National Aeronautics and Space Administration
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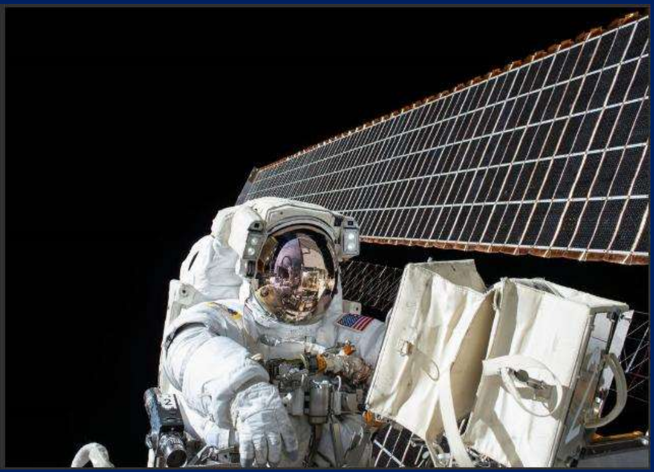
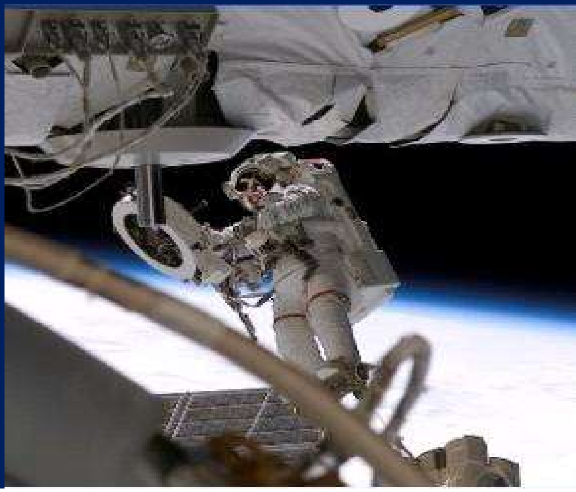
Skeletal Effects of Long-duration Spaceflight

Jean Sibonga, Ph.D.
NASA Johnson Space Center

Bone Health TeleECHO
October 6, 2020





Disclosures: NONE

Objectives

1. Describe the current surveillance program for skeletal health in l*ong-duration* astronauts.

2. Describe the effects of long-duration spaceflight on bone densitometry and bone turnover.

Slide concept courtesy of S. Amin

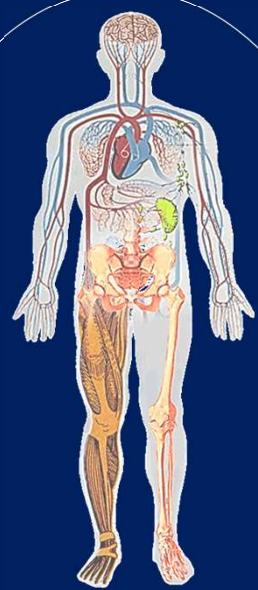
Considerations for Health & Performance Risks

Altered Gravity - Physiological Changes

Spaceflight Associated Neuro-ocular Syndrome (SANS)
Balance Disorders
Fluid Shifts
Cardiovascular Deconditioning
Muscle Atrophy
Bone Loss

Space Radiation

Acute In-flight effects (controlled by vehicle design and operational constraints)
Long term cancer risk



Integrated Human Performance

Distance from Earth

Drives the need for additional "autonomous" medical care capacity – cannot come home for treatment

Hostile/ Closed Environment

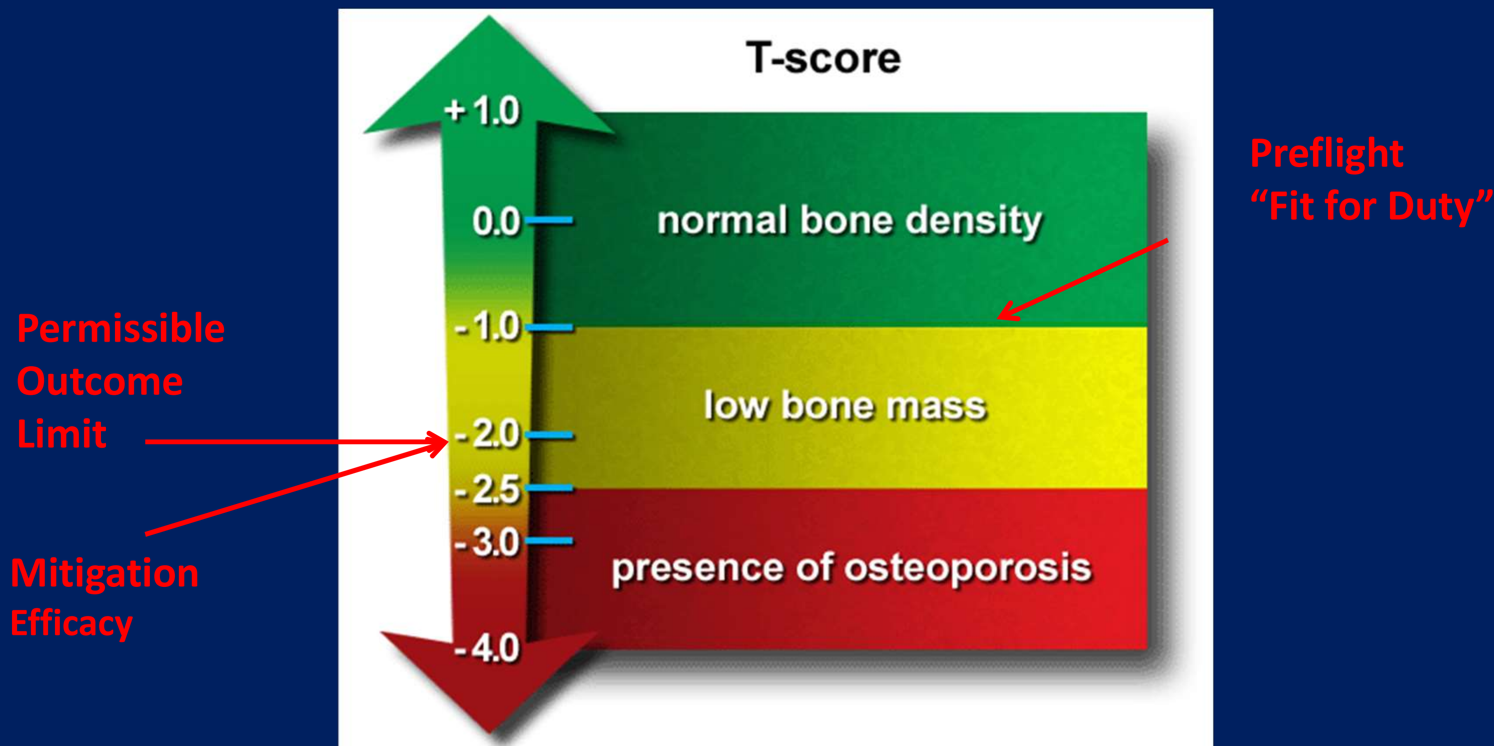
Vehicle Design
Environmental – CO_2 Levels, Toxic Exposures, Water, Nutrition/Food
Decreased Immune Function,
Microbiome Changes

Isolation & Confinement

Behavioral aspect of isolation
Sleep disorders/Team Interactions

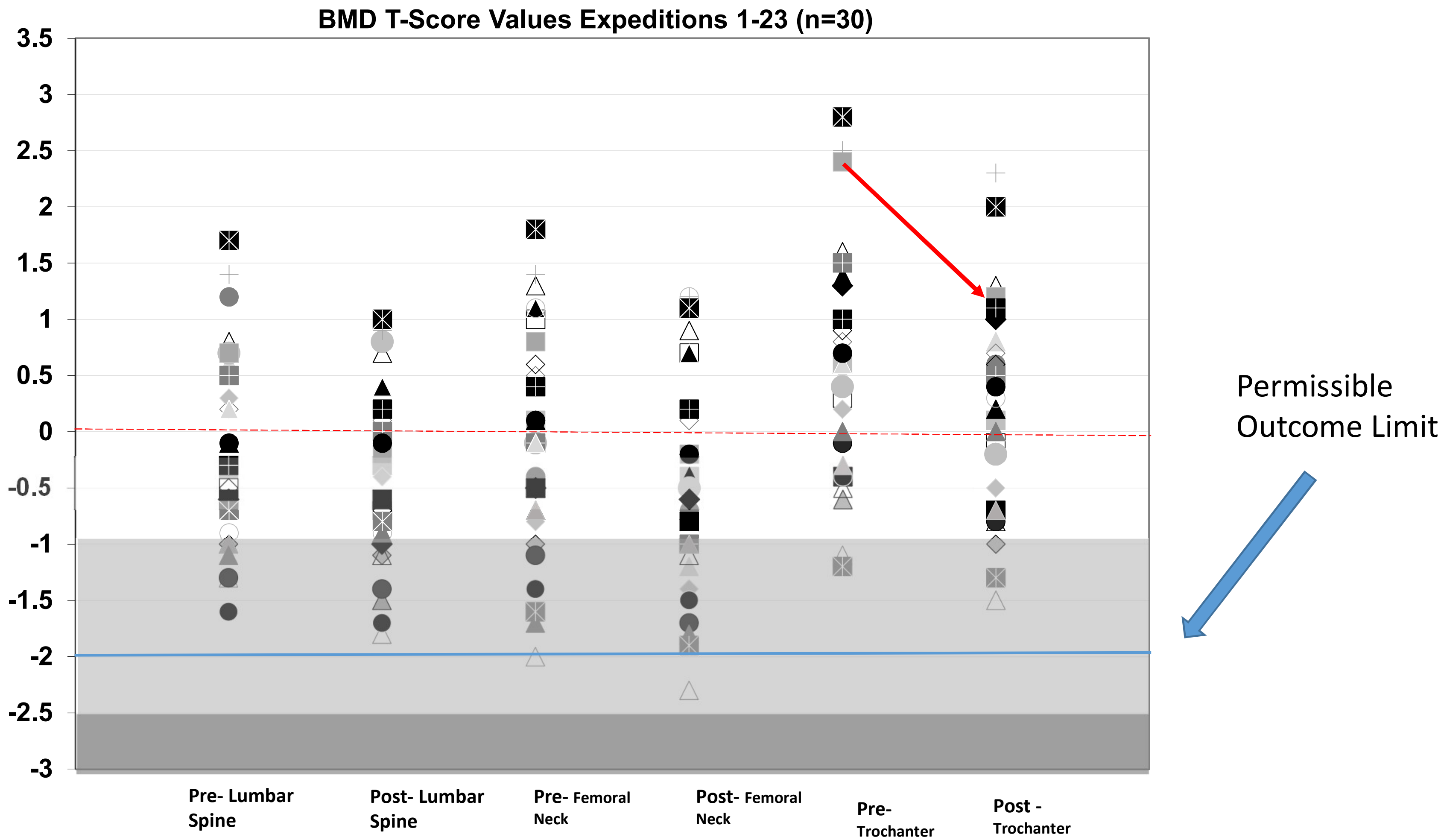
Slide courtesy E Romero; Adapted by Sibonga

NASA's Standards for Astronaut Skeletal Health. Adapting the Clinical Guidelines for Osteoporosis to set "Operating Bands."



*T-score is # Standard Deviations from mean BMD of young normal "peak bone mass"

Preflight and Postflight T-scores* Reported to Operational Medicine for LONG-Duration Astronauts



ISO, New Orleans, 2018

History: Percent change in DXA BMD as measured in cosmonauts. BMD losses are site-specific and rapid.

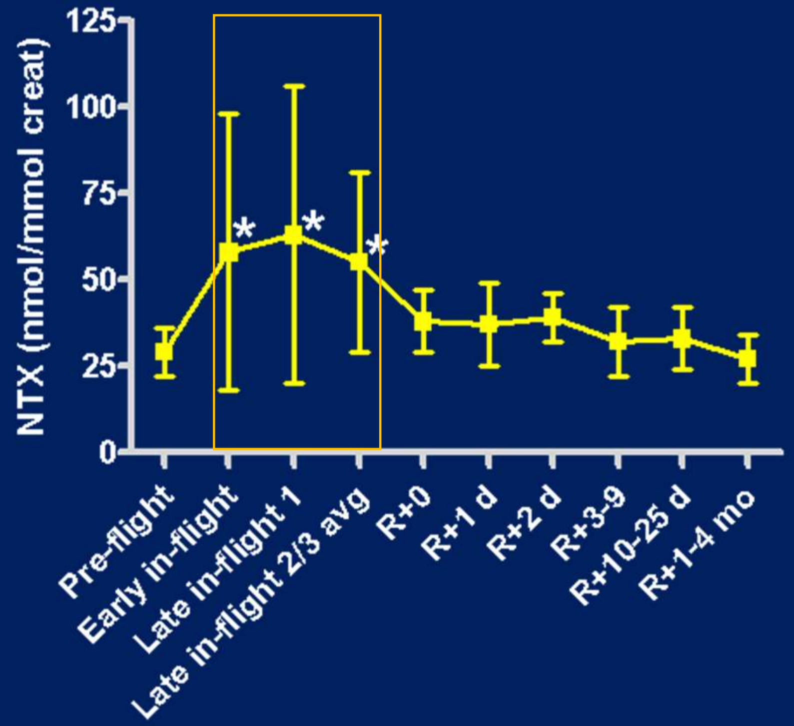
(vs. 0.5 – 1.0 % BMD loss/year in the aged)

