Bone is a Dynamic Organ

Osteoblasts

Osteoid

Osteoporosis
SKELETAL PHYSIOLOGY:
Critical Phases

• Skeletal Growth
  – Prenatal to Adolescence
  – Modeling and remodeling
  – Early and Rapid linear growth which then slows before increasing with adolescence

• Peak Bone Acquisition
  – Ages 12-18
  – Gender and compartment specific!!!!
  – Strong genetic determinants
  – Phased with linear growth

• Bone Maintenance
  – Ages 20-50: Remodeling 10% of the skeleton/yr

• Bone Loss
  – Gender and compartment specific
  – Genetic determinants may play a role
Cellular Complexity in the Bone Marrow N
Bone Remodeling Process

Osteoclasts

Lining Cells

Bone

Resorption Cavities

Osteoblasts

Osteoid

Mineralized Bone

Lining Cells
“Clastokines”

- Direct effects on osteoblasts?
- Indirect effects via the osteoclasts and coupling?

Image courtesy of R. Baron
The CNS Regulates Bone Turnover

ObR positive neurons

leptin

brainstem

5-HT

Htr1c positive neurons

VMH

SNS

adipose tissue

Bone

Osteoclast

β2AR

NE

RANKL

Osteoblast
Bone is Connected to Metabolic Homeostasis

Common Circuits:

- SNS

Bone

- BDNF

BAT

- adiponectin

"Beige or Bright"

Sarcopenia

- Pgc1a

- irisin

Osteopenia

- Wnt10b

- Igfbp2

- Cthrc1

BAT dystrophy

Lipoatrophy

unOC
The Beta Cell, Osteoblast-Osteoclast Connection

osteocalcin

beta cells

insulin

RANKL:OPG

osteoclast

osteoblast

OPG

InsR

bone matrix

Karsenty revised
Definition of Osteoporosis From BMD

<table>
<thead>
<tr>
<th>Classification</th>
<th>T-score</th>
</tr>
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<tbody>
<tr>
<td>Normal</td>
<td>-1.0 or greater</td>
</tr>
<tr>
<td>Low Bone Mass (Osteopenia)</td>
<td>Between -1.0 and -2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>-2.5 and below</td>
</tr>
<tr>
<td>Severe Osteoporosis</td>
<td>-2.5 and below with history of fragility fracture</td>
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WHO Study Group 1994
PBM is a determinant of lifetime BMD

BMD is the major determinant of future fracture

Multiple factors contribute to PBM

Genetic determinants are critical but are modifiable by environmental factors
Energy Demands in The Niche: 2 million RBCs per sec
The Marrow is Far From Inert

2,000,000 RBCs/sec
Leave the marrow

Fig. 2: The skeleton contributes to dietary fat clearance
12 weeks-old male C57BL/6J wild-type mice received a lipid gavage (olive oil) with tracer amounts of $^3$H-triolein. Fatty acid organ uptake 2 h after gavage was determined by scintillation counting. (A) Liver and brown adipose tissue (BAT) display the highest specific uptake of all organs analyzed. Parts of the skeleton (indicated in red) display specific uptake comparable to white adipose tissues, the major specialized lipid storage organ. epiWAT: epididymal white
MSC Plasticity in the Marrow Niche:

Marrow Niche

mesenchymal stromal cell (mMSC)

Prx1

Dlx5, Msx1, Runx2,

Zfps, C/EBPs, PPAR-γ,

Pre-adipocyte

Pref-1

osteoblast

osteonectin (Ocn)

adipocyte

Fabp4, Plipin, Adipq

Hypothesis: Cell Plasticity is fuel dependent
Anorexia Nervosa: A Classic Case of Limited Fuel Availability

a marrow lineage shift and skeletal fragility

Bredella et al JCEM, 2009
Osteoporosis- Obesity of Bone

Fig. 1: The skeleton is a lipid storage organ.
Environmental scanning electron microscopy (ESEM) scan from inside a mouse distal tibia. Bone marrow adipocytes appear as large, light spheres. It has long been recognized that the skeleton is a lipid storage organ: “Good news puts fat on the bones” (The Bible: Proverbs 15:30) bar: 0.25 mm
Summary

- Bone mass is determined by multiple genetic and environmental factors
- Bone remodeling is a dynamic process and is fuel dependent
- The fate of osteoblasts and adipocytes in the marrow help determine peak bone mass and bone loss
- Nutrient and environmental determinants play a major epigenetic role