Risk of Spaceflight-induced Changes to Bone, leading to In-mission Health and Performance Decrements due to Bone Fracture, and Long-Term Health Effects Secondary to Premature Skeletal Fragility. (Bone Fracture Risk)
Revision C

Human System Risk Board (HSRB)

HSRB CR SA-06093
Approved: 6/9/2025
Out of Board

Risk Custodian Team

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Risk Record

This revision:

- Provides revised content.

This information was previously reviewed/dispositioned at:

Meeting	Date	Outcomes/Direction
BRESCB & SMOCB	07/22/24	Approved to present to HSRB

Contents

1. Risk Title and Risk Statement

- **Risk Title**

  Risk of Spaceflight-induced Changes to Bone, leading to In-mission Health and Performance Decrements due to Bone Fracture, and Long-Term Health Effects Secondary to Premature Skeletal Fragility.

- **Risk Statement**

  Given the skeletal changes that occur during space missions, there is a possibility that the bones of crewmembers during and after spaceflight are not as strong as they were before the mission and a fracture may occur for activities otherwise unlikely to induce fracture prior to space missions.

2. Risk History

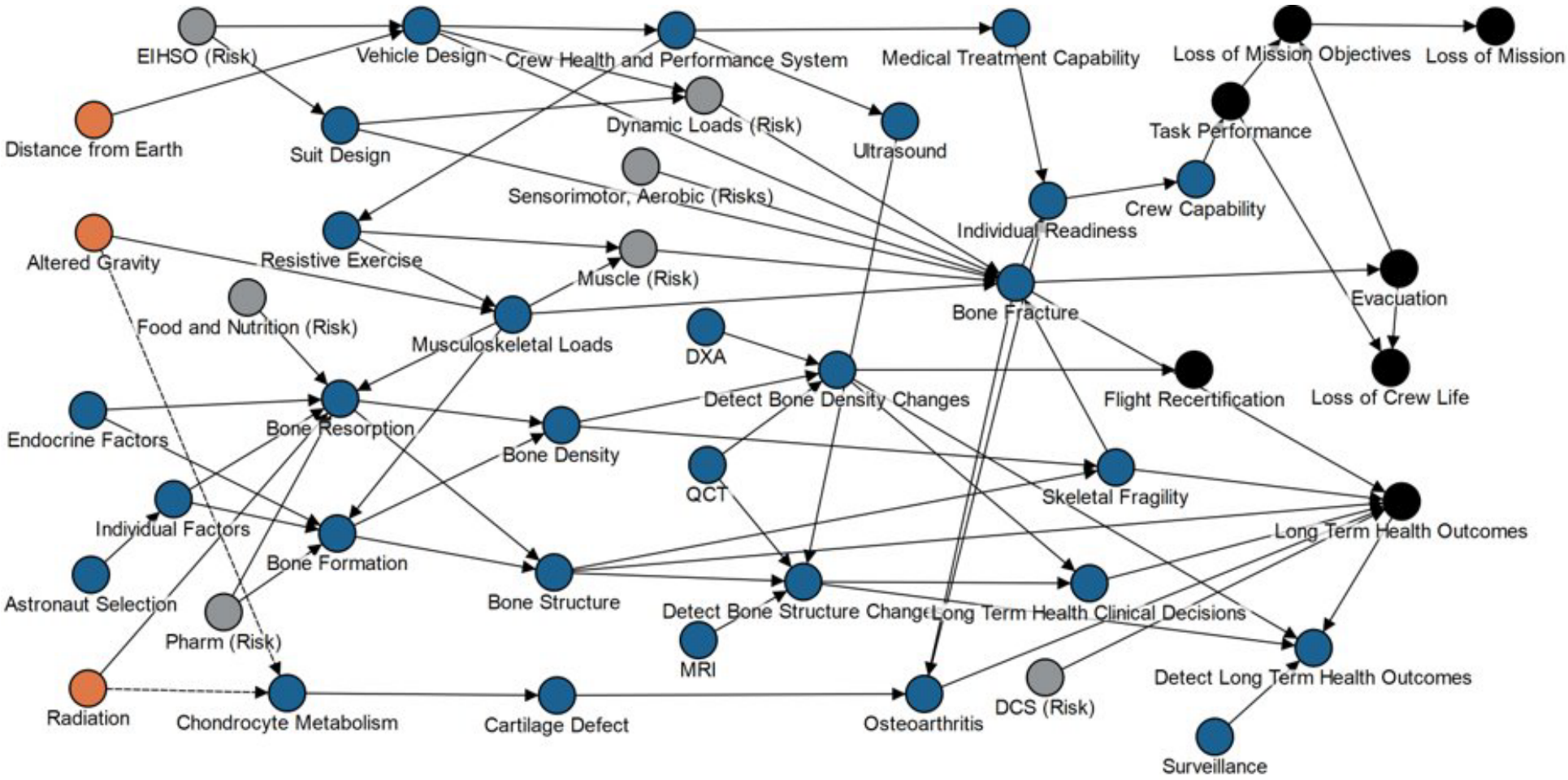
Item	Date	Outcome/Status
HSRB Risk Presentation	06/09/2025	**Decisional** – CR SA-06903 Updates to the Bone Fracture Risk, Approved with modifications Out of Board Risk; Rev C.
HSRB Risk Presentation	10/17/2024	**Informational** – CR SA-06903 package to be refined and approved to be released
HSRB Risk Presentation	05/13/2022	**Decisional** – CR SA-05096 HSRB Directed Acyclic Graphs Errata Changes; CR Approved out of board, Rev B.2
HSRB Risk Presentation	10/28/2021	**Decisional** – CR SA-04226 HSRB - Directed Acyclic Graphs: HSIA, Bone Fracture, Hearing Loss, EVA Injury, DCS, Hypoxia; CR Approved with Mods, Rev B.1
CMB Presentation	08/11/2021	CMB Concurrence on Risk Posture
HSRB Risk Presentation	06/24/2021	**Decisional** – CR SA-03265 Updates to Risk; CR Approved with Mods, Rev B.
Risk Evaluated via CR	03/22/2021	CR Evaluation period was extended through 04/12/21
HSRB Risk Presentation	03/11/2021	**Informational** – CR package to be refined and approved to be released.
HSRB Risk Presentation	03/23/2017	**Decisional** - Updates to Risk Rev A. approved with mods (LxC for new planetary DRMs); proposed Standard updates
Risk Evaluated via CR	02/17/2017	CR released for evaluation (CR-HSRB-17-003; BPSCM)
HSRB Risk Presentation	01/19/2017	**Informational** – Provided yearly updates to include new evidence
HSRB Risk Presentation	10/15/2014	**Decisional –** Action Item Closure - Approved
HSRB Risk Presentation	07/23/2014	**Decisional –** Action Item Closure - Approved
HSRB Risk Presentation	06/11/2014	**Decisional** – Approved baseline
Risk Evaluated via CR	05/23/2014	Baselined integrated risk
Risk Evaluated via CR	03/13/2014	**Withdrawn –** Proposed to baseline information due to changes in risk process, LxC assessment was tabled. Provide risk disposition and LxC via CR.
HSRB Risk Presentation	01/15/2014	**Informational** – Introduce the integration of the two previously baselined bone risks: "Bone Fracture & Early Onset Osteoporosis Due to Spaceflight into one risk.

3. Executive Summary

- This Risk update is premised upon the following points:
    1) Fracture is not contingent upon a pathological skeletal condition (e.g., diagnosis of osteoporosis),
    2) Deconditioning resulting from multiple physiological sources may contribute to events that could result in the overloading of bone leading to fracture.
- The primary evidence for this Risk is grouped into three parts:
    - Fracture Analysis: Increases in the Relative Rate of hip and spine fractures in the postflight period following long-duration (LD) spaceflights (vs. "non-LD" spaceflights) suggest that exposure to LD flights (> 90-100 days duration) increases Directed fracture risk in skeletal sites already at higher risk for age-induced fragility.
    - Hip QCT Study: As demonstrated in the hip bone*, Quantitative Computed Tomography (QCT) provides supplemental views of bone changes that occur with LD spaceflight and with recovery on Earth that are not detected by required testing by DXA (dual-energy x-ray absorptiometry).
    - Bisphosphonate (Bis) Extension Study: Exercise on the Advanced Resistive Exercise Device (ARED) does build cortical bone but does not mitigate bone resorption due to spaceflight (with enhanced detection by QCT) as well as the combination of Bis + ARED.
- Based upon the greater relative rate of hip and spine fractures, and the limited ability to assess countermeasure mitigation by a reduction in fracture outcomes (as a metric), this package provides evidence that countermeasure efficacy could be assessed based upon the ability to preserve astronauts at their preflight skeletal health, i.e., quantify mitigation of spaceflight-induced changes to bone. Estimations of fracture probability are based upon scenarios where an astronaut may be
    1) Deconditioned during prolonged periods (> 90 –100 days) of unmitigated bone resorption, and then
    2) Exposed to mechanical-loaded events or physical activities to which deconditioned astronaut has a risk of sustaining a fracture.
- There have been no in-mission bone fractures during spaceflight. It is the opinion of this Risk Custodian Team that the lack of fractures does not negate the risk of future fracture in spaceflight.
- The disposition recommendation for many DRM categories is "Requires Characterization." QCT was approved by the AMB for pre- and post-flight occupational surveillance via MedB in April 2024. Implementation is pending.

**spine changes also but pilot study restricted proof-of-concept to hip only.*

4. Bone Fracture Risk DAG



Directed Acyclic Graph (DAG) for Bone Fracture.

Bone Fracture Risk DAG: Narrative

- The Risk of Bone Fracture is primarily concerned with the Hazard of **Altered Gravity** which affects Applied Loads by increasing the # of physical events and physiological changes that could result in injurious trauma and also by uncoupling bone remodeling as an adaptive response to spaceflight, characterized by rapid bone loss. Secondary Hazards are Distance from Earth and Radiation.

- The Bone Fracture DAG centers around the **Bone Fracture** node that has two types of inputs. Those that affect applied loads to bone , and those that make bone more fragile, i.e., **Skeletal Fragility**.
  - Nodes that affect applied loads to bone include:
    - **Musculoskeletal Loading** is affected by **Altered Gravity**, the **Resistive Exercise** designed into the **Crew Health and Performance System**, and the effects of the **Muscle (Risk)** on the bone.
    - **Vehicle Design** and **Suit Design**
    - **Dynamic Loads (Risk)** governs the loads experienced in landing scenarios for planetary surfaces. This is heavily influenced by **Vehicle Design** and **Suit Design** as well.
    - **Sensorimotor, Aerobic (Risks)** can influence the likelihood of experiencing high applied loads from falling or operational errors.
    - **Muscle (Risk)** includes the muscular loads on the bone as well as muscular atrophy, which can influence fall risk. This is dependent on the **Resistive Exercise** designed into the **Crew Health and Performance System**.
  - Nodes that affect **Skeletal Fragility** include:
    - **Bone Density** refers to mineral measured within a specific volume (3D) or projected area (2D) of bone.
    - **Bone Structure** refers to the 3D distribution of bone mass at both the whole bone and microstructural level.
    - Changes to **bone density and structure** occur as a result of unbalanced **Bone Remodeling** shown as two sub-nodes**:**
      - **Bone Resorption** is executed by Osteoclast cells which can be influenced by **Musculoskeletal Loading**, **Endocrine Factors** (such as parathyroid syndrome), **Individual Factors**, medications-- represented by **Pharm (Risk)**, and Nutritional Status -- represented by **Food and Nutrition (Risk).**
      - **Bone Formation** is executed by Osteoblast cells, and which can be influenced by all of the same nodes.
    - **Food and Nutrition (Risk)** that can influence bone resorption in order to maintain calcium homeostasis.

- It is hypothesized that **Chondrocyte Metabolism** is affected by **Altered Gravity** and **Radiation.** These connections are shown as dotted lines because of the limited collection of evidence to substantiate this assertion. Additional evidence may support a predisposition to **Cartilage Defects** and **Joint Damage** that can influence **Individual Readiness and Crew Capability** for example**,** when dealing with joint pain. **Joint Damage** can also occur, or contribute to, some cases of **Bone Fracture**.

- **Skeletal Fragility** is a manifestation of osteoporosis and can contribute to **Long Term Health Outcomes**. Similarly chronic joint pain such as arthritis can contribute to **Long Term Health Outcomes**.

- **Modalities of bone** monitoring performed before and after flights, such as **DXA**, **QCT**, and **MRI,** enable us to **Detect Bone Density Changes** and **Detect Bone Structure Changes**. Detecting these can lead to **Long Term Health Clinical Decisions** such as orthopedic interventions, changes in physical activity, or medication use that can decrease the likelihood or severity of **Long-Term Health Outcomes. Currently there is no arrow connecting Detect Bone Structure Changes to Flight Recertification because an identified clinical trigger (Orwoll E JBMR, 2013) has not been accepted by NASA stakeholders. Research into new metrics for bone health and fracture prediction is in progress.**
- **Ultrasound** may provide an option to **Detect Bone Structure Changes** occurring in flight if the capability is designed into the **Crew Health and Performance System**.

5. Risk Summary

Primary Hazard:
Altered Gravity

Secondary Hazard(s):
Radiation
Hostile Closed Environment
Distance from Earth

Countermeasures in use:
Prevention
Selection standard, exercise, task design, diet (calcium/vit D sufficiency), pharmaceuticals. *Engineering-out risks of excessive mechanical loading (e.g., fall or injury risks). Awareness & knowledge.*

Monitoring
Preflight and postflight *DXA, (QCT pending implementation). Ultrasound* development for on-orbit monitoring for disruptions in trabecular microarchitecture. MRI* potential for assessing loss of trabecular bone connectivity. On-orbit assessment of bone turnover biomarkers.*

Intervention
Pharmaceuticals, post-mission rehab.

* technologies in development/require validation for bone changes due to disuse or mechanical unloading

Contributing Factors
Physiological deconditioning (e.g., neuromuscular, visual, and gait impairments contribute to injury risk) and clinical factors (e.g., sub-optimal nutrition and muscle atrophy contribute to bone breakdown), radiation, insufficient accommodations for occupant safety and operational tasks, and detailed mission design (mission design will be closely monitored; when such details are made available, the team will ensure sub-optimal design choices are not implemented to the detriment of human health and performance).

State of Knowledge

Fracture risk (OPS) increases with likelihood of applied loads to bone **>** bone strength. Fracture risk (LTH) is focused on detection of skeletal fragility. Low areal Bone Mineral Density (aBMD) has been widely used to assess skeletal fragility due to age-related bone loss. Diagnosis by aBMD is recognized by terrestrial medicine to be insufficient (requires monitoring index of Bone Quality), especially for men <50 years and pre-menopausal women. Extensive pre/post flight aBMD measurements exist for International Space Station (ISS) astronauts; exercise regimens using ARED/T2 (Advanced Resistive Exercise Device/Treadmill 2) 6 days/week have attenuated deficits in postflight aBMDs. Notably, the minimum aBMD Permissible Outcome Limit (POL) bone health standard was met before ARED/T2 were implemented on the ISS suggesting that postflight aBMD alone is not useful as a POL. Measured changes in putative biomarkers of Bone Quality, e.g., trabecular bone density and microarchitecture, whole bone structure, and estimates of bone strength, with and without pharmaceuticals, are limited to research studies.

