The Calciotropic Hormones

Arjumand Warsy
M.Sc 560

A.S. Warsy
Bone mineral Homeostasis

• A highly integrated and complex endocrine system maintains calcium, phosphate, and magnesium homeostasis in all vertebrates.
• It involves:
  • Parathyroid hormone (PTH) and
  • Calcitonin (CT),
  • 1,25-dihydroxycholecalciferol, 1,25(OH)₂D³.
• Other hormones, such as insulin, cortisol, growth hormone (GH), thyroxine, epinephrine, estrogen, testosterone, somatomedin, and inorganic phosphate, together with some compounds not yet identified and certain physical phenomena, have roles in modifying and regulating organ response to PTH, CT, and 1,25(OH)₂D³.

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Calcium level in plasma

• Concentrations of total calcium in normal serum generally range between 8.5 and 10.5 mg/dL (2.12 to 2.62 mM) and levels above this are considered to be hypercalcemia, concentrations less than the normal range produce hypocalcaemia.
**Calcium balance.** On average, in a typical adult approximately 1g of elemental calcium (Ca$^{+2}$) is ingested per day. Of this, about 200mg/day will be absorbed and 800mg/day excreted. Approximately 1kg of Ca$^{+2}$ is stored in bone and about 500mg/day is released by resorption or deposited during bone formation. Of the 10g of Ca$^{+2}$ filtered through the kidney per day only about 200mg appears in the urine, the remainder being reabsorbed.
Calcium Distribution in Blood Plasma:

- Calcium is distributed in 3 major fractions: ionized, protein-bound, and complexed.
- The ionized fraction ($Ca^{2+}$), is the only biologically active form, constitutes 46-50% of the total calcium.
- The protein-bound fraction, roughly equivalent to the ionized fraction in amount, is biologically inert.
- However, the calcium bound to albumin (80%) and globulin (20%) is an important source of readily available $Ca^{2+}$, calcium can dissociate from its binding sites as a first line of defense against hypocalcemia.

\[
\% \text{ protein-bound } Ca^{2+} = 8 \times \text{ albumin (g/dL)} + 2 \times \text{ globulin (g/dL)} + 3
\]

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Calcium in the blood

– Partly bound to plasma proteins (about 45%) notably albumin,
– Partly bound to small anions such as phosphate and citrate (about 10%)
– and partly in the free or ionized state (about 45%)

• The normal range of ionized calcium is 4.65-5.25 mg/dL (1.16-1.31 mM).
• When protein concentrations, and especially albumin concentrations, fluctuate substantially, total calcium levels may vary, whereas the ionized calcium may remain relatively stable.

The ionized calcium is metabolically active ie subject to transport into cells and capable of activating cellular processes

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Importance of calcium ion

• \( \text{Ca}^{++} \) is essential for numerous cellular functions including:
  – cell division,
  – cell adhesion,
  – plasma membrane integrity,
  – protein secretion,
  – muscle contraction,
  – neuronal excitability,
  – glycogen metabolism,
  – and coagulation.

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Ca^{++} homeostasis

• The extracellular fluid (ECF) concentration of calcium is tightly maintained within a rather narrow range

• Tight regulation of the ECF calcium concentration is maintained through the action of calcium-sensitive cells which modulate the production of hormones

• These hormones are:
  – Parathyroid hormone
  – Calcitonin
  – Vitamin D

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• PTH, CT, and 1,25 (OH)2D3, regulate the flow of minerals into and out of the extracellular fluid compartment through their actions on intestine, kidney, and bone.
Phosphate:

- Only 15% of the plasma phosphate is bound to proteins in the blood.
- The rest is ultrafilterable and consists mainly of free $\text{HPO}_4^{2-}$ and $\text{NaHPO}_4^{-}$ (85%), with free $\text{H}_2\text{PO}_4^{-}$ making up the remainder (15%).
- Phosphorus has a wider range of normal plasma values (2.5 – 4.5 mg/dL).
- Increases or decreases in dietary phosphorus are promptly reflected in corresponding increases or decreases in serum phosphorus and urinary phosphorus excretion.

