BONE LOSS IN LONG-DURATION SPACEFLIGHT: MEASUREMENTS AND COUNTERMEASURES

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ISS TOP DISCOVERIES IN MICROGRAVITY

BONE LOSS: MEASUREMENTS AND COUNTERMEASURES

- **Thomas Lang,** UC San Francisco, CT imaging studies
- **Joyce Keyak PhD**, UC Irvine, Finite Element Modeling
- **Scott M Smith PhD**, NASA JSC, Nutrition and Exercise Countermeasures
- **Adrian LeBlanc PhD**, USRA, Exercise and Pharmacologic Countermeasures
- **Jean Sibonga PhD**, NASA JSC, Bone and Mineral Laboratory
- **Peter Cavanagh PhD**, U of Washington, Exercise and Musculoskeletal Biomechanics

MOTIVATION

- Bone loss is a well-known medical consequence of long-duration spaceflight, anticipated long before the first space missions

- Loss of bone mass is associated with loss of bone strength
    - Increased risk of fracture
        - In elderly men and women, each 10% decrease in bone mineral density results in a 2-3 fold increase in fracture risk
        - A mission related fracture would be a potentially life-threatening or mission-compromising event
        - Extensive bone loss during a mission may compromise long-term bone health in the decades after service is complete

- Release of calcium from skeleton increases risk of renal stone development

EARLY STUDIES OF BONE LOSS IN SPACEFLIGHT

Skylab (early 70's): metabolic studies show loss of calcium and loss of bone from heel using early bone densitometry.
Salyut missions showed loss of bone in heel

MIR (1985-2001): first systematic study of bone loss using modern DXA technology. 19 cosmonauts measured pre- and post-flight at Star City.
Key finding: Cosmonauts lost 1-1.5%/month bone density in hip and 1%/month from spine. Losses comparable to yearly post-menopausal women (LeBlanc et al J Musc Neur Int 2000)

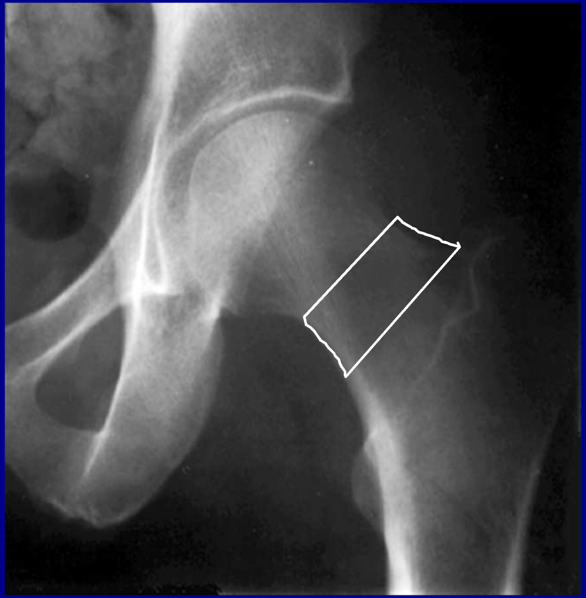
Head down bedrest studies: 90-day bedrest simulations of spaceflight showed bone loss similar to MIR. Bone loss was not reduced in subset of subjects who had a carefully controlled moderate exercise program (Leblanc J Bone and Min Res 1990), and was only reduced by an intense program of resistance exercise (Shackeford et al J App Phys 2004)

BONE LOSS AND COUNTERMEASURES:
NASA SUPPORTED HUMAN STUDIES ON THE ISS

- Studies of bone loss:
- Previous studies had focused on bone mass.
- New studies would move beyond bone mass to bone architecture, bone loading and strength
    - "Subregional assessment of bone loss in the axial skeleton in long-term spaceflight" (Thomas Lang)
    - "The Effect of Long-Duration Spaceflight on the Biomechanics of the Proximal Femur" (Thomas Lang)
    - "Foot Reaction Forces During Space Flight" (Peter Cavanagh)
- Countermeasure prescriptions
    - Combination of exercise and nutrition (Scott M Smith, PhD)
    - Bisphosphonate as a countermeasure to bone loss (Adrian Leblanc)

DUAL-ENERGY X-RAY ABSORPTIOMETRY

- Pros
  - Widely available
  - Inexpensive
  - Excellent reproducibility
  - Low x-ray exposure
- Cons
  - 2-D density (g/cm^2) at various sites
  - Combines trabecular and cortical bone
  - Does not account for bone geometry
  - Does not evaluate bone strength per se



QCT: IMAGING TO QUANTIFY BONE ARCHITECTURE AND STRENGTH

- Volumetric bone density of cortical and trabecular bone
  - Equivalent concentration of CaHA in g/cm3
- Bone geometry
  - Cross-sectional areas
  - Tissue volumes
  - Bone dimensions
- Bone strength estimates
  - Simple estimates of bending of compressive strength
  - Finite element modeling (FEM)

