Whole Bone Modeling Using Bone Mineral Data
or
Bones Are Not Amorphous Blobs

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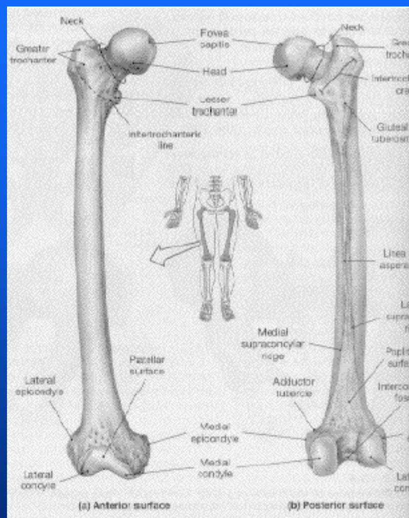
The Fundamental problem

- Bones get less dense as we age
- Old people with low density bones fracture easily
- Space-flight rapidly causes bones to get less dense
- Does space flight produce the same effects on bone as aging?



The Human Femur

Bone loss causes fragility of proximal (upper) end of femur

Fractures are major cause of death (indirect) and disability in elderly

Concern that space-flight might have similar consequences

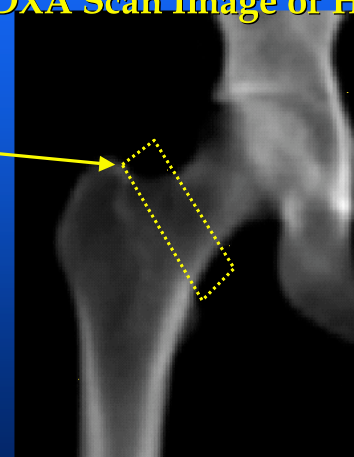
Bone Dynamics

- Bone is a dynamic tissue and is constantly being absorbed and rebuilt throughout life.
- Because bones get less dense with age physicians interpret this as an imbalance between resorption and formation.
- Old people with low density bones fracture easily so it is assumed that bone density is a measure of likelihood of fracture.

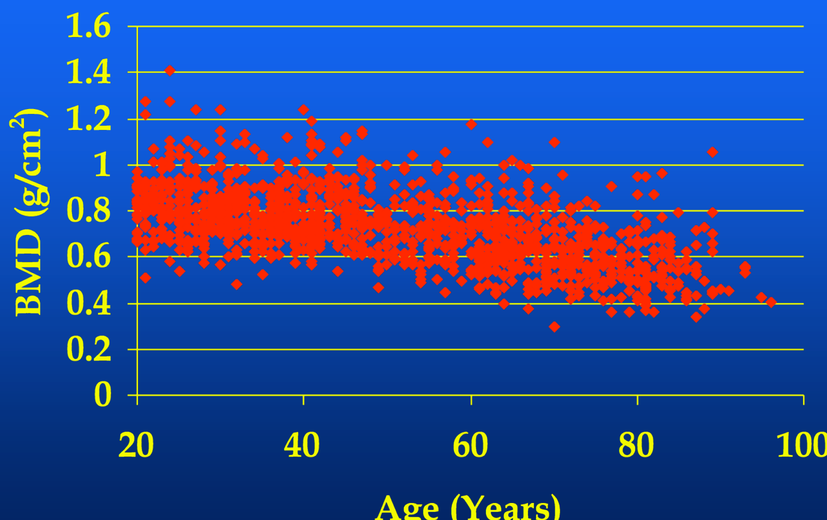
Current Bone “Density”Measurements

- Digital image with all soft tissues subtracted and only bone mineral present
- Pixel values represent areal mass in g/cm^2
- Areal mass is averaged over part of region containing bone (femoral neck region shown)
- Result approximates volumetric density and is called bone mineral density (BMD)
- BMD is (roughly) size independent thus permits comparison of dissimilar individuals

DXA Scan Image of Hip



Femoral Neck BMD



Learning Objectives for this Lecture

- Why do bones get less dense as we age?
  - Does this necessarily mean that bones are getting weaker?
- Why do astronauts lose bone?
  - Are their bones getting weaker?
- What factors are common between aging and microgravity and how do they differ?

Reduced Bone Strength is an Engineering Problem

Possible reasons:

1. The *material* is less able to withstand loading stresses

Or

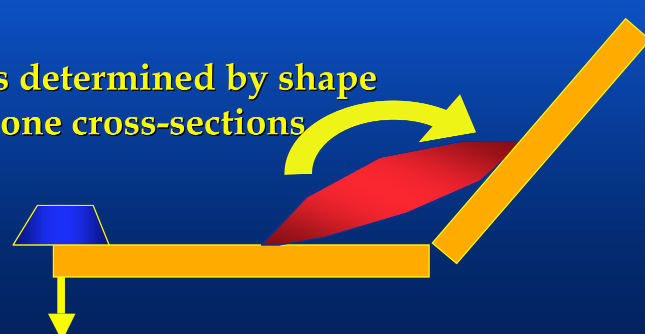
2. The *structure* is altered to increase loading stresses

Material vs. Structural Properties

- Evidence exists that bone material strength declines with age but effect disappears when corrected for porosity
- No good evidence that space-flight influences material properties
- (no reliable way to measure *in vivo* anyway)
- <u>Without question</u> bone *structure* changes with age and as a result of space-flight

An Engineering Perspective

- Long bones act as inefficient levers, with actions due to muscle forces
- Greatest mechanical stresses are in bending and torsion
- Bone density and BMD are <u>not</u> measures of strength.
- Structural strength is determined by shape and dimensions of bone cross-sections



Stress & Strain

- Local concentration of loading force usually in a cross-section
- Defined as force per unit area ($N/m^2 = Pa$)
- Depends on load and areal properties of cross-section

➡ Can be predicted from geometric measurements of cross-section

- Distortion of object shape and dimensions due to stress
- It is believed that <u>strain magnitude</u> (and frequency) are the stimuli for bone resorption and formation

At a given location, stress depends on:

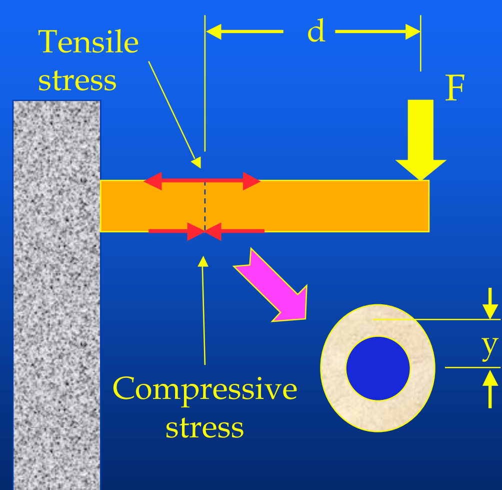
- Properties of cross-section
- Bending Moments (moment arm lengths and force magnitudes)

Bending stresses in cantilever beam

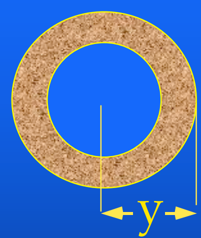
$$\sigma = \frac{My}{I}$$

I = Cross-sectional Moment of Inertia

M = F x d



Maximum Bending Stress

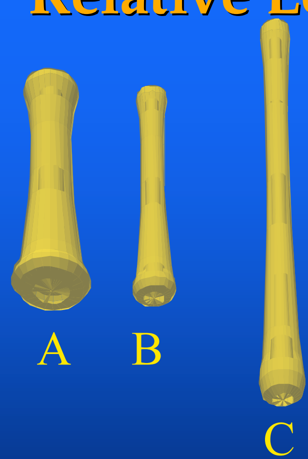


M = bending moment
I = cross-sectional moment of inertia
y = distance from centroid to surface
Z = section modulus

$$\sigma_{max} = \frac{My}{I} = \frac{M}{Z}$$

Section Modulus predicts maximum stress (σ) on subperiosteal (outer) surface

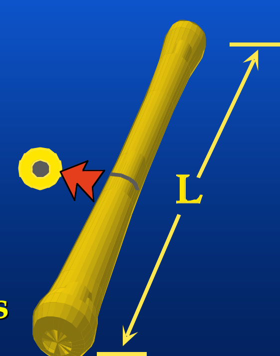
Relative Long Bone Strength



Intuitively
A>B>C

Strength in Bending

$$\text{Strength} = \frac{Z}{L}$$



Z = section modulus

Structural Changes in Adulthood

- Bone material is continually undergoing resorption and formation (remodeling).
- Bones adapt to changes in mechanical loading through life (modeling).

The Mechanism: Skeletal Loading and Strain Stimuli

- Stresses cause loaded bones to distort slightly
- These minute changes in shape or dimension are strains
- Strains are detected at the cellular level
- Bone is adapted to maintain a specific level and frequency of daily strain

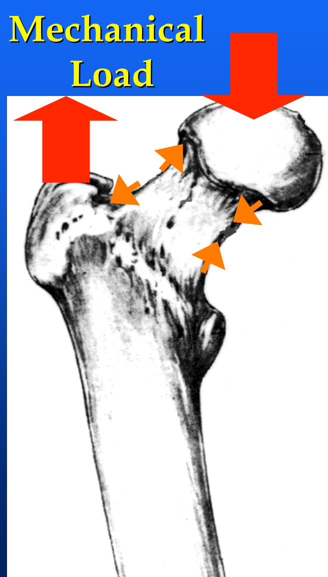
Frost's Mechanostat (or how Wolff's Law works)

- Bone *adapts* to keep average daily strains within a "normal" range.
- Strains above range cause new bone formation – stimulate bones to get stronger.
- Strains below range cause bone to be lost – stimulate bones to get weaker.

