Bone Changes During Spaceflight: The Path to Risk Reduction

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Residents in Aerospace Medicine

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At the end of this lecture, you should understand:

• The progression of bone research on the path to risk reduction for the human system.

• The view of DXA BMD as a surrogate for fracture risk in terrestrial medicine. Why “loss” is not measured by this test.

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

• Bold research approaches to a hip fracture surrogate in the context of NASA’s constraints.
Characterizing Bone Changes 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**

SPA=Single Photon Absorptiometry  
DXA=Dual-energy X-ray Absorptiometry  
QCT=Quantitative Computed Tomography  
pQCT = peripheral QCT  
BTO=biochemical markers of bone turnover
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
Two Functions of the Skeleton*

- Internal support for the body
- Attachment for muscles / tendons for motion
- Protects vital organs
- Encloses blood-forming elements in marrow
- Mineral reservoir for Calcium (Ca^{2+}) homeostasis

*What potential risks to human health & performance?
Four identified “Bone” health risks for exploration missions.

1. Early Onset Osteoporosis (fragility fractures)
2. Bone Fracture (trauma fractures)
3. Formation of Renal Stones
4. Intervertebral Disc Injury (or Damage)
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)
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 Sibonga 10
Combined Medical and Research Tests:
Intervention Requirement?, Clinical Triggers?, Surveillance Recommendations

1. What additional measure(s) do we need to monitor?
2. How frequently? For how long?
3. How should Med Ops use research data in its clinical practice?

Bone Research @ NASA

- Ground-Analog Research
- Flight validation Research
- Astronauts Clinical Care

BONE SUMMIT 2010 and 2013
Take Home Messages from Bone Summit (2010)

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 unique.
5. Clinically-accepted tests have limitations.
6. NASA’s medical standards for bone health (based upon terrestrial guidelines) are not applicable to long-duration astronauts.
7. Recommended exploring the transition of research approaches to clinical arena.
Risk: Different types of fractures

“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.
RISK FOR FRAGILITY FRACTURES: Does spaceflight result in irreversible changes to bone that combine with age-related losses? Then, what do we measure?

Peak Bone Mass

Age-related Loss

Bone mass (g/ calcium)

Menopause-induced Loss

Males

Females

Riggs BL, Melton LJ: Adapted from Involutional osteoporosis
Oxford Textbook of Geriatric Medicine
ADAPTED SLIDE COURTESY OF Dr. S. AMIN, Mayo Clinic
Increased risk in astronauts?

Limited time to count incidence of fractures.

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Increased risk in astronauts?
NASA measures Bone Mineral Density [BMD] by DXA as a surrogate for fracture just as clinical world. –T-scores (Not BMD change). circa 2000
“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 STRENGTH IS INFLUENCED BY ADDITIONAL FACTORS THAT ARE NOT MEASURED BY DXA AREAL BMD.
Diagnostic Guidelines Not Meaningful for Astronauts for peri- and postmenopausal women and men > 50 years.

BMD T-Score Values* Expeditions 1-25 (n=33)
*Comparison to Population Normals
Age is important risk factor for bone loss but the utility of BMD for < 50 years not clearly evident.

Kanis et al. JBMR 9(8):1137, 1994

* The use of DXA BMD for surveillance of active astronauts is a unique application.
Risk for osteoporotic fractures is lower at younger ages.

Given the probability of fracture drives the requirement for interventions, the necessity for testing younger aged is not evidence-based.

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.
What could be measured to define a rare risk in younger persons?

Uncertainty exists. Are the long-duration astronauts at risk?
<table>
<thead>
<tr>
<th>Mission</th>
<th>Years</th>
<th>Imaging Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemini</td>
<td>1968-72</td>
<td>SPA heel and wrist</td>
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<td>Apollo</td>
<td>1965-66</td>
<td>X-ray densitometry, SPA heel and wrist</td>
</tr>
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<td>Skylab</td>
<td>1973-74</td>
<td>SPA heel and wrist</td>
</tr>
<tr>
<td>ISS</td>
<td>2000-present</td>
<td>DXA, QCT, HR3DpQCT (ESA)</td>
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<tr>
<td>Soyuz/Salyut</td>
<td>1974-85</td>
<td>SPA, DPA</td>
</tr>
<tr>
<td>Mir</td>
<td>1974-85</td>
<td>DXA whole body, CT of lumbar spine, BMD</td>
</tr>
</tbody>
</table>

