BONE STRUCTURE AND HORMONAL CONTROL

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Bone

**Woven bone**
1. Immature bone formed rapidly as in the fetus or repair of an injury.
2. Collagen is irregularly arranged.

**Lamellar bone**
1. Mature bone that is physically stronger.
2. Collagen is regularly arranged.
Bone Structure

- **Bone Matrix:**
  - Consists of organic and inorganic components.
  - 1/3 organic and 2/3 inorganic by weight.
    - Organic component consists of several materials that are secreted by the osteoblasts:
      - Collagen fibers and other organic materials
        - These (particularly the collagen) provide the bone with resilience and the ability to resist stretching and twisting.
Inorganic component of bone matrix

- Consists mainly of 2 salts:
  - calcium phosphate
  - calcium hydroxide
- These 2 salts interact to form a compound called hydroxyapatite.
- Bone also contains smaller amounts of magnesium, fluoride, and sodium.
- These minerals give bone its characteristic hardness and the ability to resist compression.
This bone:

a. Has been demineralized
b. Has had its organic component removed
Hormonal control
Hormones important to bone growth and homeostasis:

• Growth Hormone (GH) –
  • The thyroid hormones (e.g. thyroxine) –
    • Testosterone -
      • Estrogens -
    • Calcitonin -
  • Parathyroid hormones
    • Insulin
  • Glucocorticoids
**Hormones important to bone growth and homeostasis:**

- **Growth Hormone (GH)** - from the anterior pituitary, this hormone is necessary for normal growth and development of the skeleton. A deficiency (hyposecretion) of GH during childhood produces a dwarf. An excess (hypersecretion) produces a giant. Hypersecretion in adulthood produces acromegaly, a disorder in which the shape of many bones, especially those in the face becomes exaggerated.

- **The thyroid hormones (e.g. thyroxine)** - regulate metabolism of most cells including those in bone.

- **Testosterone** - this and other androgens are important for growth in mass and density of bone. Testosterone is present in both males and females in varying amounts.

- **Estrogens** - these hormones are important for growth in length of bone and for bone maintenance. They too are present in varying amounts in both sexes.

- **Calcitonin** - Normally important only in children, this hormone is secreted by special cells in the thyroid. Its function is to stimulate the uptake of calcium into growing bone and the deposition of bone matrix. It is not produced, nor is it effective therapeutically, in adults.
Pituitary gland
Thyroid system

Hypothalamus

Thyrotropin-releasing hormone (TRH)

Anterior pituitary gland

Thyroid-stimulating hormone (TSH)

Negative feedback

Thyroid gland

Thyroid hormones (T3 and T4)

Increased metabolism

Growth and development

Increased catecholamine effect
The image shows a close-up view of tissue sections, likely from a histological study. The left side appears to show a pattern of large, irregular shapes, possibly representing the structure of a glandular tissue. The right side is labeled with "colloid," "stroma," and "follicular cells." These terms suggest the tissue might be a thyroid gland or a similar glandular structure, where follicular cells secrete colloid, and stroma provides support.

- **Colloid**: This is the material stored within the follicles and is secreted by the follicular cells. It is typically rich in hormones produced by the gland.
- **Stroma**: This is the connective tissue framework that supports the glandular structures and allows for the diffusion of nutrients and hormones.
- **Follicular cells**: These are specialized epithelial cells that line the follicles and are involved in the production and secretion of hormones.

These annotations help in identifying the specific components and their roles within the tissue structure.
Parathyroid hormone -
- this hormone exerts the primary control in calcium homeostasis.
- Calcium is necessary in the blood for many functions and when its level falls parathyroid hormone is secreted.

This hormone uses several methods to raise calcium levels in the blood:

1) **increased Vitamin D production.** Vitamin D is a hormone whose precursor is produced in the skin in response to sunlight and then processed in the liver and kidney to become active Vitamin D3. Vitamin D3 increases calcium absorption in the gut. Without this vitamin calcium is not absorbed to any great degree.

2) **Increased reabsorption of calcium in the kidney.** Much calcium is lost to the urine, so when you need more in the blood this is an important source.

3) **Resorption of bone.** PTH increases osteoclastic activity to release calcium into the blood.
Other hormones that affect bone growth include **insulin** and the **glucocorticoids**.

