Risk of Bone Fracture due to Spaceflight Induced Changes to Bone

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RISK (pg 4)

“Given that spaceflight may induce adverse changes in bone ultimate strength with respect to mechanical loads during and post-mission, there is a possibility a fracture may occur for activities otherwise unlikely to induce a fracture prior to initiating spaceflight”

GAPS (pg 25)

1) “We don’t understand how the spaceflight environment affects bone fracture healing in flight.”
2) “We need to characterize the loads applied to bone for standard in-mission activities”
3) “We need a validated method to estimate the Risk of Fracture by evaluating the ratio of applied loads to bone fracture loads for expected mechanically loaded activities during a mission”
Determinants of whole bone strength

Quantity
size and mass ($BMD$)

Distribution
shape or geometry
cortical : trabecular mass
microstructure

Properties of Bone Matrix
mineralization
proteins
microdamage
...others?

DXA
QCT
HR-pQCT
BMD explains > 70% of whole bone strength in ex vivo human cadaver studies

Proximal Femur (sideways fall)

Vertebral body (L2) (compression + forward flexion)

Johannesdottir et al (Bone 2017)

Moro et al, CTI, 1995
Poor relationship between decline in DXA-aBMD and QCT-FEA strength at prox femur (note: this is different than in osteoporosis, where they are more closely related)

Keyak et al, 2009
Heterogeneity in bone loss

BMD T-Score Values Expeditions 1-23

Orwoll et al, 2013
Significant bone loss occurring in some individuals even with ARED/Bisphos
Profound declines in femoral strength by QCT-FEA

8/13 had > -2% decline per mo

6/13 had > -2% decline per mo

Keyak et al, 2009
How well is risk understood? Major sources of disagreement in literature?

• The risk statement should be rewritten to improve clarity
• The risk is rather poorly understood, due to
  – To date, insufficient use of state-of-the-art technology (ie QCT-FEA) to assess bone strength, reliance on a single study
  – Imprecise knowledge about the loads applied to the skeleton during flight, at re-entry and post-flight
  – Inadequate use of state-of-the-art methods to assess skeletal loading using multibody dynamic models (e.g. OpenSim, AnyBody)

• Disagreement in the literature
Estimating skeletal loads

Nelson et al 2009
Does report provide evidence that the risk is of concern?

- There are large gaps in knowledge that make definitive assessment of the risk indeterminate at this time.

- Reasonable, however, to think the risk is sufficiently high to warrant further investigation and mitigation
  - Integration of “risk of early osteoporosis” and bone changes observed during flight would make a stronger argument for the risk for bone fracture
Does the report provide evidence that the named gaps are the most critical? Are there additional gaps or missing aspects?

• Yes, the identified gaps are critical and appropriate.
• The report neglects to integrate discussion of the effects of radiation on bone, muscle and fracture healing.
• Possible gap: fracture treatment.
• The report neglects to consider the risk of injury during exercise during and after flight, especially resistance exercise (e.g. ARED).
  • 12/14 musculoskeletal injuries on ISS occurred during use of exercise equipment (Scheuring et al, 2009)
  • Loads to skeleton during use of ARED and ARED-substitutes must be quantified. Kinematic / force plate data from ISS needed.
  • Subject-specific musculoskeletal models could be employed
    – Over emphasis on hip fracture
    – Could use data from spinal cord injury to gauge maximal changes in bone & fx risk
    – Critical to understand heterogeneity in bone changes
    – Critical to continue investigating countermeasures for bone loss
Is the breadth of the cited literature sufficient?

• Yes, report summarizes knowledge regarding bone deficits following spaceflight, limitations of DXA-BMD, existing knowledge on skeletal loading in mission activities

• But, report does not adequately cite/discuss literature on several topics, including:
  – Fracture healing in microgravity (or analog models)
  – Use of multibody musculoskeletal modeling to assess loading
  – Recent literature on QCT-FEA to predict fracture risk in prospective studies
  – Recent literature on contribution of cortical and trabecular microarchitecture to skeletal fragility (e.g., HR-pQCT studies)
  – ARED reduces, but does not halt bone deterioration. Evidence of high bone turnover despite ARED use not noted. ALN use profound inhibition of bone loss, not featured in this report.

• Provide a better roadmap to address gaps?