Slide courtesy of Mayo Clinic  adapted from Dr. Jean Sibonga, NASA JSC
Measurement of bone mineral in 2-d projection of bone \([\text{BMD}_a]\) \(g/cm^2\)

- Improved precision; Low radiation; Shorter scan times; BMD measures over multiple skeletal sites

- Validated in numerous population studies for fracture prediction

- Long established, widely-applied surrogate for fracture outcome – become NASA standards, but T-scores give only Relative Risks
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 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>

*p<0.01, n=16-18

LeBlanc et al, J Musculoskeletal 2000
Effects of exercise regimens described using DXA BMD

% 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

Note: No population data linking % BMD loss to Fracture Outcome

* Updated data since 2010 Bone Summit
A Limitation: DXA Cannot distinguish changes in bone size – a contributor to bone strength.

<table>
<thead>
<tr>
<th></th>
<th>Areal (g/cm²)</th>
<th>Compressive Strength</th>
<th>Bending Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>aBMD</td>
<td>1</td>
<td>1.7</td>
<td>4</td>
</tr>
<tr>
<td>Areal</td>
<td>1</td>
<td>2.3</td>
<td>8</td>
</tr>
</tbody>
</table>

Mary Bouxsein, Ph.D. Bone Geometry and Skeletal Fragility, May 2005
Exercise changes **geometry** of whole bone (adult skeleton)- not detected by DXA.


Changes in size, changes in bone strength.

Slide courtesy of M. Bouxsein, PhD
Two Functions of the Skeleton - increasing understanding by biochemistry

Structural Framework

Mineral Reservoir

Osteoblasts

Bone Resorption

Bone Formation

Resorption Biochemical Markers

Formation Biochemical Markers

Osteoclasts
Serum and urinary biomarkers are by-products of bone turnover and bone cell activity.

**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 breakdown is increased, formation is **uncoupled** from resorption, and bone gain and loss are unbalanced*.

Reflects changes in **bone cells** but not where bone mass is lost.

* Could lead to net bone loss in skeleton.
HIGHLY-REGULATED ACTIONS OF BONE CELLS on BONE TURNOVER.

Under-filling, over-filling, balanced filling of the bone remodeling unit [BRU]
Can impact overall structural strength of whole bone (skeletal region).

Remodeling of bone at the level of a single “BRU”
Some insight gained by comparison to Earth-based disorders of increased bone resorption.
Representative manifestation on bone microarchitecture.
Clinical test not currently available for hip/spine.

(Mosekilde, 2000; Seeman, 2002; Silva, 1997; Kleerekoper, 1985)
Densitometry & Reported Measurement

DXA reports areal BMD (aBMD)

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

QCT quantifies volumetric BMD

\( \text{g/cm}^3 \) for separate cortical & trabecular bone
Research: QCT detects different rate of \( \nu \)BMD loss in separate bone compartments of hip. (\( n=16 \) ISS volunteers)

<table>
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<tr>
<th>Index</th>
<th>%/Month Change ± SD</th>
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<tr>
<td>aBMD Lumbar Spine</td>
<td>1.06±0.63*</td>
<td>Integral ( \nu )BMD Lumbar Spine</td>
<td>0.9±0.5</td>
</tr>
<tr>
<td>Trabecular ( \nu )BMD Lumbar Spine</td>
<td>0.7±0.6</td>
<td>Integral aBMD Femoral Neck</td>
<td>1.2±0.7</td>
</tr>
<tr>
<td>aBMD Femoral Neck</td>
<td>1.15±0.84*</td>
<td>Integral aBMD Femoral Neck</td>
<td>1.2±0.7</td>
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<tr>
<td>Trabecular ( \nu )BMD Femoral Neck</td>
<td>2.7±1.9</td>
<td>Integral aBMD Trochanter</td>
<td>1.5±0.9</td>
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<td>aBMD Trochanter</td>
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<td>Integral aBMD Trochanter</td>
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<td>2.2±0.9</td>
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</table>

\( ^{*}p<0.01, \quad n=16-18 \)

LeBlanc, J, Musculoskeletal Neuronal Interact. 2000; Lang, J Bone Miner Res, 2004;
Path to Risk Reduction

HOW CAN THESE RESEARCH DATA BE USED CLINICALLY IN THE ABSENCE OF FRACTURE DATA? So what?
DXA BMD increases in Postflight – but not sufficient to assess recovery of bone strength.