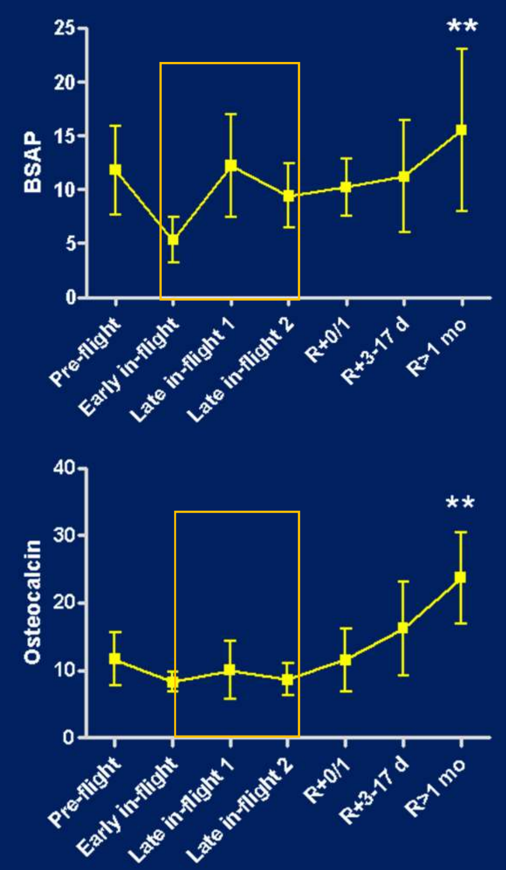
Areal BMD g/cm²	%/Month Change ± SD
Lumbar Spine	-1.06±0.63*
Femoral Neck	-1.15±0.84*
Trochanter	-1.56±0.99*
Total Body	-0.35±0.25*
Pelvis	-1.35±0.54*
Arm	-0.04±0.88
Leg	-0.34±0.33*
*p<0.01, n=16-18	

LeBlanc et al, J Musculoskeletal 2000

Bone Turnover Biomarkers

Suggest uncoupled bone remodeling in space => net bone loss

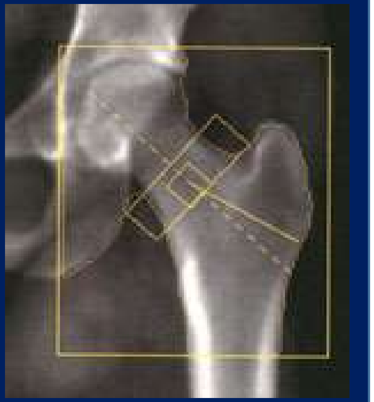




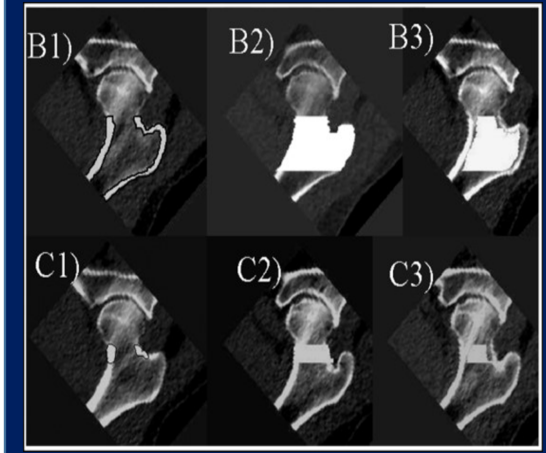
(Smith et al, JBMR 2005); adapted by Sibonga

(Mir Space Craft 1995-1998)

Research: QCT detects changes in separate cortical and trabecular bone due to spaceflight that DXA cannot detect (n=16) .

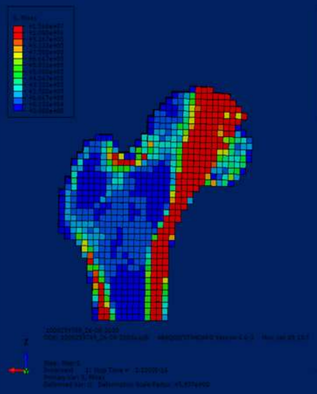


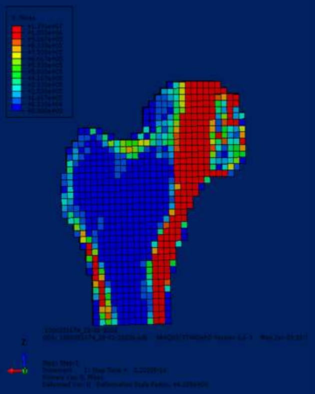
Index DXA	%/Month Change ± SD	Index QCT	%/Month Change ± SD
aBMD Lumbar Spine	1.06±0.63*	Integral vBMD Lumbar Spine	0.9±0.5
		Trabecular vBMD Lumbar Spine	0.7±0.6
aBMD Femoral Neck	1.15±0.84*	Integral vBMD Femoral Neck	1.2±0.7
		Trabecular vBMD Femoral Neck	2.7±1.9
aBMD Trochanter	1.56±0.99*	Integral vBMD Trochanter	1.5+0.9
*p<0.01, n=16-18		Trabecular vBMD Trochanter	2.2+0.9



LeBlanc, J M Neuron Interact, 2000;
Lang , J Bone Miner Res, 2004;
Vico, The Lancet 2000

Research: Finite Element Models from QCT data to estimate the "load capacity" of the hip in response to spaceflight.

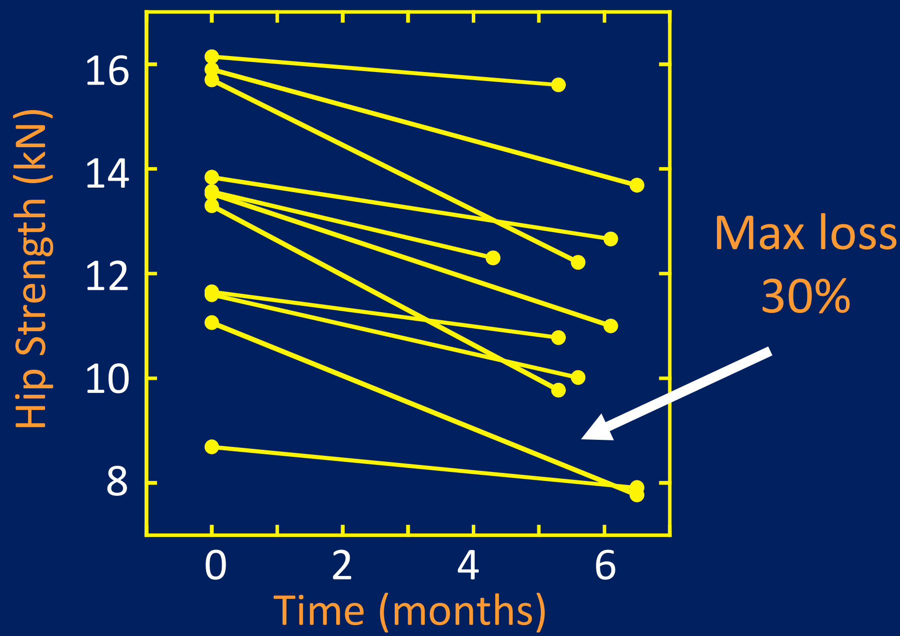




J. Keyak et al, 1998, 2001, 2005
Images courtesy of Dr. J Keyak

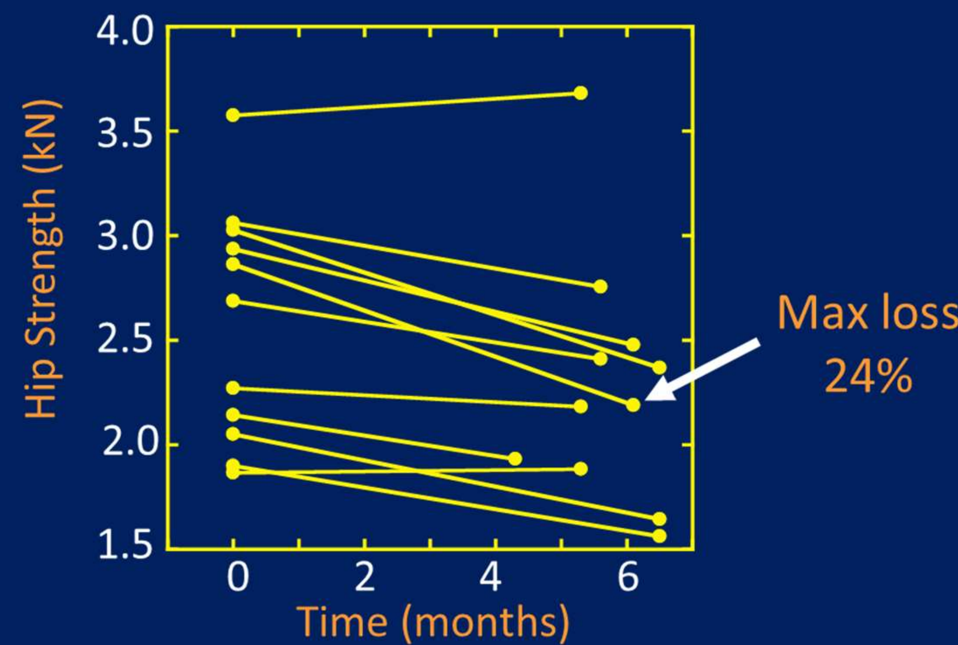
Individual Astronaut Results

Stance Loading (4 to 30% loss)



PreMean	Post Mean	P
13,200 N (2300 N)	11,200 N (2400 N)	<0.001

Fall Loading (3% gain to 24% loss)



Pre Mean	Post mean	P <
2,580 N (560 N)	2,280 N (590 N)	0.003

Keyak, Bone 2009

What does this all mean in terms of risk to human health & performance?

Bone Summit 2010 - Solicited opinions of experts in Osteoporosis & Bone Densitometry

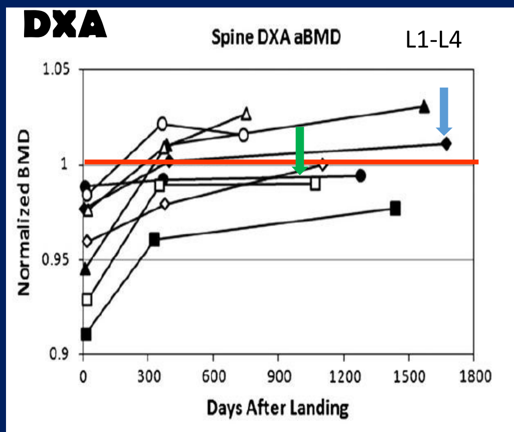
REVIEW

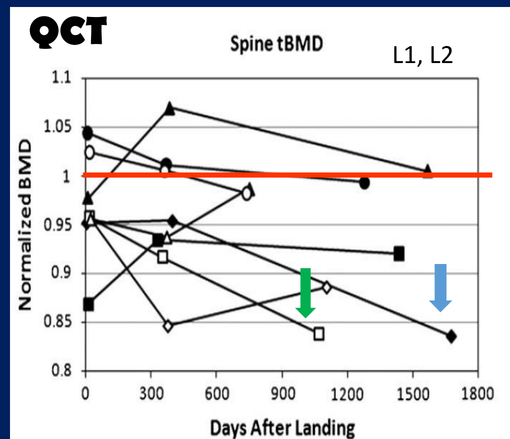
JBMR

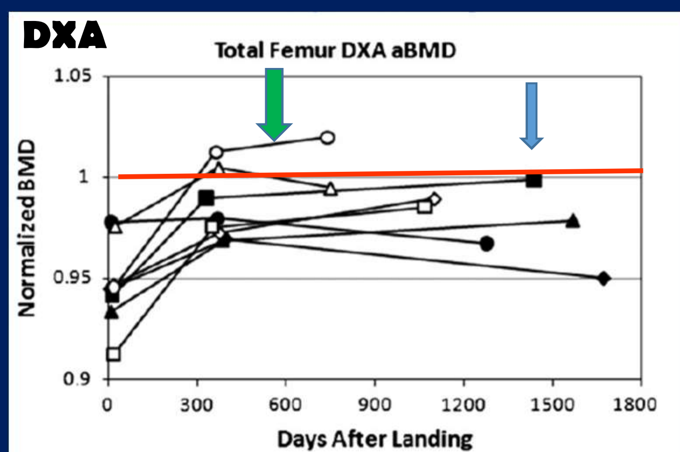
Skeletal Health in Long-Duration Astronauts: Nature, Assessment, and Management Recommendations from the NASA Bone Summit

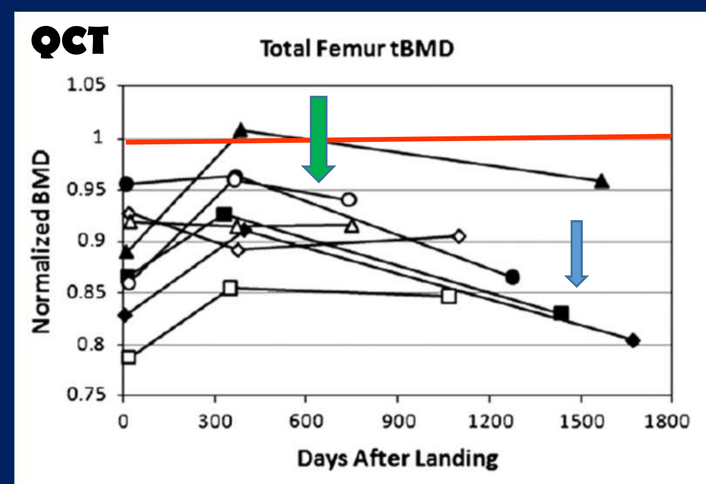
Eric S Orwoll,[1] Robert A Adler,[2] Shreyasee Amin,[3] Neil Binkley,[4] E Michael Lewiecki,[5] Steven M Petak,[6] Sue A Shapses,[7] Mehrsheed Sinaki,[8] Nelson B Watts,[9] and Jean D Sibonga[10]

