Metabolic Bone Diseases
Normal bone n mineral metabolism

- Highly vascular (receives 10% CO)
- Dynamic (constt. remodeling throughout life)
- Compact-Cancellous arrangement
- Other vital functions...hematopoiesis n homeostasis for S. Ca, Mg, PO₄
Normal bone n mineral metabolism

**Constituents:**

- **Cells** → Osteoblasts, Osteoclasts, Osteocyte
  - Hematopoietic cells

- **ECM** → Collagen (type I, fibrillar arrangement)
  → Proteins (Fibronectin, Ca-binding prot
  - Thromboplastin)
  → Minerals (Ca n PO4 hydroxy-apatite)
Normal bone n mineral metabolism

Osteoblast activity: ALP, Osteocalcin

Osteoclast activity: Collagen degradation pdt.
Calcium n Phosphorus metabolism

- Total Ca content of body = 1-2 Kg
- 99% of it in bones
- Vital for ....neuromuscular activity
  ....glandular secretions
  ....signal transduction (sec messanger)
- Total Phosphorus content of body = 500 mg
- 85% Of it in bones
- Vital for...ATP stores, NA, structural protein
  Enzymes, Co-factors
Calcium homeostasis

- Ca-channels in DCT
- Ca reabs
- CaSR in cTALH

- Bone
  + CaSR-PT gl.
  - S. Ca
  - S. PTH
  - 1,25(OH)₂D
  - Ca abs from prox small bowel
Phosphorus homeostasis

PCT reabs (Na-PO4 co-transporter)

Bone

S. PO4

Vit. D

Ca intake

Small bowel abs

S. PTH
Calcium n Phosphorus homeostasis

Hence, perturbed Ca n PO4 homeostasis can result from

1. PTH disorders
2. Vit. D disorders
3. Renal disease
4. Small bowel ds & Achlorhydria
Vitamine D

- 7- DehydroCholesterol $\rightarrow$ Vitamine D$_1$
  - UV light
- Vitamine D$_2$: Plant source
- Vitamine D$_3$: Animal source
- Vitamine D$_2$ n D$_3$....equally effective
- 25(OH)D. the major circulating n storage form
Vitamine D metabolism

$\text{PTH}$

$\downarrow$

$\text{S. Ca} \rightarrow 25(\text{OH})-1\alpha\text{-hydroxylase}$

$\downarrow$

$1,25(\text{OH})_{2}\text{Vit.D}$

$\downarrow$

$\text{Vit D Receptor (Nuclear)} \leftarrow \text{Vit D-24 hydroxylase (in most tissues)}$

$\downarrow$

$\text{Inactivated Vit. D}$
Vitamine D deficiency states

- Reduced Vit D Intake.....dietary inadequacy
  Production....sun exposure
  Absorption.....malabsorption syndrome

- Excessive loss/break-down of Vit D
  Catabolism....Phenytoin, R-cin, Barbiturates
  Enterohepaic circulation....small bowel ds or resection
Vitamine D deficiency states

- Impaired metabolism
  - 25-hydroxylation: Liver ds, INH
  - 1α-hydroxylation: CKD, Hypoparathyroidism
    - 1α-hydroxylase mutations
    - X-linked hypophosphatemic rickets
  - Target organ resis: VDR mutations
Vitamin D deficiency

- Clinical manifestations:
  - Hypocalcemia, tetany, seizures
  - Osteopenia, rickets, osteomalacia
  - Proximal myopathy
  - Pathologic bone fractures

- Diagnosis:
  - 25(OH)D (< 15 ng/mL)
  - Raised S. PTH
  - Low S. Ca, iALP (bone-specific)
  - X-ray... Osteopenia, Pseudofractures
Treatment:

- Therapeutic dose = 40,000 IU/d
- Prophylactic dose = 800 IU/d
- Various formulations and doses
  1. Clacitriol (1,25(OH)₂D₃) = 0.25-0.5 µg/d
  2. Doxercalciferol (1(OH)D₂) = 2.5-5.0 µg/d
  3. Calciferol (Vit D₂) = 50,000 IU wkly X 3 mth
     f/b 800 IU/d
  4. Inj. Vit D = 2.5 MU deep i/m Biannually

- Always add Ca with Vit D supplementation
- Normocalcemia (<1 wk); ALP n PTH in 3-6 mth
Parathyroid related disorders

- **Hyperparathyroidism:**
  1. Pr. Hyperparathyroidism
     Solitary adenoma (80%)
     MEN 1 (Wermer’s synd: Pitutary n Pancreas)
     MEN 2A (Medullary Ca thyroid + Pheochromo)
     MEN 2B (Multiple Neuromas + MCT + PCC)
  2. Sec. → CKD, Lithium therapy

- Familial hypocalciuric hypercalcaemia
Pr. Hyperparathyroidism

Clinical features:

i. Asymptomatic

ii. Bone, Stone, Groan, Mone

Bone → high turnover bone ds

→ Osteitis fibrosa cystica

→ X-ray: subperiosteal resorption

→ Histo: multinucleated osteocasts at bone surface pits

→ Formation/Resorption markers: ALP, Procollagen/Collagen telopeptide
Pr. Hyperparathyroidism

- **Stone** → Nephrocalcinosis
  → Nephrolithiasis

- **Groan** → Refractory gastritis
  → Zollinger-Ellison syndrome
  → Pancreatitis

- **Mone** → Neuropsychiatric manifestations
  → Neuropathy, Parathyroid myopathy
Pr. Hyperparathyroidism

- Diagnosis: Hypercalcemia with ↑ S. PTH
- Treatment: Medical or Surgical?

  - Medical → SERMs (Raloxifene)
    → Calcimimetics (CaSR +)

  - Annual S. Creat, DEXA scan n Biannual S. Ca
Pr. Hyperparathyroidism

- Surgery

I. Severe hyperCa (>15 mg%) or hypercalciuria (>400 mg/d)

II. Asymp hyperPTH with age < 50 yrs

III. T-score < -2.5 at any site

IV. CCL reduced by 30% or more

- Pre-op Radiolabelled Tec SPECT & intra-operative S. PTH sampling (>50% decline; 5 min. post-removal) for better localization
Familial hypocalciuric hypercalcemia

- Mutation in CaSR in PTH gland and Kidney
- Usually asymptomatic
- Must be differentiated from Pr. hyperPTH as medical therapy or surgery not useful (*K)