Calcium Metabolism
physiology of hormone
2007
Calcium metabolism

- What is the recommended daily intake?
  - 1000mg

- What is the plasma concentration?
  - 2.2-2.6mmol/L

- How is calcium excreted?
  - Kidneys - 2.5-10mmol/24 hrs

- How are calcium levels regulated?
  - PTH and vitamin D (+others)
Three Calcitropic hormones
- PTH
- 1,25 (OH)2 CC
- CT

Three targets
- Bone
- Gut
- Kidney

Three bone cells
- Osteoblasts
- Osteocytes
- Osteoclasts
Calcium homeostasis

Gut absorption → 1,25 (OH)₂ CC → Plasma → Ca++ → Bone resorption

Plasma

PTH

CT

1,25 (OH)₂ CC

Bone accretion

Calciuria
Blood Calcium is tightly regulated by:

- **PRINCIPLE ORGAN SYSTEMS**
  - GUT, BONE, KIDNEYS

- **HORMONES**
  - PARATHYROID HORMONE (PTH), VITAMIN D, calcitonin

- **INTEGRATED PHYSIOLOGY OF ORGAN SYSTEMS AND HORMONES MAINTAIN BLOOD CALCIUM**
CALCIUM PHYSIOLOGY: BLOOD CALCIUM

- Calcium flux into and out of blood
- “IN” FACTORS:
  1. intestinal absorption
  2. Bone resorption
    - “OUT” FACTORS:
      1. Renal Excretion
      2. Bone formation (Ca INCORPATION INTO BONE)
    - BALANCE BETWEEN “IN” AND “OUT” FACTORS
      - Organ physiology of Gut, Bone and kidney
      - Hormone function of PTH and vitamin D3

Organ physiology of Gut, Bone and kidney
Hormone function of PTH and vitamin D3
CALCIUM HOMEOSTASIS

DIETARY CALCIUM
THE ONLY “IN”

DIETARY HABITS, SUPPLEMENTS

INTESTINAL ABSORPTION
ORGAN PHYSIOLOGY
ENDOCRINE PHYSIOLOGY

BLOOD CALCIUM

Bone
Organ, Endocrine

Kidneys
Organ Phys.
Endocrine Phys.

Urine

The Principle “Out”
Vitamin D (cholecalciferol)

- Sources of vit D
- Diet
- u.v. light on precursors in skin
- Normal daily requirement
- 400IU/day
- Target organs
  - bone - increased Ca release
  - gut - increased Ca absorption
VITAMIN D IS A HORMONE BY CLASSIC CRITERIA: MADE IN ONE PLACE (OR SEQUENTIALLY SEVERAL PLACES!), AND ACTING IN OTHER PLACES.

THIS DISTINGUISHES IT FROM OTHER “CLASSIC” VITAMINS, SUCH AS VITAMIN C, B VITAMINS, ETC., WHICH ACT AS COFACTORS IN BIOCHEMICAL REACTIONS.
**VITAMIN D SYNTHESIS**

**SKIN**

- 7-DEHYDROCHOLESTEROL
  - UV
  - VITAMIN D$_3$

**LIVER**

- VITAMIN D$_3$
  - 25-HYDROXYLASE
  - 25(OH)VITAMIN D

**KIDNEY**

- 25(OH)VITAMIN D
  - 1α-HYDROXYLASE
  - 1,25(OH)$_2$ VITAMIN D
    - (ACTIVE METABOLITE)

**TISSUE-SPECIFIC VITAMIN D RESPONSES**
VITAMIN D MECHANISM OF ACTION

VIT D / VDR

RNA POL

5' UNTRANSLATED REGION

VITAMIN D RESPONSIVE GENE

TRANSCRIPTION START SITE

IN THE NUCLEUS
FUNCTION OF VITAMIN D

TISSUE SPECIFICITY

- GUT
  - STIMULATE TRANSPORT OF CALCIUM AND PHOSPHATE IN THE SMALL INTESTINE (PRINCIPALLY DUODENUM)

- BONE
  - STIMULATE TERMINAL DIFFERENTIATION OF OSTEOCLASTS
  - STIMULATE OSTEOBLASTS TO STIMULATE OSTEOCLASTS TO MOBILIZE CALCIUM

- PARATHYROID
  - INHIBIT TRANSCRIPTION OF THE PTH GENE (FEEDBACK REGULATION)
The **Parathyroids**, associated with the thyroid but comprising separate structures.
**PTH**

- **Physiological role**
- **Production related to plasma calcium levels**
- **Control of calcium levels**
  - target organs
    - bone - increased Ca/PO4 release
    - kidneys
      - increased reabsorption of Ca
      - increased excretion of PO4
    - gut - indirect increase in calcium reabs by stimulating activation of vitamin D metabolism
The four parathyroid glands are embedded in the surface of the thyroid gland.
They secrete **parathyroid hormone (PTH)**, a peptide:

- Raises blood calcium levels.
- Secretion regulated by calcium in the blood.
- Causes osteoclasts to break down bone, releasing Ca\(^{2+}\) into the blood.
- Stimulates the kidneys to reabsorb Ca\(^{2+}\).
- Stimulates kidneys to convert **vitamin D** to its active form that to stimulate the uptake of Ca\(^{2+}\) from food in the intestine.
- PTH and calcitonin are **antagonistic** hormones.
A lack of PTH causes hypoparathyroidism, a **tetany**:

- Calcium levels in the blood drop.
- There are convulsive contractions of the skeletal muscles.
Fig. 45.9

The diagram illustrates the regulation of blood calcium level through the hormone Calcitonin and PTH. When the blood calcium level is high:

- Calcitonin is released by the thyroid gland, stimulating Ca^{2+} deposition in bones to reduce Ca^{2+} uptake in kidneys.

