

Bone Disease After Spinal Cord Injury



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

Richard K. Shields PT, PhD, FAPTA
Carver College of Medicine
The University of Iowa

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Andy Littmann PT, cPhD
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Prevalence and Cost

- Spinal cord injury (SCI) impacts ~ two hundred thousand individuals and costs society ~ 5 billion dollars annually¹.
- Muscle atrophies quickly and bone mass begins to decline at a rate of 2-4% per month²
- The hazard for mortality is estimated to be 78% higher for people with SCI who sustain a lower extremity fracture³.

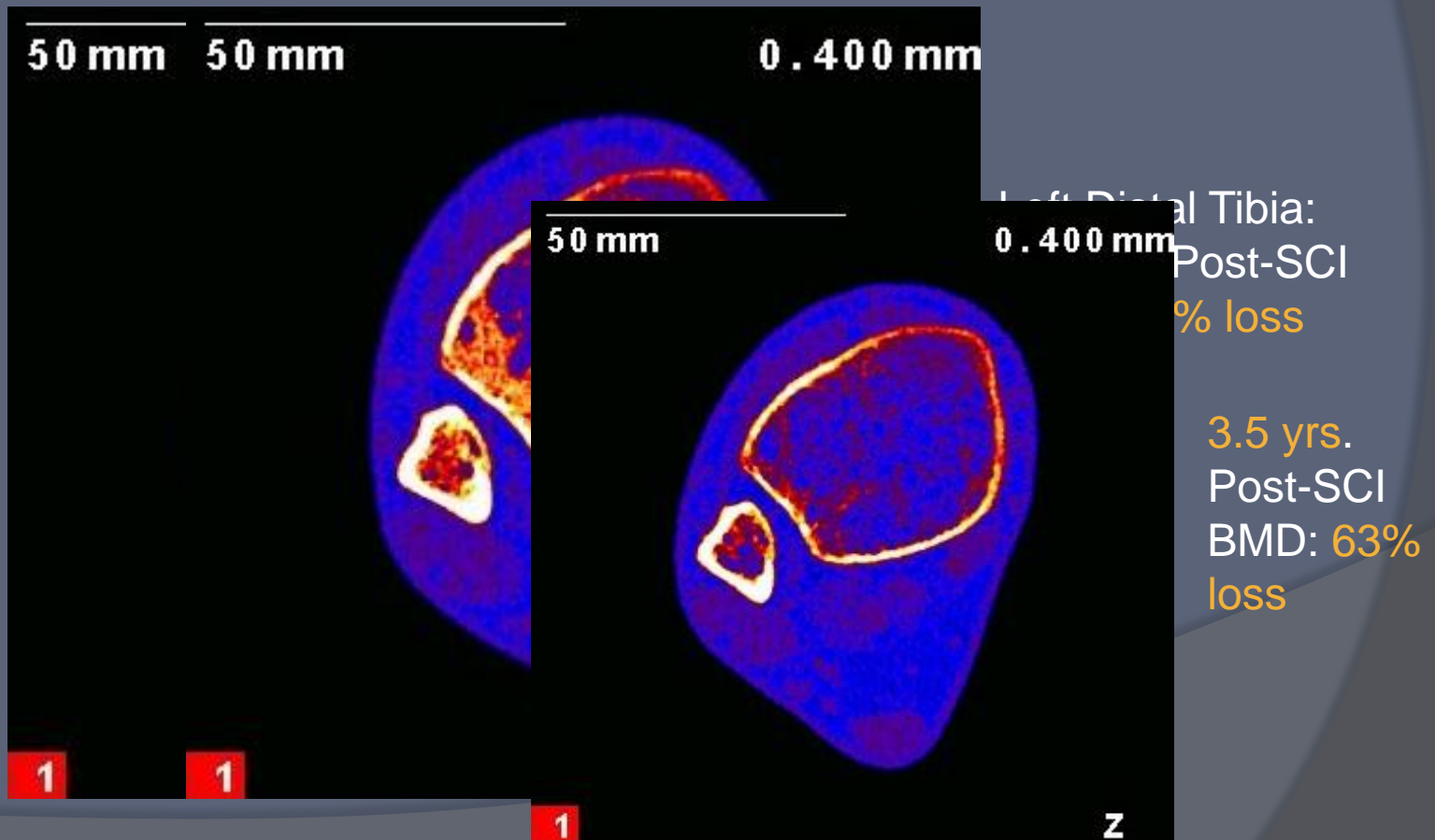
1. Stover SL, DeLisa JS, Whiteneck GG. Spinal cord injury: Clinical outcomes from the model systems. Gaithersburg, MD: Aspen Publishers, Inc.; 1995.
2. Wilmet E, Ismail AA, Heilporn A, Welraeds D, Bergmann P. Longitudinal study of the bone mineral content and of soft tissue composition after spinal cord section. *Paraplegia* 1995;33:674-677.
3. Krause JS, Carter RE, Pickelsimer EE, Wilson D. A prospective study of health and risk of mortality after spinal cord injury. *Arch Phys Med Rehabil* 2008;89:1482-1491.

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.

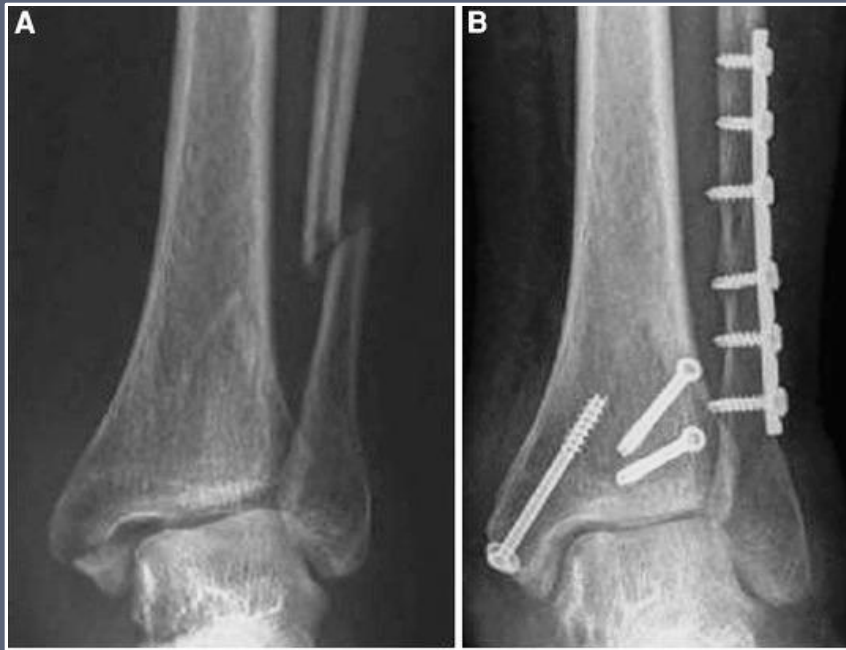
Skeletal Plasticity

- Example: Post-SCI bone loss

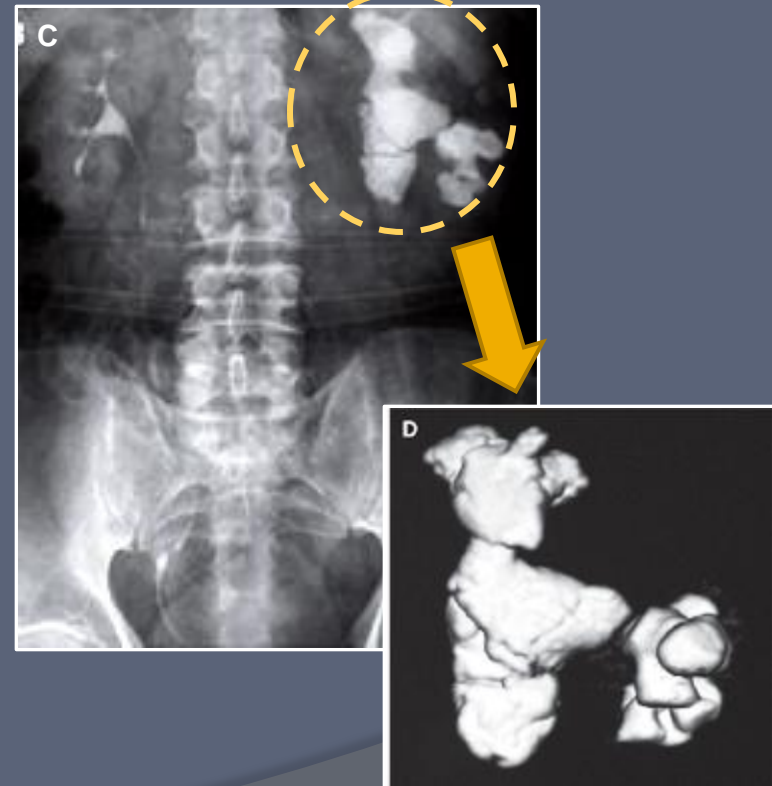


Bone Loss and Complications

Fractures



Kidney Stones



Musculoskeletal Deterioration



Shields RK, Physical Therapy 2003

What is the Mechanism of Bone Loss After SCI?

Endocrine?

Mechanical?

Neural?

Vascular?

