Effect of Microgravity on Bones: Challenges to Addressing Risks to Human Health & Performance

Endocrine Grand Rounds McGuire Veterans Affairs Medical Center

Jean D. Sibonga, Ph.D.
Lead, Bone Discipline
Human Research Program [HRP]
Johnson Space Center, Houston, TX
May 14, 2014
Overview

• NASA’s challenges to addressing skeletal risks due to spaceflight: 3 C’s

• Unique Skeletal Adaptations to Spaceflight

• Recommended Forward Actions for Risk Assessment and Management
Overview

- NASA’s challenges to addressing skeletal risks due to spaceflight: 3 C’s
- Unique Skeletal Adaptations to Spaceflight
- Recommended Forward Actions for Risk Assessment and Management
Mitigating Risks for the Human System in HRP

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

- NASA Spaceflight Human System Standards
- Exploration Missions & Architectures

- Prioritization & Implementation Approach
  - Constrained by:
    - Need dates
    - Budgets
    - Research platform availability

- Results and Deliverables
- Solicitations & Directed Research
- Integrated Research Plan

- Inst of Medicine
- Standing Review Panels

- Customer Review
- Peer Review

HRP slide courtesy C. Kundrot
Adapted Sibonga 2012
How should Space Medicine use Research Data in clinical care of astronauts?

1. Review of all Medical and Research Data.
2. What additional measure(s) for Op risk surveillance? “Bone Quality”

Bone Research @ NASA

Flight validation Research

Ground-Analog Research

Astronauts Clinical Care

BONE SUMMIT 2010, 2013
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 Sibonga10
How do we manage here to prevent condition here.

- 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
Issue: Recommendations in the absence of data.

Cooper and Melton, 1992

SLIDE COURTESY OF Dr. S. AMIN, Mayo Clinic
Take Home Messages from Bone Summit

1. Bone is a complicated tissue.
2. NASA’s constraints – not likely to reach Level of Evidence.
3. Astronauts are understudied group.
4. Spaceflight effects on bone are unique.
5. Clinically-accepted tests have limitations (JAMA).
6. Bone medical standards (based upon terrestrial guidelines) are not applicable to long-duration astronauts and require modification.
7. NASA circumstances may require transition of research technologies to clinical decision-making.
Bone Discipline Lead Briefs NASA HQ Chief Health & Medical Office [OCHMO]

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

Risks

Gaps

Exploration Missions & Architectures

NASA Spaceflight Human System Standards

Bone Summit 2010

Results and Deliverables

Solicitations & Directed Research

Integrated Research Plan

HRP slide courtesy C. Kundrot
Adapted Sibonga 2012
Use of the Research Clinical Advisory Panels [RCAP] to focus NASA’s Human Research for Bone Risks

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

- Risks

- Gaps

- Exploration Missions & Architectures

- NASA Spaceflight Human System Standards

- Results and Deliverables

- Solicitations & Directed Research

- Integrated Research Plan

- Clinically-relevant Research Tasks

- Closure Metrics

HRP slide courtesy C. Kundrot
Adapted Sibonga 2012
The long-duration astronaut – not typical subject to evaluate osteoporosis (4/2013).

- Typical space mission duration – $159 \pm 32$ days (range 49-215d)
- Average Age – $47 \pm 5$ years (range 36 – 56)
- Male to Female Ratio – 4.4 : 1
- Current total # per astronauts in corps – 59 of 365
- # repeat fliers – 6
- BMI – Male BMI $25.7 \pm 2.2$ (range 21.2 to 30.7); Female BMI $22.2 \pm 2.3$ (range 20.1 to 25.9)
- Wt and Ht- Males: Males: $81 \pm 9$ (64 to 101); $176 \pm 6$ (163 to 185)
- Females: $64 \pm 7$ (54 to 81), $169 \pm 4$ (163 to 178)
- % Body Fat: Males $20 \pm 4$ (9 to 27); Females $27 \pm 8$ (19 to 41)

*MEDICAL PRIVACY A MAJOR CONSTRAINT*
NASA Standards for Crew Health
Based on World Health Organization (WHO)
Note: T-scores \textit{(Not BMD change)}.

