0.3% / month

Lumbar Spine 1%/ month

Hip 1.5% / month

*L p<0.01, n=16-18 Leblanc et al, 2000.
Subsequently, application of Dual-energy X-ray Absorptiometry [DXA] BMD @ Johnson Space Center to:

- monitor astronaut skeletal health,
- characterize skeletal effects of long-duration spaceflight,
- evaluate efficacy of bone loss countermeasures, and
- verify restored health status
DXA BMD increases in Postflight – does that suggest a recovery of bone strength?

Sibonga et al. BONE 41:973-978, 2007
Serum and urinary biomarkers reflect bone turnover and suggest changes in cellular activities.
Bone Turnover Markers: suggest uncoupling of remodeling -- may result in net loss in bone mass *from skeleton.*
Calcium-regulating Hormones – Endocrine system is “normal” but perturbed.

Nutrition SM0, unpublished data; Courtesy Dr. SM Smith
Circa 2000, NASA adapts the only & best clinical guidelines available for Primary Osteoporosis as standards of bone health in astronauts. 

**T-scores** (Not BMD change).

*T-score* is # Standard Deviations from mean BMD of young normal “peak bone mass”
Clinical Guidelines used by NASA:

DXA-based T-scores not appropriate, informative or predictive for fracture in astronaut population.
Limited Knowledge Base: The long-duration astronaut – not typical subject to screen for osteoporosis (1/2015).

- Typical space mission duration – 160 ± 32d (range 49-215d)
- Average Age – 47 ± 5 y (range 36 – 56)
- Male to Female Ratio – 4.7 : 1 (56:12)
- Current total # per astronauts in corps – 68 of 365
- # repeat fliers – 7
- BMI – Male BMI 25.7 ± 2.2 (range 21.2 to 30.7) Female BMI 22.3 ± 2.3 (range 20.1 to 25.9)
- Wt and Ht- Males: Males: 82 ± 9 (63 to 103); 177 ± 6 (163 to 188) Females : 65 ± 7 (54 to 81), 169 ± 4 (163 to 178)
- % Body Fat: Males: 23 ± 4 (14 to 31) Females: 29 ± 6 (22 to 44)

• **YOUNGER PERSONS DO NOT FRACTURE.**
Age is important risk factor for bone loss and fracture probability. The DXA as diagnostic clinical test is not for premenopausal females or males < 50 years.

Kanis et al JBMR 9(8):1137, 1994
DXA as a Research Tool – Cannot distinguish effect of ARED exercise from bisphosphonates.
Bisphosphonates mitigate urinary calcium excretion by suppressing bone degradation.
Meanwhile, Terrestrial Observation of Reduced Sensitivity of DXA Test: “T-score Osteoporosis” Misses Over 50% of Fragility Fractures

Only 44% of women (21% of men) who sustain non-vertebral fractures have “osteoporosis” by BMD*

*Also disconnects evident with clinical trials—reduced ability to monitor therapeutic response to pharm agents.
Disconnects with BMD and Fracture risk in terrestrial medicine:
Fracture probability is influenced by additional factors that are not measured by DXA areal BMD.
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 Quality: What is it and Can we measure it?”

May 2005
Different QCT modalities to capture bone structure.

Example, GE QCT scanner

Lunar
Hip 1.2-1.5 mSv/ HIP
2-6 days  ISS background

Stratec peripheral QCT
5 slices tibia 0.5 mRem

ScanCo
High Resolution “HR” peripheral QCT
< 0.5 mRem per site
**QCT Research:** Space induces compartment-specific losses in bone sub-regions (n=16)

<table>
<thead>
<tr>
<th>Index DXA</th>
<th>%/Month Change ± SD</th>
<th>Index QCT</th>
<th>%/Month Change ± SD</th>
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</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></td>
<td></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></td>
<td></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></td>
<td></td>
<td>Trabecular vBMD Trochanter</td>
<td>2.2±0.9</td>
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*p<0.01, n=16-18

DXA areal BMD and QCT trabecular volumetric BMD of Total Proximal Femur: Discordant Recovery Patterns 2-4 Years Post-flight

FEM – a computational tool to estimate failure loads ("strength") of complex structures.

i) Models generated from QCT data. ii) Applied to astronauts (n=11) in collaboration with QCT study.


Images courtesy of Dr. J Keyak
Individual Results
Stance Loading (4 to 30% loss in strength)

Max loss 30%

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Hip Strength (kN)</th>
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<tbody>
<tr>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>8</td>
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</table>

PreMean 13,200 N (2300 N) | Post Mean 11,200 N (2400 N) | P <0.001
Individual Results
Fall Loading (3 gain to 24% loss in strength)

Max loss 24%

Pre Mean 2,580 N (560 N)
Post mean 2,280 N (590 N)
P < 0.003
Overview

• What makes Bone complicated?

• What makes space effects so unique?

• What steps are recommended to manage fracture risk in astronauts given NASA constraints?
If clinical test is insufficient, how can we predict \textit{when} fragility premature fractures might occur in astronauts?

Cooper and Melton, 1992
Convening a panel of Policy Makers in BMD/Osteoporosis Field
1. What specific measure(s) do we need to monitor in lieu of incidence?

