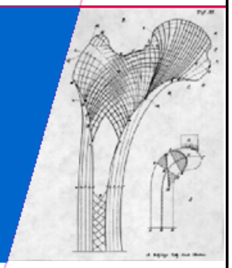
Bone remodeling Experiments

Bert van Rietbergen



Technische Universiteit Eindhoven University of Technology

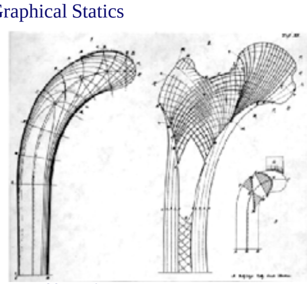
Where innovation starts

Bone has a specific density and structure

Wolff's Law: mass and orientation of trabecular structure are adapted to its mechanical load

Wolff,1892

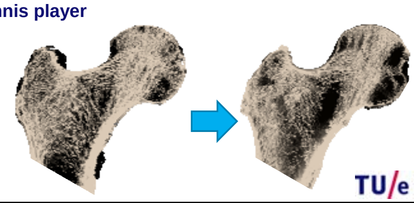
Graphical Statics



von Meyer & Culmann,1866/67

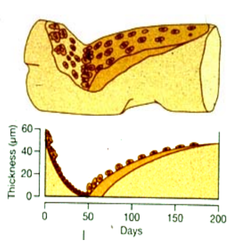
But density and structure can change as a result of changes in loading

- Disuse will lead to loss of bone
  - wheelchair
  - micro-gravity
  - bedridden
- Overuse leads to formation of bone
  - exercise
  - tennis player

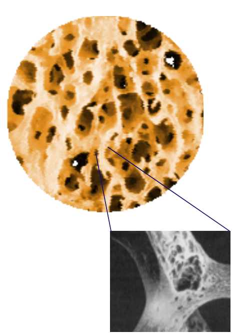


Mechanism: osteoclast/osteoblast

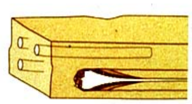
Trabecular bone

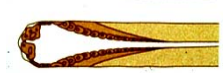


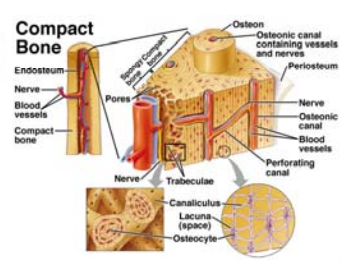
Remodeling



Mechanism: osteoclast/osteoblast

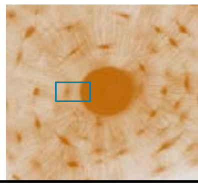




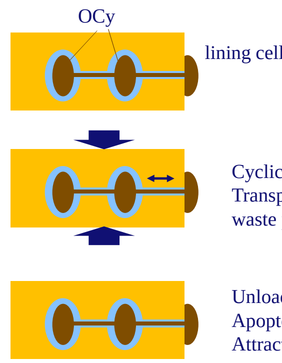


Mechanism: osteocytes

- Generally accepted that ostecytes are mechanosensors and regulate the remodeling process because they:
  - are sensitive to mechanical load
  - are sensitive to fluid flow
  - are the most abundant cell type in bone
  - can regulate OCl and OBl activity



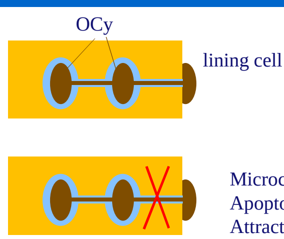
Osteocytes as mechanosensor



Cyclic loading: fluid flow
Transport of nutrients and waste products

Unloading: no fluid flow
Apoptosis of OCy
Attracts OCl

Osteocytes as mechanosensor



Microcracks: no fluid flow
Apoptosis of OCy
Attracts OCl

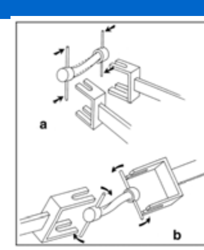
But...

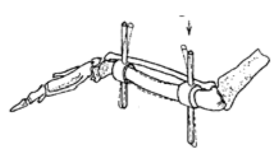
- How is this process regulated?
- How can this process leads to mechanically ‘optimized’ structures?
- How can cells at the scale of 10 microns produce 'optimal' structures at a scale 100-1000 times larger?

