Marodyne MEDICAL

Low Intensity Vibration as a Non-Drug Intervention for Musculoskeletal Injuries and Disease

November, 2014
The Scientific Basis of LIV Therapy

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Stony Brook University, New York

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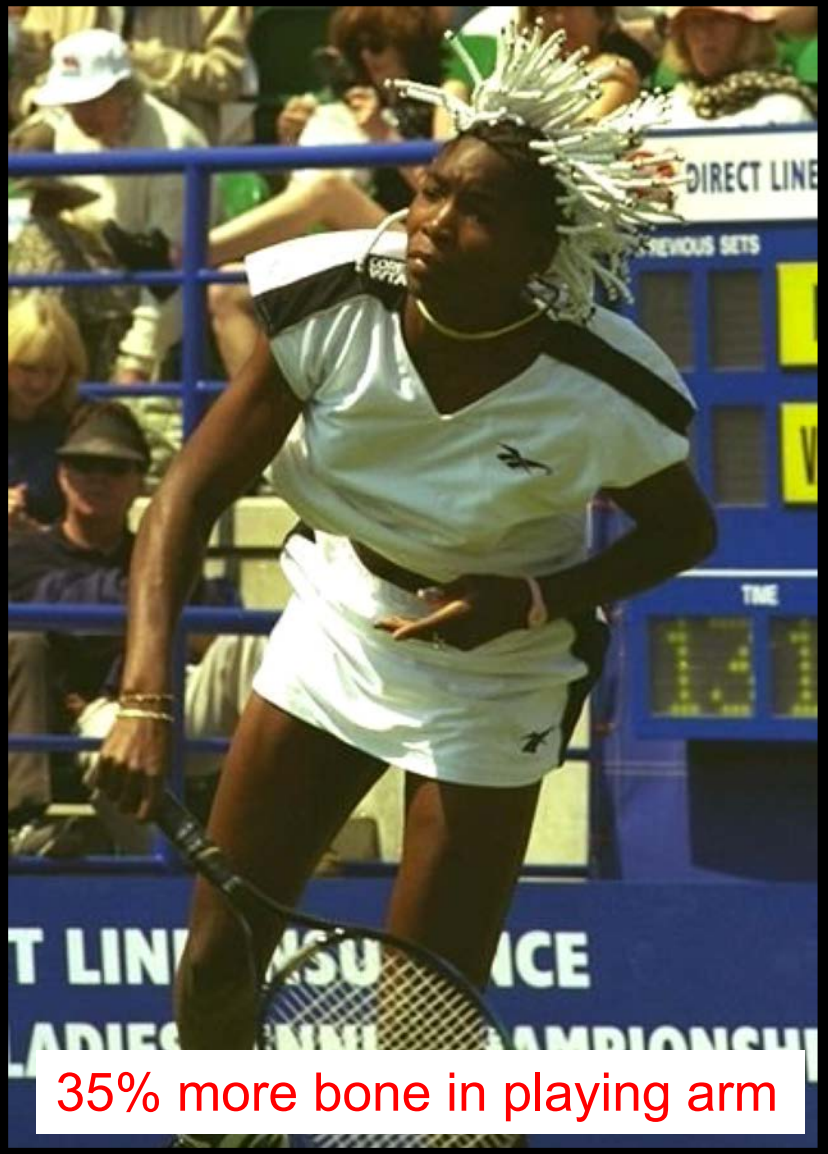
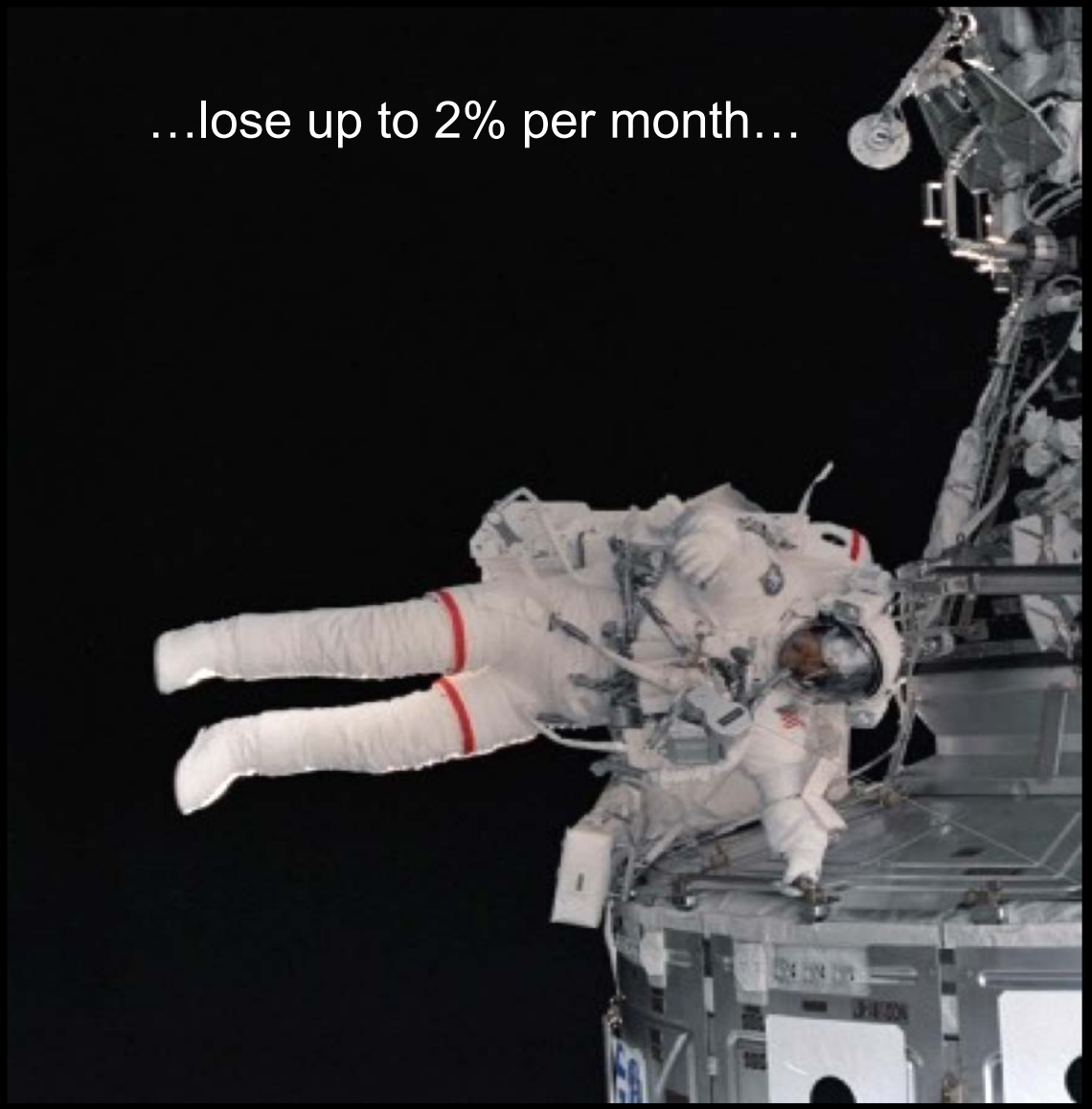
Wolff's Law: Form follows function in bone….



Jones et. al. 1977

…lose up to 2% per month…



Lang et. al., 2004

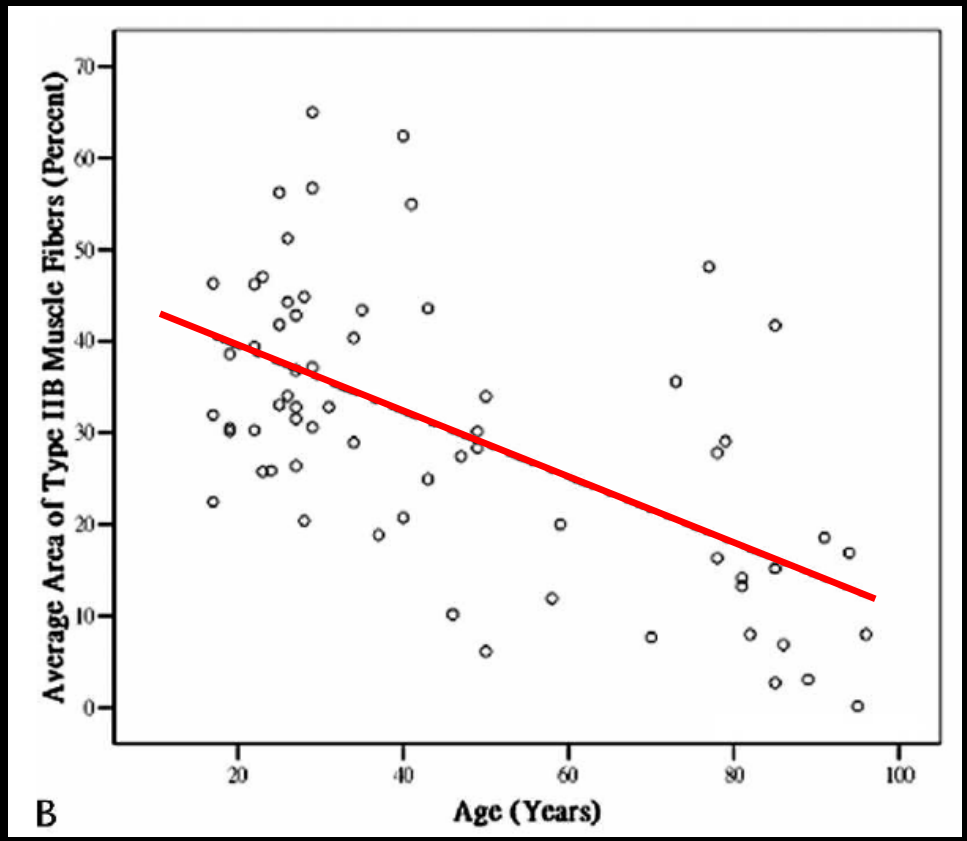
Muscle

Age-associated Decrease of Type IIA/B Human Skeletal Muscle Fibers

Wing-Sze Lee, BSc; Wing-Hoi Cheung, PhD; Ling Qin, PhD; Ning Tang, FRCSEd(Orth); and Kwok-Sui Leung, MD

M; Age 25

M; Age 63

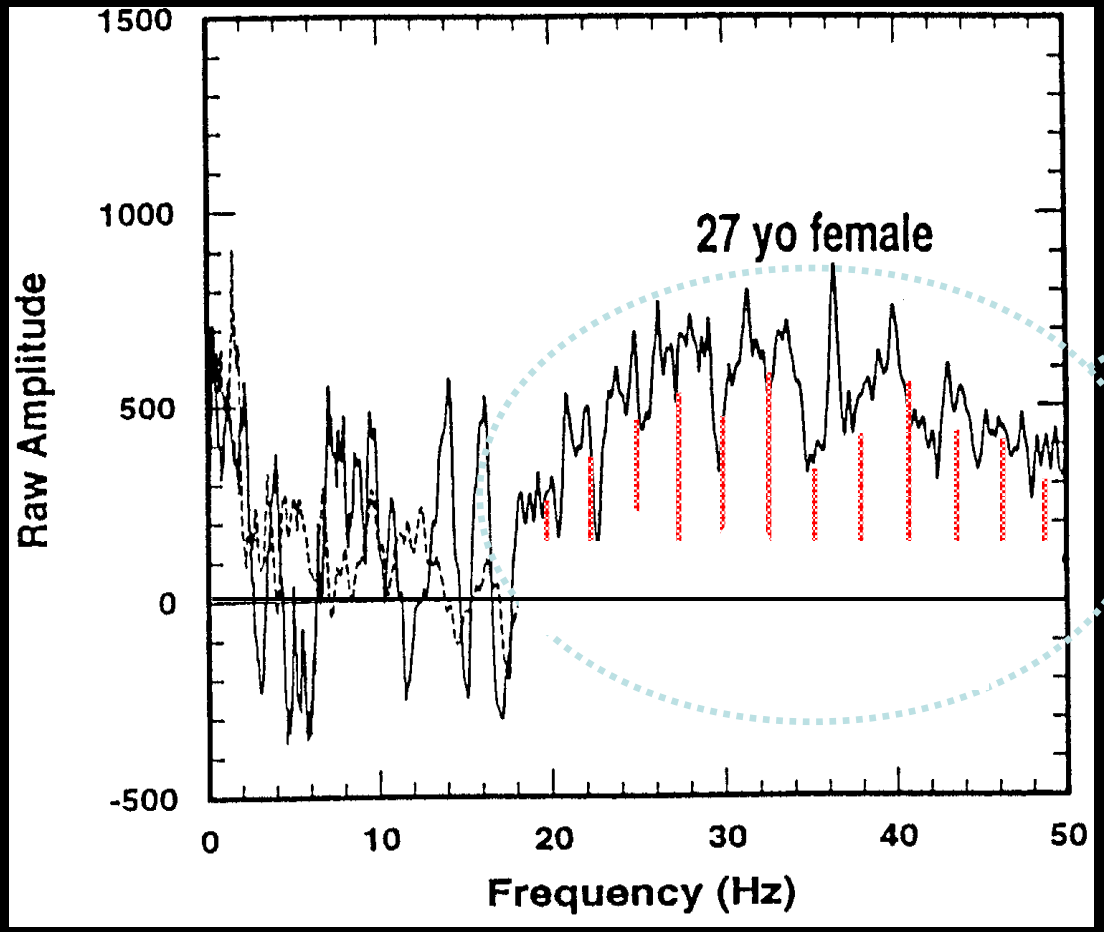


Type IIb

CORR; 2006

Contractile spectra of postural muscle

deteriorates as a function of age

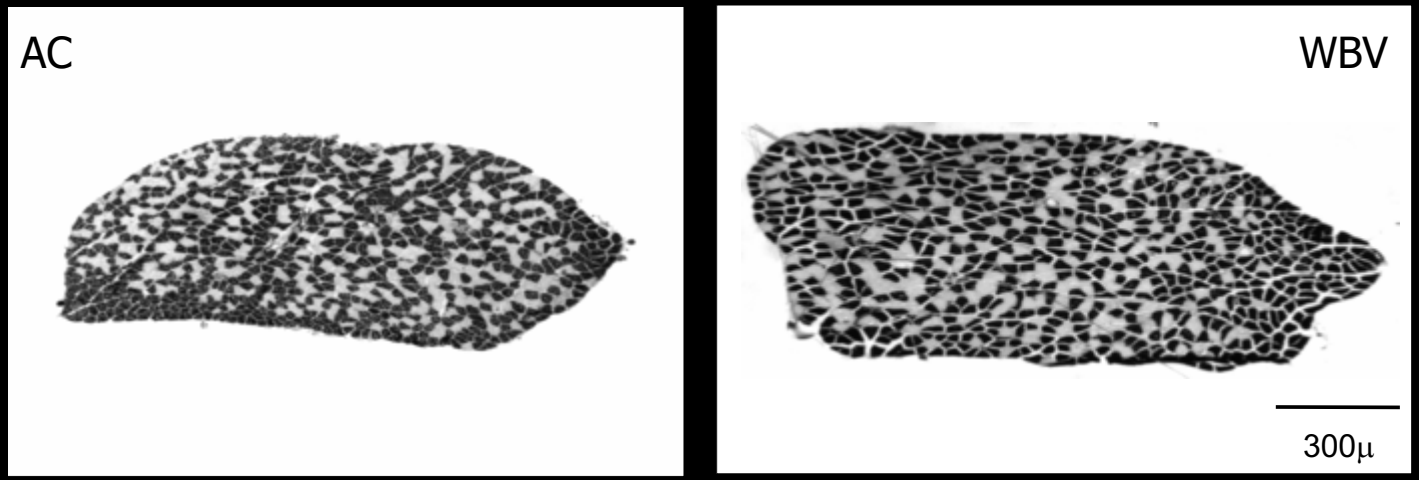


Mechanical content in 20-50 Hz band

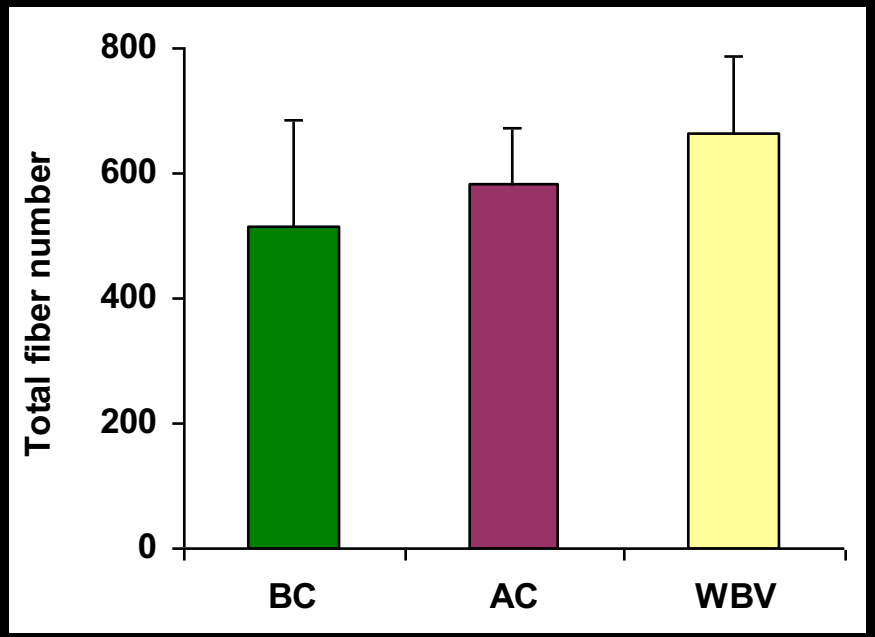
Does fibre-type specific sarcopenia suppress regulatory signals to bone?

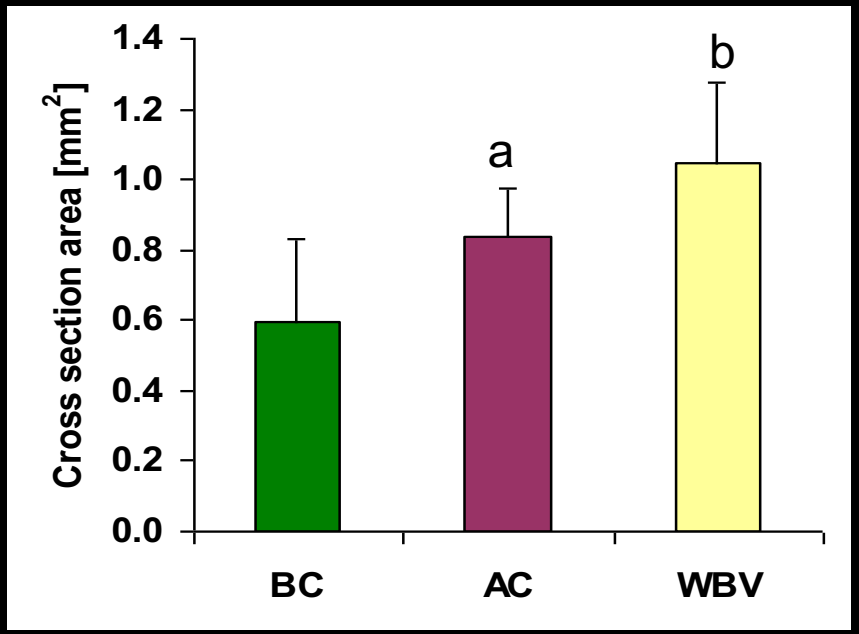
Huang et. al., *J. Geront. 1999*

LIV influences on the musculoskeletal *system*



ATPase staining (pH10.4)w/ Type II as black





>30% increase in cross-sectional area of muscle ($p<0.05$), trend of increase in fiber # and area

(mean+SD, n=12)