L x C Drivers Summary: The assumption of a low severity (non-displaced/minimally displaced) fracture was made for all free-flight DRMs and Lunar Surface DRMs. The assumption of a more severe fracture (more than minimally displaced) fracture was made for the Mars Planetary DRM**. Ops Likelihood per all DRMs:** Very low likelihood of fracture due to low applied fall loads in missions with low G. This likelihood increases with surface operations. The likelihood of crush fractures due to unmitigated kinetic energy in space is unknown but anticipated to be lower in smaller spacecrafts. Mission durations > 100 days experience a higher decline in bone mass. **Ops Consequence per DRM:** LEO, LO, LOS short, Mars Prep: Due to low applied loads to bones, if a fracture occurred, assumed to be low-severity. LEO, LO, LOS short: Evacuation possible in hours to days. Mars Prep: Evacuation capability is variable and inflight treatment may be inadequate or non-existent. LOS (long), Mars Planetary: Higher applied loads may result in assumed more severe fracture, significant performance impacts. Evacuation capability is variable and inflight treatment may be inadequate or non-existent. **LTH Likelihood per DRM:** LEO, LO short, LOS short**:** Likelihood of post-mission fracture due to spaceflight is very low due to limited mission duration and experience from ISS flyers. LO long, LOS long, Mars Prep: Likelihood is high due to long mission durations (evidence of possible irreversible trabecular changes on QCT for similar durations), increased exposure to ionizing radiation beyond LEO contributing to stimulated bone resorption, unproven resistive exercise device, possible decreased estrogen protective effect (as observed with E2 -suppressed menstrual cycling with oral contraceptives), and no anti-resorptive countermeasure. Mars Planetary: Probability of bone fractures after return to Earth is very high due to aforementioned + prolonged mission duration. **LTH Consequence all DRMs:** Most crew could return to baseline aBMD within 3 years but unknown recovery of "Bone Quality" such as trabecular microarchitecture. Risk for premature fractures may result in minor, short-term impact on quality of life and/or career related medical conditions manageable with outpatient medical treatments. The risk for irreversible loss of trabecular connectivity at the hip is unknown but strongly suggested by postflight HR-pQCT measurements at ankle and absence of recovery of QCT-measured hip trabecular bone at R + 2 yrs.

General Assumptions

- Assume that NASA Standards 3001 have been met unless otherwise stated
- Countermeasures equivalent to current ISS countermeasures are in use unless otherwise stated
- Based on the HSRB LxC Matrix and the HSRB DRM Categories

- Assumption of Fracture Severity (this assumption is unchanged from the prior risk update):
  - The SEVERITY OF FRACTURE drives *both likelihood and consequence*.
    - **<u>Free-Flight (Non-Surface DRMs):</u>**
      - Given the small volume of the vehicle and low applied loads in microgravity, any fracture that could occur is assumed to be of low severity (non-displaced or minimally displaced).
    - **<u>Surface Operations (Surface DMRs):</u>**
      - **<u>Lunar Surface Operations</u>, we are assuming a <u>low-severity</u> fracture (non-displaced or minimally displaced)**
        - Drivers include:
          - Lower **applied loads** due to 1/6G, expected ergonomic design of the suit protecting from injury, thoughtful design of EVA activities and engineering out risk for injury with tools/equipment.
      - **<u>Mars Surface Operations</u>, we are assuming <u>a more severe fracture</u> (More than minimally displaced)**
        - Drivers include:
          - Higher **applied loads** due to increase from 1/6 à 1/3G, and more intense activities expected on Mars vs. the Lunar Surface (based on the HEO Mars Task list).
          - Increased **skeletal fragility** due to much longer exposure to microgravity/radiation.

6. LxC Quick Look

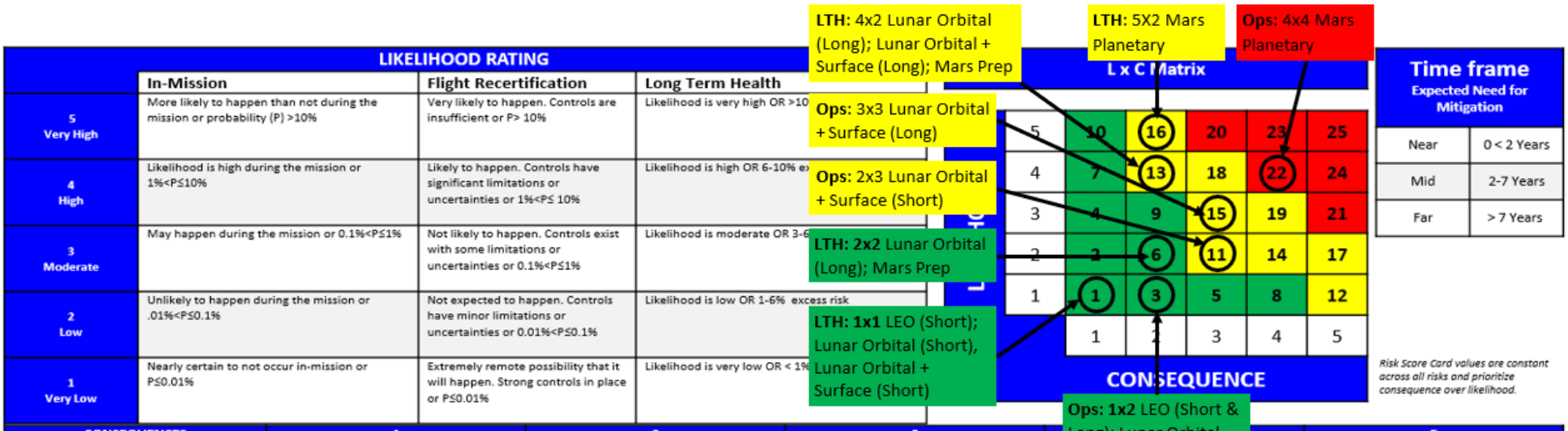
Previous (Approved February 2023)

DRM Categories	Mission Type and Duration	LxC OPS	Risk Disposition	LxC LTH	Risk Disposition
Low Earth Orbit (LEO)	Short (<30 days)	**1x2**	Accepted	**1x1**	Accepted
	Long (30 d - 1 yr.)	**1x2**	Accepted	**2x2**	Requires Characterization
Lunar Orbital (LO)	Short (<30 days)	**1x2**	Accepted	**1x1**	Accepted
	Long (30 d - 1 yr.)	**2x2**	Requires Characterization	**4x2**	Requires Characterization
Lunar Orbital + Surface (LOS)	Short (<30 days)	**2x3**	Accepted	**1x1**	Accepted
	Long (30 d - 1 yr.)	**3x3**	Requires Characterization	**4x2**	Requires Characterization
Mars	Preparatory (<1 year)	**2x2**	Requires Characterization	**4x2**	Requires Characterization
	Planetary (730-1224 days)	**4x4**	Requires Characterization	**5x2**	Requires Characterization

Current (No Changes)

DRM Categories	Mission Type and Duration	LxC OPS	Risk Disposition	LxC LTH	Risk Disposition
Low Earth Orbit (LEO)	Short (<30 days)	**1x2**	Accepted	**1x1**	Accepted
	Long (30 d - 1 yr.)	**1x2**	Accepted	**2x2**	Requires Characterization
Lunar Orbital (LO)	Short (<30 days)	**1x2**	Accepted	**1x1**	Accepted
	Long (30 d - 1 yr.)	**2x2**	Requires Characterization	**4x2**	Requires Characterization
Lunar Orbital + Surface (LOS)	Short (<30 days)	**2x3**	Accepted	**1x1**	Accepted
	Long (30 d - 1 yr.)	**3x3**	Requires Characterization	**4x2**	Requires Characterization
Mars	Preparatory (<1 year)	**2x2**	Requires Characterization	**4x2**	Requires Characterization
	Planetary (730-1224 days)	**4x4**	Requires Characterization	**5x2**	Requires Characterization

7. HSRB Risk likelihood x Consequence Matrix



LIKELIHOOD RATING	In-Mission	Flight Recertification	Long Term Health
5 Very High	More likely to happen than not during the mission or probability (P) >10%	Very likely to happen. Controls are insufficient or P> 10%	Likelihood is very high OR >10
4 High	Likelihood is high during the mission or 1%<P≤10%	Likely to happen. Controls have significant limitations or uncertainties or 1%<P≤ 10%	Likelihood is high OR 6-10% ex
3 Moderate	May happen during the mission or 0.1%<P≤1%	Not likely to happen. Controls exist with some limitations or uncertainties or 0.1%<P≤1%	Likelihood is moderate OR 3-6
2 Low	Unlikely to happen during the mission or .01%<P≤0.1%	Not expected to happen. Controls have minor limitations or uncertainties or 0.01%<P≤0.1%	Likelihood is low OR 1-6% excess risk
1 Very Low	Nearly certain to not occur in-mission or P≤0.01%	Extremely remote possibility that it will happen. Strong controls in place or P≤0.01%	Likelihood is very low OR < 1%

L x C Matrix					
5	10	16	20	23	25
4	7	13	18	22	24
3	4	9	15	19	21
2	2	6	11	14	17
1	1	3	5	8	12
	1	2	3	4	5

CONSEQUENCES		1	2	3	4	5
IN MISSION	Crew Health Impact OR Mission Objectives Impact	Temporary discomfort / Insignificant impact to crew performance and operations – no additional resources required	Minor injury/illness that can be dealt with by crew without ground support, minor crew discomfort / Minor impact to crew performance and operations – requires additional resources (time, consumables)	Significant injury/illness or incapacitation that requires diagnosis and/or treatment support from ground, may affect personal safety / Significant reduction in crew performance, threatens loss of a mission objective	ember requiring extended medical intervention and support, may result in temporary disability / Severe reduction of crew performance that results in loss of multiple mission objectives	Death or permanently disabling injury/illness affecting one or more crewmember (LOCL/LOC) / Loss of mission due to crew performance reductions or loss of crew
FLIGHT RECERT	Crew Flight Recertification Status	Immediate flight recertification status	Flight recertification status within 3 months with limited intervention	Flight recertification status within 1 year with nominal intervention or restricted flight status	Flight recertification status requires extended medical intervention and takes > 1 year	Unable to be Recertified for Flight Status, premature career end
LONG TERM HEALTH	Health Outcomes OR Quality of Life	Career related short term self-resolving medical conditions / No impact on quality of life OR independence in activities of daily living	Career related medical conditions manageable with outpatient medical treatments / Minor, short-term impact on quality of life OR rare support required for activities of daily living	Treatable career related medical condition that requires hospitalization for management / Moderate long-term impact on quality of life OR may require some time-limited support for activities of daily living	Chronic career related medical condition requiring intermittent hospitalization or nursing care / Major long-term impact on quality of life OR requires intermittent support for activities of daily living	Career related premature death or permanent disability requiring institutionalization / Chronic debilitating impact on quality of life OR requires continuous support for activities of daily living

Assumptions for Long Term Health Risk Matrix:

- *Long Term Health extends from the end of the post mission time period and covers an astronaut's lifetime.*
- *Conditions considered within the LTH Risk Matrix are those that 1) are related to the astronaut career, 2) are beyond those expected as part of natural aging, and 3) include acute, chronic and latent conditions.*
- *Quality of Life is defined as impact on day-to-day physical and mental functional capability and/or lifetime loss of years*

8. Risk Postures

Low Earth Orbit (< 30 Days) Operations

1x2	Accepted

- **LxC Drivers for Likelihood:** Short mission duration, low applied loads to bone, large vehicle volume accommodates moving masses.

- **LxC Drivers for Consequence:** Low applied load, assumed less severe fracture, evacuation (hours), resources available for treatment.

- **Rationale for Risk Disposition:** No further risk reduction necessary at this time. Underlying fracture risk in mission depends on expected applied loads and degree of skeletal fragility.
    - Applied Loads to bone:
        – Minimal applied loads (in microgravity low risk for fracture with mechanical overloading of bones). If a fracture occurred, assumed less severe due to low applied loads.
    - Skeletal fragility:
        – No historical fractures in spaceflight. In DRMs < 100 days a smaller decline in total bone mass is expected.

- **DRM Specific Assumptions:** Low severity fracture (non-displaced or minimally displaced); evacuation possible in hours to days.

- **DRM Specific Evidence/Level of Evidence:** 1-Strong

Low Earth Orbit (< 30 Days) Long Term Health

1x1	Accepted

- **LxC Drivers for Likelihood:** Short mission duration.

- **LxC Drivers for Consequence:** Post-flight interventions available if required.

- **Rationale for Risk Disposition:** No further risk reduction necessary at this time. The primary driver for long term health consequences is skeletal fragility.
    - Skeletal Fragility
        – In DRMs < 100 days there is a smaller decline in total bone mass. Bone mass change not likely beyond measurement error of DXA detection. Any BMD loss likely to be recovered

- **DRM Specific Assumptions:** N/A

- **DRM Specific Evidence/Level of Evidence:** 1-Strong

Low Earth Orbit (30 d – 1 yr) Operations

1x2	Accepted

- **LxC Drivers for Likelihood:** Longer mission duration (< 100 days, low risk; > 100 days, increased risk); low applied loads; large vehicle volume accommodates moving masses.

- **LxC Drivers for Consequence:** Evacuation (hours), resources available for treatment.

- **Rationale for Risk Disposition:** No further risk reduction necessary at this time. Underlying fracture risk in mission depends on expected applied loads and degree of skeletal fragility.
    - Applied Loads to bone:
        – Minimal applied loads (in microgravity low risk for fracture with mechanical overloading of bones). If a fracture occurred, assumed less severe due to low applied loads
    - Skeletal fragility:
        – No historical fractures in spaceflight. In DRMs < 100 days a smaller decline in total bone mass is expected. DRMS > 100 days, bone changes that increase fragility have been shown to occur, but low applied loads make fracture less likely.

- **DRM Specific Assumptions:** Assumed no anti-resorptive agent. Evacuation possible in hours to days. Low-severity fracture (non-displaced or minimally displaced).

- **DRM Specific Evidence/Level of Evidence:** 1 - Strong

Low Earth Orbit (30 d – 1 yr) Long Term Health

2x2	Requires Characterization

- **LxC Drivers for Likelihood:** Longer mission duration (< 100 days, low risk; > 100 days, increased risk); lack of recovery at R+2y by QCT.

- **LxC Drivers for Consequence:** Possible prolonged, or absent, recovery to baseline at > R+2y; modification of lifestyle to avoid bone fracture.

- **Rationale for Risk Disposition:** No further risk reduction necessary at this time. The primary driver for long term health consequences is skeletal fragility.
    - Skeletal Fragility
        – Long- duration LEO flight BMD losses have been successfully managed post-flight. The range of bone losses/structural changes varies based on the individual but is increased with increased flight duration > 100 days, with an expected plateau at TBD timing. Rapid loss increases the risk for irreversible trabecular bone changes, which requires further characterization. Fracture analysis indicates increased RR of post-flight fracture in long-duration flyers (90d+). Terrestrial treatment capability available and TREAT* Astronauts Act in place.

- **DRM Specific Assumptions:** Assumed no anti-resorptive agent.

- **DRM Specific Evidence/Level of Evidence:** 2 - Moderate

Lunar Orbital (< 30 Days) Operations

1x2	Accepted

- **LxC Drivers for Likelihood:** Short mission duration; low applied loads; small vehicle volume; increased radiation.

- **LxC Drivers for Consequence:** Evacuation capability (days), resources available for treatment.