JBMR

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: *Molecular and Integrative Physiology of the Musculoskeletal System*

Bone and muscle loss after spinal cord injury: organ interactions

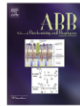
Weiping Qin,^{1,2} William A. Bauman,^{1,2,3} and Christopher Cardozo^{1,2,3}

Archives of Biochemistry and Biophysics xxx (2010) xxx-xxx

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Archives of Biochemistry and Biophysics

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



Review

Fat and bone[☆]

Ian R. Reid^{*}

Department of Medicine, Faculty of Medical and Health Sciences, University of Auckland, Private Bag 92019, Auckland, New Zealand

J Musculoskelet Neuronal Interact 2010; 10(1):56-63

Review Article

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

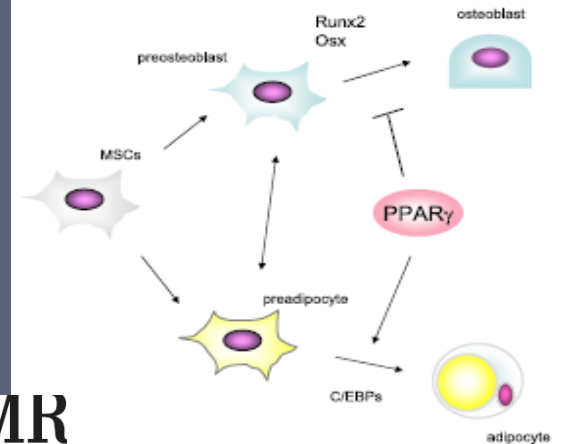
Clinic and Laboratory of Experimental Medicine and Endocrinology (LEGENDO), K.U. Leuven, Herestraat 49-ON1-bus 902, 3000 Leuven, Belgium

Lipids (2010) 45:345-355
DOI 10.1007/s11745-010-3397-0

ORIGINAL ARTICLE

Expression of Genes Associated with Bone Resorption is Increased and Bone Formation is Decreased in Mice Fed a High-Fat Diet

Ying Xiao · Jue Cui · Ya-Xin Li · Yong-Hui Shi · Guo-Wei Le



PPAR γ regulates MSC allocation. Determination of lineage allocation Cs is regulated by several transcription factors including PPAR γ and T/enhancer binding proteins (C/EBPs), which govern adipogenesis, (myt-related transcription factor), and Osx (osterix), which are necessary for osteoblastogenesis. PPAR γ favors adipogenesis and suppresses osteogenesis partly through inhibiting Runx2 function, resulting in the reduced osteoblast pool in bone marrow.

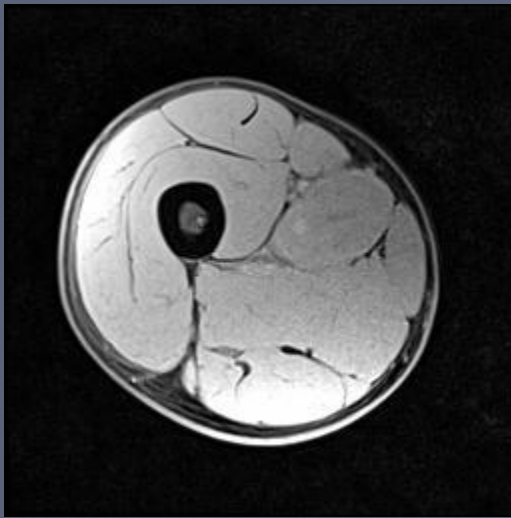
Influences on bone

- Genetics
- Endocrine
- Neural
- Mechanical

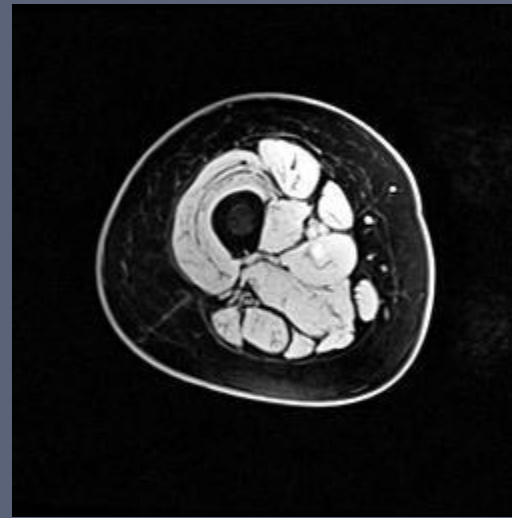
Mechanical

- ⦿ Active
 - Muscle (force/load dependent)
 - Requires electrical stimulation (nerve)
 - Dose
- ⦿ Passive
 - Vibration
 - Standing with no muscle force
 - Braces
 - Dose
- ⦿ All methods involve upregulated/down regulated molecular signaling pathways

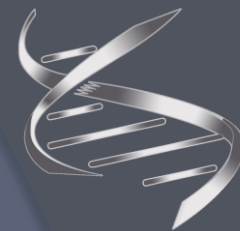
Muscle as a Master Organ: Mechanical, Neural, Vascular, Endocrine