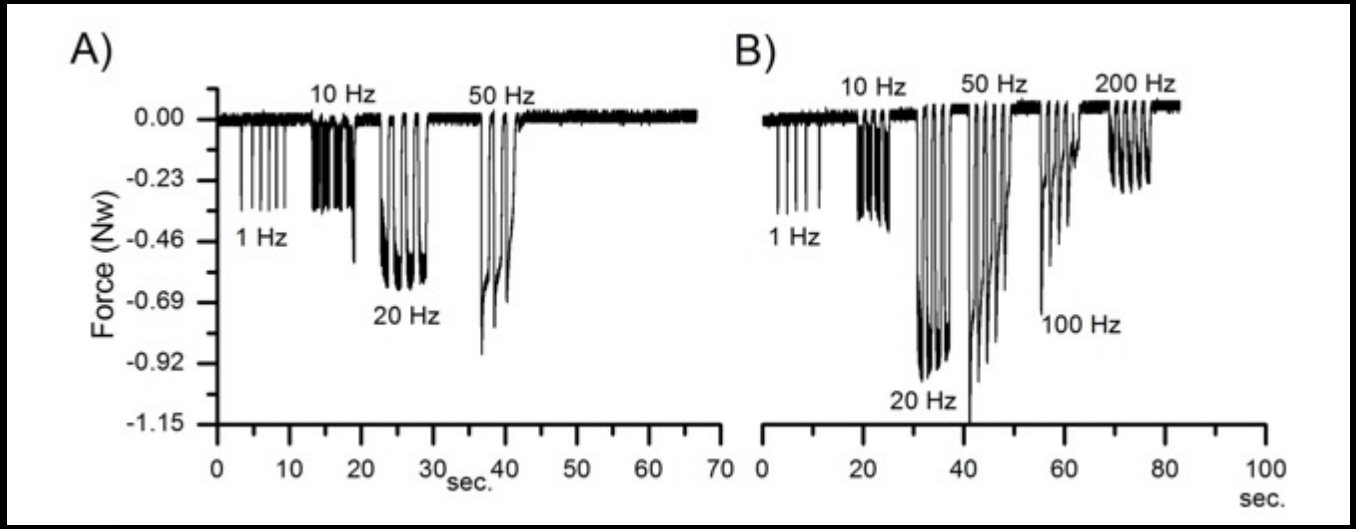
Lie et. al., 2008

LIV promotes Force:Muscle activity

In collaboration with Dr. James Bibb, UTSW

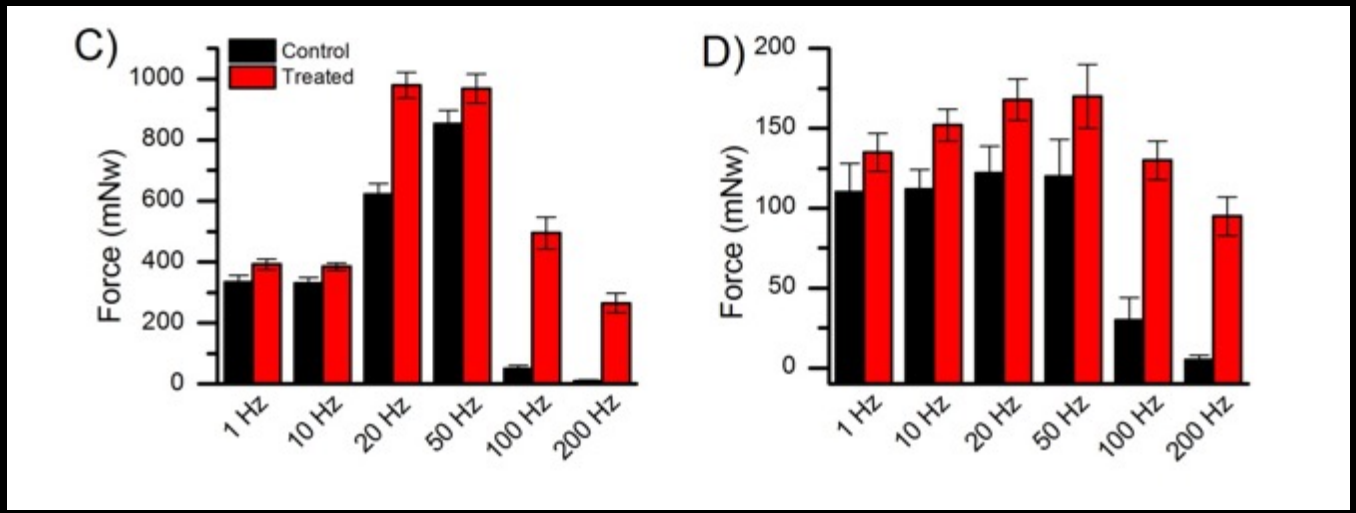
Control

LIV



Young Mice

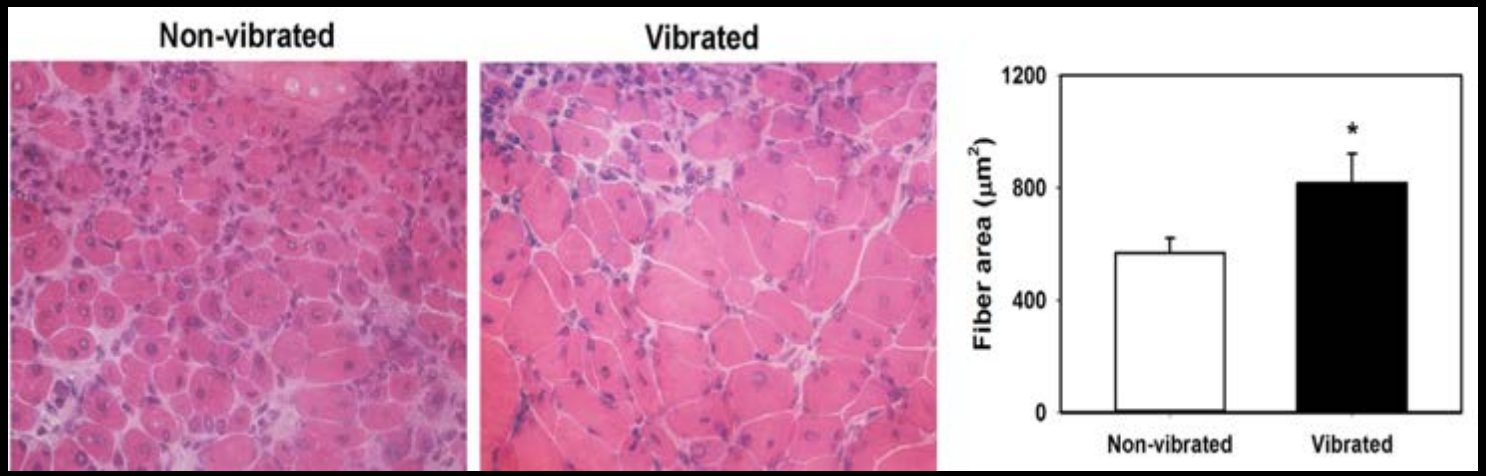
Old Mice



Bibb et al., 2014; J. Biomechanics, In Press

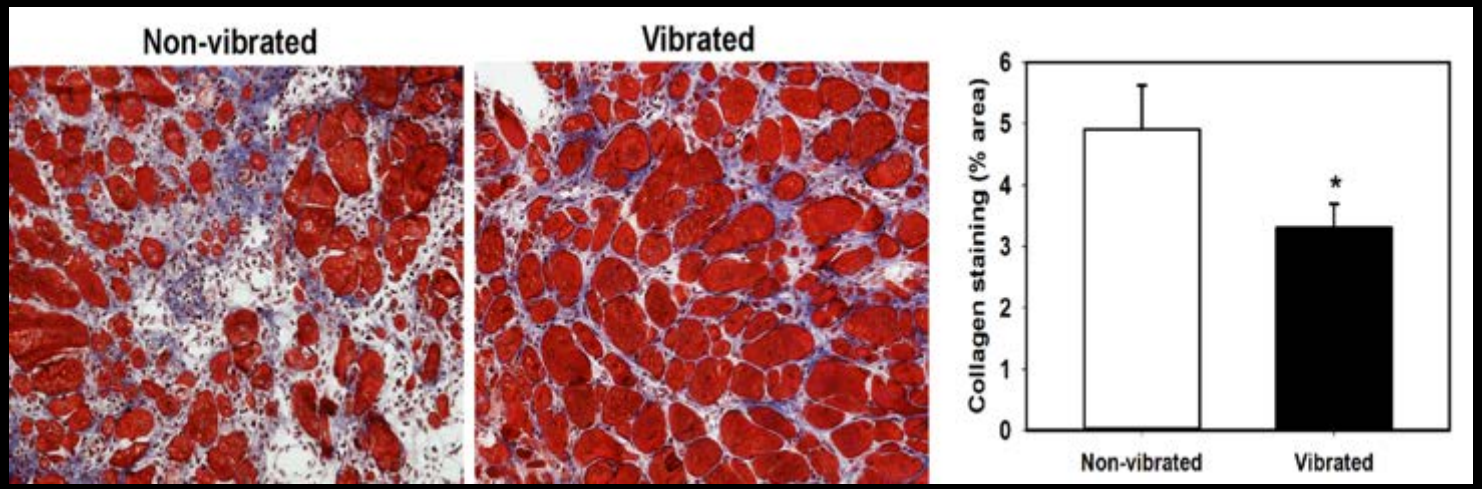
LIV augmentation of muscle healing following laceration injury

H&E

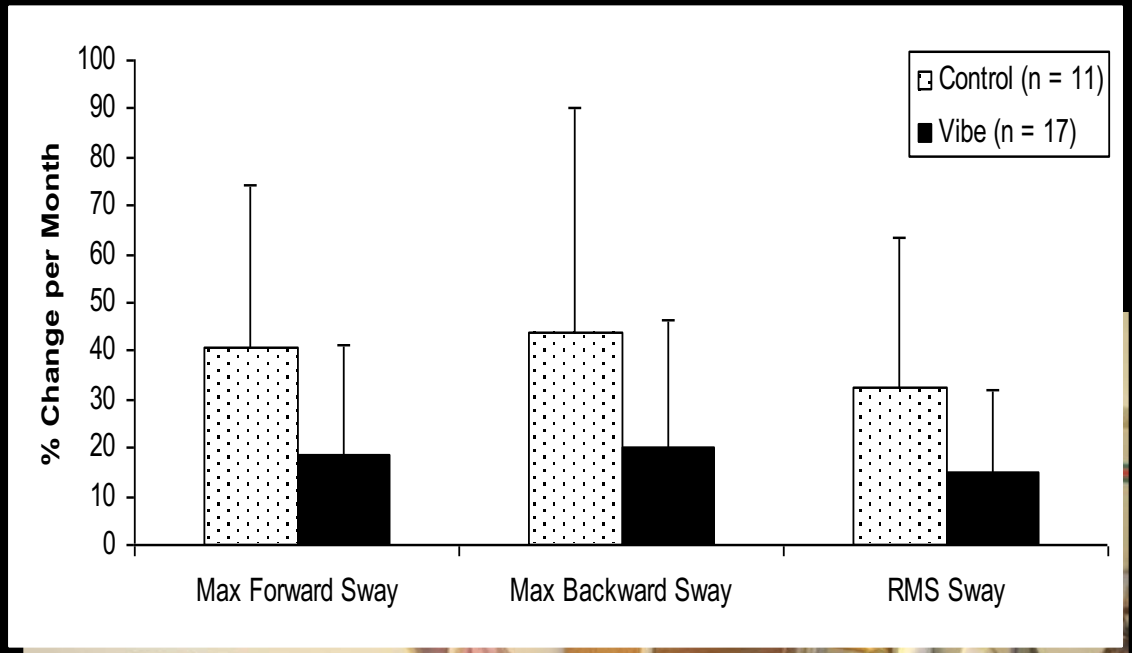


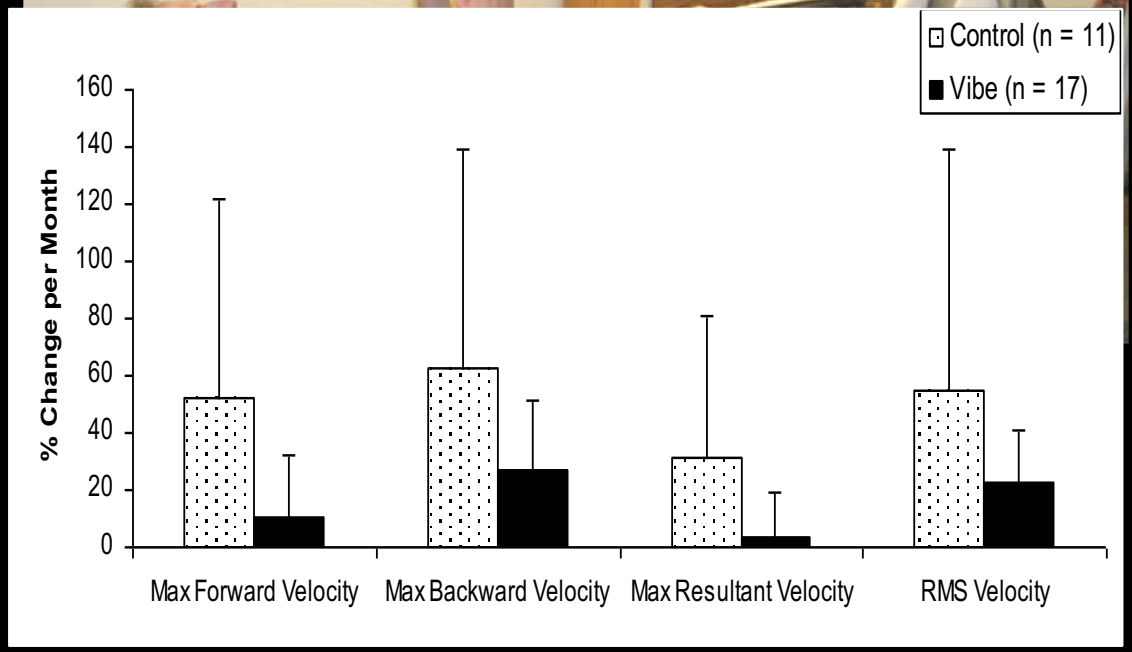
14 days post-injury

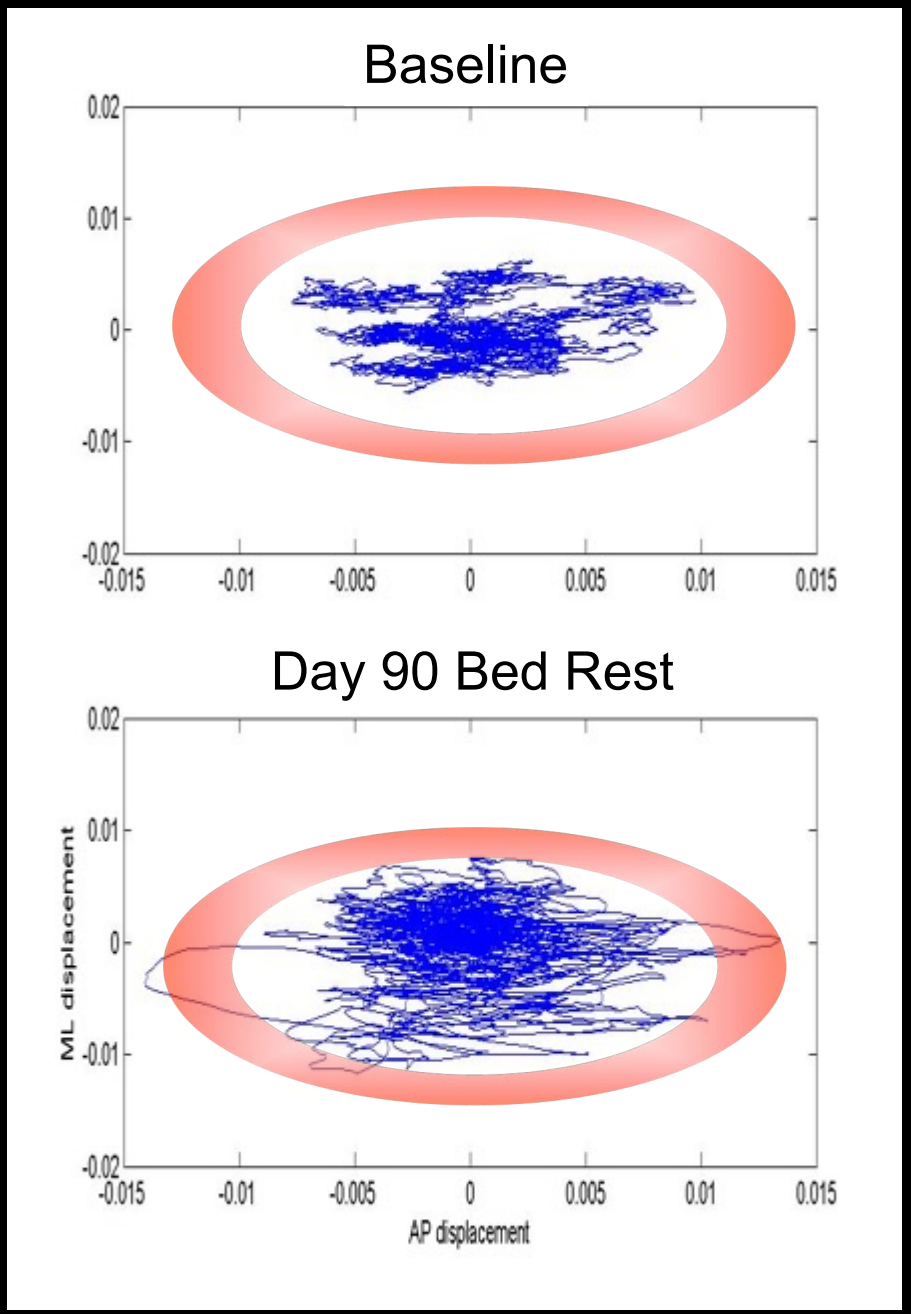
Trichrome



Koh & Judex, 2013, unpublished data





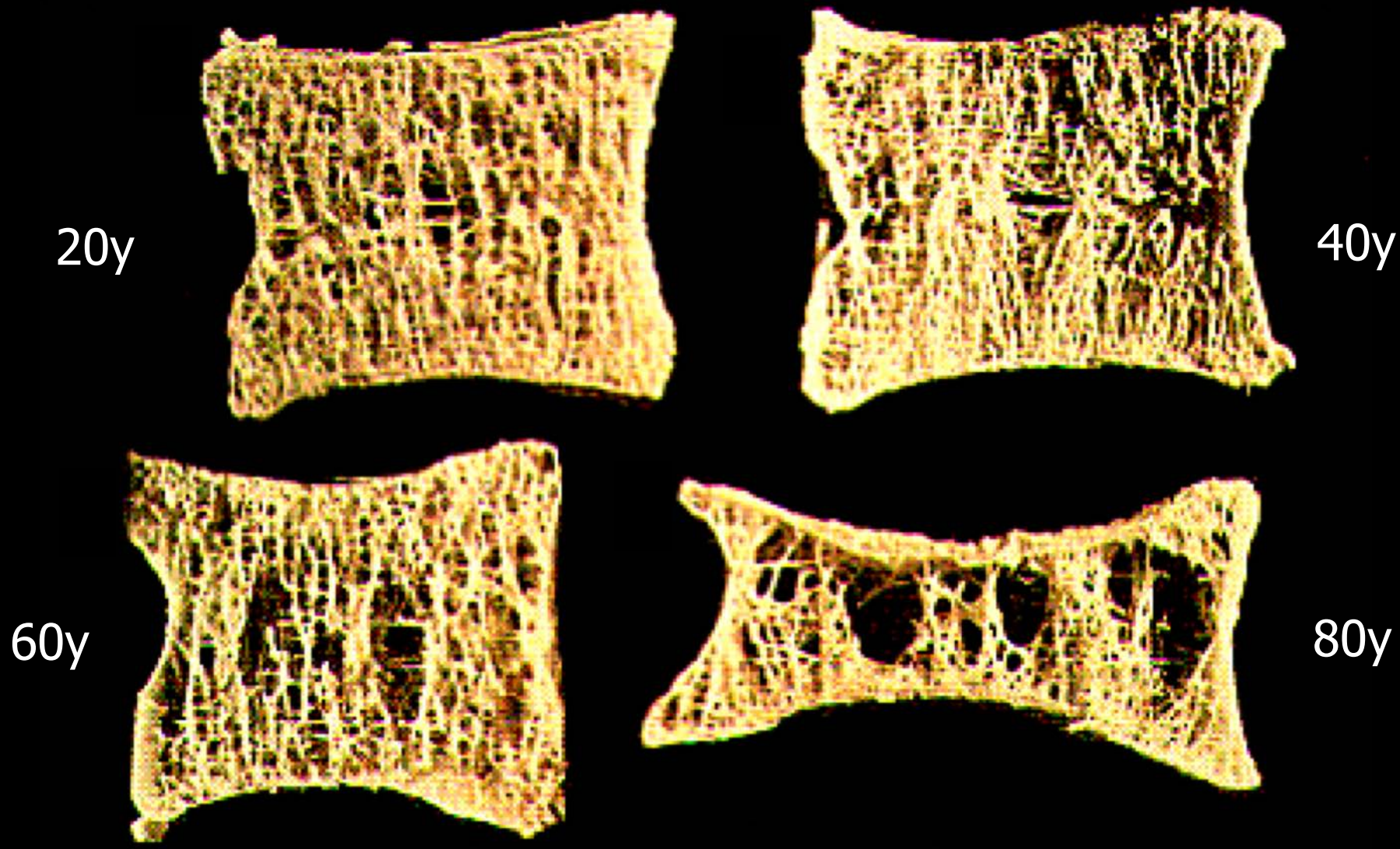


LIV retention of postural stability

Muir et. al., Gait & Posture, 2011

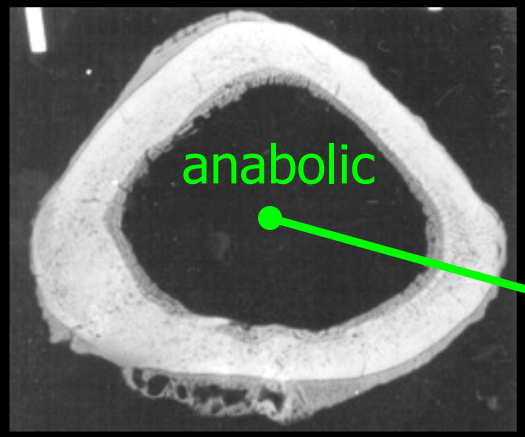
Bone

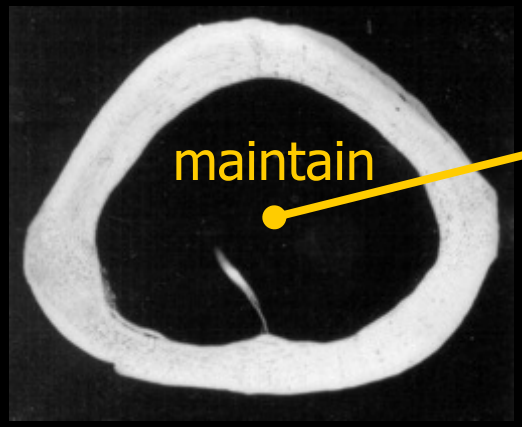
Osteoporosis: Reduced bone quality & quantity elevates fracture risk

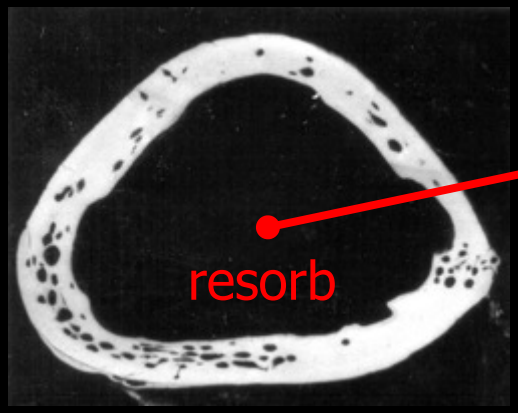


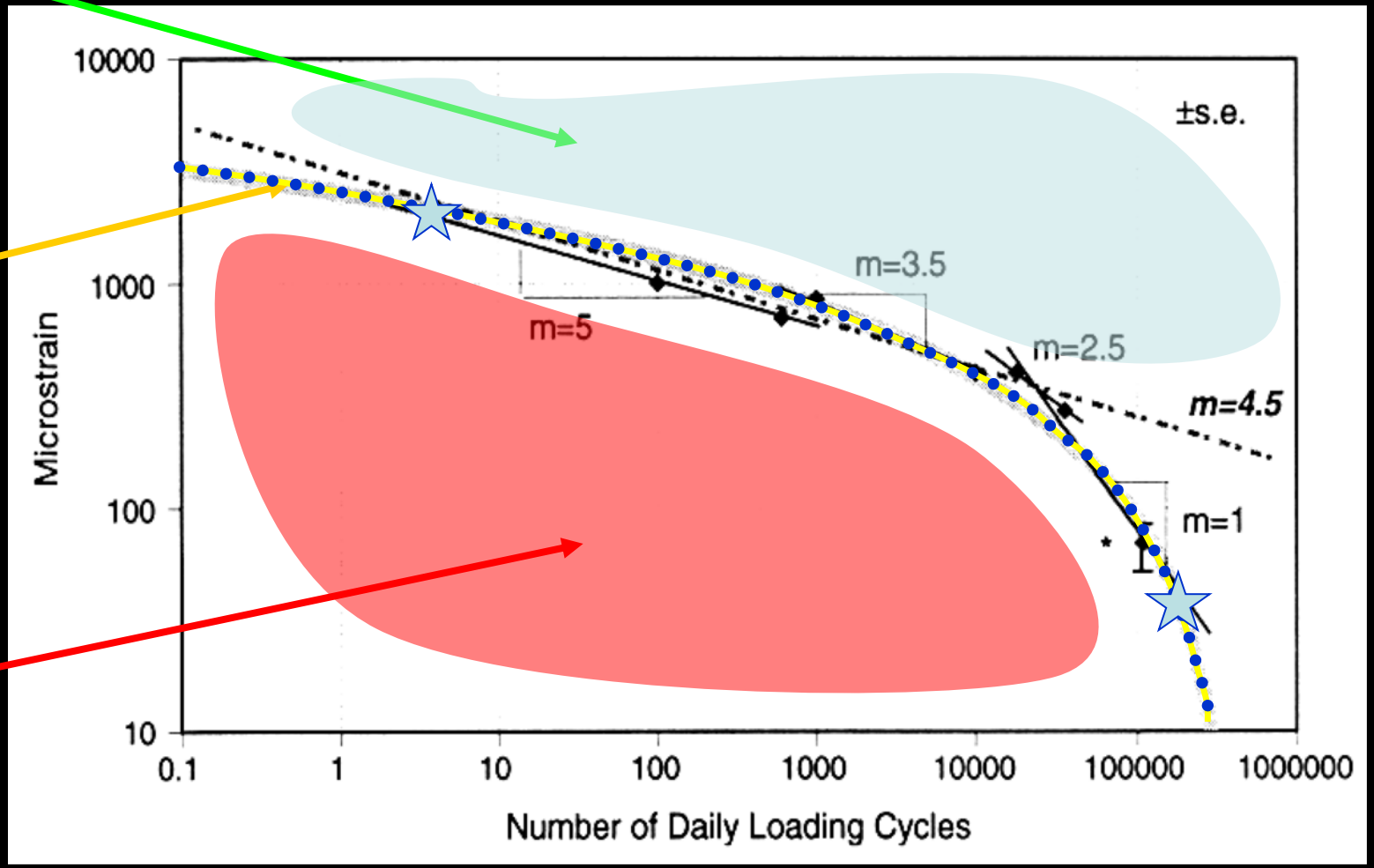
Expansion of the marrow space by fat…

Bone can be maintained with a few large loading cycles, or thousands of extremely small ones