- **Rationale for Risk Disposition:** No further risk reduction necessary at this time. Underlying fracture risk in mission depends on expected applied loads and degree of skeletal fragility.
    - Applied Loads to bone:
        - Minimal applied loads (in microgravity low risk for fracture with mechanical overloading of bones). Small vehicle volume makes risk of crush fracture unlikely. If a fracture occurred, assumed less severe due to low applied loads.
    - Skeletal fragility:
        - No historical fractures in spaceflight. In DRMs < 100 days a smaller decline in total bone mass is expected.

- **DRM Specific Assumptions:** Assumed evacuation time to Earth is 3-11 days; Low-severity fracture (non-displaced or minimally displaced), minor fractures could be stabilized prior to return; increased exposure to ionizing radiation

- **DRM Specific Evidence/Level of Evidence:** 1 - Strong

Lunar Orbital (< 30 Days) Long Term Health

1x1	Accepted

- **LxC Drivers for Likelihood:** Short mission duration**.**

- **LxC Drivers for Consequence:** Post-flight interventions available if required.

- **Rationale for Risk Disposition:** No further risk reduction necessary at this time. The primary driver for long term health consequences is skeletal fragility.
    - Skeletal Fragility
        - In DRMs < 100 days there is a smaller decline in total bone mass and exposures to applied loads are minimal (in microgravity low risk for fracture with mechanical overloading of bones. No detectable bone mass change by DXA. Any BMD loss likely to be recovered.

- **DRM Specific Assumptions:** N/A

- **DRM Specific Evidence/Level of Evidence:** 2 - Moderate

Lunar Orbital (30 d – 1 yr) Operations

2x2	Requires Characterization

- **LxC Drivers for Likelihood:** Mission duration, (< 100 days, low risk; > 100 days, increased risk); unproven resistive exercise device; low applied loads; small vehicle volume; increased radiation.

- **LxC Drivers for Consequence:** Evacuation capability (days); performance/resource impact, resources available for treatment.

- **Rationale for Risk Disposition:** Underlying fracture risk in mission depends on expected applied loads and degree of skeletal fragility.
    - Applied Loads to bone:
      – Minimal applied loads (in microgravity low risk for fracture with mechanical overloading of bones. Small vehicle volume makes risk of crush fracture unlikely. If a fracture occurred, assumed less severe due to low applied loads.
    - Skeletal fragility:
      – No historical fractures in spaceflight. In DRMs < 100 days a smaller decline in total bone mass is expected. DRMS > 100 days, bone changes that increase fragility have been shown to occur, but low applied loads make fracture less likely. The magnitude of possible contributions to skeletal fragility are uncharacterized for this DRM (radiation, resistive exercise).

- **DRM Specific Assumptions:** Assumed no anti-resorptive agent; evacuation time to Earth is 3-11 days; Low-severity fracture (non-displaced or minimally displaced), minor fractures could be stabilized prior to return; increased exposure to ionizing radiation

- **DRM Specific Evidence/Level of Evidence:** 2 - Moderate

Lunar Orbital (30 d – 1 yr) Long Term Health

4x2	Requires Characterization

- **LxC Drivers for Likelihood:** Mission duration (< 100 days, low risk; > 100 days, increased risk); increased radiation; unproven resistive exercise device; QCT not recovered at R+2y; landing, dynamic loads; irreversible loss of trabecular connectivity.

- **LxC Drivers for Consequence:** Possible prolonged, or absent, recovery to baseline at > R+2y; increased risk of fracture post-flight.

- **Rationale for Risk Disposition:** The primary driver for long term health consequences is skeletal fragility. Long term impact of bone changes due to lunar spaceflight are uncharacterized. Characterization requires a comprehensive surveillance plan including measures such as additional imaging (i.e., QCT) and biochemical assays. Risk for irreversible changes is high; disruptions in trabecular microarchitecture, a defined characteristic of osteoporosis, may result in premature skeletal fragility in astronauts. Reductions in cortical bone volume and thickness and postflight increases in cross-sectional cortical bone growth are both seen with unknown impact to LTH. The risk for future fracture events likely increases with longer spaceflights. Terrestrial treatment capability available and monitoring of former astronauts that participate in LSAH.

- **DRM Specific Assumptions:** Assumed no anti-resorptive

- **DRM Specific Evidence/Level of Evidence:** 2 - Moderate

Lunar Orbital + Surface(< 30 Days) Operations

2x3	Accepted

- **LxC Drivers for Likelihood:** Short mission duration; increased applied loads, surface hazards; increased radiation; low number of EVAs (~5); exploration Extravehicular Mobility Unit (xEMU) assumed with more leg movement; lander vehicle design.

- **LxC Drivers for Consequence:** Evacuation time (3-11 days); EVAs —5 (Assumption avg 1/wk); resources available for treatment

- **Rationale for Risk Disposition:** No further risk reduction necessary at this time. Underlying fracture risk in mission depends on expected applied loads and degree of skeletal fragility.
    - Applied Loads to bone:
        – Surface hazards and activities increase risk of mechanical overloading of bones. EVA suit could attenuate energy of falls but may also present increased or repetitive movement that could contribute to fracture mechanism. If a fracture occurred, assumed not severe due to low applied loads.
    - Skeletal fragility:
        – No historical fractures in spaceflight. In DRMs < 100 days a smaller decline in total bone mass is expected. The magnitude of possible contributions to skeletal fragility are uncharacterized for this DRM (radiation, resistive exercise).

- **DRM Specific Assumptions:** Assumed no MKS injury on landing; EVAs — 5 (Assumption avg 1/wk); evacuation time to Earth is 3-11 days; Low-severity fracture (non-displaced or minimally displaced), fracture could interfere with EVA activities; minor fractures could be stabilized prior to return; increased exposure to ionizing radiation

- **DRM Specific Evidence/Level of Evidence:** 2 - Moderate

Lunar Orbital + Surface (< 30 Days) Long Term Health

1x1	Accepted

- **LxC Drivers for Likelihood:** Short mission duration; partial gravity may provide some proportional protection.
- **LxC Drivers for Consequence:** No technology to assess loss of trabecular connectivity in deeply embedded bones.
- **Rationale for Risk Disposition:** No further risk reduction necessary at this time. The primary driver for long term health consequences is skeletal fragility. In DRMs < 100 days there is a smaller decline in total bone mass and exposures to applied loads are minimal (in microgravity low risk for fracture with mechanical loading). Bone mass change not likely beyond measurement error of DXA detection. Any BMD loss likely to be recovered.
- **DRM Specific Assumptions:** Assumed no anti-resorptive
- **DRM Specific Evidence/Level of Evidence:** 2 - Moderate

Lunar Orbital + Surface (30 d – 1 yr) Operations

3x3	Requires Characterization

- **LxC Drivers for Likelihood:** Mission duration, (< 100 days, low risk; > 100 days, increased risk);unproven resistive exercise device; Increased radiation; xEMU assumed with more leg movement; lander vehicle design; Increased applied loads, surface hazards; IMM risk 0.1% < P < 1%.
- **LxC Drivers for Consequence:** Evacuation time (3-11 days); EVAs 3-4/wk. (20-24hrs/wk.), resources available for treatment.
- **Rationale for Risk Disposition:** Underlying fracture risk in mission depends on expected applied loads and degree of skeletal fragility.
    - Applied Loads to bone:
        – Higher loads in 1/6G with potential for unmitigated kinetic energy and crush injury during surface activities. EVA suit could attenuate energy of falls but may also present increased or repetitive movement that could contribute to fracture mechanism. Fracture could interfere with EVA activities.
    - Skeletal fragility:
        – In DRMs < 100 days a smaller decline in total bone mass is expected. DRMS > 100 days, bone changes that increase fragility have been shown to occur. The magnitude of possible contributions to skeletal fragility are uncharacterized for this DRM (radiation, resistive exercise).

- **DRM Specific Assumptions:** No MSK injury on landing; No anti-resorptive; evacuation time to Earth is 3-11 days; Low-severity fracture (non-displaced or minimally displaced). Minor fractures could be stabilized prior to return; increased exposure to ionizing radiation.

- **DRM Specific Evidence/Level of Evidence:** 2 - Moderate

Lunar Orbital + Surface (30 d – 1 yr)
Long Term Health

4x2	Requires Characterization

- **LxC Drivers for Likelihood:** Mission duration (< 100 days, low risk; > 100 days, increased risk); unproven resistive exercise device; increased radiation; unproven resistive exercise device; QCT not recovered at > R+2y; landing, dynamic loads; irreversible loss of trabecula; partial gravity, some protection.

- **LxC Drivers for Consequence:** Possible prolonged, recovery to baseline at > R+2y; increased fracture risk post-flight.

- **Rationale for Risk Disposition:** The primary driver for long term health consequences is skeletal fragility. Long term impact of bone changes due to lunar spaceflight are uncharacterized. Characterization requires a comprehensive surveillance plan including measures such as additional imaging (i.e., QCT) and biochemical assays. Risk for irreversible changes is high disruptions in trabecular microarchitecture, a defined characteristic of osteoporosis, may result in premature skeletal fragility in astronauts. Reductions in cortical bone volume and thickness and postflight increases in radial cortical bone growth are both seen with unknown impact to LTH. The risk for future fracture events likely increases with longer spaceflights. Terrestrial treatment capability available and monitoring of former astronauts that participate in LSAH.

- **DRM Specific Assumptions:** Assumed no anti-resorptive

- **DRM Specific Evidence/Level of Evidence:** 2 - Moderate

Mars Preparatory (<1 yr.)
Operations

2x2	Requires Characterization

- **LxC Drivers for Likelihood**: Longer mission duration; unproven resistive exercise devices; increased radiation; small volume vehicle, no resupply; contingency EVA only, in microgravity, not on surface

- **LxC Drivers for Consequence:** Evac time days - weeks, resources available for stabilization, but definitive treatment may be unavailable.

- **Rationale for Risk Disposition:** Underlying fracture risk in mission depends on expected applied

loads and degree of skeletal fragility.

- Applied Loads to bone:
  – Small vehicle and lack or resupply reduce risk for crush fracture loads. Contingency EVA only.
- Skeletal fragility:
  – In DRMs < 100 days a smaller decline in total bone mass is expected. DRMS > 100 days, bone changes that increase fragility have been shown to occur. The magnitude of possible contributions to skeletal fragility are uncharacterized for this DRM (radiation, unproven resistive exercise).

- **DRM Specific Assumptions:** Assumed no anti-resorptive; Low-severity fracture (non-displaced or minimally displaced); long evacuation time; on orbit treatment capabilities yet to be determined; increased exposure to ionizing radiation.

- **DRM Specific Evidence/Level of Evidence:** 2 - Moderate

Mars Preparatory (<1 yr.) Long Term Health

4x2	Requires Characterization

- **LxC Drivers for Likelihood:** Mission duration (< 100 days, low risk; > 100 days, increased risk); increased radiation; unproven resistive exercise device; QCT not recovered at R+2y; landing, dynamic loads; irreversible loss of trabecular connectivity.

- **LxC Drivers for Consequence:** Possible prolonged, or absent, recovery to baseline at > R+2y. Lifestyle modification to prevent fractures due to physical activities mechanically overloading bones.

- **Rationale for Risk Disposition:** The primary driver for long term health consequences is skeletal fragility. Long term impact of bone changes due to interplanetary spaceflight are uncharacterized. Characterization requires a comprehensive surveillance plan including measures such as additional imaging (i.e., QCT) and biochemical assays. Risk for irreversible changes is high; disruptions in trabecular microarchitecture, a defined characteristic of osteoporosis, may result in premature skeletal fragility in astronauts. Reductions in cortical bone volume and thickness are seen with unknown impact to LTH. The risk for future fracture events likely increases with longer spaceflights. Terrestrial treatment capability available and monitoring of former astronauts that participate in LSAH.

- **DRM Specific Assumptions:** Assumed no anti-resorptive.

- **DRM Specific Evidence/Level of Evidence:** 3 - Weak

Mars Planetary (730-1224 d)

4x4	Requires Characterization

Operations

- **LxC Drivers for Likelihood:** Longer mission duration; Unproven resistive exercise device; Increased Radiation; Larger applied loads, surface hazards; IMM data 1-3% risk (with uncertainty ~5%).

- **LxC Drivers for Consequence:** EVAs — 2 crew x 20, 8 hr. days (Assumption avg 1-2/month); Evac time - Mission Duration, resources available for stabilization, but definitive treatment may be unavailable.

- **Rationale for Risk Disposition:** Underlying fracture risk in mission depends on expected applied loads and degree of skeletal fragility.
    - Applied Loads to bone:
        – Mars mission tasks listed by Human Exploration and Operations Mission Directorate (HEOMD) increases expected applied loads beyond those of fall from standing. Protective effects of 1/3G are uncharacterized. Awareness and effective HSIA processes may reduce risk for injury during missions. Fracture could interfere with EVA activities.
    - Skeletal fragility:
        – DRMS > 100 days, bone changes that increase fragility have been shown to occur. The magnitude of possible contributions to skeletal fragility are uncharacterized for this DRM (radiation, unproven resistive exercise).

- **DRM Specific Assumptions:** Assumed no anti-resorptive; long evacuation time; on orbit treatment capabilities yet to be determined; More severe fracture (more than minimally displaced), fracture could interfere with EVA activities.

- **DRM Specific Evidence/Level of Evidence:** 3 - Weak

Mars Planetary (730-1224 d) Long Term Health

5x2	Requires Characterization

- **LxC Drivers for Likelihood:** Prolonged mission duration (> 100 days, increased risk); irreversible loss of trabecular connectivity; increased radiation; unproven resistive exercise device; QCT lack of recovery at > R+2y; unknown if partial gravity offers any protection.

- **LxC Drivers for Consequence:** Limited technology to assess changes in deeply embedded bones; Possible prolonged, or absent, recovery to baseline may be at > R+2y; Lifestyle modification to prevent fracture.

- **Rationale for Risk Disposition:** The primary driver for long term health consequences is skeletal fragility. Long term impact of bone changes due to interplanetary spaceflight are uncharacterized. Characterization requires DXA, QCT, biochemical assays and surveillance. Characterization requires a comprehensive surveillance plan including measures such as additional imaging (i.e., QCT) and biochemical assays. Risk for irreversible changes is high;

disruptions in trabecular microarchitecture, a defined characteristic of osteoporosis, may result in premature skeletal fragility in astronauts. Reductions in cortical bone volume and thickness are seen with unknown impact to LTH. The risk for future fracture events likely increases with longer spaceflights. Terrestrial treatment capability available and monitoring of former astronauts that participate in LSAH.