Discordant recovery patterns after spaceflight between DXA vs. QCT in 8 ISS astronauts => a "clinical trigger." *Rejected*









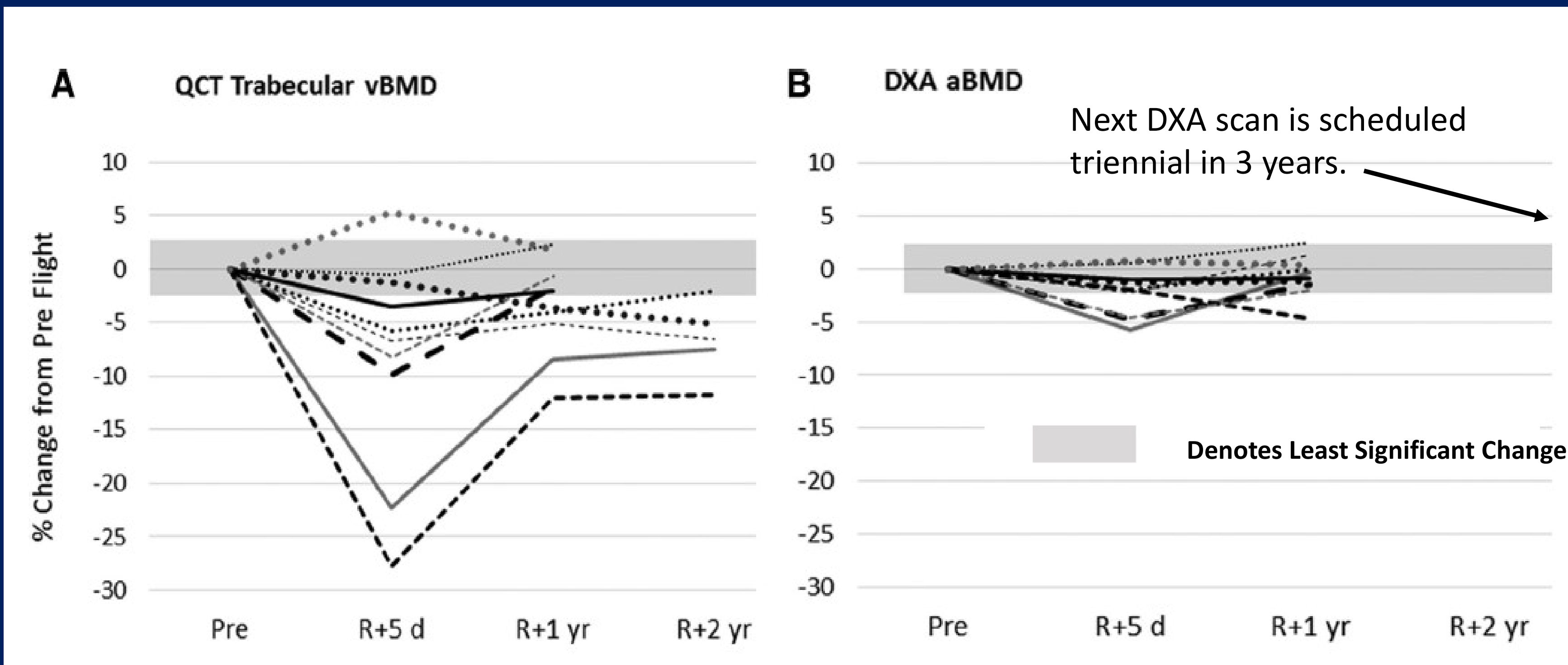
Carpenter, D et al. Acta Astronautica, 2010. Adapted by Sibonga

A pilot study to support inclusion of Hip qCT scans.

* Sibonga et al., J Clinical Densitometry 2019.

Use of Quantitative Computed Tomography to Assess for Clinically-relevant Skeletal Effects of Prolonged Spaceflight on Astronaut Hips

Jean D. Sibonga,[1] Elisabeth R. Spector,[2] Joyce H. Keyak,[3] Sara R. Zwart,[4] Scott M. Smith,[1] and Thomas F. Lang[5]*



Bisphosphonates vs. Resistive Exercise

2110 Osteoporos Int (2013) 24:2105–2114

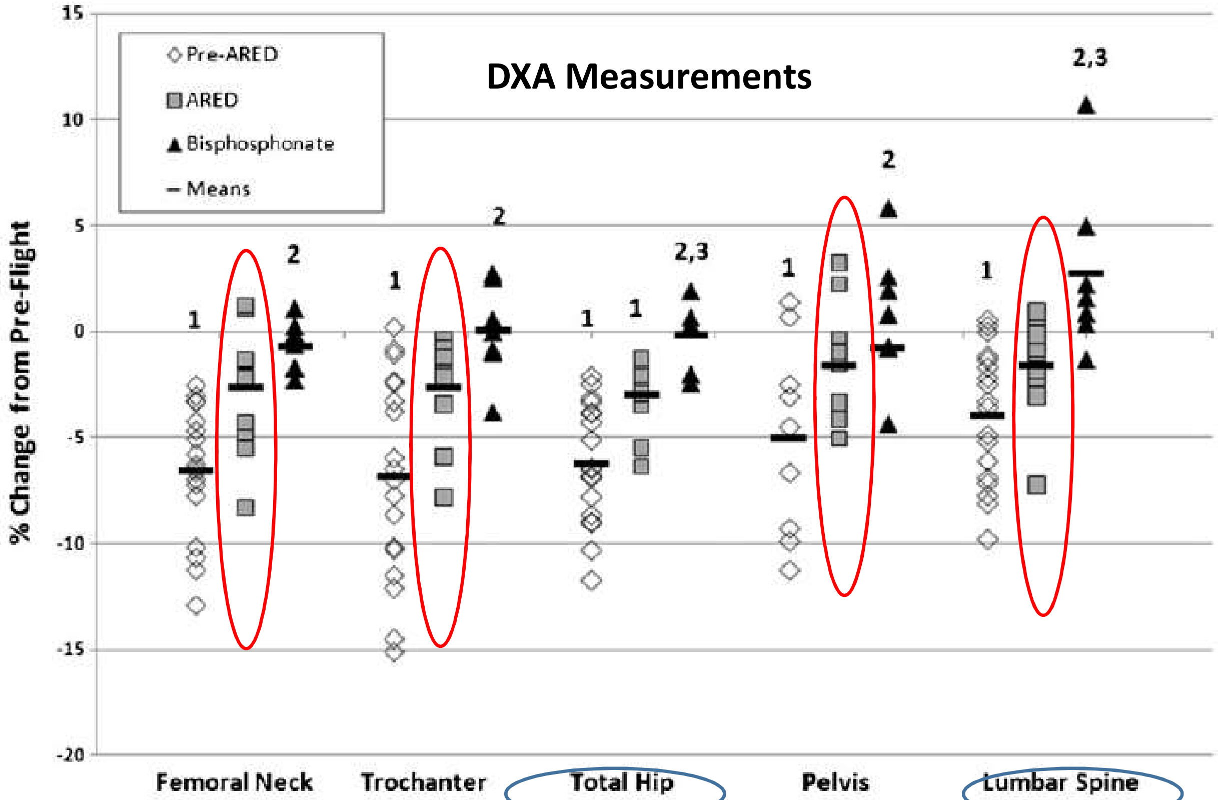
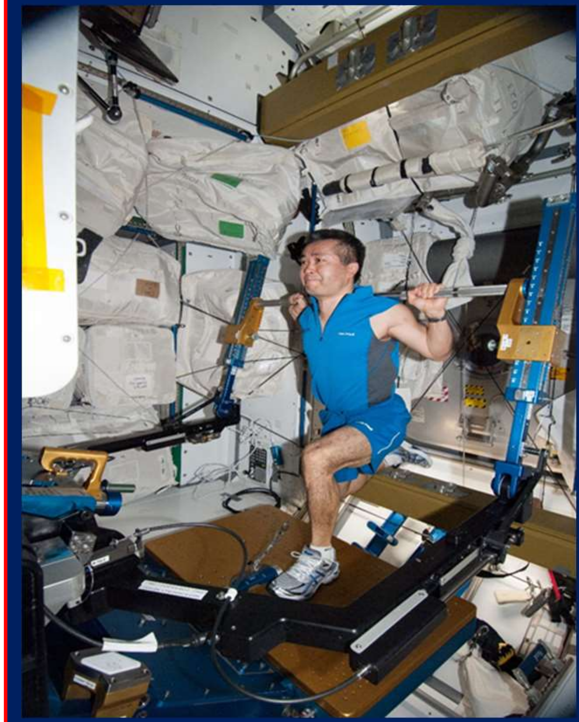
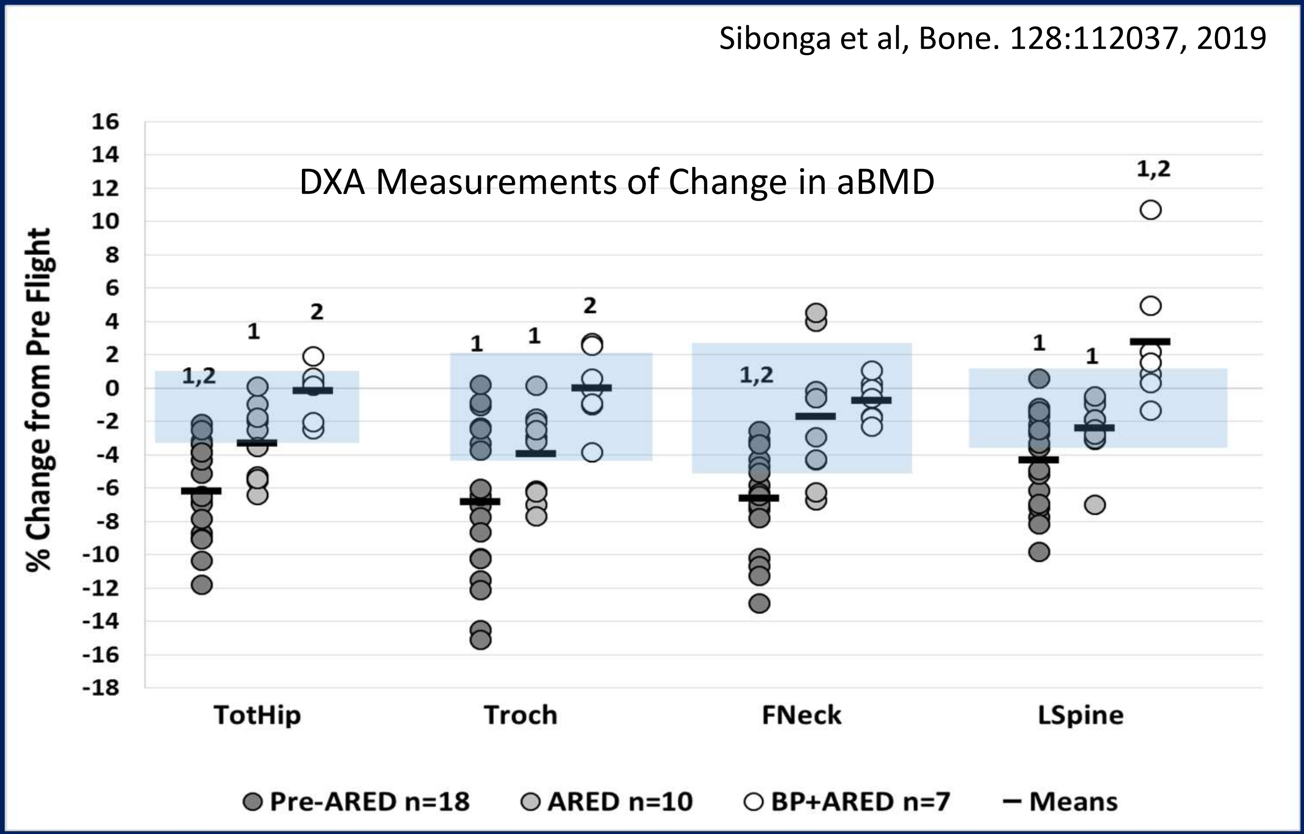


Fig. 1 Change in DXA BMD after long-duration space flight. *1* $p<0.05$, pre vs. post; *2* $p<0.05$ (bisphosphonate group significantly different from pre-ARED); *3* $p<0.05$ (bisphosphonate group significantly different from ARED). Pre-ARED ($n=18$); ARED ($n=11$); bisphosphonate ($n=7$)



ARED: Advanced Resistive Exercise Device

Extended flight study: addition of BP to ARED preserves more astronauts at preflight DXA measurement than ARED alone.