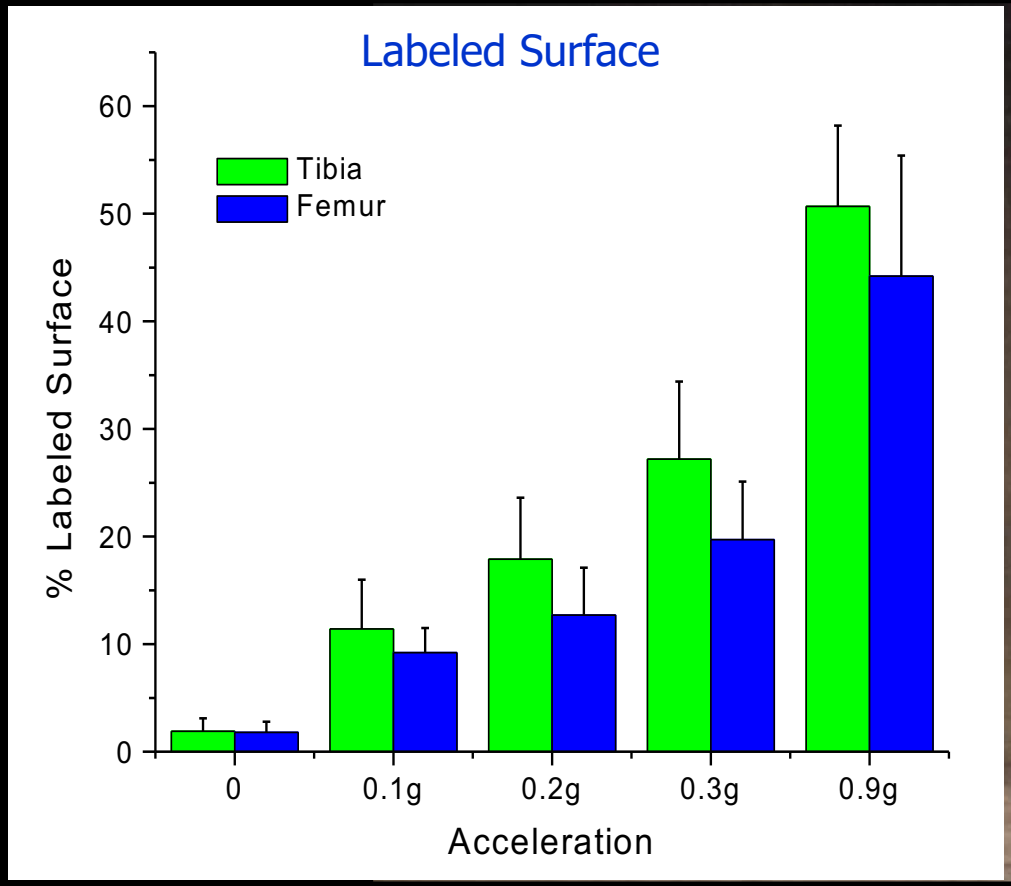


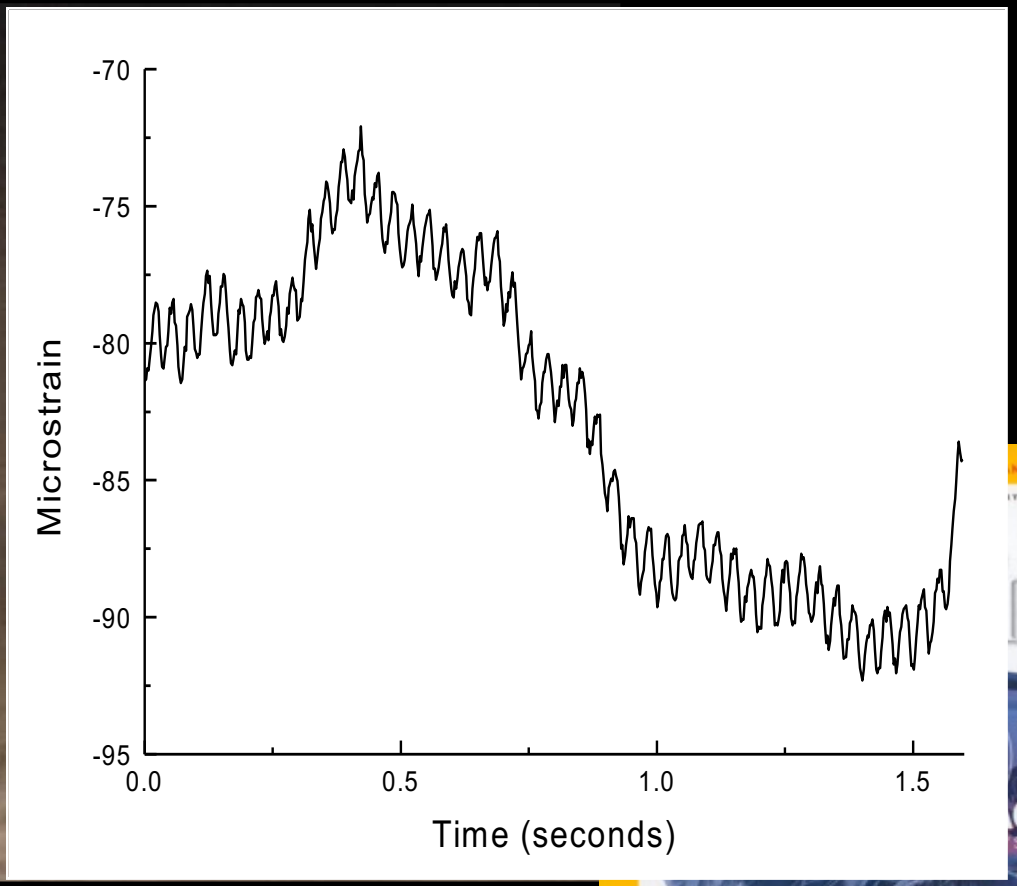




Qin et. al., *JOR, 1998*

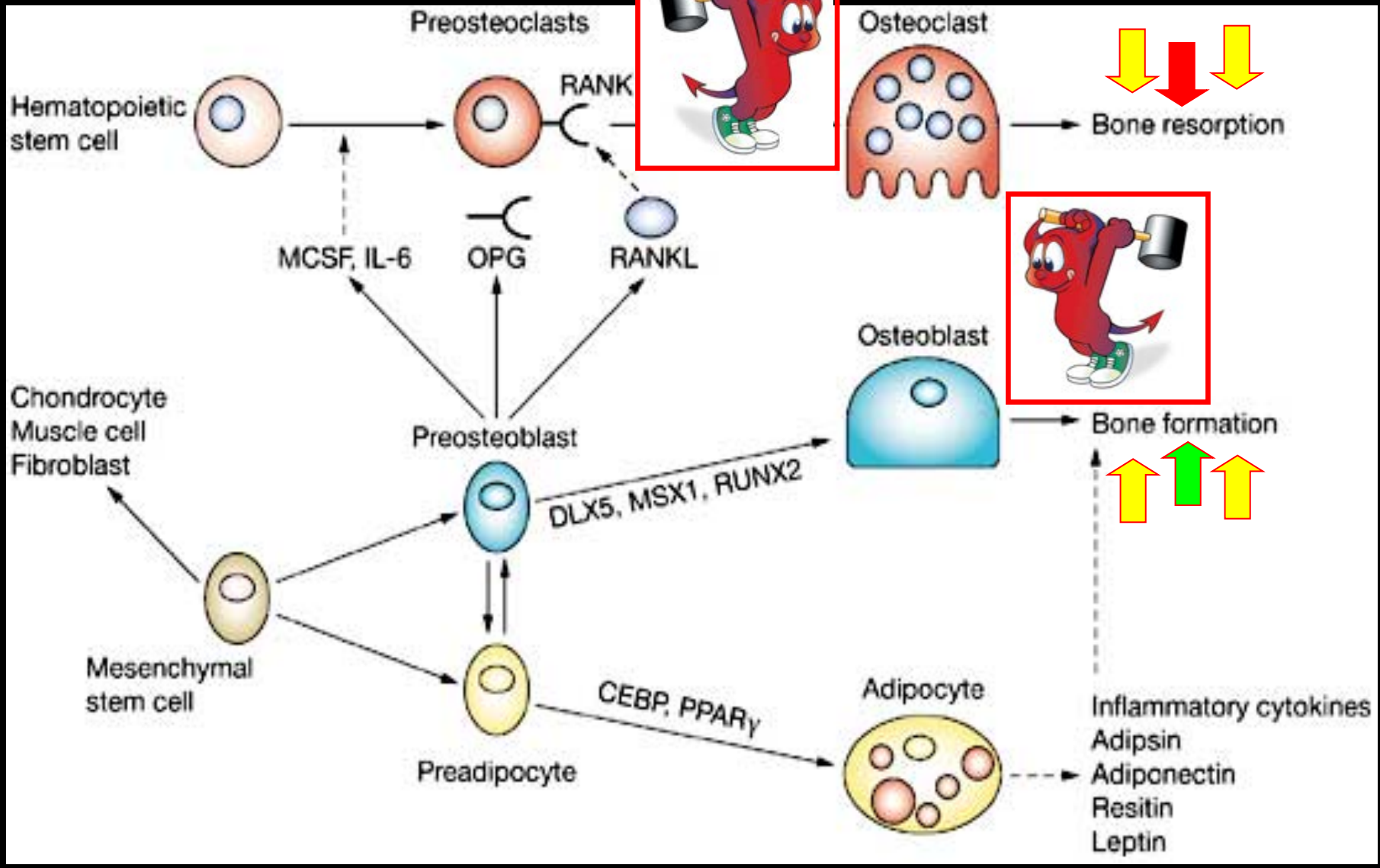
Delivering mechanical signals to the skeleton





3 microstrain induced in the turkey tibia, 30Hz @ 0.3g

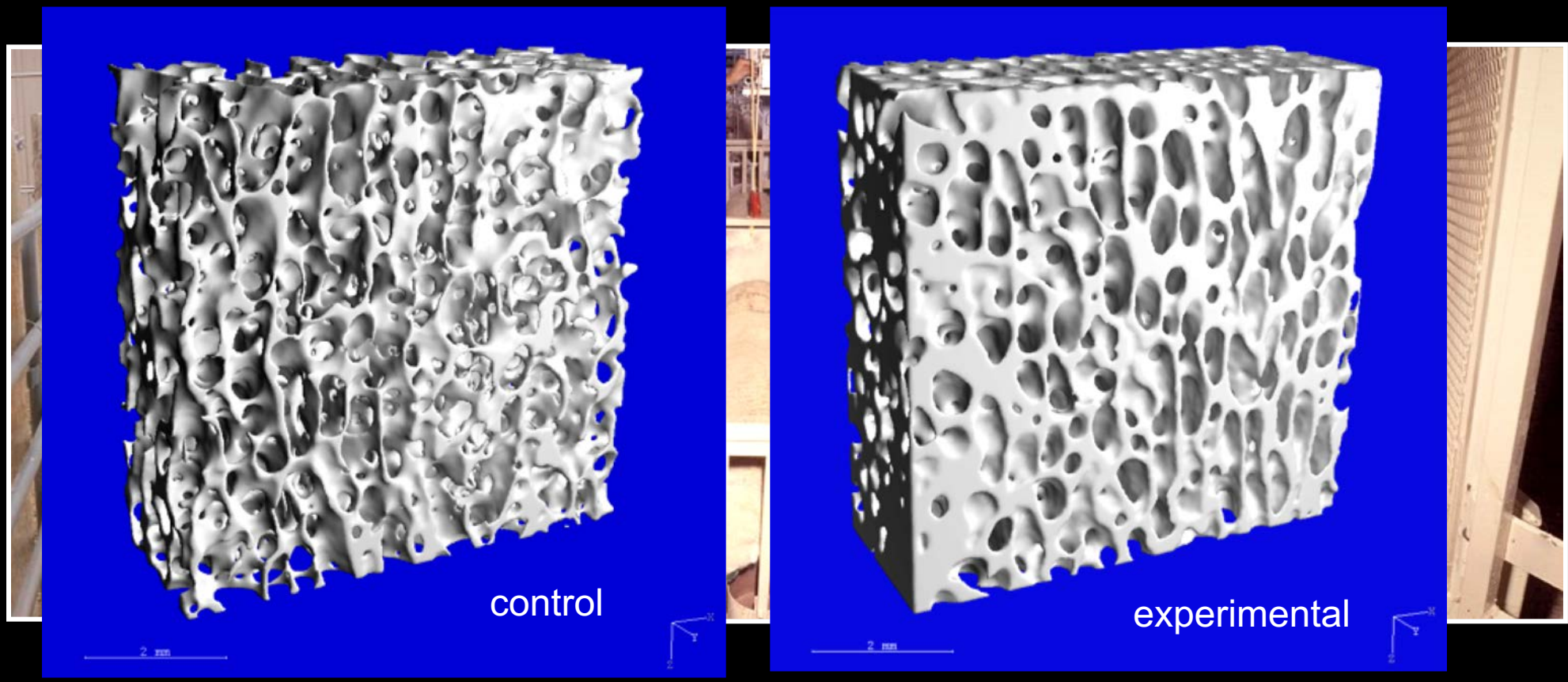
Can exercise stem this musculoskeletal deterioration?



Rosen & Bouxsein, Nat. Rev. Rheum, 2006

Anabolism

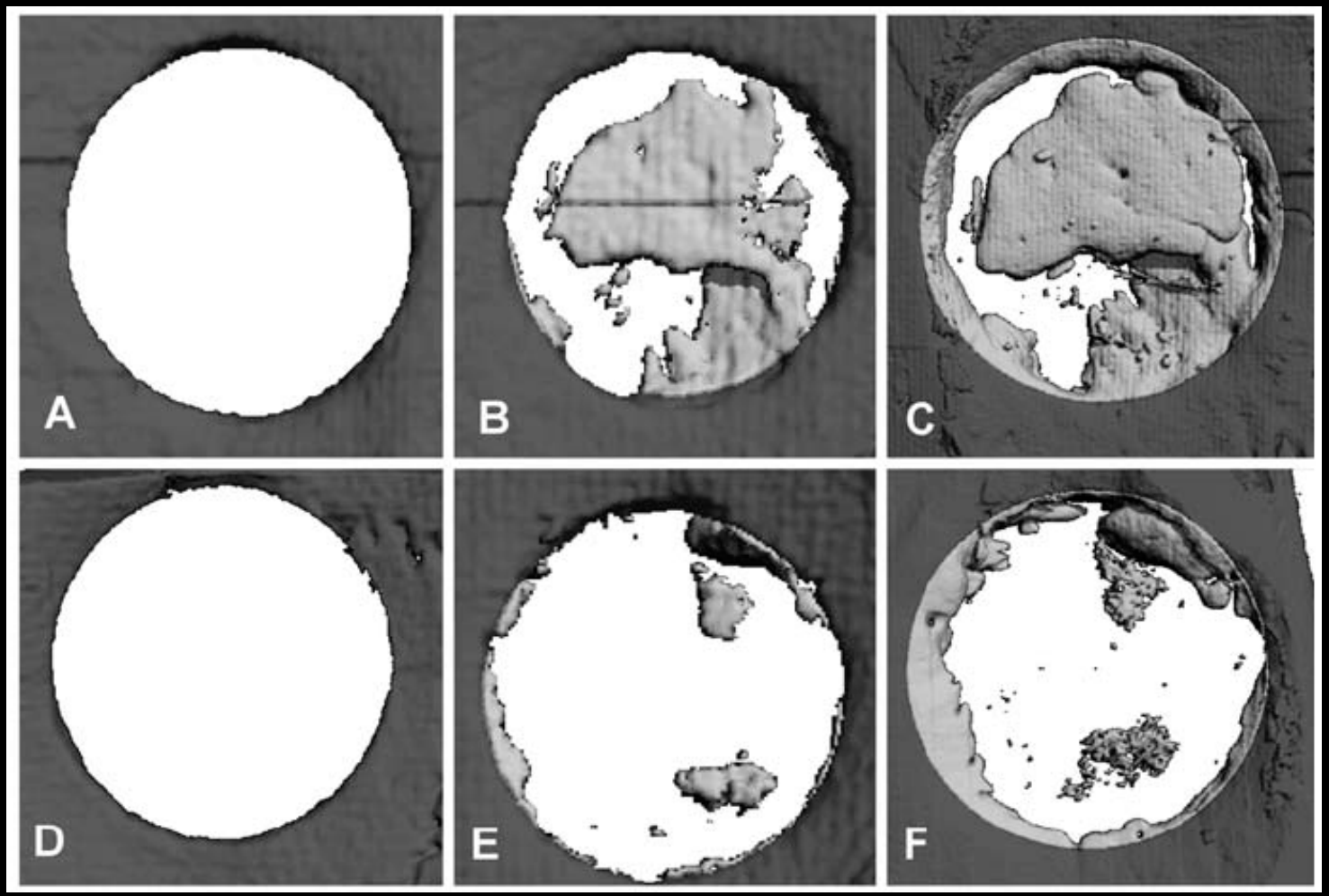
Low mechanical signals strengthen long bones



45% increase in trabecular bone volume
12% increase in stiffness
27% increase in strength

Rubin et. al., *Nature, 2001*

Enhancing bone regeneration with extremely small accelerations

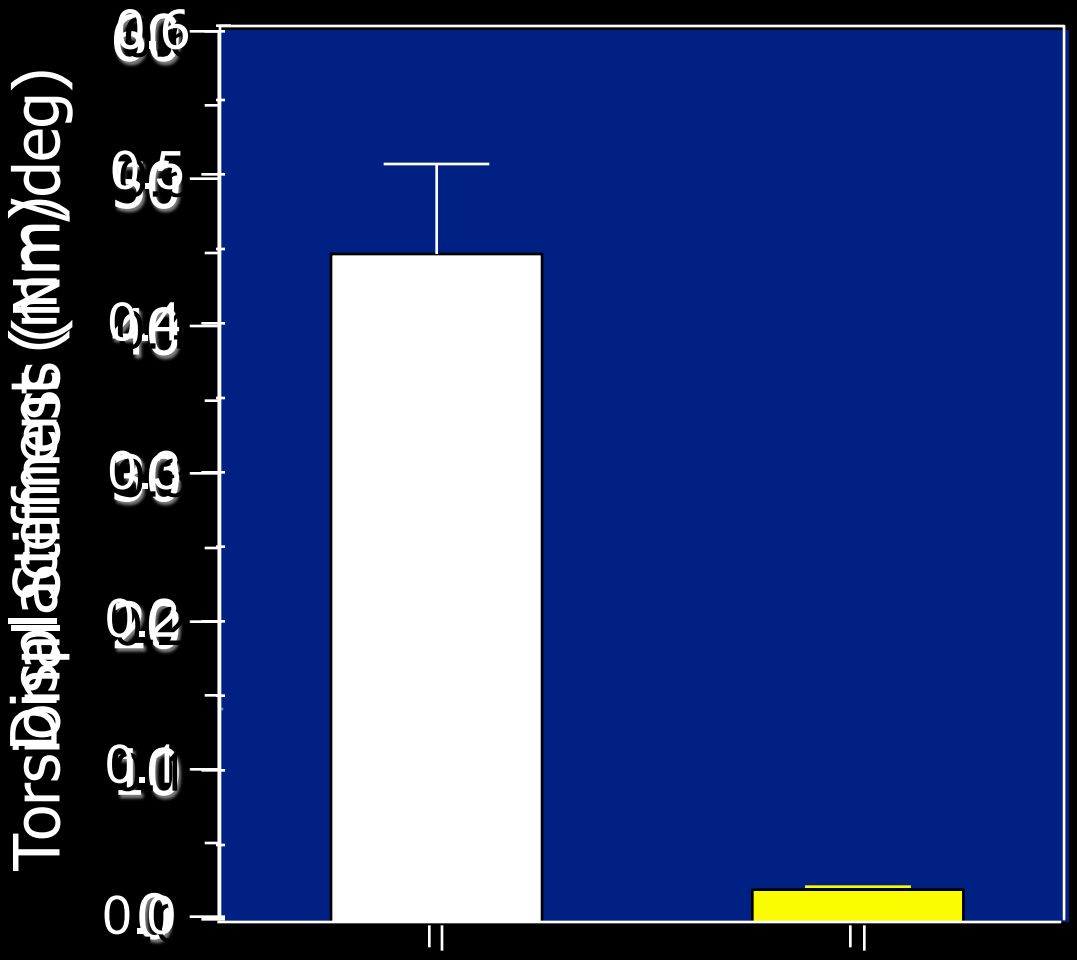


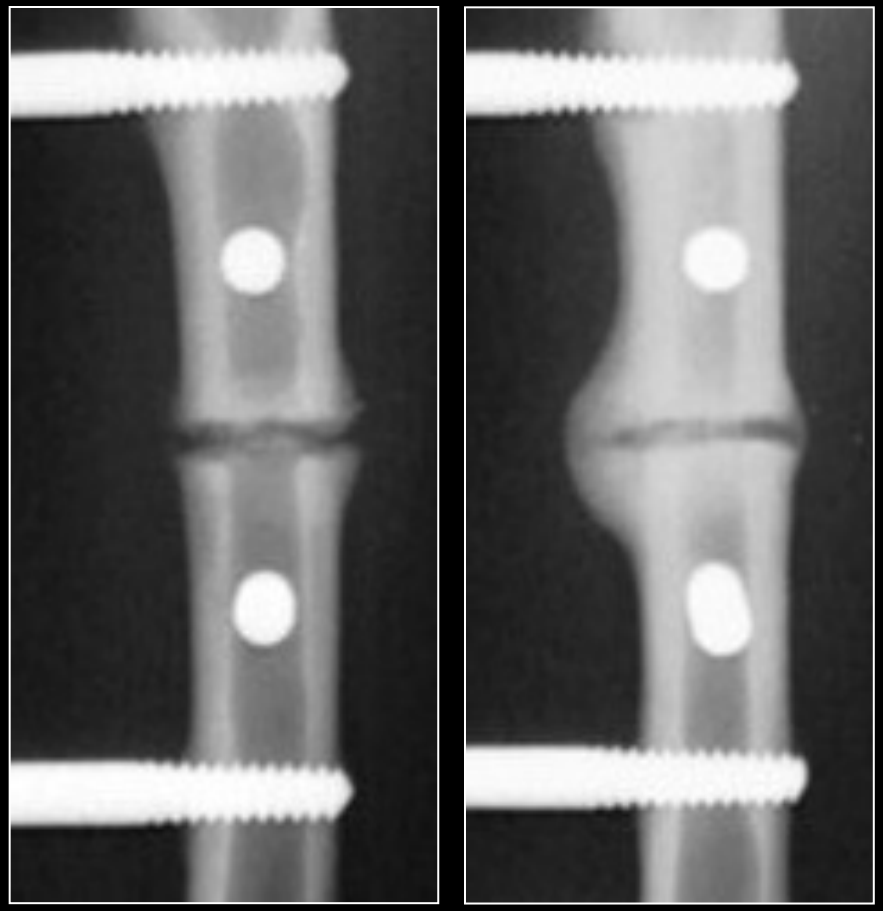
In vivo μCT scans of 5mm defects in the rat cranium