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Parathyroid Hormone

- Voice Box
- Upper Parathyroids
- Lower Parathyroids
Parathyroid glands

- There are four parathyroid glands which are normally the size and shape of a grain of rice.
- The parathyroid gland are behind the thyroid.
- Small glands located in the neck behind the thyroid.
- Normal parathyroid glands are the color of spicy yellow.

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There are three types of cells in the parathyroid gland: adipocytes, chief cells and oxyphil cells.

A reticular connective tissue framework surrounds and supports these cells.

The main secretory cell is the chief cell. These cells secrete parathyroid hormone. Unfortunately these cells have no distinguishing features.
Thyroid and parathyroid
Parathyroid Hormone (PTH)

- PTH is a glycoprotein hormone
- It has 84 amino acid, arranged as a linear polypeptide with a molecular weight of 9500.

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Biosynthesis

- Preproparathyroid hormone (preproPTH) - 90 aa.
- The hydrophobic 23-amino-acid "pre" sequence acts to bind the polyribosome-precursor complex to the endoplasmic reticulum, providing access to the cisternal space and, presumably, to the enzyme ("clipase") that removes the "pre" sequence, leaving the 90-amino-acid-proPTH structure.
- The proPTH is converted to PTH in the Golgi apparatus by proteolytic removal ("tryptic clipase") of the remaining 6-amino-termino acid sequence.
- Cleaved into an 84 amino acid protein → stored and released from the parathyroid glands.
• The 84-amino-acid polypeptide is ready for secretion either in a secretory granule or in its free form.

• Intracellular stores of PTH may be regulated by a degradative pathway that is stimulated by high and inhibited by low extracellular calcium.

• In the plasma, PTH is broken down further into a short, active NH2-end (AAs 1-34) component and an inactive COOH-end (AAs 35-84) component.
Control of Secretion

- PTH is rapidly released from the parathyroid gland in response to decreases in the plasma ionic Ca++. It acts on kidney and bone and indirectly on intestine to restore the concentration of this Ca++ to just above the normal set point, which in turn inhibits secretion of the hormone.
- The concentration of extracellular Ca++ is the major regulatory of PTH secretion.
- Other factors influence secretion only indirectly through increasing or decreasing extracellular ionic calcium.
- Prolonged hypomagnesemia markedly inhibits secretion of PTH and may be associated with hypocalcemia.

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PTH secretion

• A decrease in the normal levels of calcium in the blood causes the chief cells of the parathyroid gland to secrete more parathyroid hormone which stimulates osteoclasts to mobilize bone resulting in an increase in the level of calcium in the blood.

• Parathyroid hormone also increases Ca++ reabsorption in the kidney

• and decreases the reabsorption of phosphate ions.

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Low concentration of calcium in blood

Release of parathyroid hormone

- Efflux of calcium from bone
- Decreased loss of calcium in urine
- Enhanced absorption of calcium from intestine

Increased concentration of calcium in blood
Ca\textsuperscript{++} and PTH secretion

- Ca\textsuperscript{++} is a universal messenger that controls a variety of cell functions, including secretion. In most secretory cells, rise of the cytoplasmic Ca\textsuperscript{++} concentration stimulates secretion. However, the parathyroid cell is an exception to this rule, cytoplasmic Ca\textsuperscript{++} is an inhibitory messenger for parathyroid hormone secretion.
Under basal conditions the cytoplasmic Ca\textsuperscript{2+} concentration is about 10 000-fold lower than the extracellular concentration. This low concentration is maintained by the activity of a Ca\textsuperscript{2+}-pumping ATPase (PMCA) and a Na\textsuperscript{+}/Ca\textsuperscript{2+} exchange mechanism in the plasma membrane. There is also a Ca\textsuperscript{2+}-pumping ATPase in the endoplasmic reticulum (SERCA). Activation of voltage-operated Ca\textsuperscript{2+} channels (VOC) results in influx of Ca\textsuperscript{2+} through the plasma membrane and a prominent rise of cytoplasmic Ca\textsuperscript{2+}, which is the major mechanism explaining the release of blood glucose-regulating hormones (orange). Intracellular messengers like inositol trisphosphate (IP\textsubscript{3}) and cyclic ADP ribose (cADPr) acting on specific receptors can also release Ca\textsuperscript{2+} from the endoplasmic reticulum. These receptors are also sensitive to Ca\textsuperscript{2+} itself causing Ca\textsuperscript{2+}-induced Ca\textsuperscript{2+} release (CICR). When the Ca\textsuperscript{2+} content of the endoplasmic reticulum decreases there is activation of store-operated Ca\textsuperscript{2+} in the plasma membrane (SOC). We study all these aspects of Ca\textsuperscript{2+} signalling and their importance for hormone release and other physiological processes.
Ca++ and PTH

