Probabilistic Risk Assessment for Bone Fracture - Bone Fracture Risk Module (BFxRM)

Angelo Licata, MD PhD – The Cleveland Clinic
Jerry G. Myers, Jr. PhD – NASA Glenn Research Center
Beth Lewandowski, PhD – NASA Glenn Research Center

November 4, 2013
Agenda

- Historical fracture likelihood assessment [DXA, FRAX]
- Limitations on the reliance of BMD
- Concept and application of the NASA Bone Fracture Risk Model (BFxRM)
- Discussion on expanding capabilities to fracture risk modeling
Why Develop a Risk Tool

• History of fracture probability calculation
  – Typically aimed at clinical/treatment planning

• Original development of DXA / T-score system
  – Postmenopausal Caucasian women, elderly
  – To assess risk for fragility fracture
  – High prevalence of disease osteoporosis
  – Highest risk for those ≤ - 2.5 s.d. from population mean [ T-score]
  – Reference population may not be analogous to the astronaut corps
    • young healthy, physically fit, work in unique environment, engage in unique activity
- Became surrogate marker of a disease and architectural change, strength loss
BMD Limitations in Predicting Bone Strength

- Discordance between DXA and bone strength or [resistance to fracture], other factors of importance

- “quality” and loading

![Diagram showing the relationship between bone density, bone quality, bone strength, forces generated by loading of daily activity, and fracture](image_url)
The Loading Environment

Micro-g Translation

Stance
Walking
Ladder/Stair
Ascent/Decent

“Drop Landing”

Lateral/Posterolateral
Fall Impacting the Hip
Or
Abnormal Lifting
Medicine’s interest in topic arose late. Why? Data from clinical studies revealed unexpected observations.
Bone Quality – Age Dependence

Similar BMD in young and old does not carry the same fracture risk (i.e., age and bone quality).

Hui et al., J Clin Invest, 1988
Clinical Observation about DXA and Strength

- Vertebral fracture reduction with various anti-resorption therapies is very similar across drug classes but the increases in BMD are different.

- Significant reduction of vertebral fractures occurs within the first year of anti-resorption therapy in pivotal clinical studies but BMD does not increase much at all.

- Fracture risk with glucocorticoid [steroids] drugs maybe high even with normal BMD.

- Increased BMD does not always coincide with increased strength (e.g., sodium fluoride, osteopetrosis, diabetes mellitus).
What about the FRAX model?

• **WHO FRAX model is being promoted for use in helping to understand fracture risk in clinical evaluation of patients.**
  – An amalgamation of bone density data with dichotomous clinical risk factors
  – Can it be used for Astronauts?

• **Concerns exist that FRAX**
  – Includes variables and conditions that are not generally a concern of the astronaut corps.
  – Age ranges only slightly overlap the age range of the astronaut corps.
  – Assumes a different loading environment – limited analogy
  – Likelihoods are specified in terms of generalized 10-year risk level which makes application of the assessment questionable for in mission likelihood estimates.

• **Although good clinical tool, FRAX is likely not applicable to the astronaut corps.**
  – What are other potential alternatives
• Integrated Medical Model PRA application:
  • Probability and consequences of medical risks.
  • Integrate best evidence in a quantifiable assessment of risk.
  • Identify medical resources necessary to optimize health and mission success considering 83 medical conditions.
• **Simulation Probabilistic Risk Assessment (PRA)**
  - Physical models + physiological data + probabilistic simulations
  - Integration through Monte Carlo Simulation
  - Account for interacting contributions
  - Acts as integrator for contributing conditions
Bone Fracture Risk Model (BFxRM) for Assessing In Flight Fracture Risk

• What can we do to estimate astronaut risk of fracture?
• Real and Present Concern: Skeletal Fracture
  – Weakened bones
  – Unique and off-nominal loading states
• Lack of In Flight Injuries
  – Predictive data is limited
• Fracture risk
  – Likelihood (unknown) + Severity (known)
• Our Question is:
  – What is the fracture likelihood in space (ISS, Orion) and on planetary activities (Moon and Mars)?
  – Can such assessments be extended to the BMD recovery period after return?
GOAL
• Capture the state of knowledge of the likelihood of fracture
  – Incorporating mission related factors, environmental influences, and best available clinical and biomedical knowledge
  – Represent this in such a way as to communicate the state of knowledge to risk assessment efforts while acceptably representing the state of uncertainty of that knowledge.
  – Aligns to NASA PRA engineering analysis