Bone *Remodeling*

- Occurs mainly on <u>internal</u> bone surfaces throughout life
- Rates are influenced by hormones and by skeletal loading
  - Increased loading *suppresses* remodeling
  - Decreased loading *stimulates* remodeling
- Skeletal loading is diminished in the elderly relative to when they were stronger and more active
- Space-flight removes skeletal loading from most of the body (except upper extremities)
- Expect remodeling on internal bone surfaces to be stimulated in both cases

Remodeling in presence of load



- Bone is temporarily removed from internal surfaces
- Bending strains increase on <u>external</u> surfaces
- New bone is added to external surfaces (modeling)
- Bone diameter increases to compensate internal bone loss

Effects of normal modeling on bone density

- Less bone needs to be added to external surface than removed from internal surface
- Bone gets less dense because it is bigger in diameter and because less bone needed to maintain section modulus

Bone Modeling and Changing Load

- New bone formation resulting from increased strain stimuli
- Because long bones are mainly loading in bending, maximum strains are on the *outer* surface
- New bone formation (modeling) occurs on the *outer* surface of bone

Adaptation to Increased Loading

- Strains throughout the bone should increase.
- Rates of remodeling should decrease
- May expect bone to get bigger and cortex thicker.
- Section modulus should increase
- Density may or may not increase depending on details of changes.

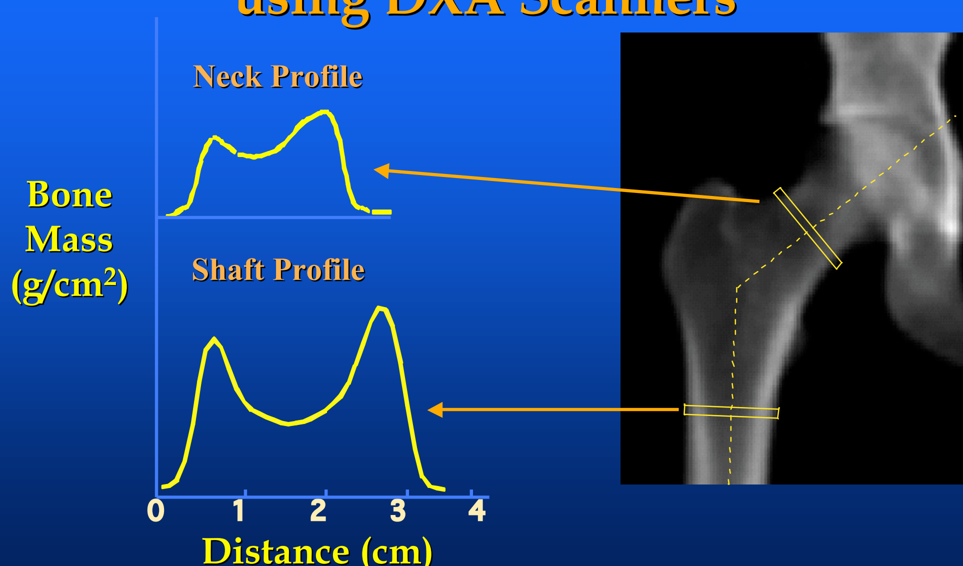
Adaptation to Decreased Load

- Strains decrease through bone
- Remodeling increases from internal surfaces
- Bone should be lost from internal surfaces and cortices should get thinner
- Both section modulus and density should decrease

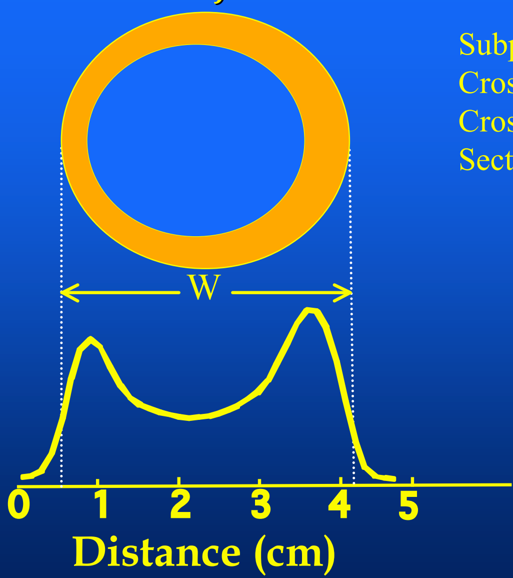
Space-Flight Effects

- H_o: In the absence of loading (except that due to exercise countermeasures)
  - Expect increased rates of internal bone loss
  - Expect no modeling on outer surface
  - Section modulus and density should decrease

Geometry from mass profiles using DXA Scanners



Mass Projection of Shaft Cross-Section



Subperiosteal width
Cross-sectional area
Cross-sectional moment of inertia
Section Modulus

$$I_x = \int (x - x_c) dA$$

$$A = \int dA$$

Properties measured from bone mass profiles

At all cross-sectional regions:

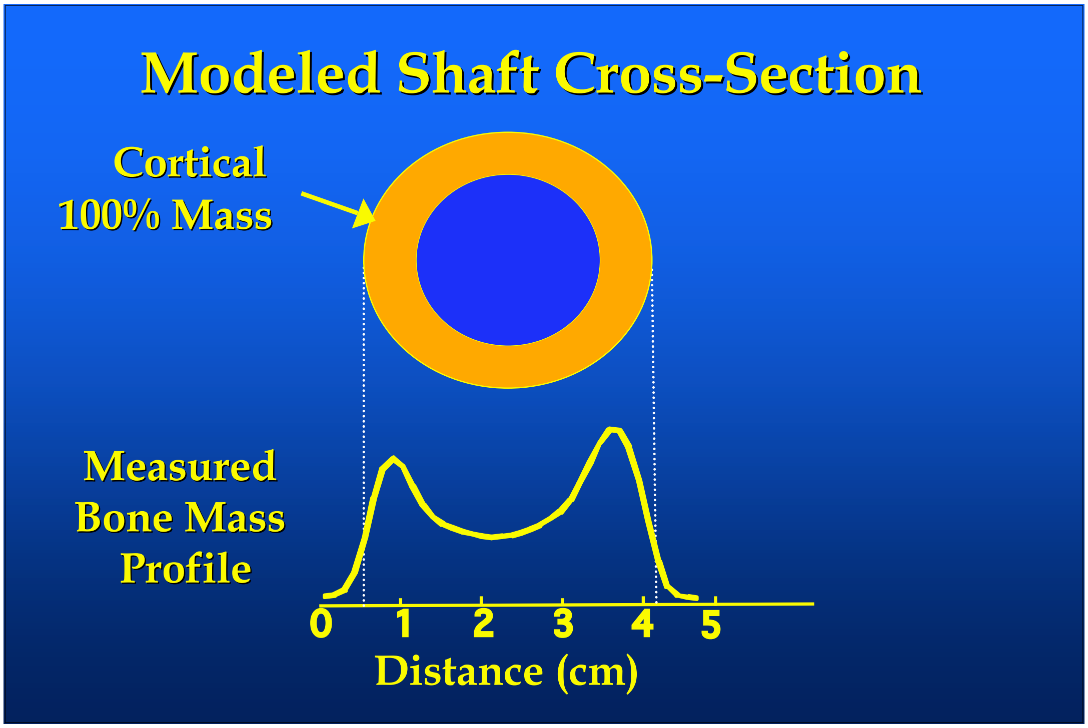
- BMD
- Subperiosteal Width
- Cross-Sectional Area (cortical bone equivalent)
- Section Modulus

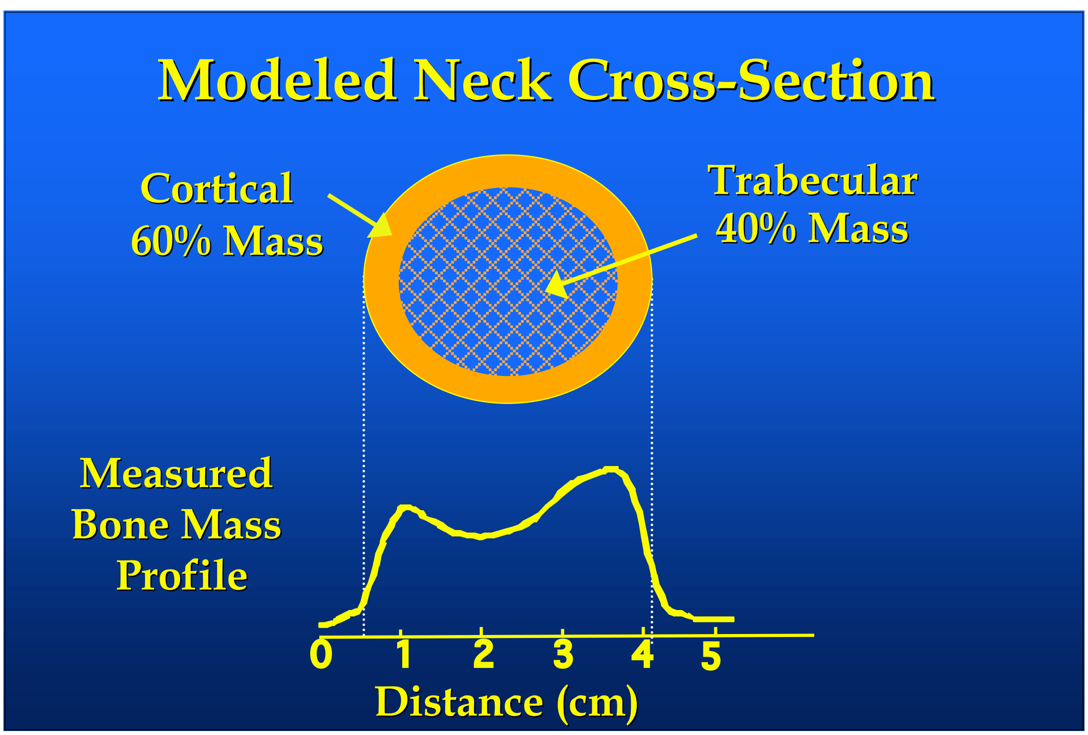
Need for a model of the cross-section

- Measured properties don't completely describe the cross-section.
- In absence of complete data (picture of cross-section) we need a model.
- Model assumes reasonable shape and has geometry measured from DXA data.
- Validity depends on how well model corresponds to actual cross-section.