- **DRM Specific Assumptions:** Assumed no anti-resorptive

- **DRM Specific Evidence/Level of Evidence:** 3 - Weak

9. Overall Assessment of the Evidence

- New technologies – evidence for Fracture risk assessment is being actively investigated
- The previously presented evidence of 2021 has been written up as manuscripts for peer-reviewed submission for journal publication.
- Peer-review provides critical vetting of the interpretation of data acquired from a unique cohort (for which there is minimal baseline characterization) exposed to a rare and novel skeletal insult (e.g., spaceflight).
- **Risk for Fracture Due to Spaceflight-Induced Changes to Bone: The Case for Bisphosphonate Use in Astronauts Flying Long-Duration Missions.** Manuscript published ejournal Cells. 8/2024 Authors: Reece Rosenthal, BS; Victor S. Schneider, MD; Jeffrey A. Jones, MD; Jean D. Sibonga, PhD.
  - *This submission focuses on the cell biology of spaceflight-induced bone loss and the cellular mechanism of action of the bisphosphonate class of drugs which specifically target osteoclasts (without the rebound-effect after treatment cessation associated with denosumab, another anti-osteoclastic drug). The important message is that the cellular mechanism of action of bisphosphonates is "intact" during spaceflight.*
- **Increased Rates of Hip and Spine Fractures Associated with Longer Spaceflight Duration.** Submitted to (3/25) for potential publication in Mayo Clinic Proceedings. Authors : Tristen N. Taylor, Millennia Young, Elisabeth R. Spector, Amy J. Kreykes, and Jean Sibonga.
  - *Presented as poster at ASBMR Annual Meeting 2022 Austin, TX. This manuscript is the first to report 1)increased rate in astronauts of hip and spine fracturs – skeletal sites that are clinically predisposed to age-related bone loss, 2) a comparison of fracture events monitored over ranges of person-years relative to long-duration SF exposure and 3) a comparison of fracture data within the astronaut cohort (LD vs. non-LD exposure) in addition to terrestrial age-matched terrestrial populations.*

- Manuscripts submitted by 3/25

Use of DXA-based Software to Identify Astronauts at Risk for Persisting Spaceflight-induced Bone Loss. Heenam Goel[1], Elisabeth Spector[2], Greg Yardley[2], Samuel Mosiman[3], Diane Krueger[3], Neil Binkley[3], Jean Sibonga[4]. [1]CentraCare, St. Cloud, MN, USA [2]KBRWyle, Houston TX [3]University of Wisconsin, Madison, USA [4]NASA Johnson Space Center, Houston TX. Short Communication manuscript under refinement to be submitted to Osteo International. ***Pilot validation of modified DXA software to identify astronauts at R + 1 yr who did not recover hip Trabecular BMD by QCT at R + 2 yrs – the use of DXA will limit the number of astronauts who may need further verification by more sensitive QCT***

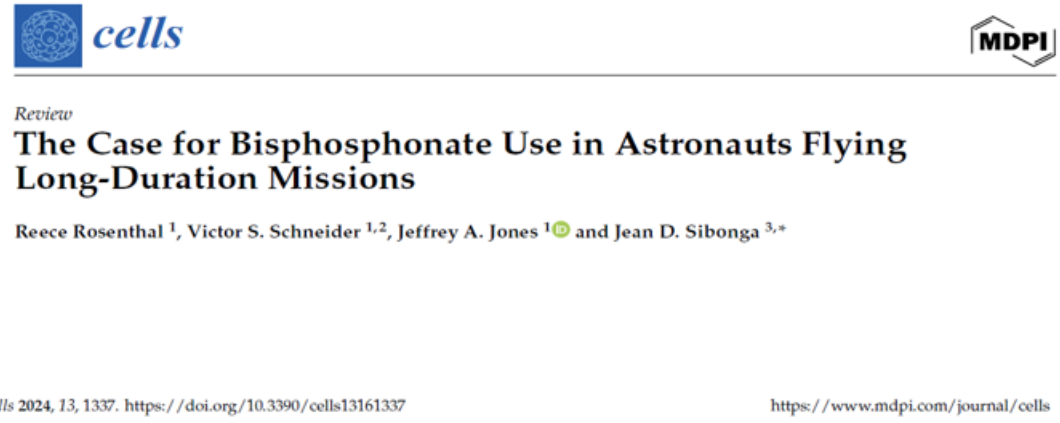
Spaceflight Effects on Astronaut Trabecular Bone Score of the Lumbar Spine. KD Anderson[1], ER Spector[3], R Ploutz-Snyder[4], G. Yardley[2],NB Watts[5], D Hans[6], JD Sibonga[2]. [1]Rush University Medical Center, Chicago, IL [2]NASA Johnson Space Center, Houston, TX, [3]KBR, Houston, TX ,[4]University of Michigan School of Nursing, Ann Arbor, MI [5]Mercy Health, Cincinnati, OH. [6]Lausanne University and Hospital, Lausanne, VD, Switzerland Penultimate manuscript under review for ATP submitted 1/24 to Osteo International.

Programmatic Utility of QCT scans: Evaluating efficacy of in-flight countermeasures to preserve astronaut preflight skeletal status. KD Anderson,1 E.R. Spector,3 T. Lang,4 A.D. Leblanc,5 J.D. Sibonga,*1 1National Aeronautics Space Administration (NASA) Johnson Space Center, Houston, TX, Houston, TX, 2KBrWyle, Houston, TX, 3University of California, San Francisco, CA, 4Baylor College of Medicine, Houston, TX Penultimate manuscript under review for ATP to be submitted to journal npj Microgravity . ***This manuscript extends the utility of QCT to evaluate the efficacy of in-***

flight countermeasures (pre- and postflight monitoring) to mitigate SF–induced skeletal changes to both cortical and trabecular bone.

10. State of Knowledge – New Evidence

- Investigations for new and continued evidence for the Bone Fracture risk are in progress



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Review

The Case for Bisphosphonate Use in Astronauts Flying Long-Duration Missions

Reece Rosenthal [1], Victor S. Schneider [1,2], Jeffrey A. Jones [1] and Jean D. Sibonga [3,*]

Cells **2024**, *13*, 1337. https://doi.org/10.3390/cells13161337 https://www.mdpi.com/journal/cells

11. Metrics

- The metrics for risk progress are:
  - the calculated fracture incidence rate (by SK Biostatistician), adjusted for age and period considered "at risk" (follow-up time)
  - the hip and spine fractures in LD astronauts (>90-100 days spaceflight exposure) reported to and documented by the LSAH and
  - expressed as rate of fracture incidence relative to both non-LD astronauts and similarly aged, sex-specific terrestrial cohort.*
- The previously presented metrics (above) are included in the manuscript for publication (Taylor et al).
- Proposed alternative metric for countermeasure efficacy – effective mitigation (within measurement error to test) of spaceflight-induced changes to bone.

  - *Only fractures in males in this presentation to preserve data privacy.

12. Risk Mitigation Framework – Color Changes

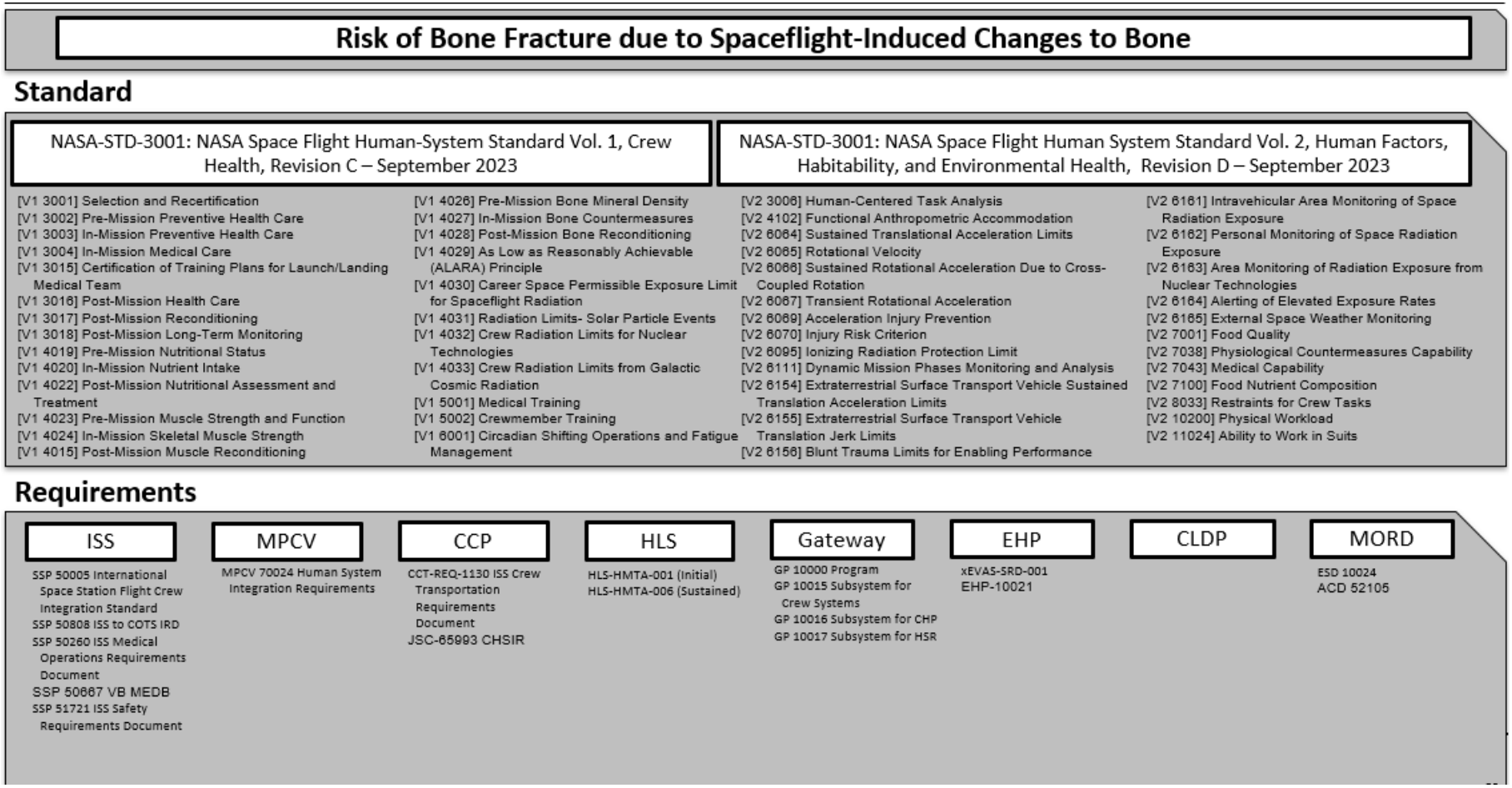
- **How do we know when we go from red → yellow? Mars planetary DRM**
  - Requires further characterization. Trabecular changes are strongly suspected based upon Analogy to terrestrial populations, but no non-invasive monitoring test exists to assess these changes in deeply embedded bones.
  - Risks associated with bisphosphonates reduce acceptance of this systemic, anti-resorptive pharmaceutical agent (not a panacea).
  - Astronauts still continue to lose bone mass in spite of ARED exercise. Cannot predict who will/will not lose. As an alternative to treating everyone –
  - Continue Preflight to postflight characterization of bone changes (DXA areal BMD and bone turnover biomarkers, QCT parameters bone mass of 3D bone morphology)
  - Determine acceptable metrics for spaceflight-induced skeletal changes that incorporate changes to bone structure in addition to bone mineral density (T-scores in the younger-aged astronaut population are not predictive of fracture risk)
  - Develop capability to conduct real-time biochemical assays of bone turnover to identify astronauts who are not responding, and to prompt countermeasure use or modification
  - Develop an in-flight monitoring device to characterize the progressive loss of trabecular connectivity and better assess the efficacy of current countermeasures/modify countermeasures moving forward
  - Identify mission tasks that are likely to put the astronaut at risk for mechanically over-loading the skeletal sites
  - Modify assessment of countermeasures by their ability to maintain crewmembers at pre-flight measurement levels (within the % measurement error of test/technology)

- **In the absence of fracture outcomes clearly linked to spaceflight-induced changes**, stakeholders reluctant to use countermeasures with any risks. Data provided by a "bone health monitoring device" for deeply embedded bones during DRMs are critical for individualizing the countermeasure prescriptions.

- **How do we know when we go from yellow → green?** Use of the above-mentioned technology for deeply embedded bones during spaceflight, and with ground-based imaging technologies after spaceflight, to inform the type and timing of post-flight therapies (e.g., to prevent further bone loss and/or restore bone mass).
  - Modify assessment of countermeasures by their ability to maintain crewmembers at pre-flight measurement levels (within the % measurement error of test/technology)

- **In the absence of fracture outcomes clearly linked to spaceflight-induced changes**, stakeholders reluctant to use countermeasures with any risks. Data provided by a "bone health monitoring device" for deeply embedded bones during DRMs are critical for individualizing the countermeasure prescriptions real-time.

13. Risk → Standard → Requirements Flow



14. Proposed Standard Updates

- Consistent with assessing countermeasure efficacy based upon mitigating spaceflight-induced changes (within measurement error of test), may consider future modification of standard to include a "least significant change" standard as similarly implemented in densitometry field.

15. High Value Risk Mitigation Targets

The results of the research studies revealed the following targets for further characterization:

- Expand characterization (QCT, DXA, biochemical assays) of hip bone (pre- to postflight loss and postflight recovery).
- Characterization of the anti-resorptive countermeasures (including but not limited to pharmaceuticals) in the astronaut population.
- Capability to monitor for changes in trabecular bone architecture of deeply embedded bones (i.e., hip and spine) during spaceflight. Would inform need for real-time intervention to prevent an irreversible loss of trabecular connectivity.

16. Conclusions

- QCT scans characterize changes in Hip Bone Quality (i.e., attributes of bone that contribute to bone strength, and potentially fracture risk, independent of DXA-measured areal BMD).
- Data to-date, suggest that an anti-resorptive countermeasure could suppress bone loss due to breakdown of bones by osteoclasts; if unabated, astronauts may be at risk for irreversible losses in trabecular connectivity which cannot be resolved by QCT. These changes require further characterization.
- Emerging technologies to assess for irreversible changes to trabecular bone microarchitecture of deeply embedded bones should be taken advantage of, once validated.
- Resistive exercise on ARED does not mitigate systemic bone breakdown during spaceflight but in some cases have preserved astronauts at their preflight skeletal status - consistent with effective stimulation of bone formation. Further characterization of resistive exercise devices is warranted.
- Difficult to substantiate with actual fracture outcomes that countermeasures can mitigate the risk (i.e., reducing # of hip/spine fractures). Propose verifying countermeasure efficacy to mitigate/prevent 1) spaceflight-induced changes to bone tissue (e.g., to within the measurement error of testing modalities) and 2) elevations in biomarker(s) for bone resorption.
- Need to characterize the effects of a hypobaric/slightly hypoxic exploration atmosphere environments to bone physiology in space

17. Recommendations Accepted

- ❖ The Risk Record of the Bone Fracture Risk provides:
  - Revised content

18. Acronyms and Abbreviations

aBMD	areal Bone Mineral Density
Aerobic Risk	Risk of Reduced Physical Performance Capabilities Due to Reduced Aerobic Capacity
Afib	Atrial Fibrillation
ARED	Advanced Resistive Exercise Device
BF	Bone Formation
Bis	Bisphosphonate
BMD	Bone Mineral Density
BR	Bone Resorption
BRESCB	Biomedical Research and Environmental Science Control Board
BSAP	Bone Specific Alkaline Phosphatase
BZK	Benzalkonium chloride
CB	Astronaut Office (Division Code)
CHP	Crew Health and Performance
CI	Confidence Interval
CK	Flight Integration Division (Division Code)
CMs	Countermeasures
CR	Change Request
DAG	Directed Acyclic Graph
DCS	Decompression Sickness
DCS Risk	Risk of Decompression Sickness
DRM	Design Reference Mission
DXA	dual-energy x-ray absorptiometry
EBWG	Evidence Base Working Group
EVA	Extravehicular Activity
EVA Risk	Risk of Injury and Compromised Performance Due to EVA Operations
FD	Flight Day
FEA	Finite Element Analysis
Food - Nutrition Risk	Risk of Performance Decrement and Crew Illness Due to Inadequate Food and Nutrition
Fx	Fracture
g/dl	grams per deciliter
GI	gastrointestinal
HEO	Human Exploration and Operations Mission Directorate
HRP	Human Research Program
HSIA Risk	Risk of Adverse Outcome Due to Inadequate Human Systems Integration Architecture