CONCEPT
• Estimate the probability of loading event during mission
• Estimate the skeletal strength at the time of loading (pre-, in- or post-mission)
• Estimate the skeletal loading with regard to the type of load and astronaut parameters
• From well established studies, develop a “transfer function” that translates Fracture Risk Index (FRI) to a probability of fracture
• Monte Carlo simulation to integrate model and data components
• Develop a probability density function (PDF) of the representative probability of fracture per mission
Model Validation and Predictive Results

- Validation: Compared to two published data sets
- Applied to 4 design reference missions
  - Wrist most likely fracture location
  - Highest sensitivities: Space suit properties
- Succeeds
  - Representing state of knowledge
  - Quantitates BMD as bone quality metric

BFxRM - Applications

• In flight
  – Same logic used for wrist fracture due to translation activities on ISS
  – Used to predict ISS evacuation rate in IMM

• Post-Flight
  – Increased likelihood of fracture
    • Includes post-flight BMD recovery
    • Specific loading scenarios
      – Elevated, unprotected falls
      – Translational impacts – Bicycle

• Support of Injury Criteria Definition
  – Supplied input for fitness for duty standards review
  – Injury loading thresholds – off-nominal Orion landing

• Countermeasures induce changes to in-flight injury likelihood resulting from
  – Improved exercise with ARED and T2
  – Use of Bisphosphonates
Suggested Discussion Questions

• Is there further utility in the BFxRM approach
  – Assessing ongoing astronaut fracture risk
    • Inflight (mission activity)
    • Post-flight (daily activity on return to earth)

• What additional capabilities (variables) should be implemented to improve the clinical assessment potential of this approach?
  – Currently rely on idealized loading scenarios and DXA for maximum bone loading for the loading scenario.
  – How would integration with FEM or other combination of “quality parameters” increase the predictive capability and acceptance of the simulation? What quality of data is available in these areas?

• What type of Verification, Validation and Credibility assessment would make this approach clinically acceptable for decision support?
  – NASA STD 7009 is being used as the basis for FDA and NIH-IMAG model credibility assessment approaches
EXTRAS
Integrated Medical Model (IMM)

Potential Medical Condition

Evaluate with IMM

Likelihood of occurrence, probable severity of occurrence, and optimization of treatment and resources.

- Probability and consequences of medical risks.
- Integrate best evidence in a quantifiable assessment of risk.
- Identify medical resources necessary to optimize health and mission success considering 83 medical conditions.
Sources of Model Data

• **Limitations**
  – Small n - “Attributable” data

• **Observed Data**
  – Open literature
  – In flight observations
  – Ground studies

• **Expert Opinion**
Femoral Neck – Fall to the side

Hip mass

Stiffness and damping of hip pad and ground


Lumbar Spine – Fall, landing on two feet

Stiffness and damping of lumbar spine

Load on Spine

CoM

Load on


Lumbar Spine – Trunk flexed, holding a load

Upper body mass

Pelvis and leg mass

Stiffness of leg

Foot mass

Stiffness and damping of ground

• **Active Response**
  – Taking action to arrest fall impact
    • Re-orienting during fall
    • Reaching out to break fall with arm
  – Active response successfully occurs 72% of the time: Hsiao and Robinovitch, 1998
    • Successful if occurs in time frame to attenuate the load to the hip
    • Higher likelihood in reduced g
  – With a successful active response
    • Load Attenuation at hip is 12% +/-37% : Sabick et al (1999)
  – Wrist fracture becomes a concern
• Accepted that bone loss occurs at an accelerated rate in microgravity
  – Especially at the femoral neck, trochanter and lumbar spine
  – Time course usually represented as linear
• Controversy as to the extent of loss
  – Consensus is that it does not go on indefinitely
  – Unclear what ultimate level is reached
• Assumption: Maximum limit corresponds to the maximum bone loss seen terrestrially
  – Combining observations of NHANES III and Cummings, JBMR 2004;19S1:S89
    • 60% ± 17% (max 69%)
    • Review of Spinal Cord Injury Data indicates that this level of loss is high