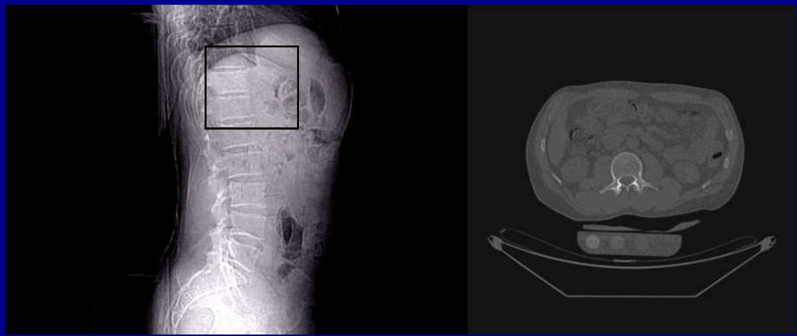
Joyce H. Keyak, PhD UC Irvine

SUBREGIONAL ASSESSMENT OF BONE LOSS IN THE AXIAL SKELETON IN LONG-TERM SPACEFLIGHT

- 16 International Space Station Crewmembers with pre-flight, post-flight (within 3 weeks of landing) and one year measurements
- Data gathered between 2001-2005
- DXA of spine and hip at JSC
- Volumetric QCT of the proximal femur and spine performed at Methodist Hospital, Baylor College of Medicine

QCT IMAGING

Image acquisitions



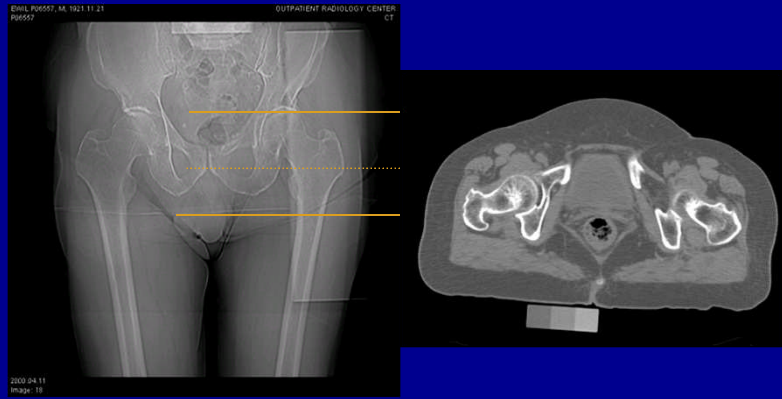
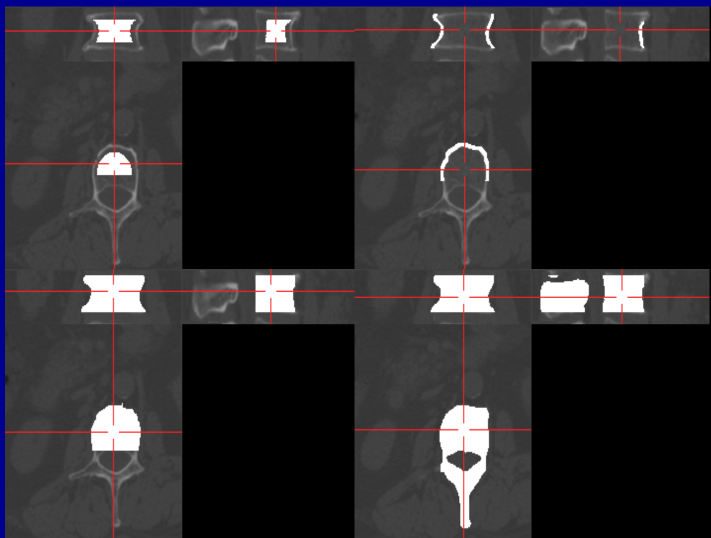
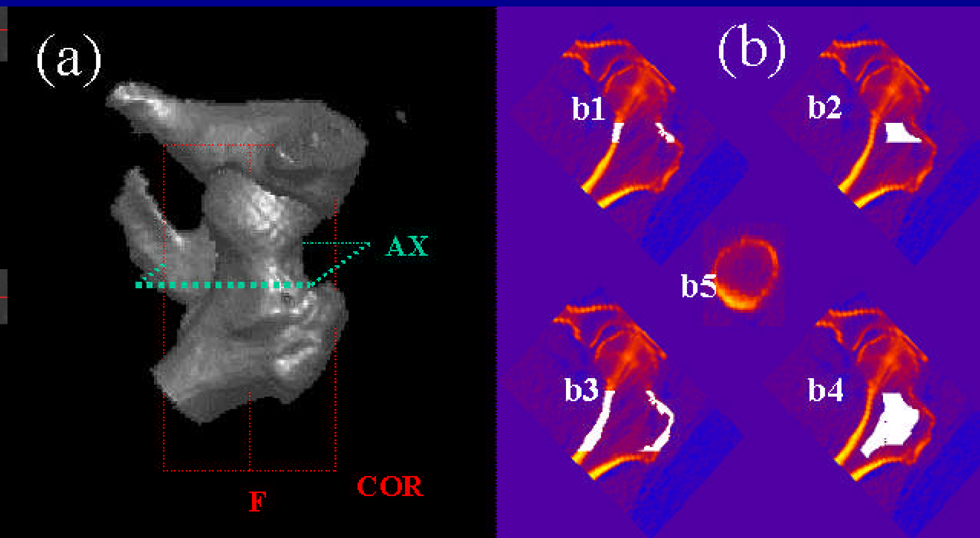