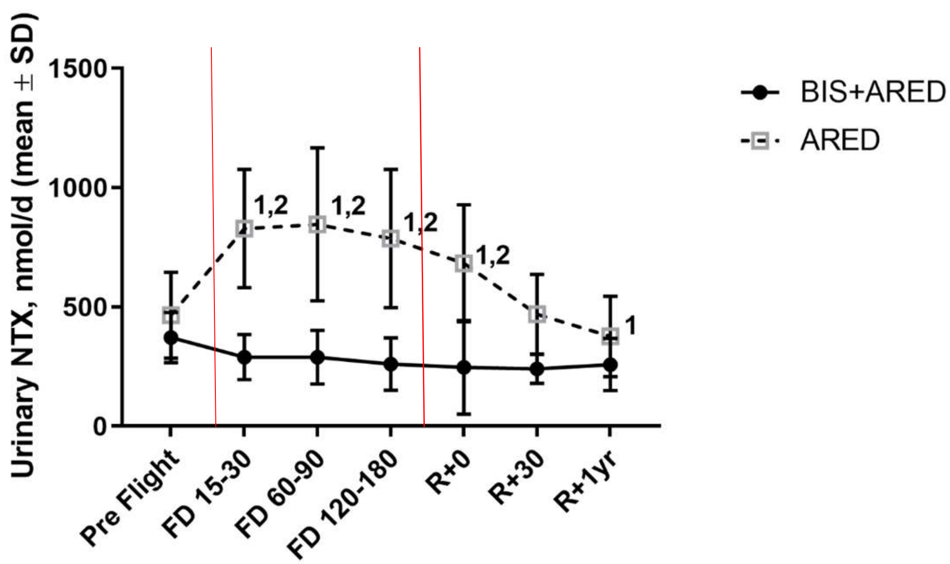
S

1 Pre vs. Post, $P < 0.05$
2 Delta change vs. ARED, $P < 0.05$

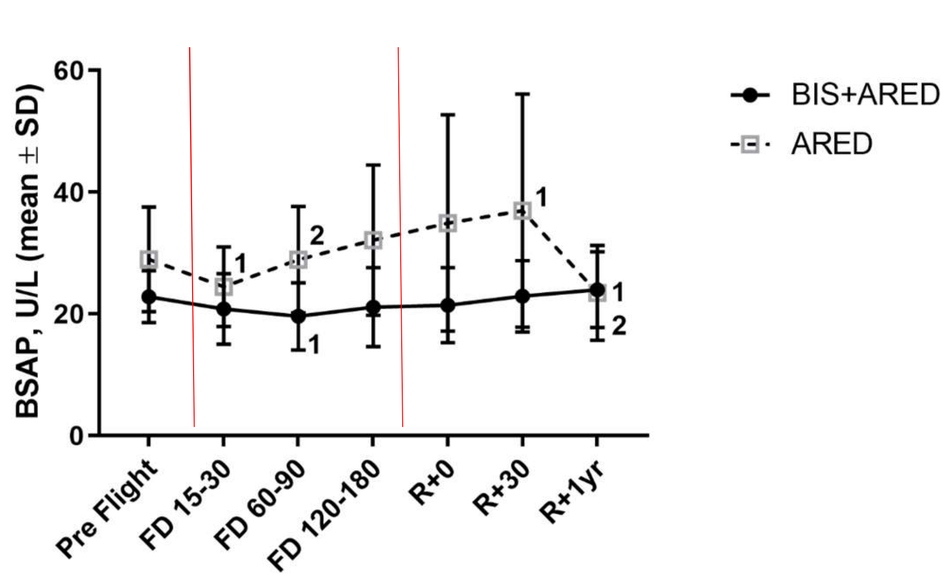
Denotes Least Significant Change

Resistive exercise does not suppress stimulation of bone resorption during spaceflight.

Urinary NTX

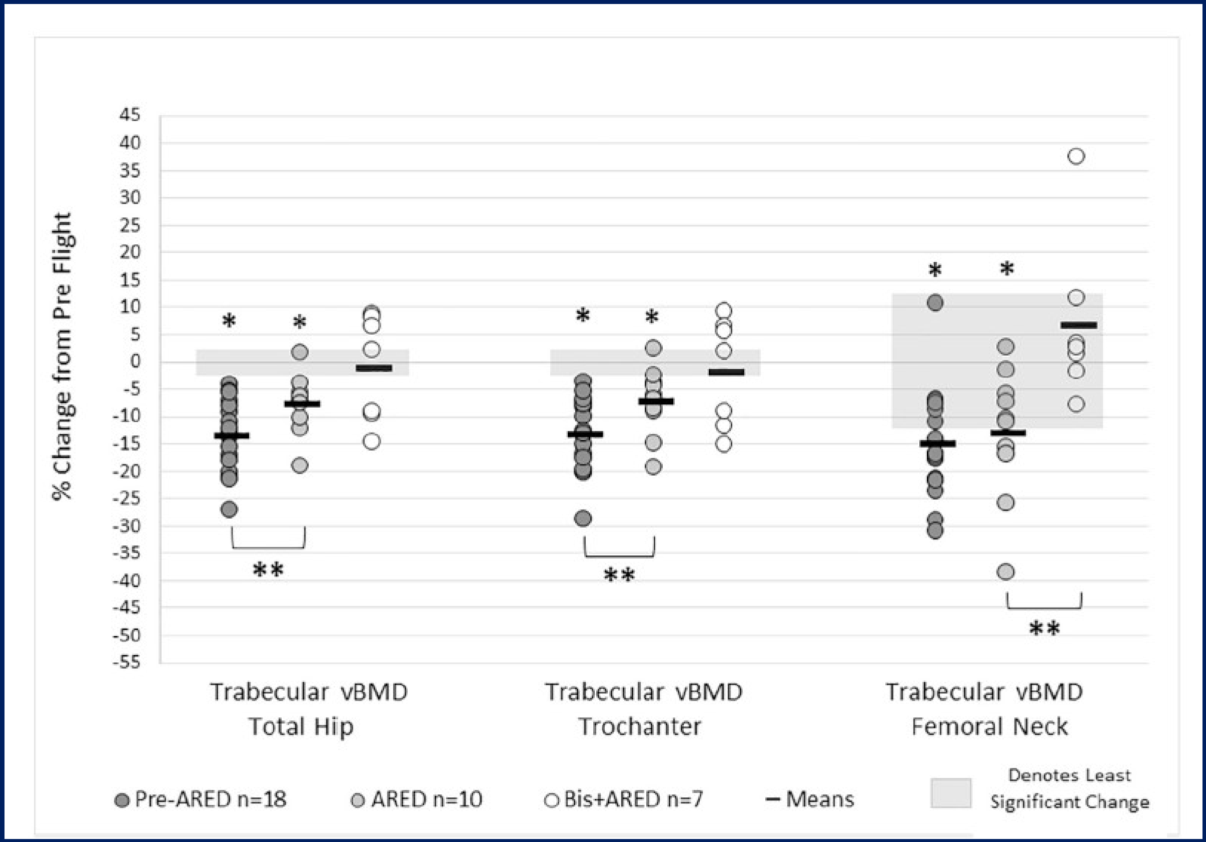


Serum BAP



Sibonga et al, Resistive exercise in astronauts on prolonged spaceflights provides partial protection against spaceflight-induced bone loss. Bone. 128:112037, 2019

QCT data reveals that BP protects against trabecular bone loss (not with ARED alone) and BP enhances the effect of ARED for femoral neck. *Why protect trabecular bone?*

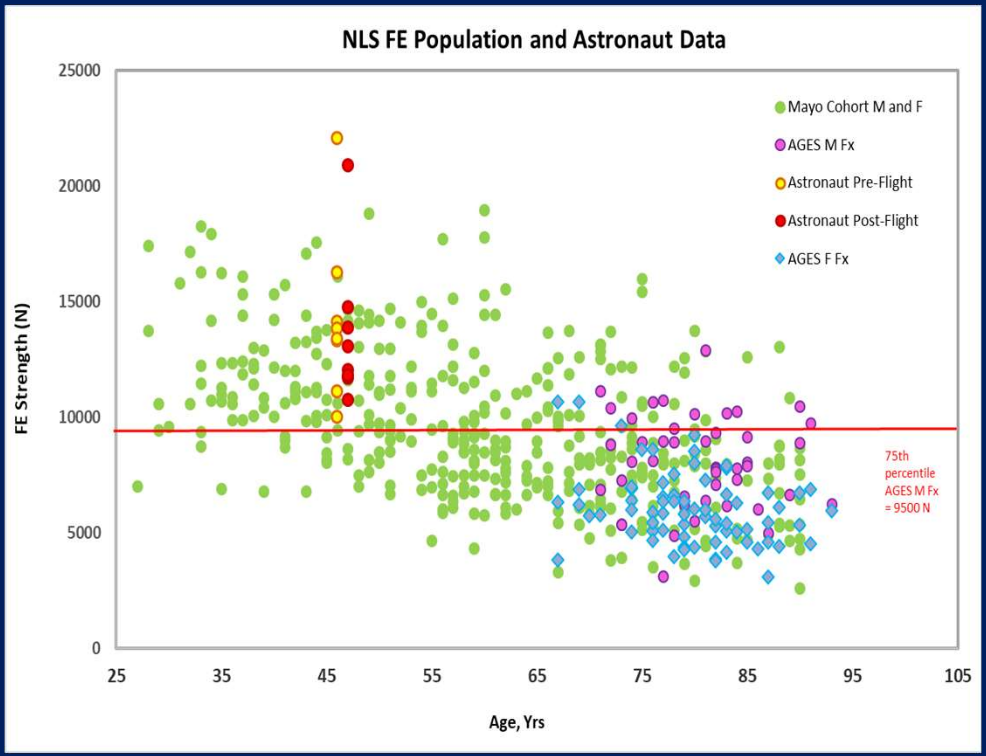


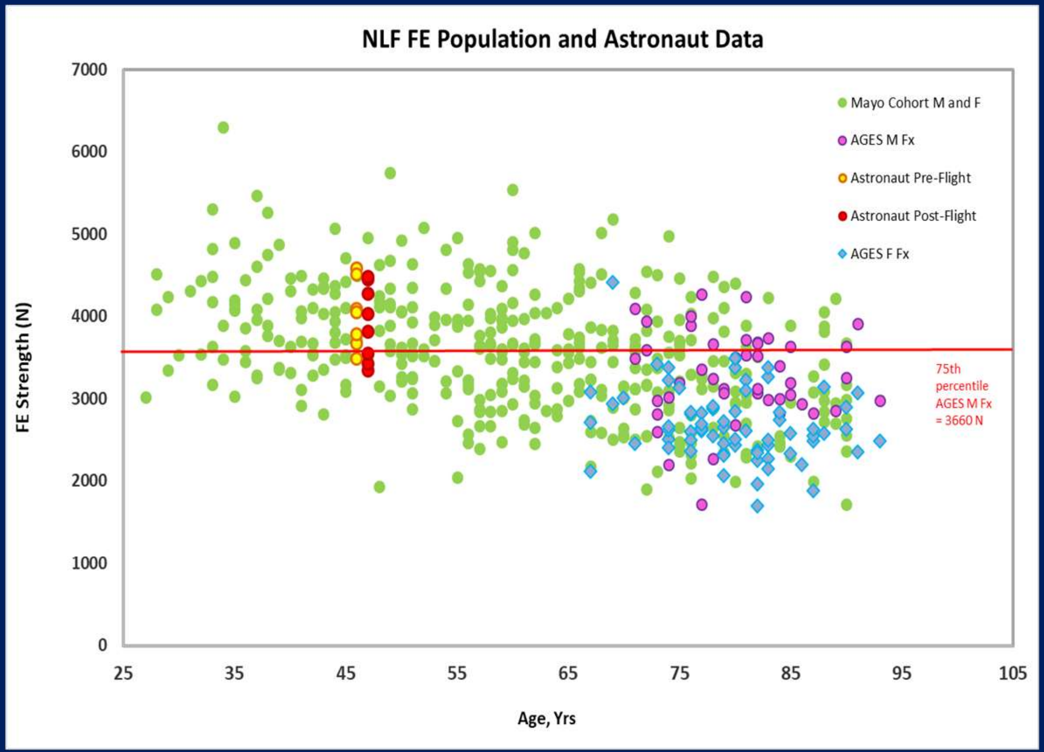
*Pre vs. Post, *P* < 0.05

**ARED + Alendronate vs. Pre-ARED, *P* < 0.05,
ARED + Alendronate vs. ARED, *P* < 0.05,
ARED vs. Pre-ARED, *P* < 0.05

Denotes Least Significant Change

Postflight FE Hip Load Capacity in Astronauts vs. Aging Populations – A new permissible outcome limit?





Michalski AS, Amin S, Cheung AM, Cody DD, Keyak JH, Lang TF, Nicolella DP, Orwoll ES, Boyd SK, Sibonga JD. Hip load capacity cut-points for Astronaut Skeletal Health NASA Finite Element Strength Task Group Recommendations. **Npj Microgravity. 2019 Mar 14;5(1):6.**

Recommendations for monitoring/maintaining skeletal health in astronauts.

- Supplement the DXA evaluation with QCT scans of bone loss during and recovery after spaceflight, and for countermeasure efficacy.*

- Offer an anti-resorptive bisphosphonate (zoledronic acid) as a countermeasure to prevent bone loss, to preserve astronauts at their preflight Bone Mineral Density (BMD) and to mitigate a risk for irreversible disruptions to trabecular microarchitecture.

- Add the analysis of Finite Element (FE) models (of QCT data) to estimate skeletal integrity --- to enhance programmatic decision-making (e.g., countermeasure efficacy).

*QCT recommendation for hip and possibly for vertebral testing TBD.


Thank you. Questions?

References

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- Orwoll ES, Adler RA, Amin S, et al (2013) Skeletal health in long-duration astronauts: Nature, Assessment and Management Recommendations from the NASA Bone Summit. J Bone Mineral Res. 28(6):1243-1255.
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- Smith SM, Wastney ME, O'Brien KO et al (2005) Bone markers, calcium metabolism and calcium kinetics during extended-duration space flight on the Mir space station. J Bone Miner Res 20(2):208-218.

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- Elisabeth R. Spector (NASA JSC)
- Greg Yardley (NASA JSC)
- Sara Zwart, Ph.D. (NASA JSC)
- Bone Summit RCAP (Research & Clinical Advisory Panel)

Emily Morey-Holton, Ph.D
David J. Baylink, M.D.

Back-up slides for Q & A

JSC Crew Surgeon's Point of View

1. Enhance our Crew's health
2. Understand changes associated with spaceflight.
3. Prevent mission impact and impact to crew's health and career.

