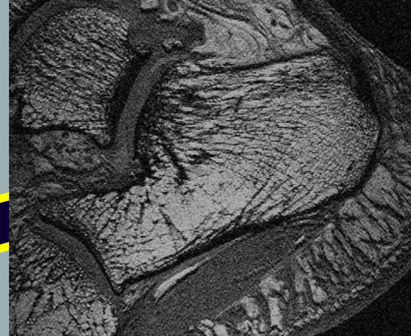
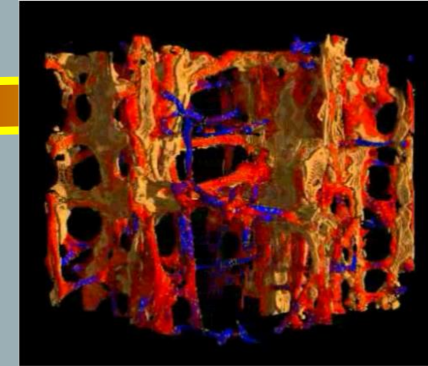
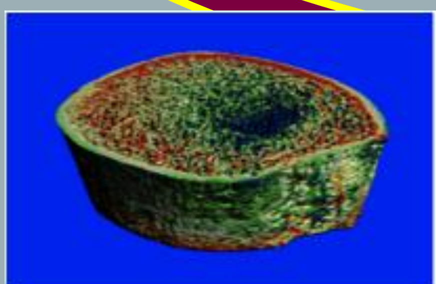




EVIDENCE REPORT: RISK OF EARLY ONSET OSTEOPOROSIS DUE TO SPACE FLIGHT



Sharmila Majumdar, PhD
Musculoskeletal and Quantitative Imaging Research Group
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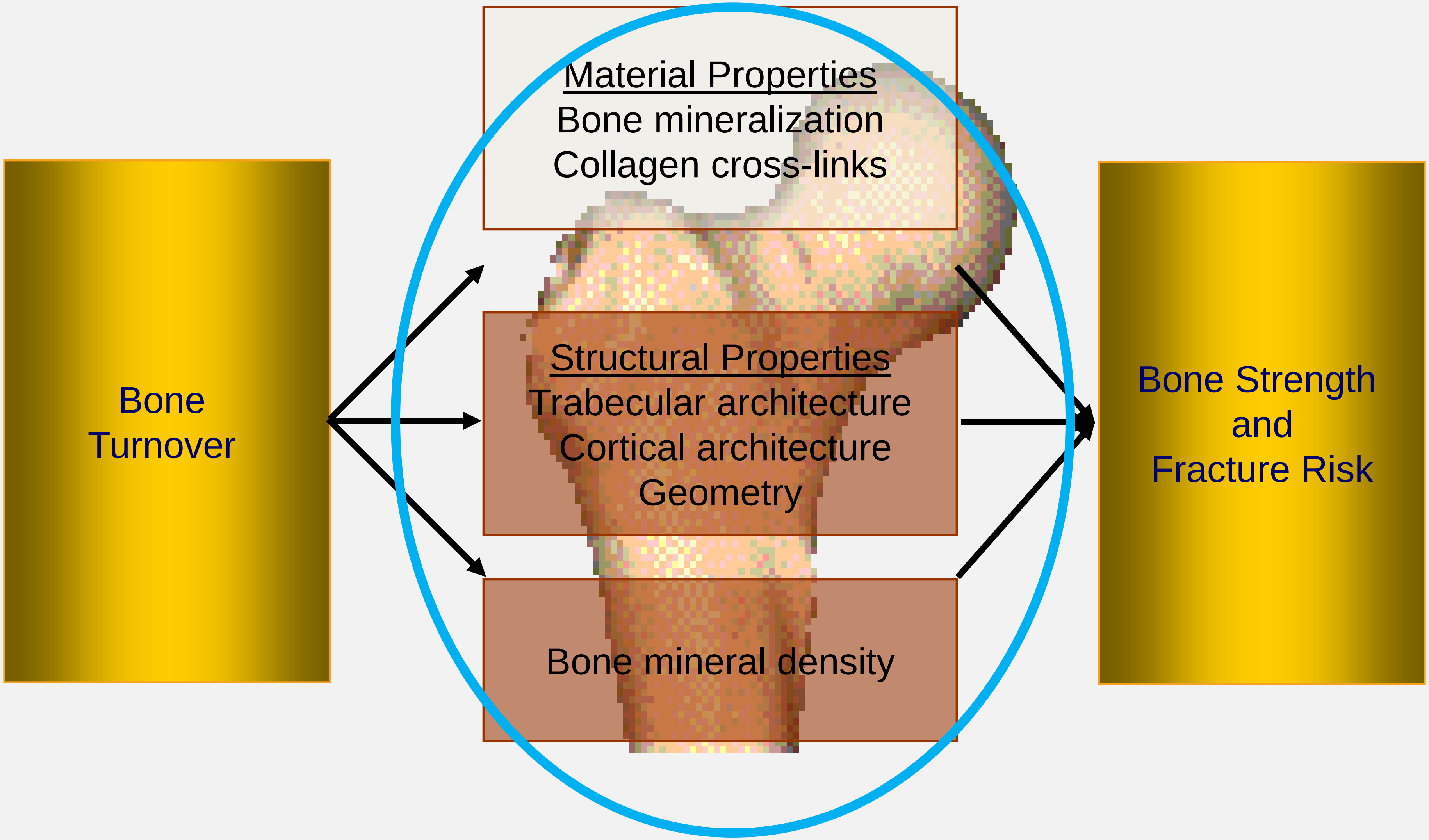
University of California, San Francisco, USA