Recent SCI
3 Days



Chronic SCI
1 year



Regular Muscle Activity

PGC1 alpha

Fast Myosin

Myostatin

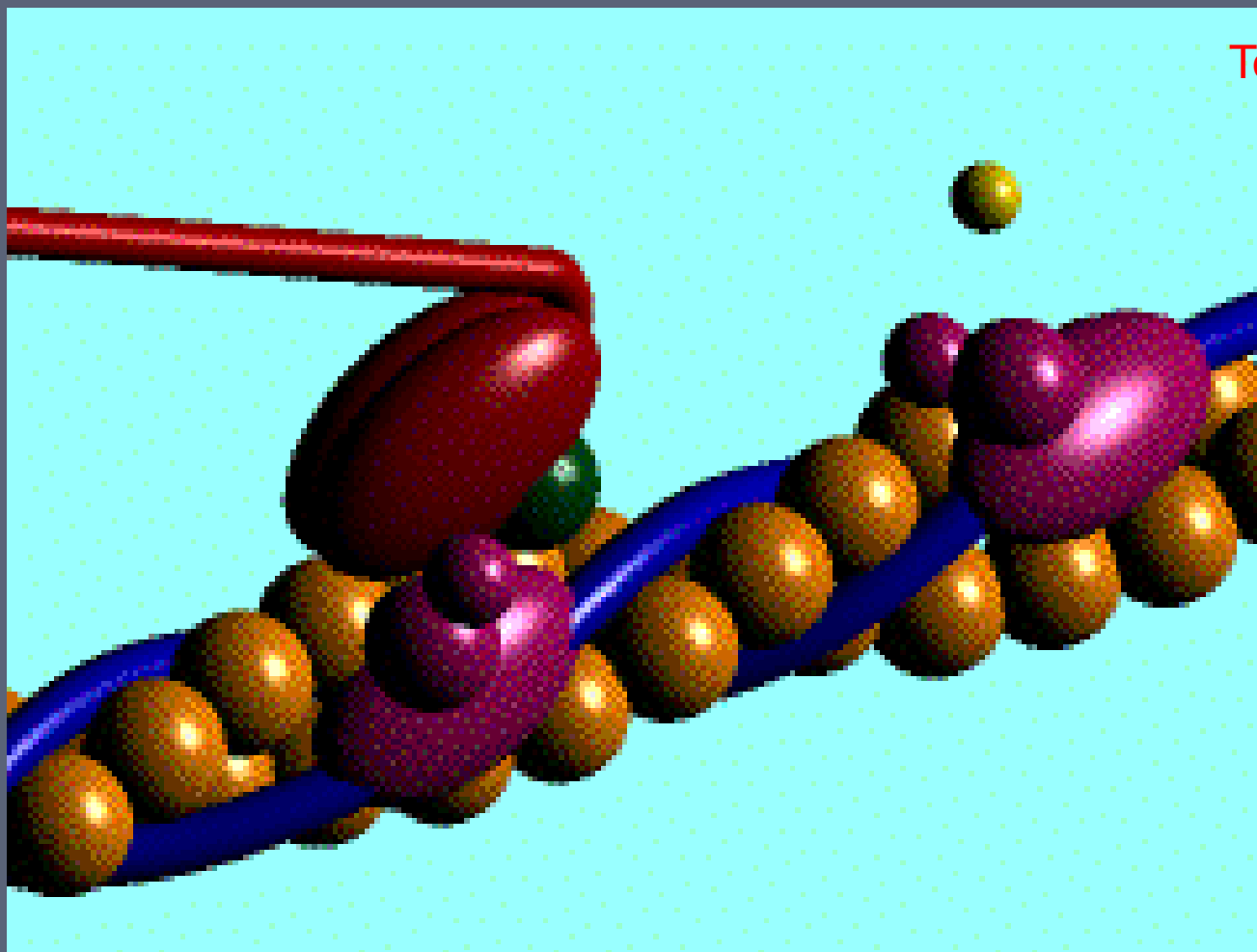
Slow Myosin

Torque/Force

Eccentric

Concentric

Isometric

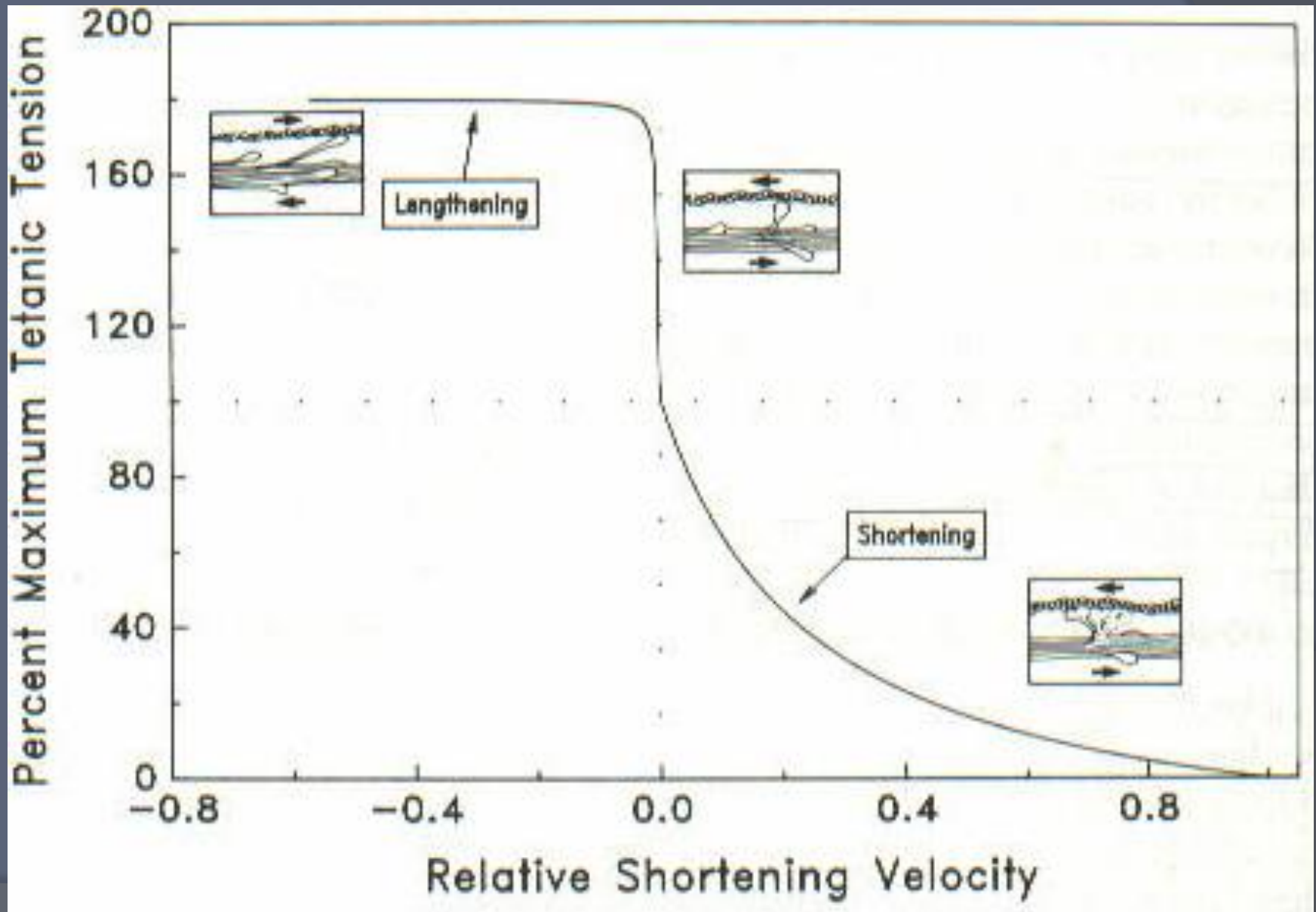


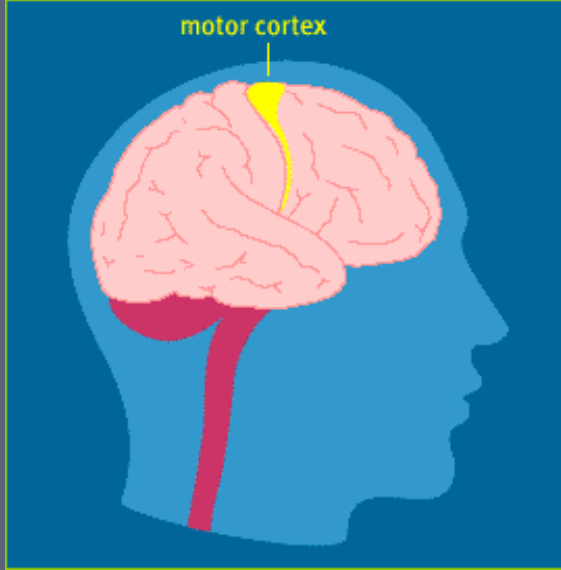
IGF-1

Mitochondria

Glucose

Force – Velocity Curve for Muscle



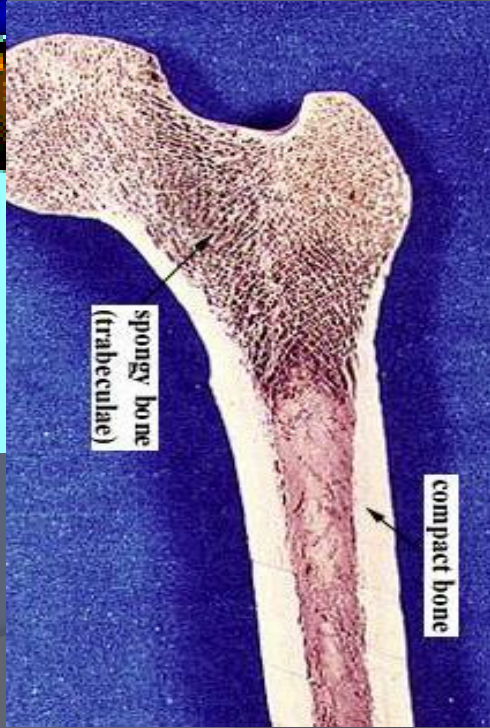
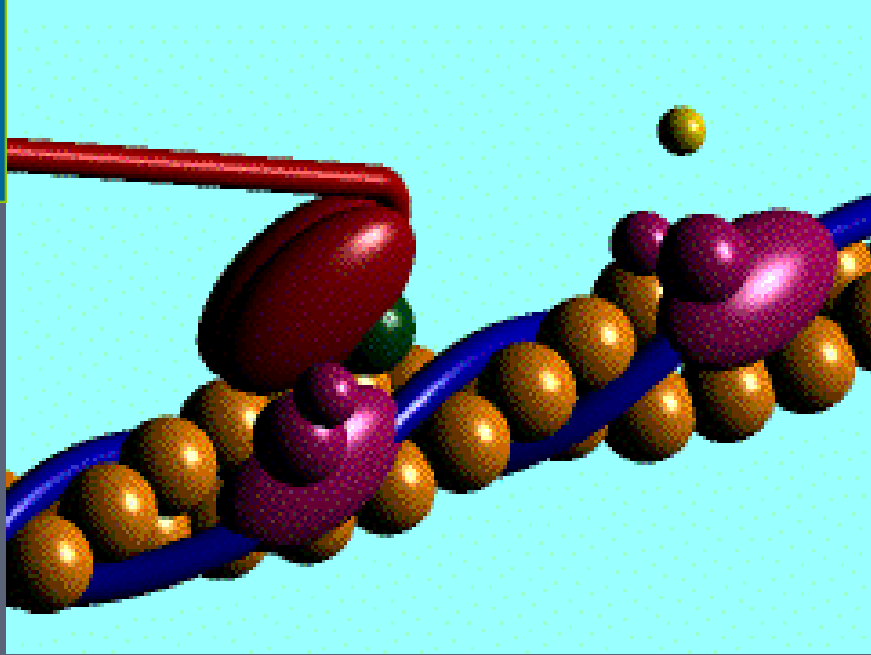


Repetitive Velocity Load Length

Transducer

concentric

Bone



Nerve

eccentric

isometric

Muscle

Work Rest Cycle

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%

J Neuro-rehab 2007
Spine 2006
Muscle and Nerve 2006
J Neurophys 2006
J Appl Physiol 2006
J Appl Physiol 2008
Osteoporosis Int 2010
Neuroscience Letters 2011
Arch Phys Med 2011

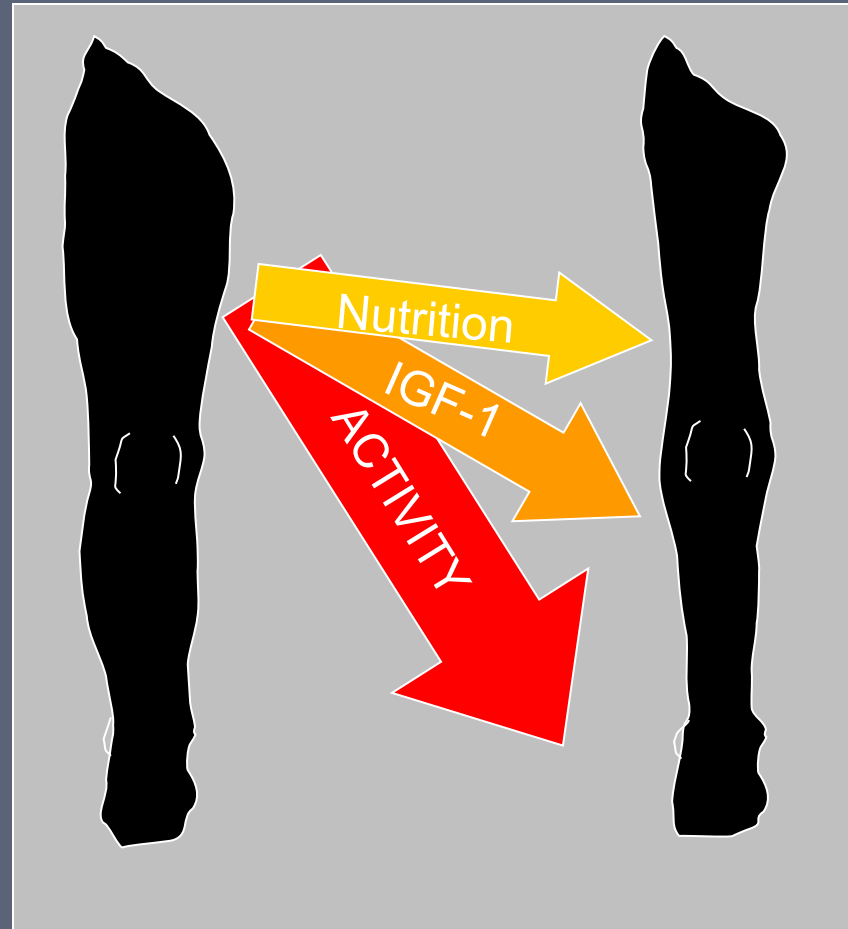
Rationale for the Intervention?

Muscle stress
Bone stress
Frequency
Current
Work-rest
Adherence

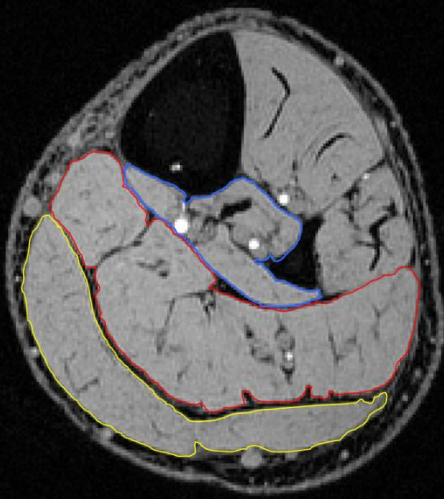
1-1.5 times
Body weight



Within Subject Control Systemic Factors



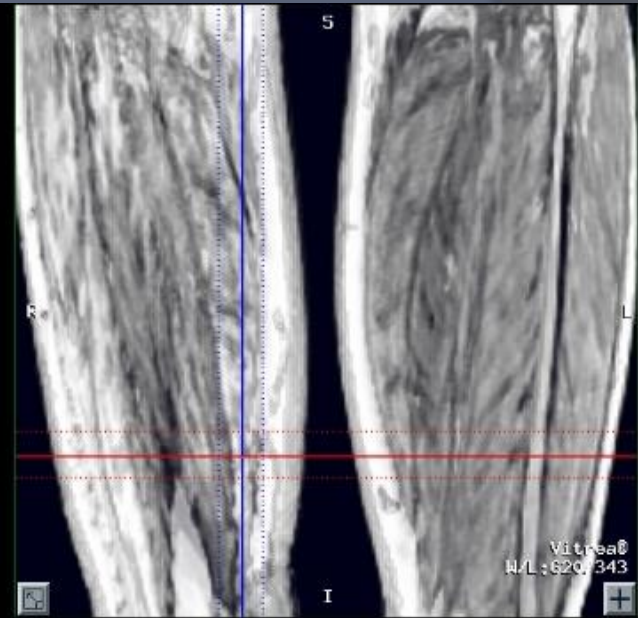
After 3 Years....