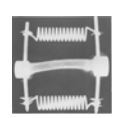
Experimental bone adaptation strategies

- Overloading strategies @ normal strain-rates
  - Turkey ulna loading
  - Rat ulna loading
  - Rat tail loading
  - Rat exercise
  - Sheep ulnar osteotomy
  - Hypergravity
- Unloading strategies
  - Rat tail suspension
  - External fixation
  - Rat hindlimb neurectomy/botox treatment
  - Rat microgravity
  - Human bed-rest
- High-frequency strategies
  - Rat ulna
  - Sheep vibration platforms
  - Human

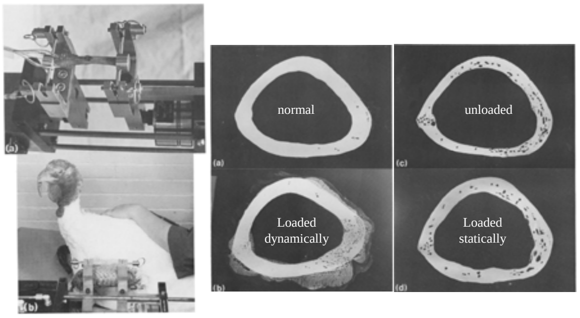
Turkey ulna loading







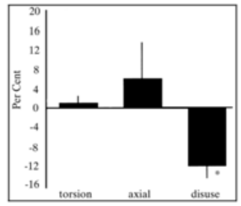
Turkey ulna loading



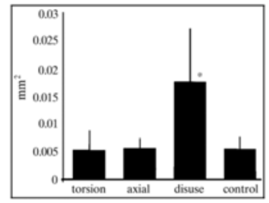
Turkey ulna loading

Torsion versus axial

Change in total area

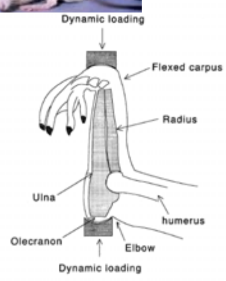


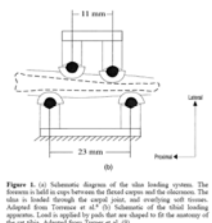
Mean pore size



Rubin et al., JBJSA, 1998

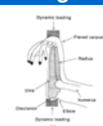
Rat ulna/tibia loading



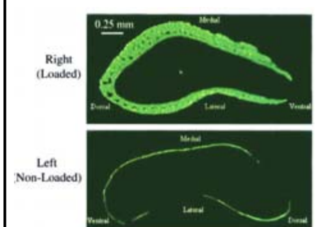


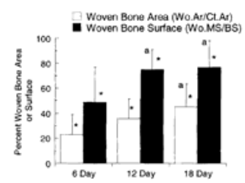
Turner et al., Bone, 1999

Rat ulna loading
Fatigue test



Fatigue loading:
- 13 N @ 2Hz
- -2400/+1700 µstrain
- stop when reaching 60% increase in displacement



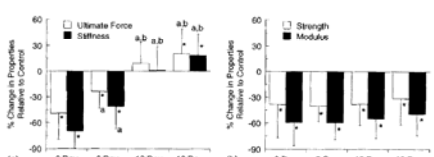


Rat ulna loading
Fatigue test

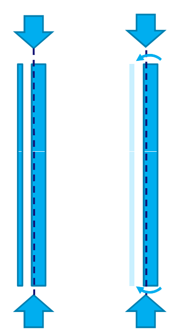
3-point bending

extrinsic

intrinsic

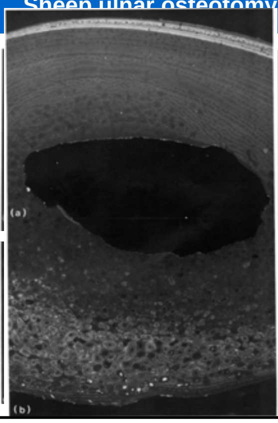


Sheep ulnar osteotomy



Lanyon et al., J.Biomech., 1982

Sheep ulnar osteotomy



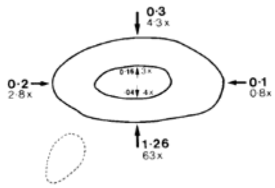
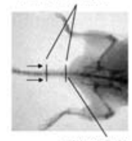
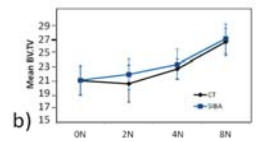


Fig. 4. The mean thickness (mm) of periosteal new bone deposited at the arrowed sites in the radius in animals allowed 50 weeks for adaptive remodelling after ulnar osteotomy. In each case the factor by which this exceeds the amount of new bone deposited on the contralateral radius over the same period in the same animals is shown in smaller type.

