Bone Changes During Spaceflight: The Path to Risk Reduction

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Johnson Space Center, Houston, TX
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

Mean Ca (mg/day)

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, Robert A Adler, Shreyasee Amin, Neil Binkley, E Michael Lewiecki, Steven M Petak, Sue A Shapses, Mehrsheed Sinaki, Nelson B Watts, and Jean D Sibonga
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

Flight validation Research

Ground-Analog 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)

Load > Bone Strength = FRACTURE (Key Causality – BIOMECHANICS)

You don’t have to be OLD.

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?

![Graph showing bone mass over age with peaks for males and females, and losses due to age-related and menopause-induced factors.](image)

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.

Cooper and Melton, 1992

SLIDE COURTESY OF Dr. S. AMIN, Mayo Clinic
“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: Kanis JA et al. Osteoporosis Int. 2001;12:989-995
Slide Courtesy of S. Petak, MD.
Uncertainty exists. Are the long-duration astronauts at risk?

WHAT COULD BE MEASURED TO DEFINE A RARE RISK IN YOUNGER PERSONS?
History of Bone Imaging in Space

<table>
<thead>
<tr>
<th>Gemini</th>
<th>Space Shuttle</th>
<th>ISS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mercury</td>
<td>Apollo</td>
<td>Skylab</td>
</tr>
<tr>
<td>X-ray densitometry</td>
<td>SPA heel and wrist</td>
<td>SPA heel and wrist</td>
</tr>
<tr>
<td></td>
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<td>1974-85</td>
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<tr>
<td>Soyuz/Salyut</td>
<td>Mir</td>
<td>1974-85</td>
</tr>
<tr>
<td>1974-85</td>
<td></td>
<td>DXA whole body</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT of lumbar spine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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 [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

Whole Body 0.3% / month

Lumbar Spine 1% / month

Hip 1.5% / month
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.

Effect of geometry on long bone strength

<table>
<thead>
<tr>
<th></th>
<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>1.7</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></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.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Periosteal Apposition</th>
<th>Endosteal Apposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periosteal Diameter</td>
<td>100 %</td>
<td>110 %</td>
<td>100 %</td>
</tr>
<tr>
<td>Endosteal Diameter</td>
<td>100 %</td>
<td>100 %</td>
<td>90 %</td>
</tr>
<tr>
<td>Compressive Strength</td>
<td>100 %</td>
<td>148 %</td>
<td>125 %</td>
</tr>
<tr>
<td>Bending Strength</td>
<td>100 %</td>
<td>168 %</td>
<td>116 %</td>
</tr>
</tbody>
</table>

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

Structural Framework

Mineral Reservoir

Resorption Biochemical Markers

Formation Biochemical Markers

Osteoblasts

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

(Smith et al, JBMR 2005); adapted by Sibonga

* 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 vBMD loss in separate bone compartments of hip. (n=16 ISS volunteers)

<table>
<thead>
<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 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>Trabecular vBMD Femoral Neck</td>
<td>2.7±1.9</td>
</tr>
<tr>
<td>aBMD Trochanter</td>
<td>1.56±0.99*</td>
<td>Trabecular vBMD Trochanter</td>
<td>2.2±0.9</td>
</tr>
</tbody>
</table>

*p<0.01, n=16-18

LeBlanc, J Musculoskelet 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*.

Sibonga et al. BONE 41:973-978, 2007
DXA & QCT Spine in 8 ISS astronauts:
Expanding our Understanding of Recovery After Spaceflight

Clinical Evidence: QCT measures are independent predictors of hip fracture to supplement aBMD.
DXA BMD not as good of 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 the relationship between time (months) and hip strength (kN), with a trend line indicating a decrease in hip strength over time.
Individual Results

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

**Time (months)**

**Hip Strength (kN)**

- 4.0
- 3.5
- 3.0
- 2.5
- 2.0
- 1.5

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

Stance: R²=0.23
Fall: R²=0.05

Which is better?
Which is better?
Fracture risk by 1 measurement or by > 1 measurement?
It’s not complicated.

Finite Element Strength
BMD
Geometry
Material Properties
Loading

Individualized Fracture Risk
Finite Element Strength
BMD
Material Properties
Geometry

Bone Strength Surrogate
aBMD

Relative 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.

