Bone Health Monitoring in Astronauts: Recommended Use of Quantitative Computed Tomography [QCT] for Clinical and Operational Decisions

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On behalf of the NASA Bone Summit Panel for Early Onset Osteoporosis in Long-Duration Astronauts.
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BASIS FOR BONE SUMMIT
Does spaceflight induce enduring changes to bone that combine with age-related losses?

![Graph showing peak bone mass and age-related loss for males and females.]

- **Peak Bone Mass**
- **1° Age-related Loss**
- **Males**
- **Females**


Slide courtesy of Amin adapted by Sibonga.
Risk: Do age-related fractures occur prematurely due to previous exposure to long-duration spaceflight.

Cooper and Melton, 1992

Slide courtesy of Amin; adapted
To-date, subclinical effect, but T-scores are inappropriate and not informative for long-duration astronauts.
Clinical Significance: Impact of Age-related Hip Fractures

- 50% of survivors post-hip fracture require institutional care or functional assistance

- Decreased quality of life and negative health outcomes for men and women with vertebral deformity

  Poor Osteoporosis Intl. 1995; Matthis Osteoporosis Intl. 1998; Scane Osteoporosis Intl. 1999

**Men tend to do worse**

- Twice as likely to die in hospital following hip fracture than women

- 1 year mortality rate following hip fracture is higher compared with women (31-35% vs. 17-22%)

Notably, spaceflight-induced skeletal changes could also impact fracture risk after return to earth if recovery of bone strength is not sufficiently established.

- In the post-mission period when the LD astronaut returns to preflight level of physical activity

- In the aging astronaut before or concurrent with age-related bone loss.*

* age-related bone loss is sex-specific (see figure) with females losing bone mass earlier with the onset of menopause.
Given the **following**, it becomes more critical to reduce the uncertainty with how bone mass and bone structure change due to spaceflight and with recovery on earth after a mission.

“An *asymptomatic* systemic bone disease characterized by low bone mass and **microarchitectural deterioration** of bone tissue, with a consequent increase in bone fragility and susceptibility of fracture”

Am J Med 1993; Consensus Development Conference: diagnosis, prophylaxis and treatment of osteoporosis

“Bone strength reflects the integration of two main features: bone density and **bone quality**.”

JAMA, 2001

“….Bone quality, in turn, is stated to refer to **architecture, turnover**, damage accumulation, (e.g., microfractures) and mineralization….”

Osteoporosis Intl. 2002

“Bone Quality: What is it and Can we measure it?”

Focused ASBMR- NIH Forum, May 2005

“**Structural determinants** of vertebral fracture risk.”

But, how does Space Medicine use emerging research technologies and data in clinical practice? Action to convene a panel of clinical experts for a Bone Summit on Early Onset Osteoporosis in Long-Duration Astronauts.

Bone Summit Panel will be asked to:

- **Consider the Cohort**: Long-duration Astronauts - not the typical target population for evaluating osteoporosis or for determining age-related fracture risk.

- **Understand the Constraints**: NASA has a limited and insufficient dataset to describe the multi-factorial effects of prolonged spaceflight (small n, limited technologies, restricted data collection).

- **Recommend a Therapeutic Course of Action**: Panelists need to be leaders in the field of bone, knowledgeable in densitometry data and bone loss risk factors.

- **Recommend Approaches for Occupational Risk Surveillance**: what should NASA do now to address an occupational health risk that may manifest later?
Bone Summit Panel Members

- **Eric Orwoll, MD**
  - Endocrinology and Male Osteoporosis
- **E. Michael Lewiecki, MD, FACP, FACE**
  - Endocrinology, ISCD
- **Neil Binkley, MD, CCD**
  - ISCD, Geriatrics and Vitamin D
- **Shreyasee Amin, MD**
  - Rheumatology, Male Osteoporosis and Epidemiology
- **Sue Shapses, PhD**
  - Nutritional Sciences and Weight-loss
- **Robert A. Adler, MD**
  - Male Osteoporosis and Epidemiology
- **Steven Petak, MD, JD, FACE**
  - Endocrinology, ISCD (contracted by NASA)
- **Mehrsheed Sinaki, MD**
  - Physical Medicine & Rehabilitation
- **Nelson B. Watts, MD**
  - Endocrinology, ISCD

Left to Right, Top Row down
Individual “charts” of operational & medical data were compiled from a subset of LD-astronauts representing novel scenarios or skeletal responses (females, repeat fliers, ARED users, with QCT data, with bone strength data, with > 10% loss in hip or spine). Following this critical review, the panel was asked to address the following charge:

- Can a clinical trigger be identified, from the evidence-to-date, that would require medical response and/or a possible intervention to prevent early onset osteoporosis?