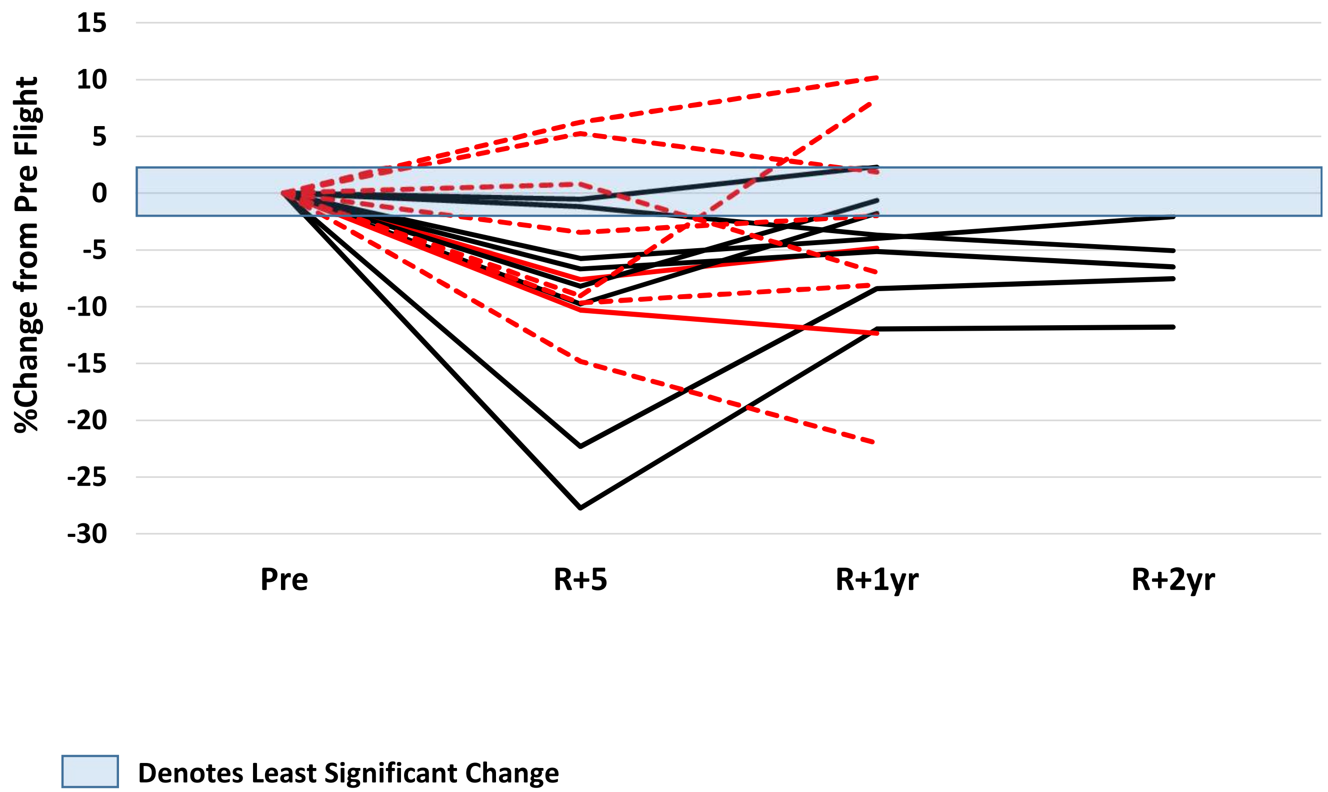
The Cohort of Long-duration (LD) Astronauts (4/2019)
(Not typical patient with age-related bone loss.)

- Prolonged immobilization (spaceflight)– **161 ± 39d (range 49-340d)**
- Younger Average Age – **47 ± 5 y (range 36 – 58)**
- Predominantly males – **4.8 : 1 (76:16)**
- Low total # per LD astronauts in corps – **~92 (80) of 365**
- # repeat fliers, greater risk? – **12 (10 with 2 flights; 2 with 3 flights)**
- BMI – **Male BMI 25.8 ± 2.2 (range 21.2 to 32.6) Female BMI 20.1 ± 2.6 (range 20.1 to 28.5)**
- Wt (kg) and Ht (cm): **Males: 81 ± 9 (63 to 103); 177 ± 6 (163 to 188) Females : 66 ± 8 (54 to 83), 169 ± 4 (163 to 178)**
- %Body Fat: **Males: 24 ± 4 (14 to 32) Females: 30 ± 6 (22 to 44)**

Tally includes Mir and ISS to Exp 57, US and IP astronauts; no cosmonauts. Excludes short-duration astronauts.

Hip Trb vBMD loss: Influence of in-flight alendronate on loss and recovery at R + 1 yr.

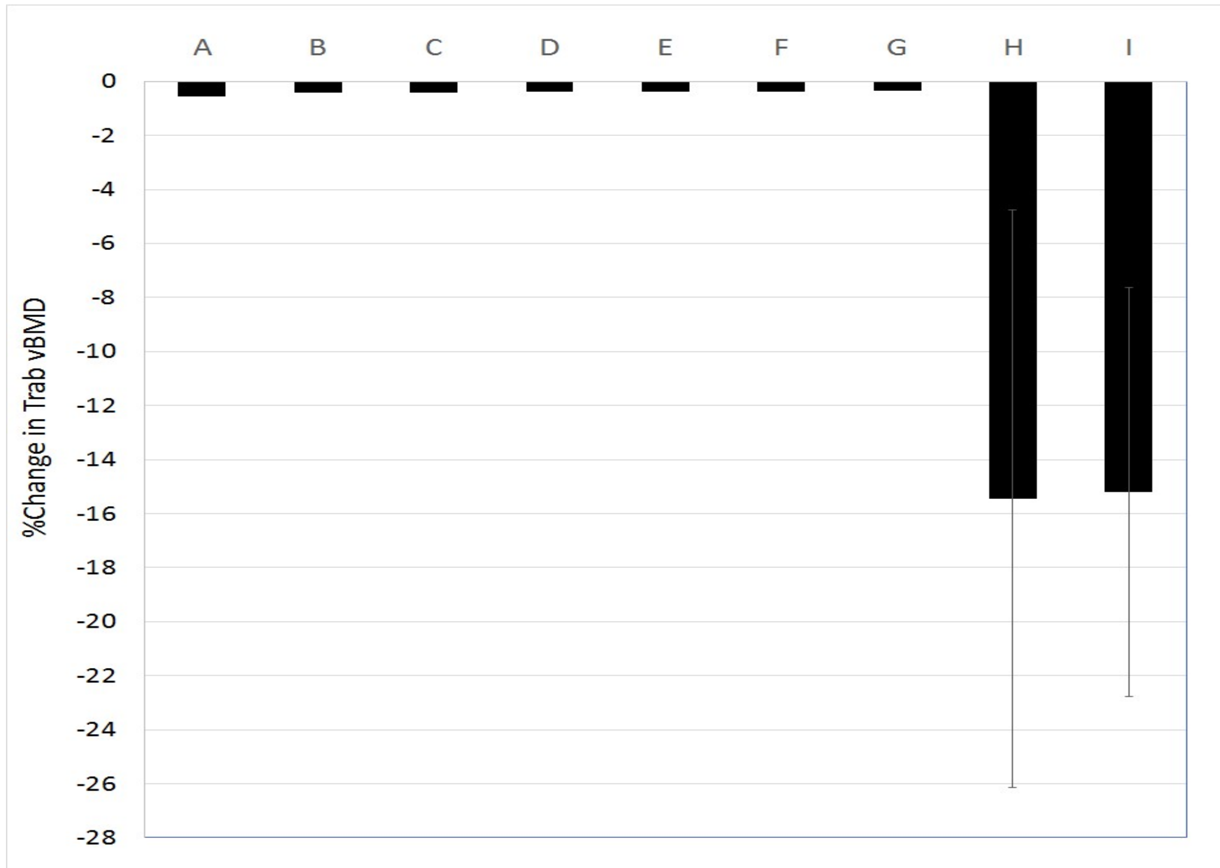
QCT Trb vBMD %ch in ARED Astronauts with Scans Through at Least R+1Yr
Hip with Greatest Loss n=17
Includes 7 Bisphosphonate Subjects (Dashed Lines)



Loss rate of trabecular bone mass in astronauts > than terrestrial populations.*

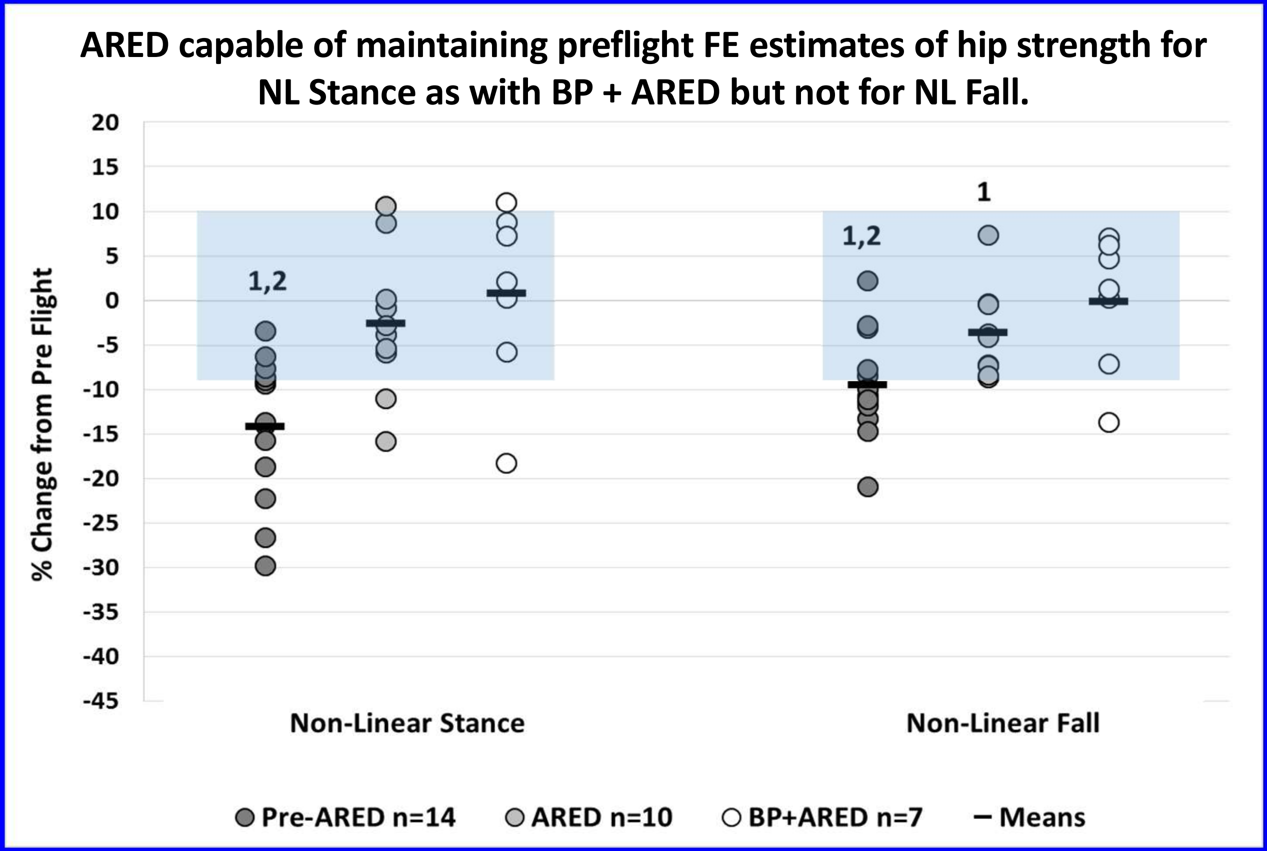
A 20-90 yrs F, cross-sectional study, Nicks et al., 2013;
B ~75 yrs F, longitudinal study, Johannesdottir 2014(;
C 20-90 yrs F, cross-sectional study, Riggs et al., 2004;
D 20-89 yrs F, cross-sectional study, Khoo et al., 2016(;
E 55-85 yrs F, cross-sectional study, Genant et al., 2017(;
F ~75 yrs M, longitudinal study, Johannesdottir et al., 2014(;
G 20-90 yrs M, cross-sectional study, Riggs et al., 2004;
H Pre-ARED ISS Astronauts (n=18), longitudinal study, Lang et al., 2004(;
I All available astronaut hip QCT data from multiple studies post-ARED (n=11).

Sibonga et al. J Clin Densitometry, 2019.



* All normalized to 6-months.