Image Analyses

Spine



Hip



3D FINITE ELEMENT MODELING

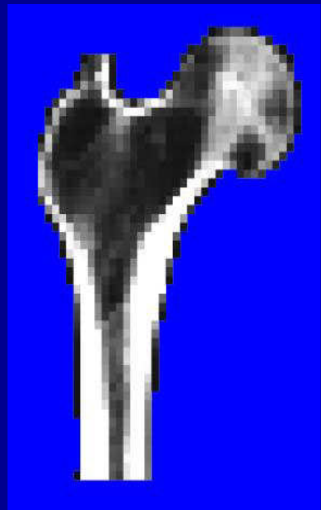
3D finite element model of hip derived from CT scan

Elastic modulus and strength derived for each QCT voxel parametrically from BMD

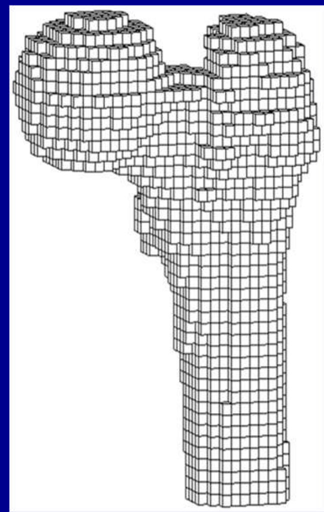
TABLE 1. Mechanical Property Relationship

Relationship	Type of Bone
E (MPa) $= 14900\rho_{ash}^{1.86}$	Trabecular and cortical
S (MPa) $= 102\rho_{ash}^{1.80}$	Trabecular and cortical
ε_{AB} (mm/mm) $= 0.00189 + 0.0241\rho_{ash}{}^{*}$	Trabecular
ε_{AB} (mm/mm) $= 0.0184 - 0.0100\rho_{ash}{}^{*}$	Cortical
E_p (MPa) $= -2080\rho_{ash}^{1.45*}$	Trabecular
E_p (MPa) $= -1000^{*}$	Cortical
σ_{min} (MPa) $= 43.1\rho_{ash}^{1.81}$	Trabecular and cortical