- Insulin stimulates bone formation
- Glucocorticoids inhibit osteoclast activity.
**Testosterone**

is primarily secreted in the testicles of males and the ovaries of females, although small amounts are also secreted by the adrenal glands.

In the testes the **leydig cells** [interstitial cells of Leydig] produce the testosterone

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**Estrogens**

- are produced primarily by developing follicles in the ovaries, the corpus luteum, and the placenta.
- Follicle-stimulating hormone (FSH) stimulates the production of estrogen in the granulosa cells of the ovaries.
- Some estrogens are also produced in smaller amounts by other tissues such as the liver, adrenal glands, and the breasts.
- Fat cells also produce estrogen.
At puberty, the rising levels of sex hormones (estrogens in females and androgens in males) cause osteoblasts to produce bone faster than the epiphyseal cartilage can divide.

This causes the characteristic growth spurt as well as the ultimate closure of the epiphyseal plate.

Estrogens cause faster closure of the epiphyseal growth plate than do androgens.

Estrogen also acts to stimulate osteoblast activity.
TUBAL VESSELS
ANASTOMOSIS OF UTERINE AND
OVARIAN ARTERIES
HELCINE BRANCHES
OVARIAN ARTERY
UTERINE BLOOD VESSELS
OVARIAN BLOOD VESSELS
FALLOPIAN TUBE
OVARIAN ARTERY
OVARIAN BLOOD VESSELS

Testosterone
LH
FSH
Anterior pituitary
Parathyroid Hormone

- Released by the cells of the parathyroid gland in response to low blood \([\text{Ca}^{2+}]\). Causes blood \([\text{Ca}^{2+}]\) to increase.
- PTH will bind to osteoblasts and this will cause 2 things to occur:
  - The osteoblasts will decrease their activity and they will release a chemical known as osteoclast-stimulating factor.
  - Osteoclast-stimulating factor will increase osteoclast activity.
- PTH increases calcitriol synthesis which increases \(\text{Ca}^{2+}\) absorption in the small intestine.
- PTH decreases urinary \(\text{Ca}^{2+}\) excretion and increases urinary phosphate excretion.
Normal parathyroid glands as seen during a thyroidectomy. The large arrow points to the superior parathyroid. The thinner arrow points to the inferior parathyroid. The forceps points toward the recurrent laryngeal nerve. The patient's head is toward the right.
Parathyroid gland, chief and oxyphil cells
Hormonal control of remodelling

- Hormonal control of remodelling acts to maintain blood calcium homeostasis rather than integrity of skeleton

- Blood calcium homeostasis
  - **Parathyroid hormone (PTH)** released when blood Ca\(^{2+}\) low - stimulates osteoclasts
    - Also promotes Ca\(^{2+}\) absorption in GI tract and reduces filtration at kidney
  - **Calcitonin** released when blood Ca\(^{2+}\) high
    - **inhibits** osteoclasts
    - **stimulates** osteoblasts

1. High level of Ca\(^{2+}\) in blood stimulates thyroid gland parafollicular cells to release more CT.
2. Low level of Ca\(^{2+}\) in blood stimulates parathyroid gland chief cells to release more PTH.
3. PARATHYROID HORMONE (PTH) promotes resorption of Ca\(^{2+}\) from bone matrix into blood and retards loss of Ca\(^{2+}\) in urine, thus increasing blood Ca\(^{2+}\) level.
4. CALCITRIOL stimulates increased absorption of Ca\(^{2+}\) from foods, which increases blood Ca\(^{2+}\) level.
5. PTH also stimulates the kidneys to release CALCITRIOL.
6. CALCITONIN inhibits osteoclasts, thus decreasing blood Ca\(^{2+}\) level.
Calcitonin = thyrocalcitonin

- Released by the C cells = clear cells = parafollicular cells of the thyroid gland in response to high blood [Ca^{2+}].
- Calcitonin acts to "tone down" blood calcium levels (reduce calcemia).
- Calcitonin causes decreased osteoclast activity which results in decreased breakdown of bone matrix and decreased calcium being released into the blood.
- Calcitonin also stimulates osteoblast activity which means calcium will be taken from the blood and deposited as bone matrix.