Properties modeled

- Shape of cross-section
- Proportion of trabecular and cortical bone.
- Endocortical diameter
- Cortical thicknesses


Modeled Shaft Cross-Section
Cortical
100% Mass
Measured
Bone Mass
Profile
0 1 2 3 4 5
Distance (cm)


Modeled Neck Cross-Section
Cortical
60% Mass
Trabecular
40% Mass
Measured
Bone Mass
Profile
0 1 2 3 4 5
Distance (cm)

Adaptive Modeling vs. BMD Loss

- BMD measurements tell us that we lose bone throughout adult life.
- Bone loss should dynamically alter levels of mechanical strain in the skeleton.
- With consistent skeletal loading our bones should adapt and should not get weaker.
- This adaptive modeling should be evident in the bone geometry (not necessarily in BMD).

Some Examples:

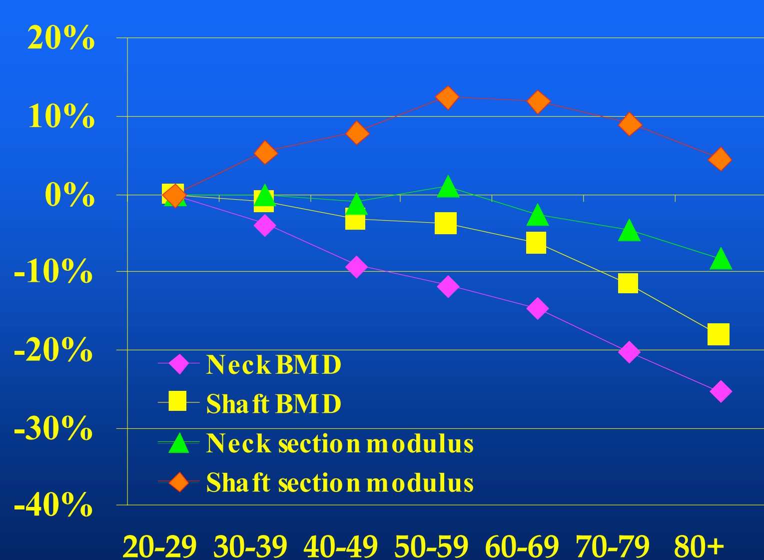
Study Populations:

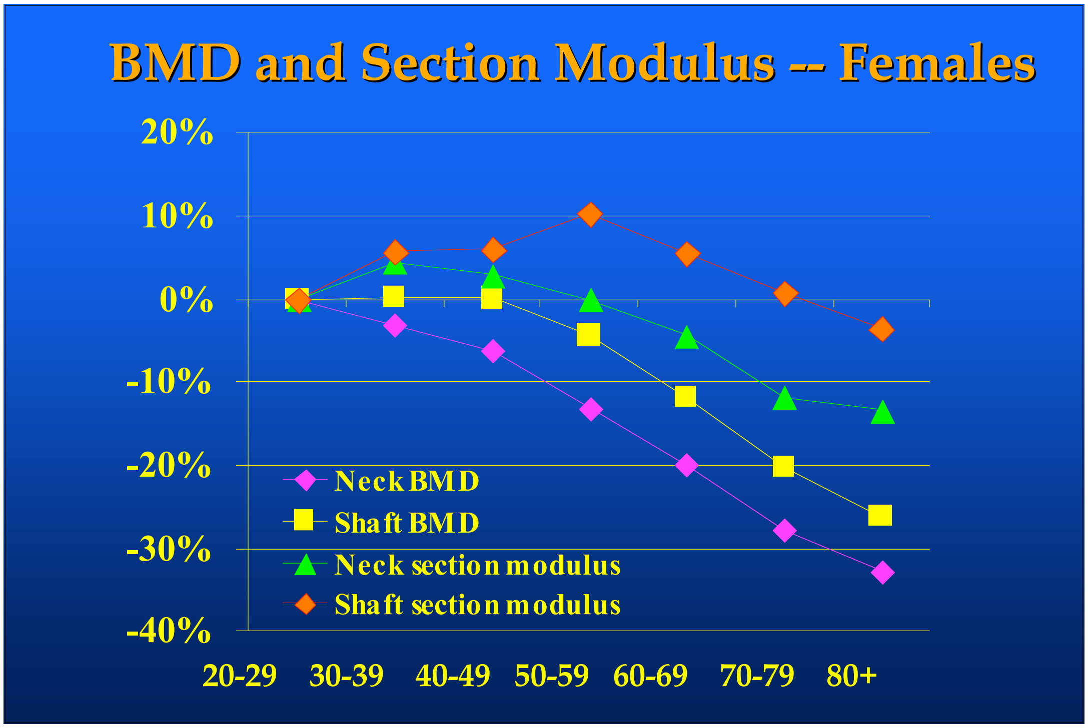
- National Health and Nutrition Examination Survey (NHANES III)
- Study of Osteoporotic Fractures (SOF)
- Russian Cosmonauts on Mir Space Station

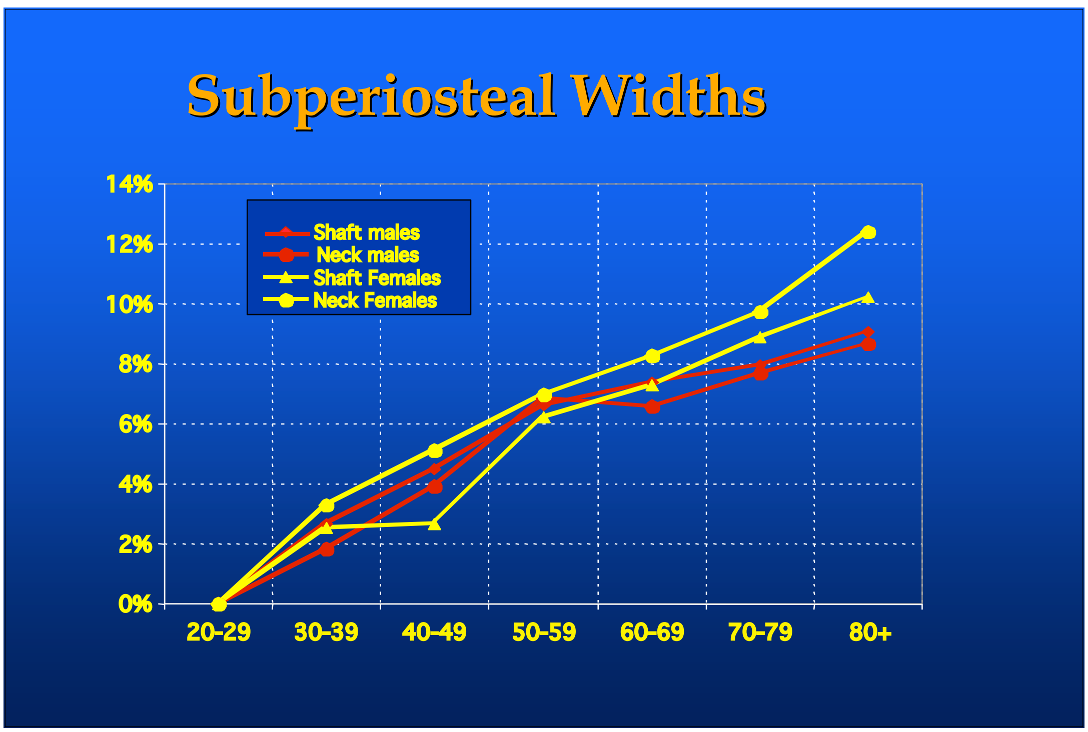
NHANES III: A structural view of normal aging in the hip

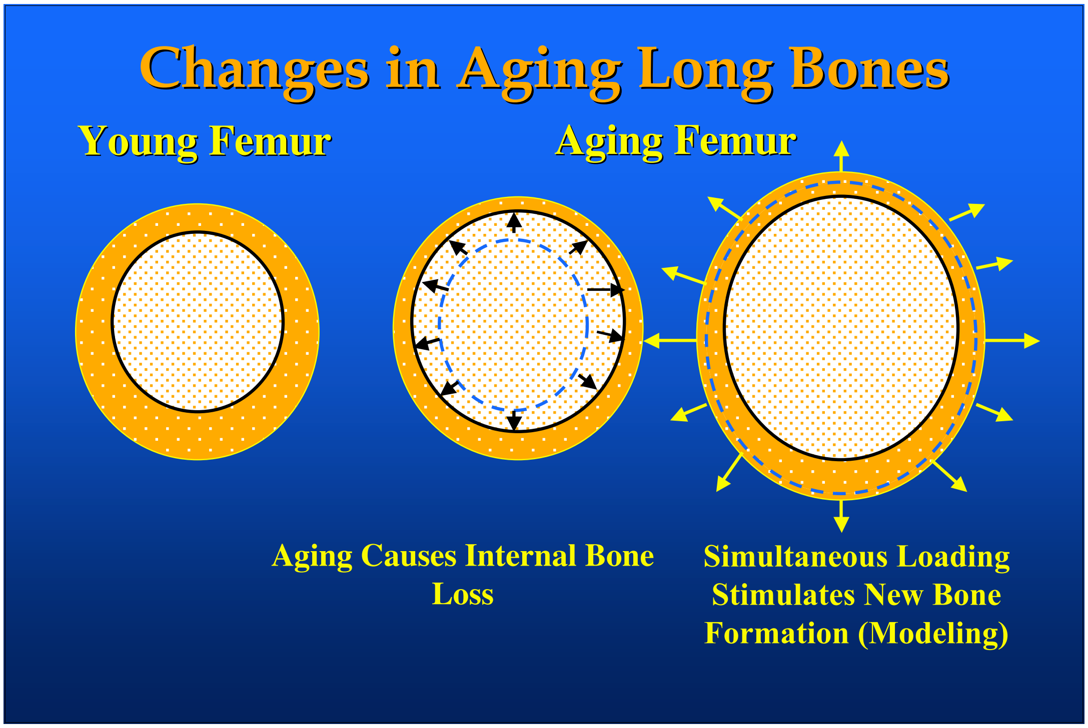
- Cross-sectional sample of US population >14,000 hip DXA scans.
- White sub-sample including 2719 males and 2904 females age 20-90+.
- Data courtesy of Dr. Anne Looker, US National Center for Health Statistics, and Dr. Heinz Wahner, Mayo Clinic