Hwang et. al., 2009

Augmentation of healing fractures by low level signals

(30Hz, 25 micron displacement on sheep tibia)

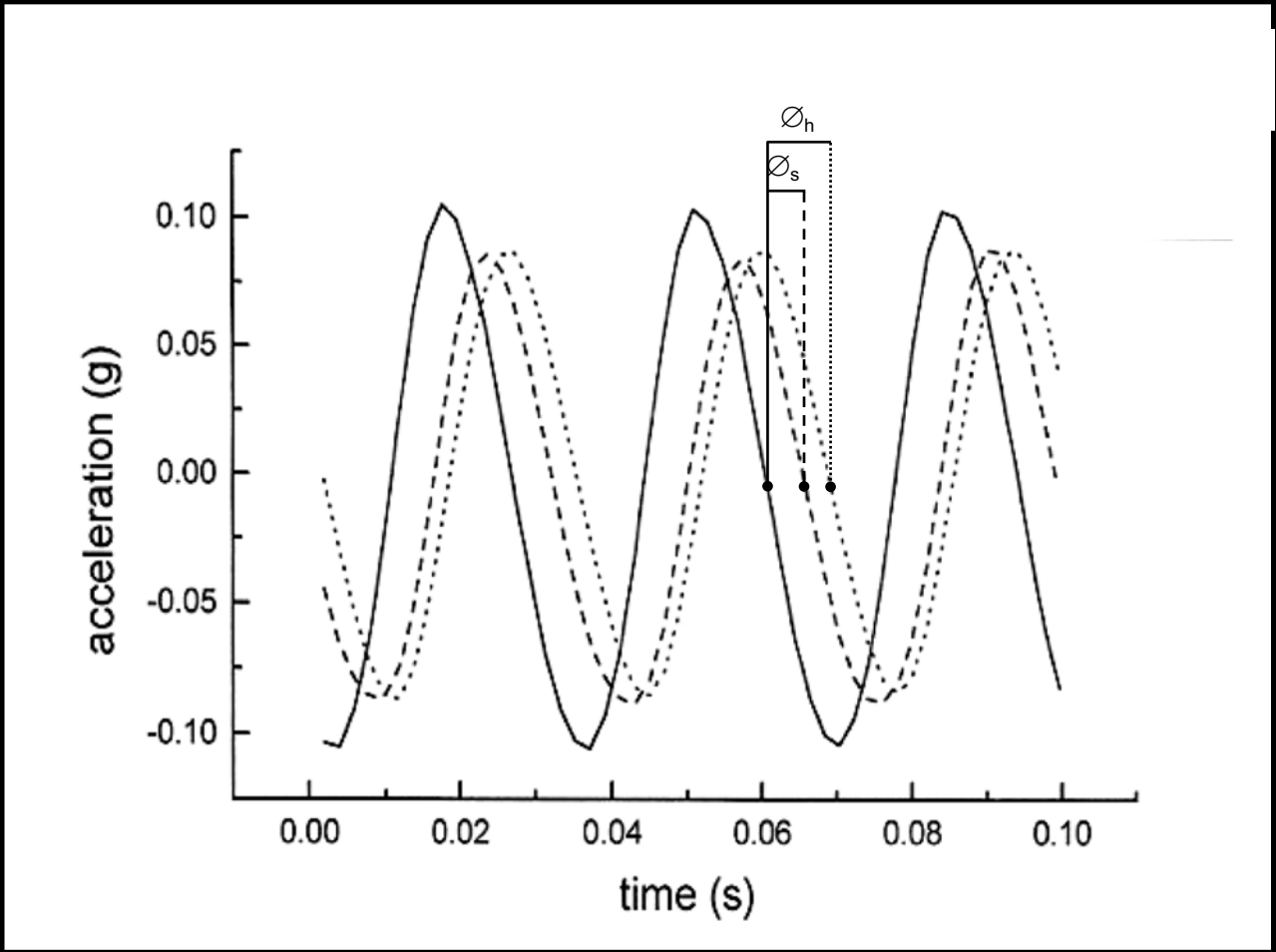




Goodship et. al., *JOR, 2009*

Transmissibility of low-level signals to hip and spine

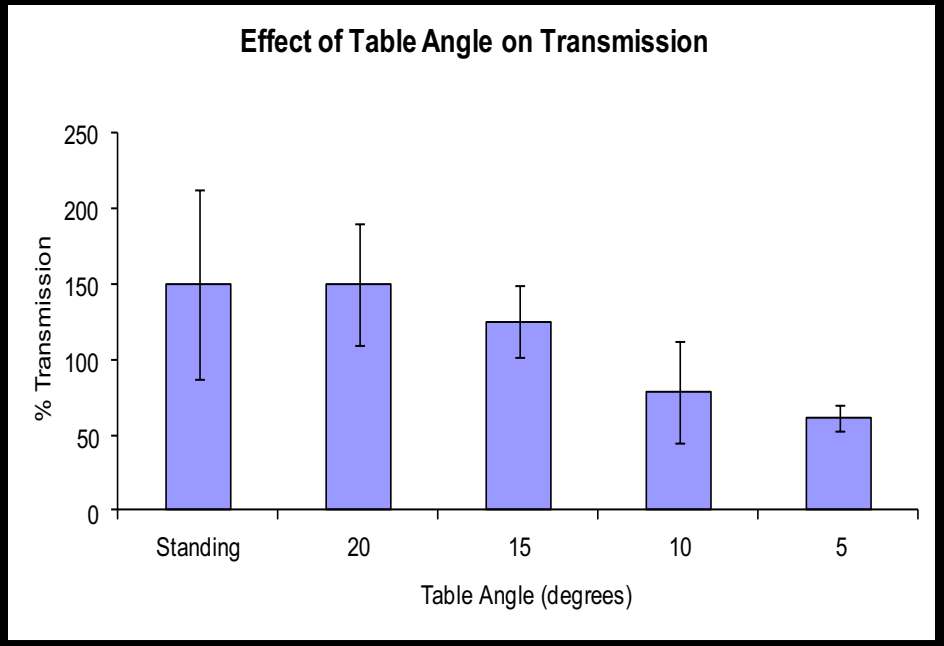
In collaboration with Dr. M. Pope & T. Hansson, Gothenburg, Sweden



Rubin et. al., Spine, 2003

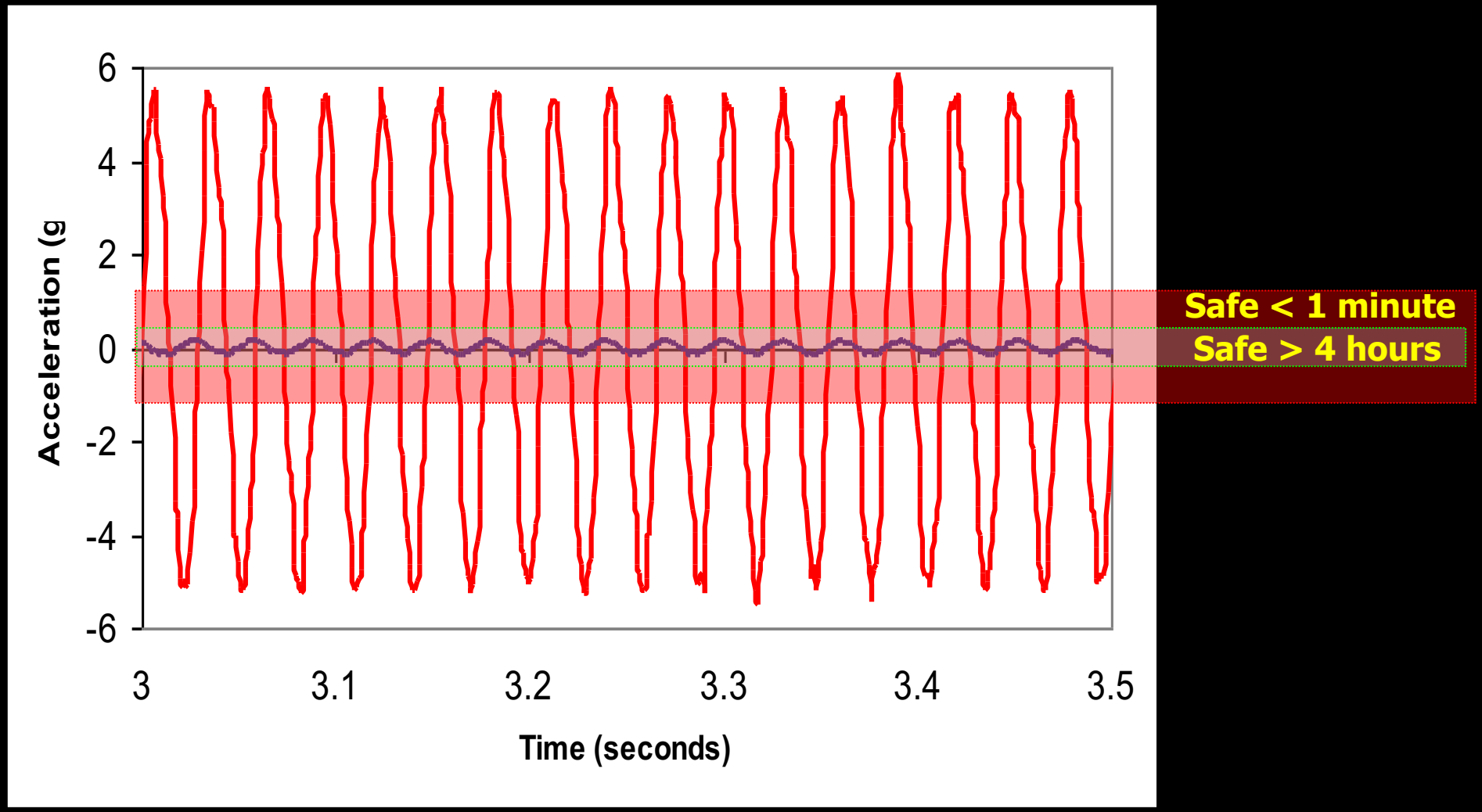
Delivering the LIV signal to a subject in a standard hospital bed

US Army Grant currently under review for the use of the LIV technology in the suppression of bone loss and adiposity gain in SCI subjects



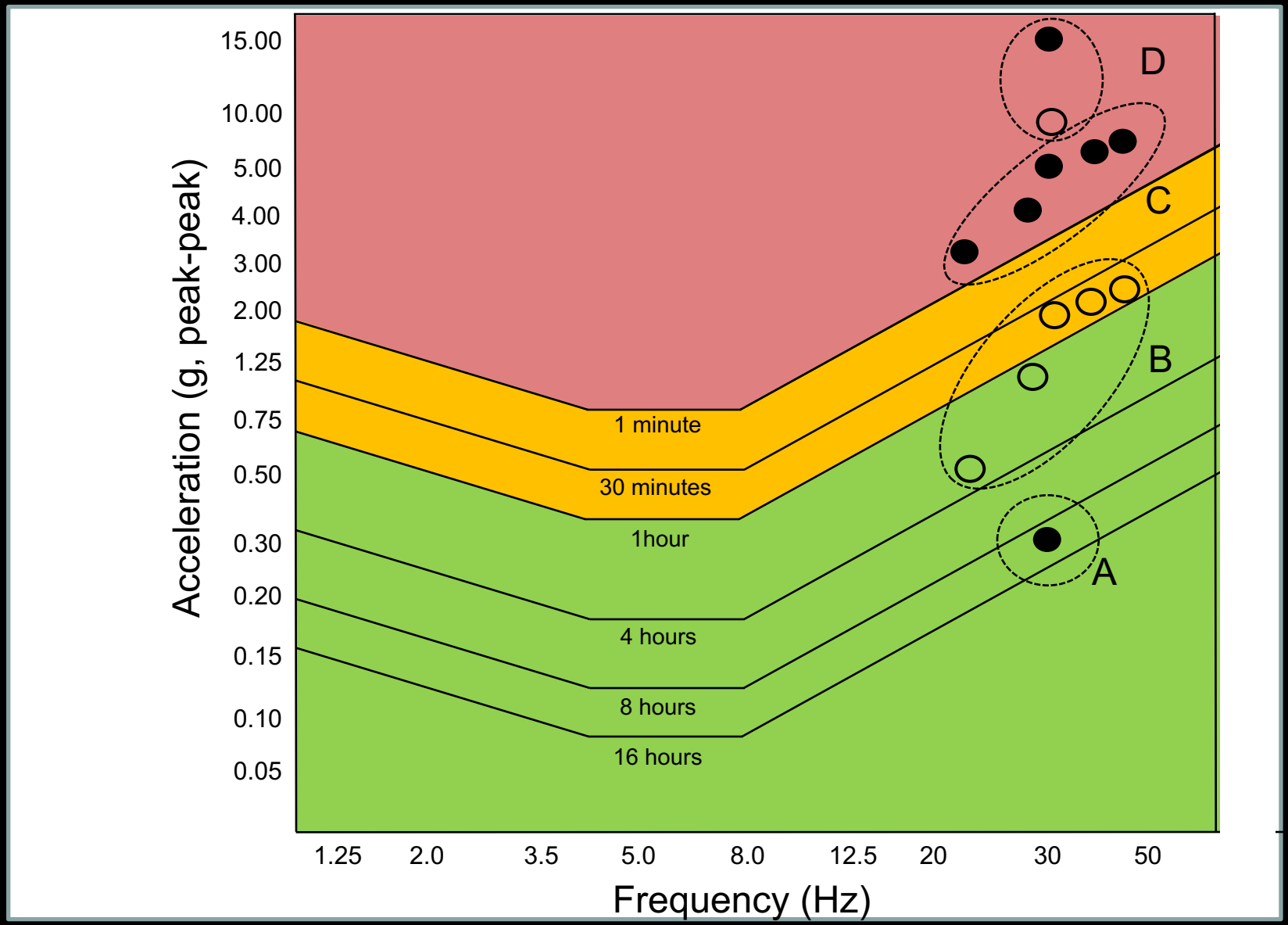
Is it safe? ISO-2631 Human Tolerance Limits for Vibration

FDA has concluded LIV signal a "non-significant risk device"



Acceleration exposure of PowerPlate v. Marodyne device

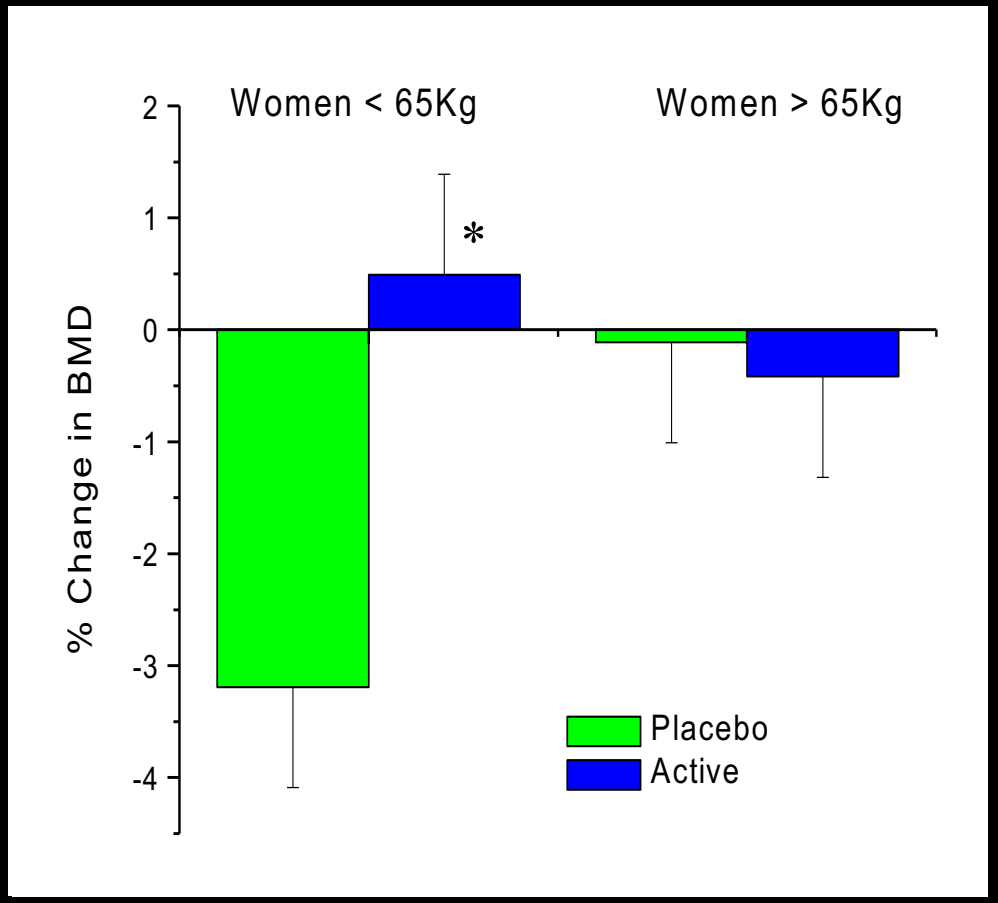
Is it safe? ISO-2631 Human Tolerance Limits for Vibration



Muir et. al., JSMS, 2013

Inhibition of bone loss in a post-menopausal population

In collaboration with Drs. R. Recker & D. Cullen, Creighton University

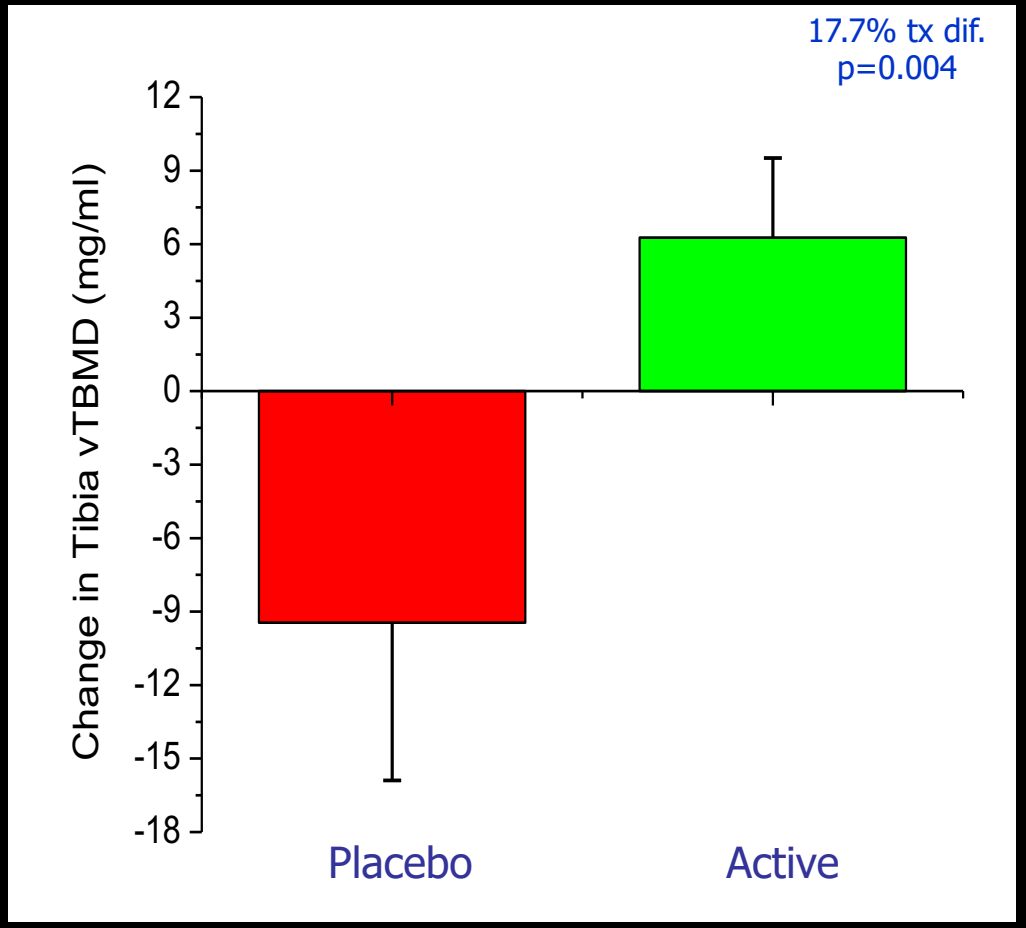


One year, 20 m/d, 30Hz @ 0.2g

Rubin et. al., 2004

Inhibition of osteoporosis in children with cerebral palsy

In collaboration with Drs. K. Ward & Z. Mughal, St. Mary's Hospital, Manchester U.K.