- Stimulate the uptake of calcium into growing bone and the deposition of bone matrix
- Calcitonin stimulate osteoblast to produce bone and store calcium

Secretion of calcitonin is stimulated by:
- increase in serum calcium
- Gastrin and pentagastrin

More specifically, calcitonin lowers blood Ca^{2+} levels in three ways:
- Inhibits Ca^{2+} absorption by the intestines
- Inhibits osteoclast activity in bones
- Inhibits renal tubular cell reabsorption of Ca^{2+} allowing it to be secreted in the urine

- Vitamin D regulation
- calcitonin protects against calcium loss from skeleton during periods of calcium mobilization, such as pregnancy and, especially, lactation
Calcitonin Negative Feedback Loop

Increased Blood $[\text{Ca}^{2+}]$ → Increased calcitonin release from thyroid C cells.

- Decreased osteoclast activity
- Increased osteoblast activity
Increase in Blood Calcium

- Increases secretion of calcitonin

Decrease in Blood Calcium

- Increases secretion of parathyroid hormone
Calcium

- Important signal molecule
- Part of intercellular cement that holds cells together at tight junction
- Cofactor in the coagulation cascade
- Affects the excitability of neurons

Calcium is the most abundant mineral in the human body.

- The average adult body contains in total approximately 1 kg, 99% in the skeleton in the form of calcium phosphate salts.
- The extracellular fluid (ECF) contains approximately 22.5 mmol, of which about 9 mmol is in the serum.
- Approximately 500 mmol of calcium is exchanged between bone and the ECF over a period of twenty-four hours.
- The amount of total calcium varies with the level of serum albumin, a protein to which calcium is bound.

The serum level of calcium is closely regulated with a normal total calcium of 2.2-2.6 mmol/L (9-10.5 mg/dL) and a normal ionized calcium of 1.1-1.4 mmol/L (4.5-5.6 mg/dL).
Calcium Balance in the Body

Small intestine
- Dietary calcium
  - Calcium in feces
  - Calcium in urine
  - Some calcium is secreted into the small intestine.
  - Cells: [Ca$^{2+}$] $0.001$ mM

Bone
- [Ca$^{2+}$]
- Calcitonin
- PTH
- Calcitriol
- Cortisol

Electrochemical gradient
- Active transport

ECF
- [Ca$^{2+}$] $2.5$ mM

Kidney
- Ca$^{2+}$ in kidney tubules
- Ca$^{2+}$ in urine

KEY
- PTH = parathyroid hormone
Calcium Balance

Osteoclasts are responsible for bone resorption

Osteoclasts secrete acid and enzymes.

Nuclei

Area of bone resorption

Enzymes, H⁺ dissolve bone.

Bone matrix
Calcium Balance

- **Parathyroid hormone**
  - Mobilizes calcium from bone
  - Enhances renal reabsorption
  - Indirectly increases intestinal absorption
- **Vitamin D (Calcitriol)**
- **Calcitonin (from Thyroid)**
Calcium regulation

Parathyroid glands

Increased calcium in blood

Parathyroid hormone

Bones

+ Calcium reabsorption

Kidneys

+ Calcium reabsorption

1,25 hydroxy-vitamin D

Intestines

+ Calcium absorption
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.
Bone homeostasis

- **Bones continually being remodelled**
  - 5-7% of bone mass turned over each week

- **Remodelling regulated by two control mechanisms:**
  - Hormonal control of blood Ca\(^{2+}\) homeostasis
  - Mechanical stress
Nutritional Effects on Bone

- Normal bone growth/maintenance cannot occur w/o sufficient dietary intake of calcium and phosphate salts.
- Calcium and phosphate are not absorbed in the intestine unless the hormone calcitriol is present.
- Calcitriol synthesis is dependent on the availability of the steroid cholecalciferol (a.k.a. Vitamin D) which may be synthesized in the skin or obtained from the diet.
- **Vitamins C, A, K, and B_{12}** are all necessary for bone growth as well.
**Different Forms of Vitamin D**

**Cholecalciferol**

*Cholecalciferol* is the naturally occurring form of vitamin D. Cholecalciferol is made in large quantities in your skin when sunlight strikes your bare skin. It can also be taken as a supplement.

**Calcidiol**

**25(OH)D or 25D** Calcidiol Made in Liver AFTER BEING ABSORBED BY SKIN OR INJECTION

Calcidiol (25-hydroxyvitamin D) is a prehormone in your blood that is directly made from cholecalciferol. When being tested for vitamin D deficiency, calcidiol is the only blood test that should be drawn. When someone refers to vitamin D blood levels, they are referring to calcidiol levels. Your doctor can order calcidiol levels but the lab will know calcidiol as 25-hydroxyvitamin D.

