Bone Disease After Spinal Cord Injury

Capitalizing on Tissue Plasticity to Impact Bone Health After Spinal Cord Injury

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Prevalence and Cost

- Spinal cord injury (SCI) impacts ~ two hundred thousand individuals and costs society ~ 5 billion dollars annually\(^1\).
- Muscle atrophies quickly and bone mass begins to decline at a rate of 2-4% per month\(^2\).
- The hazard for mortality is estimated to be 78% higher for people with SCI who sustain a lower extremity fracture\(^3\).

Objectives of Presentation

- Attendees will become aware of our work exploring mechanical methods to prevent bone loss in humans with SCI.
- Attendees will appreciate issues of dose-response, feasibility, and outcomes of timely delivered stress in humans with SCI.
- Attendees will understand the complexities of mechanisms that contribute to osteogenic responses in humans with SCI.
Skeletal Plasticity

- Example: Post-SCI bone loss

- Left Distal Tibia:
  - 6 mos. Post-SCI: BMD: 9% loss
  - 16 mos. Post-SCI: BMD: 46% loss
  - 3.5 yrs. Post-SCI: BMD: 63% loss
Bone Loss and Complications

Fractures

Kidney Stones
Musculoskeletal Deterioration

Shields RK, Physical Therapy 2003
What is the Mechanism of Bone Loss After SCI?

- Mechanical?
- Neural?
- Vascular?
- Endocrine?

Myostatin (GDF-8) as a key factor linking muscle mass and bone structure

M.N. Elkasrawy and M.W. Hamrick

The White Adipose Tissue Connection With Calcium and Bone Homeostasis

Roger Bouillon and Brigitte Decallonne

Clinic and Laboratory of Experimental Medicine and Endocrinology (LEGENDO), K.U. Leuven, Herestraat 49-ON1-bus 902, 3000 Leuven, Belgium
Influences on bone

- Genetics
- Endocrine
- Neural
- Mechanical

Qin, Bauman, Cardoza, 2010
Mechanical

- Active
  - Muscle (force/load dependent)
    - Requires electrical stimulation (nerve)
    - Dose

- Passive
  - Vibration
  - Standing with no muscle force
  - Braces
    - Dose

- All methods involve upregulated/downregulated molecular signaling pathways
Muscle as a Master Organ: Mechanical, Neural, Vascular, Endocrine

Recent SCI
3 Days

Chronic SCI
1 year
Regular Muscle Activity

- PGC1 alpha
- Fast Myosin
- Myostatin
- Slow Myosin
- IGF-1
- Mitochondria
- Glucose
- Torque/Force
- Eccentric
- Concentric
- Isometric
Force – Velocity Curve for Muscle
Study 1: Can Mechanical Stress through Muscle Contraction Prevent Bone Changes after SCI?

- Started within 6 weeks post SCI.
- Trained one leg for 2+ years (N=10)
- Intervention: 35 minutes/day electrical stimulation; Dose Specific
- Compliance: 82%
Rationale for the Intervention?

Muscle stress
Bone stress
Frequency
Current
Work-rest
Adherence

1-1.5 times
Body weight
Within Subject Control
Systemic Factors
After 3 Years….

Untrained  Trained

40% increase
T1 = < 6 wks; T2 = .5 years; T3 = 1 year; T4 = 1.5 years; T5 = 2.0; T6 = 2+

Bone Density (pQCT) Untrained versus Trained

Left Leg-Untrained  Right Leg-Trained  32% greater BMD

Shields RK...J Neurophysiol. 2006
Untrained

Trained

Neural?
Muscle Cytokines?
Mechanical?
Muscle-Bone Signaling

Hamrick et al. 2011
Down Regulated MSTN Gene
### Microarray: mRNAs Most Decreased by Right Soleus Training

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Protein</th>
<th>Relative mRNA Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTN3</td>
<td>alpha actinin 3</td>
<td>0.13 ± 0.03</td>
</tr>
<tr>
<td>PVALB</td>
<td>parvalbumin</td>
<td>0.26 ± 0.20</td>
</tr>
<tr>
<td>MSTN</td>
<td>myostatin</td>
<td>0.34 ± 0.03</td>
</tr>
<tr>
<td>TSPAN8</td>
<td>tetraspanin 8</td>
<td>0.34 ± 0.09</td>
</tr>
<tr>
<td>SH3RF2</td>
<td>SH3 domain containing ring finger 2</td>
<td>0.36 ± 0.09</td>
</tr>
<tr>
<td>HCN1</td>
<td>hyperpolarization activated cyclic nucleotide-gated K⁺ channel</td>
<td>0.37 ± 0.03</td>
</tr>
<tr>
<td>AQP4</td>
<td>aquaporin 4</td>
<td>0.37 ± 0.04</td>
</tr>
<tr>
<td>SH2D1B</td>
<td>SH2 domain containing 1B</td>
<td>0.41 ± 0.09</td>
</tr>
<tr>
<td>MYLK2</td>
<td>myosin light chain kinase 2</td>
<td>0.41 ± 0.10</td>
</tr>
<tr>
<td>MYL5</td>
<td>regulatory myosin light chain (fetal skeletal muscle)</td>
<td>0.42 ± 0.07</td>
</tr>
</tbody>
</table>

#### qPCR Analysis

- **Right Soleus mRNA Level**
- **(Relative To Left Soleus mRNA Level)**

**Graph**:
- ACTN3
- MSTN
Oxidative Phosphorylation Signaling Pathway
Activating muscle to stress bone in stance?

- Safer? Feasible?
- Benefits? (Psychological, bladder, skin)
- Multi-segmental?
- Passive, Active, Active Resistive Stance?
Methodology
5 Groups: 3 yrs N=32

1. No SCI
2. Acute
3. Hi: 100% X BW
4. Low: 40% X BW
5. Untrained: No stand

Shields et al. Clinical Biomechanics, 2004
No SCI
Acute
Hi
Low
Untrained

Osteoporosis International, 2011 in press
Unilateral 30 Minutes/Day

Trained 27% larger than Untrained
Untrained vs Trained

NOTE: Untrained received passive standing: 40% of body weight
CT
VTA Technique
Volumetric
Topological
Analysis
Distal Femur

- Trabecular BMD (mg/cm³)
  - Trained
  - Untrained

- Surface Width (microns)
  - Trained
  - Untrained

- Surface-to-Curve Ratio
  - Trained
  - Untrained
Muscle contractions induce important mechanical signals to the skeletal system of individuals with SCI.

The greater the mechanical signal, the greater the effect on bone. ~ 150% of BW compressive load from muscle contraction appears effective in reducing bone loss in areas that are stressed.

There are minimal systemic effects (paracrine) on bone with localized stimulation, but large localized effects which appear to be due to load/electrical activation of tissue.

When contrasted with the literature for cycling, the magnitude of effect for bone appears enhanced when muscle force is optimized through isometric contractions.

More research is needed to develop feasible activity based interventions with the appropriate dose to sustain the health of the musculoskeletal extremities of people with SCI.
Thank you
Unilateral Training