Disorders of Ca/P metabolism
Osteoporosis

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Objectives

- Body distribution of Ca\(^{2+}/P\)
- Function of Ca\(^{2+}/P\)
- Hormonal regulation of Ca\(^{2+}\)
  - Parathyroid hormone (PTH)
  - Vitamin D (Calcitriol)
  - Calcitonin
- Disorders of Bone Ossification
  - Rickets
  - Osteomalacia
  - Osteoporosis
Body distribution of Ca\(^{2+}\)

- Total Ca content in adult body is 25 000 mmol (approx. 1.5% - 2.2% of body weight)
- 99% of Ca is found in bones and teeth
- Rest in extracellular fluid (approx 22.5 mmol)

**Plasma calcium:**
1. Protein bound fraction- 33%
2. Complex with citrate and phosphate- 2%
3. Ionised form- 65%

Ca\(^{2+}\) turnover

[Diagram showing calcium intake, absorption, secretion, and deposition]
Major functions of Ca$^{2+}$

- Calcification of bone and teeth
  - Hydroxyapatite crystals - \((\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2)\)
- Muscle Contraction
- Role in neuromuscular transmission
- Role in blood coagulation
- Maintenance of Cell Membrane
- Calcium as second messenger

Body distribution of P

- "Metabolic Twin" Of Calcium
- Both Regulated Via Vitamin D & PTH
- P Comprises Approximately 1% Of Body Weight
- Approximately 80% In Bones & Teeth
- Approximately 20% In All Cells (ATP)
Major functions of P

- Vital role in cellular metabolism
- Part of cellular energetics (ATP)
- Phosphorylation of enzymes
- PO₄ buffer system

The principle of 3s in regulation of Ca²⁺/P metabolism

- Three types of bone cells
- Three regulating hormones
- Three target organs
3 Types of Bone Cells

Schematic view of bone formation/re-absorption and the corresponding conditions associated with its disorder.
3 Regulating Hormones

- Parathyroid hormone
- Calcitonin
- $1,25\,(OH)_2\,D_3$ (Vit. D$_3$)

Regulating Hormones

1. Parathyroid hormone (PTH) increases serum Ca$^{2+}$
   - Mobilizes Ca$^{2+}$ from bones (Increased resorption)
   - Increases renal excretion of PO$_4^-$, decreases excretion of Ca$^{2+}$
2. Calcitonin (CT) decrease serum Ca^{2+}
   - Inhibiting the release of Ca^{2+} via bone resorption.

3. 1,25 (OH)_{2} D_{3} (Vit. D_{3}) decrease serum Ca^{2+}
   - Inhibiting the release of Ca^{2+} via bone resorption.
3 Target organs

Three sites are involved in regulation of plasma Ca\(^{2+}\)

- Intestine
- Bone
- Kidneys

Target organs

1. INTESTINE

- Low Plasma (Ca\(^{2+}\)) leads to increased 1, 25 (OH)\(_2\) D3, leads to increased Ca\(^{2+}\) absorption
- High Plasma (Ca\(^{2+}\)) Leads to Decreased 1, 25 (OH)\(_2\) D3, leads to decreased Ca\(^{2+}\) absorption
Target organs

2. BONE

- Low plasma (Ca\(^{2+}\)) leads to increased PTH → increased bone resorption → increased plasma Ca\(^{2+}\)
- High plasma (Ca) leads to increased Calcitonin → decreased bone resorption → leads to decreased plasma Ca\(^{2+}\)

3. KIDNEYS

- Low plasma (Ca\(^{2+}\)) leads to decreased renal Ca\(^{2+}\) excretion → increased plasma Ca\(^{2+}\)
- High plasma (Ca\(^{2+}\)) leads to increased renal Ca\(^{2+}\) Excretion → leads to decreased plasma Ca\(^{2+}\)
Calcium Homeostasis summary

1. Osteoclasts break down bone and release calcium into the blood, and osteoblasts remove calcium from the blood to make bone. PTH regulates blood calcium levels by indirectly stimulating osteoclast activity, resulting in increased calcium release into the blood. Calcitonin plays a minor role in calcium maintenance by inhibiting osteoclast activity.

2. In the kidneys, PTH increases calcium reabsorption from the urine.

3. In the kidneys, PTH also promotes the formation of active vitamin D, which increases calcium absorption from the small intestine.

Etiology of Hypercalcemia

- Hyperparathyroidism
  - Primary
    - Adenoma
    - Hyperplasia
    - Carcinoma
  - Other Forms
    - Familial Hypocalciuric Hypercalcemia
    - Tertiary hyperparathyroidism

- Other Endocrinopathias
  - Thyrotoxicosis, adrenal insufficiency, pheochromocytoma, ectopic PTH secretion

- Drug induced
  - Vitamin A and D, Milk-Alkali syndrome, Thiazide diuretics
  - Lithium therapy

- Immobilization (low gravity – space flights)
Signs of Hypercalcemia

- Central nervous system dysfunctions
- Muscle weakness
- Bowel hypomotility and constipation
- Increased gastrin secretion and peptic ulcer disease
- Pancreatitis
- Acute and chronic insufficiency
- Nephrogenic diabetes insipidus
- Nephrolithiasis
- Shortening of the QT interval
- Corneal Ca$^{2+}$ deposition (Band keratopathy)