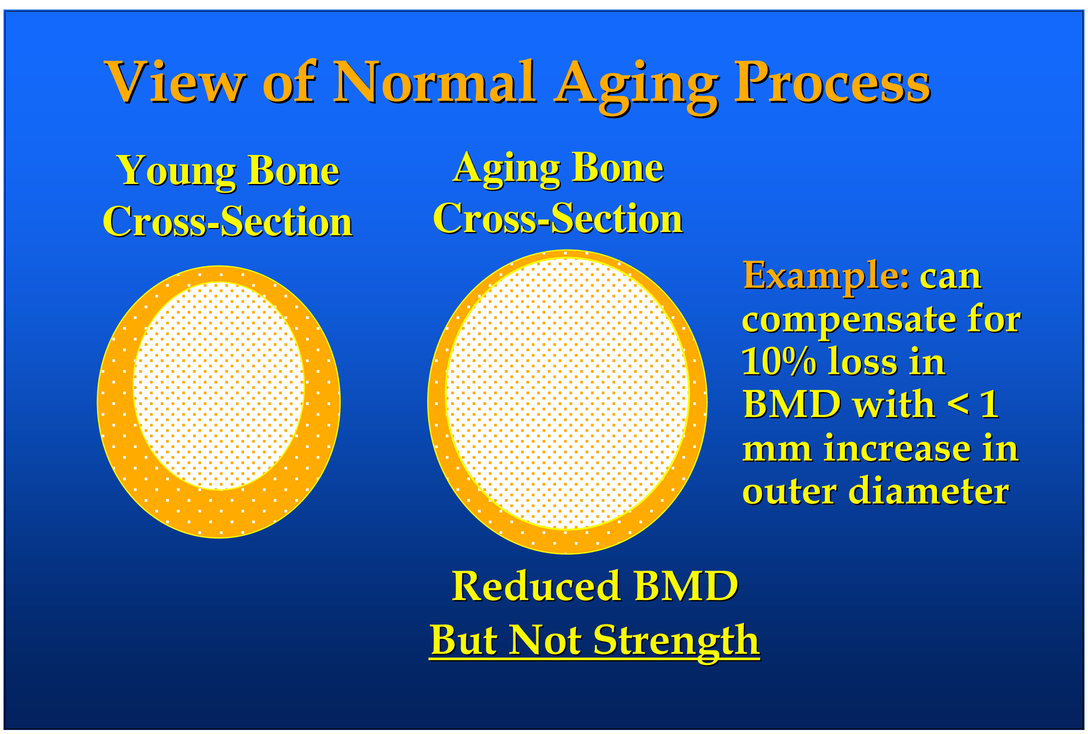
BMD and Section Modulus -- Males




BMD and Section Modulus -- Females
20%
10%
0%
-10%
-20%
-30%
-40%
Neck BMD
Shaft BMD
Neck section modulus
Shaft section modulus
20-29
30-39
40-49
50-59
60-69
70-79
80+


Subperiosteal Widths
14%
12%
10%
8%
6%
4%
2%
0%
Shaft males
Neck males
Shaft Females
Neck Females
20-29
30-39
40-49
50-59
60-69
70-79
80+


Changes in Aging Long Bones
Young Femur
Aging Femur
Aging Causes Internal Bone Loss
Simultaneous Loading Stimulates New Bone Formation (Modeling)


View of Normal Aging Process
Young Bone Cross-Section
Aging Bone Cross-Section
Example: can compensate for 10% loss in BMD with < 1 mm increase in outer diameter
Reduced BMD
But Not Strength

Frost's Mechanostat Implies:

- If skeletal loading is static:
  Bone strength should be maintained
- If skeletal loading increases:
  Bone strength should improve
- If skeletal loading decreases:
  Bone strength should decline

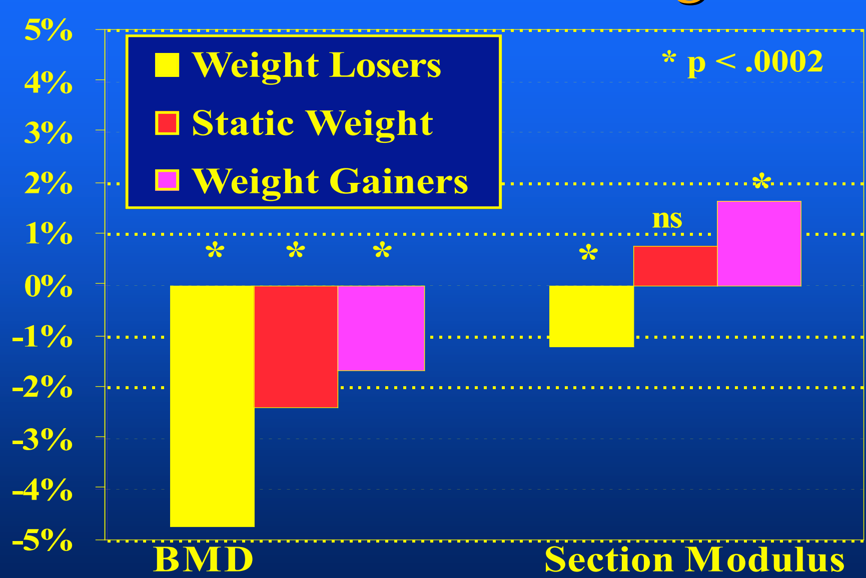
The Classic Hip Fracture Case

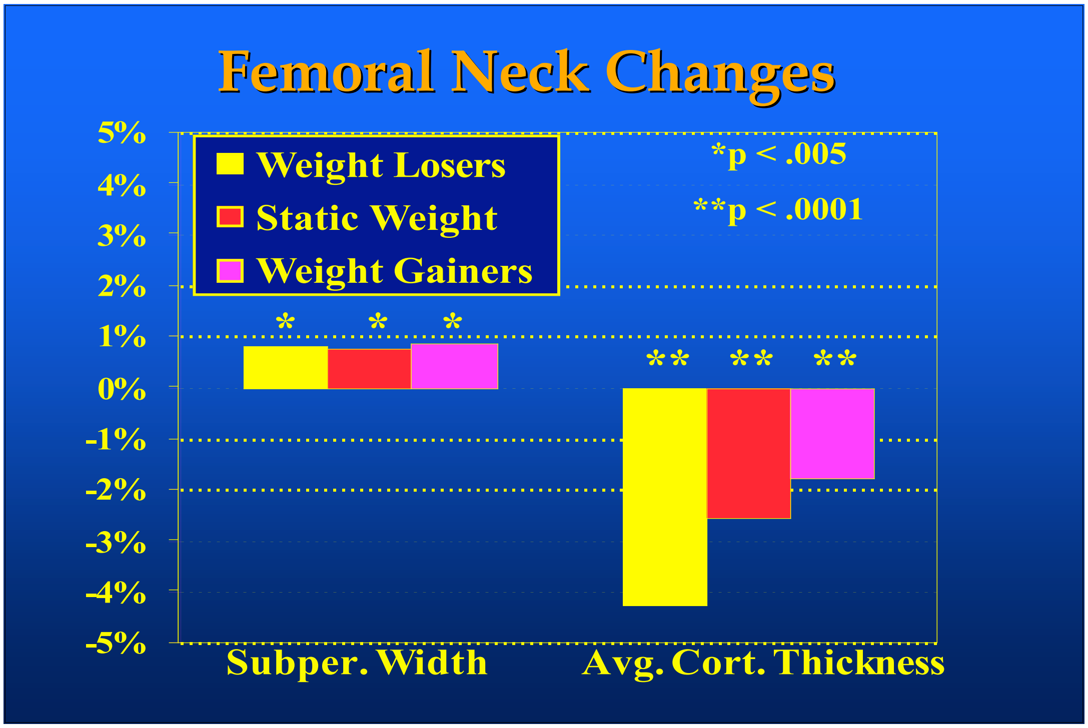
- An elderly woman who is:
  - Physically inactive
  - Low body weight
  - Reduced muscle mass
- Her skeletal loading is considerably reduced from levels when she was younger and more active.