Untrained

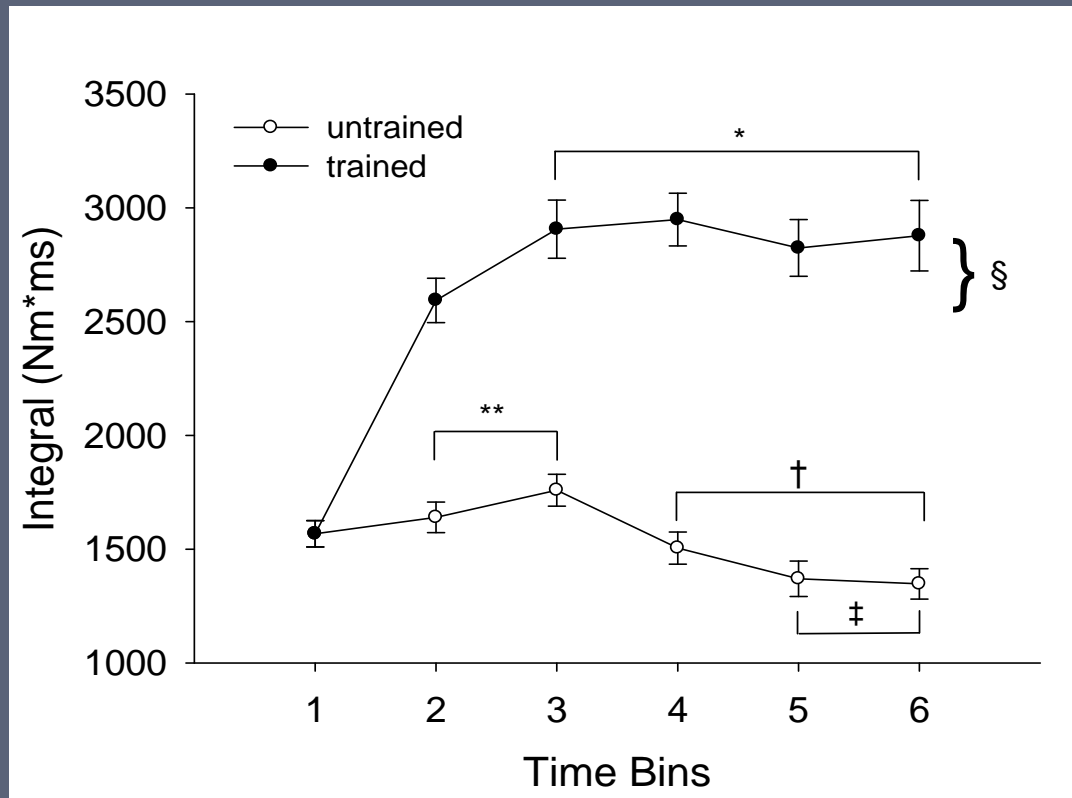


Trained



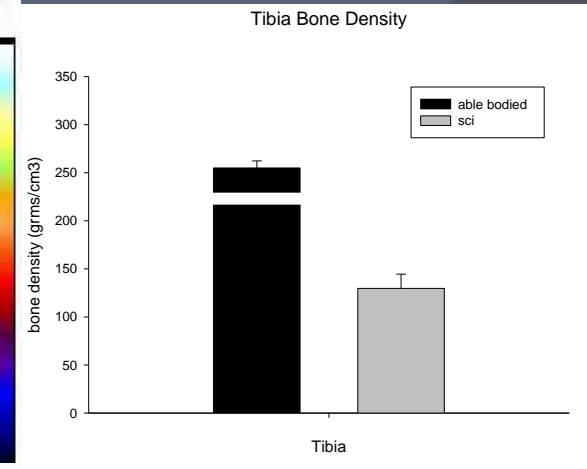
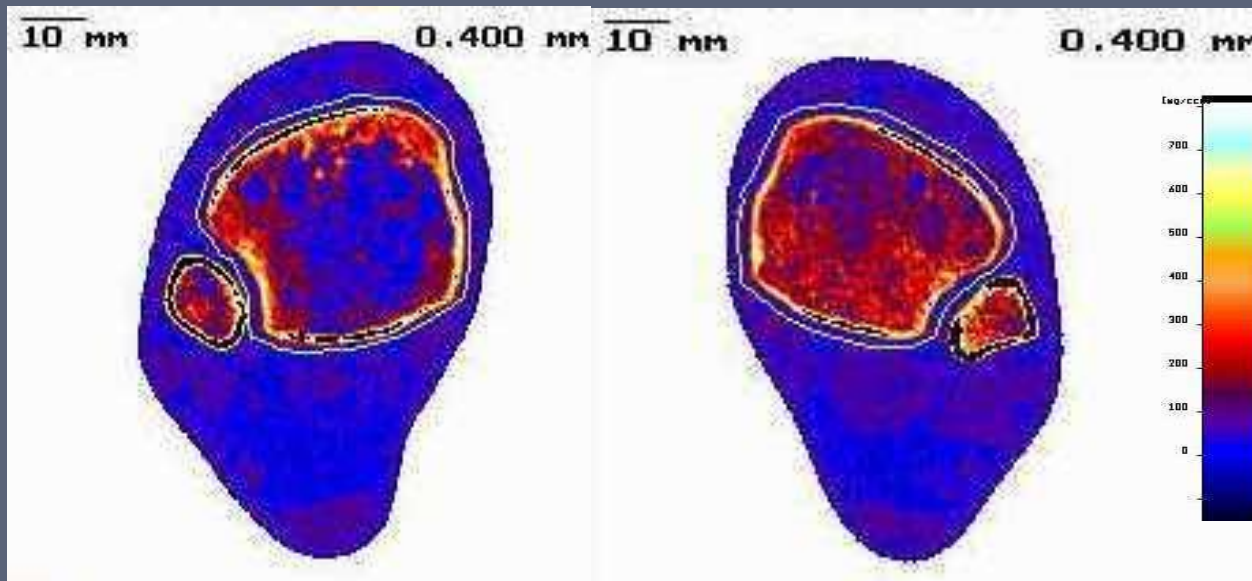
40% increase