Etiology of Hypocalcemia

PTH deficiency

- Acquired
  - Thyroidectomy
  - Parathyroidectomy
  - Radiation

- Hereditary
  - Developmental defect of parathyroid glands (DiGeorge)
  - Autosomal dominant hypocalcemia (activating mutation of calcium receptor gene)
Etiology of Hypocalcemia

Vitamin D
- Deficiency
  - Nutritional deficiency and lack of skin exposure
    - Osteomalacia
  - Rickets Type 1
    - Hereditary vitamin D deficiency due to lack of 1-alpha hydroxylase
    - Renal insufficiency
- Resistance
  - Rickets Type II
    - Target organ unresponsiveness to vitamin D due to defect in receptor

Signs of Hypocalcemia
- Tetany, Stiff gait, muscle fasciculations and generalized tremors
- Facial rubbing and pawing
- Generalized seizures
- Drooling (cats)
- Hyperthermia**
- Panting and Hyperventilation**
- Puerperal tetany usually occurs postpartum but can occur near the end of pregnancy
Tetany

- Caused by low serum Ca$^{2+}$
- Severe, Intermittent Spastic Contractions Of Muscles: Pain
- Trousseau's Sign: Characteristic Flexion of Wrist & Thumb Due to Muscle Spasm
- Milk Tetany in Newborns Fed Undiluted Cow's Milk which has an Increased P/Ca Ratio, Leads to Increased Serum P and Decreased Serum Ca

Hypocalcemia - causes an increase in membrane permeability to Na, depolarizing membranes to threshold. The resulting over-excitation stimulates muscles constantly leading to tetany
Disorders of Bone Ossification

- **Rickets**
  - calcium salts are not deposited properly
  - bones of growing children are soft
  - bowed legs, skull, rib cage, and pelvic deformities result

- **Osteomalacia**
  - new adult bone produced during remodeling fails to ossify
  - hip fractures are common

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**Rickets**

- Vitamin D deficiency remains the major cause of rickets among young infants in most countries, because breast milk is low in vitamin D.
- Studies indicated that the disease occurs among older toddlers and children and probably is attributable to low dietary calcium intakes, which are characteristic of cereal-based diets.
Osteopenia and Osteoporosis

- 34 million Americans have Osteopenia

Metabolic Bone Disease

- Osteoporosis definition
  - Porous, Fragile Bones
  - Bone Mineral Density (BMD) is very low (> 2.5 SD below average)
- Affects > 10 million in the U.S.; 80% are women
- Common In Postmenopausal Women
- Immobilization Leads to Decreased Bone Formation

~ 34 million Americans have Osteopenia
BMD Changes with Age

- Two stages
  - Formation
  - Resorption
- Two types of bone
  - Trabecular
  - Cortical

Boughton, 1999; Notelovitz, 1993; PDR, 1998; Smith, 1993; Wardlaw, 1993
Types of Osteoporosis

- **Primary**
  - **Type I**
    - increased bone resorption that primarily affects trabecular bone
    - decreased production of estrogen that coincides with menopause
  - **Type II**
    - proportionate loss of trabecular and cortical bone
    - afflicts men and women over the age of 70 years and is called senile osteoporosis
- **Secondary** (Result of other disease or medications)

Donohue, 1999; Glaser & Kaplan, 1997; Kulak, et al., 2000; NIH, 2000; NOF, 2000; Peterson, 2001
Risk Factors You Can Not Change

- Gender
- Ethnicity
- Body Size
- Age

Risk Factors You Control

- Exercise
- Not Smoking
- Avoid alcohol
- Diet
- Sex Hormones Medications
Diagnostics

- Osteoporosis is preventable and treatable, therefore early diagnosis and treatment is important.
- Most common technique is Dual Energy X-ray Absorptiometry (DEXA scan)
  - Precise measurement/high resolution
  - Sensitive to changes
  - Simple to perform, no pain or discomfort
  - Less Radiation

DEXA Scan
Consequences of Osteoporosis

- Vertebral Fractures
- Loss of height
- Acute and chronic back pain
- Morphologic changes
  - *kyphosis
  - *loss of waistline
  - *protruding abdomen
- Physiologic changes
  - *Digestive function
  - *Breathing difficulties
- Increased mortality

Consequences of Osteoporosis

- Nonvertebral fractures
  (Example-hip,wrist,arm)
- Pain
- Loss of independence
- Possible entry in a nursing home
- Surgical complications
Hormone Replacement Therapy (HRT)

- **Estrogen has a powerful effect on bones**
- The National Osteoporosis Foundation supports estrogen replacement therapy in women at or near the onset of menopause. Estrogen replacement therapy might slow the rate of bone loss. Because estrogen replacement therapy does have side effects, women and their physicians should assess the risks and benefits before starting this treatment.

Fosamax

- Fosamax® (alendronate sodium) is the first in a new class of FDA-approved drugs called aminobisphosphonates to treat osteoporosis in post-menopausal women.
- Decreases osteoclast activity, maintains a lower post-menopausal rate of bone loss and increases bone density.
- Positive effects three months after use
- May reverse the progression of osteoporosis.
Thank you!