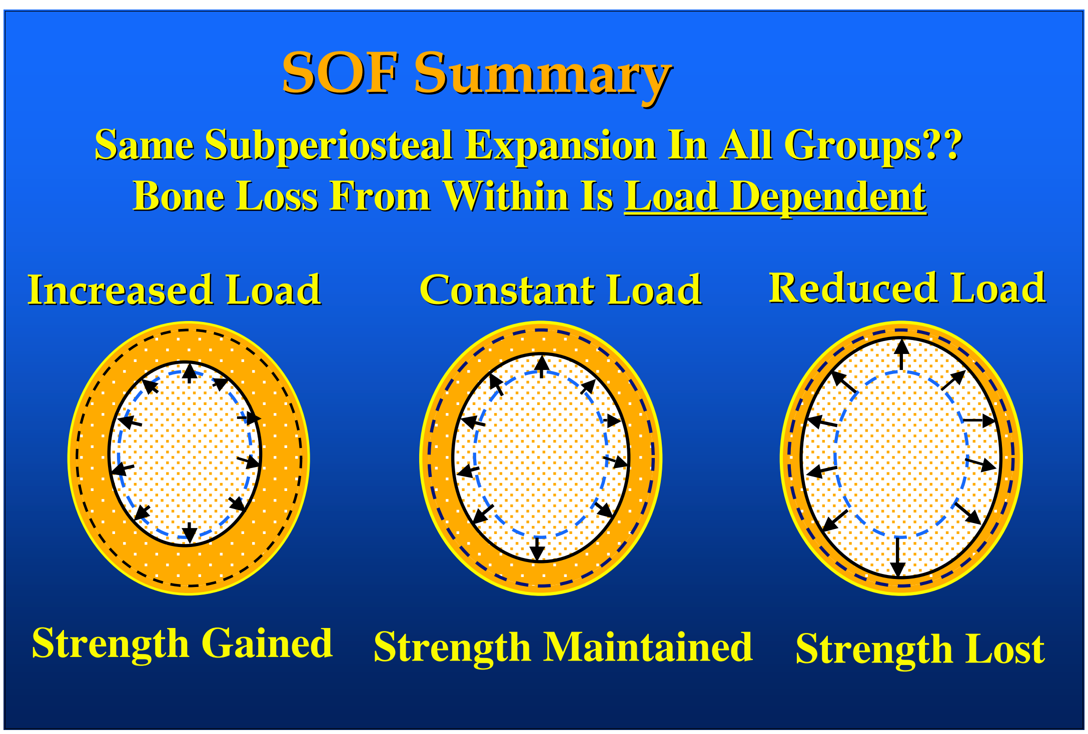
SOF: The Loading Hypothesis

- Longitudinal sample of white post-menopausal women ages > 65 at entry.
- Two hip scans averaging 3.6 years apart on 1876 subjects.
- Subjects categorized by weight change:
  - Static ($\pm$ 1 kg of base-line) N = 479
  - Gainers N = 654
  - Losers N = 743
- Data Courtesy of Drs. Steve Cummings and Katie Stone, University of California at San Francisco

Femoral Neck Changes




Femoral Neck Changes
5%
4%
3%
2%
1%
0%
-1%
-2%
-3%
-4%
-5%
Weight Losers
Static Weight
Weight Gainers
*p < .005
**p < .0001
*
*
*
**
**
**
Subper. Width
Avg. Cort. Thickness


SOF Summary
Same Subperiosteal Expansion In All Groups??
Bone Loss From Within Is Load Dependent
Increased Load
Constant Load
Reduced Load
Strength Gained
Strength Maintained
Strength Lost

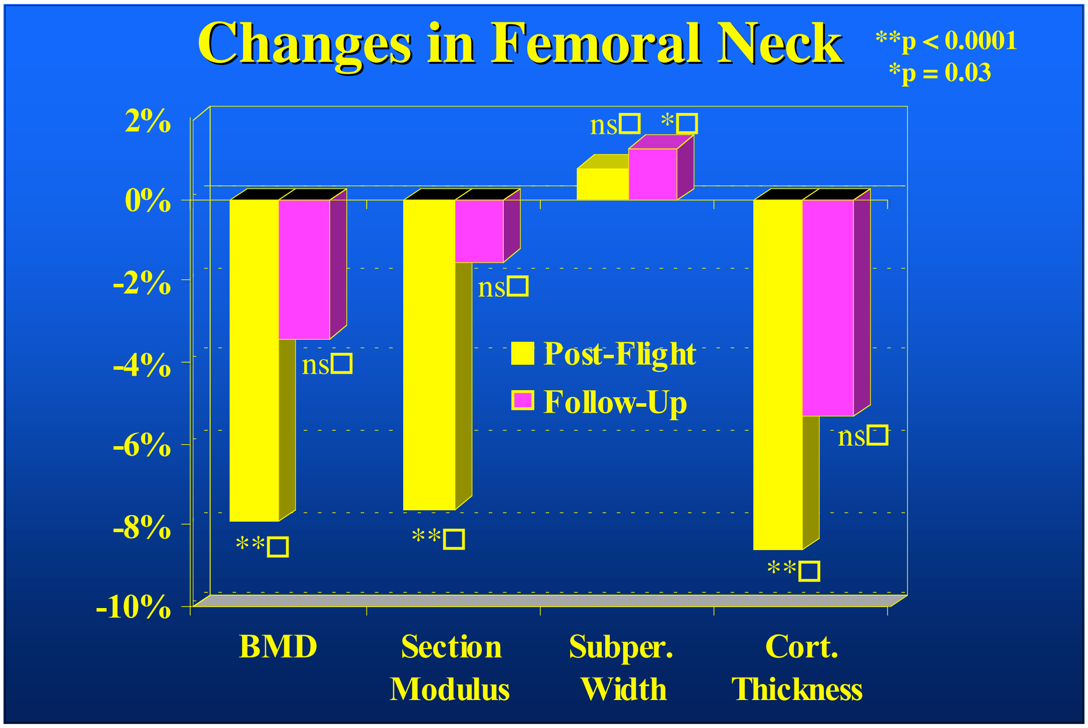
What If Loading Is Eliminated? (i.e., H_o for Space-Flight)

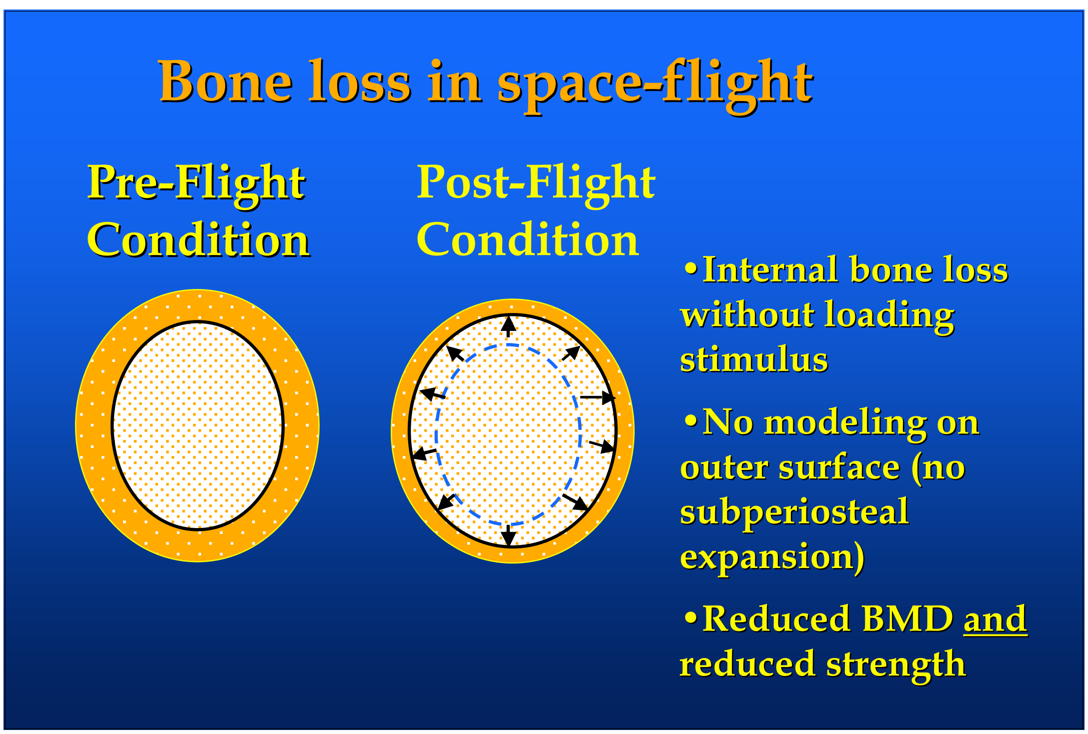
Since loading stimulates subperiosteal modeling and controls rate internal remodeling (bone loss)

- Accelerated internal bone loss
- No subperiosteal expansion
- Both BMD and bone strength should be reduced

Effects of Space-Flight

- Pre and post flight hip data on 19 Russian Cosmonauts.
- Average of 178 (126-312) days on Mir Space Station.
- Follow-up data on 8 Cosmonauts (~1.5 yr post flight)
- Data courtesy of Drs. Adrian Leblanc, Linda Shackelford, Victor Schneider and V. Oganov.