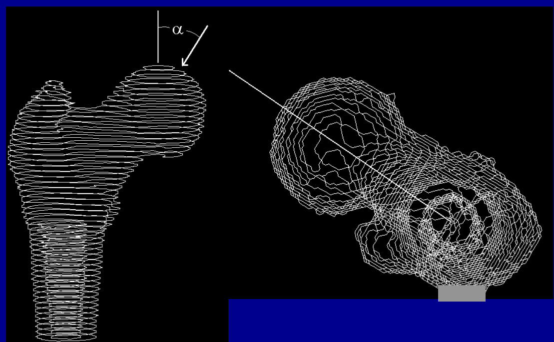
Map of material properties



Finite element model derived from QCT scan



Loading Conditions

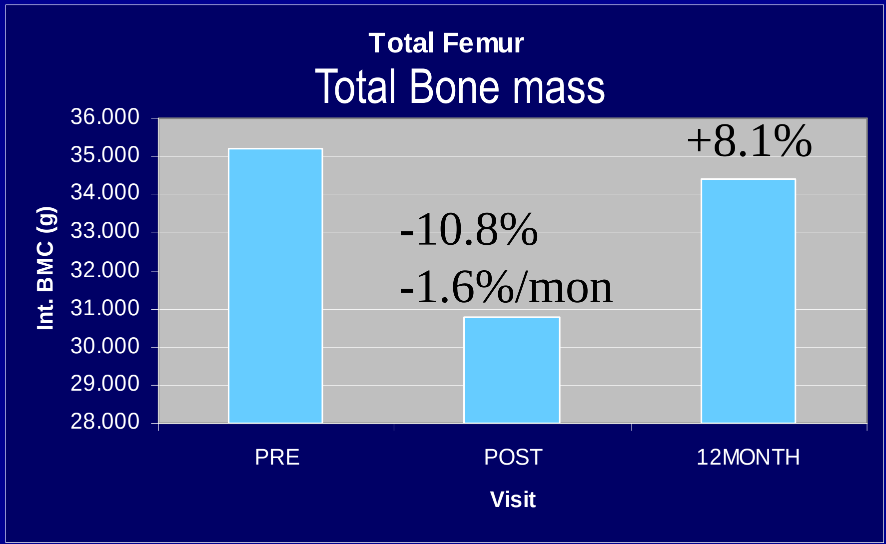


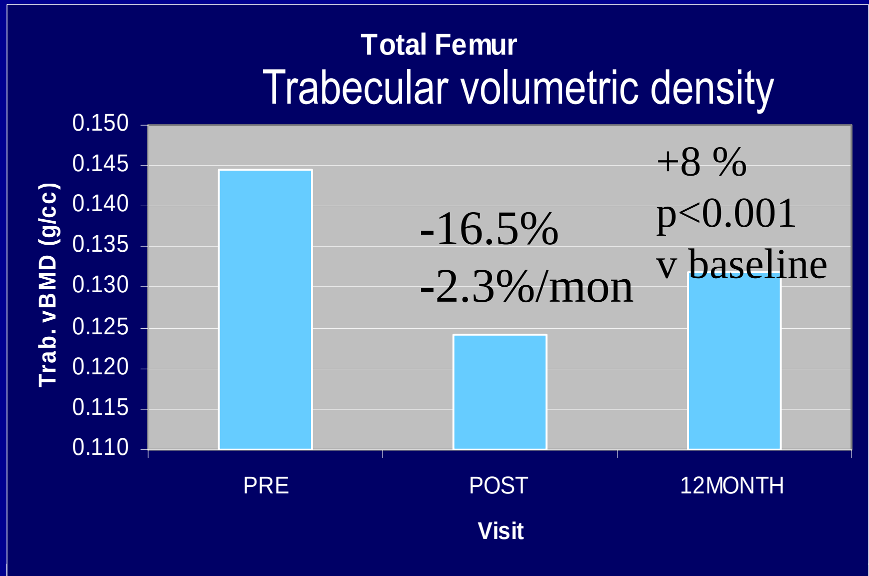
Stance Fall

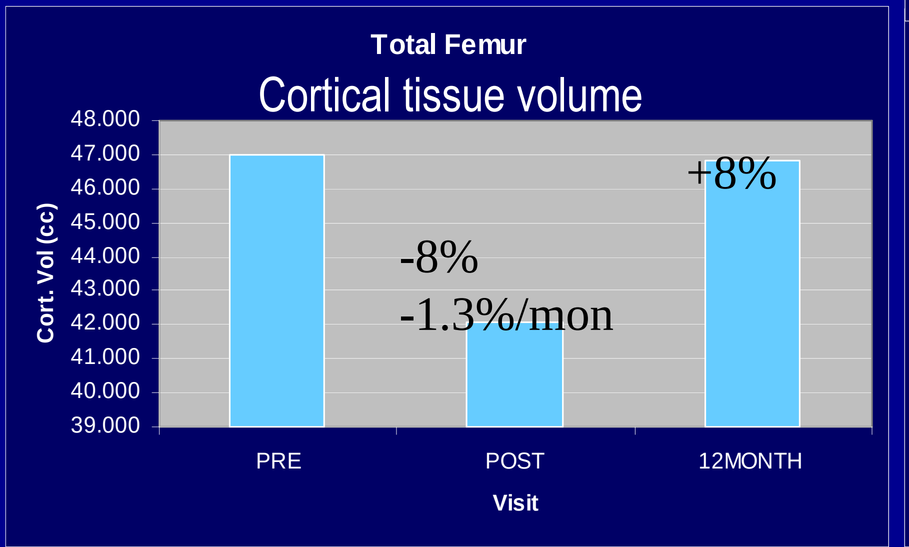
JH Keyak

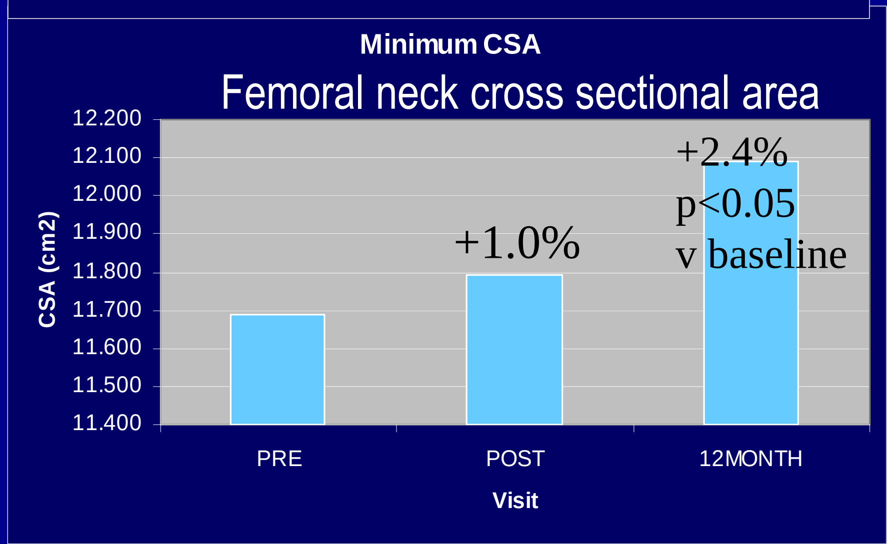
VQCT BONE LOSS RESULTS

Lang et al J Bone and Miner Research 2006



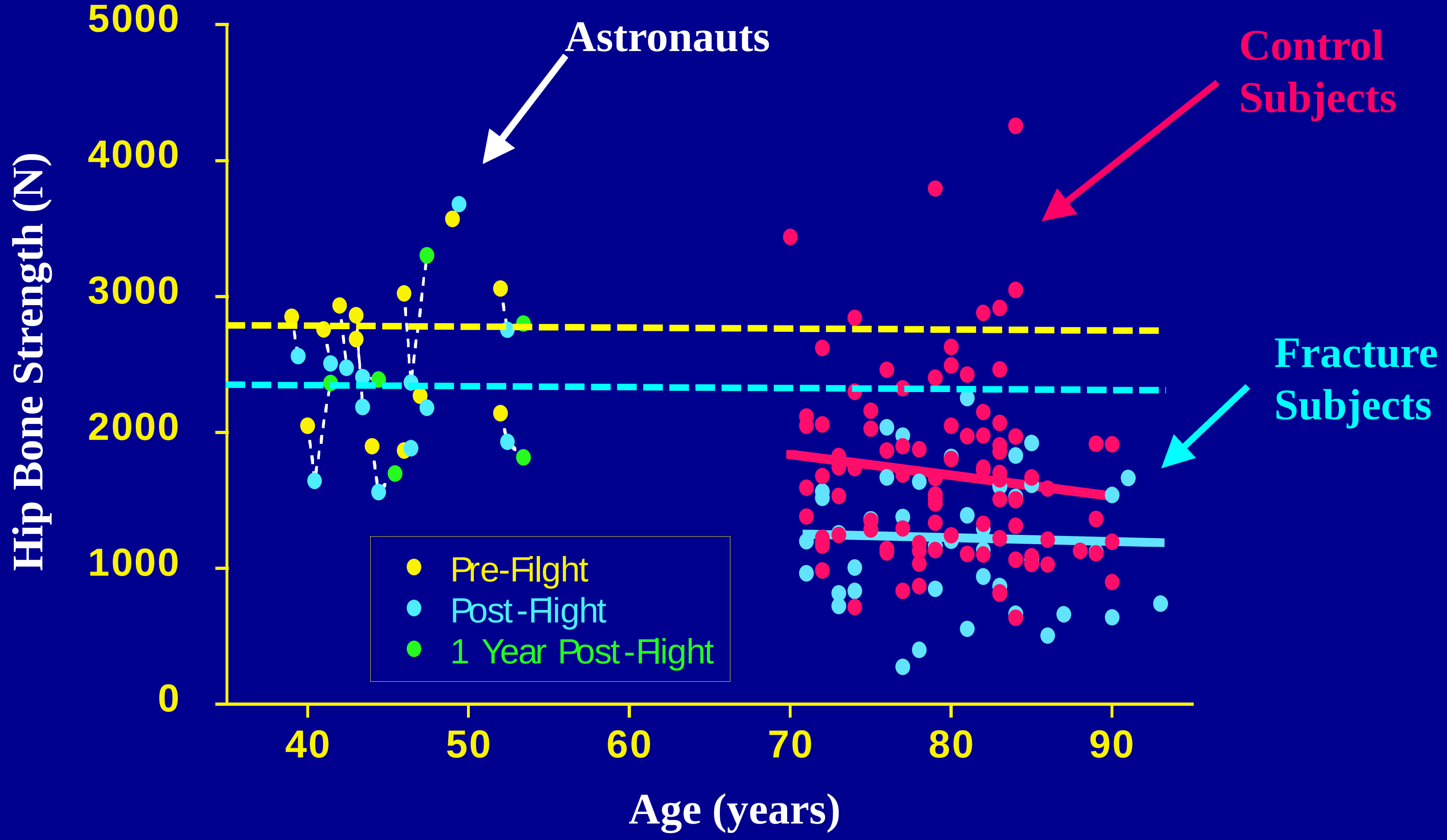






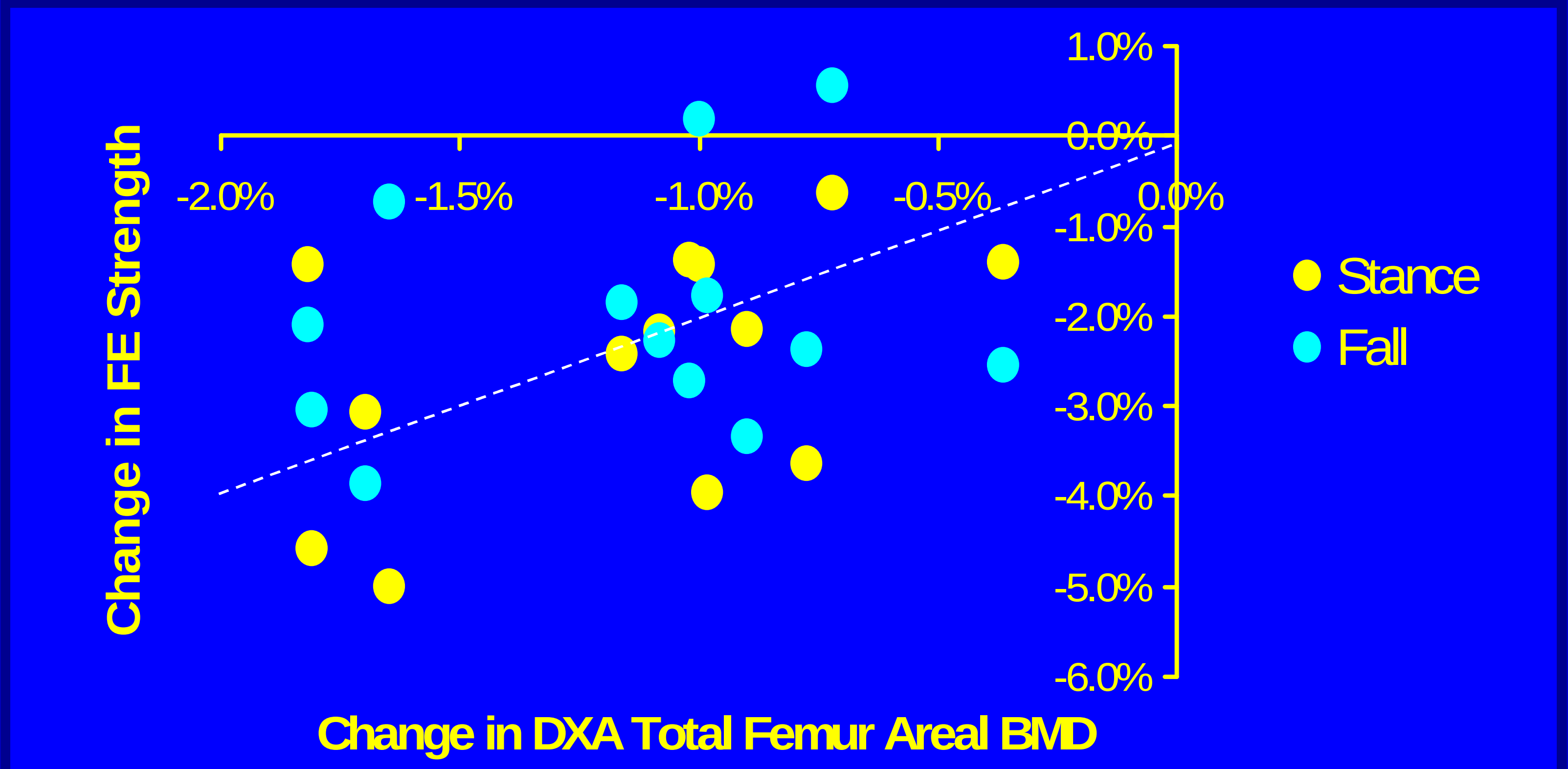
HIP BONE STRENGTH: FALL LOADING IN MEN

Joyce H. Keyak PhD



LOW CORRELATIONS BETWEEN DXA CHANGES AND HIP BONE STRENGTH CHANGES.

Per Month Decrease in FE Strength vs. DXA Areal BMD Stance, R^2=0.23 Fall, R^2=0.05



Joyce Keyak PhD

BONE LOSS MEASUREMENTS DISCUSSION

- Early ISS crews had experienced similar rates of bone loss to MIR crew
- Trabecular and cortical bone compartments changed at different rates