BONE STRENGTH FRAMEWORK

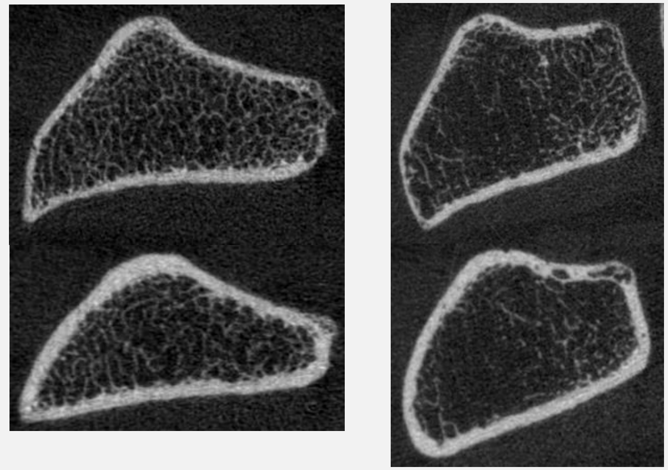


Adapted from Felsenberg D et al. Clin Ther. 2005;27:1–11.

HIGH-RESOLUTION PQCT

Scanco XtremeCT, 82µm voxels, ~3min scan, 3 µSv

Report is loud and clear: DXA has limitations, QCT, FEA provides additional information

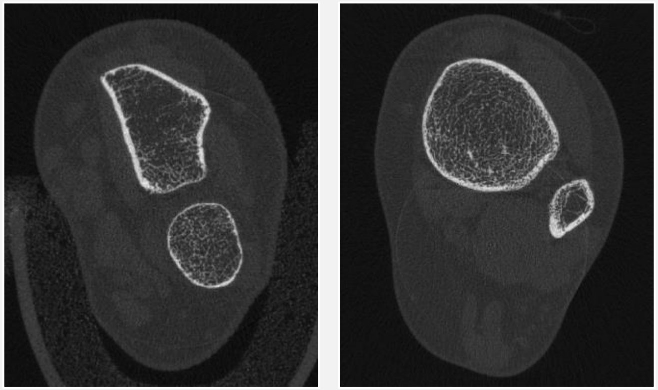


Both subjects: UD Radius BMD = 0.40

HRpQCT				
BV/TV		**0.13**	**0.08**	**54**
Tb.N	**(1/mm)**	**2.00**	**1.10**	**58**
Tb.Th	(mm)	0.07	0.07	4
Tb.Sp	**(mm)**	**0.43**	**0.84**	**64**
SD	**(mm)**	**0.18**	**0.56**	**104**
Ct.Th	(mm)	0.67	0.64	5
$vBMD_{tot}$	(mg/cc)	316	233	30
$vBMD_{cort}$	(mg/cc)	838	857	2
$vBMD_{trab}$	(mg/cc)	161	93	54
DXA BMD	(mg/cm^2)			
Spine		0.95	0.83	14
Femur Neck		0.66	0.60	11
Femur Troch		0.59	0.60	1
Femur Total		0.86	0.77	12
Radius UD		**0.40**	**0.40**	**0**
Radius 1/3		0.64	0.61	5