- Serum Ca++ levels are the most important regulators of PTH. Hypocalcemia is the major stimulus

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased Serum Ca(^{2+})</td>
<td>→ Increased PTH</td>
</tr>
<tr>
<td>Increased Serum PO(_4^-)</td>
<td>→ Increased PTH</td>
</tr>
</tbody>
</table>

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Calcium sensing receptor

• The PT glands detect ECF Ca via a Ca-sensing receptor (CaSR). This receptor has a large NH2-terminal extracellular domain which binds ECF Ca, seven plasma membrane-spanning helices and a cytoplasmic COOH-terminal domain. It is a member of the superfamily of G protein coupled receptors and in the parathyroid chief cells is linked to various intracellular second-messenger systems. Transduction of the ECF calcium signal via this molecule leads to alterations in PTH secretion.

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The Ca sensing receptor (CaSR) is the principal regulator of PTH release.

- The CaSR is located on the chief cell of the parathyroid gland and is the principal regulator of PTH release. When the CaSR is inactive, vesicles move into the cell membrane and release their stores of PTH. As the CaSR is activated by increasing serum calcium levels, release of PTH is inhibited.

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Ca++ Sensing receptor
CaSR

Chief cell of the parathyroid gland

PTH vesicle

Calcium-sensing receptor (CaR)
Plasma Ca++ and PTH metabolism

• A change in ECF Ca++ also produces a change in PTH metabolism in the parathyroid cell.
• This response is slower than the secretory response.
• A rise in Ca++ will promote enhanced PTH degradation and the release of bioinert mid-region and COOH fragments,
• A fall in Ca++ will decrease intracellular degradation so that more intact bioactive PTH is secreted. Bioinactive PTH fragments, which can also be generated in the liver, are cleared by the kidney.
• With sustained low ECF calcium there is a change in PTH biosynthesis which represents an even slower response.
• Thus, low ECF calcium leads to increased transcription of the gene encoding PTH and enhanced stability of PTH mRNA
• Sustained hypocalcemia can eventually lead to parathyroid cell proliferation and an increased total secretory capacity of the parathyroid gland. Although sustained hypercalcemia can conversely reduce parathyroid gland size, hypercalcemia appears less effective in diminishing parathyroid chief cells once a prolonged stimulus to hyperplasia has occurred.
Functions of Parathyroid Hormone

The major function of PTH is to correct hypocalcemia, by:
1. conservation of calcium by the kidney,
2. release of calcium from bone,
3. enhanced absorption of calcium from the gut (indirectly via vitamin D), and
4. reduction in plasma phosphate.
Control of PTH secretion and PTH action
Role of Parathyroid Hormone Target Tissues

- Under normal circumstances, PTH prevents serum calcium from falling below physiologic concentrations by stimulating calcium movement from intestinal and renal tubular lumina and from the bone fluid compartment into the blood.
- Its effects on bone and kidney are direct, PTH acts indirectly on the intestine, through the mediation of Vitamin D.
- Stimulates the conversion of $25(0H)D_3$ to $1,25(OH)_2D_3$ in the kidney via a $25(OH)D_3$, 1α-hydroxylase in the mitochondria of the renal tubule.
- The $1,25(OH)_2D_3$ thus formed stimulates intestinal calcium absorption. PTH also prevents serum phosphate levels from rising above normal physiologic concentrations by increasing renal tubular excretion of phosphate.
## Actions of PTH

