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Metabolic Bone Disease

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M2 Musculoskeletal

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BONE STRUCTURE

• Extracellular matrix
  – Osteoid (type 1 collagen)
  – Mineral crystals

• Bone architecture
  – Cortical bone
  – Trabecular (cancellous) bone
OSTEOBLASTS

• Arise from connective tissue progenitors
• Produce extracellular matrix proteins: type 1 collagen and osteocalcin
• Responsible for mineralization: alkaline phosphatase
• Stimulated by growth factors: TGF-β, IGF-1
OSTEOCLASTS

- Multinuclear cells arising from hematopoietic precursors
- Contact with bone at ruffled border: acid environment and lysosomal enzymes
- Activity stimulated by IL-1, IL-6 and TNF
BONE REMODELING

• Begins with osteoclastic activity (7-10 days)
• Followed by osteoblastic bone reformation (3 months)
• Mechanical loading is an important stimulus
• Immobilization increases resorption and blocks formation
Normal Bone Remodelling

Resorption

Reversal

Formation

Resting
OSTEOPOROSIS

The clinical syndrome caused by a decrease in bone mass. The remaining bone is histologically normal.
OSTEOPOROSIS: ETIOLOGY

• Positive family history, thin body habitus, poor nutrition, Caucasian and Asian race, fair skin and cigarette smoking all predict increased risk

• Glucocorticoids decrease bone formation and induce hypogonadism
OSTEOPOROSIS:
CLINICAL MANIFESTATIONS

• Early osteoporosis is asymptomatic
• As skeletal integrity declines, fractures occur, often with minimal trauma
• Vertebral compression fractures are most common, hip and wrist fractures also are major problems
• End stage disease associated with marked dorsal kyphosis
Osteoporosis: A Significant Public Health Problem
Onset and Advanced Osteoporotic Patients
OSTEOPOROSIS: INCIDENCE

- 40% of 50 year old Caucasian and Asian women will have an osteoporotic fracture during their lifetime.
- 13% of men and Black women will have such a fracture.
- 1/3 of these fractures will be hip fractures, a condition associated with 5-20% mortality.
OSTEOPOROSIS: DIAGNOSIS

- Plain films provide very poor assessment of bone density
- Density best measured with bone densitometry (DEXA) measurements
- Criteria for diagnosis is bone density more than 2.5 standard deviations below the mean for young normals
BONE MARKERS

• Osteoblast: Alkaline phosphatase and osteocalcin

• Osteoclast: Pyridinoline crosslinks and N-telopeptide
CAUSES OF OSTEOPENIA

• Hypogonadism, both in men and women
• Cushing's syndrome
• Hyperparathyroidism
• Hyperthyroidism
• Osteomalacia
• Multiple myeloma
OSTEOPOROSIS: PREVENTION

• Adequate calcium intake in susceptible individuals

• Avoid hypogonadism

• Weight bearing exercise
OSTEOPOROSIS: TREATMENT

- Fall prevention
- Calcium supplementation
- Vitamin D
OSTEOPOROSIS: TREATMENT

• Gonadal steroid replacement
  – Major, well established effects to decrease osteoclastic activity
  – Long term therapy increases bone mass and decreases fracture risk
OSTEOPOROSIS: TREATMENT

• Raloxifene
  – Selective estrogen receptor modulator
  – Increases bone density and decreases fracture risk
  – Probably not as potent as estrogen
OSTEOPOROSIS: TREATMENT

- Raloxifene
  - No trophic effect on breast or uterus
  - May cause or worsen hot flashes
  - Increased risk of thromboembolic disease
OSTEOPOROSIS: TREATMENT

- Bisphosphonates: Alendronate, Risedronate, Ibandronate and Zoledronic Acid
  - Potent inhibitors of osteoclast activity
  - Promote significant increase in bone density and decrease fracture risk by about 50%
  - Rare instances of erosive esophagitis and gastritis
  - Osteonecrosis of the mandible
OSTEOPOROSIS: TREATMENT

• Calcitonin
  – Available as a nasal spray
  – Slows bone loss, usually does not restore bone
  – May provide pain control for acute fracture
  – Occasional nausea, vomiting, flushing
OSTEOPOROSIS: TREATMENT

• Parathyroid hormone (Teriparatide)
  – Potent stimulator of osteoblast activity
  – Increases bone mass up to 13%
  – Reduces fracture risk by about 50%
  – Given as a single daily injection
  – Low incidence of side effects, hypercalcemia, nausea
GLUCOCORTICOID-INDUCED OSTEOPOROSIS

• Adequate calcium and vitamin D

• Gonadal steroid replacement

• Bisphosphonates
OSTEOMALACIA and RICKETS

Clinical syndromes that result from inadequate bone mineralization
OSTEOMALACIA: ETIOLOGY

• Vitamin D deficiency or resistance
  – Inadequate intake and sunlight
  – Malabsorption
  – Severe liver disease
  – Renal failure
  – Hereditary syndromes
OSTEOMALACIA: ETIOLOGY

• Phosphate deficiency
  – Renal tubular disorders
  – Tumor associated osteomalacia
  – X-linked hypophosphatemia
  – Phosphate binders
OSTEOMALACIA: ETIOLOGY

• Inhibitors of mineralization
  – Aluminum
  – Fluoride
VITAMIN D DEFICIENCY

• Vitamin D deficiency leads to decreased absorption of calcium by the GI tract.

• As serum calcium starts to fall, secondary hyperparathyroidism occurs.
VITAMIN D DEFICIENCY

- Elevated Pth levels may maintain serum calcium in the normal range, but at the cost of phosphaturia, hypophosphatemia and increased bone reabsorption.

- Low serum phosphate results in inadequate bone mineralization and osteopenia.
VITAMIN D DEFICIENCY

• In severe cases, secondary hyperparathyroidism is not adequate to maintain serum calcium levels, and hypocalcemia occurs.
OSTEOMALACIA: CLINICAL MANIFESTATIONS

- Bone pain and pathologic fractures
- Decreased bone density
- Hypophosphatemia, increased alkaline phosphatase, and increased PTH
OSTEOMALACIA: CLINICAL MANIFESTATIONS

- Late hypocalcemia
- Pseudofractures
- In children, bowing of the legs and rachitic rosary, short stature
OSTEOMALACIA: DIAGNOSIS

- Low levels of 25-hydroxyvitamin D
- Elevated parathyroid hormone and alkaline phosphatase
- Bone biopsy
OSTEOMALACIA: EVALUATION

- Careful diet and sunlight history
- Renal function
- Fecal fat determination
- Anti IgA tissue transglutaminase antibodies. Small bowel biopsy
PAGET’ S DISEASE OF BONE

- Common disorder of increased bone turnover
- Etiology unknown
- Increased bone resorption with compensatory increased bone formation leads to thick, abnormal bones
PAGET’S DISEASE:
CLINICAL MANIFESTATIONS

- Many patients asymptomatic
- Bone pain and deformity
- Fractures
- Arthritis
- Nerve compression
- Osteogenic sarcoma
PAGET’S DISEASE: DIAGNOSIS

- Increased alkaline phosphatase
- Characteristic radiographic appearance
- Bone scan to determine extent of disease
PAGET’S DISEASE: TREATMENT

• Only indicated for symptoms or high fracture risk

• Bisphosphonates are often helpful

• Calcitonin is also of value, but not as effective as bisphosphonates