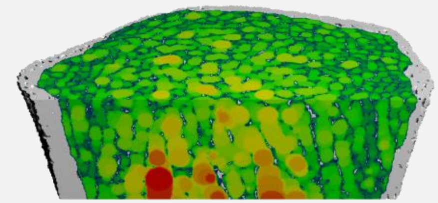
Journal of Bone and Mineral Research
Volume 23, Issue 4, pages 463-474, 26 NOV 2007 DOI: 10.1359/jbmr.071116

HR-PQCT IMAGE ANALYSIS



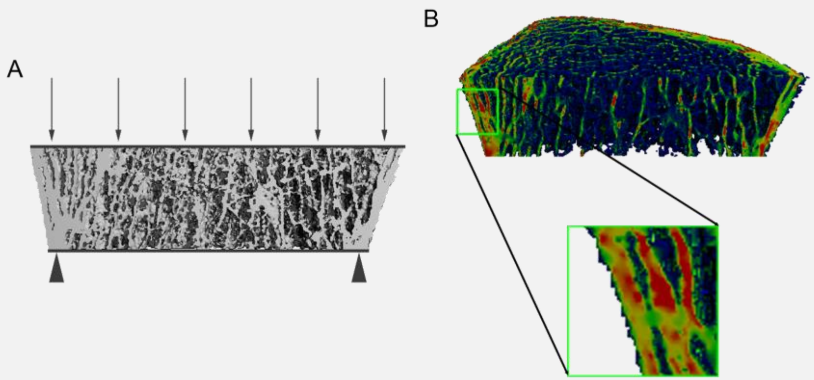
radius tibia

Scanco analysis



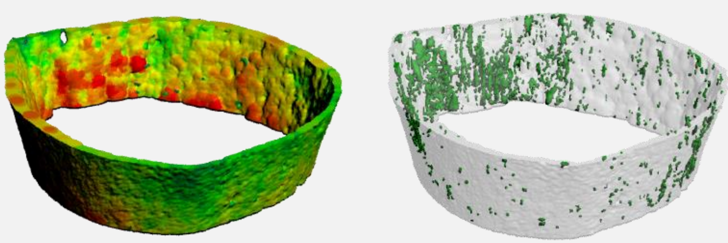
BMD, Ct.Ar, Tb.N

Linear Finite Element Analysis



Stiffness (K), Estimated Failure Load (F), Cortical Load Fraction (Ct.LF)