<table>
<thead>
<tr>
<th>Renal effects:</th>
<th>Bone effects:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Increases Ca(^{2+}) reabsorption in distal tubule</td>
<td>• Increases bone resorption</td>
</tr>
<tr>
<td>• Decreases PO(_4^-) reabsorption in distal tubule</td>
<td>• Facilitates bone formation</td>
</tr>
<tr>
<td>• Increases 1-alpha-hydroxylase (which facilitates the production of 1,25-(OH)(_2)-Vit D)</td>
<td></td>
</tr>
</tbody>
</table>

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A. **Effects of PTH on Kidney:**

1. To increase renal tubular reabsorption of calcium and magnesium, and
2. To increase phosphate and bicarbonate excretion by inhibiting their proximal tubular resorption.

- **Hormone:** induced bicarbonaturia tends to produce acidosis, which decreases the ability of circulating albumin to bind calcium, thus increasing Ca++ by physiochemical means.

- **Release of phosphate from bone**, which occurs obligatory during hormone-induced Ca mobilization from bone, **does not produce hyperphosphatemia.**
Contd…

- PTH, either stimulates renal tubular 25(OH)D₃, 1α-hydroxylase to convert the major circulating metabolite of cholecalciferol, 25(OH)D₃, to its major biologically active metabolite, 1,25(OH)₂D₃.

- This latter compound acts directly on intestinal mucosal cells to increase calcium absorption and on bone to increase resorption.

- PTH increases urinary excretion of cAMP.
B. Effects of PTH on Bone:

- PTH increases the net release of calcium and phosphate from bone into extracellular fluid.

- This is direct result of the hormone's effect on the differentiation of activities of bone cells (osteogenic precursors, osteoblasts, osteoclasts, and osteocytes).
Bone resorption

• Bone resorption is the normal destruction of bone by osteoclasts, which are indirectly stimulated by PTH.

• Stimulation is indirect since osteoclasts do not have a receptor for PTH; rather, PTH binds to osteoblasts, the cells responsible for creating bone.

• Binding stimulates osteoblasts to increase their expression of RANKL, which can bind to osteoclast precursors containing RANK, a receptor for RANKL.

• The binding of RANKL to RANK stimulates these precursors to fuse, forming new osteoclasts which ultimately enhances the resorption of bone.
Calcium ion concentration decreases

Secretion of parathyroid hormone

Effect on intestines
- Increased calcium ion absorption

Effect on bone
- Osteoclast activity increases

Effect on kidney
- Calcium ion retention in renal tubules
- Phosphate ion secretion from renal tubules

Blood calcium ion concentration increases
- Normal calcium ion concentration

Blood phosphate ion concentration increases
- Normal phosphate ion concentration
Mechanism of Action

- PTH binds to specific plasma membrane receptors of target cells.
- Activates membrane-bound adenylate cycalase to convert ATP to cAMP.
- Activates intracellular phosphorylations.
Calcitonin
Calcitonin

- Calcitonin is a polypeptide hormone.
- As the level of calcium in the blood rises, the amount of calcitonin secreted by the C cells of the thyroid increases.
- Calcitonin stimulates osteoblasts to form bone taking calcium out of the circulation.
- At the same time, calcitonin inhibits the mobilization of bone (and calcium) by osteoclasts.
- The end result is a decrease in the level of calcium in the blood thus helping to maintain proper blood calcium levels.
**Structure & Biosynthesis**

- Calcitonin (CT), a 32-amino-acid polypeptide with a molecular weight of 3700 and a disulfide bridge between residues 1 and 7 is biosynthesized and secreted by (parafollicular, "C") cells.