DXA & QCT Spine in 8 ISS astronauts: Expanding our Understanding of Recovery After Spaceflight

DXA & QCT Femoral Neck

Clinical Evidence: QCT measures are independent predictors of hip fracture to supplement aBMD.

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

Dennis M Black,1 Mary L Bouxsein,2 Lynn M Marshall,3 Steven R Cummings,4 Thomas F Lang,5 Jane A Cauley,6 Kristine E Ensrud,7 Carrie M Nielson3 and Eric S Orwell3 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,1,2 Judith Adams,3 Klaus Engelke,4 Mounir Aout,5 Martine Cohen-Solal,6 Catherine Bergot,2 Didier Haguenauer,7 Daniele Goldberg,8 Karine Champion,9 Redha Aksouh,1 Eric Vicaut,5 and Jean-Denis Laredo1,2
DXA BMD not as good of a predictor of hip fractures for the “complicated patient” i.e., non-age-related bone loss

- Different patterns of bone “loss” (cortical vs. trabecular) with different metabolic disorders … analogous to spaceflight effects

Seeman, JCI 1992
Slide courtesy of Dr. Amin, MD
Dual Photon Absorptiometry (DPA)
Describing changes in hip bone strength with Finite Element Modeling/Analysis: Emerging data from population studies.


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 changes in hip strength over time (0 to 6 months), with individual measurements indicating a general trend of decreasing strength.
Individual Results

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

Max loss 24%
Astronaut Data (n=11): Space effects on surrogates of bone strength do not correlate.

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.

- aBMD
  - Bone Strength Surrogate
  - Relative Fracture Risk

- BMD
  - Geometry
  - Material Properties
  - Loading
  - Finite Element Strength
  - Individualized Fracture Risk

Which is better?
Fracture risk by 1 measurement or by > 1 measurement?
It’s not complicated.
Additional cut-points for Bone Health: FE Modeling 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.

[Graph showing data for All Male Subjects under Stance Loading.

Data slide courtesy of Keyak. NOT FOR DISTRIBUTION]
Probabilistic Risk Assessments for Bone Fracture: NASA’s Model for Fracture Likelihood

Biomechanics and Mission Operations

Bone Loss in Space

Estimate of Fracture Probability

Probability of Fracture

Probability of event

Probability bone will fail to support load

Clinical and Engineering Characteristics of Bone Strength

Slide courtesy of J Myers; Adapted by Sibonga
WHAT IS OUR PATH TO RISK REDUCTION?

For Exploration Class Missions
<table>
<thead>
<tr>
<th>Osteo 1: GUIDED, NEW</th>
<th>A new acceptable bone health standard using an improved surrogate for bone strength needs to be defined for the flight environment.</th>
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<tbody>
<tr>
<td>Osteo 2: REPHRASED, MERGED</td>
<td>What is the incidence &amp; prevalence of early onset osteoporosis or fragility fractures due to exposure to spaceflight?</td>
</tr>
<tr>
<td>Osteo 3: GUIDED, MERGED</td>
<td>We need a validated, clinically-relevant method for assessing the effect of spaceflight on osteoporosis or fracture risks in long-duration [LD] astronauts.</td>
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<tr>
<td>Osteo 4: MERGED</td>
<td>We don’t know the contribution of each risk factor on bone loss and recovery of bone strength, and which factors are the best targets for countermeasure application.</td>
</tr>
<tr>
<td>Osteo 5: REPHRASED</td>
<td>We need an in flight capability to monitor bone turnover and bone mass changes during spaceflight.</td>
</tr>
<tr>
<td>Osteo 6: NEW</td>
<td>How do skeletal changes due to spaceflight modify the terrestrial risk of osteoporotic fractures?</td>
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<tr>
<td>Osteo 7: MERGED</td>
<td>We need to identify options for mitigating early onset osteoporosis before, during and after spaceflight.</td>
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**Bone Medical Standards update, Clinical Practice Guidelines [CPG]**