CRTX Analysis*

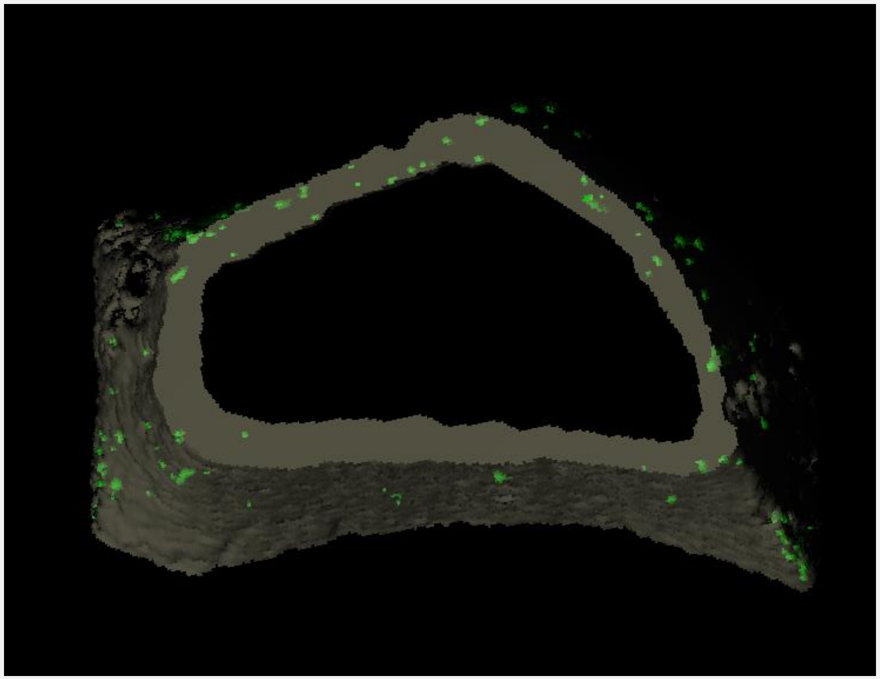


Ct.Th*, Ct.Po.V, Ct.Po

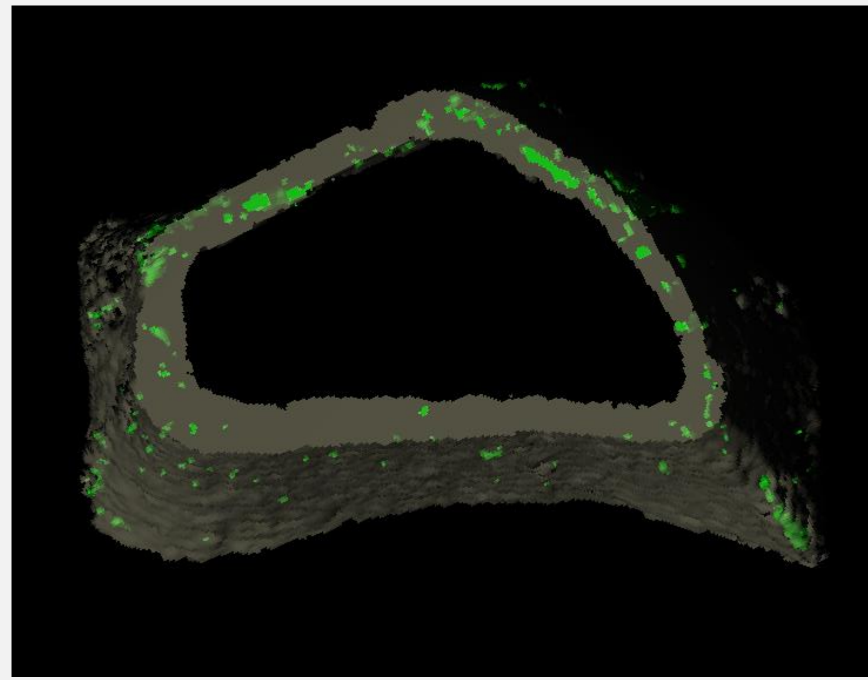
* Burghardt et al., Bone 2010

PROGRESSION OF INTRA-CORTICAL BONE LOSS

Baseline

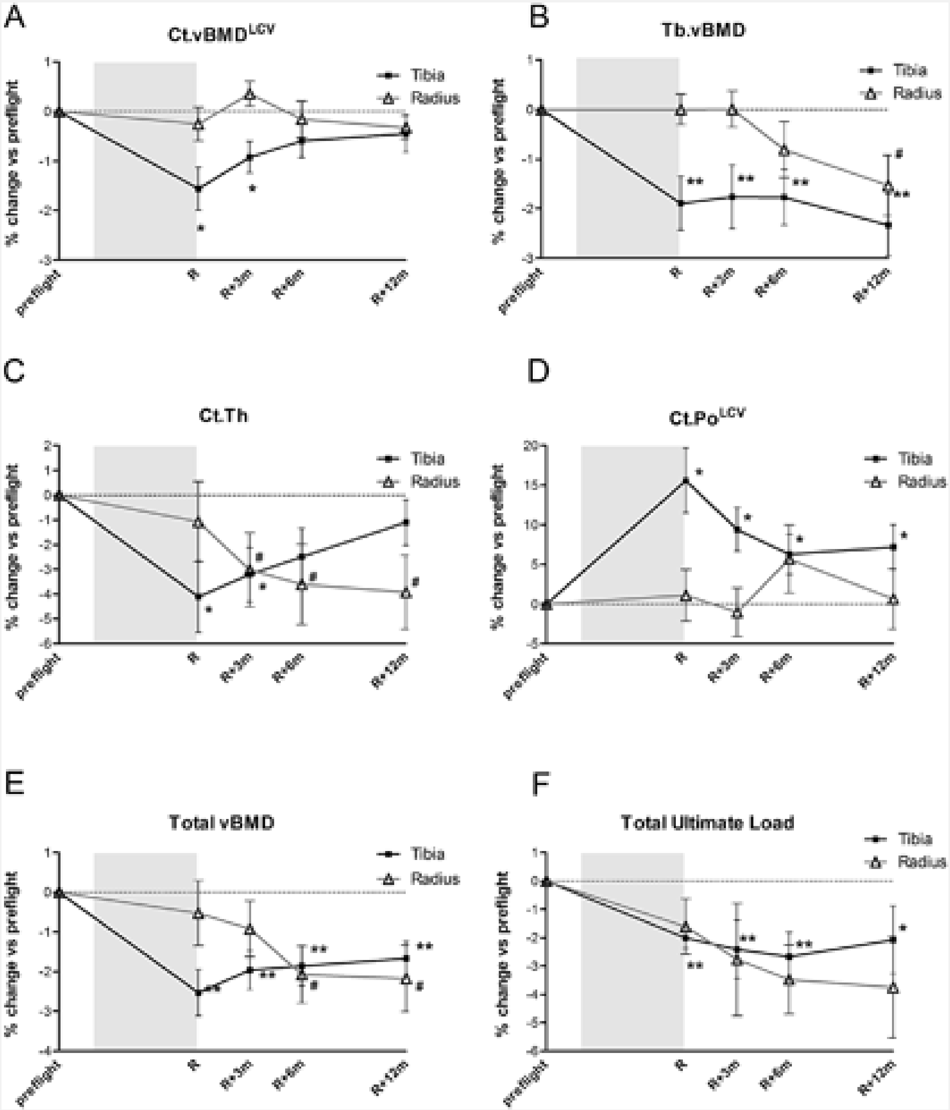


24-months



Ct.Po.V	➡	+156.6
Ct.Po.Dm	➡	%
Failure Load	➡	**-8.3 %**

CORTICAL AND TRABECULAR BONE MICROSTRUCTURE DID NOT RECOVER AT WEIGHT-BEARING SKELETAL SITES AND PROGRESSIVELY DETERIORATED AT NON-WEIGHT-BEARING SITES DURING THE YEAR FOLLOWING INTERNATIONAL SPACE STATION MISSIONS



In the distal tibia:

- cortical bone thickness and density eventually recovered
- cortical porosity and trabecular bone failed to recover
- leading to deficits in ultimate load

The distal radius:

- preserved at landing
- progressive fragility during the postflight follow-up

Bone remodeling markers:

- regained preflight levels within 6 months after landing
- declined to lower than preflight values between 6 and 12 months

Vico et. al. Journal of Bone and Mineral Research
28 JUN 2017 DOI: 10.1002/jbmr.3188

CORTICAL AND TRABECULAR BONE MICROSTRUCTURE DID NOT RECOVER AT WEIGHT-BEARING SKELETAL SITES AND PROGRESSIVELY DETERIORATED AT NON-WEIGHT-BEARING SITES DURING THE YEAR FOLLOWING INTERNATIONAL SPACE STATION MISSIONS

- Bone modifications and its' association with biochemical markers:
  - occur in a time-specific, site-specific and compartment-specific manner,
  - weight-bearing bones being the most affected.

- Crew members who practiced aerobic and resistance exercises for 2 hours daily using ARED + improved diet
  - attenuate bone loss (similar to DXA) compared to prior missions, but loss was not eliminated

- Bone deterioration - in space include ***irreversible features***
- Recovery follow-up after return to Earth vary based on loading, and the effect of cumulative exposures warrants further evaluation