2. What’s the clinical trigger?

3. What should be the clinical response?

Desired Deliverable: Clinical Practice Guidelines

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

Journal of Bone and Mineral Research
Vol. 28, No. 6, June 2013, pp 1243–1255
What measurements should be performed to describe spaceflight changes?

- 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
Probabilistic Risk Assessments [PRA]: When is fracture most likely?

- **Age (yr)**
- **Bone mass (g/calcium)**
- **Peak Bone Mass**
- **OPS**
- **LTH**
- **Due to Overloading of bones (biomechanics)**
- **Due to Irreversibility of space effects**
- **Age-related Loss**
- **Menopause-induced Loss**
- **Males**
- **Females**

Nigo BL, Melton LJ: Adapted from Involutional osteoporosis, Oxford Textbook of Geriatric Medicine. ADAPTED SLIDE COURTESY OF Dr. S. AMIN, Mayo Clinic.
Also, immediate (TBD) period after return – attributed to sub-clinical change in bone strength with no change in level of physical activity.
Clinical Evidence: QCT measures are independent predictors of hip fracture to supplement aBMD in the aged.

Proximal Femoral Structure and the Prediction of Hip Fracture in Men: A Large Prospective Study Using QCT*

Dennis M Black, Mary L Bouxsein, Lynn M Marshall, Steven R Cummings, Thomas F Lang, Jane A Cauley, Kristine E Ensrud, Carrie M Nielson and Eric S Orwell for the Osteoporotic Fractures in Men (MrOS) Research Group

In Vivo Discrimination of Hip Fracture With Quantitative Computed Tomography: Results From the Prospective European Femur Fracture Study (EFFECT)

Valérie Danielle Bousson, Judith Adams, Klaus Engelke, Mounir Aout, Martine Cohen-Solal, Catherine Bergot, Didier Haguenaier, Daniele Goldberg, Karine Champion, Redha Aksouh, Eric Vicaut, and Jean-Denis Laredo
Subsequently, Clinical Advisory Panel recommends the following:

1. Clinical Trigger: The failure to measure recovery of trabecular BMD of hip by two years after return in astronaut.

2. Clinical response: Seek an evaluation by an osteoporosis specialist. Correction of risk factor or possible intervention.

3. Overall, QCT measures provide useful information regarding causation of hip fracture, evaluation of hip fracture risk and possible targets for intervention. Good candidate for “Risk Surveillance.”

Science Rationale:

- QCT + FEM outperforms DXA and QCT for estimating fracture loads

R²=.66 QCT

R²=.57 DXA

R²=.84 FEM
Investigate FE estimates of hip strength as new surrogate for bone health for individualized assessments—likely to capture more effects of spaceflight that affect bone integrity.

Finite Element Strength

- aBMD
- BMD
- Material Properties
- Geometry
- Loading

Bone Strength Surrogate

Relative Fracture Assessment

Individualized Fracture Assessment
Recommendation: Explore emerging data from population studies using FE bone strength to predict fractures and return to panel with findings for clinical operating bands of astronaut health.


- Position on the use of QCT for clinical decision making is being deliberated by International Society of Clinical Densitometry [ISCD] as of **Feb. 2015.** Data from clinical studies (n=22 reports of qCT and/or FEM) in this meta analysis.
Exploring Finite Element Models [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.

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.

Data slide courtesy of Keyak. NOT FOR DISTRIBUTION
High Resorption $\rightarrow$ Disrupts Microarchitecture $\rightarrow$ Fractures*
GAPS persist.

Predisposed to "codfish" fx

Male Astronauts? Spaceflight Effect? The Hip?
Bone Microarchitecture: Need to “discover” technology to monitor for a Non-permissible outcome because irreversible.

Images courtesy of Ralph Müller, PhD, Switzerland

Adapted by Sibonga
Summary: Forward Actions for Bone Risk Management

1. Collect QCT data for risk surveillance – for operational and clinical decisions – based upon evidence from randomized controlled trials.

2. QCT provides opportunity for Finite Element Models, the analysis of which generates a “hip strength index” which could be used in a NASA-developed Probabilistic Fracture Assessment Module.

3. Explore FEM data from population studies to identify a possible hip strength cut-point as a modified astronaut standard for hip strength.

4. Search/validate new technologies for surveillance of unique bone measures (e.g., microarchitecture)

5. Note: Following a review of QCT data 9 additional astronauts (case reports), Bone Summit Panel maintained its recommendation to use QCT for surveillance.
Closing Remark

Bone Discipline Goal: To reduce the uncertainty of spaceflight-induced fracture risks in astronauts.

- Expand the definition of spaceflight effects on bone loss and recovery.
- Because of constraints, transition innovative technologies and analyses available to measure additional bone parameter and increase our ability to predict fractures.
Thank you.

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- Robert Wermers, M.D. (Mayo Clinic)

Emily Morey-Holton, Ph.D
David J. Baylink, M.D.
Pilot Study: Hip QCT

1. Hypothesis: QCT will distinguish the effects of biochemical from mechanical countermeasures. **Important to use QCT to evaluate Countermeasures that affect different bone types.**

2. Translate QCT data to *hip strength* with FEM.

*From J. W. Jaworski*
*Images Courtesy of D Carter, PhD*