When the blood calcium level is low:

- PTH is released by the parathyroid gland, stimulating Ca^{2+} release from bones, increasing Ca^{2+} uptake in kidneys, and increasing Ca^{2+} uptake in intestines.

The system aims to maintain homeostasis by adjusting these processes to keep the blood calcium level within a normal range.
Parathyroid hormone (PTH) Physiology

- PTH FUNCTIONS to preserve normal blood calcium (and phosphate)
  - PTH STIMULATES BONE RESORPTION AND, THUS, INCREASES BLOOD CALCIUM
  - PTH STIMULATES RENAL TUBULAR REABSORPTION OF CALCIUM, AND THUS, INCREASES BLOOD CALCIUM
  - PTH STIMULATES RENAL 1α-HYDROXYLATION OF 25(OH)VITAMIN D, THUS INDIRECTLY STIMULATING INTESTINAL ABSORPTION OF CALCIUM
CALCIUM, PTH, AND VITAMIN D FEEDBACK LOOPS

If BLOOD Ca FALLS:
- SUPPRESS PTH
- BONE RESORPTION
- URINARY LOSS
- 1,25(OH)_2 D PRODUCTION
- NORMAL BLOOD Ca

If BLOOD Ca RISES:
- STIMULATE PTH
- BONE RESORPTION
- URINARY LOSS
- 1,25(OH)_2 D PRODUCTION
Calcitonin

- **Physiological role**

- **Levels increased when serum Ca >2.25mmol/L**

- **Target organs**
  - Bone - suppresses resorption
  - Kidney - increases excretion
There are 3 principle tissues that function prominently in calcium homeostasis. Disorders of these tissues, or of the calcitropic factors that affect their function may result in disorders of calcium metabolism.

- Intestines
- Kidneys
- Bone
Factors affecting bone turnover

- **Other hormones**
  - **Oestrogen**
    - gut - increased absorption
    - bone - decreased re-absorption
  - **Glucocorticoids**
    - gut - decrease absorption
    - bone - increased re-absorption/decreased formation
  - **Thyroxine**
    - stimulates formation/resorption
    - net resorption
Skeletal System

- Bones are made of several tissues
- Primarily made of collagen and hydroxyapatite - $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$
- About 206 bones in the human body
- What is the composition of bone?

- The matrix
  - 40% organic
    - Type 1 collagen (tensile strength)
    - Proteoglycans (compressive strength)
    - Osteocalcin/Osteonectin
    - Growth factors/Cytokines/Osteoid
  - 60% inorganic
    - Calcium hydroxyapatite

- The cells
  - osteo-clast/blast/cyte/progenitor
Functions of Skeletal System

- **SUPPORT:** Hard framework that supports and anchors the soft organs of the body.

- **PROTECTION:** Surrounds organs such as the brain and spinal cord.

- **MOVEMENT:** Allows for muscle attachment therefore the bones are used as levers.

- **STORAGE:** Minerals and lipids are stored within bone material.

- **BLOOD CELL FORMATION:** The bone marrow is responsible for blood cell production.
Rickets

- Disease of children due to a lack of vitamin D.
- Calcium is not deposited in bones.
- Bones become soft.
- Bowing of the bones, and other deformities occur.
Osteomalacia

- “Rickets” of adults.
- Due to a lack of vitamin D.
- Calcium is not deposited in the bones.
- Bones become brittle.
Homeostatic Imbalances

Osteoporosis

• Bone reabsorption is greater than bone deposition.
• Due to any of the following:
  • Lack of estrogen in women.
  • Lack of exercise to stress the bones.
  • Inadequate intake of calcium and phosphorus.
  • Abnormalities of vitamin D metabolism.
  • Loss of muscle mass.
## Risk factors for osteoporosis

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<tr>
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<td>Alcoholism</td>
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<td>Genetic predisposition</td>
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<td>Family history</td>
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<td>Immobilization</td>
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<td>- Heparin</td>
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<td>- Corticosteroids</td>
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Osteoporosis
Vertebral bone

Vertebral fracture

Normal vertebrae
Osteoporotic fracture of femoral neck
Prevention of osteoporosis

- Diet rich in calcium 1.2 g/d
- Vitamin D 400 IU/d
- Exercise
  - 40 min walk
  - 4 times a week
- Sunshine
Age Related Dysfunctions

Arthritis:

Osteoarthritis - 90% of pop. By age 40
chronic inflammation of articular cartilage
can be normal age-dependent change
can also be pathology due to ?
Age-related changes
decrease blood supply
trauma
Osteoarthritis

Loss of Cartilage

Normal Knee
CAUSES OF HYPERCALCEMIA

- HORMONAL
  - PRIMARY HYPERPARATHYROIDISM
  - HYPERVITAMINOSIS D
  - PARANEOPLASTIC (e.g., PTHrP, cytokines)

- NON-HORMONAL
  - RENAL FAILURE

- DRUGS
  - THIAZIDES, LITHIUM, OTHERS
Thank you