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-</td>
<td>1 2 3 4 5 6 7 8 9</td>
</tr>
<tr>
<td>Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-</td>
<td>10 11 12 13 14 15 16 17 18 19</td>
</tr>
<tr>
<td>Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-</td>
<td>20 21 22 23 24 25 26 27 28 29</td>
</tr>
<tr>
<td>Gly-Thr-Pro-NH₂</td>
<td>30 31 32</td>
</tr>
</tbody>
</table>

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Calcitonin Synthesis
Parafollicular (C) cells in thyroid gland
Synthesis of calcitonin
• Human CT is cleaved from a high-molecular-weight precursor that also contains 2 other peptides, katacalcin and calcitonin gene-related peptide (CGRP).
Processing of Calcitonin Gene

The primary transcript has two poly-A sites, one is in the brain, the other is in the thyroid. In the brain, the splicing omits the exon 4, and results in exons 1, 2, 3, 5, 6 and polyA. In the thyroid, the splicing with exon 4, generates shorter transcripts with exons 1, 2, 3, and 4.
Control of Secretion

• CT is rapidly released by the "C" cells in response to small increases in plasma ionic calcium.
• It acts on kidney and bone to restore the level of Ca\(^{++}\) to just below a normal set point, which in turn inhibits secretion of the hormone.
• CT is a physiologic antagonist of PTH.
• The hormones act in concert to maintain the normal concentration of ionic calcium in extracellular fluid.
• There is a positive correlation between plasma calcium and plasma immunoreactive CT (iCT) in normal subjects when plasma calcium is increased above the normal range.
Metabolism & Circulation

Forms

• CT exists in several molecular forms both in tissue and in plasma.
• Fragments consists of as many as 4 or 5 immunoreactive forms which have molecular weights large than the 32-amino-acid CT.
• It is likely that some of these forms are polymers of CT with interchain disulfide molecular linkages.

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Role of Calcitonin

• Calcitonin prevents abnormal increase in both serum calcium and serum phosphate.

• It decreases the translocation of calcium from the renal tubule and bone fluid compartment into the blood and thus can be considered as a counter regulator of PTH.
# Actions of major calcium-regulating hormones

<table>
<thead>
<tr>
<th>Parathyroid hormone (PTH)</th>
<th>Bone</th>
<th>Kidney</th>
<th>Intestine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increases resorption of calcium and phosphate</td>
<td>Increases resorption of calcium, decreases reabsorption of phosphate; increases conversion of 25OHD3 to 1,25(OH)2D3; decreases resorption of bicarbonate.</td>
<td>No direct effects</td>
</tr>
<tr>
<td>Calcitonin (CT)</td>
<td>Decreases resorption of calcium and phosphate</td>
<td>Decreases resorption of calcium and phosphate. Questionable effect on vitamin D metabolism.</td>
<td>No direct effects.</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Maintains Ca2+ transport system.</td>
<td>Decreases resorption of calcium</td>
<td>Increases absorption of calcium and phosphate.</td>
</tr>
</tbody>
</table>

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Calcitonin Receptor

Cartoon of Calcitonin Receptor

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Calcitonin and Fracture Reduction

• Continuous use of calcitonin is associated with a persistent decrease in the rate of bone resorption, which is associated with decreased resorptive activity and the number of osteoclasts.

• The Prevent Recurrence of Osteoporotic Fractures (PROOF) trial, the largest randomized controlled trial of nasal calcitonin, demonstrated a reduction in vertebral fractures for those individuals taking 200 IU/d, but there was no significant decline for those receiving 100 or 400 IU/d. Intranasal calcitonin has not been shown to significantly decrease nonvertebral fracture rates after 5 years.

• Calcitonin was previously available only as a subcutaneous or intramuscular injection; however, a nasal spray preparation of salmon calcitonin was approved for treatment of osteoporosis. The most common side effect of the nasal spray preparation is rhinitis, with rare instances of mucosal ulceration. The nausea seen in some patients receiving injectable calcitonin does not appear to occur with intranasal preparations.
Calcitonin is used for treatment of osteoporosis

- Calcitonin is used therapeutically in the treatment of osteoporosis.
- Recent studies have shown that other tissues are capable of producing calcitonin, such as the pituitary gland, the mammary gland, and even the perichondrium/periosteum which line endochondral growth plate.
Osteoporosis, a disease that makes bones more fragile, is responsible for more than 1.5 million fractures annually, including:

- About 700,000 vertebral fractures
- Over 300,000 hip fractures
- About 250,000 wrist fractures

Bones naturally destroy and rebuild themselves over a lifetime. Here is a section of a healthy bone.