**Calcitriol**

**1,25(OH)2D3 or 1,25D3** Calcitriol is made from calcidiol in both the kidneys and in other tissues and is the most potent steroid hormone derived from cholecalciferol. Calcitriol has powerful anti-cancer properties. It is sometimes referred to as the active form of vitamin D. Calcitriol levels should never be used to determine if you are deficient in vitamin D.
Nutritional rickets: lack of sunlight, lack of dietary vitamin D₂ and D₃

7-dehydrocholesterol

Skin

Ultraviolet light

Cholecalciferol (vitamin D₃)

Liver

Vitamin D₃-25 hydroxylase

Calcidiol (25[OH]D₃)

Kidney

25(OH)D₃-1-α-hydroxylase

Calcitriol (1,25(OH)₂D₃)

Vitamin D-dependent rickets, type II affects receptors and increases calcitriol.

Both ergocalciferol and cholecalciferol are metabolized in liver

Intestines

- Increased calcium absorption
- Increased phosphorus absorption
- Decreased magnesium absorption
- Parathyroid glands
- Decreased PTH synthesis
- Decreased PTH secretion

Bone

- Increased mineralization indirectly via increased calcium absorption in intestinal lumen
- At high doses: increased osteoclastic bone

Parathyroid glands

- Increased PTH synthesis
- Increased PTH secretion

Vitamin D-dependent rickets, type I

Vitamin D₃ (fish, meat)

Vitamin D₂ (supplements)

25-hydroxyvitamin D₃

1,25-dihydroxycholecalciferol
# Calcium Balance

## Parathyroid Hormone (PTH)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell of origin</td>
<td>Parathyroid glands</td>
</tr>
<tr>
<td>Chemical nature</td>
<td>84-amino acid peptide</td>
</tr>
<tr>
<td>Biosynthesis</td>
<td>Continuous production, little stored</td>
</tr>
<tr>
<td>Transport in the circulation</td>
<td>Dissolved in plasma</td>
</tr>
<tr>
<td>Half-life</td>
<td>Less than 20 minutes</td>
</tr>
<tr>
<td>Factors affecting release</td>
<td>↓ Plasma Ca(^{2+})</td>
</tr>
<tr>
<td>Target cells or tissues</td>
<td>Kidney, bone, intestine</td>
</tr>
<tr>
<td>Target receptor</td>
<td>Membrane receptor acts via cAMP</td>
</tr>
<tr>
<td>Whole body or tissue action</td>
<td>↑ Plasma Ca(^{2+})</td>
</tr>
<tr>
<td>Action at cellular level</td>
<td>↑ Vitamin D synthesis; ↑ renal reabsorption of Ca(^{2+}); ↑ bone resorption</td>
</tr>
<tr>
<td>Action at molecular level</td>
<td>Rapidly alters Ca(^{2+}) transport but also initiates protein synthesis in osteoclasts</td>
</tr>
<tr>
<td>Onset of action</td>
<td>2–3 hours for bone, with increased osteoclast activity requiring 1–2 hours for intestinal absorption; within minutes for kidney transport</td>
</tr>
<tr>
<td>Feedback regulation</td>
<td>Negative feedback by ↑ plasma Ca(^{2+})</td>
</tr>
<tr>
<td>Other information</td>
<td>Osteoclasts have no PTH receptors, so are affected by PTH-induced paracines. PTH is essential for life; absence causes hypocalcemic tetany.</td>
</tr>
</tbody>
</table>
Endocrine Control of Calcium Balance

- **Endogenous precursors**
  - Sunlight on skin
  - Vitamin D
    - Liver
    - 25-hydroxycholecalciferol (25(OH)D₃)
      - Kidney
      - Parathyroid hormone
      - 1, 25-dihydroxycholecalciferol (1,25(OH)₂D₃, or calcitriol)
        - Bone, distal nephron, and intestine
          - ↑ Plasma Ca²⁺