Torque



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

Bone Density (pQCT) Untrained versus Trained

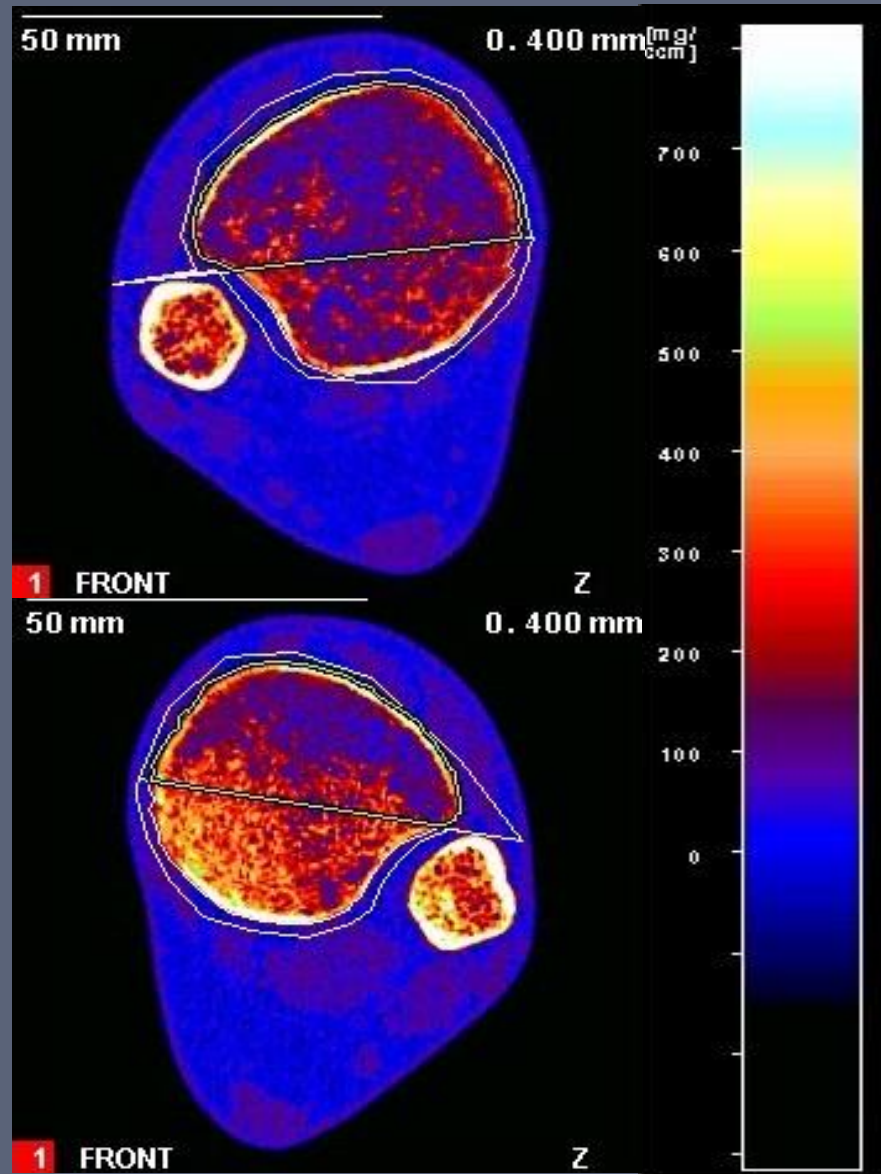


Left Leg-Untrained

Right Leg-Trained

32% greater BMD

Untrained

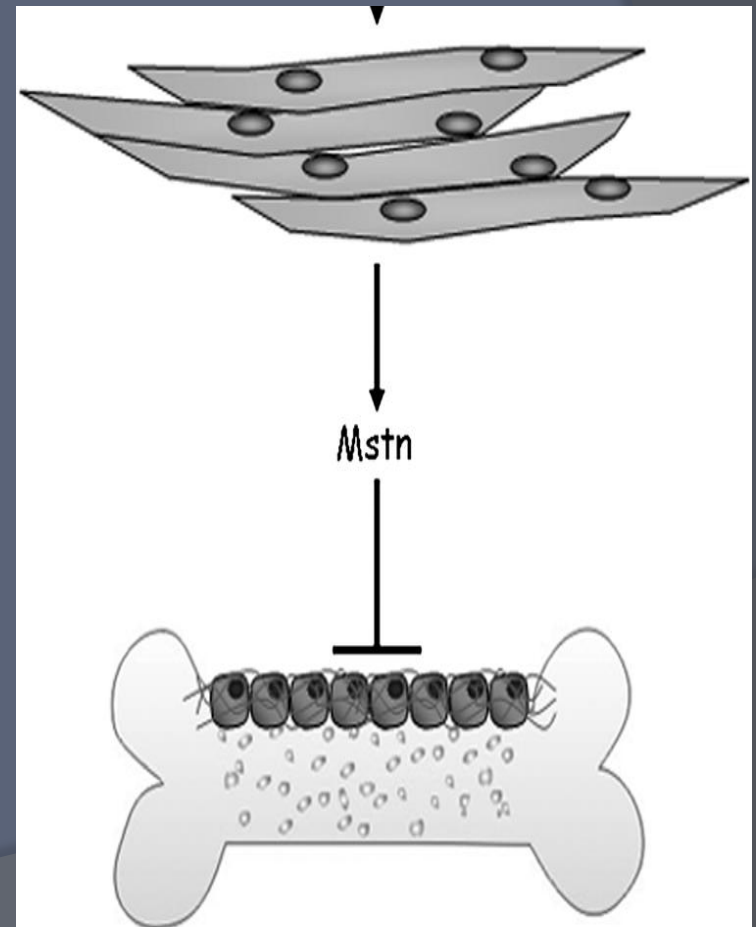
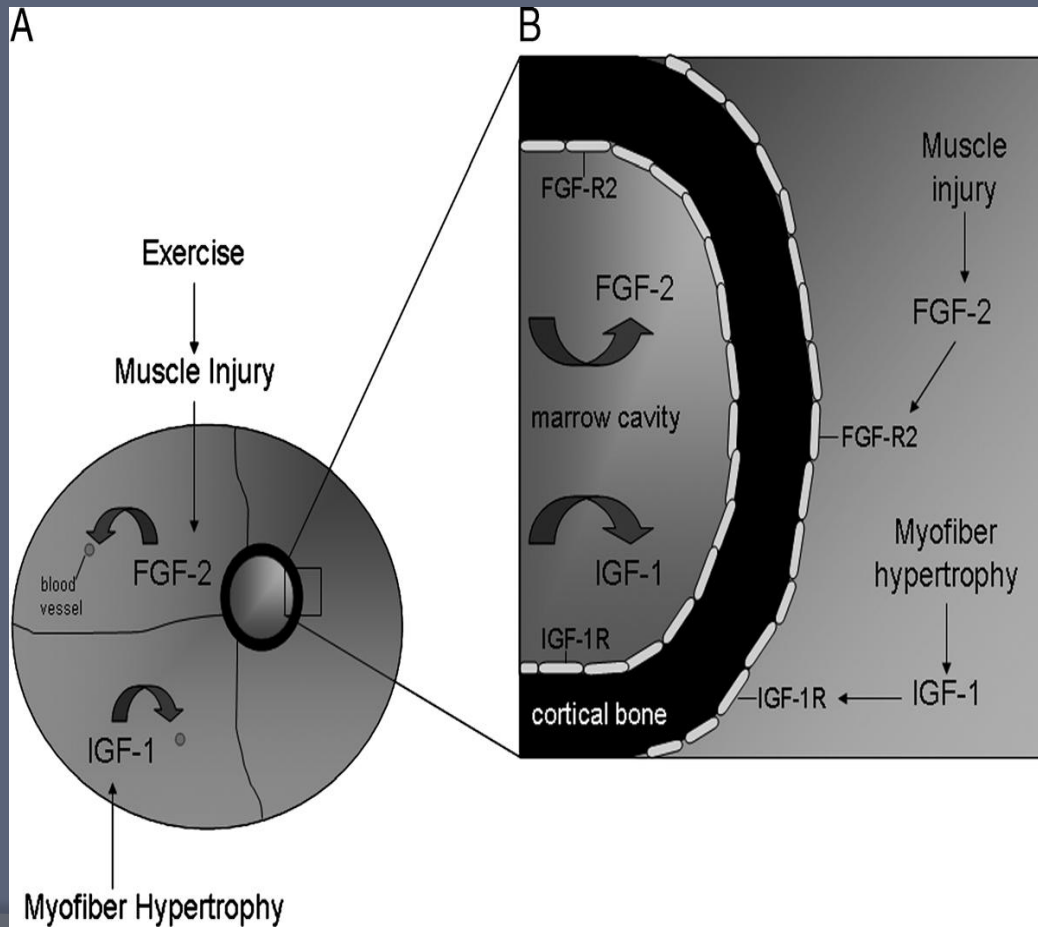


Neural?
Muscle Cytokines?
Mechanical?

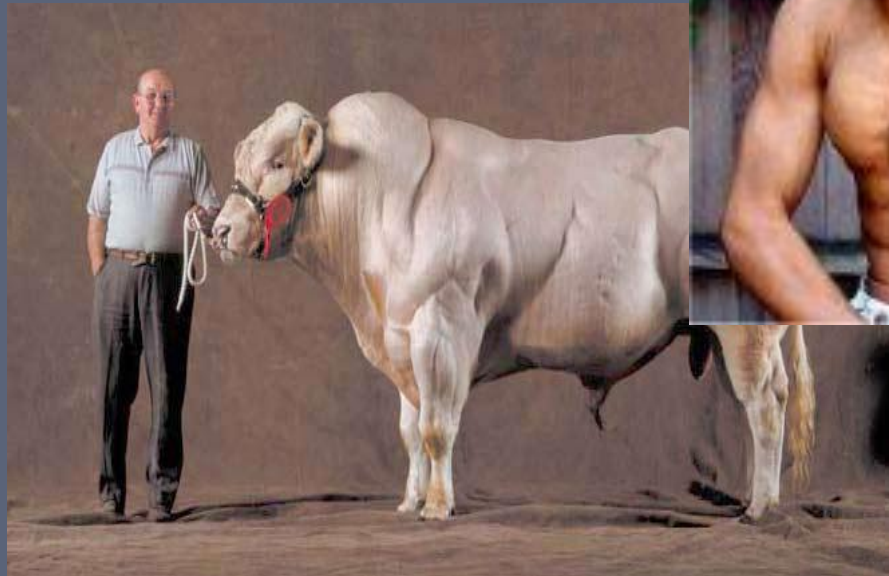
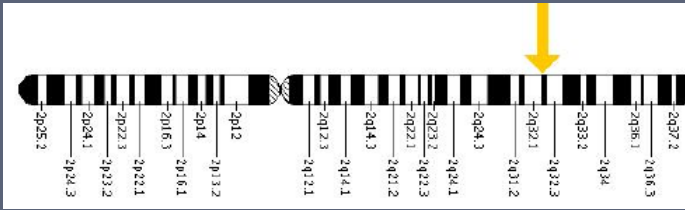
Trained

Muscle-Bone Signaling

Hamrick et al. 2011



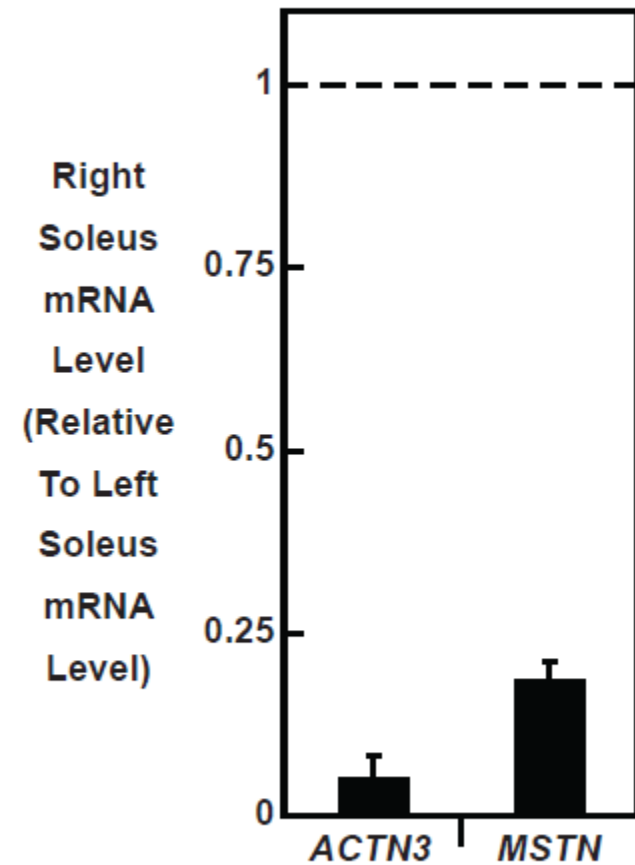
Down Regulated MSTN Gene



A Microarray: mRNAs Most Decreased by Right Soleus Training

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

C qPCR Analysis



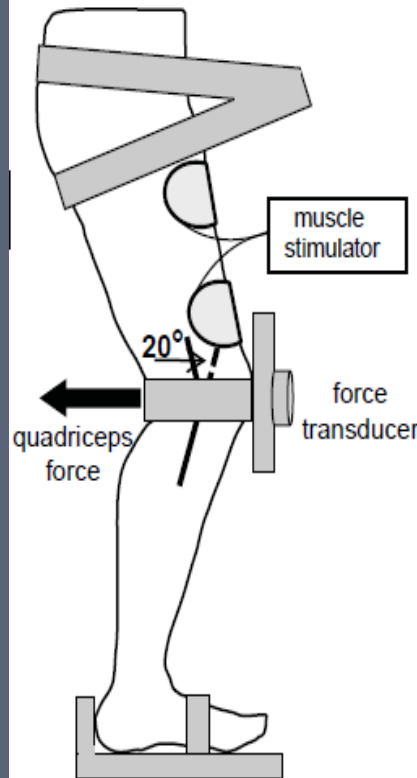
Activating muscle to stress bone in stance?