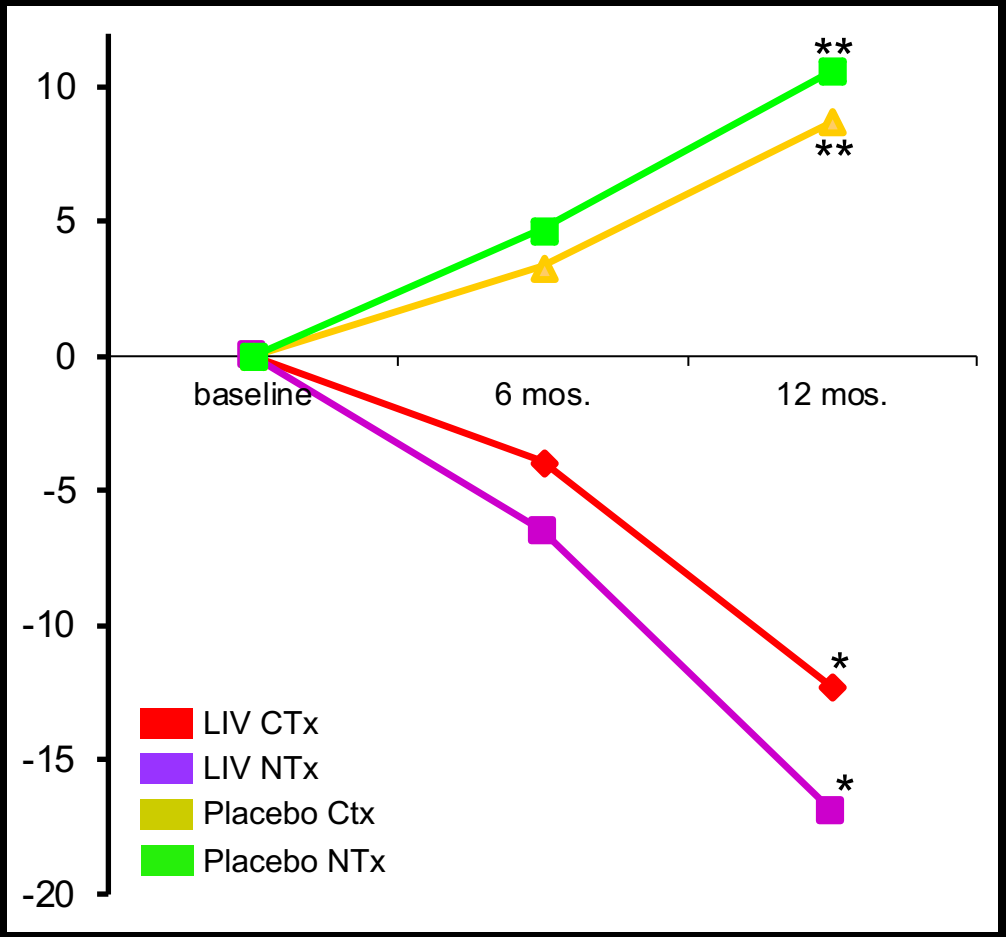
20 subjects, mean age: 9.1y
10 placebo, 10 active; 0.3g
Six Months, 4.4 minutes per day

Ward et. al., *JBMR, 2004*

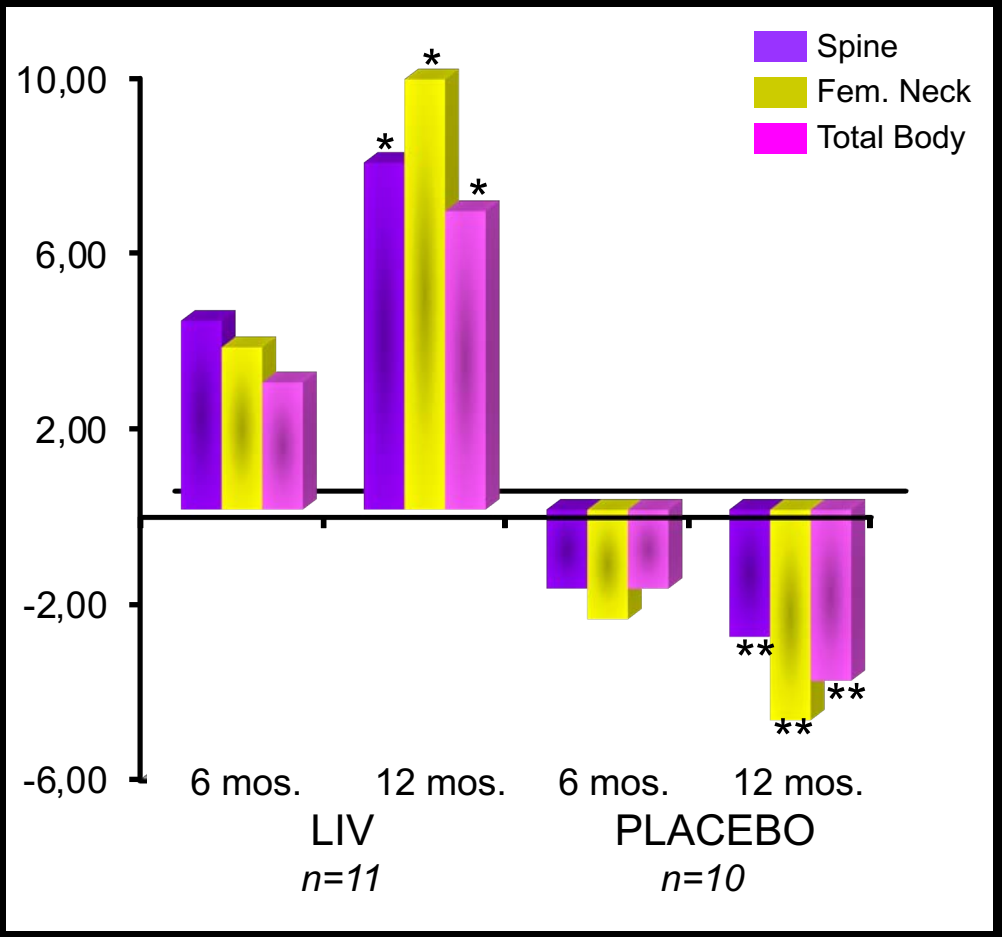
Anabolic response to LIV in children with Duchenne Muscular Dystrophy

In collaboration with Professor Maria Luisa Bianchi and Colleagues, Milan, Italy

Ambulatory, 9.3y ± 3.9y, One year study, All treated w/ glucocorticoids



% Change in Bone Resorption Markers



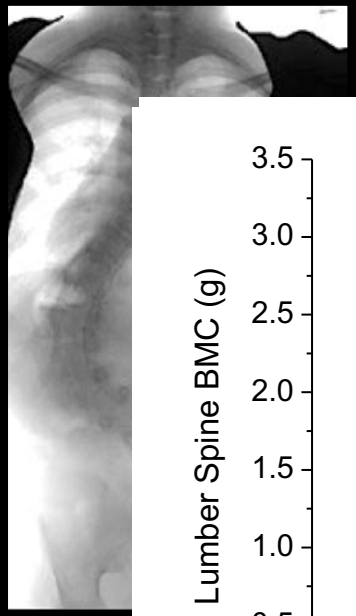
% Change in Bone Mineral Density

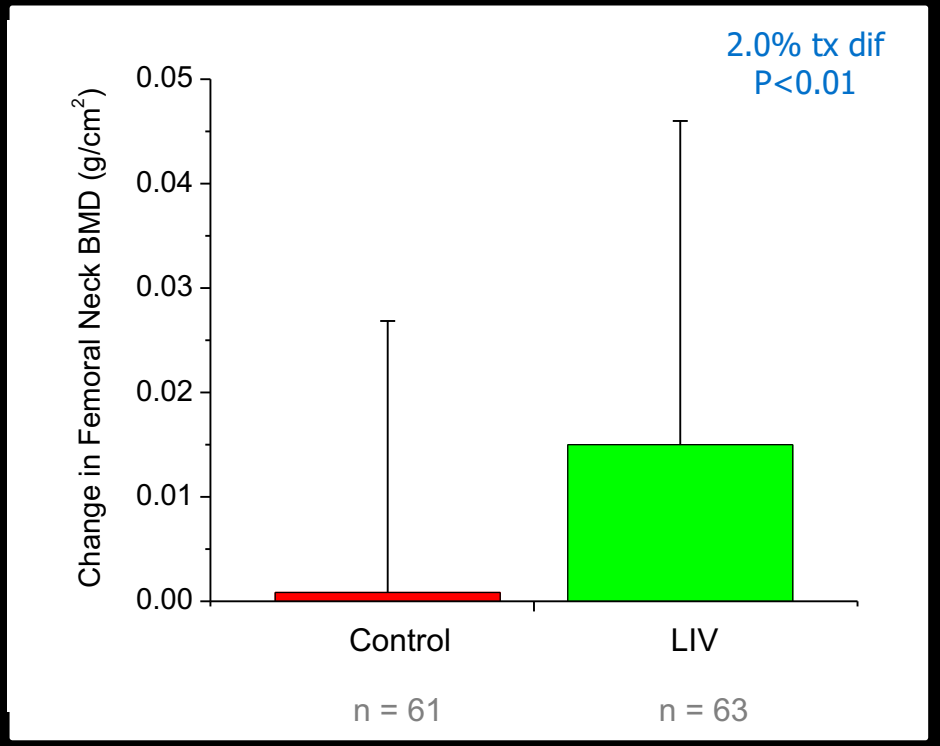
Bianchi et al., ASBMR 2013: poster LB-SU03

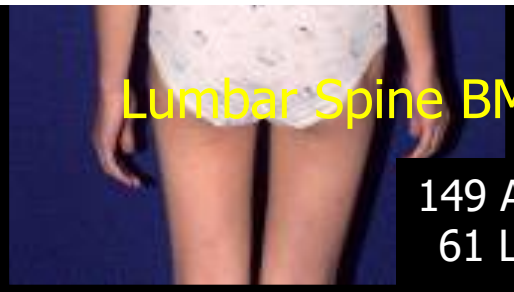
* p<0.02 ** p<0.05

Promotion of bone density in Adolescent Idiopathic Scoliosis

Professors T.P. Lam, L. Qin & J. Cheng; Chinese University of Hong Kong







Lumbar Spine BMC

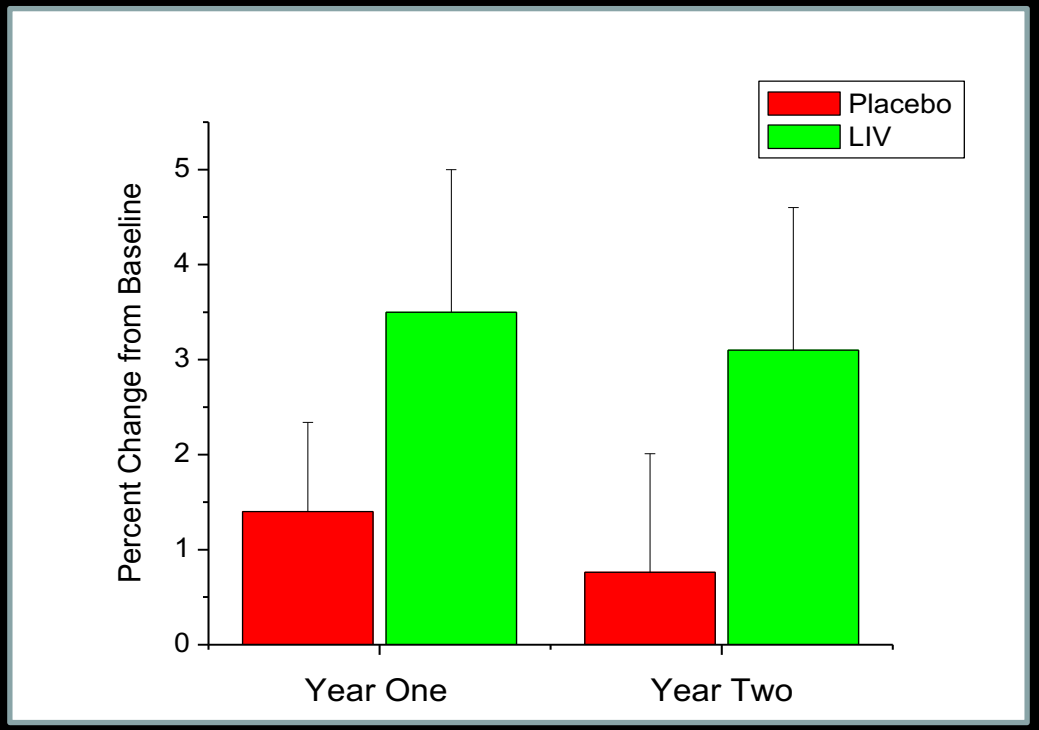
Femoral Neck BMD

149 AIS girls, 15-25y
61 LIV; 0.3g, 30Hz
One year
20 minutes per day

Lam et. al., *Ost. Int. 2012*

Inhibition of bone loss in the frail elderly

In collaboration with Drs. D. Kiel & M. Hannan, Harvard Medical School

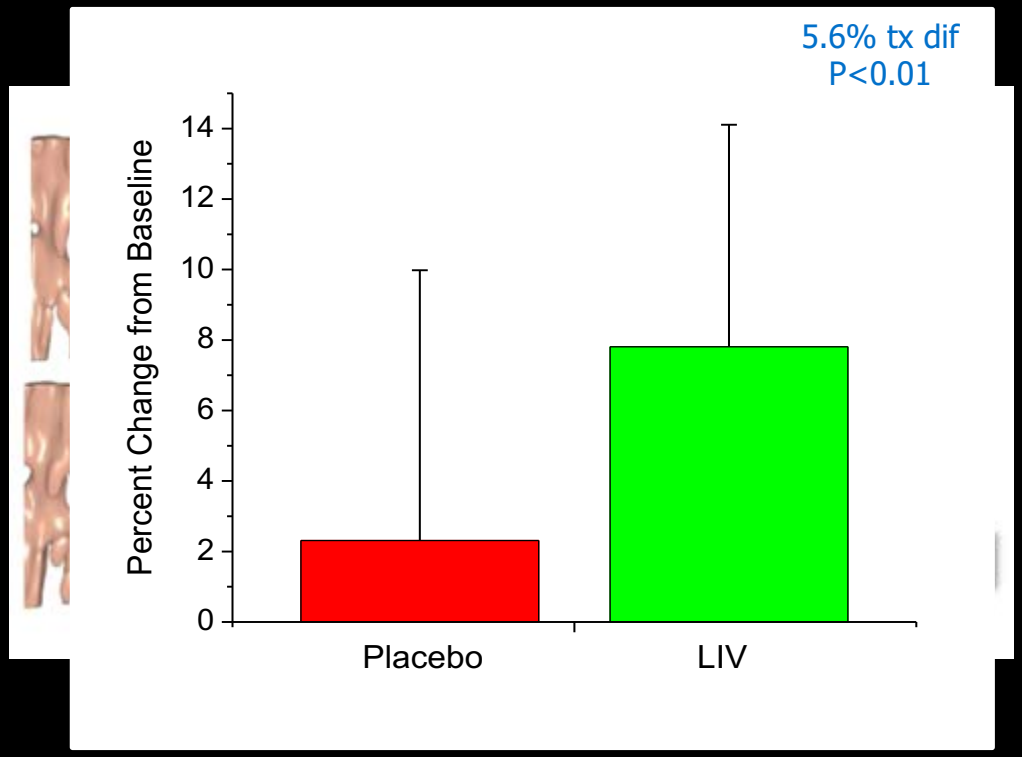


Percent change from baseline of
Total Femoral Trabecular Bone Density

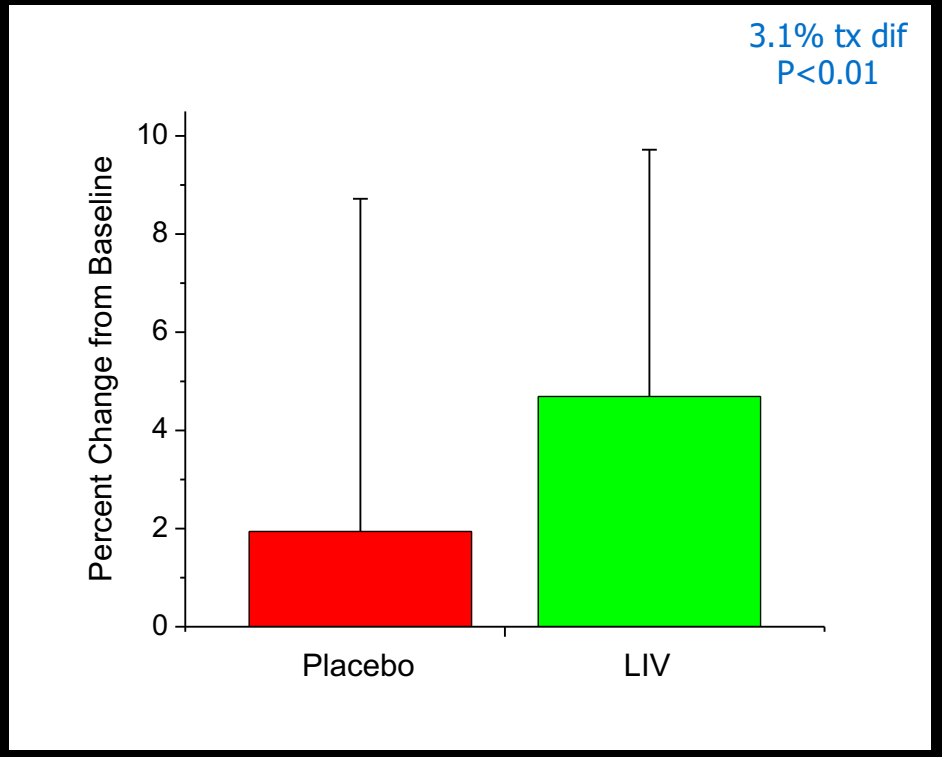
N>50 per group
Means ± s.e.; nsd

Promotion of bone *quality* in end-stage renal disease

In collaboration with Professors M. Leonard and F. Wehrli, CHOP & U-Penn



Tibial Strength

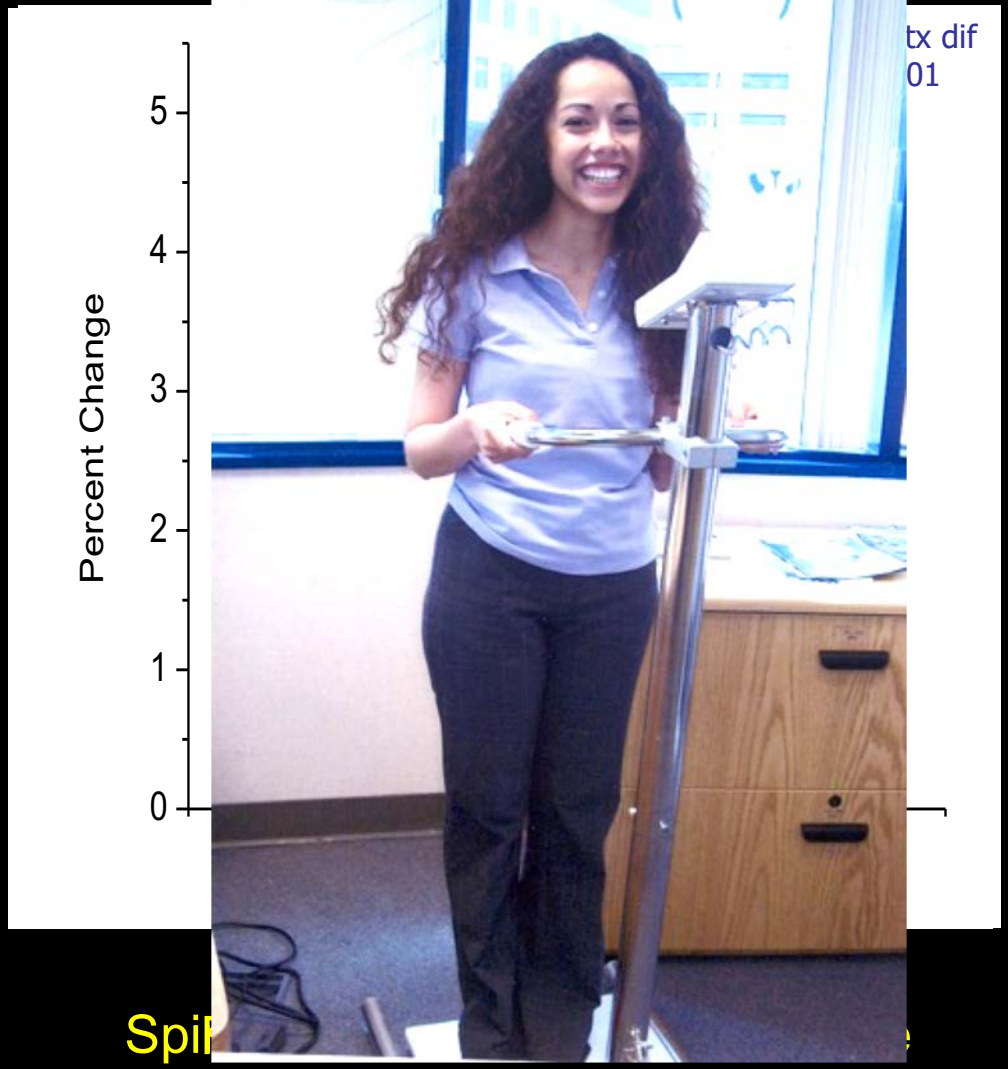


Tibial Stiffness

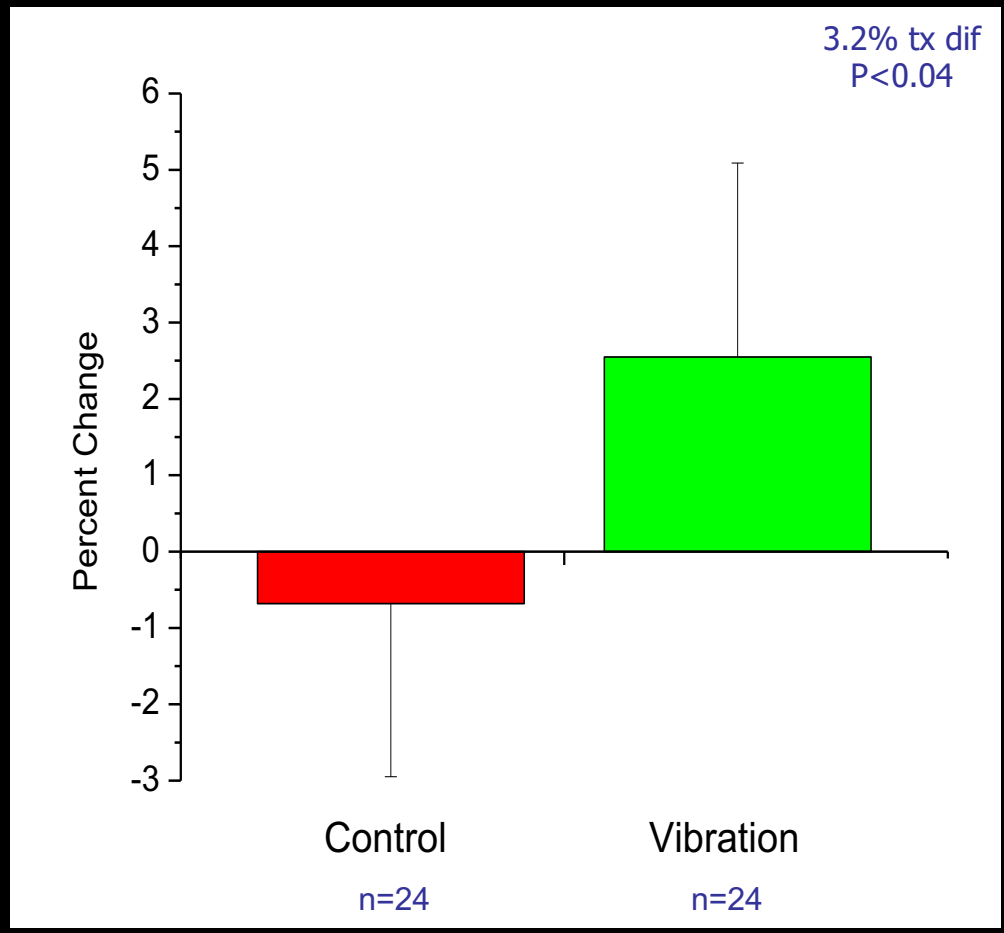
Rajapakse et. al., *ASBMR 2012*

Enhancement of the musculoskeletal *system* in young osteopenic women

In collaboration with Dr. V. Gilsanz, Children's Hospital of Los Angeles, CA



Spi

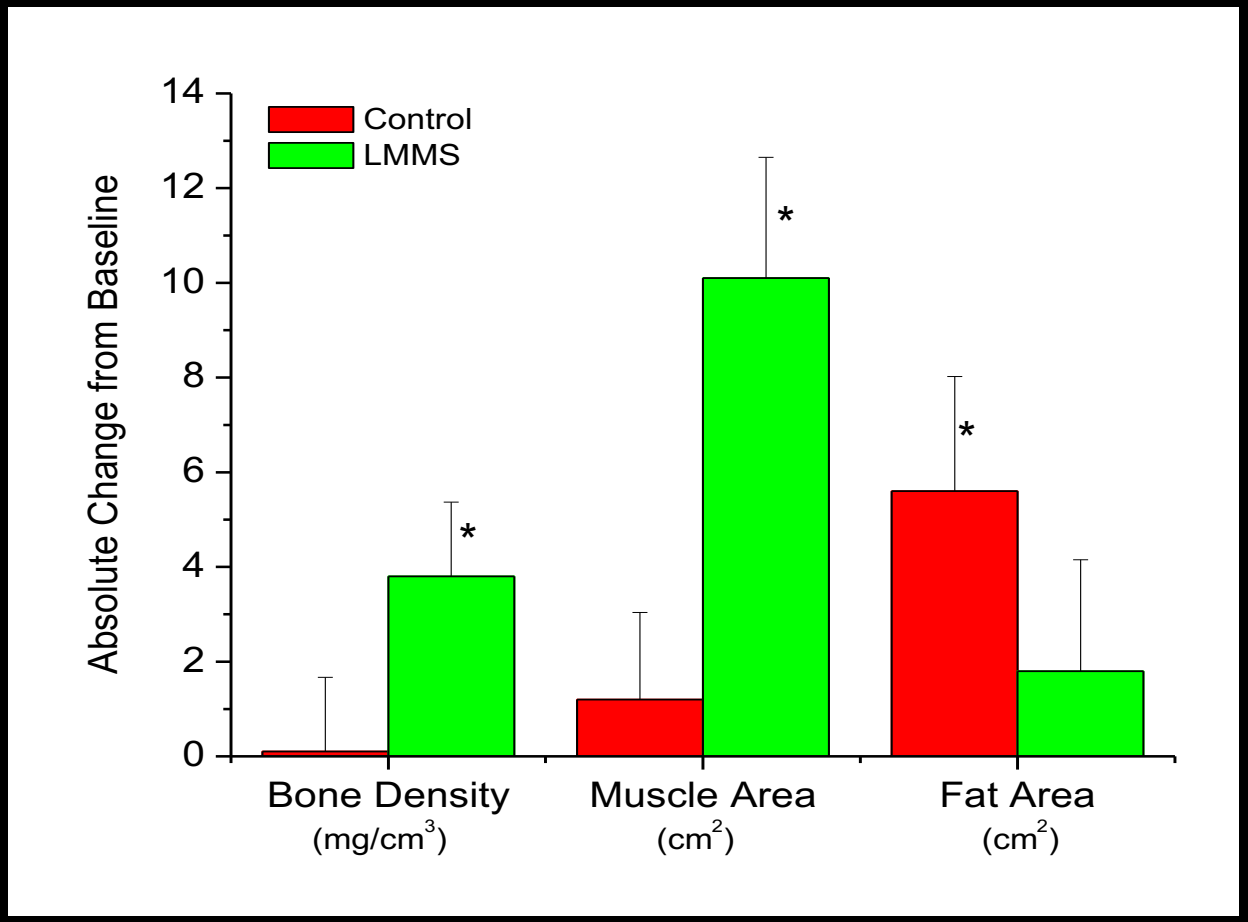


Spine: Cancellous Bone Density

Gilsanz et. al., *JBMR, 2006*

Can low mechanical signals influence fat metabolism?