Changes in Femoral Neck
**p < 0.0001
*p = 0.03
2%
0%
-2%
-4%
-6%
-8%
-10%
ns
*
ns
ns
ns
**
**
**
Post-Flight
Follow-Up
BMD
Section Modulus
Subper. Width
Cort. Thickness

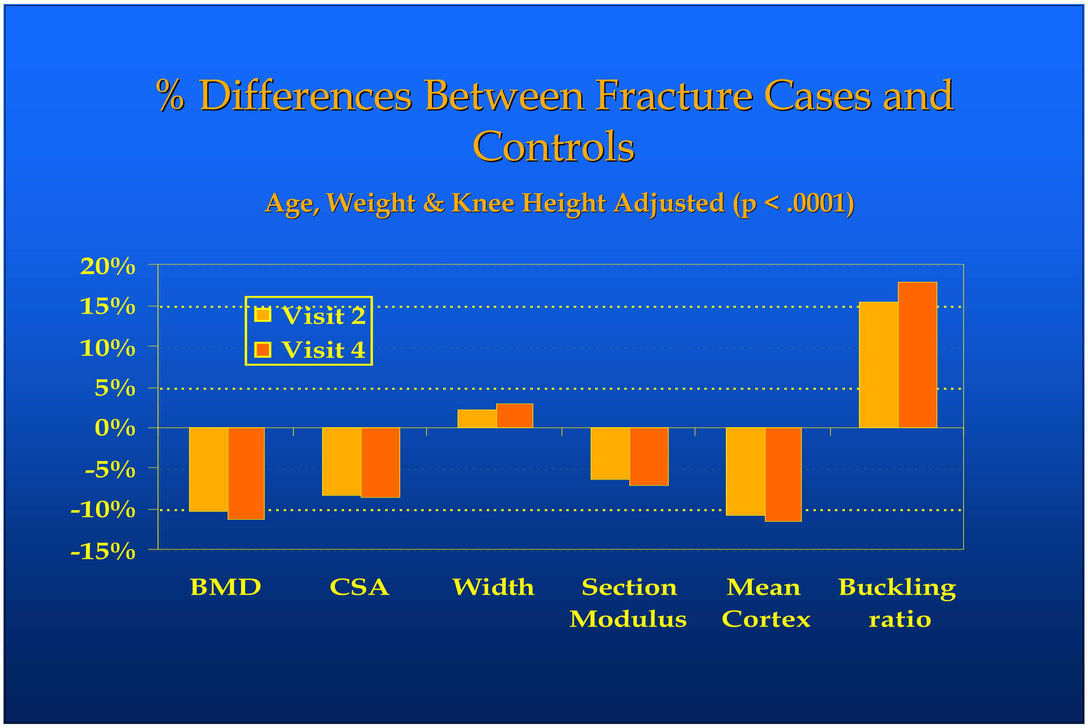

Bone loss in space-flight
Pre-Flight Condition
Post-Flight Condition
•Internal bone loss without loading stimulus
•No modeling on outer surface (no subperiosteal expansion)
•Reduced BMD and reduced strength

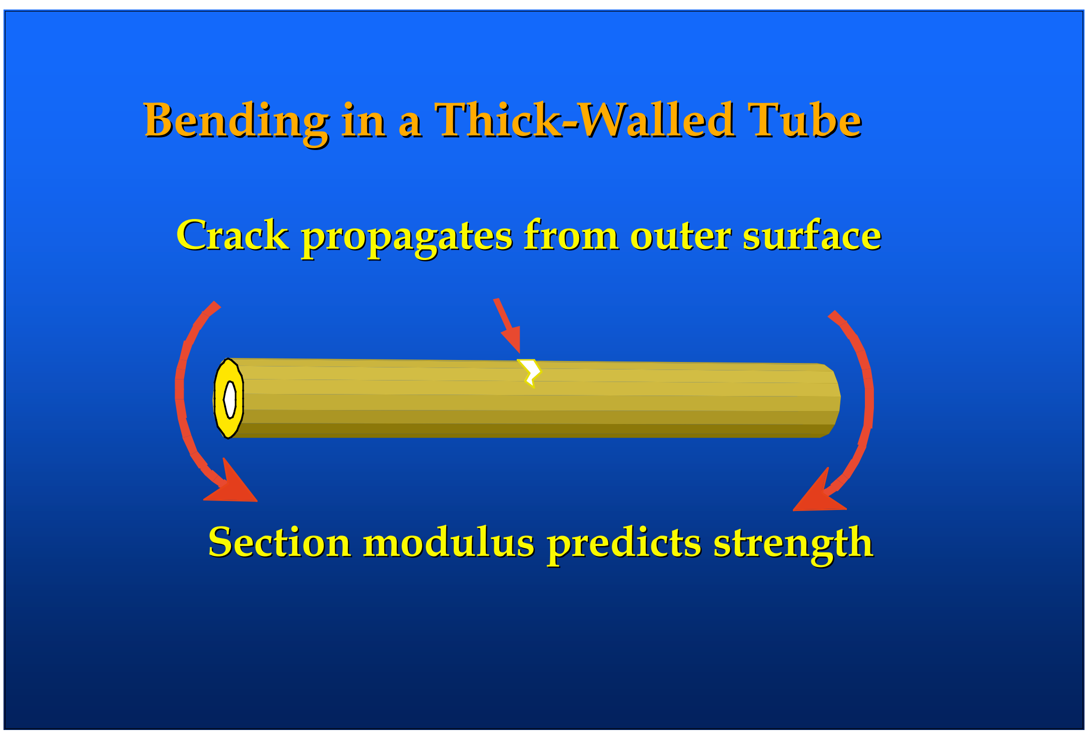
So What do we know about bone loss?

- Bones adapt to loading conditions, getting stronger or weaker as load demands change
- Loss of bone doesn't necessarily mean loss of strength -- bones get more mechanically efficient as we age
- The homeostatic endpoint that the body strives to maintain is the section modulus
- Absence of load (space flight) removes stimulus for adaptive modeling, bones get weaker as bone is lost

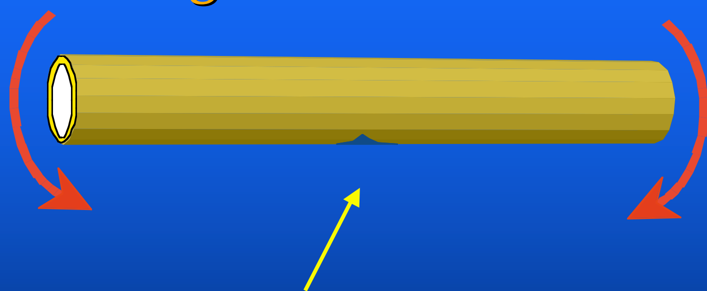
Differences Between Fracture Cases and Controls

- 121 hip fracture cases compared to 4082 controls
- Results adjusted for age, knee-height and weight


% Differences Between Fracture Cases and Controls
Age, Weight & Knee Height Adjusted (p < .0001)
20%
15%
10%
5%
0%
-5%
-10%
-15%
Visit 2
Visit 4
BMD
CSA
Width
Section Modulus
Mean Cortex
Buckling ratio


Bending in a Thick-Walled Tube
Crack propagates from outer surface
Section modulus predicts strength

Bending in a Thin-Walled Tube

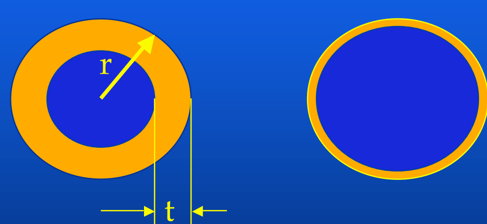


Folds inward on inner surface
(crumpling or local buckling)

<u>Section Modulus Overestimates Strength</u>

Defining Thin-Walled tubes

Buckling Ratio = $\frac{r}{t}$



Buckling considered for ratios > 10 in hollow tubes
For trabecular filled volumes (femoral neck) critical value unknown but probably higher

Local Buckling In the Femoral Neck

- How thin does the cortex need to be?
  - At visit 4 after adjustment for age and body size, cases averaged 24.3 vs 20.6 in controls (18% higher).

Overall Conclusions:

- Depending on skeletal loading, geometric changes may compensate for net bone loss.
- Structural adaptation appears to be the case for most post-menopausal women – indeed most do not fracture.
- Progression toward fragility may actually be a <u>consequence</u> of the adaptation to reduced loading as follows:

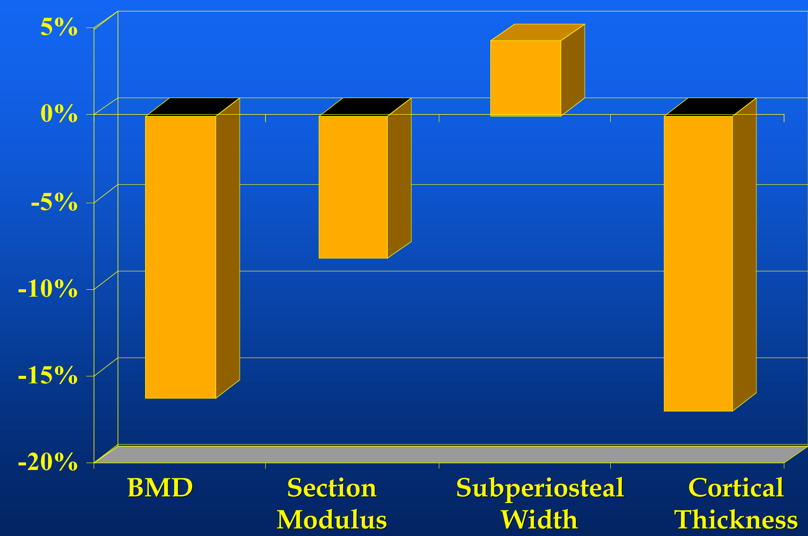
But what about elderly hip fractures?

- Why do they fracture if bone is adapting to their loading?
- One would expect that bone have some margin for overload.
- Could bones fail in other than pure bending?

Evidence from Hip Fracture Cases

- 57 hip fracture cases compared to 125 random controls
- Results adjusted for age
- With and without adjustment for weight (Cases were lighter on average)
- SOF data courtesy of Dr. Steven Cummings, analysis by Dr. Katie Stone

SOF Hip Fracture Cases Relative to Random Controls

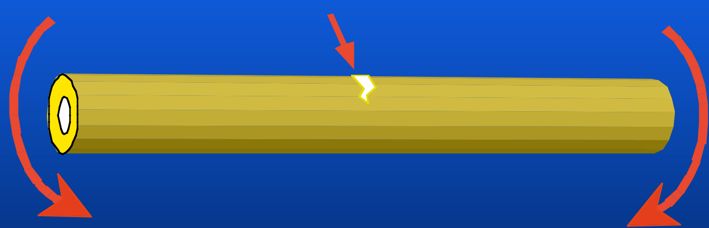


Progress Toward Fragility

- Skeletal loading is reduced
- Mechanostat accelerates
  - Endocortical resorption
  - Subperiosteal expansion?
- Section modulus adapts to reduced load but
- Cortex thins to point where failure occurs not in pure bending (perhaps in local buckling??)