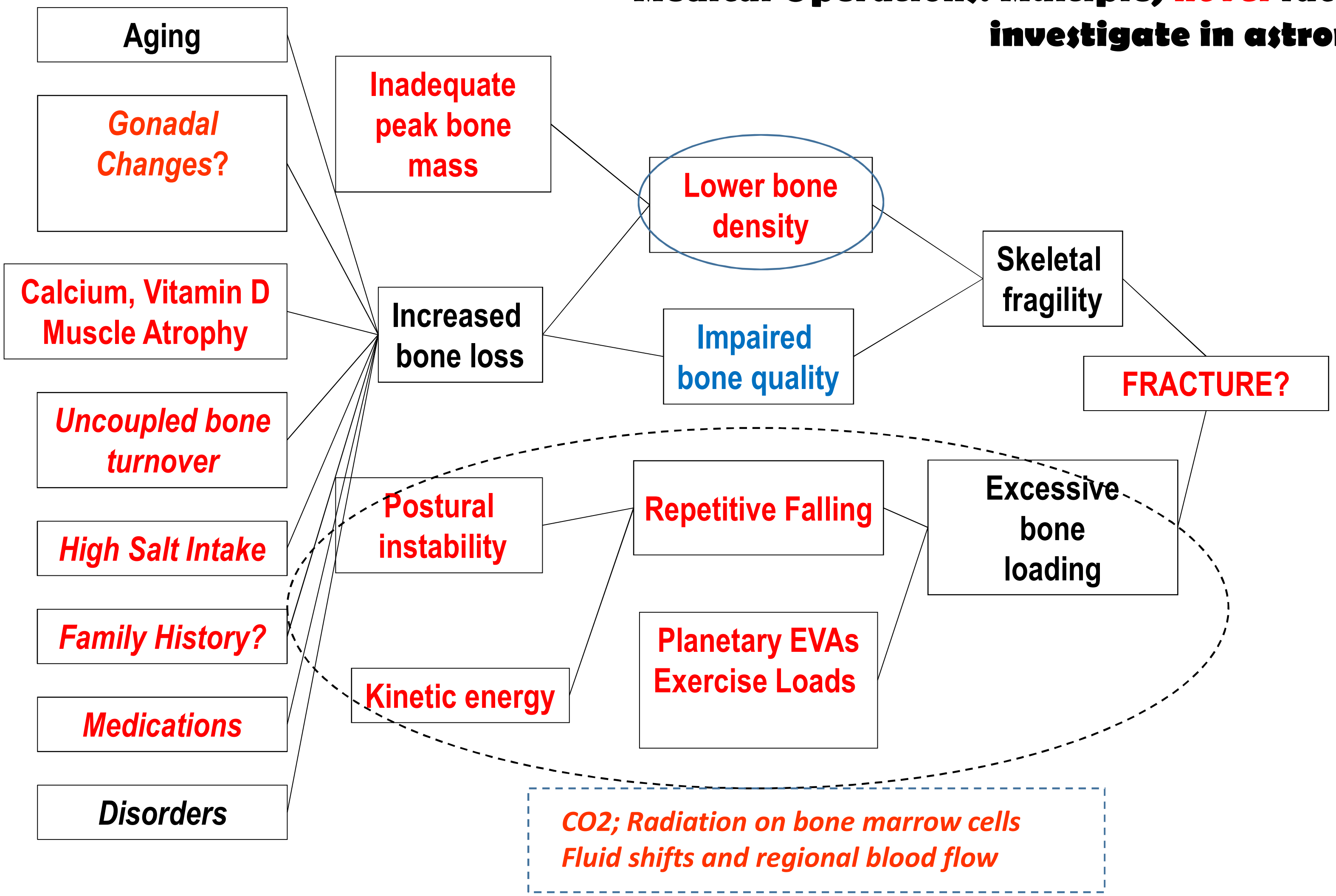
QCT- Finite Element Strength after Space Flight
(useful but very limited).



1 Pre vs. Post, *P* < 0.05
2 ARED + Alendronate vs. Pre-ARED, *P* < 0.05
3 ARED + Alendronate vs. ARED, *P* < 0.05
4 ARED vs. Pre-ARED, *P* < 0.05

Denotes Least Significant Change

Medical Operations: Multiple, *novel* factors to investigate in astronauts.

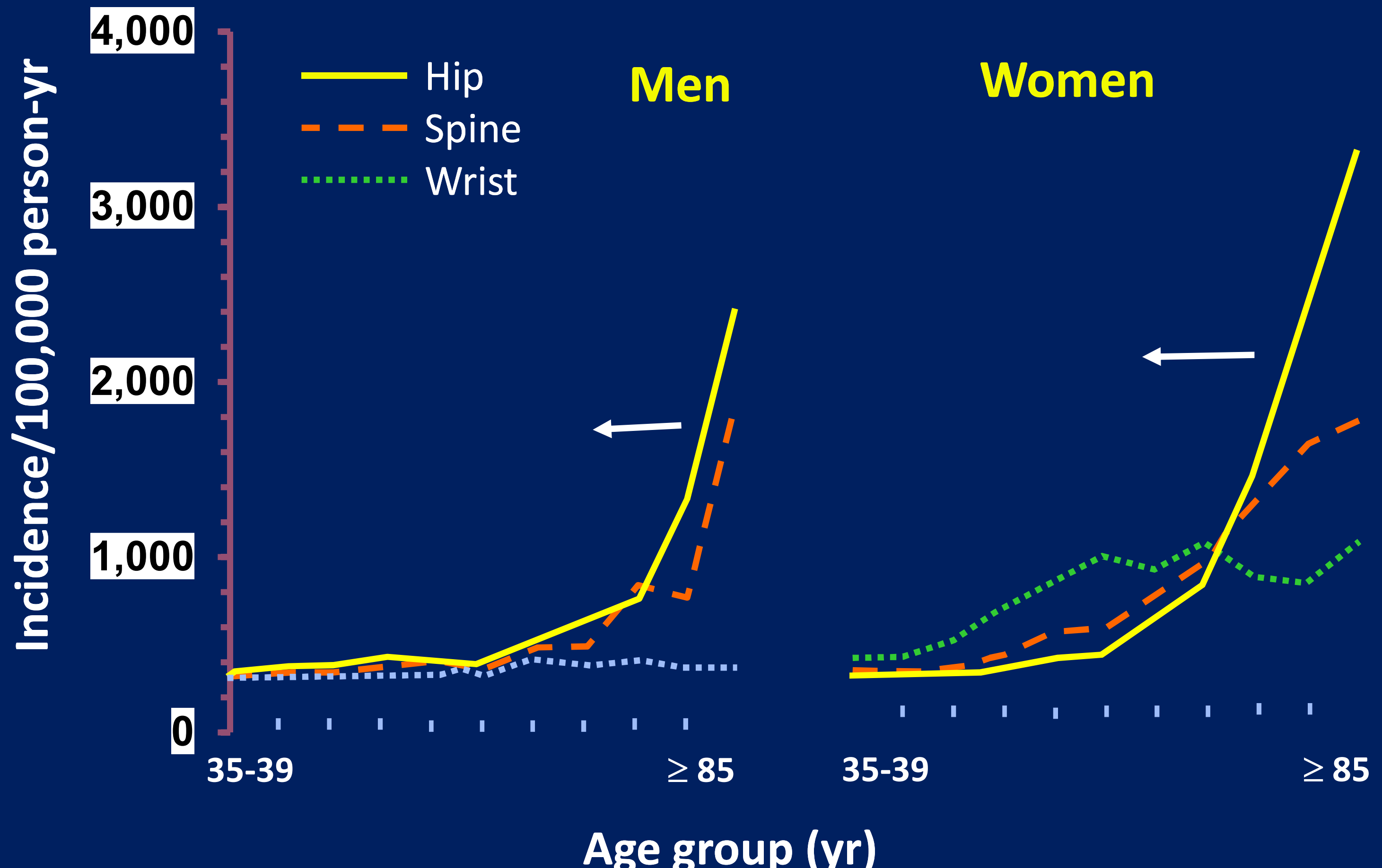


Adapted from: Pathogenesis of Osteoporosis-Related Fractures (NOF) Cooper C, Melton LJ

What about fracture?

"NASA also does not have a driving problem supported by data that suggests there is an increased fracture incidence among astronauts as they age after spaceflight exposure ." The risk is accepted.

Fracture Incidence Associated with Terrestrial Age-related Bone Loss (Primary Op). Premature fractures in astronauts?

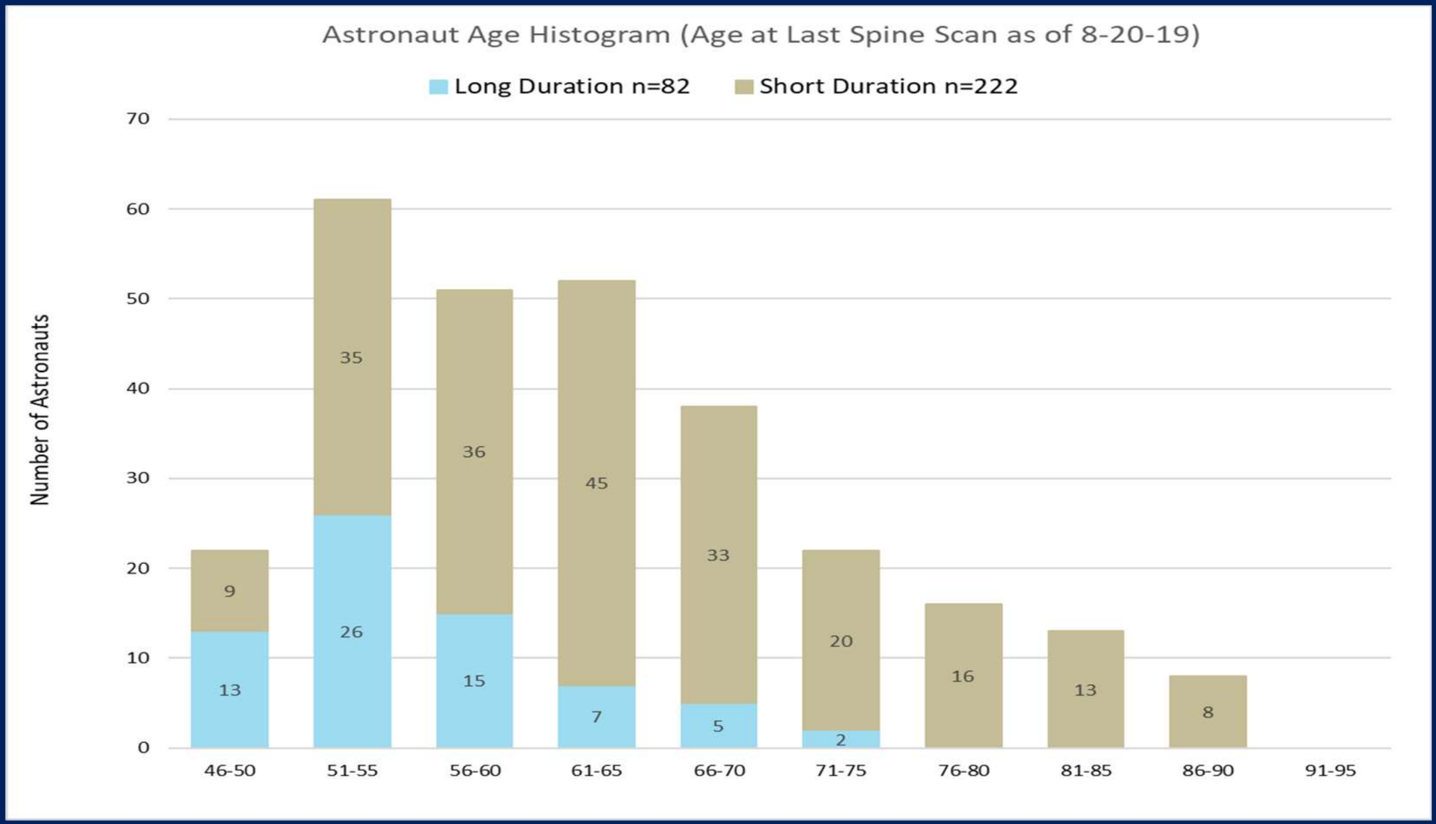


SLIDE COURTESY OF Dr. S. AMIN, Mayo Clinic

Cooper and Melton, 1992

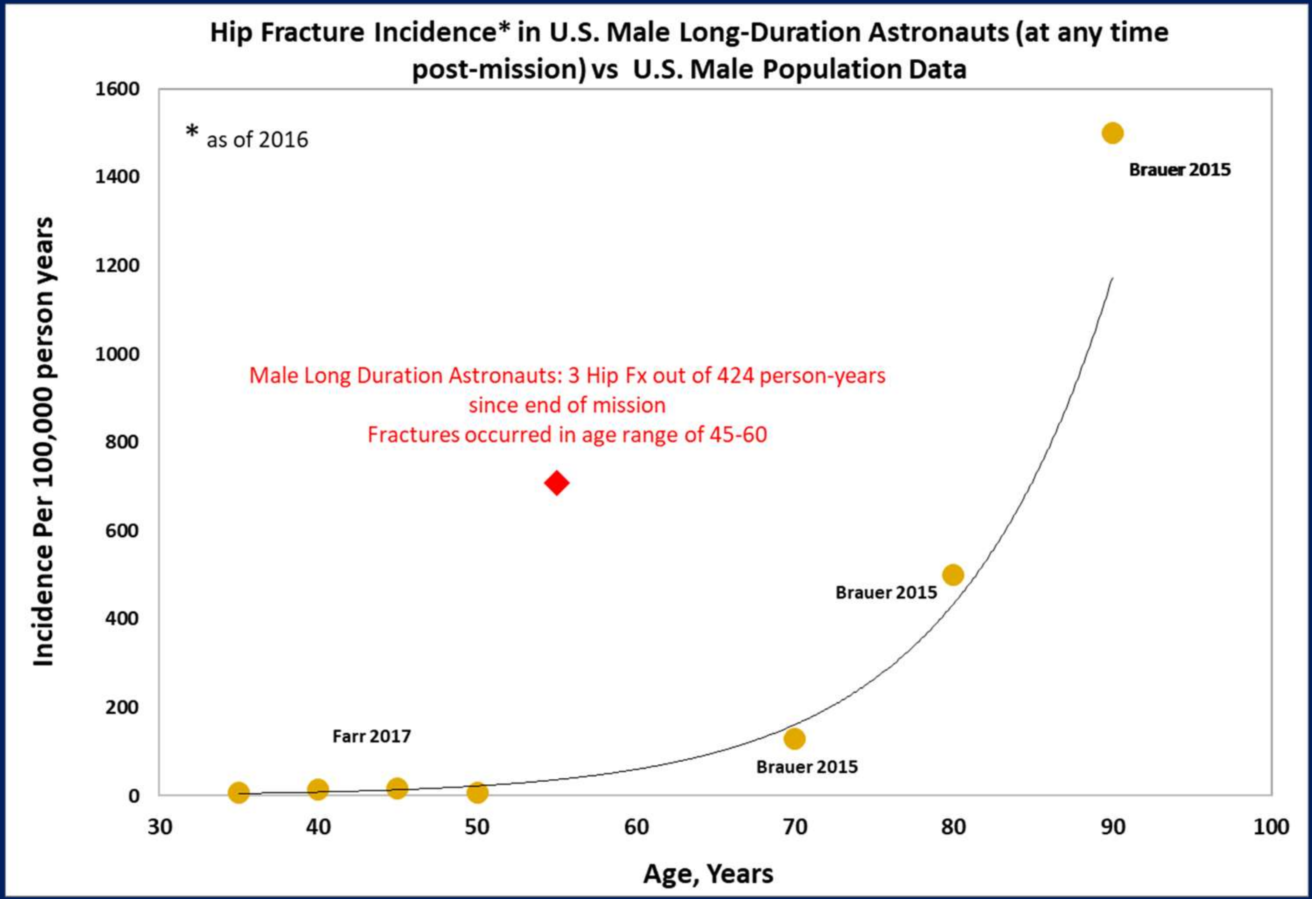
Challenge: Limited # LD Astronauts* to assess fracture incidence