    - Trab bone loss >> cortical bone loss
- Recovery of bone mass comprises changes in bone structure
    - Increase in bone size
    - Impaired recovery of trabecular bone
    - Hip structure looks “older”
- Hip bone strength loss higher than predicted by DXA
    - Some individuals lost over 30% of their hip strength over the course of a 6 month mission.

PROBLEMS WITH COUNTERMEASURES: EARLY ISS MISSIONS

- Early crews used the interim resistive exercise device (iRED), a treadmill, and an exercise bicycle
  - For bone, crews carried out squats and deadlifts on the iRED
  - Treadmill running used tensioned loading devices to load subject on to treadmill with goal of 80% of body weight
- The iRED had limited modes of usage, variable load over range of motion, and a maximum load capacity of 297 lbs
- “Foot reaction forces in spaceflight” (PI: Peter Cavanagh)
  - 4 astronauts on mission wore leggings equipped with insole load measurement device to measure foot forces and estimate lower extremity loads
  - Foot forces in treadmill running were less than half those experienced on earth
  - In resistance exercise, loads on lower extremity ranged from 0.2-1.3 body weight
  - 30% of prescribed exercise time resulted in measureable loading
- Early ISS crews consumed 70-80% of their energy requirements, resulting in 5-10% loss of body weight

ADVANCED RESISTANCE EXERCISE/NUTRITION

Advanced Resistive Exercise Device (aRED) was launched to orbit in 2008

- 600 lb maximum load
- Constant load across range of motion
- Larger selection of motion

Exercise/Nutrition Countermeasure Study
Scott M Smith, PhD

Vitamin D dose of 800 IU/day

Food frequency questionaire (FFQ) was employed to record intake of basic dietary components: energy, protein, water, sodium, calcium, iron, and potassium.