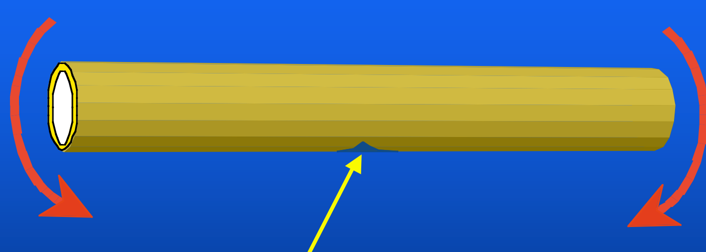
Bending in a Thick-Walled Tube

Crack propagates from outer surface



Section modulus predicts strength

Bending in a Thin-Walled Tube



Folds inward on inner surface
(crumpling or local buckling)

<u>Section Modulus Overestimates Strength</u>

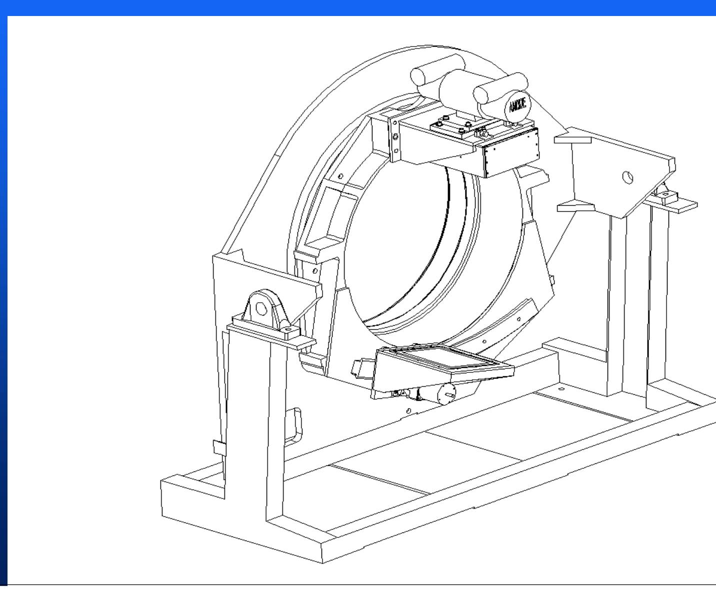
Questions About Local Buckling

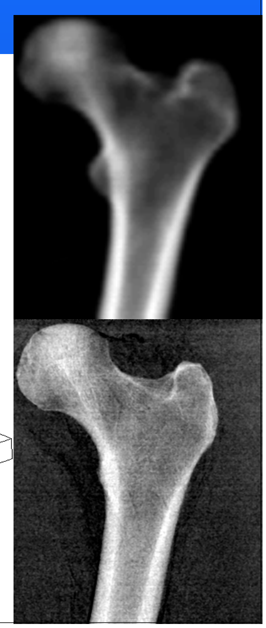
- When does this transition occur?
- How thin does the cortex need to be?
- What is the role of trabecular bone in prevention of local buckling?
- Can this effect be measured with DXA data?

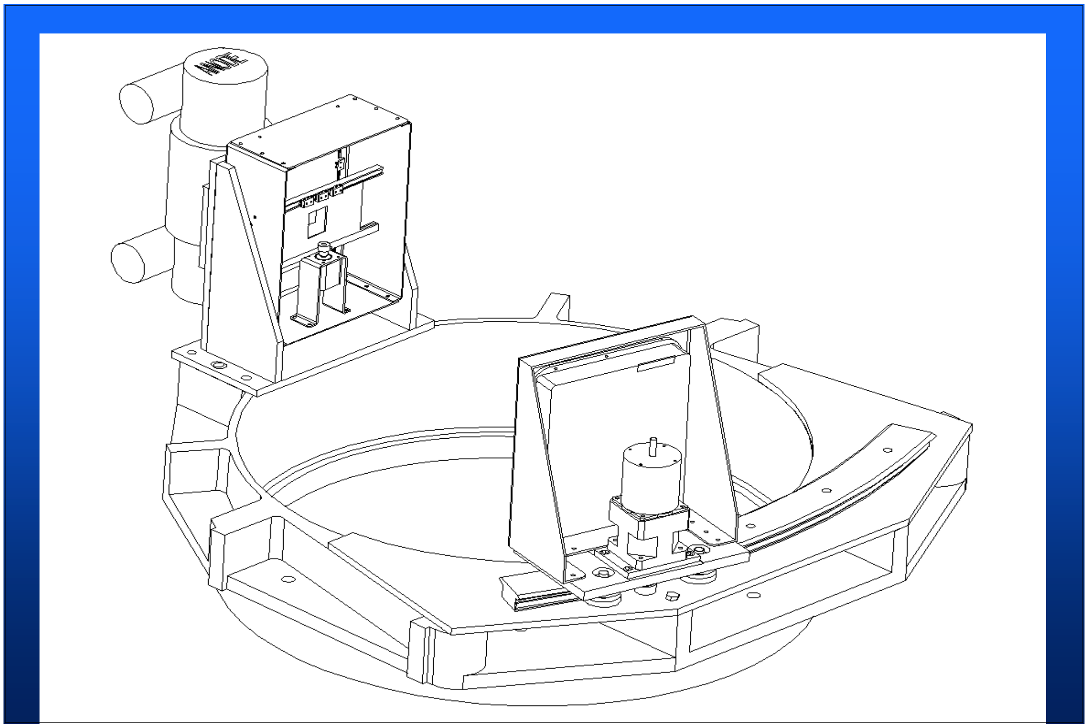
Caveats

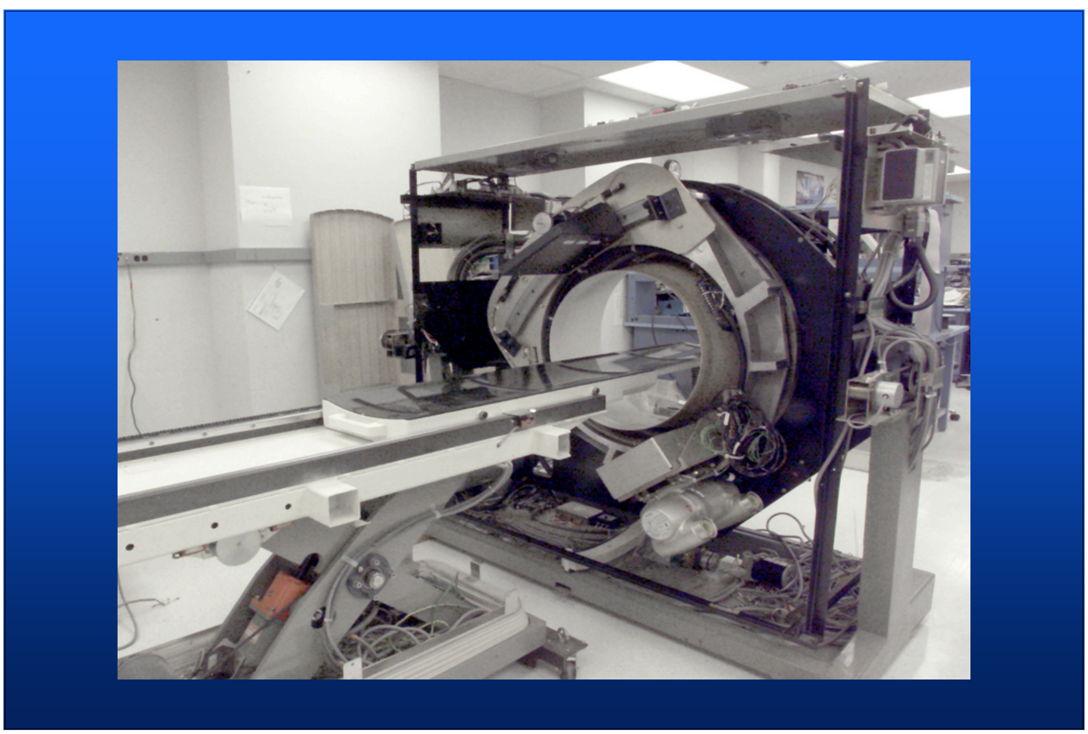
- Structural geometry can be measured with current DXA scanners but not very well
- Small changes in dimensions are structurally important, but can't be reliably measured with current DXA scanners