HSRB	Human System Risk Board
IMM	Integrated Medical Model
ISCD	International Society for Clinical Densitometry
ISS	International Space Station
IV	Intravenous
IVA	intravehicular
LD	Long Duration
LEO	Low Earth Orbit
LO	Lunar Orbital
LOCL	Loss of Crew Life
LOM	Loss of Mission
LOMO	Loss of Mission Objectives
LOS	Lunar Orbital + Surface
LSAH	Long Term Surveillance of Astronaut Health
LTH	Long-Term Health
LxC	Likelihood and Consequence
MSK	musculoskeletal
Muscle Risk	Risk of Impaired Performance Due to Reduced Muscle Size, Strength & Endurance
N	number of subjects
NASA-STD-3001	NASA-STD-3001, Space Flight Human-System Standard
nmol/d	nanomoles per day
NTX	Amino Terminal Telopeptide
Ops	Operations
Pharm Risk	Risk of Ineffective or Toxic Medications During Long-Duration Exploration Spaceflight
POL	Permissible Outcome Limit
PTH	Parathyroid Hormone
R+	Return +
REID	Risk of Exposure-induced Death
RR	Relative Risk
SANS Risk	Risk of Spaceflight Associated Neuro-ocular Syndrome
SD	Space Medicine Operations Division (Division Code)
SDS	Single dose syringe
SE	Standard error
Sensorimotor Risk	Risk of Impaired Control of Spacecraft/ Associated Systems and Decreased Mobility Due to Sensorimotor/Vestibular Alterations Associated with Space Flight
SF	Human Systems Engineering & Integration Division (Division Code)
SK	Biomedical Research and Environmental Sciences Division (Division Code)
SMO	Supplemental Medical Object
SMOCB	Space Medicine Operations Control Board

SPEL	Space Permissible Exposure Limit
SQ	sub-cutaneous
T2	Treadmill 2
U/L	Units per Liter
vBMD	Volumetric Bone Mineral Density
xEMU	Exploration Extravehicular Mobility Unit
ZA	Zoledronic acid

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Appendix – Existing Evidence Base

Existing Evidence — Rev B

Analysis of Astronaut Fracture Data (New Evidence)

- Data were analyzed on 262 astronauts over 8433.6 person-years splitting across
  - No spaceflight (262 individuals and 1882.7 person-years)
  - Non-LD spaceflight (232 individuals and 6121.3 person-years)
  - LD spaceflight (42 individuals and 429.6 person-years)
- The number of fractures was modeled using count regression (Negative Binomial or Poisson) adjusting for:
  - The repeated measures within individuals across the groupings
  - The differing lengths of follow-up for each individual
  - Age at start of follow-up for each of the groupings
    - Age at selection for No Spaceflight group; age at landing from first mission (LD or non-LD groups)
    - Overall estimates were predicted for the average age
    - Once astronaut is exposed to LD spaceflight, astronaut is no longer considered in non-LD group.
- Evidence found for an *increased* rate of *hip* and *spine* fractures for *LD (> 90 days) follow-up as compared to non-LD (< 90 days) follow-up*.
- Similar rates of fractures for LD and non-LD at other sites.

* This fracture analysis is not broken down by IRED vs. ARED. This was suggested as future work during the HSRB presentation on March 11, 2021.

Relative Rate for Fracture Incidence (All Types) in Astronauts per Spaceflight Exposures (New Evidence)

- Higher rate of fracture (Fx) before any flight.
- Total Fx – Non-LD vs No Spaceflight:
  - RR 0.56 (95%CI*: 0.40, 0.79)
- Adjusted for age – predicted at average age at the start of follow-up
- Adjusted for repeated individuals and differing lengths of follow-up time.

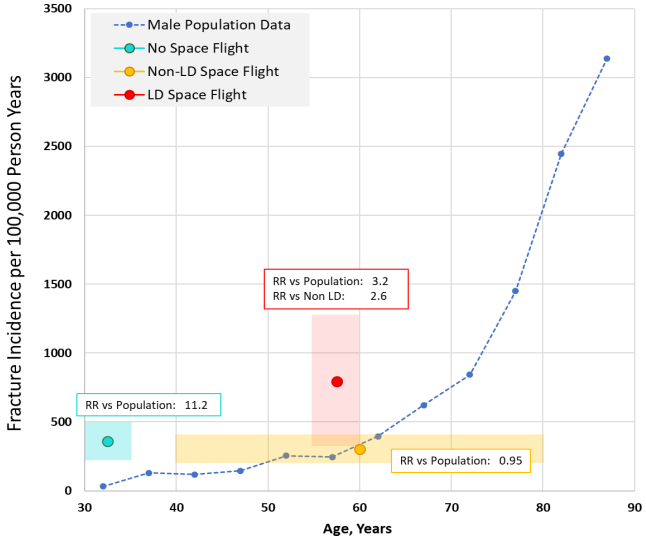
*Confidence Interval

Analysis of LSAH Astronaut Fracture Data (New Evidence)

- Higher rate of hip and spine Fx associated with LD flight (>90 days).
- LD vs non-LD spaceflight:
  - Hip – Relative Rate (RR) 3.4 (95%CI: 1.0, 12.0)
  - Spine Events – RR: 3.4 (95%CI: 1.0, 11.6)
- Adjusted for age – predicted at average age at the start of follow-up.
- Adjusted for repeated individuals and differing lengths of follow-up time.

Spine (Thoracic + Lumbar) Fracture Incidence – Astronaut vs Terrestrial Population Data

Shaded Boxes around the mean (circle):



Height represents ± Standard Error (SE) around incidence rate

Width represents approximate age range of recorded fractures

Dot represents average age of recorded fractures

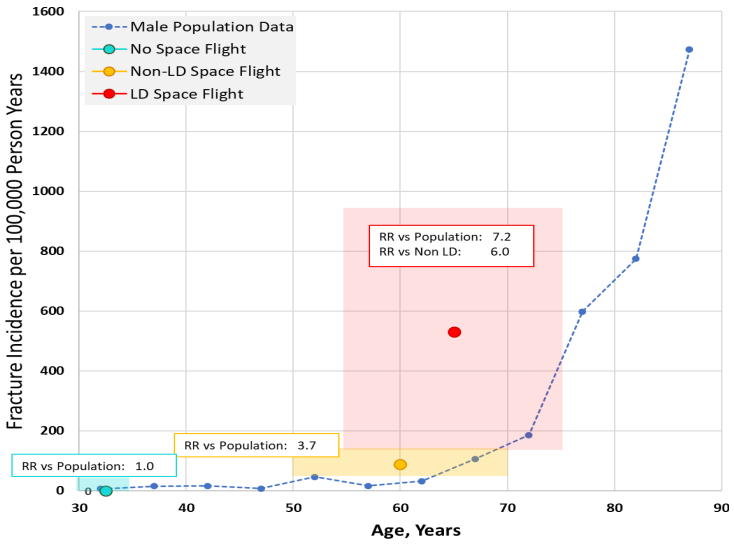
Only Males

No SF: 6 out of 1675 person years (4 fracture events)
Non-LD SF: 17 out of 5626 person years (15 fracture events)
LD SF: 3 out of 377 person years (3 fracture events)

Graph based upon data from Amin et al., 2014 J Bone Miner Res, and Farr et al, J Bone Miner Res 2017 .

Hip Fracture Incidence – Astronaut vs Terrestrial Population Data

Shaded Boxes around the mean (circle):



Height represents ± Standard Error (SE) around incidence rate

Width represents approximate age range of recorded fractures

Dot represents average age of recorded fractures

Population data are from Amin 2014 J Bone Miner Res, Farr 2017 J Bone Miner Res

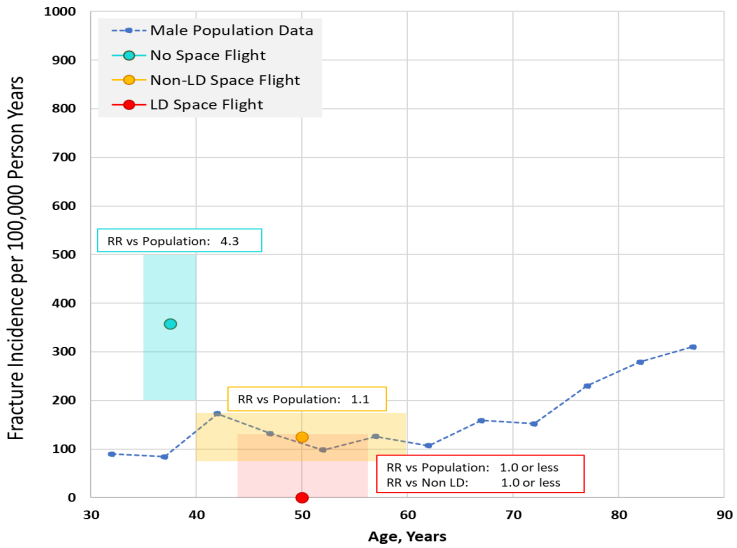
Only Males

No SF: 0 out of 1675 person years
Non-LD SF: 5 out of 5626 person years (includes 1 fx where SF exposure was >50 but <90d)
LD SF: 2 out of 377 person years

Graph based upon data from Amin et al., 2014 J Bone Miner Res, and Farr et al, J Bone Miner Res 2017 .

Wrist Fracture Incidence – Astronaut vs Terrestrial Population Data

Shaded Boxes around the mean (circle):



Height represents ± Standard Error (SE) around incidence rate

Width represents approximate age range of recorded fractures

Dot represents average age of recorded fractures

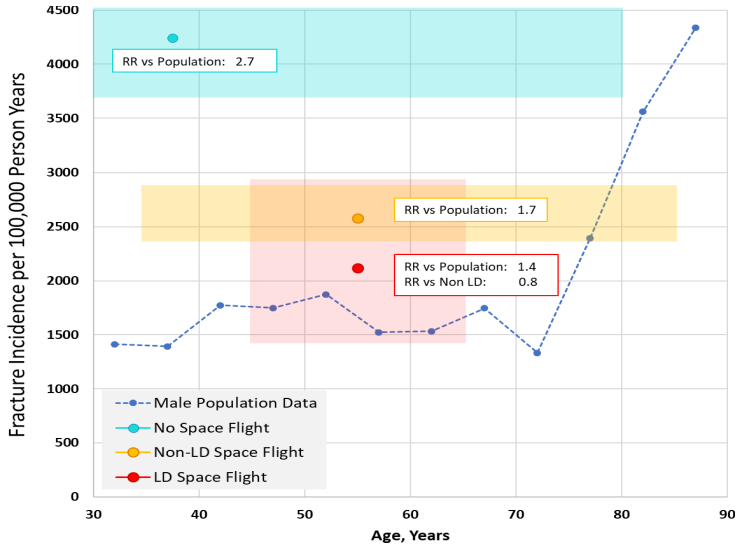
Only Males

No SF: 6 out (Ctrl) years (6 fracture events)
Non-LD SF: 7 out years (6 fracture events)
LD SF: 0 out of 377 person years

LD – Long Duration
Graph based upon data from Amin et al., 2014 J Bone Miner Res, and Farr et al, J Bone Miner Res 2017 .

All Fractures (excl. hip and spine) Incidence – Astronaut Data vs Terrestrial Population Data

Shaded Boxes around the mean (circle):



Height represents ± Standard Error (SE) around incidence rate

Width represents approximate age range of recorded fractures

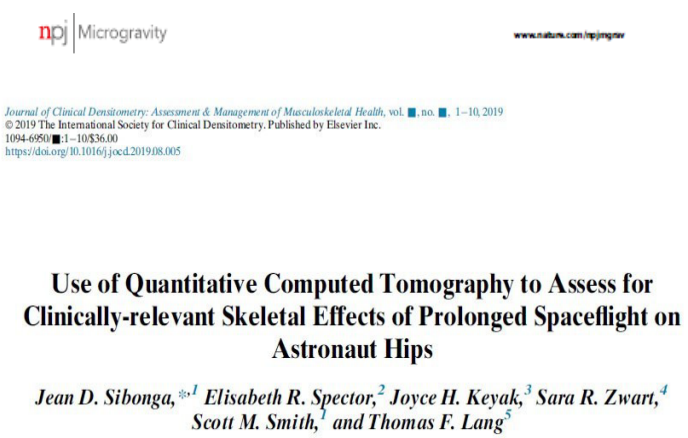
Dot represents average age of recorded fractures

Only Males

No SF: 71 out of 1675 person years (67 fracture events)
Non-LD SF: 145 out of 5626 person years (127 fracture events)
LD SF: 8 out of 377 person years (8 fracture events)

LD – Long Duration
Graph based upon data from Amin et al., 2014 J Bone Miner Res, and
Farr et al, J Bone Miner Res 2017

Human Research Program Research (New Evidence)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www.nature.com/npjmgrav

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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]*


Bone 137 (2020) 115321

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

ELSEVIER

Full Length Article

Hip load capacity and yield load in men and women of all ages

J.H. Keyak[a,b,c,*], T.S. Kaneko[a], S. Khosla[d], S. Amin[e,f], E.J. Atkinson[g], T.F. Lang[h], J.D. Sibonga[i]

Bone 128 (2019) 112037

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

ELSEVIER

Full Length Article

Resistive exercise in astronauts on prolonged spaceflights provides partial protection against spaceflight-induced bone loss

J. Sibonga[a,*], T. Matsumoto[b], J. Jones[c], J. Shapiro[d], T. Lang[e], L. Shackelford[a], S.M. Smith[a], M. Young[a], J. Keyak[f], K. Kohri[g], H. Ohshima[h], E. Spector[i], A. LeBlanc[c]

BMD Data from Extended Bis SMO (DXA and QCT) (New Evidence)

- ❖ ARED alone does not fully preserve preflight skeletal status

See Figures 1 and 2 in Sibonga et al., *Bone*, 2019

Amino Terminal Telopeptide (NTX) and Bone Specific Alkaline Phosphatase (BSAP) from Extended Bis SMO (New Evidence)

- ❖ Elevated bone resorption during spaceflight is not suppressed by ARED exercise.