Five subjects exercising on aRED, and having optimized nutritional intake were compared to 12 iRED exercisers and MIR cosmonauts

Bone density, body mass, lean mass, bone formation and resorption markers, and vitamin D levels were monitored

Benefits for Bone From Resistance Exercise and Nutrition in Long-Duration Spaceflight: Evidence From Biochemistry and Densitometry

Scott M Smith,[1] Martina A Heer,[2,3] Linda C Shackelford,[1] Jean D Sibonga,[1] Lori Ploutz-Snyder,[4] and Sara R Zwart[4]

J Bone and Miner Res 2012

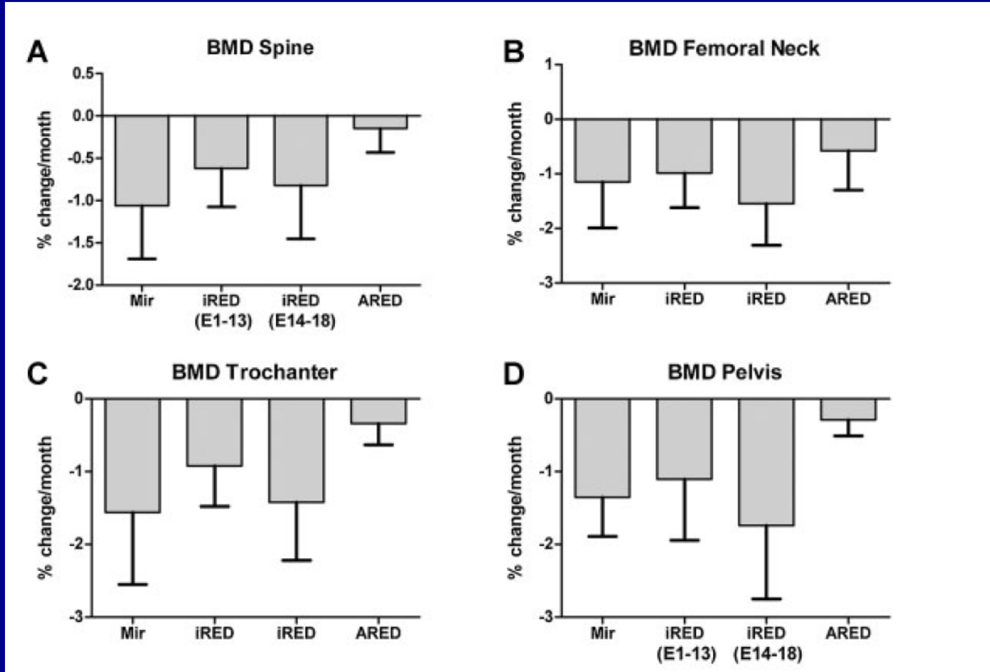
In 5 aRED exercisers, data suggest lower rate of bone loss than MIR or iRED

All groups showed increased rates of bone resorption

aRED exercisers returned with higher lean mass and lower fat mass

aRED users maintained higher energy intake, greater %required energy intake and higher intake of protein

Across all subjects, inflight energy and protein intake were inversely correlated with bone loss in hip and pelvis



Comparison of hip bone density changes in MIR crew, iRED users and aRED users

BISPHOSPHONATES AS A COUNTERMEASURE TO BONE LOSS

Bisphosphonates, such as alendronate (FOSAMAX™) have been used since the mid 90's to treat osteoporosis, showing 30-50% reduction of fracture rates

Bisphosphonates inhibit the action of osteoclasts that resorb bone and which show increased activity in disuse

Alendronate attenuated bone loss in a earlier bedrest study (LeBlanc et al, J Bone and Miner Research 1999)

NASA project to evaluate use of alendronate to reduce or prevent bone loss in ISS crew (PI: Adrian LeBlanc)

Seven ISS crew members from NASA and JAXA took 70 mg alendronate/wk starting 3 weeks prior to launch and continuing through flight. All subjects exercised on aRED

Subjects imaged with DXA and QCT pre and post-flight. QCT images analyzed with bone density and FEM software

Bisphosphonates as a supplement to exercise to protect bone during long-duration spaceflight

