Osteoporosis
Reparative growth of the bone

- Bone is continuously remodeled
  - Internal remodeling (no change in shape)
  - Endosteal resorption
  - For metabolic maintenance
  - For repair of fatigue damage

- Bone formation is in excess of bone resorption during early growth and adolescence due to
  - High concentrations of GH, estrogen, androgens, IGF-I
Internal remodeling is a component of reparative growth

- Bone formation is in balance with bone resorption during young adulthood because of:
  - high concentrations of GH, estrogen, androgens, IGF-I
  - high muscle mass and physical activity
- Bone formation falls short of bone resorption after the third decade of life
Osteoporosis is a consequence of bone metabolism in old age

- Loss of bone mineral and lamellar structure
- A consequence of unbalanced coupling of bone formation and bone resorption
- Expressed more in trabecular bone of the axial skeleton than in appendicular bones
  - due to high rate of internal remodeling
  - due to greater amount of trabecular bone
- Increases risk of bone fractures
Reasons for remodeling

- repair of fatigue microdamage
- 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- calcium is withdrawn from the bone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
Functions of calcium in the body

- plasma constituent
- excitability of muscle, nerve cells
- intracellular signalling
- mineral component of bone (99% of total Ca)
- Plasma and bone calcium are regulated separately
Plasma calcium

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

- Two counter-regulating hormones
  - Parathyroid hormone
  - Calcitonin
Counter-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
Organs that participate in plasma calcium homeostasis:

- Calcium is secured from intestine, bone or kidney
- Plasma Ca regulation takes precedence to bone mineral balance
Hormonal control

- PTH action on bone
  - recruits osteoclasts
  - activates differentiated osteoclast phenotype
  - action is indirect
    » via osteoblasts
    » via stromal marrow cells
Hormonal control

- PTH action on bone
  - osteolytic when levels high and stimulation continuous
  - osteogenic when concentrations low and stimulation is intermittent
Coupling of resorption and bone formation by PTH

- **Osteolytic actions**
  - collagenase clears osteoid
  - osteoclast recruitment

- **Osteogenic actions**
  - stimulation of bone growth factors
Hormonal control

VitD3 action on bone

- recruits osteoclasts lining cells (osteoblasts) clump and resorb organic osteoid
- activates differentiated osteoclast phenotype and promotes resorption
- action is indirect
  » via osteoblasts
  » via stromal marrow cells
- promotes mineralization via intestinal Ca absorption
Osteoclast differentiation

- Derivatives of blood cell lines
  - monocytes
  - macrophages

- Fusion into multinucleated cell
Osteoclast differentiation: ruffled border

- Vacuolar H+-ATPase acidifies bone surface
Messengers of osteoclast recruitment & differentiation

- Produced by marrow stromal cells and osteoblasts
  - cytokines IL-1, IL-6, basic FGF
  - prostaglandins of the E series
Hormonal control

- PTH action on kidney
  - stimulates the last stage of synthesis of vitamin D3
  - increases calcium reabsorption

- Vitamin D
  - is made in the skin by UV B
  - ingested in the diet as D3 or D2
Vit D3 (calcitriol)

- Stores of dehydrocholesterol in dermis
- UV B from sunlight forms cholecalciferol
- Liver makes 25-(OH)VitD3
- Kidney makes 1,25-(OH)_2VitD3 in response to PTH
Hormonal control

- Vit D3 action on the intestine
  - synthesis of transport proteins:
    - calbindins
    - integral membrane Ca binding protein
  - Ca++ pump
  - Increased intestinal absorption of Ca
Hormonal control of bone turnover by estrogen

- Important role of estrogen in preventing osteoclastic bone resorption
  - inhibits production of cytokines
    - IL-1
    - IL-6
  - inhibits production of prostaglandin E2
- inhibits recruitment & differentiation of osteoclasts
Hormonal control of bone turnover by estrogen
Circumstances leading to bone mineral loss and osteoporosis

- Pregnancy and lactation
- Inadequate calcium intake
- Inadequate vitamin D intake
- Inadequate caloric intake
- Withdrawal of steroid hormones
- Reduced bone loading or immobilization
Calcium intake in North America

- Women of all age groups eat between 50 and 60% of calcium RDA.
- Substitution of sodas for milk prevents the build-up of skeletal mass during adolescence.
- Calcium absorption becomes less efficient in old age because of diminished stomach acid secretion.
- 2.5 lbs in the body; regulated in plasma; essential for muscle, nerve, hormone functions
- Deficiency: contractile problems, osteoporosis (low intake by women)
- Where? Milk products, dark-green & leafy veggies (oxalates!)
- RDA: 1200-1500 mg young and old, 1000 others
Vitamin D deficiency is prevalent in the US

- No Vit D (0% photoproducts) made in winter in northern latitudes
- Inadequate intake of vitD enriched milk
- Reduced intestinal absorption of VitD
Vitamin D: the aging factor

- Old individuals (blue) make less vit D with the same sun exposure
- RDA for aged may need to be increased to 800 IU
Reproductive hormone withdrawal with age

- 1 to 3% annual mineral loss from mid 30’s
- Accelerated mineral loss during early menopause (5 to 7%)
  - due to removal of suppression by estradiol of bone resorption
Conditions leading to osteoporosis

- Increased bone turnover
  - estradiol and androgen withdrawal
  - inadequate mechanical loading
  - inadequate quantity and quality of diet
  - inadequate vitD3 synthesis and action

- loss of bone density

- loss of horizontal trabeculae in the axial skeleton
Vertebral compression fracture

- Horizontal trabeculae are lost
- Vertical trabeculae prone to buckling
Prevention of osteoporosis: build up a healthy bone mass in 20’s
Treatment of osteoporosis

- Estrogens
  - early treatment is more effective in preventing up to 50% of cancellous and 35% of cortical bone loss
  - optimal duration: 20 years/indefinitely
  - side-effects
    » cancer of the uterus
    » venous thrombosis
  - antagonism with progesterone
Treatment of osteoporosis

- Partial estrogen agonists (anti-estrogens)
  - antiestrogenic in uterus and breast
  - estrogenic action in bone
  - tamoxifen
  - side effects
    - venous thrombosis
    - hepatotoxic
  - phytoestrogens
Treatment of osteoporosis

- Androgens
- Combination of androgen and estrogen
- Calcitonin
Treatment of osteoporosis

- Dietary supplements
  - increased vitD3 RDA to 800 IU
  - increased calcium supplementation to 1200 mg
Treatment of osteoporosis

- **Exercise**
  - high resistance exercise to
    » increase muscle mass
    » increase bone loading
  - partially counteracts bone loss in loaded appendicular bones