Journal of Bone and Mineral Research
28 JUN 2017 DOI: 10.1002/jbmr.3188

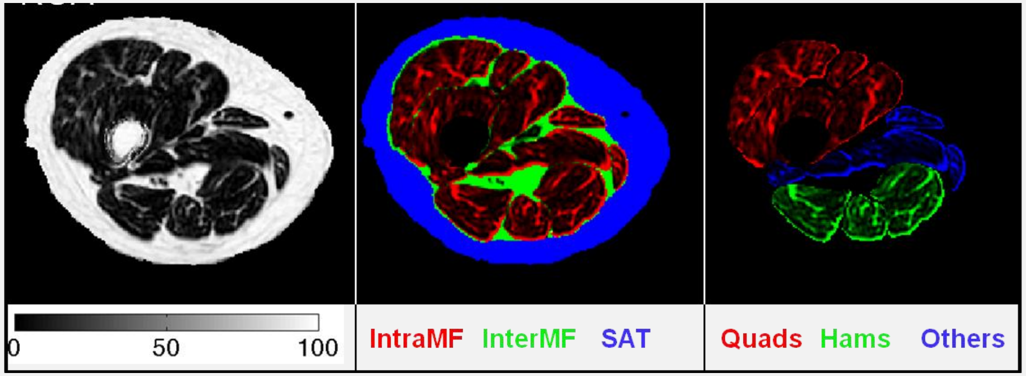
REPLACEMENT OF DAILY LOAD ATTENUATES BUT DOES NOT PREVENT CHANGES TO THE MUSCULOSKELETAL SYSTEM DURING BED REST. CAVANAGH ET. AL. BONE REPORTS, 2016

- Subjects were confined to 6-degree head-down bed rest for 84 days
- The exercise group performed individually prescribed 1 g loaded locomotor exercise to replace their free-living daily load.
- Pre-and post-bed rest muscle volumes – MR:
  - Exercise group lost - 7.2% ± 5.9 and - 13.8% ± 6.1 compared to control - 23.3% ± 5.9 and - 33.0 ± 8.2 in total quadriceps and gastrocnemius muscle volume.
- Both groups significantly lost strength in several measured activities ($p < 0.05$).
- The declines in peak torque during repeated exertions of knee flexion and knee extension were significantly less in the exercise group than in the control group ($p < 0.05$).

PROLONGED SPACE FLIGHT-INDUCED ALTERATIONS IN THE STRUCTURE AND FUNCTION OF HUMAN SKELETAL MUSCLE FIBRES. FITTS ET. AL. J. PHYSIOL. 2010

- Fibre atrophy - 20% in the soleus type I fibres - contributor to the loss of peak force < 35%.
- Exercise countermeasures - incapable of providing high intensity to adequately protect fibre and muscle mass; ability to perform strenuous exercise compromised?

MUSCLE CHANGES IN SPACE-FLIGHTS
THE MUSCLE-BONE CONNECTION



- Mean isokinetic strength declined 8-17% following spaceflight
- One month after return to Earth, strength had improved, but small deficits of 1-9% persisted.
- Mean strength losses were as much as 7% less in crewmembers who flew after the Advanced Resistive Exercise Device (ARED) but we not eliminated.
- MR measures showed:
  - Size of most muscle regions significantly decreased 3–10% compared with baseline
  - These changes were reversed within 30–60 days after landing.
  - Post-flight swelling and elevation of calf muscle transverse relaxation time persisted for several weeks after flight, which suggests possible muscle damage or fatty infiltration.

Isokinetic Strength Changes Following Long-Duration Spaceflight on the ISS.
English KL, Lee SM, Loehr JA, Ploutz-Snyder RJ, Ploutz-Snyder LL.
Aerosp Med Hum Perform. 2015 Dec;86(12 Suppl):A68-77
Muscle volume, MRI relaxation times (T2), and body composition after spaceflight.
LeBlanc A, Lin C, Shackelford L, Sinitsyn V, Evans H, Belichenko O, Schenkman B, Kozlovskaya I, Oganov V, Bakulin A, Hedrick T, Feeback D.
J Appl Physiol (1985). 2000 Dec;89(6):2158-64

OSTEOSARCOPENIA: WHERE BONE, MUSCLE, AND FAT COLLIDE. H. P. HIRSCHFELD, ET. AL. OSTEO. INTER. 2017

- Basic and clinical research suggests a “crosstalk” between the two tissues, with fat being a major player that affects this interaction.
- The musculoskeletal unit interacts mechanically and physically but also biochemically via paracrine and endocrine communication.