- For occupational risk surveillance, recommend skeletal measures for monitoring the risk for premature age-related fractures in this population.

* Abbreviated for the theme of this IAA presentation
Flight and Earth-based Population Studies

DATA BACKGROUND
DXA BMD Summary

Rapid (1-1.5%/mo) and site-specific BMD loss (local not metabolic).

Total BMD loss over 6 mo mission > 2 y loss in sex- and age-matched population on earth

Loss is variable.
Recovery is variable.
Recovery is prolonged.
Indicates: Multiple Risk Factors at play.
QCT measures loss vBMD in trabecular bone compartment which DXA technology cannot (n=16 ISS)

NOT detectable by DXA

<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>
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<td>Trabecular vBMD Lumbar Spine</td>
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<td></td>
<td>0.7±0.6</td>
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<td>aBMD Femoral Neck</td>
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<td>1.2±0.7</td>
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<td>2.7±1.9</td>
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<tr>
<td>aBMD Trochanter</td>
<td>1.56±0.99*</td>
<td>Integral vBMD Trochanter</td>
<td>1.5±0.9</td>
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<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 in Population Study and in Astronauts

Suggests that femoral neck total area increases by outward displacement when cortex thins with aging – risk of space effects combining with aging effects.


Lang et al, JBMR, 2006
QCT: Trabecular BMD at hip does not appear to show a recovery 2-4 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?

Results: Lower trabecular BMD is an independent predictor of hip fracture in elderly men. Overall, QCT measures provide useful information regarding causation of hip fracture, evaluation of hip fracture risk and possible targets for intervention.
Panel reviewed

EXPERT PANEL RECOMMENDATIONS
Recommended Clinical Trigger in Astronauts

- **Recommended Postflight Clinical Trigger**: lack of recovery in trabecular compartment of hip at R+ 2 years (*regardless of DXA T-score*). Astronaut/flight doc seeks consult with endocrinologist (Petak) for evaluation and possible recommendation for intervention.

- **Rationale**: Concern for irreversible deficits to this bone compartment – an independent fracture predictor.
QCT scans for Occupational Risk Surveillance

NASA’s constraints may be the circumstances in which “research technologies should be transition to clinical realm.”

- **Required to detect clinical trigger** and for Countermeasure Evaluation: clinical trigger based upon trabecular bone compartment – not detectable by DXA but by QCT

- QCT’s **additional** measures reduce the uncertainty for fracture risk and for countermeasure efficacy

- **Added** benefits: facilitates *individualized* estimations of bone strength by Finite Element Modeling (preliminary findings exist in flight evidence base). Can inform rehabilitation approaches.
Why Apply Finite Element Modeling [FEM] to QCT data (a computational tool for complex structures) to assess failure loads of whole hip bone.
FEM may provide single best composite number to estimate bone strength because it integrates multiple factors.

Finite Element Strength

Geometry

Material Properties

BMD

Loading

Individualized Fracture Risk
Astronaut data: surrogates of bone strength do not correlate suggesting that FEM can detect changes due to space that DXA surrogate cannot.

Use of QCT Technology for Clinical and Operational Decisions

Recommendations from an Expert Panel for Consideration by NASA

CANDIDATE SELECTION TO ASTRONAUT CORPS

Is DXA T-score above -1?
- yes: Accept into Corps
- possible: Ineligible for Corps
- no: no

Is L1-1y DXA T-score above -1.5?
- yes: L1-(3-12) mo. QCT*: FE strength and trabecular recovery
- no: No pre-flight intervention required
- possible: Endocrine Evaluation for possible Tx.

Is R1+0y DXA T-score above -2?
- yes: yes
- no: no
- possible: no

Is R1+0.5y DXA T-score within 2% of preflight?
- yes: yes
- no: no
- possible: no

Is R1+1.0y DXA T-score within 2% of preflight?
- yes: yes
- no: no
- possible: no

Is R1+2y DXA T-score within 2% of preflight?
- yes: yes
- no: no
- possible: no

Conduct R1+3y DXA
- yes: yes
- no: no
- possible: no

Conduct routine DXA every 3 years from date of DXA indicating recovery within 2% of preflight
- yes: yes
- no: no
- possible: no