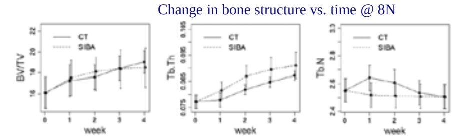
Rat tail loading



BV/TV vs. loading



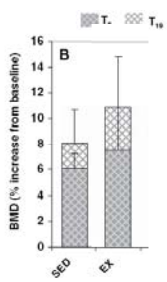
Change in bone structure vs. time @ 8N



Lambers et al., 2011

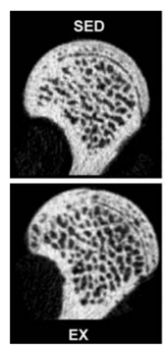
Rat exercise backpack

- Backpack: 20% BW
- Running 15 min/day
- 19 weeks

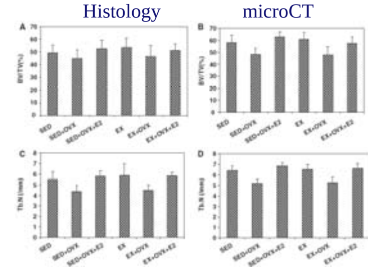


Tromp et al., Calc.Tiss., 2006

Rat exercise backpack



Histology microCT



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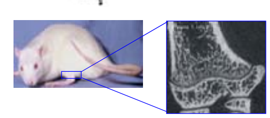
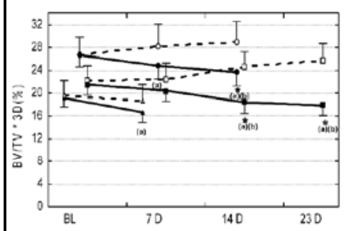
Tail suspension

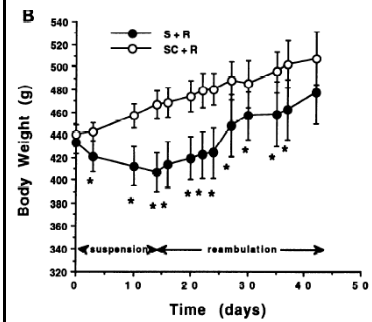


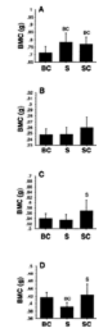
Tail suspension



David et al., 2003; Barou et al., 2002

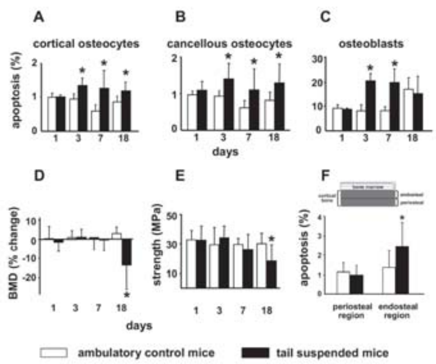
Tail suspension:





Vico et al., 1995

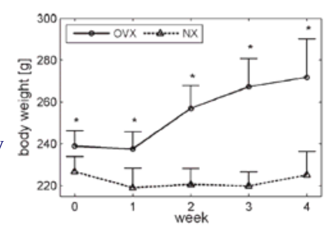
Tail suspension



Aguirre et al., JBMR, 2006

Rat neurectomy

unilateral sciatic neurectomy



Brouwers et al., 2009

Rat neurectomy

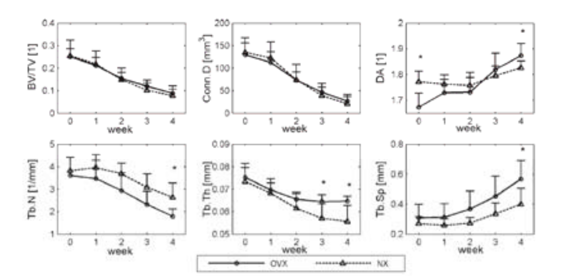
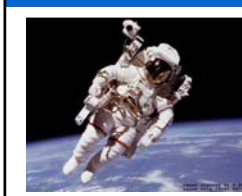


Figure 2. Structural parameters in the metaphyseal proximal tibia (mean ± SD). Asterisk indicates a significant difference between the OVX and NX groups at that time point.