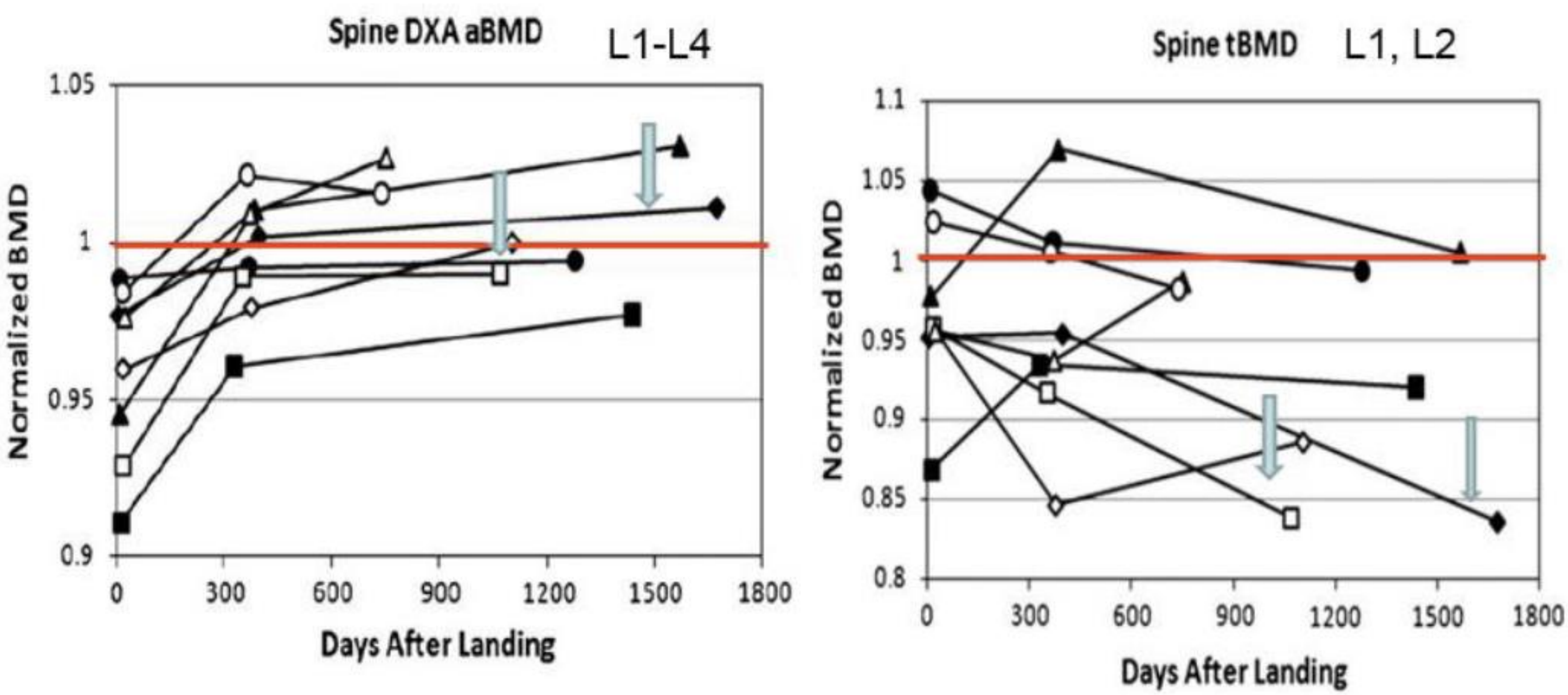
MUSCLE STRENGTH IS PROTECTIVE AGAINST OSTEOPOROSIS IN AN ETHNICALLY SAMPLE OF ADULTS. MCGRATH ET. AL. J STRENGTH COND RES. 2017 JUN 22.

- Increased muscle strength reduced the odds of osteoporosis among both males and females in a nationally-representative, ethnically diverse sample of adults.

FURTHER RESEARCH WARRANTED

Report covers the disadvantages of DXA, inclusion of QCT and FEA, (Fig. 13a report).