(2019 updated)

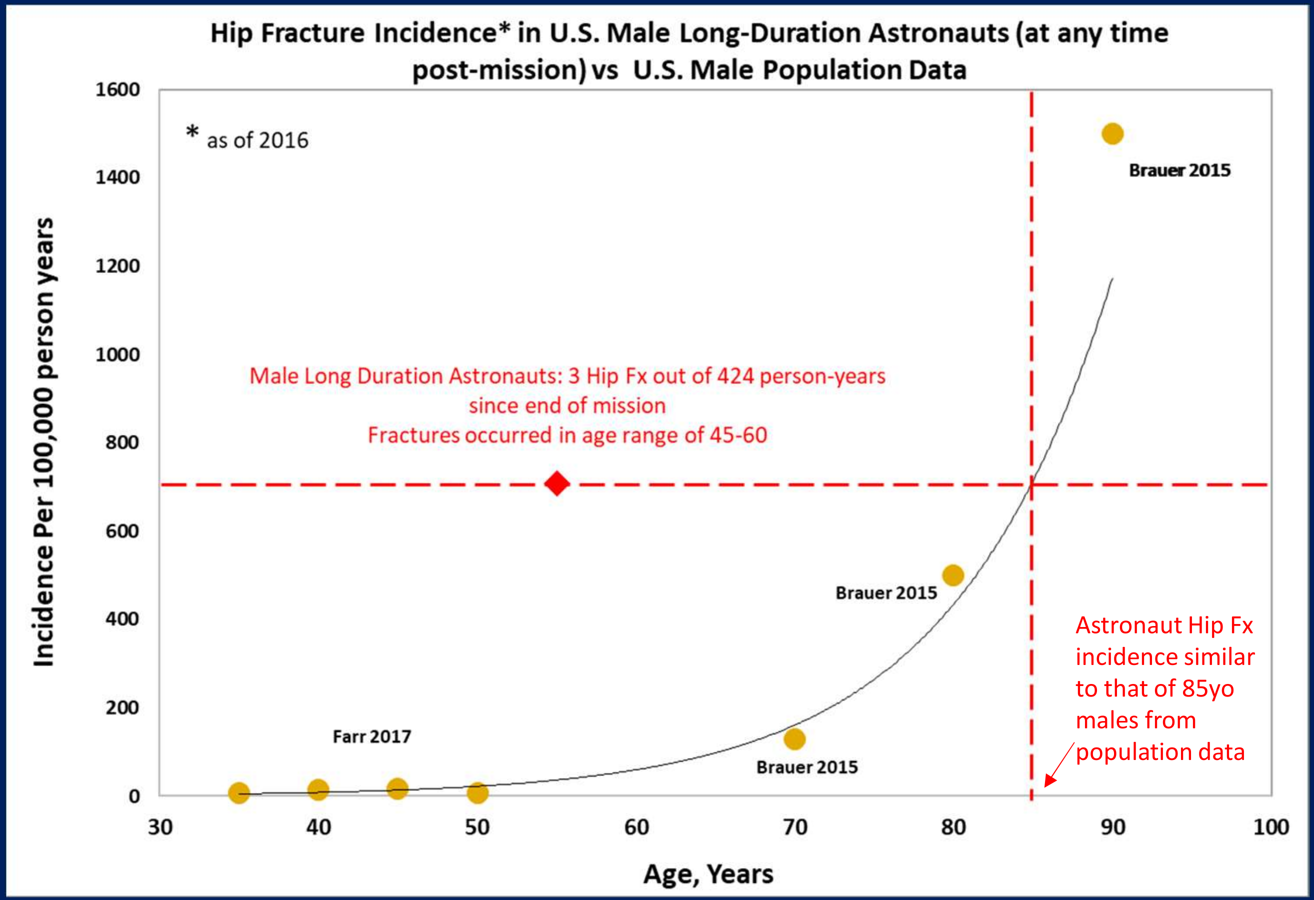


* Males and Females

Alternative Fracture Analysis – In Progress* (unpublished)



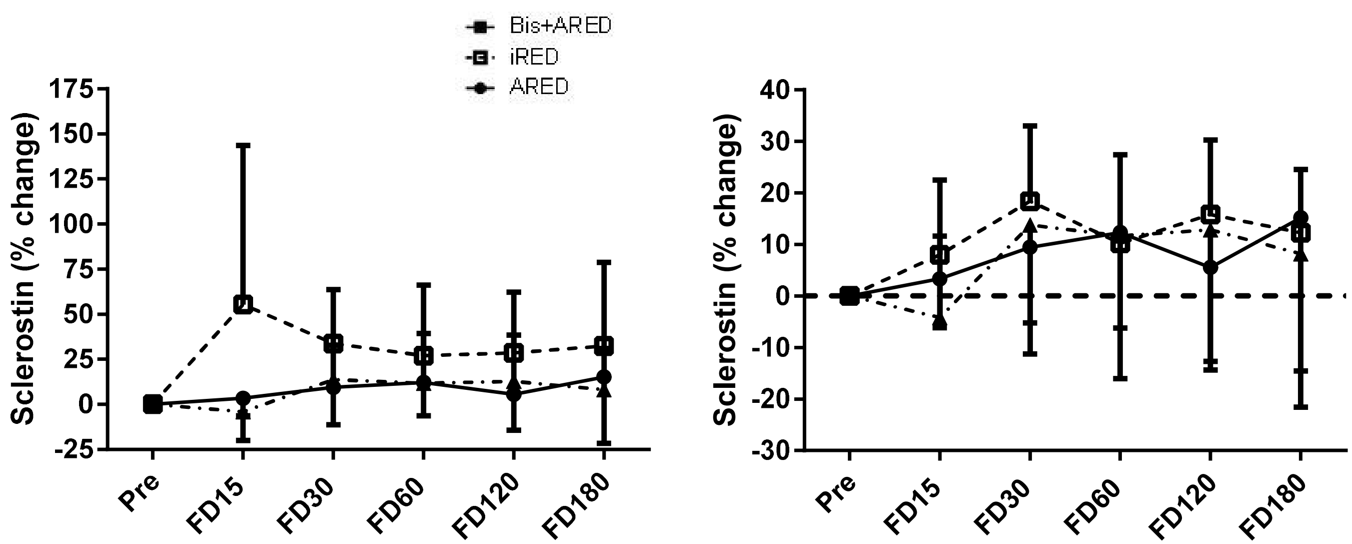
*Presented at ASBMR Annual Meeting Orlando, FL 2019


Hip Fracture Incidence* in U.S. Male Long-Duration Astronauts (at any time post-mission) vs U.S. Male Population Data
* as of 2016
Incidence Per 100,000 person years
Age, Years
Male Long Duration Astronauts: 3 Hip Fx out of 424 person-years since end of mission
Fractures occurred in age range of 45-60
Farr 2017
Brauer 2015
Brauer 2015
Brauer 2015
Astronaut Hip Fx incidence similar to that of 85yo males from population data
0
200
400
600
800
1000
1200
1400
1600
30
40
50
60
70
80
90
100

The Bone RCAP: Explore the emerging data from population studies to propose how *Finite Element Models of QCT data could be used to reflect fracture risk due to spaceflight.*

- **Male-female differences in prediction of hip fracture during finite element analysis.** Keyak JH, Sigurdsson S, Karlsdottir G, Oskarsdottir D, Sigmarsdottir A, Zhao S, Kornak J, Harris TB, Sigurdsson G, Jonsson BY, Siggeirsdottir K, Eiriksdottir G, Gudnason V, Lang TR. Bone. 2011;48(6):1239-1245.
- **Association of hip strength estimates by finite –element analysis with fractures in women and men**. Amin S,, Kopperdahl DL, Melton LJ 3rd, Achenbach SJ, Therneau TM, Riggs BL, Keaveny TM, Khosla S. J Bone Miner Res. 2011;26(7):1593-1600.
- **Age-dependence of femoral strength in white women and men.** Keaveny TM, Kopperdahl DL, Melton III LJ, Hoffmann PF, Amin S, Riggs BL, Khosla S. J Bone Miner Res. 2010;25(5):994-1001.
- **Osteoporotic Fractures in Med Study Group. Finite element analysis of the proximal femur and hip fracture risk in older men**. Orwoll ES, Marshall LM, Nielson CM, Cummings SR, Lapidus J, Cauley JA, Ensrud K, Lane N, Hoffmann PR, Kopperdahl DL, Keaveny TM J Bone Miner Res. 2009;24(3):475–483.

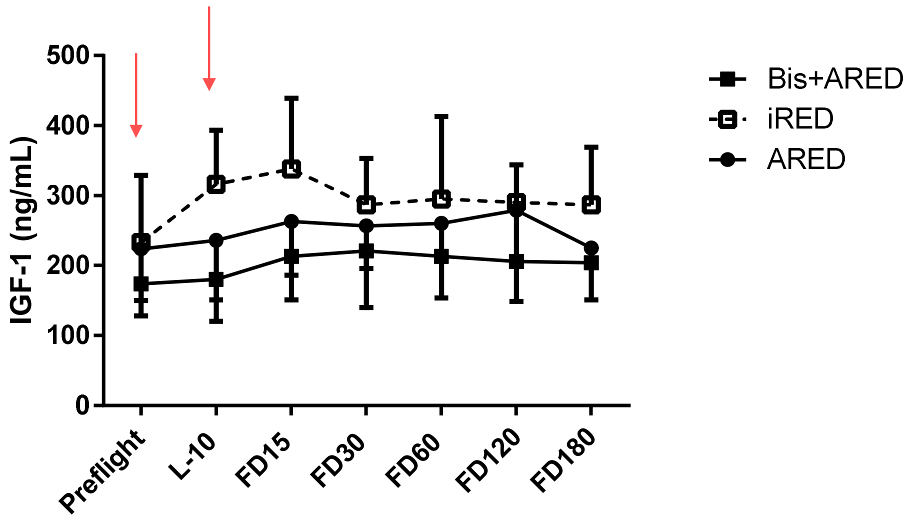
Albeit not clear, Sclerostin may contribute to the uncoupling of bone turnover.

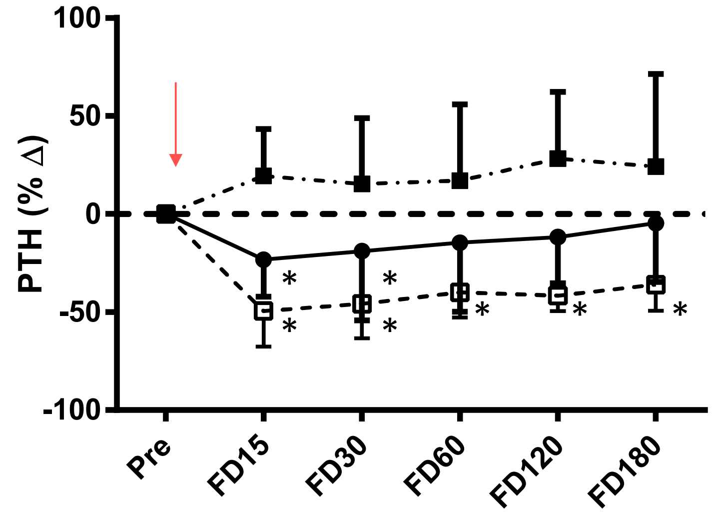


p<0.06 -- 15% increase above preflight

Smith et al. Bone 2015.
Figures Courtesy of Smith & Zwart

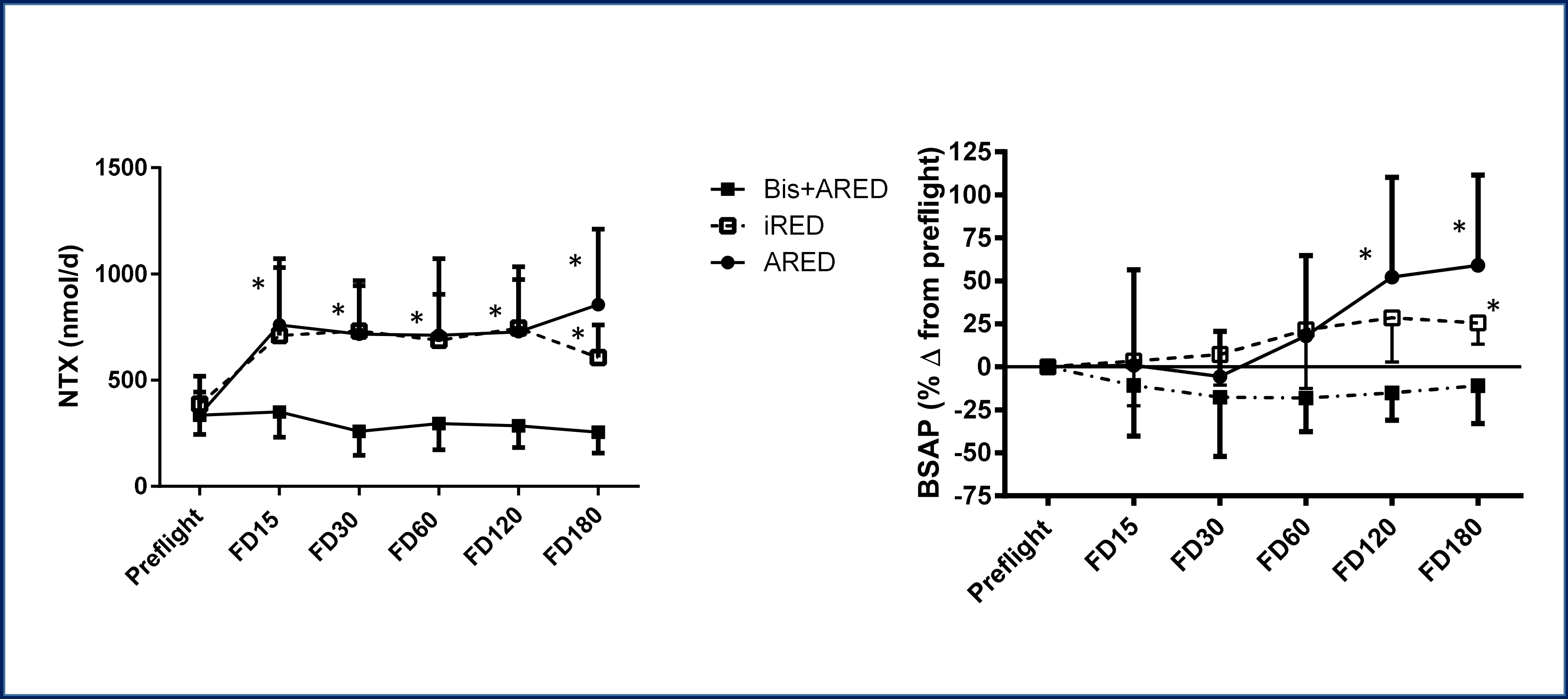
Interpreting Biochemical Data: 1) Increased IGF1 vs. preflight in all groups 2) Suppressed PTH in exercise groups.