LeBlanc et al Osteoporosis Internat 2013

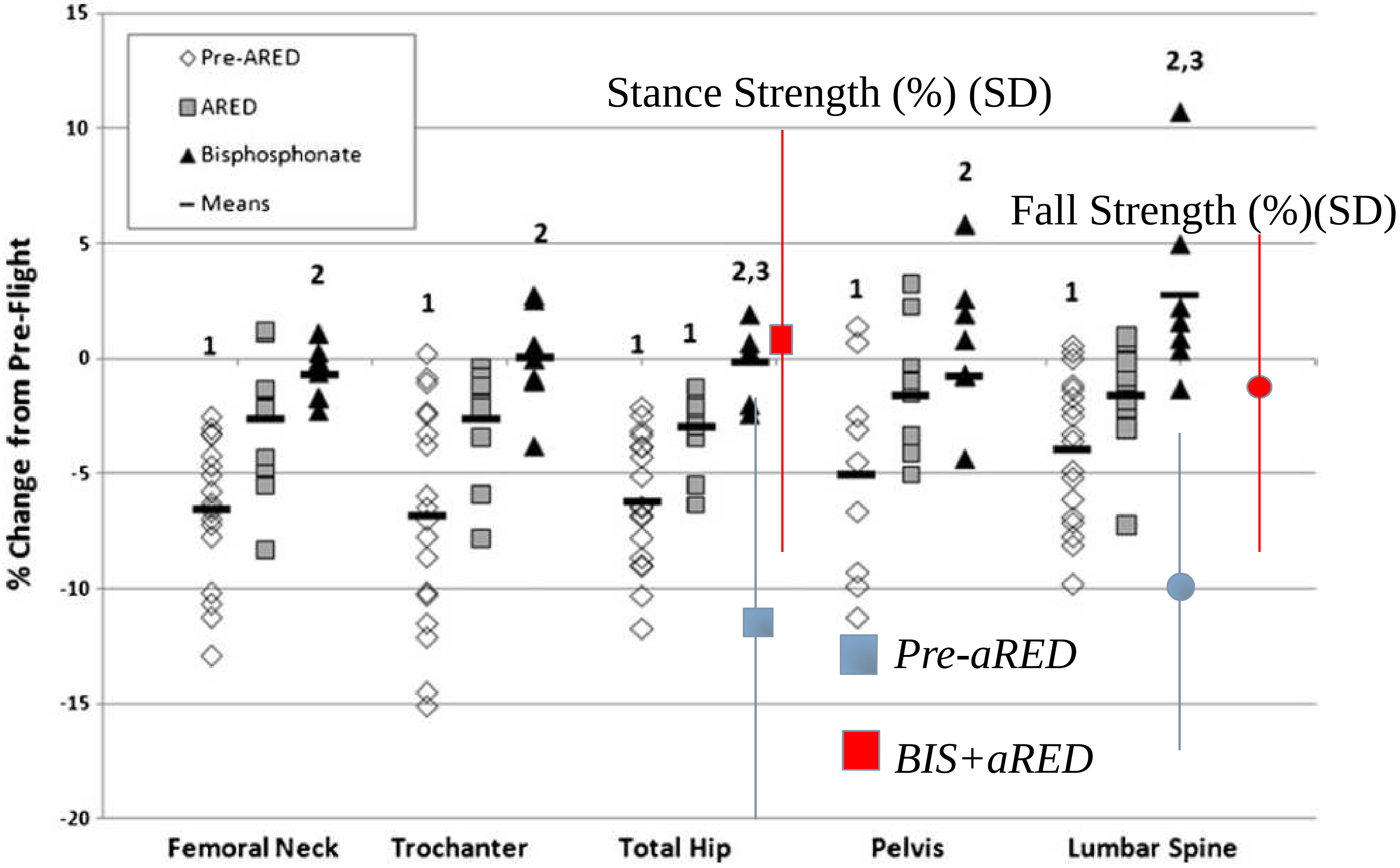


Fig. 1 Change in DXA BMD after long-duration space flight. *1* $p<0.05$, pre vs. post; *2* $p<0.05$ (bisphosphonate group significantly different from pre-ARED); *3* $p<0.05$ (bisphosphonate group significantly different from ARED). Pre-ARED ($n=18$); ARED ($n=11$); bisphosphonate ($n=7$)

COUNTERMEASURE KEY POINTS

- High intensity resistance exercise appears to reduce loss of bone density, although bone turnover is still elevated
- Data support importance of fulfilling required energy and protein intake for reducing bone loss
- Bisphosphonate study showed that even with aRED exercise, statistically significant hip bone loss occurs
- Alendronate, combined with aRED, prevented bone loss at the hip, as documented by DXA, QCT and FEM.
- Overall, data document that it is possible to prevent bone loss, mitigating changes in hip structure that may compromise bone health in later life

TRANSLATING FINDINGS TO MEDICAL OPERATIONS IN EXPLORATION ERA

- Smaller spacecraft and different mission profiles imply logistical constraints
- Optimal combination of drug and exercise to reduce drug dose and exercise dose
- Emerging osteoporosis medications may offer reduced gastrointestinal side effects compared to bisphosponates
- Combination of drugs and exercise to reduce loads and risk of injury
- Develop state of the art bone health standards that incorporate new quantitative methods such as Finite Element Modeling (Jean Sibonga, PhD)
    - Finite Element Cut Point Task Group: Panel of leading clinicians are helping to develop new guidelines for using QCT and FEM data to assist flight physicians in assessment of astronaut skeletal health
    - Evidence –based recommendations recently published in key bone journal (Orwoll et al, J Bone and Miner Res 2013)

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Bone Loss Studies (QCT/FEM)

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Countermeasure Studies

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