- Safer? Feasible?
- Benefits? (Psychological, bladder , skin)
- Multi-segmental?
- Passive, Active, Active Resistive Stance?

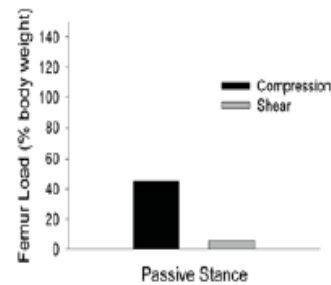
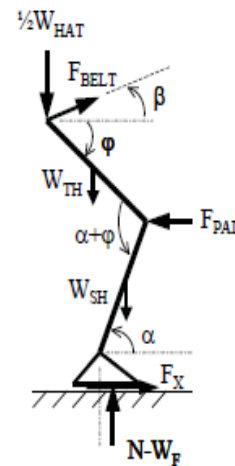
Methodology
5 Groups: 3 yrs
N=32

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

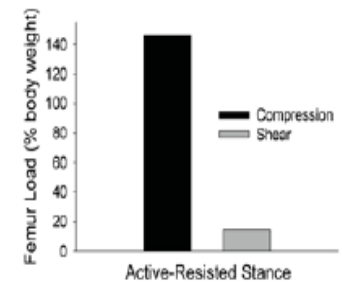
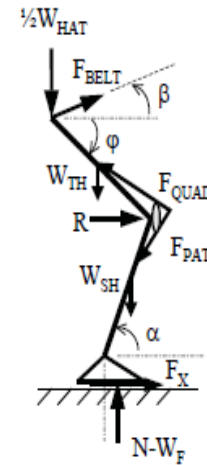
Laboratory Standing System



Passive Stance Model

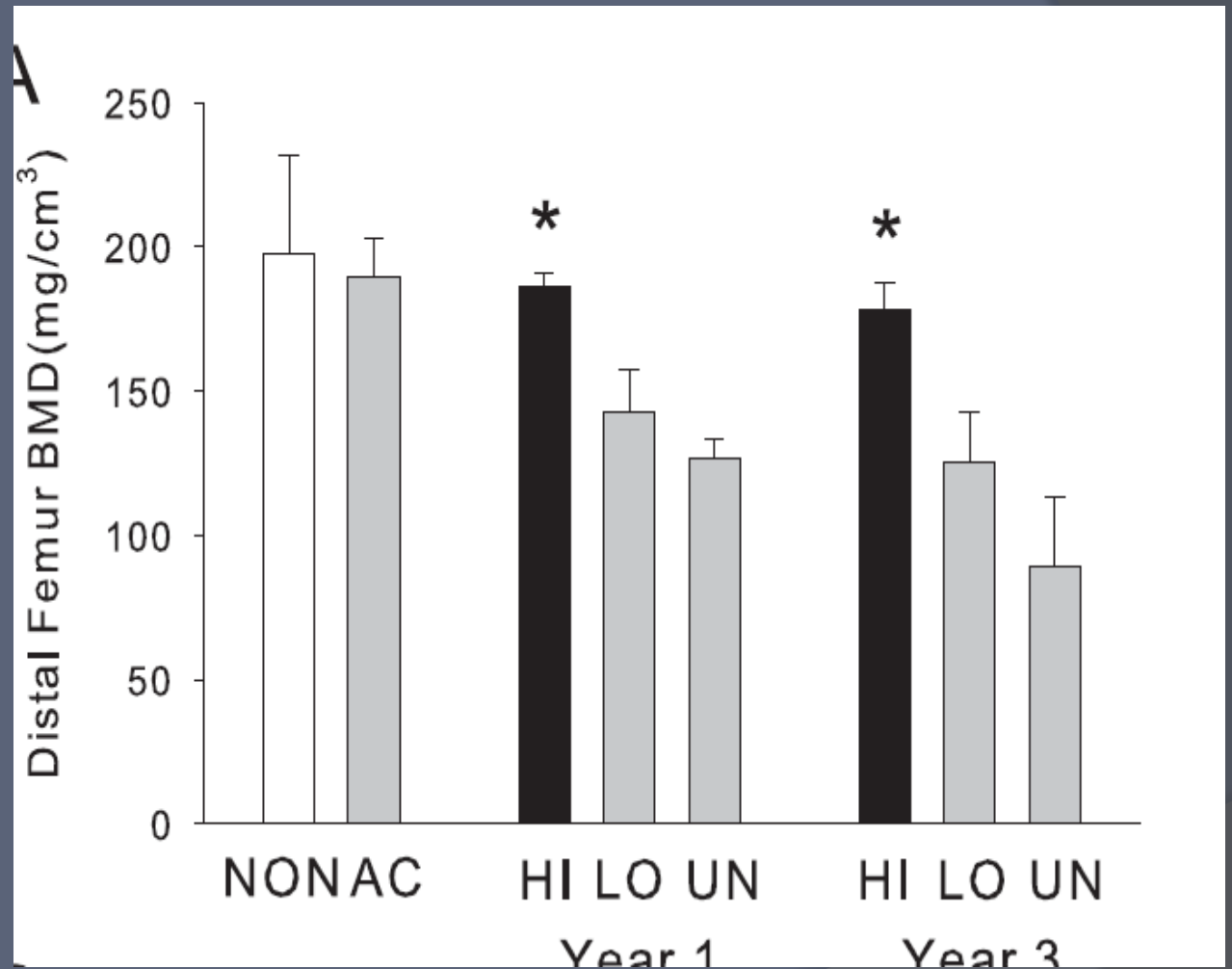


Active Stance Model



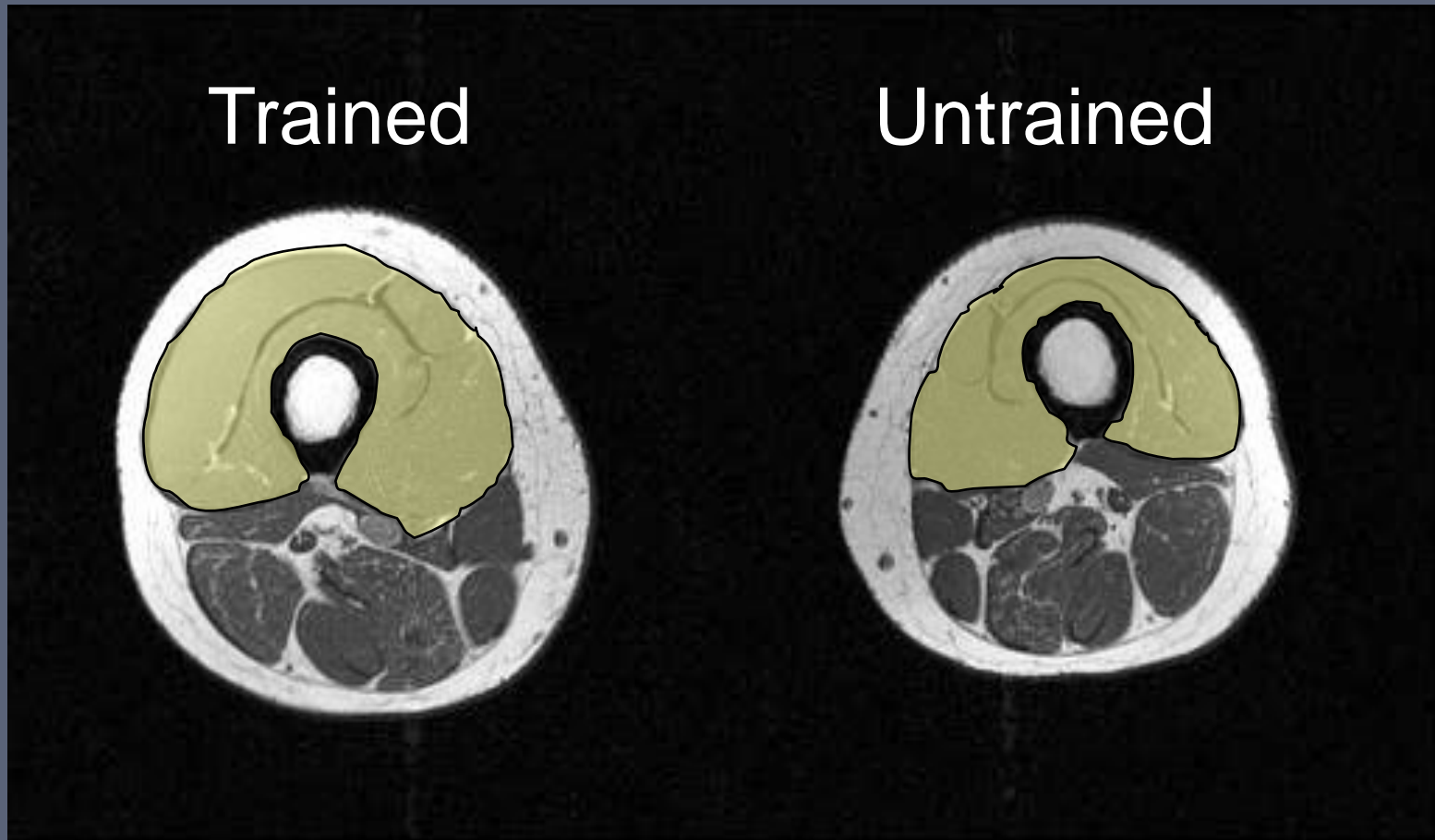
Shields et al. Clinical Biomechanics, 2004