See Fig. 6 in Sibonga et al., *Bone*, 2019

ARED Only n=10:

Consistent with Smith et al. Bone 2015. n=4-9

Hip QCT Surveillance of Bone Loss and Recovery (New Evidence)

- ❖ Pilot Study: Hip QCT reveals persistent bone deficits and delayed recovery that are not captured by DXA testing.

aBMD = Areal Bone Mineral Density

vBMD = Volumetric Bone Mineral Density

See Fig. 2 in Sibonga et al. 2020

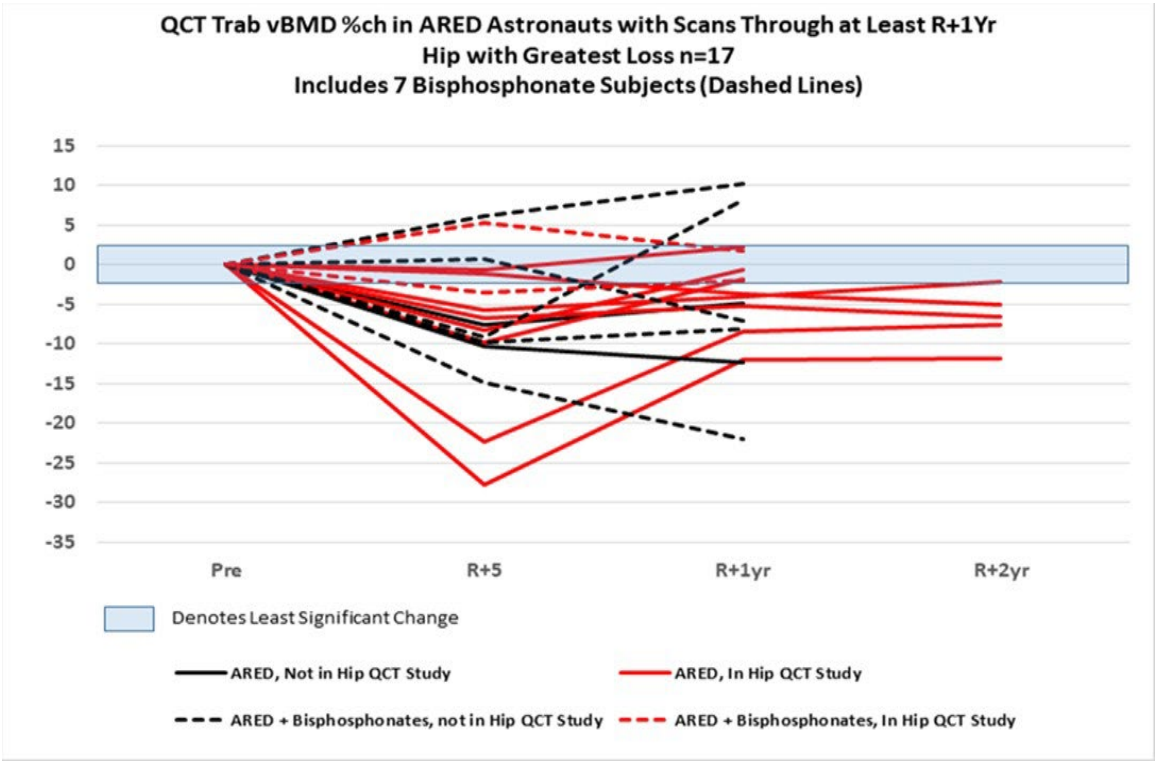
Hip QCT Biochemical Markers Bone Turnover (New Evidence)

- ❖ Persistent losses (absence of recovery) detected in Hip QCT subjects (n=4 Not Recovered of 10 total) appear to be associated with unabated bone resorption during spaceflight.

See Fig. 6 in Sibonga et al., Bone, 2019

Hip QCT data of Bone loss and Recovery <u>with</u> Extended Bis SMO (New Evidence)

- ❖ Bis Alendronate loss and recovery has high variability consistent with poor bioavailability of an oral Bis.



ARED - Advanced Resistance Exercise Device

Special HSRB Working Group to Evaluate Bone Fracture Risk Evidence

April 4, 2019 Attendees

Anton, Wilma (SA)	Fogarty, Jennifer (SA)	Sibonga, Jean (SK)
Antonsen, Erik (SA)	Pattarini, James (SD)	Van Baalen, Mary (SD)
Auñón-Chancellor,		
Serena (CB)	Rapley, Mike (CK)	Wu, Honglu (SK)

October 16, 2020 Attendees

Agarwal, Saroochi (SD)	Keune, Jessica (SD)
Anton, Wilma (SA)	Kreykes, Amy (SD)
Antonsen, Erik (SA)	Lowe, Kim (SA)
Auñón-Chancellor, Serena (CB)	Rapley, Mike (CK)
Bayuse, Tina (SD)	Shackelford, Linda (SD)
Connell, Erin (SF)	Scheuring, Richard (SD)
Coffey, Kristin (SA)	Sibonga, Jean (SK)
Fogarty, Jennifer (SA)	Van Baalen, Mary (SD)

Charge to Working Group:
As technical experts and stakeholders of the Bone Fracture Risk or its related risk areas, you are charged to evaluate the level of evidence, the quality of evidence, and the applicability of evidence that is available to support the recommendations brought forward by the Bone Fracture Risk Team.

Special HSRB Working Group to Evaluate Bone Fracture Risk Evidence - Literature Reviewed

- Axpe E, Chan D, Abegaz MF, Schreurs A-S, Alwood JS, Globus RK, et al. A human mission to Mars: Predicting the bone mineral density loss of astronauts. PLOS ONE. 2020; 15(1):e0226434
- Epstein S, Inzerillo AM, Caminis J, Zaidi M. Disorders associated with acute rapid and severe bone loss. J Bone Miner Res. 2003; 18(12):2083–94
- Farr JN, Melton LJ, Achenbach SJ, Atkinson EJ, Khosla S, Amin S. Fracture Incidence and Characteristics in Young Adults Aged 18 to 49 Years: A Population-Based Study. J Bone Miner Res. 2017; 32(12):2347–54. doi: 10.1002/jbmr.3228. Epub 2017 Oct 3. PMID: 28972667; PMCID: PMC5732068.
- Kennel KA, Drake MT. Adverse effects of bisphosphonates: implications for osteoporosis management. Mayo Clin Proc. 2009; 84(7):632–7; quiz 638
- Michalski AS, Amin S, Cheung AM, Cody DD, Keyak JH, Lang TF, et al. Hip load capacity cut-points for Astronaut Skeletal Health NASA Finite Element Strength Task Group Recommendations. NPJ Microgravity. 2019; 5:6
- Sibonga J, Matsumoto T, Jones J, Shapiro J, Lang T, Shackelford L, et al. Resistive exercise in astronauts on prolonged spaceflights provides partial protection against spaceflight-induced bone loss. Bone. 2019; 128:112037
- Sibonga JD, Spector ER, Keyak JH, Zwart SR, Smith SM, Lang TF. Use of Quantitative Computed Tomography to Assess for Clinically relevant Skeletal Effects of Prolonged Spaceflight on Astronaut Hips. J Clin Densitom. 2020; 23(2):155–64

Special HSRB Working Group to Evaluate Bone Fracture Risk Evidence - Topics

Topics Discussed to Consensus October 16, 2020:

- ❖ Review of evidence from the relevant articles
  - Rapid trabecular bone loss
  - Continued loss after spaceflight that is not captured on DXA (failure to recover at R+2 years)
  - Bisphosphonate side effects and pharmaceutical countermeasure options/challenges (see upcoming slides # 35, 36)
- ❖ Characterization with QCT
  - Radiation dose involved discussed at length

Outcome of Special HSRB Working Group to Evaluate Bone Fracture Risk Evidence

Outcome/Recommendations:

- ❖ There is a need to better characterize the risk and benefits of pharmaceutical countermeasures in the astronaut population, including but not limited to bisphosphonates.
- ❖ The HSRB defers to Astronaut Medical Board in matters of clinical pharmaceutical recommendations.
- ❖ The Working Group recommends that the HSRB endorse/recommend QCT for further risk characterization. This is as an adjunct to current Bone DXA requirements.
  - A formal dissenting opinion to this recommendation was lodged by Linda Shackelford. All other members of the working group agreed with QCT recommendation.

Dose Exposures per Recommended QCT scan protocol for 1 Bilateral Hip Scan

Representative dose exposure for a 45-year-old astronaut:

- ❖ 1 Hip Scan [Lang Protocol*, National Cancer Institute (NCI) tool]:

  Previously used in astronauts.

Sex	mSv/scan	REID (97.5%)/scan	Approx. Total mSv (3 scans)
F	0.42	0.0040	1.26
M	0.19	0.0035	0.57

DXA bilateral hip scan < 0.05 mSv
National Cancer Institute Dosimetry System for CT Version 3.0
The NASA Space Radiation Analysis Group (SRAG) is working on a side-by-side comparison of DXA vs. QCT, using the NCI tool, but this information was not yet available for release and will be forward work.

*Recommended QCT protocol will be presented to the Aerospace Medical Board for its consideration and authorization.

Exercise Countermeasures Mir and ISS

- There is a high level of individual variability to BMD changes from spaceflight
- Exercise countermeasures have improved decline in BMD (bone building)
- Bisphosphonates have additive benefit to ARED (anti-resorptive)[1]
- Despite current exercise countermeasures:
- Trabecular changes at R+2y seen on QCT, independent of DXA BMD[2,3]

1. Sibonga et al. Bone. 2019.
2. Sibonga et al. J Clin. Densitometry. 2019.
3. Carpenter et al. 2010

See also Shackelford LC. Musculoskeletal Response to Space Flight. In: Principles of Clinical Medicine for Space Flight. Pg 595. New York, NY: Springer; 2019. 2nd Edition.

Pharmaceuticals To Mitigate Bone Changes

Terrestrial Options:

- ❖ Bisphosphonates
  - Alendronate (weekly, by mouth)
  - Zoledronic acid (ZA) (Intravenous (IV) infusion pre-flight)
- ❖ Monoclonal Antibodies
  - E.g., Denosumab sub-cutaneous (SQ) injection/ 6 months and Romosozumab, SQ monthly
- ❖ Synthetic Parathyroid Hormone (PTH) Analogs
  - Ex. Teriparatide SQ daily

Spaceflight Challenges:

- ❖ Oral Bisphosphonate
  - Large footprint due to oral weekly dosing
  - Stability of medication for exploration mission
- ❖ Injectable Bisphosphonate
  - ZA given pre-flight, IV infusion
  - Efficacy for up to 5 years
- ❖ Monoclonal Antibodies
  - Requires refrigeration
  - Required re-administration during mission
  - Large footprint = SDS, BZK (Benzalkonium chloride antiseptic) wipes, needles, sharps container etc.
  - Stability of medication for exploration mission
  - Unknown if launch vibration could negatively impact proteins
- ❖ PTH Analogs
  - Requires refrigeration
  - Stability of medication for exploration mission
  - Large footprint = prefilled pens, includes 28 days of treatment; BZK wipes, needles,

sharps container etc.

- Administration concerns with multi-use pens in microgravity

Bisphosphonates

Advantages

- ❖ Alendronate has been approved for spaceflight
- ❖ Zoledronic acid could be one-time dose prior to spaceflight
- ❖ Flight studies show that they work under spaceflight (weightless) conditions
    - Cortical bone loss at R+1 in Bisphosphonate arm in recent study requires further investigation

Disadvantages

- ❖ Side effect of concern
    - Gastrointestinal (GI) upset/gastritis (PO)
    - Cortical bone mineral density decline at R+1yr (only report: Sibonga, J Clin Densitometry, 2019)
    - Musculoskeletal (MSK) pain
    - Hypocalcemia
    - Ocular inflammation
    - Osteonecrosis of the jaw
    - A-Fib (Atrial Fibrillation)
    - Sub-trochanteric fracture of the femur
    - Risks in women of child-bearing age
    - – Maternal-Fetal Medicine and Endocrinology feel the risk is low compared to the benefit

Mars Surface Task Assumptions for Risk Posture Assessments*

Potential for Increased Loads

- ❖ Falling/crashing from flight in a ballonet gondola.
- ❖ "Climb 3-meter ladder, manually while wearing surface EVA suit, to access Mars Surface Ascent Vehicle."
- ❖ "Climb crater wall/gully while carrying hand tools and wearing surface EVA suit to conduct geological research."
- ❖ "Descend crater wall/gully while carrying hand tools and wearing surface EVA suit to conduct geological research."
- ❖ Accidents occurring with Rover vehicle.
- ❖ Construction activity accidents.
- ❖ These (and similar) activities may be in excess of the loads used in Finite Element Analysis modeling that has been done in the past (Lewandowski, Nelson 2008-2009) indicating that a fracture of the hip is unlikely.

*Source: Human Exploration of Mars: Preliminary List of Crew Tasks NASA/CR-2018-220043

Integrated Medical Model (IMM) Fracture Likelihood

See Fig. 9 in Nelson et al., *Annals Biomed Engr*, 2009

Fracture Incidence Associated with Terrestrial Age-related Bone Loss (Primary Op)

Bone density is currently the best single predictor of future fracture

See Fig 1 in Melton *Bone*, 1996 reproduced in this work with permission. The original figure is from Cooper and Melton, *Trends Endocrinol & Metabolism*, 1992

Existing Evidence — Rev A

Mechanical loads to hip with Falls* were estimated by Digital Astronaut Project

Load (kN)	Fall Type
1 - 4	Tripping fall with arm/object attenuation
4 - 6	Fall height ≈ Hip height: slipping, short elevation, football tackle
> 5	Hip height with translational velocity (cycling, skiing) OR elevated fall height

Factors Affecting Hip Impact Force

- Fall Height
- Travelling Speed
- Impact Velocity
- Body Mass
- Arms/Muscles to slow fall
- Hip fat pad absorbs energy

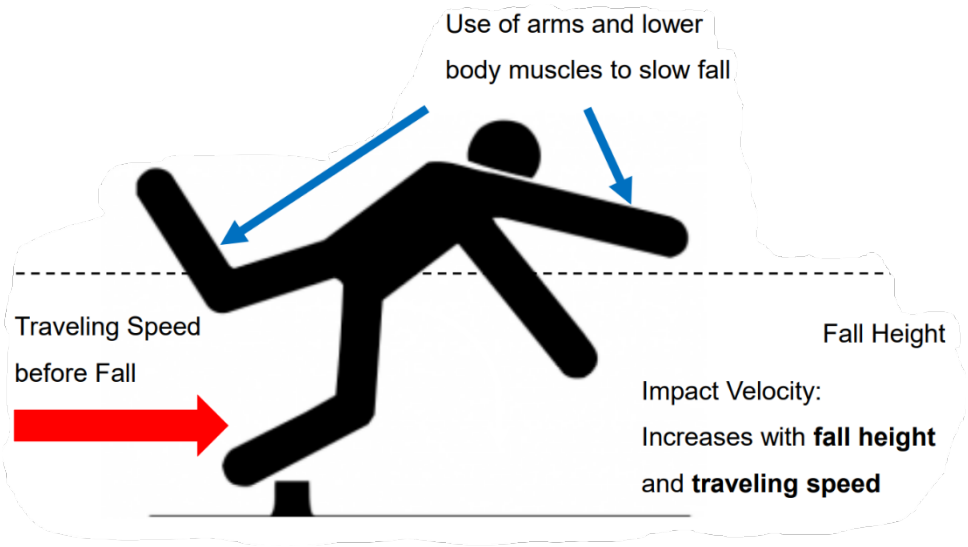
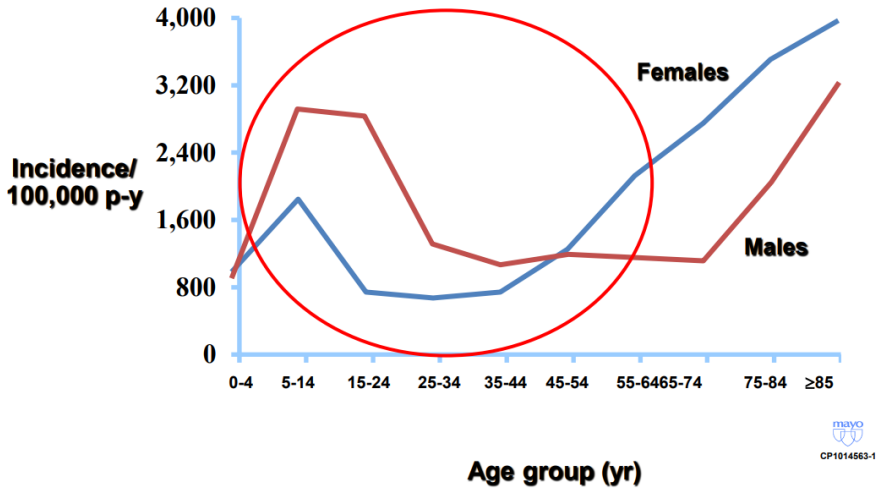


Figure courtesy of Scott Lenfest (TAMU) based upon DAP Modeling Nelson et al. Ann Biomedical Eng., 2009.