Conduct routine DXA every 3 years from date of DXA indicating recovery within 2% of preflight
- yes: yes
- no: no
- possible: no

Is QCT-1y derived FE strength at time of recertification above (TBD)?
- yes: Certified for second flight
- no: Not certified for second flight
- possible: no

Is R1+2y QCT* indicate trabecular bone recovery and/or FE strength?
- yes: yes
- no: no
- possible: yes

R1+1y QCT*: FE strength and trabecular recovery
- yes: yes
- no: no
- possible: yes

L1-(3-12) mo. QCT*: FE strength and trabecular recovery
- yes: yes
- no: no
- possible: yes

Endocrine Evaluation for possible Tx.
- yes: yes
- no: no
- possible: yes

Additional clinical info?
- yes: yes
- no: no
- possible: yes

*All designated QCT scans are for occupational surveillance purposes.
*a: Total Hip, Femoral Neck, Trochanter

Use of QCT Technology for Clinical and Operational Decisions

Recommendations from an Expert Panel for Consideration by NASA

Flight 1

Is R1+0y DXA T-score above -2?
- yes: yes
- no: no
- possible: yes

Is R1+0.5y DXA T-score within 2% of preflight?
- yes: yes
- no: no
- possible: yes

Is R1+1.0y DXA T-score within 2% of preflight?
- yes: yes
- no: no
- possible: yes

Is R1+2y DXA T-score within 2% of preflight?
- yes: yes
- no: no
- possible: yes

Conduct R1+3y DXA
- yes: yes
- no: no
- possible: yes

Conduct routine DXA every 3 years from date of DXA indicating recovery within 2% of preflight
- yes: yes
- no: no
- possible: yes

Is QCT-1y derived FE strength at time of recertification above (TBD)?
- yes: Certified for second flight
- no: Not certified for second flight
- possible: no

Is R1+2y QCT* indicate trabecular bone recovery and/or FE strength?
- yes: yes
- no: no
- possible: yes

R1+1y QCT*: FE strength and trabecular recovery
- yes: yes
- no: no
- possible: yes

L1-(3-12) mo. QCT*: FE strength and trabecular recovery
- yes: yes
- no: no
- possible: yes

Endocrine Evaluation for possible Tx.
- yes: yes
- no: no
- possible: yes

Additional clinical info?
- yes: yes
- no: no
- possible: yes

Flight 2

Is R1+0y DXA T-score above -2?
- yes: yes
- no: no
- possible: yes

Is R1+0.5y DXA T-score within 2% of preflight?
- yes: yes
- no: no
- possible: yes

Is R1+1.0y DXA T-score within 2% of preflight?
- yes: yes
- no: no
- possible: yes

Is R1+2y DXA T-score within 2% of preflight?
- yes: yes
- no: no
- possible: yes

Conduct R1+3y DXA
- yes: yes
- no: no
- possible: yes

Conduct routine DXA every 3 years from date of DXA indicating recovery within 2% of preflight
- yes: yes
- no: no
- possible: yes

Is QCT-1y derived FE strength at time of recertification above (TBD)?
- yes: Certified for second flight
- no: Not certified for second flight
- possible: no

Is R1+2y QCT* indicate trabecular bone recovery and/or FE strength?
- yes: yes
- no: no
- possible: yes

R1+1y QCT*: FE strength and trabecular recovery
- yes: yes
- no: no
- possible: yes

L1-(3-12) mo. QCT*: FE strength and trabecular recovery
- yes: yes
- no: no
- possible: yes

Endocrine Evaluation for possible Tx.
- yes: yes
- no: no
- possible: yes

Additional clinical info?
- yes: yes
- no: no
- possible: yes
Discussion

• NASA has a responsibility for the health of astronauts.
• QCT Surveillance will enable the collection of scientific knowledge, especially for measures that have been validated in population studies.
• QCT will increase the evaluation of bone changes due to space and with aging to address risks for current and future missions and risks to long-term health.
• Criticality to reduce uncertainty: Federal Employee Workman’s Compensation requires a 3-5 year window to establish causality between occupational hazard and injury or disease.
Concluding Comments

How much uncertainty is acceptable to manage the skeletal risks for early onset osteoporosis and for bone fracture? Increased understanding of spaceflight effects on bone by the Space Life Sciences Directorate:

- Will better inform decision-making (both clinical and operational),
- Will help direct focused and efficient countermeasure research and validation,
- Will improve the delineation of spaceflight causality substantiating occupational risk or injury,
- May lead to the translation of research technologies to earth-based medicine.