No SCI
Acute
Hi
Low
Untrained



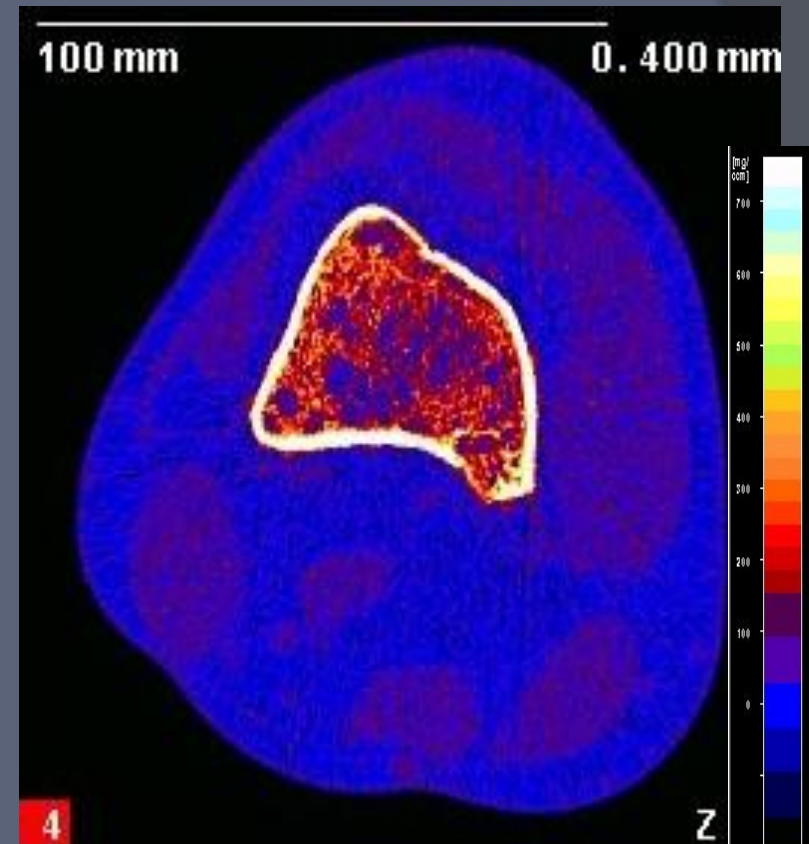
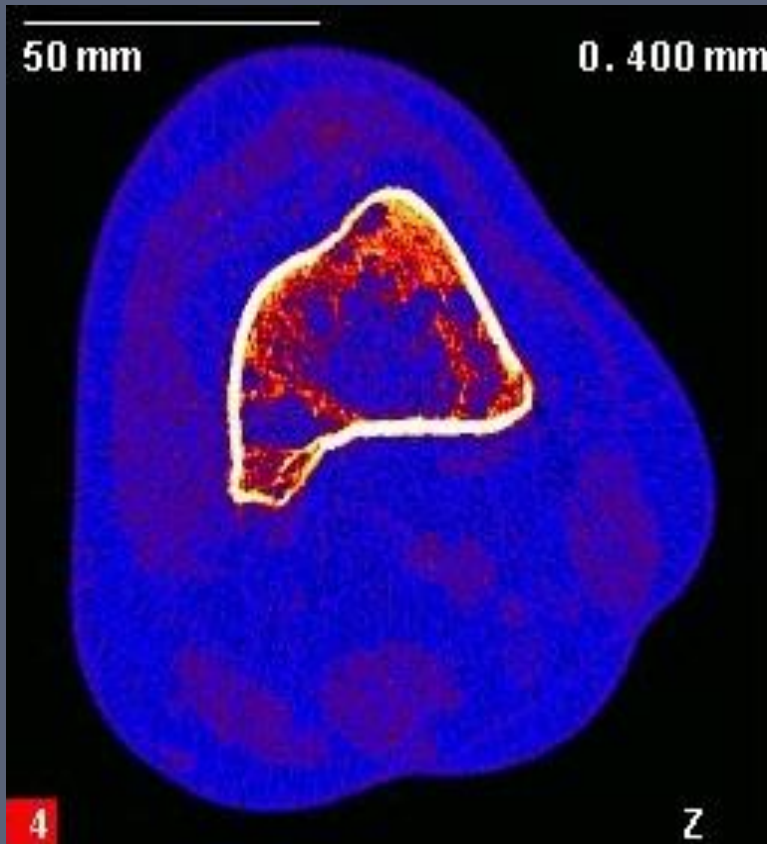
Osteoporosis International, 2011 in press

