Exercise, Bisphosphonates & Bone Strength: Is the Bone problem solved?

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I have no financial relationships to disclose.

I will discuss the off-label investigational use of bisphosphonates.
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)
Four Identified “Bone” health risks for exploration missions.

1. Early Onset Osteoporosis
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Osteoporosis: Premature fractures in astronauts?

Cooper and Melton, 1992

SLIDE COURTESY OF Dr. S. AMIN, Mayo Clinic
NASA Standards for Crew Health Based on World Health Organization (WHO) – T-scores (Not BMD change).

T-score

-4.0
-3.0
-2.5
-2.0
-1.0
0.0
+1.0

Presence of osteoporosis
Low bone mass
Normal bone density

Permissible Outcome Limit

Disconnected discovered in population studies.

Fracture cases

Fitness For Duty

Non fractures
Diagnostic Guidelines Not for Astronauts
for peri- and postmenopausal women and men > 50 years.

BMD T-Score Values* Expeditions 1-25 (n=33)
*Comparison to Population Normals
Dual-energy X-ray Absorptiometry [DXA]  
Cannot distinguish changes in bone size

Effect of geometry on long 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</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.7</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>4</td>
<td>8</td>
</tr>
</tbody>
</table>

Mary Bouxsein, Ph.D. Bone Geometry and Skeletal Fragility, May 2005
IS NASA USING THE RIGHT TEST FOR EVALUATING RISK?
DXA – BMD cannot address operational concern — Exercise vs. Pharmaceuticals?
Quantitative Computed Tomography [QCT]

QCT MONITORING OF SPACEFLIGHT EFFECTS
DXA vs. QCT Spine:
Discordant Recovery Patterns After Spaceflight

DXA vs. QCT Femoral Neck: Discordant Recovery Patterns After Spaceflight

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
Astronaut Data (n=11): Space effects on surrogates of bone strength do not correlate.

Stance: $R^2=0.23$

Fall: $R^2=0.05$

Summary

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

• As long as countermeasure efficacy is assessed by a surrogate measure of bone strength (DXA – BMD) vs. an estimate of bone strength (e.g., FE models), then there is a risk of underestimating fracture probability and countermeasure efficacy.
Thank you.

QUESTIONS? COMMENTS?
Backup Slides
FEM of QCT data integrates multiple factors associated with fracture to provide a single composite number to estimate bone strength.
ARED exercise appears to mitigate decline in areal BMD.

(J Bone Mineral Research. Smith et al 2012) * this is not ref for figure.
Exploring 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.

All Male Subjects
Stance Loading

Data slide courtesy of Keyak. NOT FOR DISTRIBUTION

REPRESENTATIVE POPULATION DATA
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>
Take Home Messages

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 complex.
5. Clinically-accepted tests have limitations.
6. Bone medical standards (based upon terrestrial guidelines) are not applicable to long-duration astronauts and require modification.
Clinical Trigger: Failure to Recover
Hip Trabecular Bone Loss

Based upon: Lower trabecular BMD was an independent predictor of hip fracture in aged men in randomized controlled trial.

Note: QCT measures do not outperform BMD for fracture prediction…
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><strong>HR</strong></td>
</tr>
<tr>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Trabecular bone, volumetric BMD (g/cm²)</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.
Mineralization  Remodeling rate  ECM properties
Loading conditions  Chemical composition
Microdamage  Activation frequency
Microarchitecture  Ultrastructure
Geometry  Genetic profile
BMD

Fracture Risk?

Steven Goldstein, Ph.D.
“Bone Quality: A Biomechanical Perspective”
Does spaceflight result in irreversible changes to bone that combine with age-related losses?

**Peak Bone Mass**

**Bone mass (g/calcium)**

**Age (yr)**

**Age-related Loss**

**Males**

**Females**

**Menopause-induced Loss**

Riggs BL, Melton LJ: Adapted from Involutional osteoporosis
Oxford Textbook of Geriatric Medicine
ADAPTED SLIDE COURTESY OF Dr. S. AMIN, Mayo Clinic
Inappropriate: Probability for osteoporotic fractures is lower at younger ages.

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.
DXA measurement of areal BMD \([BMD_a]\) – a 3d measure in 2d units
- Used in large prospective studies for fracture prediction
- Long established surrogate for bone strength
- Despite limitations, still considered best predictor of fracture
Limitation of DXA: cannot distinguish different geometries of bone and thus cannot reflect different levels of bone strength.
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)
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>
</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>Integral vBMD Femoral Neck</td>
<td>1.2±0.7</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>Integral vBMD Trochanter</td>
<td>1.5±0.9</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></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)

Femoral Neck

Int. BMC (g)

Volumetric Bone Mineral Density g/cm³

Femoral Neck

Int. vBMD (g/cc)

Minimum Cross-sectional Area cm²

Minimum CSA

Pre  Post  12

P < 0.05 with respect to preflight*, postflight*

Slide adapted from T. Lang, JBMR 2006.
## 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>$p$</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
Individual Results

Stance Loading (4 to 30% loss in strength)

![Graph showing hip strength over time with max loss of 30%](image-url)
Individual Results

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

Max loss 24%
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.

The long-duration astronaut - an atypical subject to evaluate osteoporosis risk.

- Typical space mission duration – $163 \pm 32d$ (range 90-215d)
- Average Age – $46.5 \pm 4.5\ y$ (range 36.8 – 55.3)
- Male to Female Ratio – $3.8 : 1$
- Current total # per astronauts in corps – 34 of 331
- # repeat fliers – 4
- BMI – Male BMI $25.9 \pm 2.2$ (range 20.6 to 30.6); Female BMI $22.6 \pm 2.2$ (range 20.4 to 25.4)
- Wt and Ht- Males: Males: $81 \pm 9\ kg$ (range 62 to 101 kg), $177 \pm 6\ cm$ (range 163 to 185 cm); Females: $65 \pm 7\ kg$ (57 to 80 kg), $170 \pm 4\ cm$ (range 165 to 178 cm)
- MEDICAL PRIVACY OF THE ASTRONAUT.
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.