Smith et al. Bone 2015.
Figures Courtesy of Smith & Zwart

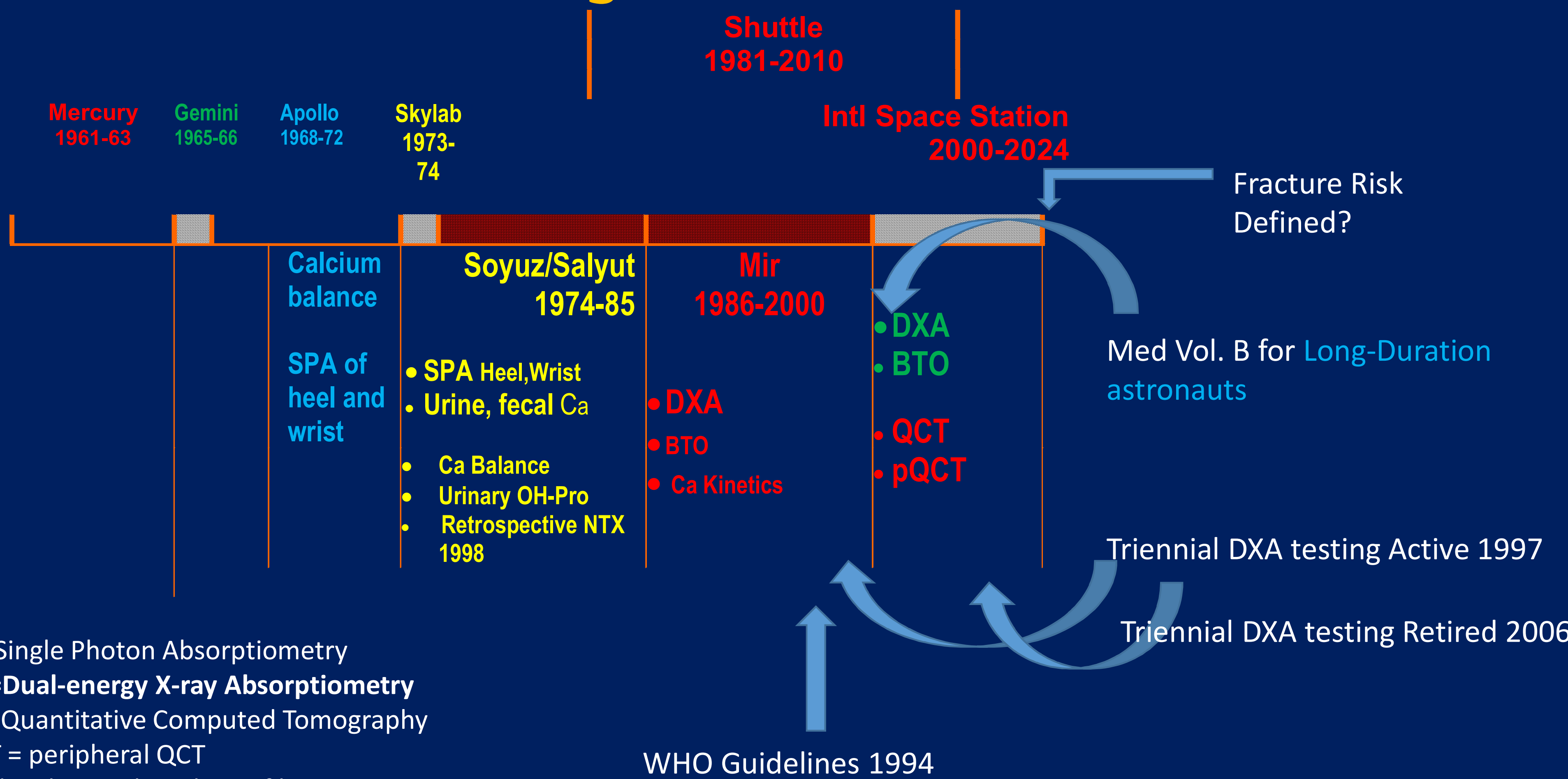
Updated Trends in Biochemistry : Influence of resistive exercise +/- bisphosphonates.
n=4-9



Smith et al. Bone 2015.
Figures Courtesy of Smith & Zwart
JSC Nutritional Biochemistry Lab

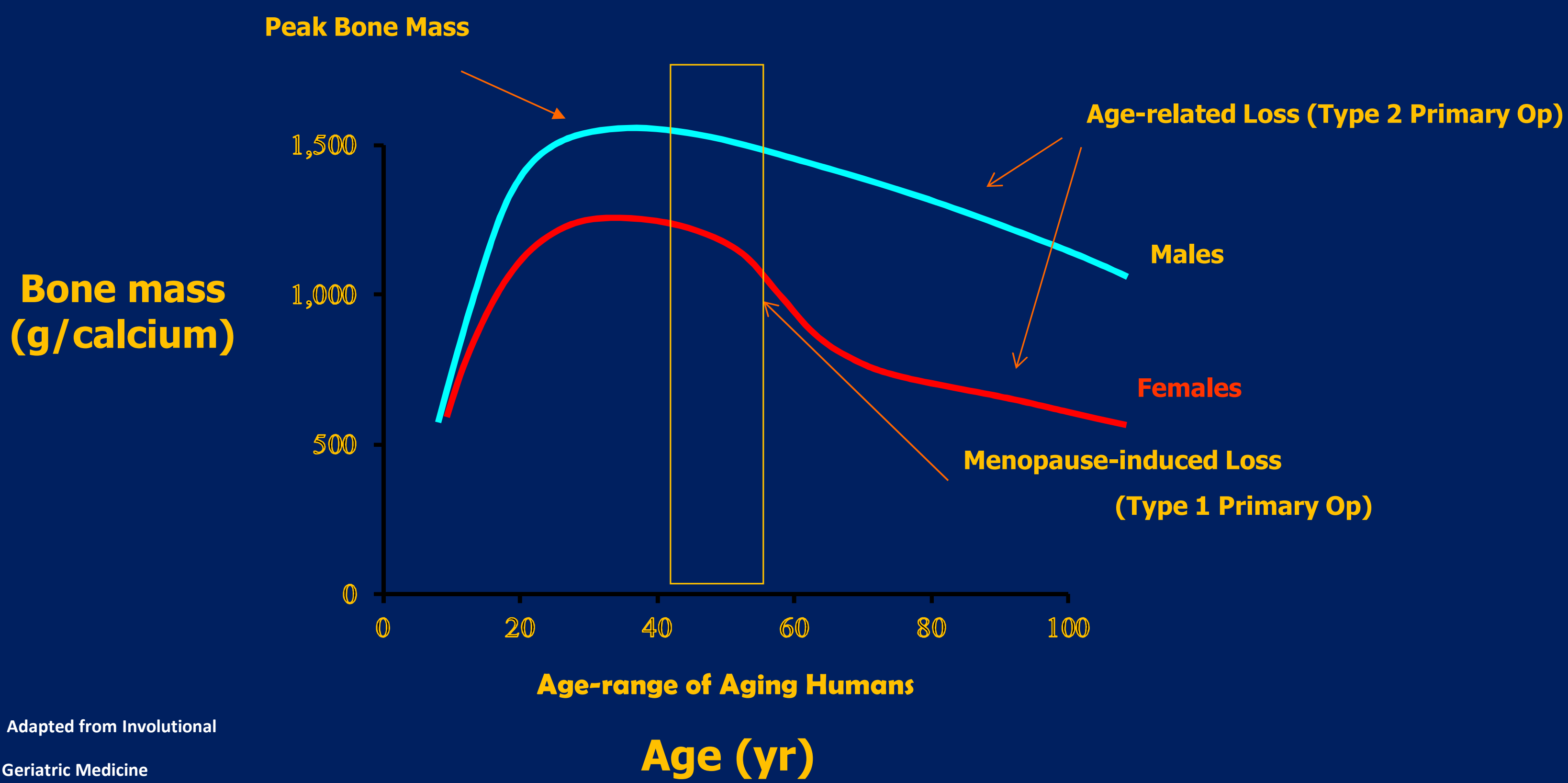
IRED – Interim Resistive Exercise Device (300 lbs of resistive force)
ARED – Advanced Resistive Exercise Device (600 lbs of resistive force)
Bis + ARED – combined therapies of resistive exercise and an oral bisphosphonate

History: Monitoring Skeletal Health in Astronauts
Is it enough for Mars Mission?



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

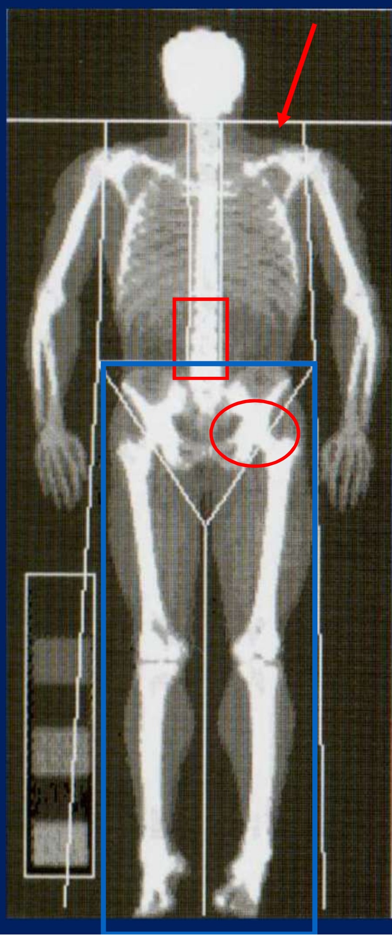
What index should NASA monitor in Long-duration astronauts to assess fracture probability?



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

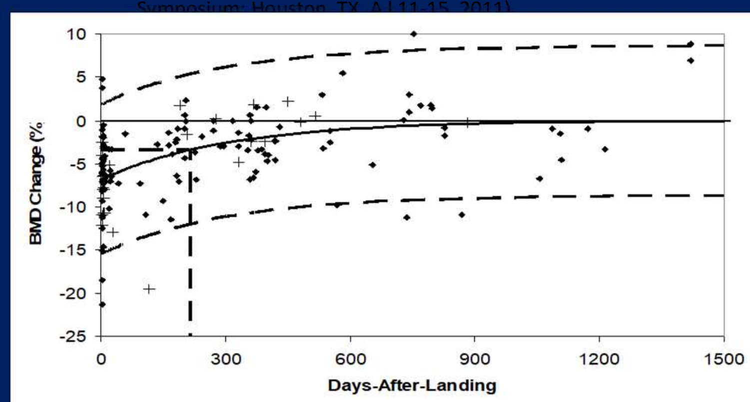
DXA BMD reveals changes that are unique & complex.

Resistive Exercise can reduce expected declines.



BMD Site	Mean Immediate Post Flight BMD (% change/month)			Mean Three Year Post Flight BMD (% change/month)		
	Predicted	Observed	p-value	Predicted	Observed	p-value
Total Hip	1.063 (0.05)	0.994 (-0.76)	<0.001	1.066 (0.02)	1.047 (-0.03)	<0.001
Lumbar Spine	1.081 (0.11)	1.016 (-0.58)	<0.001	1.085 (0.03)	1.069 (-0.00)	0.11
Ultra-Distal Radius	0.558 (-0.05)	0.550 (-0.20)	0.12	0.541 (-0.08)	0.551 (-0.04)	0.005
Mid-Shaft Radius	0.755 (0.19)	0.741 (-0.00)	0.04	0.749 (0.02)	0.741 (0.00)	0.28
Total Body	1.288 (-0.04)	1.262 (-0.26)	0.009	1.284 (-0.01)	1.261 (-0.05)	0.19

Total BMD **loss** greater and **persist** **(n=14)** compared to BMD changes predicted from algorithms derived from Earth-based population. (Amin, 18th International Academy of Astronautics Humans in Space Symposium; Houston, TX, Jul 11-15, 2011)



Loss is variable.
Recovery is variable.
Recovery is prolonged.
Indicates: Multiple Risk Factors at play.
(Sibonga, 2009)

*