WHO/ISCD* Guidelines developed for peri-, postmenopausal women and men > 50 yrs. DXA screening & surveillance unique to NASA

*Intl Society Clinical Densitometry
Fig. courtesy of S. Petak, MD

Adapted from:
Adapted from: Pathogenesis of Osteoporosis-Related Fractures (NOF) Cooper C, Melton LJ

- Aging
- Gonadal Changes?
- Muscle Atrophy
- Ca/Nutrition/Vit D
- Increased and unbalanced bone resorption

**Operationally-induced Factors**
- Skeletal fragility
- Fracture Probability

**Inadequate peak bone Mass; Family History**
- Increased bone loss
- Lower bone density
- Impaired bone quality/Stress risers

**CO2; Radiation on bone marrow cells Fluid shifts and regional blood flow**

**Postural instability**

**Kinetic Energy of Mass**

**Exercise Loads**

**EVA Suit**

Adapted from: Pathogenesis of Osteoporosis-Related Fractures (NOF) Cooper C, Melton LJ
Overview

- NASA’s challenges to addressing skeletal risks due to spaceflight: 3 C’s
- Unique Skeletal Adaptations to Spaceflight
- Recommended Forward Actions for Risk Assessment and Management
Diagnostic guidelines using areal BMD T-scores - not appropriate or predictive for fracture in astronaut population.

BMD T-Score Values* Expeditions 1-25 (n=33)
*Comparison to Population Normals
Paradigm Shift

• “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
Dual-energy X-ray Absorptiometry [DXA] BMD @ Johnson Space Center

- Monitor astronaut skeletal health
- Characterize skeletal effects of long-duration spaceflight
- Evaluate efficacy of bone loss countermeasures
- Verify restored health status
What are the risks for using inappropriate DXA-BMD based guidelines?

• Unnecessarily disqualifying applicants to Astronaut candidacy.

• Not fully understanding the effects of spaceflight on hip and spine integrity.

• Inadequately evaluating efficacy of countermeasures.
**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>
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</thead>
<tbody>
<tr>
<td>Lumbar Spine</td>
<td>-1.06±0.63*</td>
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<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
DXA BMD increases in Postflight – but not sufficient to assess recovery of bone strength.

Sibonga et al. BONE 41:973-978, 2007
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><strong>Periosteal Diameter</strong></td>
<td>100%</td>
<td>110%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Endosteal Diameter</strong></td>
<td>100%</td>
<td>100%</td>
<td>90%</td>
</tr>
<tr>
<td><strong>Compressive Strength</strong></td>
<td>100%</td>
<td>148%</td>
<td>125%</td>
</tr>
<tr>
<td><strong>Bending Strength</strong></td>
<td>100%</td>
<td>168%</td>
<td>116%</td>
</tr>
</tbody>
</table>

Slide courtesy of M. Bouxsein, PhD – Bone Quality, 2005
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)
Bone Turnover Markers suggest a net loss in bone mass in the skeleton.
Calcium-regulating Hormones – Endocrine system is “normal” but perturbed.

Nutrition SMO, unpublished data; Courtesy Dr. SM Smith
% 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

* Updated data since 2010 Bone Summit
Bisphosphonates as a Countermeasure to Spaceflight Effects - mitigates of urinary calcium excretion

**Urinary Calcium During and After Space Flight**

- **Mir n = 6**
- **Bisphos + ARED n = 5 to 7**
- **IRED n = 4 to 8**
- **ARED n = 2 to 5**

* %Change in Mean Urinary Calcium vs. Pre Flight

* p<0.05, significant difference vs. Pre-Flight

Slide courtesy of Dr. A. LeBlanc
Densitometry & Reported Measurement

DXA reports areal BMD (aBMD) $g/cm^2$ averaged for cortical + trabecular bone

QCT quantifies volumetric BMD $g/cm^3$ for separate cortical & trabecular bones
DXA vs. QCT Spine: Discordant Recovery Patterns in Astronauts After Spaceflight

aBMD – areal bone mineral density g/cm²

tBMD – trabecular volumetric bone mineral density g/cm³

Why the clinical concern?


\[\text{aBMD} - \text{areal bone mineral density} \ g/cm^2\]

\[\text{tBMD} - \text{trabecular volumetric bone mineral density} \ g/cm^3\]
QCT measures are independent predictor of hip fracture.