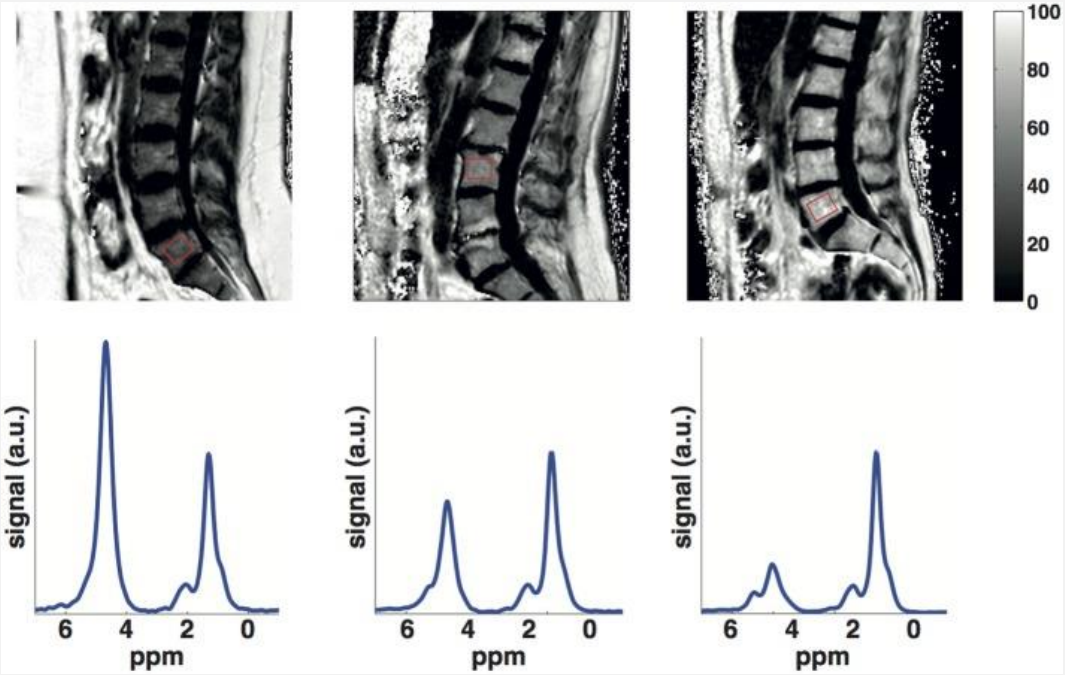
- **Response to technical issues per Tony Keaveny: NASA QCT data on older scanner: Yes. The precision of <1% forBMD, many teretsrial studies done on the same platform, FEA precision 3-4%. Fig. 13a shows very large changes that do not recover post flight).**



FURTHER RESEARCH WARRANTED

- **Additional thoughts:**
- Cortical and trabecular bone, structure and strength loss, recovery in all parts of the skeleton.
- Counter-measures provide some mitigation, but not fully.
  - Many open questions regarding, frequency of exercise, dosing, injury to muscle, muscle response due to changes?
  - Anti-resorptive therapies in space - do they work in the same way.
- Muscle/bone connection remains to be evaluated.
  - Fiber changes?
- Radiation induce bone/muscle changes.

FURTHER RESEARCH WARRANTED



- Bone/bone marrow (cellular changes) (MR and CT)
  - Fat fraction increases (+2.5, $p<0.05$), persists after 1 year in vertebrae women in space.
  - Rats in space had 32% < trabecular bone area; 306% > marrow fat. Bone formation spaceflight was insufficient to balance increased resorption - defective coupling.
  - hypothesis - spaceflight mesenchymal stem cells are diverted to adipocytes at the expense of forming osteoblasts.

Trudel G, et. al. J Appl Physiol (1985). 2009 Aug.
Keune JA, et. al. NPJ Microgravity. 2016 Apr 28.

RESPONSES TO QUESTIONS POSED

- How well is the risk understood? What, if any, are the major sources of disagreement in the literature pertaining to this risk?
- Does the evidence report provide sufficient evidence, as well as sufficient risk context, that the risk is of concern for long-term space missions?
- Does the evidence report provide evidence that the named gaps are the most critical presented?
- Are there any additional gaps or aspects of existing gaps that are not addressed for this specific risk?
  - Technologies beyond QCT, FEA, for cortical and trabecular micro-architecture
  - Multi-tissue interactions
- Does the evidence report address relevant interactions among risks?
  - Muscle-bone, bone marrow-bone, nutritional imbalance and bone, radiation and bone, cartilage, ligaments, disc, - bone and fracture
- Is the breadth of the cited literature sufficient?