**Surveillance Program to data mine evidence of increased risk for fragility of low trauma fractures.**

**Data for medical standards; surveillance data for CPG formulation; Clinical trigger; surveillance data**

**Risk Characterization/Quantification**

**Prototype In-flight monitoring device for bone mass and for bone biomarkers**

**Risk Characterization: Probabilistic Risk Assessment Model/Tool to generate LxC; Input for clinical practice guidelines**

**Integrated suite of countermeasures nutrition, exercise and pharmaceuticals**
Schedules: ISS 2024

• Standards Update By FY14 End

• Spaceflight Effects Characterized (as reasonably can be achieved) ~ FYs 19-20

• Countermeasures (validated efficacy for mitigating risk factors during flight, e.g., declines in BMD, turnover and strength) By FY 23
Summary

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

• If skeletal integrity is assessed solely by a surrogate measure of bone strength (DXA – BMD) vs. an estimate of bone strength (e.g., FE modeling), then there may be a risk of underestimating fracture probability and poorly estimating countermeasure efficacy.

• In order to proceed down the path to risk reduction [PRR], Bone Research needs to take innovative approaches to characterizing risk and countermeasure effects.
Thank you.

QUESTIONS? COMMENTS?
Backup Slides
Study on Risk Surveillance: Hip QCT

- Test feasibility of QCT protocol for surveillance of clinical trigger.

- Accumulate surveillance data for development of clinical practice guidelines (QCT and FEM)

- **Research**: Demonstrate how QCT can delineate biochemical from mechanical countermeasures. “Proof of Concept” Pilot Study

Figures courtesy of T. Lang (UCSF) and D. Carter (Stanford U)
AGE-REGRESSIONS: Trabecular bone loss occurs at earlier age than expected.


Slide courtesy S. Khosla, adapted by Sibonga
Use of Osteoporosis Policy-makers help to translate research data to CPGs in absence of fracture data.
Effects on Different Compartments of Bone (cortical vs. trabecular BMDs)

Monitoring Drug Therapy

- PTH
- Combo
- Alendronate

1 yr follow-up PATH
n=238 women

Increase at 1 year (%)

- BMD DXA
- Integral QCT
- Trabecular QCT

Bars indicate 95% confidence intervals

Black et al. NEJM 2003
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.
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.
Different ways to **unbalance** remodeling at bone surface.

Different levels of cell number and cell activities ending in deficit of bone at the BRU.
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>
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<tbody>
<tr>
<td>Model A (HR per SD decrease)</td>
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<tr>
<td>--------------------------------</td>
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<tr>
<td>HR  95% CI p</td>
</tr>
<tr>
<td>Trabecular bone, volumetric BMD (g/cm²)</td>
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<tr>
<td>Percent cortical volume</td>
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<tr>
<td>Minimum cross-sectional area (cm²)</td>
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<tr>
<td>Areal BMD from DXA (g/cm²)</td>
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Area under the ROC curve for Models A, B, and C were 0.853, 0.855, and 0.860, respectively.
ARED exercise **appears** to mitigate decline in areal BMD.

(J Bone Mineral Research. Smith et al 2012) *this is not ref for figure.*
FE Standards Combine Aging and Spaceflight Changes to Hip Strength and used together with DXA BMD Standards.

<table>
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<tr>
<th>Minimum FE strength for Bone Health</th>
<th>“Go”</th>
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<tr>
<td>Minimum Permissible Outcome</td>
<td>“Wait”</td>
</tr>
<tr>
<td></td>
<td>“No Go”</td>
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</table>
Steven Goldstein, Ph.D.
"Bone Quality: A Biomechanical Perspective"
QCT Postflight – Changes in Femoral Neck structure detected 12 months after return

**Bone Mineral Content (g)**

PRE  | POST  | 12MONTH
-----|-------|--------
5.200| 5.400 | 5.600  
5.800| 6.000 | 6.200  
6.400| 6.600 |

**Volumetric Bone Mineral Density (g/cm³)**

PRE  | POST  | 12MONTH
-----|-------|--------
0.300| 0.310 | 0.320  
0.330| 0.340 | 0.350  
0.360| 0.370 |

**Minimum Cross-sectional Area (cm²)**

PRE  | POST  | 12MONTH
-----|-------|--------
5.200| 5.400 | 5.600  
5.800| 6.000 | 6.200  
6.400| 6.600 |

*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

The long-duration astronaut – not typical subject to evaluate osteoporosis (2/2013).