Young osteopenic women, 1y LIV



Inverse Interdependence of Bone and Fat Formation?

Luu et. al., *JBMR 2009*

Effects of 18-month low-magnitude high-frequency vibration on fall rate and fracture risks in 710 community elderly—a cluster-randomized controlled trial

K. S. Leung · C. Y. Li · Y. K. Tse · T. K. Choy · P. C. Leung · V. W. Y. Hung · S. Y. Chan · A. H. C. Leung · W. H. Cheung

"LIV is effective in fall prevention with improved muscle strength and balancing ability in the elderly"

Groups	Fall %	Fracture %	Balance & Mobility
LIV = 364 66% ave compliance	18.6	1.1	Improved balance and muscle strength
Exercise = 346	28.7	2.3	
Variance	P = 0.001	P = 0.171	P < 0.001

Leung et al, Osteoporosis Int, 2014

Low-Magnitude, High-Frequency Vibration Enhances Fracture Healing and Rehabilitation in Elderly with Intertrochanteric Fractures

+[1]Leung,KS; [1]Cheung,WH; [1]Mok, HW; [1] Liu, PL; [1] Chan TJ; [1] Chan SY; [1] Mak WY;
+[1] The Chinese University of Hong Kong
ksleung@cuhk.edu.hk

40 +65 yrs with unilateral throchanteric Fractures fixed with DHS or Gamma Nail

LIV Post Op Day 4 for 6mths
0.3g 20 mins 7/7
85% compliance in LIV

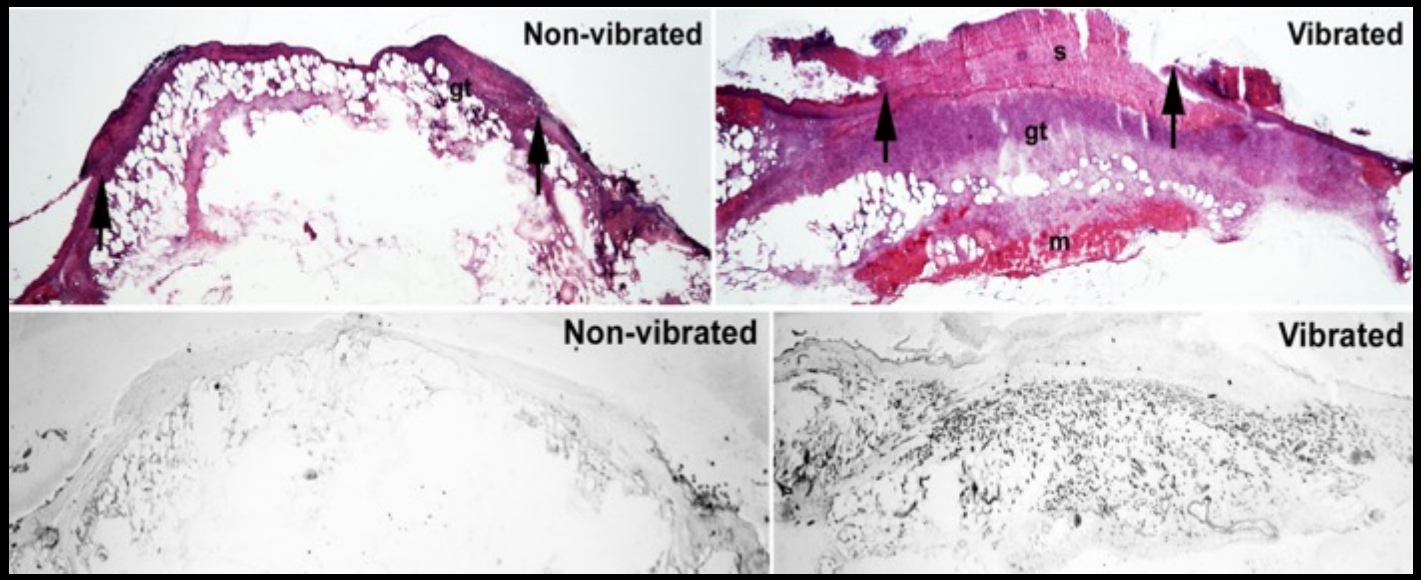
Results:	Control	LIV
2 month		Positive QoL and RoM Hip P <0.5
RANKL/OPG ratio	8.97+/-5.76	16.26 +/- 13.22
Increase Hip BMD Non Fx side		Benefit 1.43%
Fem neck loss	-4.22%	-2.53%
Fracture Healing		Early Fx impaction and IM callius
		No Pain or problem using LIV device

The above X-ray showed that fracture impaction with sliding of lag screw and appearance of intra-medullary callus in vibration group

Leung, ORS 2011

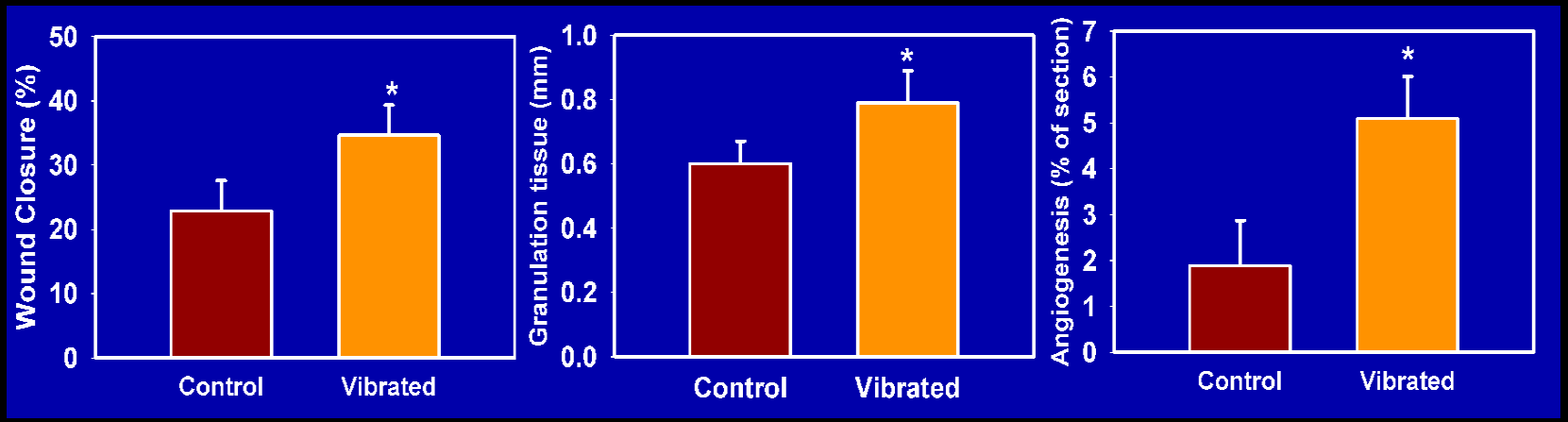
LIV enables wound healing in diabetic mice

H&E



7d post injury

CD31



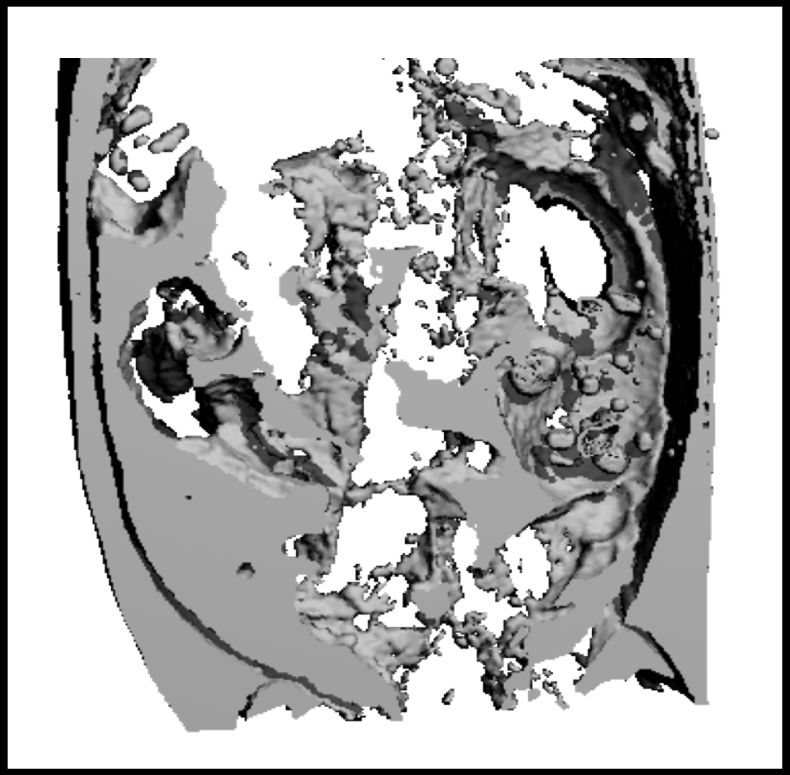
Koh & Judex, 2013, unpublished data

Adiposity

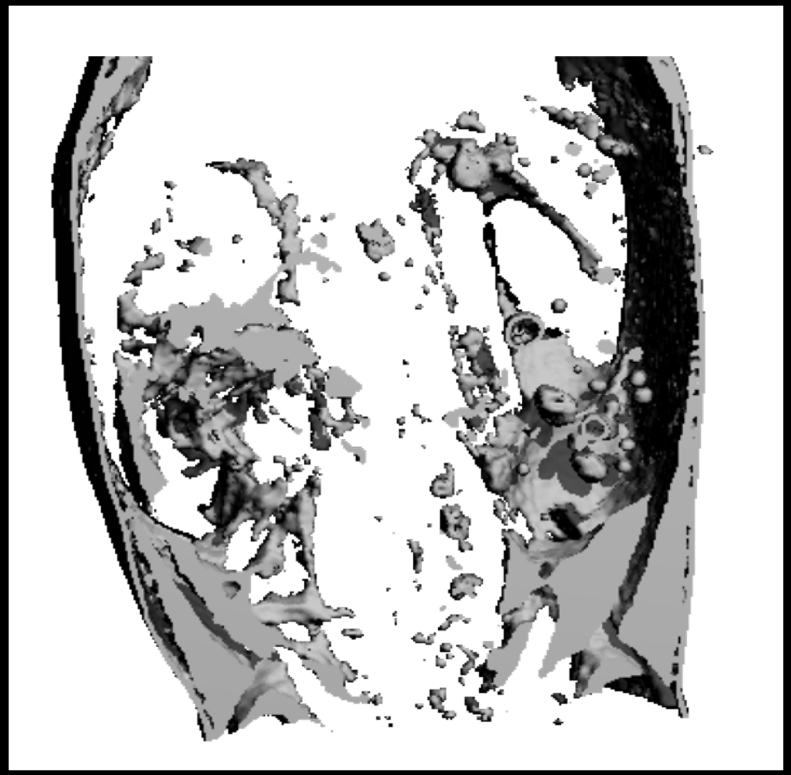
Suppression of adiposity by low-level mechanical signals

BL6 male mice, 12w stimulation, normal diet

Control



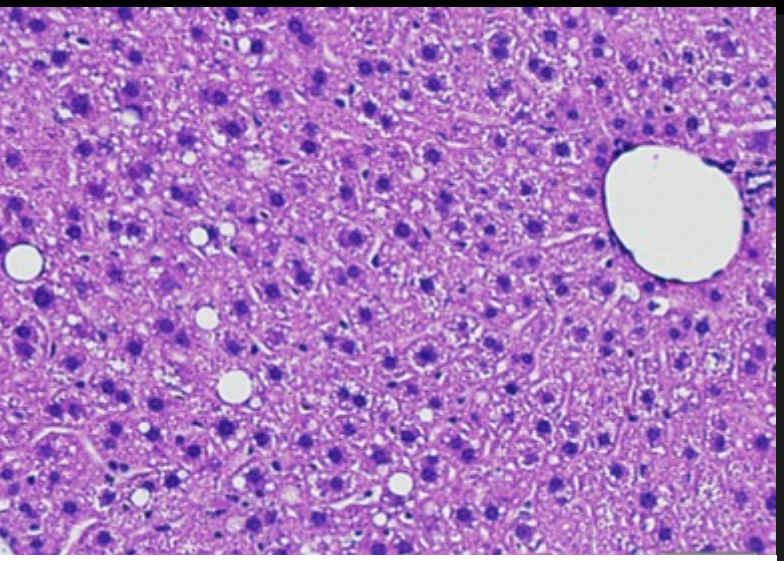
LIV



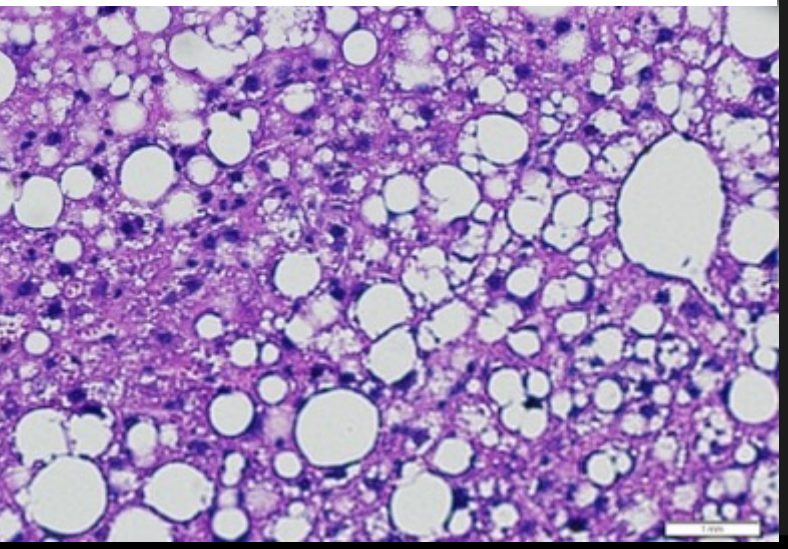
10mm

27.6% less epididymal and 19.5% less subcutaneous fat ($p<0.01$)

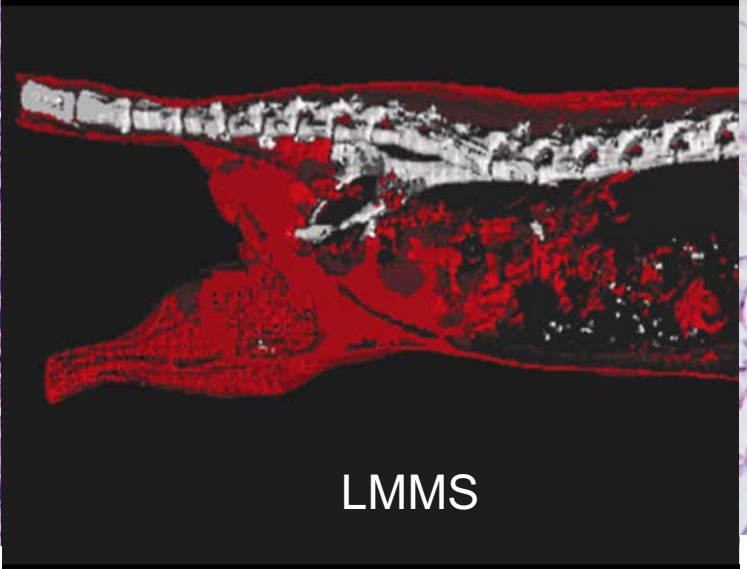
Prevention of diet induced obesity by mechanical signals