Brouwers et al., 2009

Microgravity



Long-term spaceflight: bone loss

Model:
- Bedrest studies
- Head 6º tilt down
- ~ several weeks

Human Bed-rest

Variable	N	%/Month	SD
BMD Spine	18	-1.06*	0.63
BMD Neck	18	-1.15*	0.84
BMD Troch	18	-1.56*	0.99
BMD Total	17	-0.35*	0.25
BMD Pelvis	17	-1.35*	0.54
BMD Arm	17	-0.04	0.88
BMD Leg	16	-0.34*	0.33
Lean Total	17	-0.57*	0.62
Lean Leg	16	-1.00*	0.73
Lean Arm	17	0.00	0.77
Fat Total	17	+1.79	4.66

*p<0.01

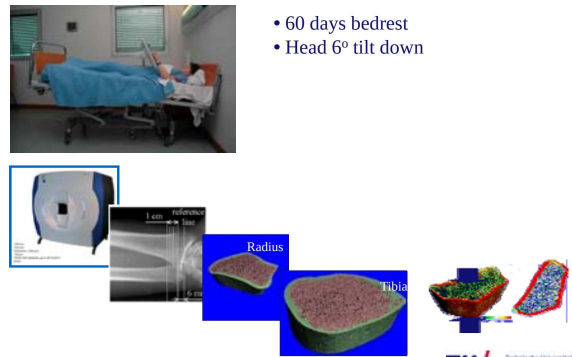
Spaceflight

Variable	N	% Change/Month	SD (slope)
BMD Spine	8	-0.87*	0.13
BMD Neck	8	-0.82*	0.17
BMD Troch	8	-1.04*	0.17
BMD Total	8	-0.35*	0.13
BMD Pelvis	8	-1.26*	0.22
BMD Arm	8	-0.61	0.39
BMD Leg	8	-0.43*	0.17
Lean Total	6	-1.04*	0.26
Lean Leg	6	-3.03*	0.35
Lean Arm	6	+0.91	0.56

* p<0.05

Bedrest

Bedrest study



- 60 days bedrest
- Head 6° tilt down

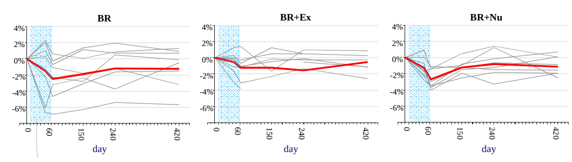
Ambrecht et al., 2009

Countermeasures

- **Exercise group: every 3rd day**
  - **Resistance training on ergometer**
  - **Aerobics training: running on a vertical treadmill**
- **Nutrition group:**
  - **Additional amounts of protein and free-leucine**

Tibia

Change in strength over time

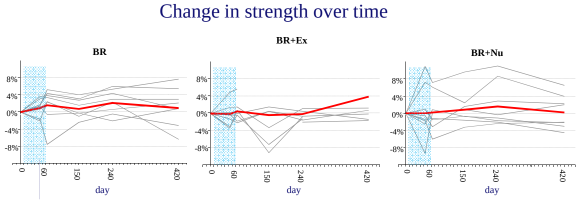


Bedrest period

Individual subjects
Group average

Radius

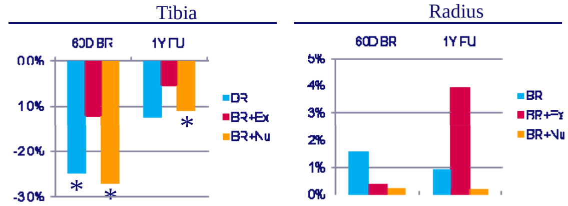
Change in strength over time



Bedrest period

Individual subjects
Group average

Anova: change in strength since baseline



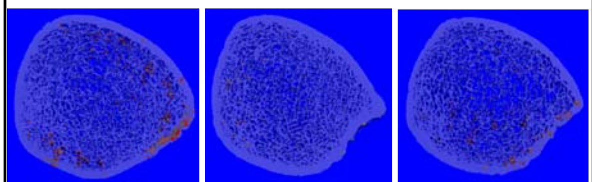
*Significantly different from baseline (p<0.05)