<table>
<thead>
<tr>
<th></th>
<th>DXA BMD g/cm²</th>
<th>%/month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar Spine</td>
<td>-1.06±0.63</td>
<td></td>
</tr>
<tr>
<td>Femoral Neck</td>
<td>-1.15±0.84</td>
<td></td>
</tr>
<tr>
<td>Trochanter</td>
<td>-1.56±0.99</td>
<td></td>
</tr>
<tr>
<td>Pelvis</td>
<td>-1.35±0.54</td>
<td></td>
</tr>
<tr>
<td>Arm</td>
<td>-0.04±0.88</td>
<td></td>
</tr>
<tr>
<td>Leg</td>
<td>-0.34±0.33</td>
<td></td>
</tr>
</tbody>
</table>

LeBanc et al, 2000

LSAH Provided: Combined NASA-MIR and ISS-Expedition 1-12

<table>
<thead>
<tr>
<th></th>
<th>%/day</th>
<th>%/month</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>FN</td>
<td>-0.035</td>
<td>-1.059</td>
<td>0.824</td>
</tr>
<tr>
<td>LS</td>
<td>-0.024</td>
<td>-0.723</td>
<td>0.737</td>
</tr>
<tr>
<td>Troch</td>
<td>-0.040</td>
<td>-1.198</td>
<td>0.717</td>
</tr>
<tr>
<td>Pelvis</td>
<td>-0.042</td>
<td>-1.260</td>
<td>0.691</td>
</tr>
</tbody>
</table>
Relationship between BMD and Ultimate Load of bone for different loading conditions


Estimating Probability of Fracture

- Follows from Davidson et al. 2006
  - Logistic regression to relate FRI to Probability of Fracture
- Define Threshold Based on Archival Literature
  - $0.5 < P < 0.95$
  - $1-\sigma < \text{FRI}=1 < 1+\sigma$

\[ P(FRI) = \frac{1}{1 + \exp(-1*(FRI - \mu) * \theta)} \]
Experimental Reduction of Uncertainty

• Analog estimates of Space suit injury protection – SILAS
  – First quantifiable analog of pressurized suit impact load attenuation

• Results
  – Attenuation characteristics dependent on Distance between hip and suit and Magnitude of the loading condition
  – Implementation in the Bone Fracture Risk Model (BFxRM)
    • Reduced epistemic uncertainty, the mean probability of fracture, and the 90th percentile by about 20%

![Graph showing attenuation vs. offset at 33kPa, 4800N with curves for experimental and 5th and 90th percentiles]
V&V - It's Really About Model Credibility!
Achieving a high level of belief or trust in the model

- **NASA-STD-7009**
  - Standard for Models and Simulations (M&S)

- **M&S Development**
  - Verification
    - Fixed and Extreme value testing to estimate numerical error
  - Validation
    - Face validation with medical experts/panels
    - Direct comparison historical, prospective and analog data

- **M&S Operations**
  - Input Pedigree
    - Highest quality of the data correlated to the scenario
  - Results Uncertainty
    - Quantified with non-deterministic analysis
  - Results Robustness
    - Quantified with rank order correlation

- **Supporting Evidence – Rigorously Documented**
  - Use History
  - M&S Management
  - People Qualifications

Note: HRP historically relies heavily SME and non-advocate review processes
• Present medical tools inappropriate

• Original development of DXA / T-score system
  – Postmenopausal Caucasian women, elderly
  – To assess risk for fragility fracture
  – Highest risk for those $\leq -2.5$ s.d. from population mean
    \[T\text{-score}\]
  – Reference population used unlike astronaut corps
    young healthy, physically fit, work in unique environment, engage in unique activity