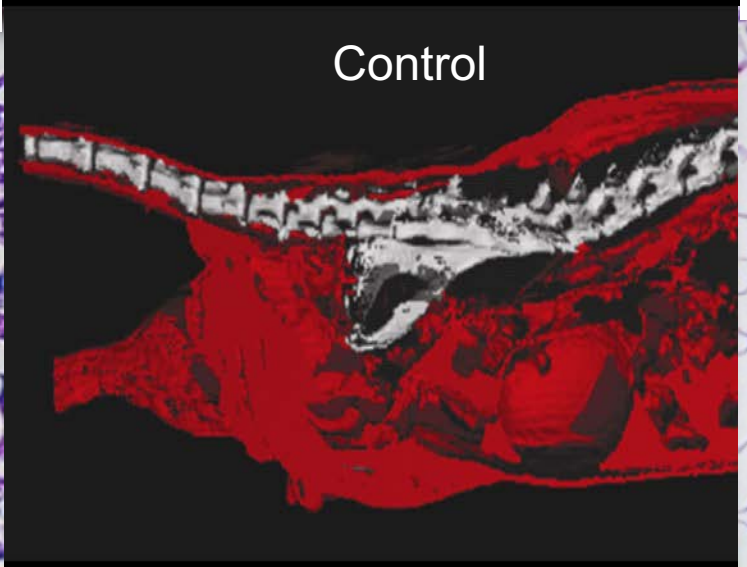


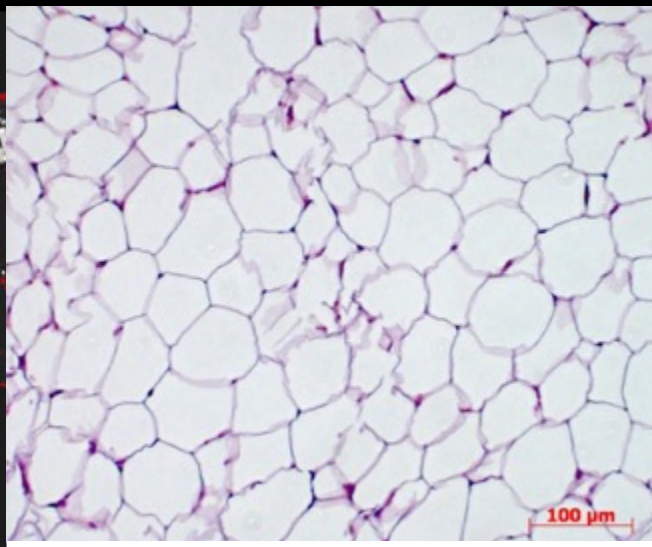
DIO Liver @ 9 months; -28%



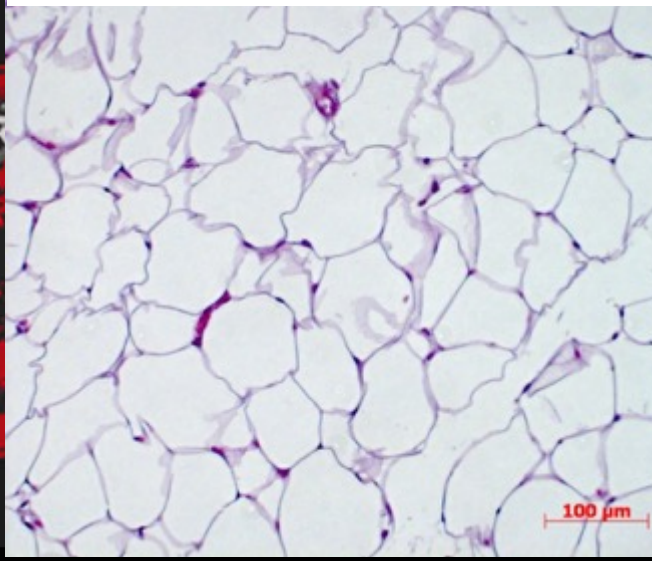
Luu et. al., 2010







Adipocyte volume -38%

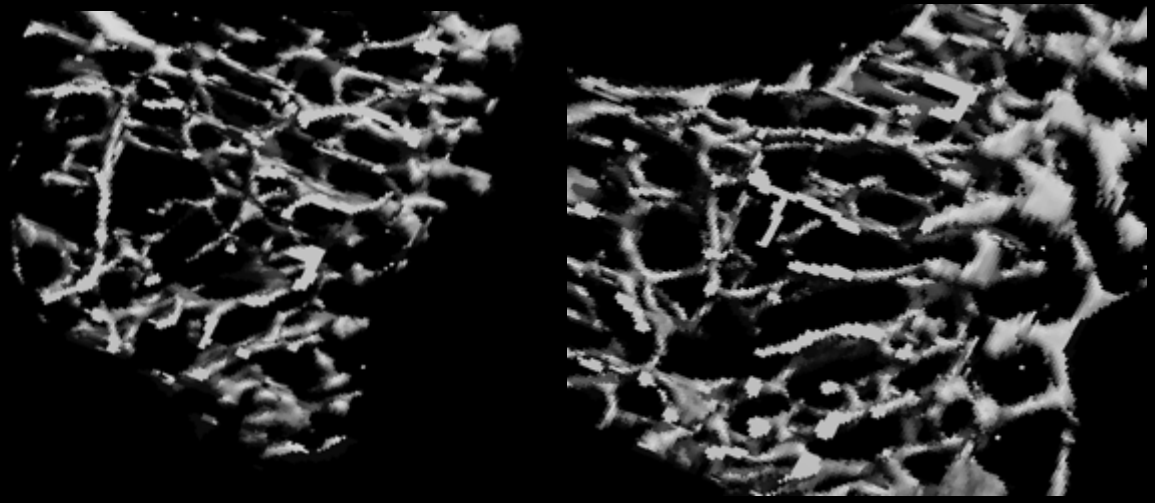


Luu et. al., 2009

Biasing the Fate Selection of the Adult Stem Cell Population

12w HFD

CT of Proximal Tibia

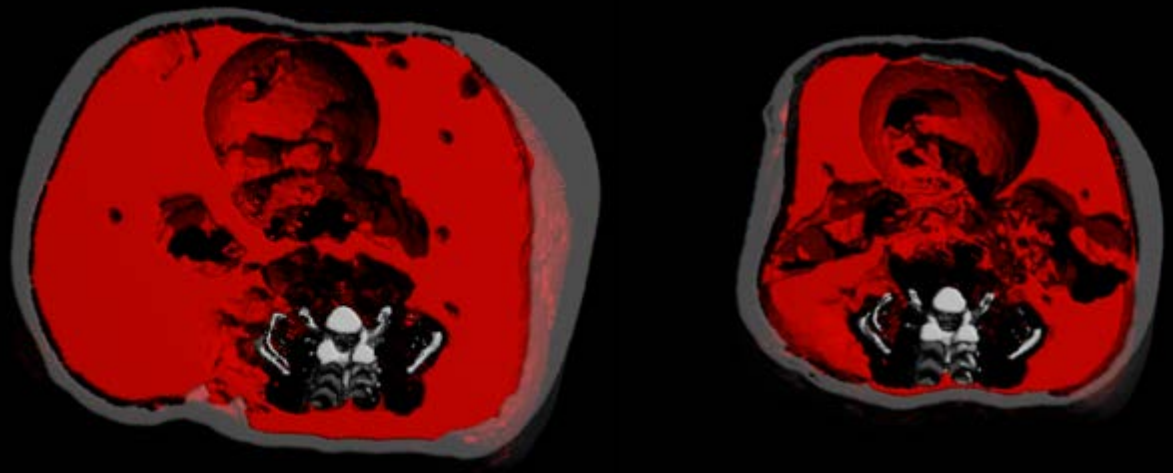


Bone Volume:
+13.3%
P<0.01

LIV Bias Towards Bone & Muscle

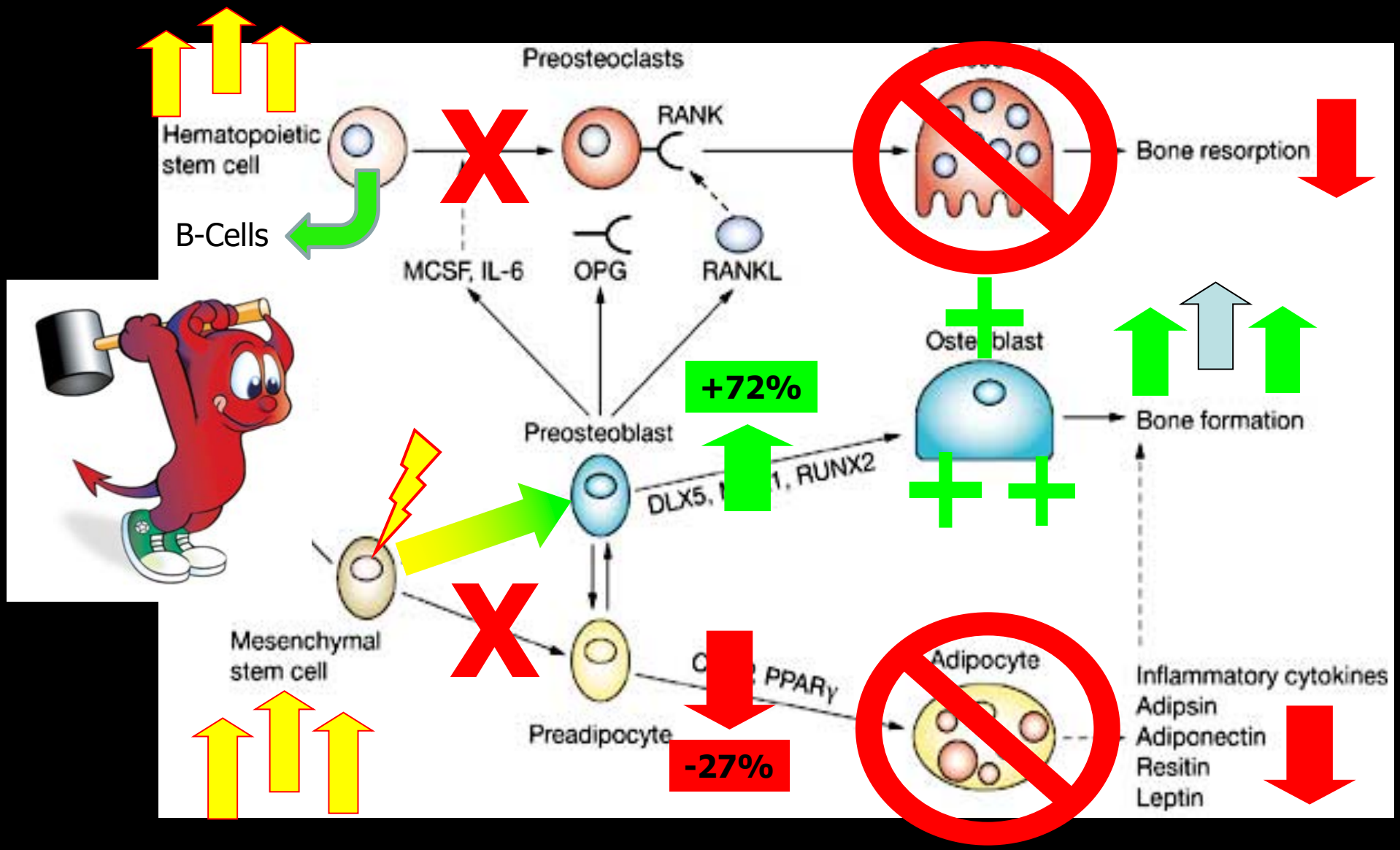
Sedentary Bias Towards Fat

CT of Adipose Burden in Torso



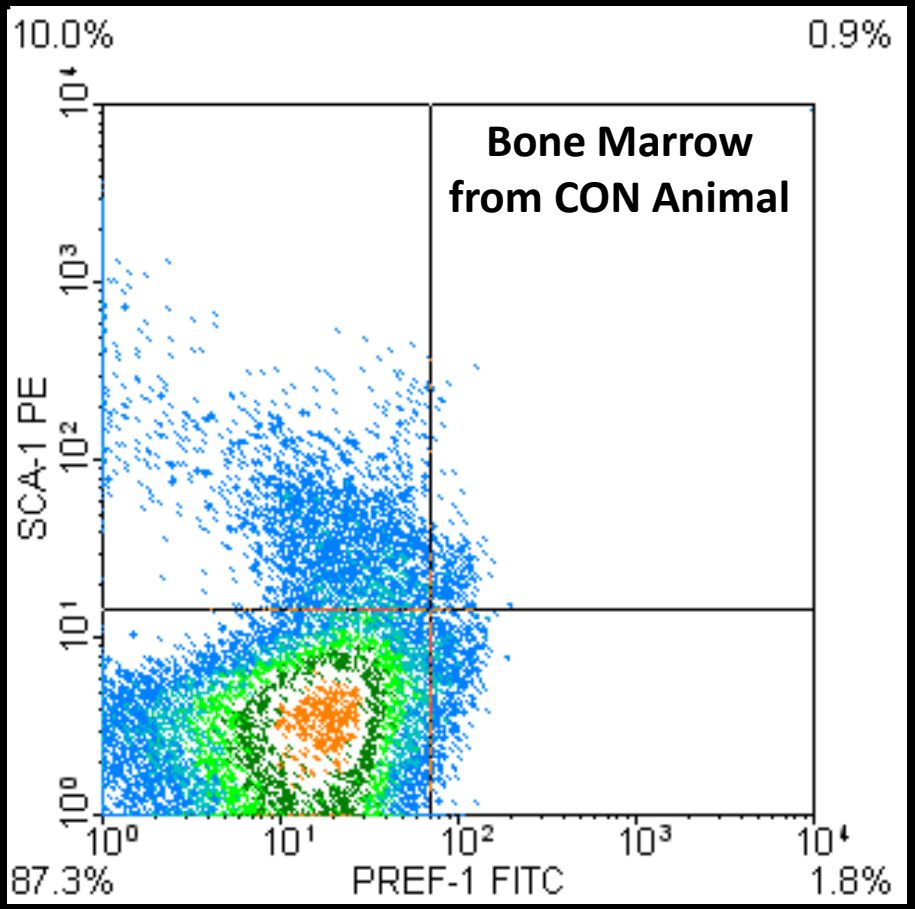
Fat Volume:
-25.4%
P<0.001

LIV Therapy biasing of MSC & HSC fate selection

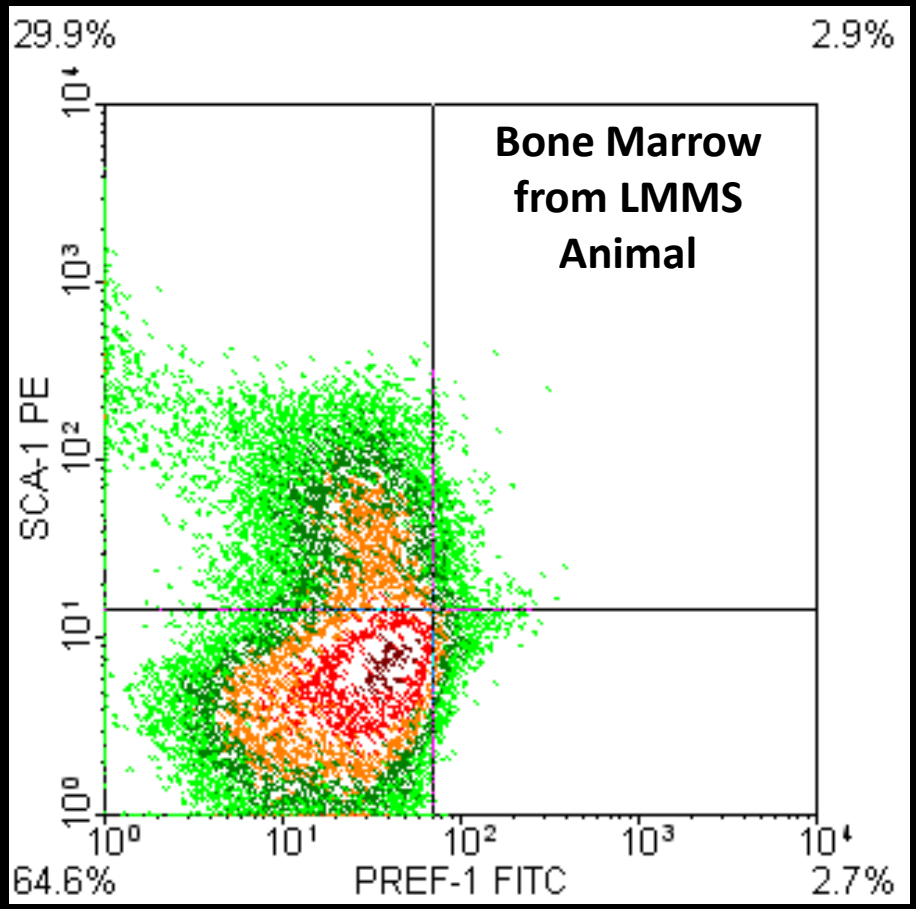


Towards a stronger and healthier musculoskeletal system

And promoting the bone marrow stem cell pool



Control



LIV

At six weeks: 37.2% increase in overall stem cell pool ($Sca1^+$; $p<0.03$)

46.1% increase in MSC pool ($Sca1^+$ & $Pref1^+$; $p<0.02$)

While Simultaneously Enhancing Bone Quantity & Quality

7w Male C57/BL6

High Fat Diet

In vitro CT @ 14w

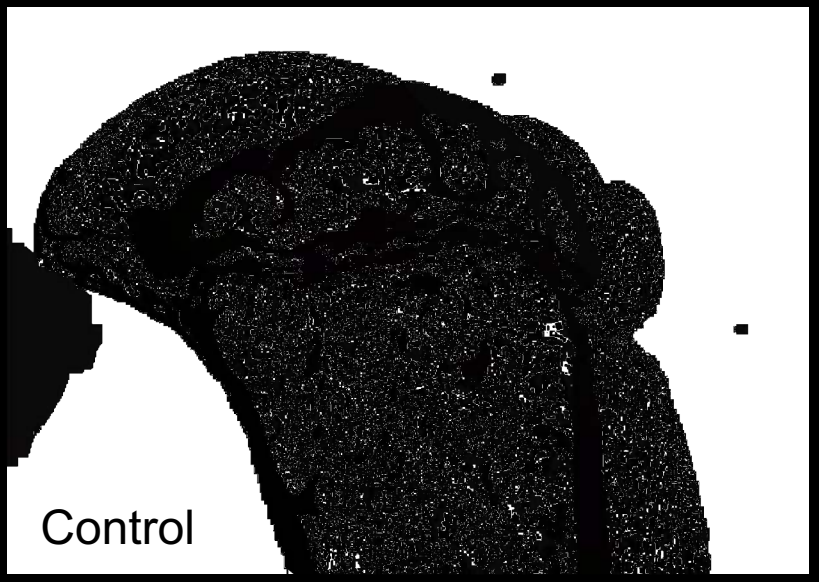
+7.3% bone volume in torso
(p=0.055)

+13.3% bone volume in tibia
(p<0.01)

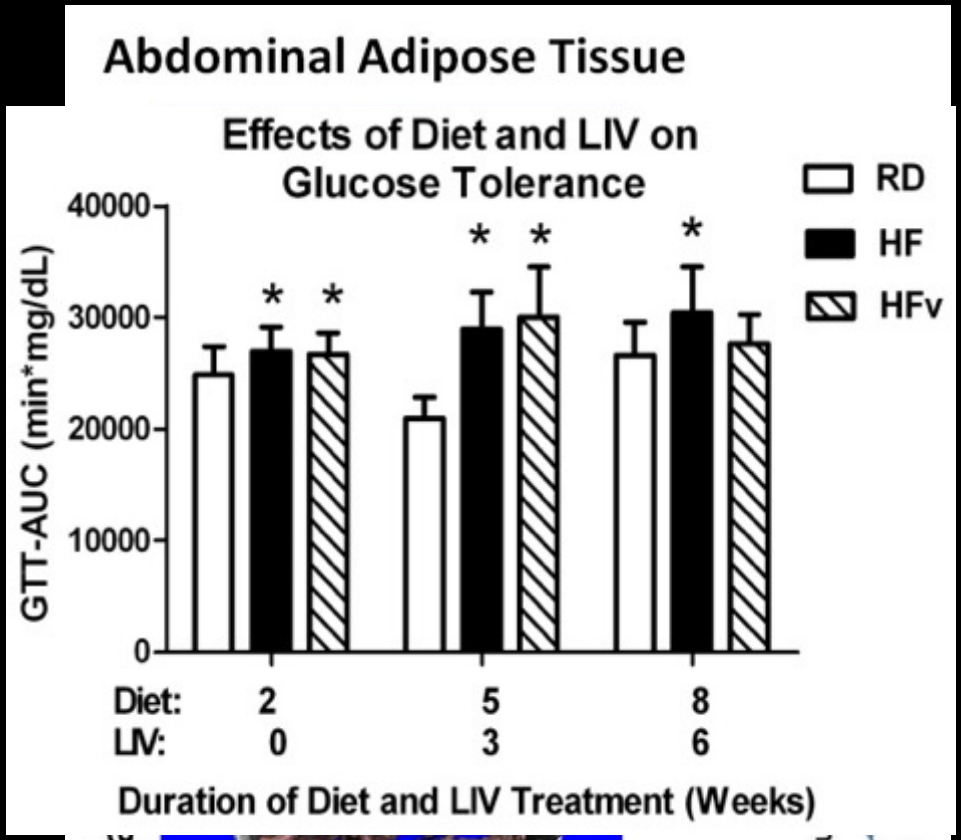
+10.4% trabecular number
(p<0.02)

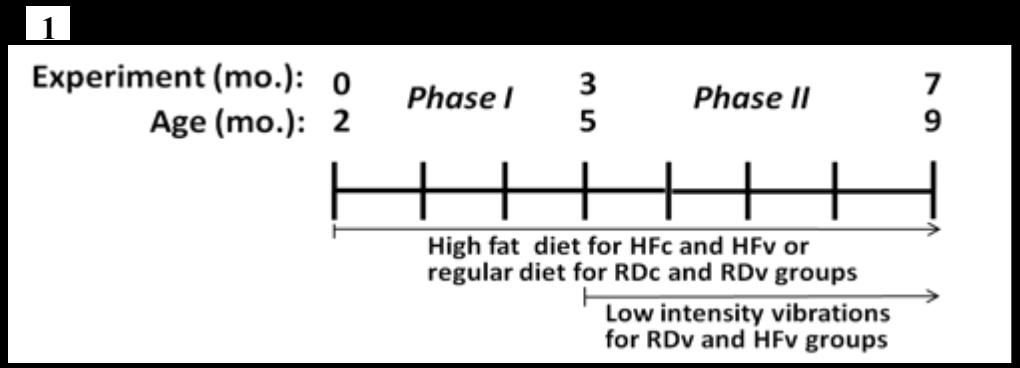
-11.1% trabecular spacing
(p<0.01)

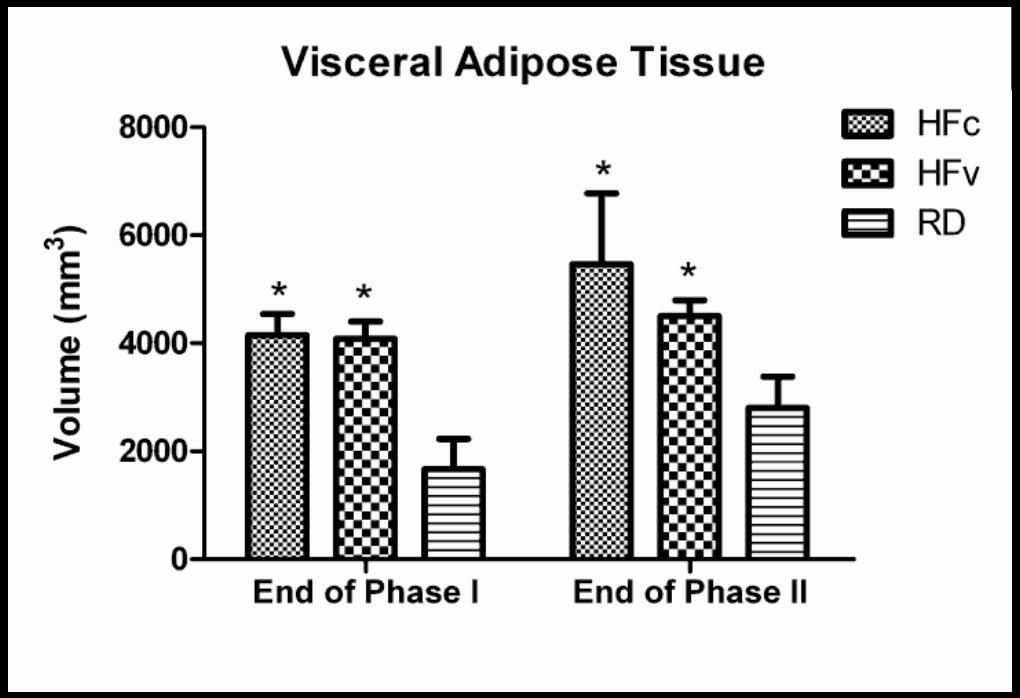
-4.9% SMI
P<0.02



Can LIV influence diabesity outcomes in mice that are already fat?