No significant differences between groups

Bone loss/gain analysis: tibia other subjects

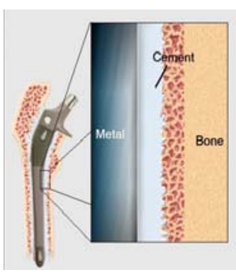
BR period

BR | BR+Ex | BR+Nu

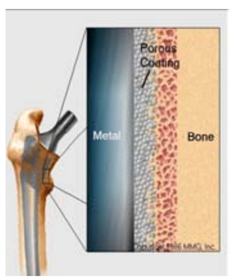


Unloading due to placement of implants

Unloading due to placement of implants

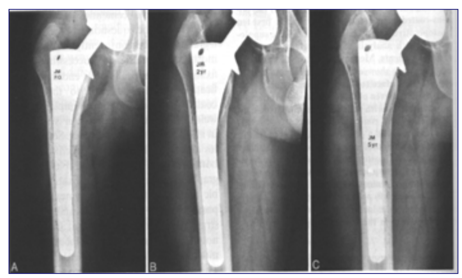


Cemented

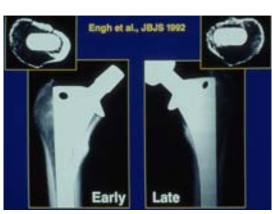


Non-cemented

Unloading due to placement of implants



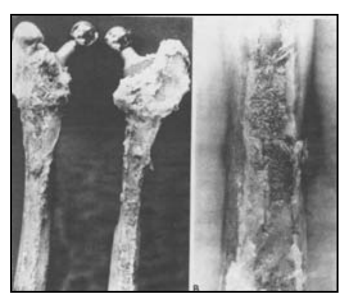
Unloading due to placement of implants



'stress shielding'

Unloading due to placement of implants

effect of implant stiffness



Bobyn et al., 1990

- Overloading strategies @ normal strain-rates
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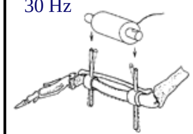
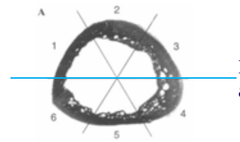
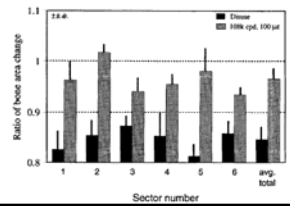
Turkey ulna high frequency loading

30 Hz



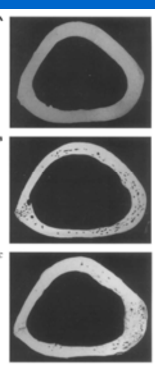


Neutral axis



Qin et al., JOR, 1998

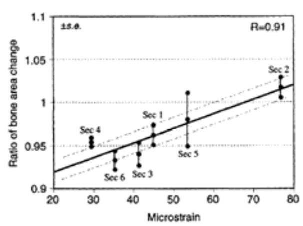
Turkey ulna high frequency loading



Control

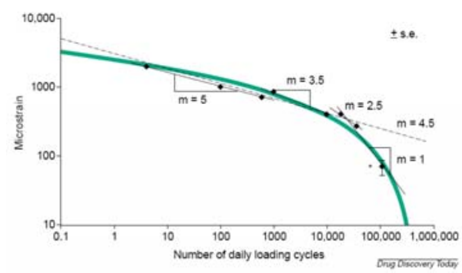
Unloaded

100 µstrain @30Hz



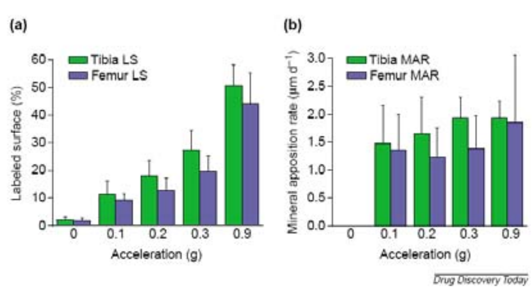
Turkey ulna high frequency loading

Strain threshold required to maintain bone mass



Rubin et al., 2001

Turkey whole-body vibration



Rubin et al., 2001

Sheep whole-body vibration

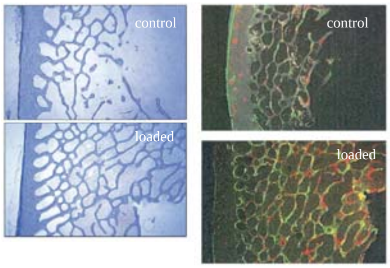
- 12 months / 5days / week
- 20 min/day
- 30Hz
- 0.3g