- **Diet**
  - fortified milk, fish oil, egg yolks

**KEY**
- **Stimulus**
- **Vitamin D pathway**
- **Efferent pathway**
- **Effector**
- **Systemic response**
<table>
<thead>
<tr>
<th><strong>Cell of origin</strong></th>
<th>C cells of thyroid gland (parafollicular cells)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemical nature</strong></td>
<td>32-amino acid peptide</td>
</tr>
<tr>
<td><strong>Biosynthesis</strong></td>
<td>Typical peptide</td>
</tr>
<tr>
<td><strong>Transport in the circulation</strong></td>
<td>Dissolved in plasma</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>&lt;10 minutes</td>
</tr>
<tr>
<td><strong>Factors affecting release</strong></td>
<td>↑ Plasma [Ca^{2+}]</td>
</tr>
<tr>
<td><strong>Target cells or tissues</strong></td>
<td>Bone and kidney</td>
</tr>
<tr>
<td><strong>Target receptor</strong></td>
<td>G protein-coupled membrane receptor</td>
</tr>
<tr>
<td><strong>Whole body or tissue action</strong></td>
<td>Prevents bone resorption; enhances kidney excretion</td>
</tr>
<tr>
<td><strong>Action at molecular level</strong></td>
<td>Signal transduction pathways appear to vary during cell cycle</td>
</tr>
<tr>
<td><strong>Other information</strong></td>
<td>Experimentally decreases plasma [Ca^{2+}] but has little apparent physiological effect in adult humans; possible effect on skeletal development; possible protection of bone Ca^{2+} stores during pregnancy and lactation</td>
</tr>
</tbody>
</table>
Calcium homeostasis of blood: 9–11 mg/100 ml

- Parathyroid glands release parathyroid hormone (PTH).
- Thyroid gland
- Osteoclasts degrade bone matrix and release Ca$^{2+}$ into blood.

Stimulus: Falling blood Ca$^{2+}$ levels

IMBALANCE

BALANCE

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Increased PTH release by parathyroid gland

- Binds to osteoblast causing decreased osteoblast activity and release of osteoclast-stimulating factor
- Increased calcitriol synthesis
- Decreased $\text{Ca}^{2+}$ excretion

- OSF causes increased osteoclast activity

- Increased intestinal $\text{Ca}^{2+}$ absorption

- Decreased bone deposition and increased bone resorption

Increased Blood $[\text{Ca}^{2+}]$

Decreased Blood $[\text{Ca}^{2+}]$
Fig. 12.4  The bone remodelling cycle. \((1,25 \text{(OH)}_2 \text{D} = 1,25\text{dihydroxyvitamin D})\)
Response to Mechanical Stress

Wolff's law - a bone grows or remodels in response to the forces or demands placed upon it.
Mechanical control of remodelling

- Hormonal control determines *when* remodelling will occur
- Mechanical stress determines *where* remodelling occurs
  - Mechanical loading reduces osteoclast sensitivity to PTH
Osteoporosis

Normal bone (left) and bone loss in osteoporosis (right)
Decalcified Bone Matrix
This cross section of a long bone shows cortical bone to the right and bone marrow to the left. The white circles in the marrow are fat cells. In this preparation calcium has been removed during tissue processing.
• Decalcified Bone Matrix
Osteoclasts (blue) are responsible for degradation of old bone.
• Be careful, do not mistake the large multinucleate osteoclast with the equally large megakaryocyte.
• The megakaryocyte (green) has a single multi-lobed nucleus.
Acromegaly

- Pituitary adenoma (CT scan or MRI)
- Hypertrophy of sweat & sebaceous glands
- Galactorrhea (prolactin)
- Cardiomegaly
- Hypertension
- Sexual dysfunction
- Peripheral neuropathy

High blood - [Growth Hormone]

- Visual field defects
- Prominent supraorbital ridge
- Large nose and jaw
- Teeth are separated or lacking
- Abnormal glucose tolerance test
- Glucosuria/polyuria
- Spade-shaped hands and feet
- Arthrosis

Fig. 38-7
Hyperparathyroidism

Increased Blood \([\text{Ca}^{2+}]\)

- Epulis (Giant cell tumour)
- Metastatic calcification
- Peptic ulcer Pancreatitis
- Muscular atrophy

- Skull decalcification ("salt- and pepper skull")
- Parathyroid ADENOMA
- Osteitis fibrosa cystica Subperiostal resorption
  - Nephrocalcinosis
  - Kidney stones (Calcium phosphate)
  - Renal infections
  - Renal failure

Fig. 30-8