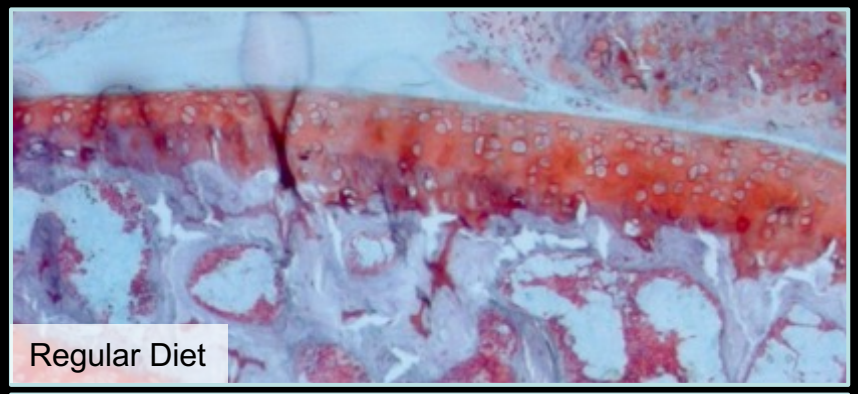


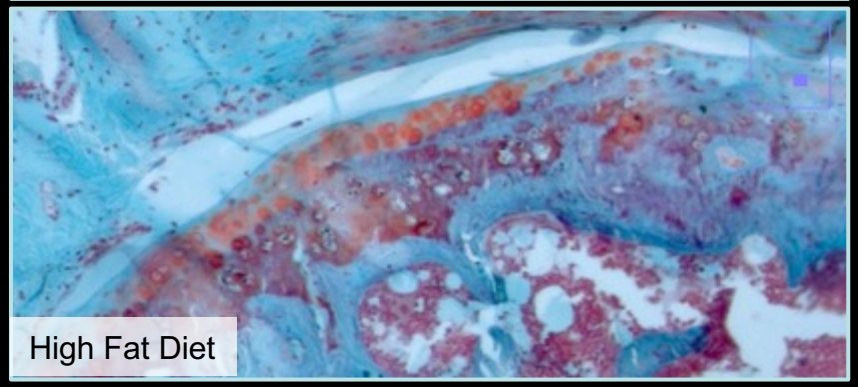


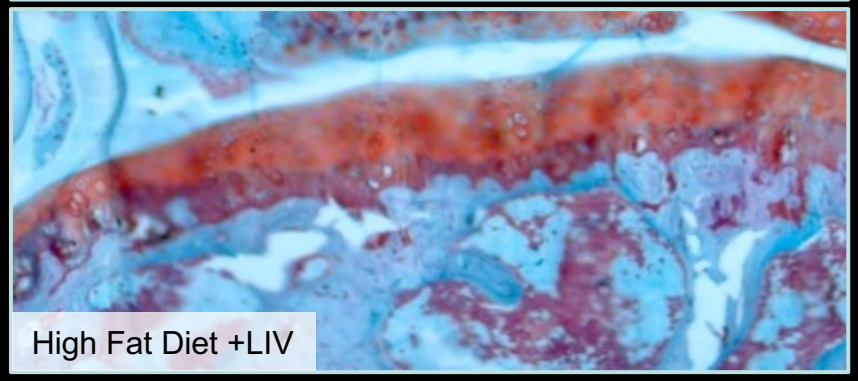


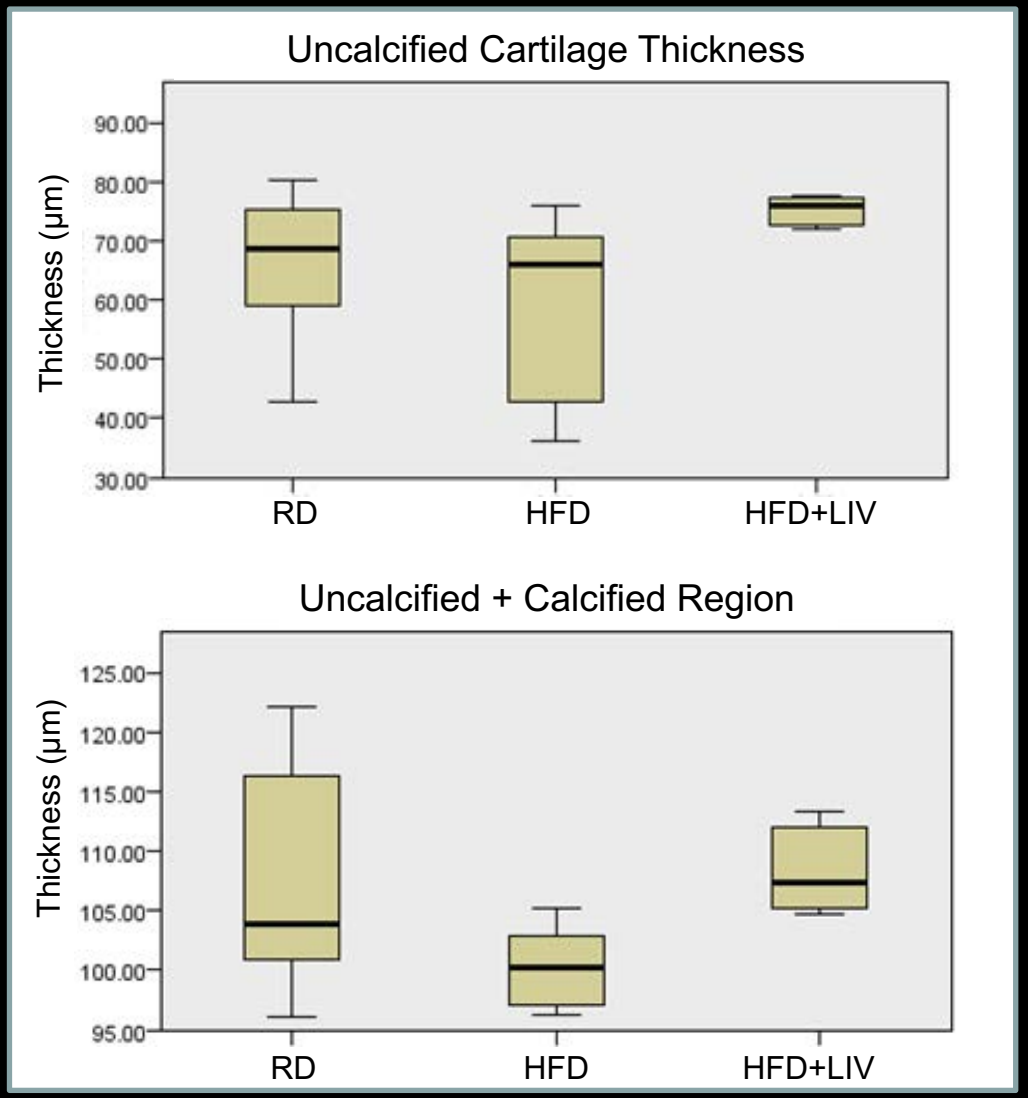
Suppression of obesity-induced osteoarthritis by LIV

(Calcification of articular cartilage slowed by LIV)





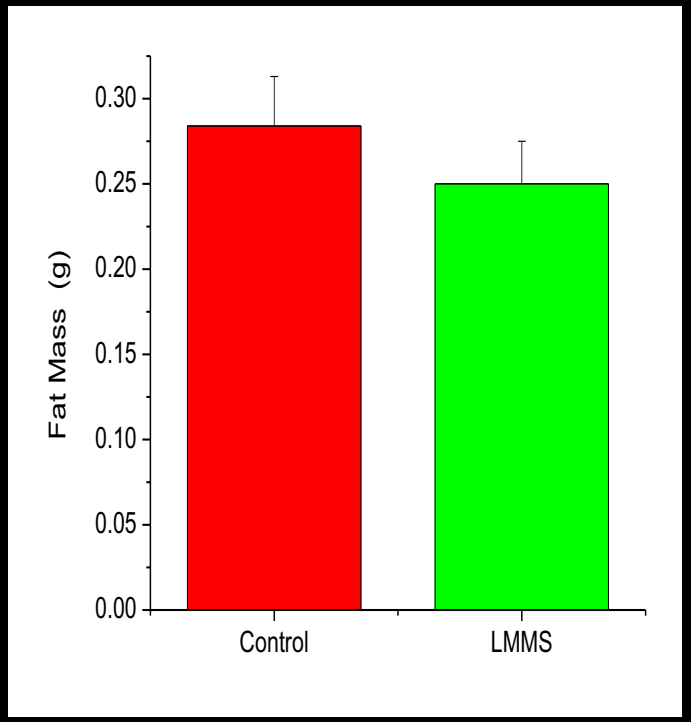


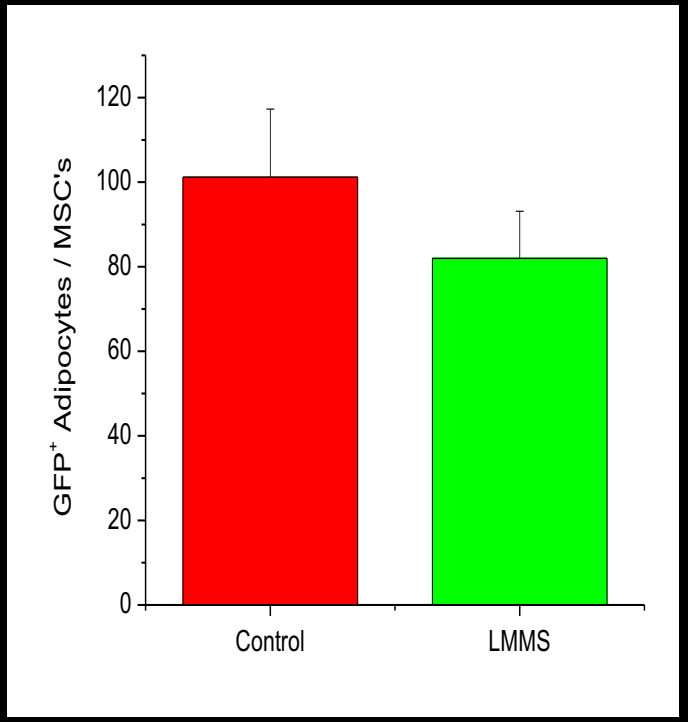


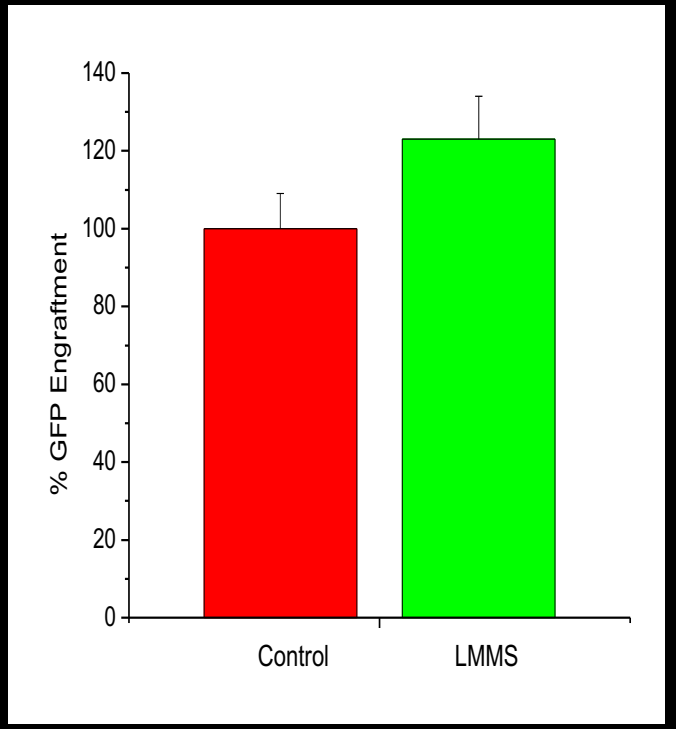
Pamon et. al. 2013, unpublished data

Mechanical influence on mesenchymal stem cells

GFP+ recipients to track MSC differentiation



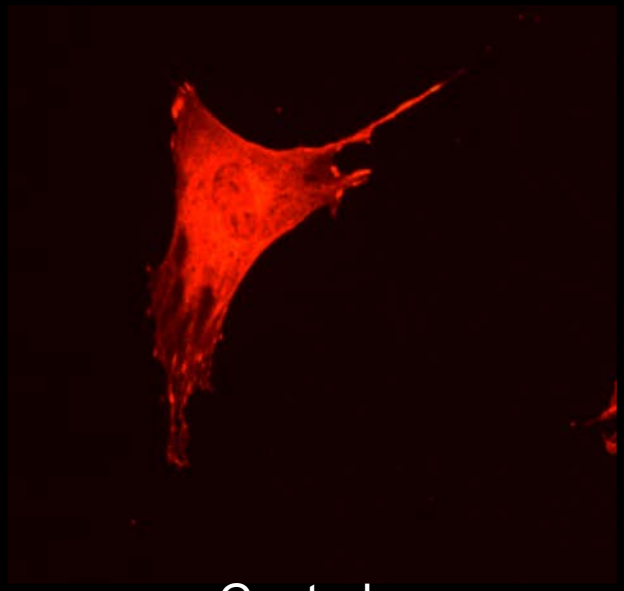




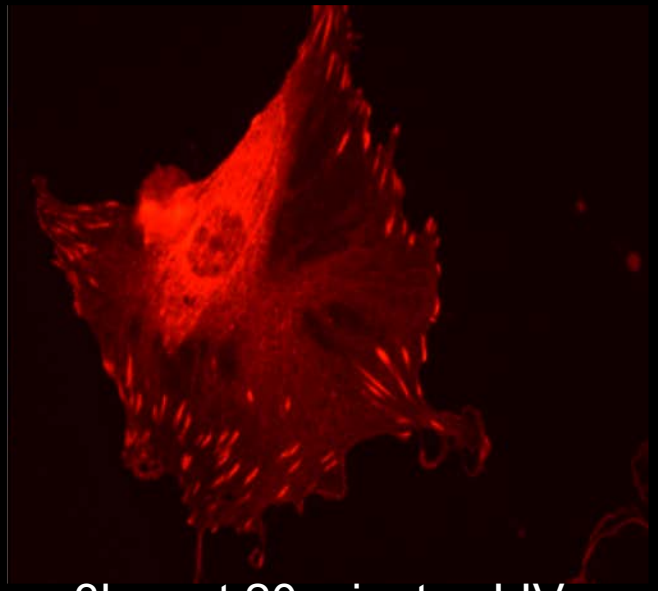
Epididymal Fat Pad	GFP+ Adipocytes	MSC Number
-12.1%	-18.9%	+23.4%
P<0.03	p<0.02	p<0.001

Lethal irradiation, marrow transplant, 6w mechanical stimulation

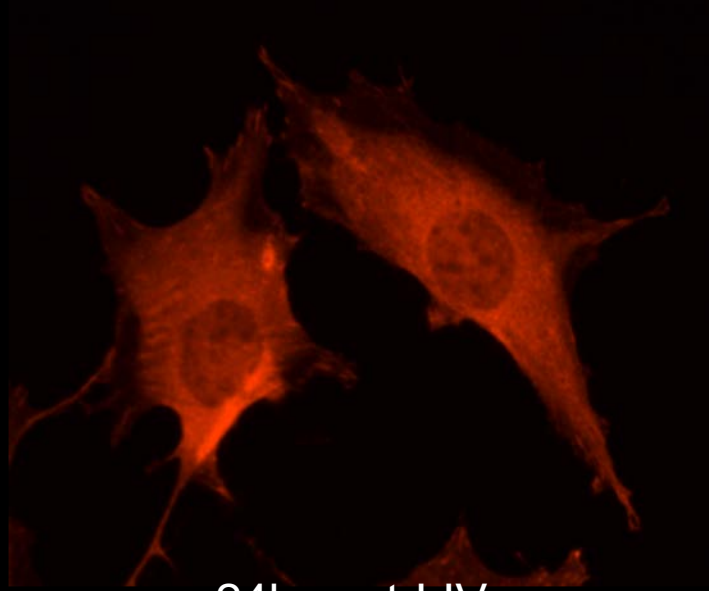
Low intensity vibration induces changes in cell architecture



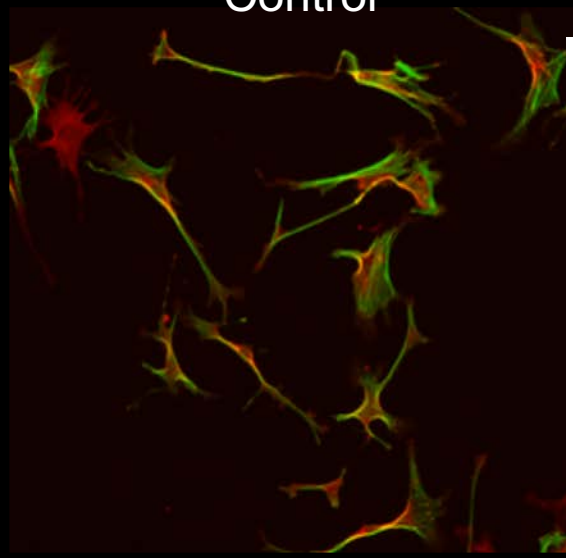
Control

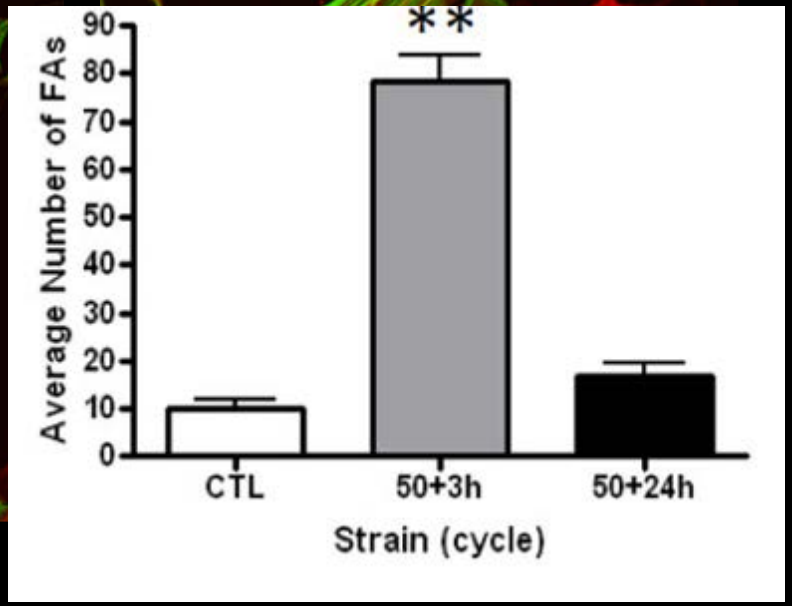


3h post 20 minutes LIV



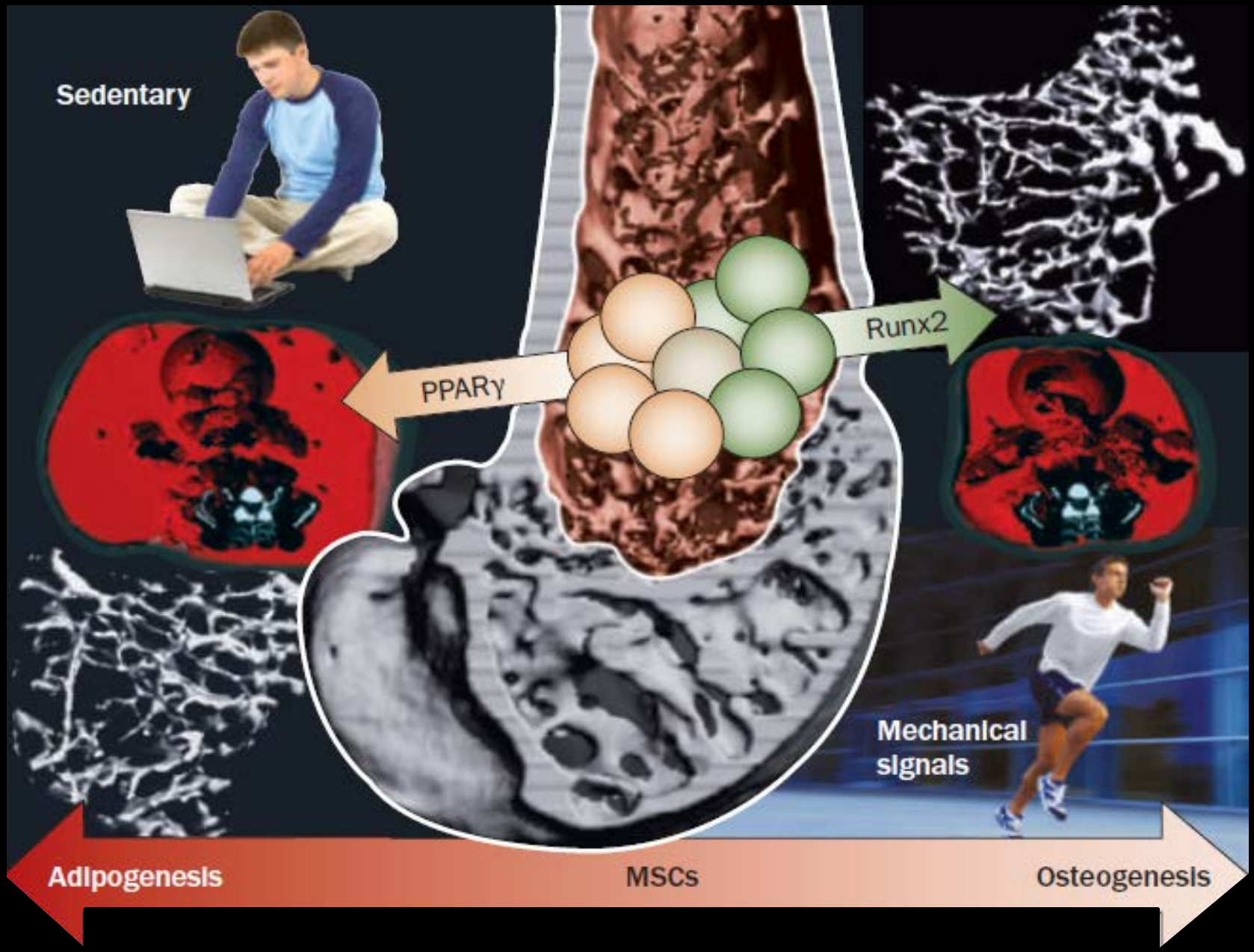
24h post-LIV

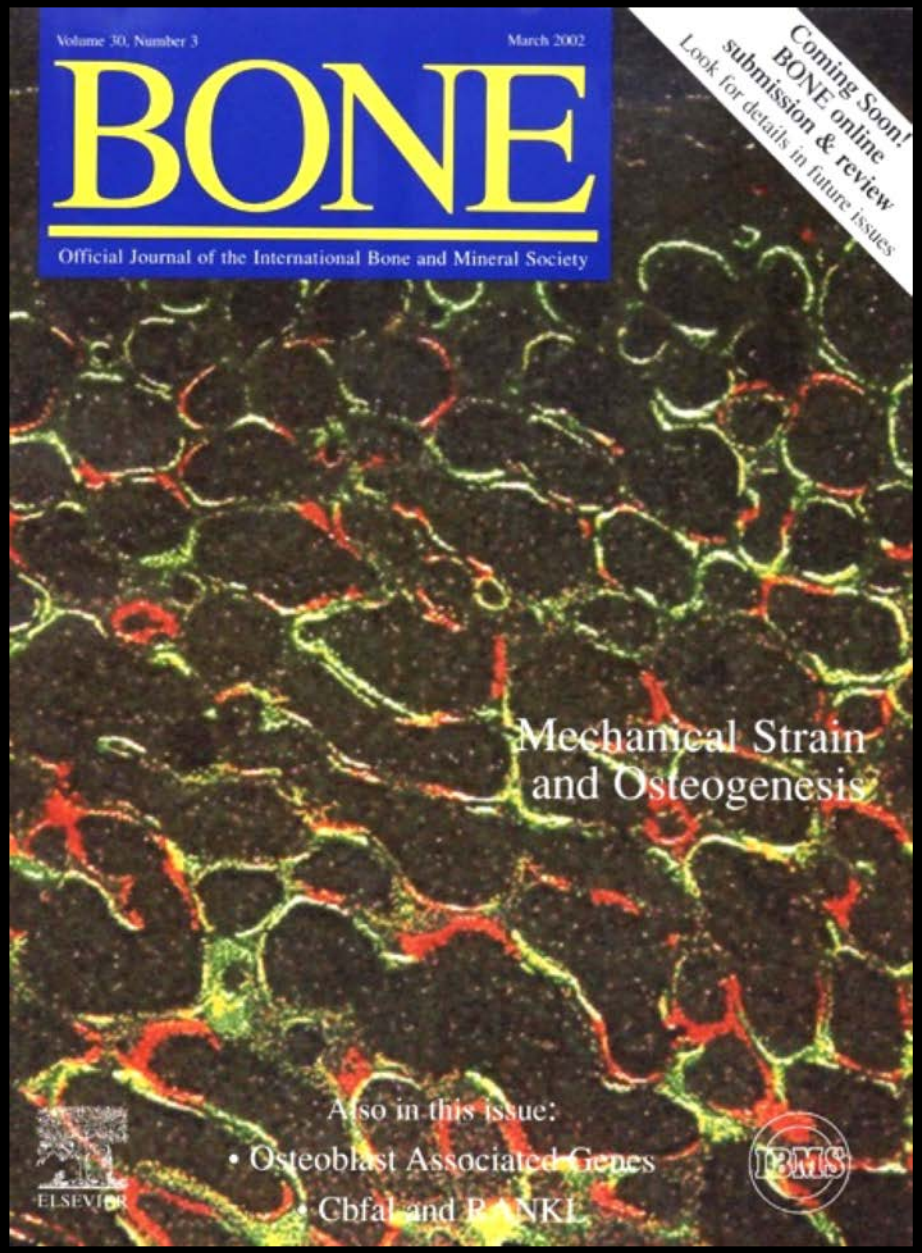




But these adaptations are transient

Sen et. al, *Stem Cells, 2011*


Sedentary
PPARγ
Runx2
Mechanical signals
Adipogenesis
MSCs
Osteogenesis



Low Intensity Vibration *can* regulate bone mass and morphology

- Omnipresent signal in the skeleton
- Targets bone cell progenitors
- Stimulate bone formation
- Suppress bone resorption
- Produce lamellar bone
- Self-targeting
- Self regulating

- *Non-drug prevention and/or treatment for osteoporosis?*