Regulation of the skeletal mass through the life span
Functions of the skeletal system

- Mechanical protection
  - skull
- Movement
  - leverage for muscles
- Mineral metabolism
  - calcium store
- Erythropoiesis
  - red blood cells in bone marrow
Changes in the skeletal system with age

- Early development
  - fetal, infancy, childhood:
  - statural skeletal growth

- Midlife
  - hypertrophic growth
  - reparative growth

- Old age
  - hypertrophic growth
  - impaired reparative growth
Skeletal growth by elongation and change in shape

Growth during fetal development, infancy, childhood and adolescence

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Early development: endochondral bone growth

- Endochondral growth and ossification
  - long bones
- Intramembranous ossification
  - flat bones
- Growth process
  - cartilage bone model formed
  - chondroblasts proliferate
  - create rough bone shape
Early development: endochondral bone growth

- Endochondral growth and ossification
  - chondrocytes differentiate
  - secrete matrix
    - proteoglycans
  - polar regions grow more actively
  - cells hypertrophy in central region
  - cells express alkaline phosphatase
  - mineral matrix kills cells
Early development: endochondral bone growth

- Endochondral growth and ossification
  - space with dead cells invaded by blood vessels
  - debris cleaned up by osteoclasts
  - invasion by osteoblasts
  - bone formation
    - diaphysis
    - epiphysis
Epiphyseal growth zone

- Zone of resting cartilage (geminative layer)
- Proliferative zone
- Hypertrophic zone
  - dying cartilage
  - invasion of blood vessels
  - osteoclast clean-up
- Mineralization by osteoblasts
What is needed for early bone growth?

- Hormonal guidance
- Adequate nutrition
- Mechanical stimulation
Hormonal mediation of early bone growth

- No involvement of growth hormone
- Important role of insulin
  - carbohydrate and amino acid uptake
  - carbohydrate metabolism for ATPs
  - cell proliferation
- Important role of IGF-II (fetal) and IGF-I (postnatal)
  - cell proliferation
  - protein synthesis
Hormonal mediation of early bone growth

- Important role of thyroid hormones (thyroxine > triiodothyronine)
  - growth of muscle and long bones
  - maturation of bones and other tissues
  - antagonism of insulin and IGF-I action

- Important maturational role of cortisol

- Insulin and T4 act on gene expression

- Insulin and T4 induce IGF synthesis
Hormonal mediation of childhood and adolescent bone growth

- Control by growth hormone and IGF-I
- GH receptors and action on germinative cells
  - differentiation of IGF-I receptors
- IGF-I hepatic and in bone
  - action on proliferative cells
Hormonal mediation of childhood and adolescent bone growth

- Control by estrogen in both genders
  - receptors on osteoblasts
  - suppression of osteoclast action
  - release of IGF-I by osteoblasts
  - closure of EGZ
Nutritional mediation of early bone growth

- Abundant nutrition is required
- Maternal circulation provides
  - energy
  - specific nutrients (calcium, amino acids)
- Inadequate nutrition results in stunting

Concerns
- heavy maternal exercise
- undernutrition during infancy

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Mechanical modulation of bone growth

- Immature or woven bone
  - coarse-fibered
  - collagen fibers show no special orientation

- First bone that develops
  - in ontogeny
  - after a break

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Mechanical modulation of bone growth

- Mature or lamellar
  - collagen fibers show special orientation in alignment with mechanical forces

- Rough cartilage bone model is shaped to withstand prevailing forces
Lamellar bone

- Cortical (compact) bone
  - shafts (diaphyses) of long bones
  - surface of flat bones
- Trabecular (spongy or cancellous) bone
  - ends and interior of long bones
Cortical (compact) bone

- 80% of skeletal mass
- Haversian system
- Concentric layers of mineral
- Endosteal cells detect strain
- Blood vessel and nerve & communicating canals
- Density and structure confer strength
Trabecular, spongy or cancellous bone