In people with osteoporosis, bones become quite porous, like this section of a bone.

Source: National Osteoporosis Foundation

Photo credit: Photo Researchers
Osteoporosis

• Osteoporosis, a disorder involving demineralization of bone usually associated with older individuals can be related to several factors:
  – 1) deficiency of dietary calcium
  – 2) reduced estrogen levels common in post-menopausal women. This may be treated with HRT, hormone replacement therapy.
  – 3) reduced activity and exercise, including:
    – 4) reduced weight bearing stress on the bones. This is important in stimulating bone growth and replacement at any age.

• Osteoporosis treatment may include calcium formulated with other minerals, hormone replacement therapy, calcitonin, and an exercise program.

• There are two types of osteoporosis:
  – 1) Post-menopausal osteoporosis - due to estrogen deficiency in post-menopausal women, this causes Calcium to be lost from the bones.
  – 2) Senile osteoporosis, in which reduced Vitamin D production in old age reduces calcium absorption. This produces PTH secretion which stimulates osteoclasts and bone loss.
Moderate Osteoporosis

A. Female, age 88 years

Severe Osteoporosis

B. Male, age 89 years
Decrease in height with age
Incidence of fractures in women

![Graph showing incidence of fractures in women by age group and type of fracture.](image-url)
Rising calcium level has not been shown to increase bone deposition by itself, but it makes it possible.

Other sources precede bone as a source of calcium.

Osteoclasts degrade bone matrix and release Ca^{2+} into blood.

Important for bone growth in children. It is now being given to older adults to help reverse osteoporosis.

Calcitonin stimulates calcium salt deposit in bone.

Falling blood Ca^{2+} levels

Calcium homeostasis of blood
9–11 mg/100 ml

Imbalance

PTH

Parathyroid glands release parathyroid hormone (PTH)

© BENJAMIN/CUMMINGS
PTH for treatment of osteoporosis

• In 1986 and in 1990, investigators published the first clinical research studies which showed that PTH, injected once daily, dramatically increased bone mass in the spine of osteoporotic men and osteoporotic postmenopausal women.

• These findings were subsequently confirmed by studies in other institutions, that demonstrated the bone building effect of PTH in both men and women.
Confirmation

• In May 2001, results of investigators were published in the New England Journal of Medicine.

• The study demonstrated that PTH is markedly better than any available treatment in reducing vertebral fractures (70% fewer than in the control) and in increasing bone density (up 13% in the spine and 6% in the femoral neck) over the course of the study (18-26 months).

• This increase in bone density and dramatic drop in the number of fractures is far superior to any other treatment available.

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Role of PTH in osteoporosis

• The effects of PTH on bone growth and resorption are both paradoxical and complex.

• Continuous high levels of PTH result in high levels of calcium in the blood and a decrease in bone density.

• However, injections of PTH administered once a day, result in an increase in bone density.
The effects of PTH are mediated by a specific receptor, found on osteoblast cells in bone and on tubule cells in the kidney. The receptor is embedded in the cell membrane and when the hormone binds to the receptor, a conformational change takes place. This initiates two cascades of biochemical events within the cell,

- increased synthesis of cAMP---leading to phosphorylation
- increased calcium uptake into the cell and enzyme activation.

At present, it is not clear whether one or both of these cascades initiates bone growth.
Parathyroid hormone related peptide

• In addition to PTH,
• A similar protein is secreted and acts locally within the bone, known as parathyroid hormone-related peptide (PTHrP).
• This acts on the same receptor as PTH, known as the PTH/PTHrP receptor.
• A second PTH receptor (PTH-2 receptor) that does not respond to PTHrP also exists. Studies are concentrating on PTH/PTHrP receptor functions.