*Does not integrate physiological deconditioning that may increase the probability of falling.

Incidence of Limb Fractures

Fracture risk in younger persons likely due to overloading bones not due to bone fragility.



Garraway et al, Mayo Clin Proc, 1979. Slide courtesy of S. Amin, MD. Adapted by Sibonga.

Current Status

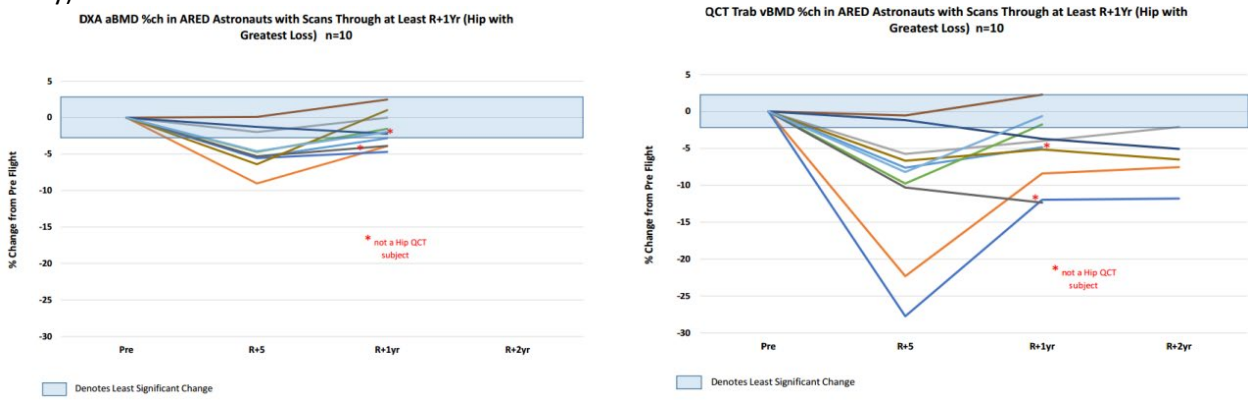
Informed Consent Briefing

QCT: 1 scan session (captures both hips)	Radiation Exposure: Effective dose = 2-6 days on ISS (1.50 mSv per session for men – 1500 microSv 1.22 mSv per session for women 1220 microSv)	Use qualified facilities and technologists.
Compared to DXA: 1 complete scan session for regional scans (WB, hip, lumbar spine, forearm, calcaneus and, VFA)	0.036-0.045 mSv (36-45 microSv) Effective dose = 1-2 hrs on ISS	
Compared to DXA: bilateral regional scans of hips.	(0.012 mSv per session for men – 12 microSv 0.0158 mSv per session for women 15.8 microSv)	

New Evidence

Hip QCT Pilot Study for Risk Surveillance

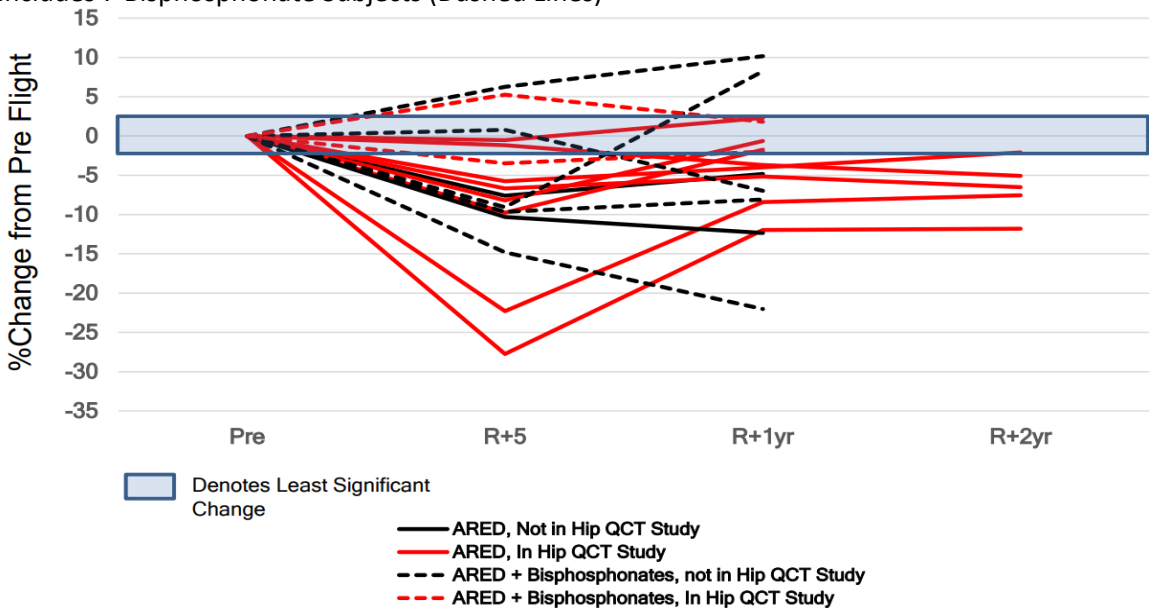
LTH Fracture Risk - Monitoring recovery with DXA measurement of aBMD of total hip (cortical + trabecular bone mass) and with QCT for trabecular vBMD of hip (clinical trigger).
DXA fails to assess for clinical trigger and misses those who may need intervention (n=2 not in Hip QCT study).



*Note: Replaced the bisphosphonate-treated subjects (n=2) to focus on exercise countermeasure effect only. Shaded area represents error for the technology –specific measurement

aBMD = areal bone mineral density; vBMD = volumetric bone mineral density

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



ARED – Advanced Resistance Device; QCT - Quantitative Computed Tomography

Clinical trigger based upon deficits in volumetric BMD (by QCT) as additional predictors of hip fracture in aged. *

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 23, Number 8, 2008
Published online on March 17, 2008; doi: 10.1359/JBMR.080316

Proximal Femoral Structure and the Prediction of Hip Fracture in Men: A Large Prospective Study Using QCT*

Dennis M Black,[1] Mary L Bouxsein,[2] Lynn M Marshall,[3] Steven R Cummings,[4] Thomas F Lang,[5] Jane A Cauley,[6] Kristine E Ensrud,[7] Carrie M Nielson[3] and Eric S Orwoll[3] for the Osteoporotic Fractures in Men (MrOS) Research Group

Journal of Bone and Mineral Research
Volume 26, Issue 4, Article first published online: 23 MAR 2011
Abstract | Full Article (HTML) | References | Supporting Information
Cited By

In Vivo Discrimination of Hip Fracture With Quantitative Computed Tomography: Results From the Prospective European Femur Fracture Study (EFFECT)

Valérie Danielle Bousson,[1,2] Judith Adams,[3] Klaus Engelke,[4] Mounir Aout,[5] Martine Cohen-Solal,[6] Catherine Bergot,[2] Didier Haguenauer,[7] Daniele Goldberg,[8] Karine Champion,[9] Redha Aksouh,[1] Eric Vicaut,[5] and Jean-Denis Laredo[1,2]

* Failure to recover triggers possible treatment to restore deficit (as per Osteoporosis endocrinologist) to prevent premature fragility fractures.

Limitations

1. 1. New Evidence based upon Models, e.g., i)Bone strength, ii) Applied loads to hip. THIS IS USEFUL MODEL FOR SPACE PROGRAM.*
2. New hip strength evidence is for one load orientation (e.g., posterolateral falls). FE MODELING IS BEST METHOD FOR ESTIMATING BONE STRENGTH (Engelke et al, J Clin Densitometry, 2015). Factor of Risk estimated more accurately.
3. Does not include fractures due to repetitive bone loading (i.e., stress fractures) or due to moving masses (i.e., crush fractures). Probability of fractures could be underestimated.
4. Cannot resolve the effect of rapid bone loss on trabecular bone microarchitecture (major concern – associated with fractures, e.g., vertebral bodies in postmenopausal females). A CRITICAL KNOWLEDGE AND TECHNOLOGY GA.

Existing Evidence — Baseline

Terrestrial State of Knowledge

- ❖ "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 quality, in turn, is stated to refer to architecture, turnover, damage accumulation, (e.g., microfractures) and mineralization…."
  - Osteoporosis Int. 2002

Bone strength is influenced by additional factors that are not measured by DXA areal BMD.

Proximal femoral structure and the prediction of hip fracture in men: a large prospective study using QCT - PubMed

In vivo discrimination of hip fracture with quantitative computed tomography: results from the prospective European Femur Fracture Study (EFFECT) - PubMed

Clinical Evidence: QCT measures are independent predictors of hip fracture to supplement aBMD.

JOURNAL OF BONE AND MINERAL RESEARCH
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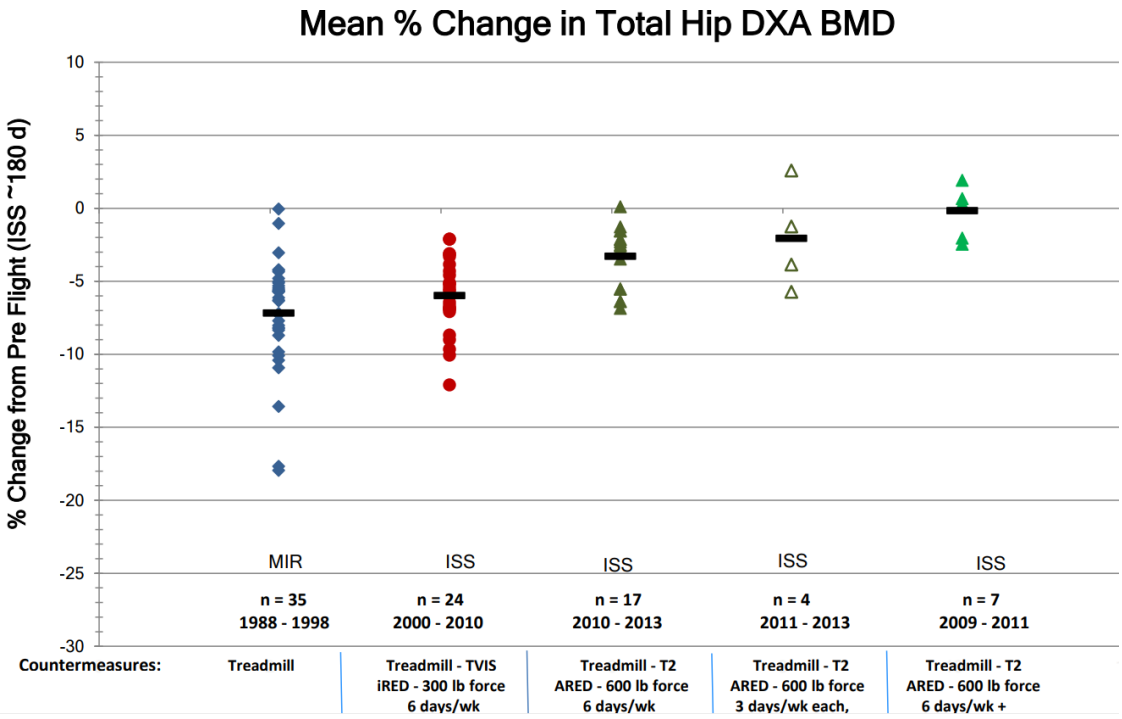
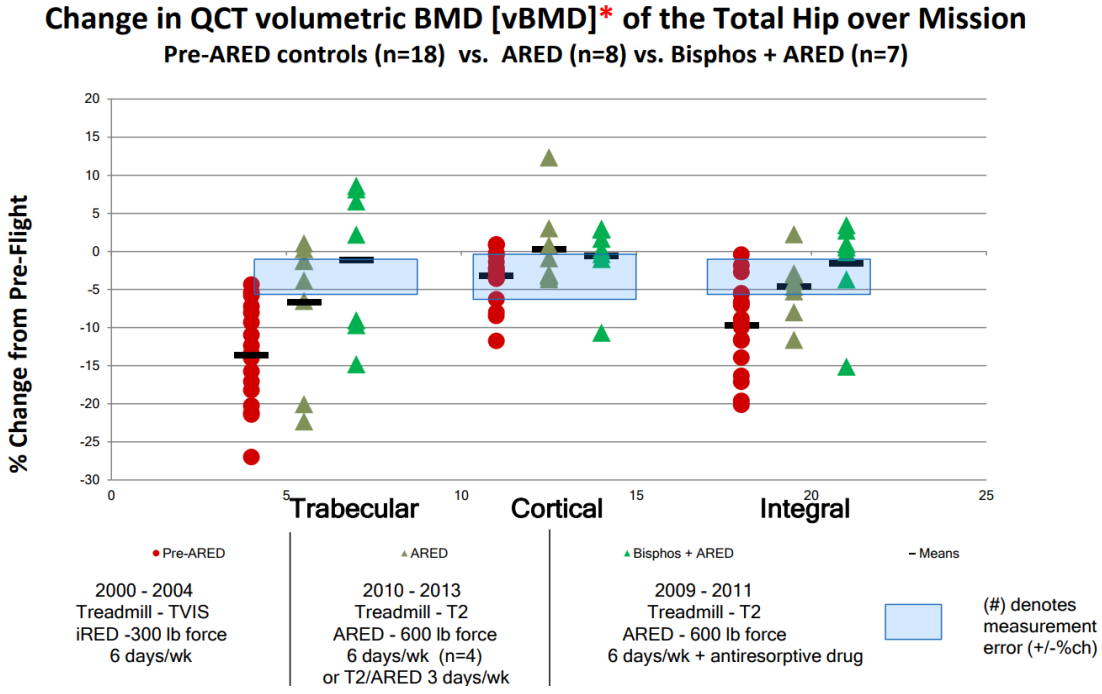
Areal BMD as a metric for the Risk of Bone Fracture due to Spaceflight



QCT monitors different effects of spaceflight on different bone compartments which impact 3d-bone structure.