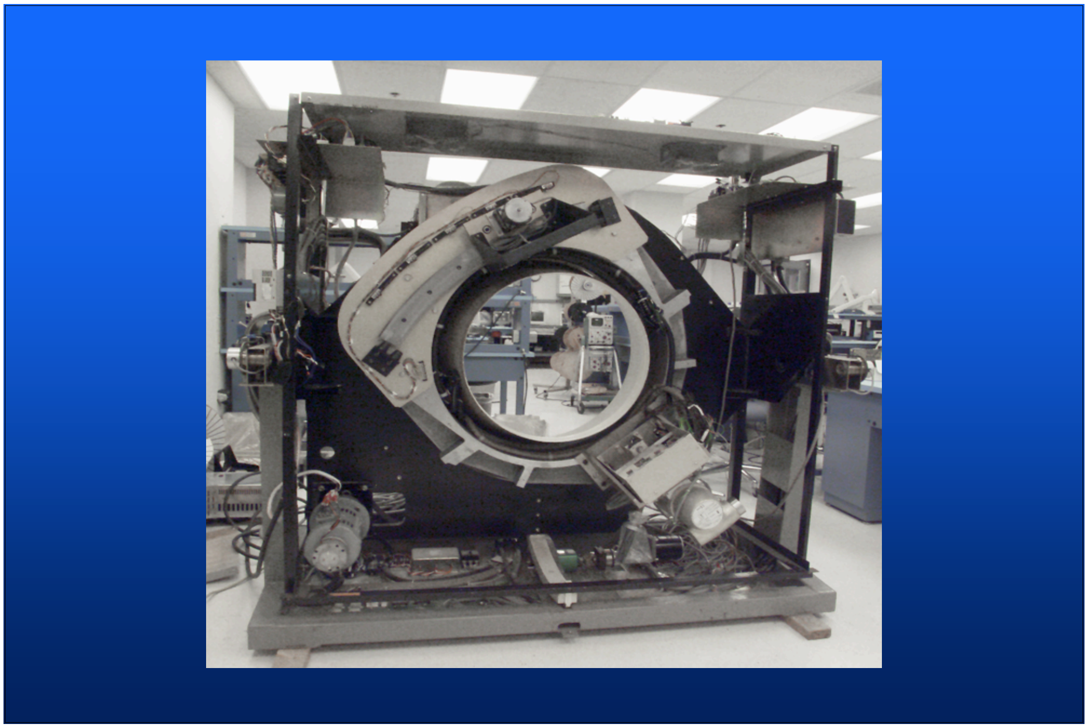
DXA Clinical Prototype Under Construction

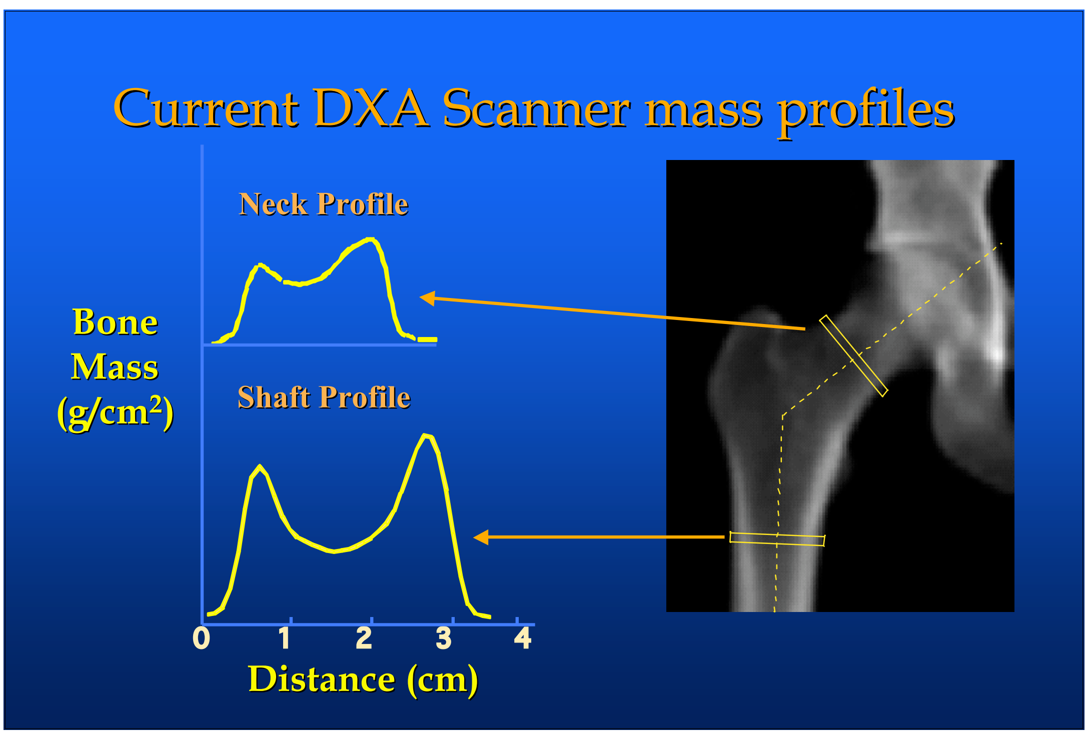


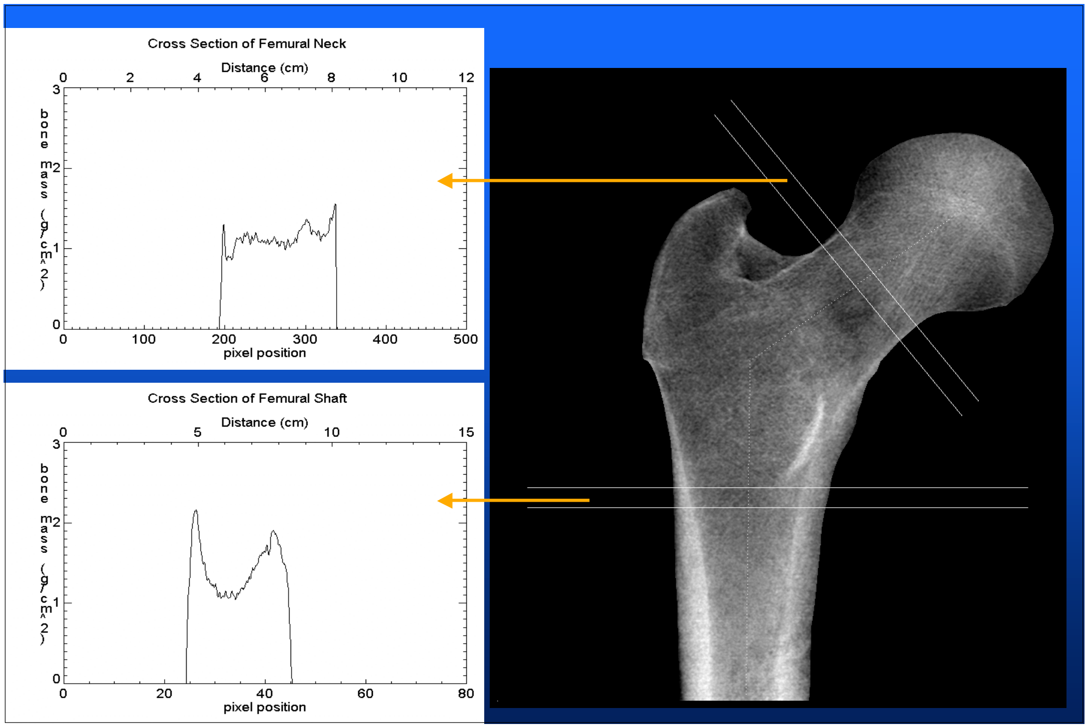




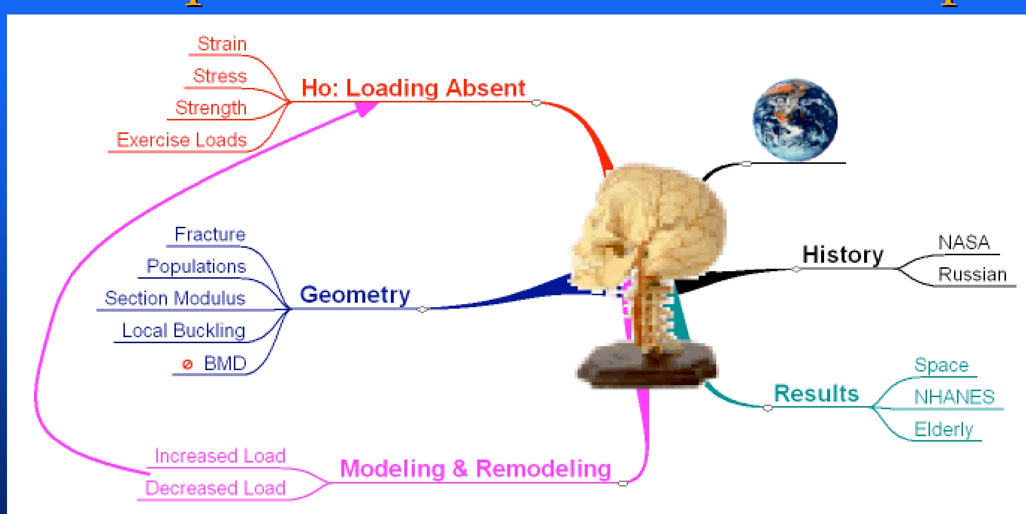





Current DXA Scanner mass profiles
Neck Profile
Shaft Profile
Bone Mass (g/cm²)
0 1 2 3 4
Distance (cm)



Completion of our Bone Mind Map



Homework

- Much we don’t know but you can speculate on, based on results of simple simulations
- Simulations can employ known effects on bone from measured data

Using Simulations of Bone Adaptation

- Simulate femoral shaft as a right cylindrical hollow tube subjected to bending:
  - Changing rates of remodeling
  - Changing load
  - Changing both load and rates of remodeling
- Examine effects on BMD, section modulus and bone diameter

Assumptions:

- Moment arms are constant in adulthood, changes in cross-sectional dimensions and load magnitudes only
- Section modulus changes linearly with load magnitude
- Remodeling changes inner radius of tubular bone (can increase or decrease we will assume only increase).

Example 1:

- Remodeling with consistent skeletal loading
- Remodeling removes bone from inner surface (increases inner radius) at a certain rate
- What increase in outer radius will result in a constant section modulus?

Geometry of hollow tube

$$I = \frac{\pi}{4}(r_o^4 - r_i^4)$$

$$A = \pi(r_o^2 - r_i^2)$$

$$BMD = \frac{A\rho_m}{2r_o}$$

ρ_m = effective mineral density of solid bone (use~1.05 g/cm^3)

Starting dimensions

For young 25 y/o adult male
r_o= 1.70 cm

r_i= 1.20 cm

For young 25 y/o adult female
r_o= 1.40 cm

r_i= 0.90 cm

Remodeling

- Assume r_i Increases at constant rate
- Measured data suggest increase of .004 cm/y in males