Unilateral 30 Minutes/Day



Trained 27% larger than Untrained

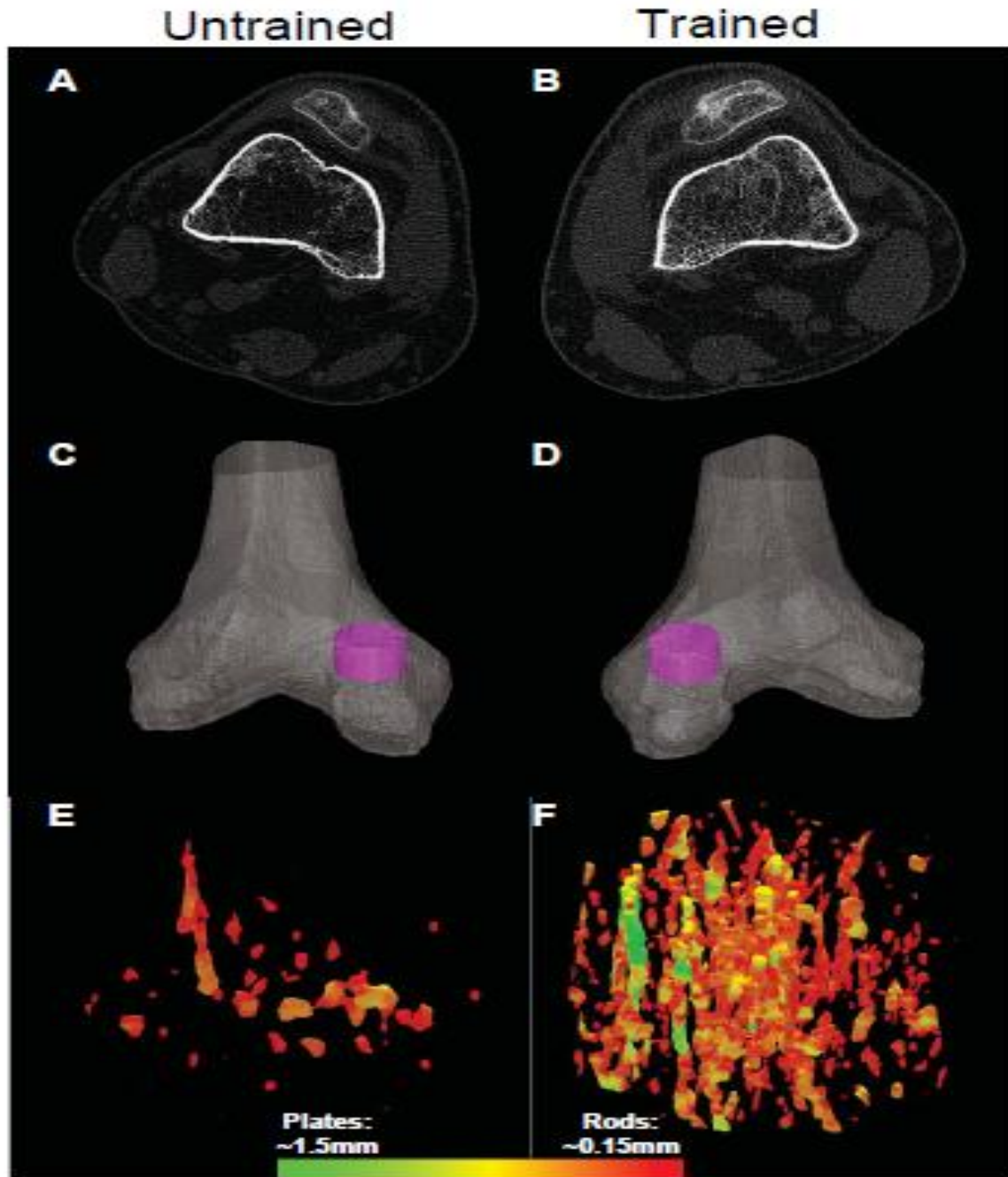
Untrained vs Trained



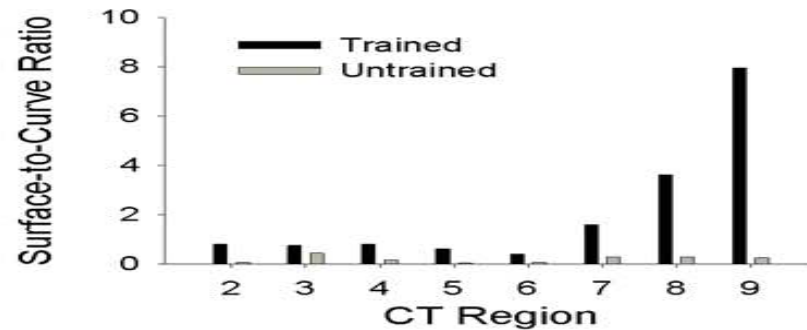
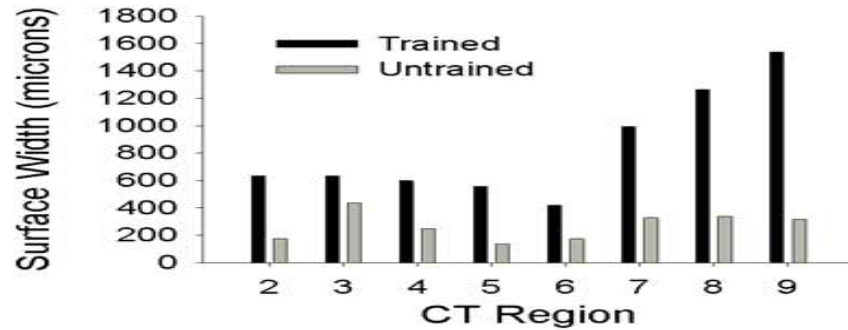
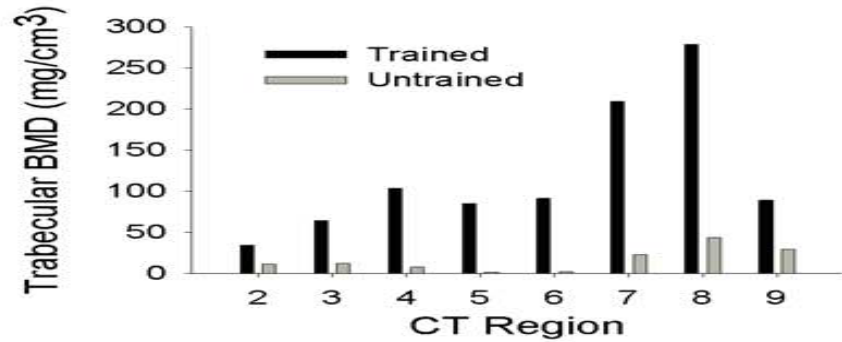
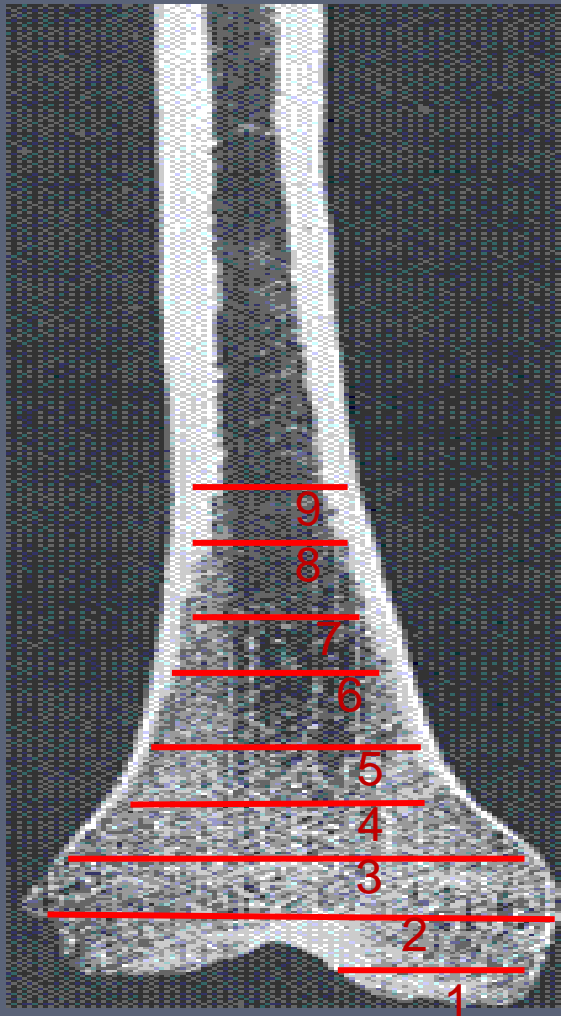
NOTE: Untrained received passive standing: 40% of body weight

CT
VTA Technique

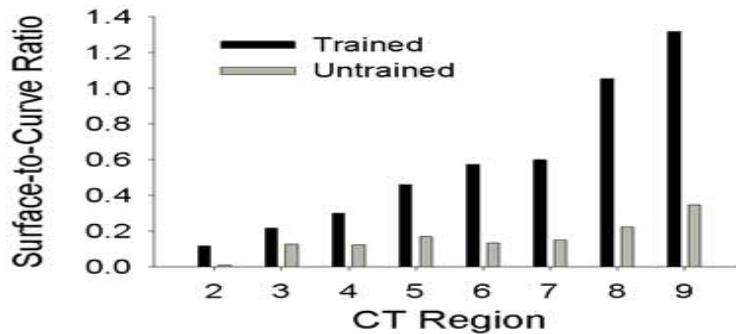
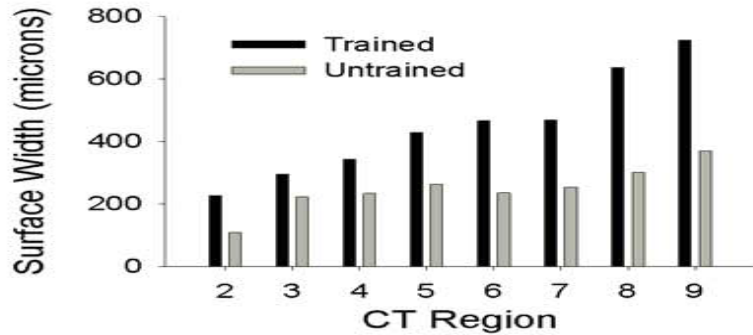
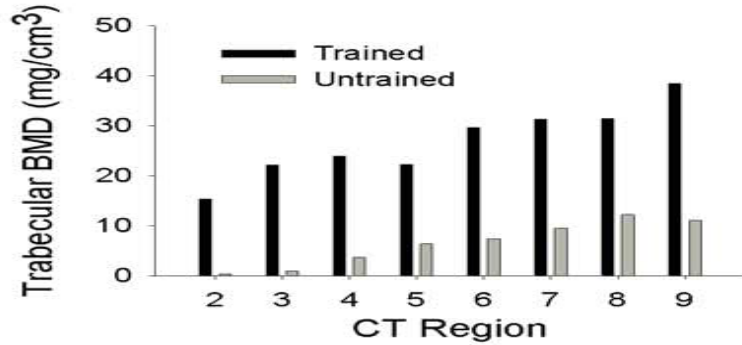
Volumetric
Topological
Analysis



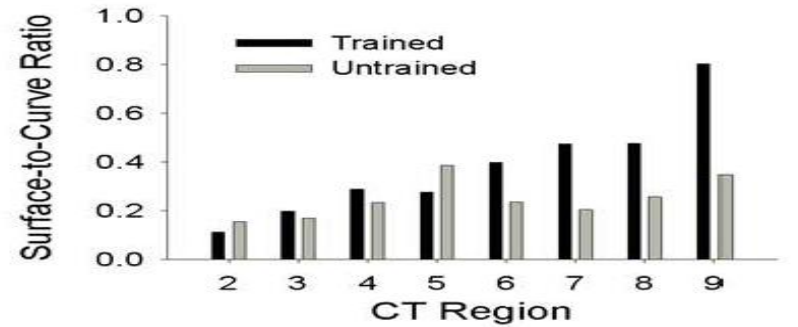
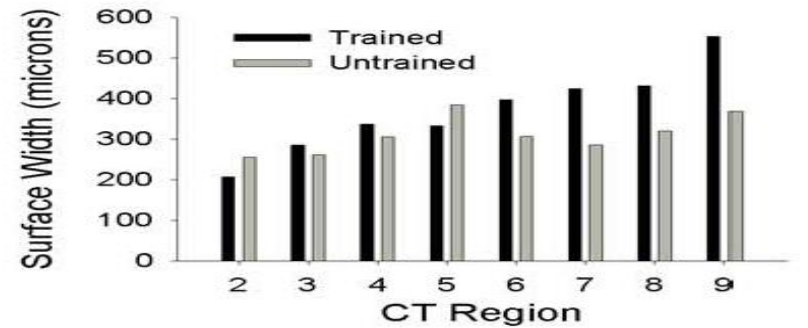
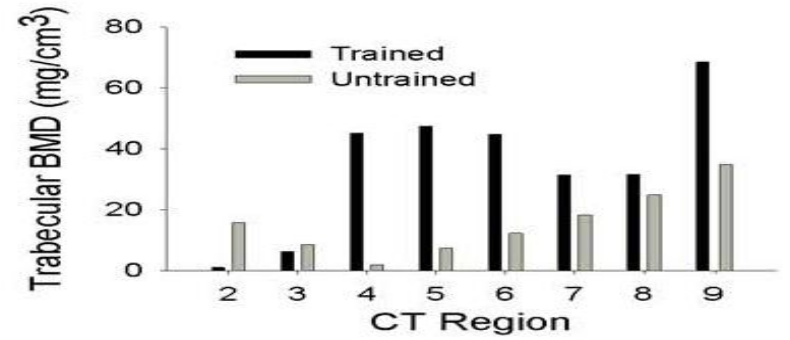
Distal Femur



Proximal tibia



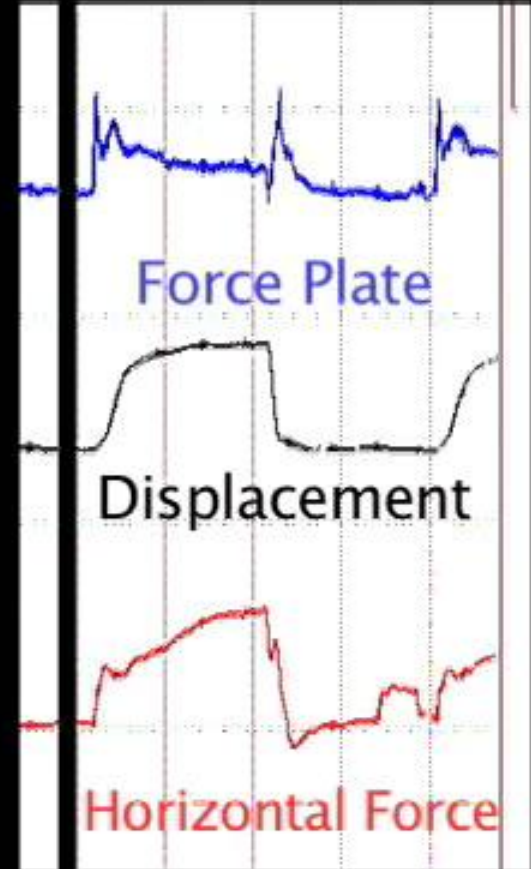
Distal Tibia



Take Home Message

- 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