ARED – Advanced Resistance Exercise Device; BMD – Bone Mineral Density; DXA - dual-energy x-ray absorptiometry; QCT - Quantitative Computed Tomography; vBMD – volumetric bone mineral density (g/cm^3 or mg/cm^3)

(*) vBMD = Volumetric Bone Mineral Density (g/cm^3 or mg/cm^3)
BMD Recovery Trochanter Delayed recovery is the clinical trigger
See Fig.1 in Sibonga et al., *Bone* 2007

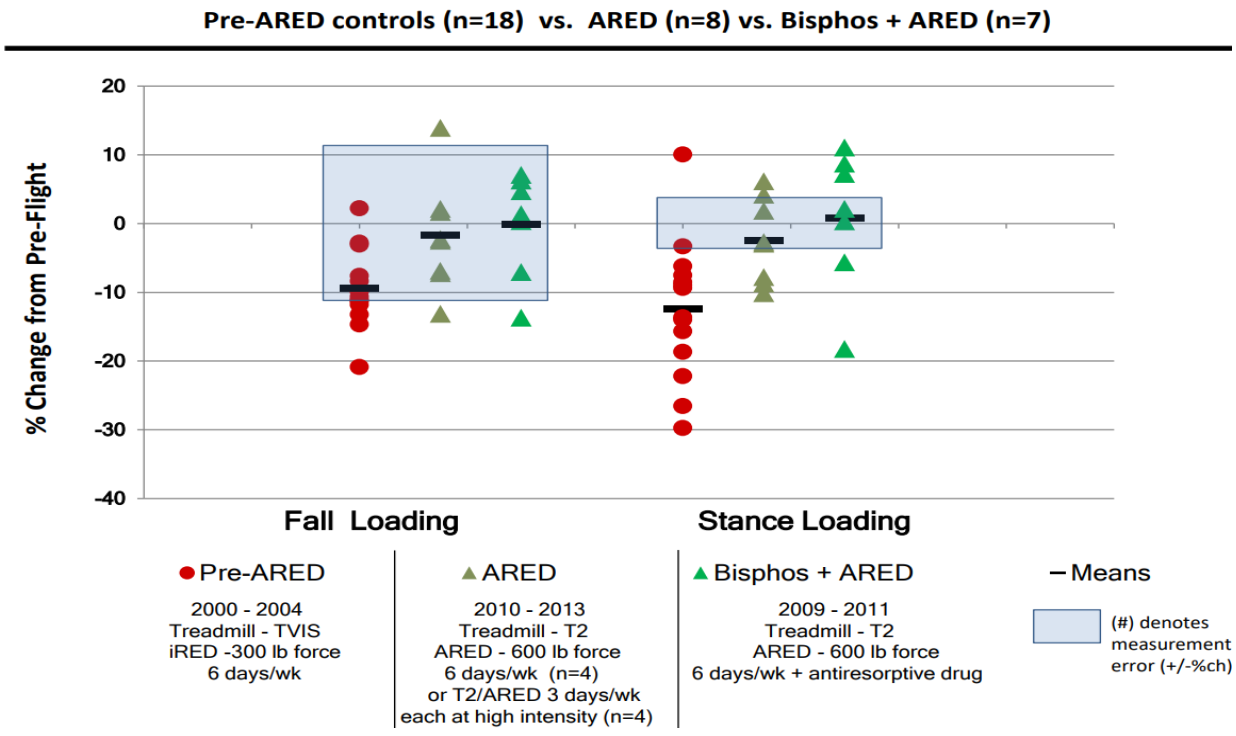
Proposed period immediately postflight return to baseline–higher probability until new fracture-based cut-points available to re-assess.
Study: Four x half-life = 15/16ths recovery 4 x 255 = 1020 days ~ 2.8 yrs
RCAP Recommendation: 2.0 ytd for trabecular BMD of all hip regions. Based upon site identified in randomized clinical trial, concern for trabecular disruption and astronaut flight data.

A Bone Mineral Density (BMD) T-score is a value that relates a measured BMD to that of a healthy young adult of the same sex. A T-score of 0 represents the BMD of a healthy 30-year-old. Scores of -1 or higher are considered normal. Scores in the range of -1 to -2.5 indicate (low bone mass. A score of -2.5 or lower are associated with osteoporosis.

Areal BMD T-scores are not appropriate or predictive for fracture in astronaut population.

Densitometry & Reported Measurement – see Fig 1 in Sibonga et al., Aerospace Med Hum Perform, 2015. for separate cortical and trabecular bones, g/cm^3 are shown in Fig 1 in Lang et al., *JBMR*, 2009.

Change in Finite Element Hip Strength over Mission



ARED – Advanced Resistance Exercise Device; Bisphos – Bisphosphonate; iRED – Interim Resistance Exercise Device; TVIS - Treadmill with Vibration Isolation and Stabilization

DXA and QCT monitor different responses to ARED and to re-ambulation in individual astronauts. DXA areal BMD alone is not sufficient index to monitor countermeasures

Finite Element Models of QCT data – "FE modeling" is a computational tool to estimate failure loads ("strength") of complex structures.

Essential Finding: Areal BMD (DXA) alone is not a sufficient metric for …

- ❖ Detecting the effects of spaceflight on hip bone structure.
- ❖ Evaluating the skeletal effects of countermeasures identifying who will fracture (absolute risk)
- ❖ Assessing fracture risk in younger persons or with non-age-related bone loss

See: Keyak, et al., *J Biomechanics*, 1998
Keyek et al., *Med Engr Physics* 2001
Keyak et al., *Current Orthopedic Practice,* 2005

Terrestrial Research Data: QCT + Finite Element Modeling [FEM] has superior capabilities for estimating mechanical strength of ex-vivo bones.

- ❖ QCT estimates fracture loads better than DXA
- ❖ FEM is a computational tool to estimate "failure" loads to complex structures.
- ❖ QCT + FEM directly estimates fracture loads – outperforming the "surrogate measures" for bone strength.

See Fig. 5 in Cody et al., *J Biomechanics*, 1999

Finite Element Models of QCT data can be analyzed to estimate bone strength.

See: Keyak et al., J Biomechanics, 1998
Keyak et al., Med Engr Physics 2001
Keyak et al., *Current Orthopedic Practice,* 2005

Not just NASA: FE bone strength proposed as new clinical surrogate for fracture to the Federal Working Group by NIH investigators (May 2013)

Estimating bone strength by QCT-based finite element analysis

- ❖ Standard engineering approach to evaluate mechanical behavior of complex structures.
  - Integrates material and 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 the effect of treatment on bone strength and to predict fracture risk in untreated subjects.

See: Keyak et al., J Biomechanics, 1998
Keyak et al., Med Engr Physics 2001
Keyak et al., *Current Orthopedic Practice,* 2005

Two methods of monitoring space-induced changes in bone strength, changes in FE Strength, and changes in areal BMD, do not correlate.

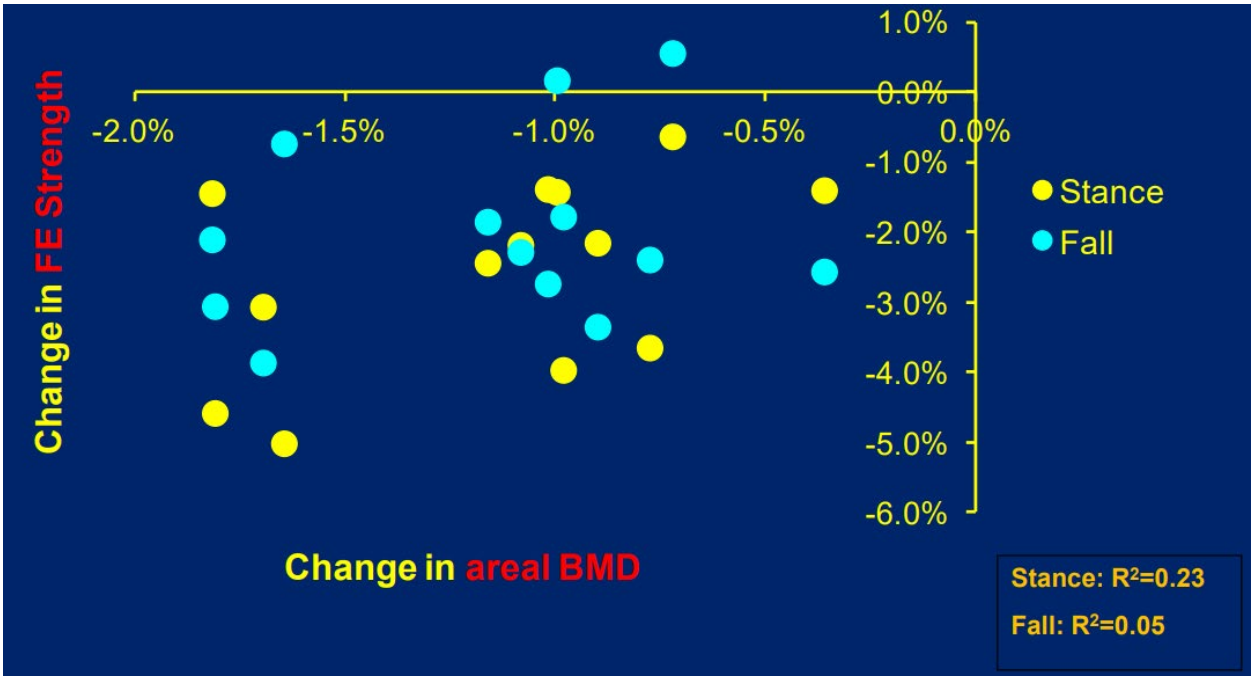
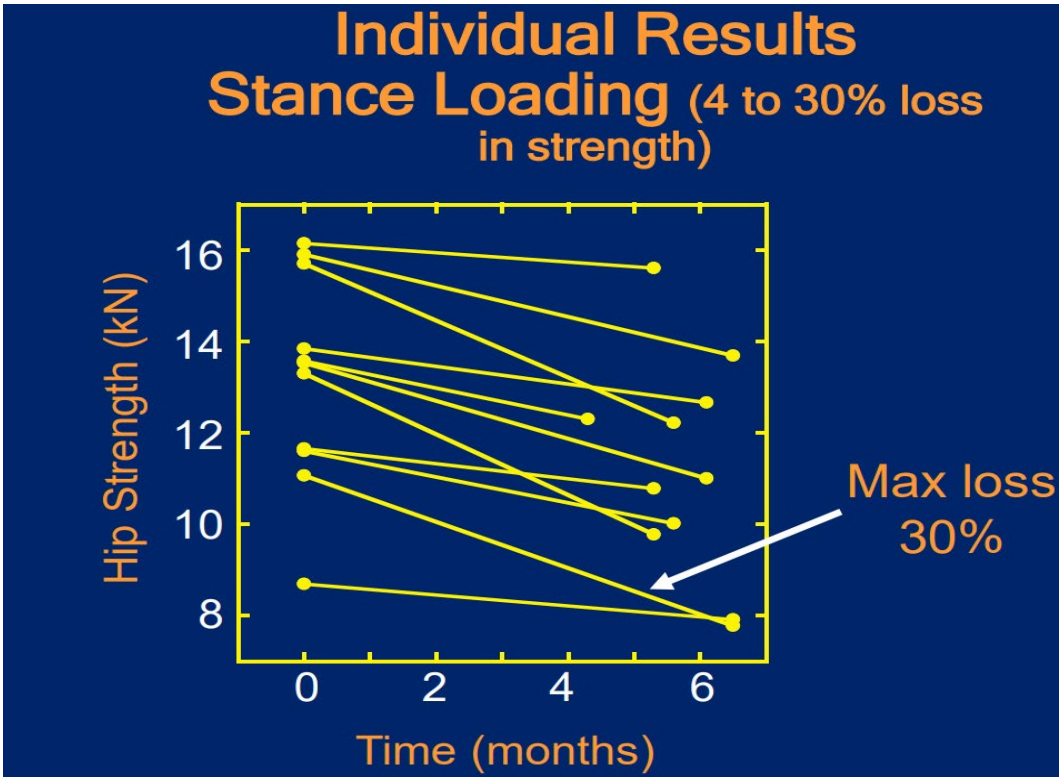
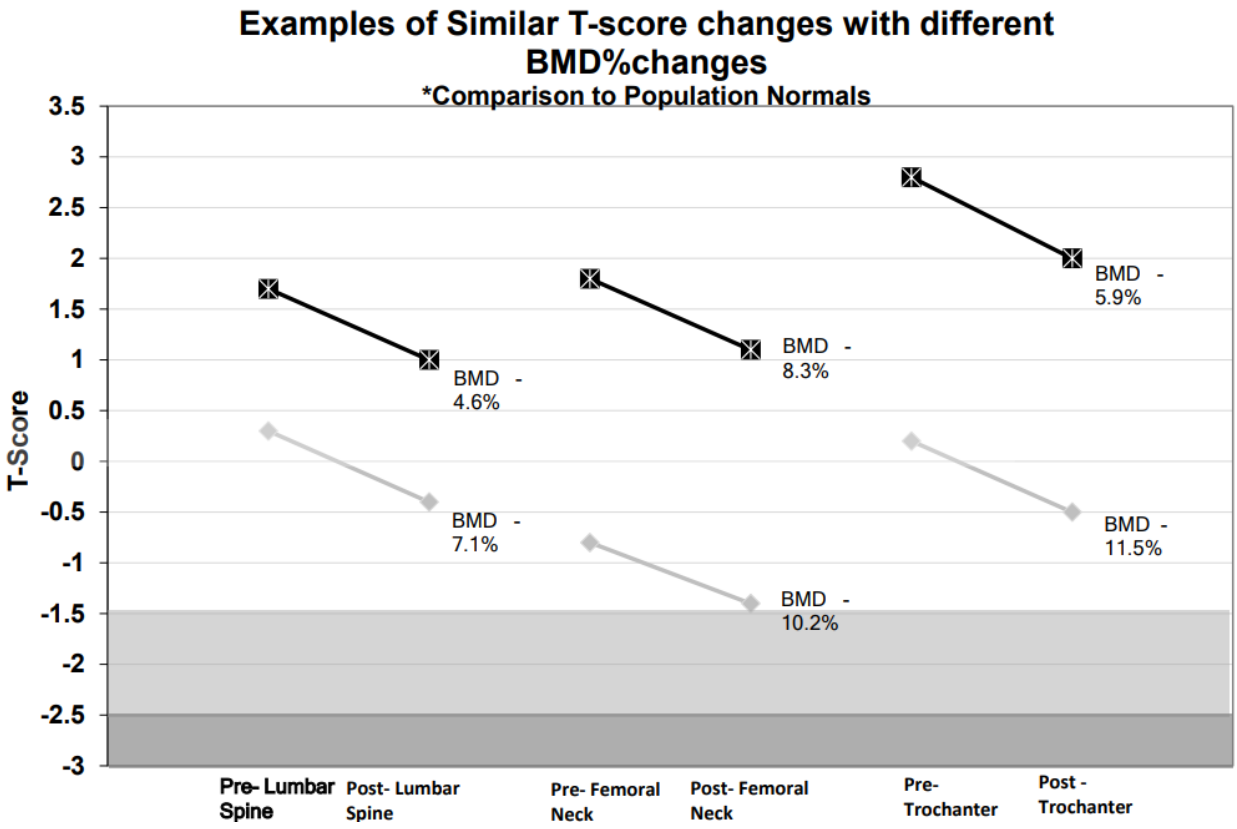


Image produced from data in Keyak et al., *Bone*, 2009 and provided courtesy of J Keyak.

BMD – Bone mineral density




Examples of Similar T-score changes with different BMD%changes
*Comparison to Population Normals
T-Score
3.5
3
2.5
2
1.5
1
0.5
0
-0.5
-1
-1.5
-2
-2.5
-3
BMD - 4.6%
BMD - 7.1%
BMD - 8.3%
BMD - 10.2%
BMD - 5.9%
BMD - 11.5%
Pre- Lumbar Spine
Post- Lumbar Spine
Pre- Femoral Neck
Post- Femoral Neck
Pre- Trochanter
Post - Trochanter