Lower trabecular hip BMD is a predictor of hip fracture in aged men* (and in women, Bousson et al 2011)

SUMMIT RECOMMENDS AS THE CLINICAL TRIGGER FOR ASTRONAUTS.

This is the basis of Hip QCT flight study.
Overview

• NASA’s challenges to addressing skeletal risks due to spaceflight: 3 C’s

• Unique Skeletal Adaptations to Spaceflight

• Recommended Forward Actions for Risk Assessment and Management
Investigate a new medical standard for BONE Finite Element Modeling [FEM]: What is it and what can it tell NASA about hip fracture risk in the long-duration astronaut?
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%
Individual Results

Fall Loading (3 gain to 24% loss in strength)
Two methods of monitoring space-induced changes in bone strength do not correlate.

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

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

EXPLORE HOW FEM PREDICTS FRACTURE IN POPULATION STUDIES
Describing changes in hip bone strength with Finite Element Modeling/Analysis: Emerging data from population studies.


FE Strength Cutoffs* 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

*Red, Yellow and Green Operating Bands

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.

Minimum FE strength for Bone Health

Minimum Permissible Outcome

Data slide courtesy of Keyak. NOT FOR DISTRIBUTION
Similar approach proposed for terrestrial medicine.

Improving Bone Quality Assessment Biomarkers Consortium Project

Dennis Black, Ph.D.
Gayle Lester, Ph.D.
Federal Working Group on Bone Diseases
May 1, 2013
A new surrogate/patient management

**Estimating bone strength by QCT-based finite element analysis (FEA)**

- Standard engineering approach to evaluate mechanical behavior of complex structures
  - Integrates material & structural info from 3D QCT scans
  - Can provide multiple strength metrics

- Cadaver studies show that FEA predicts bone strength better than DXA-BMD

- Has been used *in vivo* to assess effect of treatments on bone strength and to predict fracture risk in untreated subjects

*Melton, et al, JBMR 2008*
Summary

• DXA – may be underestimating fracture probability and poorly estimating countermeasure efficacy for the astronaut population.

• Bone Discipline Research in progress to test QCT as a surveillance technology and to derive new cut-points for baseline bone health based upon finite element modeling.

• Bone Summit Panel is trying to formulate a therapeutic course of action, and the optimal timing of intervention.

• Leveraging Level 4 Evidence (expert opinion) from Bone Summit Panel as a means of defining and managing skeletal risks in astronauts in the absence of fracture evidence.
Thank you.

Acknowledgements

NASA & EXTRAMURAL
- Shreyasee Amin, M.D. (Mayo Clinic)
- Adriana Babiak-Vasquez (NASA JSC)
- Craig Kundrot (NASA JSC)
- Harlan J. Evans, Ph.D. (NASA JSC)
- Joyce H. Keyak; Ph.D. (UC Irvine)
- Thomas F. Lang; PhD. (UC San Francisco)
- Adrian D. LeBlanc, Ph.D. (USRA)
- Jerry Myers, Ph.D. (NASA GRC)
- Robert Ploutz-Snyder, Ph.D (NASA JSC)
- Clarence Sams, Ph.D (NASA JSC)
- Richard Scheuring, M.D. (NASA JSC)
- Linda C. Shackelford, M.D. (NASA JSC)
- Scott A. Smith (NASA JSC)
- Scott M. Smith, Ph.D. (NASA JSC)
- Elisabeth R. Spector (NASA JSC)
- Robert Wermers, M.D. (Mayo Clinic)
Backup Slides
The bridge as a metaphor for bone.

The I-35W Bridge Collapse in MN

- Probable cause: inadequate load capacity, due to a design error of the gusset plates (NTSB)
  - "...the half-inch thick plates should have been an inch thick — double the size."
- Contributing factors: underestimated loads to bridge, did not anticipate construction loads, did not integrate weather/salt temperature contribution to breakdown of material properties
  - "Inadequate use of technologies for accurately assessing the condition of gusset plates on deck truss bridges."
### Fracture Probability

#### Aging
- Hypogonadism
- Menopause

#### Clinical risk factors
- Excessive bone loading
- Clinical risk factors
- High bone turnover
- Inadequate peak bone mass
- Increased bone loss
- Falls
- Skeletal fragility
- Impaired bone quality
- Propensity to fall
- Fall mechanics
- Certain activities
- Low bone density