- Typical space mission duration – \(162 \pm 36\) days (range 58-215 days)
- Average Age – \(47 \pm 5\) y (range 37 – 55)
- Male to Female Ratio – \(4.8 : 1\)
- Current total # per astronauts in corps – 55 of 331
- # repeat fliers – 5
- BMI – Male BMI \(25.8 \pm 2.0\) (range 21.2 to 30.7); Female BMI \(23.4 \pm 2.4\) (range 20.4 to 25.9)
- Wt and Ht- Males: Males: \(80 \pm 6\) (63 to 97); \(176 \pm 6\) (163 to 185)
- Females: \(67 \pm 8\) (57 to 82), \(170 \pm 4\) (165 to 178)
- % Body Fat: Males \(20 \pm 4\) (9 to 27); Females \(27 \pm 8\) (19 to 41)
Bone Remodeling Sequence

Slide courtesy of Dr. R. Wermers, Mayo Clinic
**RISK FOR FRAGILITY FRACTURES:** Does spaceflight result in irreversible changes to bone that combine with age-related losses?

- **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
<table>
<thead>
<tr>
<th>Osteo #</th>
<th>Category</th>
<th>Subcategory</th>
<th>Customers</th>
<th>Deliverables</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Standards</td>
<td>New</td>
<td>OCHMO; Space &amp; Clinical Operations; Human Health Countermeasures [HHC]</td>
<td>Bone Health Standards update, Clinical Practice Guidelines</td>
</tr>
<tr>
<td>2</td>
<td>Knowledge Gap: Risk Characterization</td>
<td>Evidence</td>
<td>OCHMO; Space &amp; Clinical Operations</td>
<td>Evidence of increased risk for fragility of low trauma fractures.</td>
</tr>
<tr>
<td>3</td>
<td>Technology Gap: Methodology &amp; bone measurements</td>
<td>Clinical care; medical informatics</td>
<td>OCHMO; Space &amp; Clinical Operations; HHC</td>
<td>Data for medical standards (including index of countermeasure efficacy); Clinical trigger; surveillance data for Space Normal;</td>
</tr>
<tr>
<td>4</td>
<td>Knowledge Gap: Data, phenomenon, mechanism</td>
<td>Risk Factor</td>
<td>HHC, Biomed Research Div; Technology &amp; Engineering Division</td>
<td>Risk Characterization/Quantification-</td>
</tr>
<tr>
<td>5</td>
<td>Mitigation Gap: detect, monitor, treat</td>
<td>Prototype Hardware</td>
<td>Med Operations; Human Health Countermeasures; Systems Engineering</td>
<td>Prototype In-flight monitoring device for bone mass and for bone biomarkers</td>
</tr>
<tr>
<td>6</td>
<td>Mitigation-surveillance</td>
<td>Computational models, software</td>
<td>OCHMO; Space &amp; Clinical Operations; HHC</td>
<td>Risk Characterization: Probabilistic Risk Assessment Model/Tool to generate LxC; Input for clinical practice guidelines</td>
</tr>
<tr>
<td>7</td>
<td>Mitigation Prevention &amp; Treatment</td>
<td>Prescription(s)</td>
<td>Bone Summit-like Panel; Med Operations; OCHMO</td>
<td>Exercise prescription, metabolic countermeasures; validated pharm agent prescription; risk factor modifications; Recommended medical intervention.</td>
</tr>
<tr>
<td></td>
<td>Protocol</td>
<td>Protocol</td>
<td>Med Operations; OCHMO; HHC</td>
<td>Integrated suite of countermeasures nutrition, exercise and pharmaceuticals</td>
</tr>
</tbody>
</table>