- 20% of skeletal mass
- More porous
- Lamellae are aligned in parallel with stress trajectories
Trabecular, spongy or cancellous bone

- Lamellae are aligned in parallel with stress trajectories
- In appendicular skeleton more than in axial
- Wolff’s law
Mechanical guidance of longitudinal bone growth

- The shape of the bone changes as the bone grows in size (modeling)
- Changes in shape are guided by changes in mechanical loading of the growing bone
Hypertrophic bone growth in adulthood

Increases in bone density and bone geometry in response to changes in stress
Hypertrophic bone growth

- occurs when bone is deformed (strained) in response to mechanical force
- Strain produces a force (stress) within the bone
- Bone will increase in density and change configuration so it can meet the force without getting deformed
Mechanical forces producing strain

- tension
- compression
- shear
Mechanical forces producing strain

- Magnitude of strain
- Capacity of bone stress resistance
Hypertrophic response in bone

- Increases in bone mineral density
- Changes in lamellar geometry so that they are aligned with stress trajectories (Wolff’s law)
Hypertrophic response in bone

- occurs through modeling within a bone metabolic unit (BMU)
- stages
  - quiescence
  - activation
  - resorption
  - reversal
  - formation
  - quiescence

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Hypertrophic response in bone

- mediated by
  - activation by stress of osteoclasts
  - secretion by osteoclasts and monocytes of cytokines IL-1, IL-6, prostaglandin E2
  - removal of unstressed parts of bone
  - secretion by osteoblasts of IGF-I, TGFbeta, \( \text{PG}_E \), osteocalcin, BMPs
  - bone formation
Reparative growth of the bone and mineral homeostasis

Maintenance of bone mass throughout life
Reparative growth of the bone

- bone is continuously remodeled for metabolic maintenance (internal remodeling)
Metabolic function of the bone

- Bone serves as a reservoir of calcium in the body.
- Calcium is withdrawn from the bone:
  - When it is needed to maintain blood calcium balance.
  - When the hormonal environment favors bone resorption.
  - When bone is insufficiently loaded.
Minerals in the body

- Ca
  - plasma constituent
  - excitability of muscle, nerve cells
  - intracellular signalling
  - mineral component of bone (99% of total Ca)

- Plasma and bone calcium regulated separately
Organs that participate in plasma calcium homeostasis:

- Calcium is secured from intestine, bone or kidney
- Plasma Ca takes precedence to bone mineral balance
Hormones that control internal remodeling

- Parathyroid hormone
  - increases plasma calcium
  - acts on
    - bone (resorption)
    - intestine (Ca absorption)
    - kidney (vitamin D synthesis and Ca reabsorption)
Hormonal control

- PTH action on bone
  - increases bone resorption by acting first on osteoblasts
  - Osteoblasts activate osteoclasts
Hormonal control

- PTH action on kidney
  - stimulates synthesis of vitamin D3
  - vitD3 stimulates synthesis of intestinal Ca transport proteins
  - increases Ca and phosphate reabsorption
Vit D3

- sunlight forms cholecalciferol
- dietary source of D3 and D2
- Liver makes 25-(OH)VitD3
- Kidney makes 1,25-(OH)\textsubscript{2}VitD3
Hormonal control

- **PTH action on the intestine**
  - VitD3 stimulates synthesis of transport protein
  - Increased intestinal absorption of Ca
Plasma calcium

- Regulated range
  - 8.6-10.2 mg/dl
  - 3 - 8 mEq/l

- Two counter-regulating hormones
  - Parathyroid hormone
  - Calcitonin
Regulation of plasma calcium

- **Parathyroid hormone**
  - released when plasma Ca is low
  - increases plasma Ca

- **Calcitonin**
  - released when plasma Ca is high
  - decreases plasma Ca
Hormonal control

Important role of estrogen in preventing
- osteoclastic bone resorption
  - inhibits production of resorptive cytokines
    - IL-1
    - IL-6
    - TNF
    - and PGE