#### Factors in Patients
- Lifestyle factors
- Genetic factors
- Medications
- Disorders

### Endocrine disorders
- Adrenal insufficiency
- Cushing’s syndrome
- Diabetes mellitus
- Thyrotoxicosis

### Gastrointestinal disorders
- Celiac disease
- Inflammatory bowel disease
- Primary biliary cirrhosis
- Gastric bypass
- Malabsorption
- GI surgery
- Pancreatic disease

### Hematologic disorders
- Hemophilia
- Multiple myeloma
- Systemic mastocytosis
- Leukemia and lymphomas
- Sickle cell disease
- Thalassemia

### Rheumatic and autoimmune diseases
- Ankylosing spondylitis
- Lupus
- Rheumatoid arthritis

### Miscellaneous conditions and diseases
- Alcoholism
- Emphysema
- Muscular dystrophy
- Amyloidosis
- End stage renal disease
- Parenteral nutrition
- Chronic metabolic acidosis
- Epilepsy
- Post-transplant bone disease
- Congestive heart failure
- Idiopathic scoliosis
- Prior fracture as an adult
- Depression
- Multiple sclerosis
- Sarcoidosis

Adapted from: Pathogenesis of Osteoporosis-Related Fractures (NOF) Cooper C
Bone fragility is influenced by factors that are not detected by DXA BMD.

BMD accounts for 50-70% bone strength

Disconnects discovered in population studies.

FRACTURE CASES

normal bone density

low bone mass

presence of osteoporosis

NON FRACTURES
Dual Photon Absorptiometry DPA

- Differences in patterns of bone “loss” (cortical vs. trabecular) for different diseases...

Seeman, JCI 1992
Slide courtesy of Dr. Amin, MD
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>Model A (HR per SD decrease)</td>
</tr>
<tr>
<td>--------------------------------</td>
</tr>
<tr>
<td>Trabecular bone, volumetric BMD (g/cm³)</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.
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.
## 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
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></td>
<td></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>
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*p<0.01, n=16-18

LeBlanc, J Musculoskelet 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)

Volumetric Bone Mineral Density g/cm³

Minimum Cross-sectional Area cm²

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th>12</th>
</tr>
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<tbody>
<tr>
<td>Femoral Neck</td>
<td></td>
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<tr>
<td>Int. vBMD (g/cc)</td>
<td></td>
<td></td>
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<tr>
<td>Visit</td>
<td>PRE</td>
<td>POST</td>
<td>12MONTH</td>
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<th></th>
<th>Pre</th>
<th>Post</th>
<th>12</th>
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<tbody>
<tr>
<td>Volumetric Bone Mineral Density</td>
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<tr>
<td>Int. vBMD (g/cc)</td>
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<td>Visit</td>
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<td>POST</td>
<td>12MONTH</td>
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<th>Post</th>
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<td>Minimum CSA</td>
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<tr>
<td>(cm²)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Visit</td>
<td>PRE</td>
<td>POST</td>
<td>12MONTH</td>
</tr>
</tbody>
</table>

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

AGE-REGRESSIONS: Bone loss occurs at earlier age than expected.

Microarchitectural Measures of Trabeculae and of Spatial Orientation

Images courtesy of Ralph Müller, PhD, Switzerland

Adapted
**Hip QCT Study**

1. **Purpose of Hip QCT Surveillance** is to implement recommendations of a clinical advisory panel of osteoporosis experts (Bone Summit 2010).

2. **Collect specific QCT surveillance data** to develop clinical practice guidelines to recommend to space medicine.

3. **Evaluate recovery** at R+1 y and, if required, R+2 y.

4. **Research Study:** Describe how in-flight countermeasures or how post-flight activities affect changes in bone strength and recovery.
Characterizing Bone Loss in Space

Mercury
1961-63

Gemini
1965-66

Apollo
1968-72

Shuttle
1981-2010

Skylab
1973-74

Soyuz/Salyut
1974-85

Mir
1986-2000

Intl Space Station
2000-present

- Calcium balance
- SPA of heel and wrist
- SPA
- Urine, fecal Ca
- Heel, Wrist
- DXA
- QCT
- pQCT
- BTO