femur

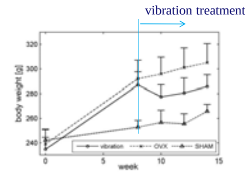
	Control	Experimental	Difference	P value
DXA				
Animal mass (kg)	71.1 ± 7.1	70.3 ± 9.4	−1.1%	n.s.
Bone mineral density (g/cm²)	0.83 ± .06	0.88 ± .05	+5.4%	0.1
pQCT				
Total density (g/cm³)	466 ± 60	496 ± 53	+6.5%	0.1
Cortical density (g/cm³)	1215 ± 51	1193 ± 49	−1.6%	n.s.
Trabecular density (g/cm³)	169 ± 37	227 ± 56	+34.2%	0.01

Rubin et al., 2002

Sheep whole-body vibration



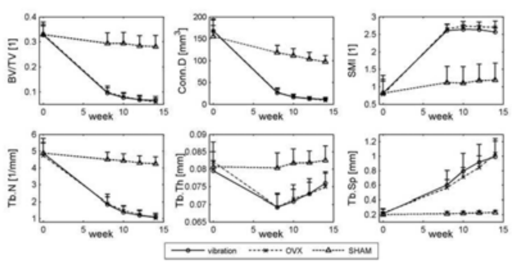
Rat whole-body vibration



- 20 min/day, 5 days/week
- 6 weeks
- 0.3g, 90 Hz

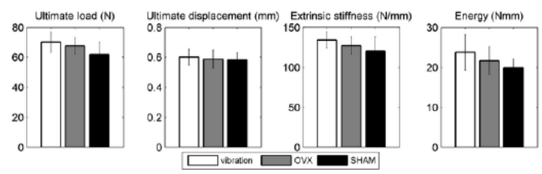
Brouwers et al., 2009

Rat whole-body vibration



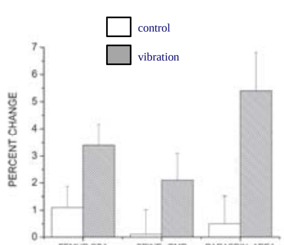
Brouwers et al., 2009

Rat whole-body vibration



Brouwers et al., 2009

Human whole-body vibration



- 48 young women (15-20y)
- 12 months
- 0.3g @ 30Hz

Gilsanz et al., 2006

Human whole-body vibration

TABLE 6. ABSOLUTE AND PERCENT CHANGE IN DXA MEASURES FOR WOMEN IN THE CONTROL AND EXPERIMENTAL GROUPS (N = 24 IN EACH GROUP)

	Absolute change			*Percent change*		
	Control	*Experimental*	p	*Control*	*Experimental*	p
Spine BMC (g)	2.14 ± 2.18	2.07 ± 1.97	0.91	3.82 ± 4.07	3.93 ± 3.84	0.92
Spine aBMD (g/cm^2)	0.02 ± 0.03	0.02 ± 0.03	0.99	2.11 ± 3.22	2.25 ± 3.19	0.88
Whole Body BMC (g)	59.5 ± 57.8	53.5 ± 53.8	0.71	3.45 ± 3.45	3.52 ± 3.34	0.94
Whole body aBMD (g/cm^2)	0.01 ± 0.02	0.01 ± 0.02	0.57	0.65 ± 1.87	0.96 ± 2.29	0.61
Trunk lean mass (g)	214 ± 1058	460 ± 1174	0.45	1.06 ± 4.93	2.19 ± 6.03	0.49
Total lean mass (g)	702 ± 1704	754 ± 2456	0.93	1.75 ± 4.07	1.61 ± 5.95	0.93

No significant differences between control and experimental subjects were identified.

Gilsanz et al., 2006

- Overloading strategies @ normal strain-rates
  - Turkey ulna loading
  - Rat ulna loading
  - Rat tail loading
  - Rat exercise
  - Sheep ulnar osteotomy
  - Hypergravity
- Unloading strategies
  - Tail suspension
  - external fixation
  - Hindlimb neurectomy/botox treatment
  - microgravity
  - bed-rest
- High-frequency strategies
  - Rat ulna
  - Sheep vibration platforms
  - Human

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But...

- How is this process regulated?
- How can this process leads to mechanically ‘optimized’ structures?
- How can cells at the scale of 10 microns produce 'optimal' structures at a scale 100-1000 times larger?

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