Data slide courtesy of Keyak. NOT FOR DISTRIBUTION

REPRESENTATIVE POPULATION DATA
Probabilistic Risk Assessments for Bone Fracture: NASA’s Model for Fracture Likelihood

Biomechanics and Mission Operations

Bone Loss in Space

Estimate of Fracture Probability

Clinical and Engineering Characteristics of Bone Strength

- Probability of Fracture
- Probability bone will fail to support load
- Probability of event

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

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

For Exploration Class Missions
### Modified Bone Gaps and Expected Deliverables
#### Risk for Early Onset Osteoporosis

<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>
</tr>
</thead>
<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>
</tr>
<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>
</tr>
<tr>
<td>Osteo 7: MERGED</td>
<td>We need to identify options for mitigating early onset osteoporosis before, during and after spaceflight.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bone Medical Standards update, Clinical Practice Guidelines [CPG]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surveillance Program to data mine evidence of increased risk for fragility of low trauma fractures.</td>
</tr>
<tr>
<td>Data for medical standards; surveillance data for CPG formulation; Clinical trigger; surveillance data</td>
</tr>
</tbody>
</table>

#### Risk Characterization/Quantification

<table>
<thead>
<tr>
<th>Prototype In-flight monitoring device for bone mass and for bone biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Characterization: Probabilistic Risk Assessment Model/Tool to generate LxC; Input for clinical practice guidelines</td>
</tr>
<tr>
<td>Integrated suite of countermeasures nutrition, exercise and pharmaceuticals</td>
</tr>
</tbody>
</table>
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.

Use of Osteoporosis Policy-makers help to translate research data to CPGs in absence of fracture data.

Evidence Base – Flight and Ground
- Science
- Clinical
- Operational experience

Risks

Gaps

Exploration Missions & Architectures

NASA Spaceflight Human System Standards

Closure Metrics

Results and Deliverables

Solicitations & Directed Research

Integrated Research Plan

Clinically-relevant Research Tasks
Effects on Different Compartments of Bone (cortical vs. trabecular BMDs)

Monitoring Drug Therapy

- PTH
- Combo
- Alendroate

Increase at 1 year (%)

BMD DXA
Integral QCT
Trabecular QCT

1 yr follow-up PATH
n=238 women

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.

<p>| 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 |</p>
<table>
<thead>
<tr>
<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>HR</td>
<td>95% CI</td>
<td>p</td>
</tr>
<tr>
<td>Trabecular bone, volumetric BMD (g/cm^3)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Percent cortical volume</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Minimum cross-sectional area (cm^2)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Areal BMD from DXA (g/cm^2)</td>
<td>4.13</td>
<td>2.67, 6.38</td>
</tr>
</tbody>
</table>

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>
<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>
Turnover

Mineralization  Remodeling rate  ECM properties
Loading conditions  Chemical composition  Activation frequency
Microdamage  Ultrastructure  Genetic profile
Microarchitecture  Geometry  BMD

Fracture Risk?
QCT Postflight – Changes in Femoral Neck structure detected 12 months after return

<table>
<thead>
<tr>
<th>Bone Mineral Content (g)</th>
<th>Volumetric Bone Mineral Density g/cm³</th>
<th>Minimum Cross-sectional Area cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoral Neck</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Int. BMC (g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRE</td>
<td>5.200</td>
<td>0.300</td>
</tr>
<tr>
<td>POST</td>
<td>5.400</td>
<td>0.310</td>
</tr>
<tr>
<td>12MONTH</td>
<td>5.600</td>
<td>0.320</td>
</tr>
</tbody>
</table>

* * P < 0.05 with respect to preflight*, postflight*

Minimum CSA

Pre Post 12

QCT Postflight – Changes in Femoral Neck structure detected 12 months after return

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 – $47 \pm 5$ years (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

- Oc Precursor
- Osteoclast
- Mononuclear Cells
- Ob Precursors
- Osteoblast
- Resting Bone Surface
- Resorption
- Reversal
- Bone Formation
- Mineralization

LC = Lining Cells  CL = Cement Line  OS = Osteoid  BRU = Bone Remodeling Unit

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

Bone mass (g/calcium)

Age-related Loss

Menopause-induced Loss

Males

Females

Age (yr)

Riggs BL, Melton LJ: Adapted from Involutional osteoporosis
Oxford Textbook of Geriatric Medicine
ADAPTED SLIDE COURTESY OF Dr. S. AMIN, Mayo Clinic
## HRP Deliverables as Category

<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><strong>Knowledge Gap: Risk Characterization</strong></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><strong>Technology Gap Methodology &amp; bone measurements</strong></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><strong>Knowledge Gap: Data, phenomenon, mechanism</strong></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><strong>Mitigation-surveillance</strong></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><strong>Mitigation Prevention &amp; Treatment</strong></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>Med Operations; OCHMO; HHC</td>
<td>Integrated suite of countermeasures nutrition, exercise and pharmaceuticals</td>
<td></td>
</tr>
</tbody>
</table>