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PTH receptor

- Regions of PTH/receptor binding (Mol Endocrinol. '95, JBC '98)
- Sites of mutation resulting in constitutive activation (J Clin Endo Metab '99)
- Sites that differ in PTH-2 receptor and affect PTHrP binding
- Sites important for signalling
PTH Activates the PTH/PTHRP Receptor by Changing its Shape

Activated receptor initiates cascades of events inside cell leading to:
- Ca^{2+} uptake
- cAMP synthesis
Vitamin D

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VITAMIN D

- A sterol
- A fat soluble vitamin
- Acts as a hormone
- Essential for action of PTH and CT

Main types:

- Vitamin D$_3$ (cholecalciferol) is primarily synthesized in the skin by ultraviolet irradiation of 7-dehydrocholesterol.
- Vitamin D$_2$ (erogalciferol), which is used to fortify dairy products, is produced by ultraviolet irradiation of the plant sterol ergosterol.

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7-dehydrocholesterol (Diet) → UV → Cholecalciferol (Skin) → Bound Cholecalciferol (Blood) → 25-hydroxycholecalciferol (Liver) → 1,25-dihydroxycholecalciferol (Kidneys) → Ca Absorption (GIT) → PTH +

25-Hydroxylase

1α-Hydroxylase

DBP
Major source – sunlight

Skin

Cholecalciferol (vitamin D₃)

7-Dehydrocholesterol

Minor source – dietary intake

Vitamin D₃ (fish, meat)
Vitamin D₂ (vitamin supplements)

Liver

25-dihydroxyvitamin D₃

Kidney

1,25-dihydroxyvitamin D₃

↑Calcium absorption (small intestine)
↑Urinary calcium re-absorption (kidney)
↑Bone mineralisation

Maintains calcium balance in the body via the action of parathyroid hormone
VITAMIN D

Concentrations of Vitamin D Metabolites:

- Normal individuals, $1,25(OH)_2D_3$ is 30 pg/mL.
- $25OHD_3$ circulates in concentrations 1000 times greater than $1,25(OH)_2D_3$ suggests that $25OHD_3$ may have intrinsic biologic importance as well.

Other Hydroxylation Pathways:

- $25(OH)D_3$ to $24,25(OH)_2D_3$ occurs mainly in the kidney.
- PTH stimulates production of $1,25(OH)_2D_3$ but suppresses that of $24,25(OH)_2D_3$.

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Role of Vitamin D

• The principal physiological role of vitamin D is to increase plasma levels of calcium and phosphate and thus maintain conditions favorable for bone mineralization. Essential for the actions of PTH and CT.
• Facilitate the absorption of calcium and phosphate by the intestine.
• Vitamin D acts as a classic steroid hormone.
• $1\text{,}25\text{(OH)}_2\text{D}_3$ receptors have also been demonstrated in bone, parathyroid glands, pancreas, pituitary, placenta, and other tissues.
The actions of Vitamin D

<table>
<thead>
<tr>
<th>Gut effects:</th>
<th>Bone effects:</th>
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<tbody>
<tr>
<td>• Increases calcium absorption</td>
<td>• Increases bone resorption</td>
</tr>
<tr>
<td>• Increases phosphate absorption</td>
<td>• Facilitates bone formation</td>
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</table>

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## Control of Vit D level

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased Serum Ca&lt;sup&gt;2+&lt;/sup&gt;</td>
<td>Increased 1,25-(OH)&lt;sub&gt;2&lt;/sub&gt;-vitamin D</td>
</tr>
<tr>
<td>Decreased Serum PO&lt;sub&gt;4&lt;/sub&gt;&lt;sup&gt;-&lt;/sup&gt;</td>
<td>Increased 1,25-(OH)&lt;sub&gt;2&lt;/sub&gt;-vitamin D</td>
</tr>
<tr>
<td>Increased Serum PTH</td>
<td>Increased 1,25-(OH)&lt;sub&gt;2&lt;/sub&gt;-vitamin D</td>
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</tbody>
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Deficiency of Vit.D: Rickets
Summary of the effect of hormones on Ca\(^{++}\) level

- A reduction in ECF calcium stimulate release of parathyroid hormone (PTH) from the parathyroid glands.
  - PTH acts to enhance bone resorption and liberate both calcium and phosphate from the skeleton.
  - PTH can also enhance calcium reabsorption in the kidney, and inhibits phosphate reabsorption producing phosphaturia.
  - Hypocalcemia and PTH itself can both stimulate the conversion of the inert metabolite of vitamin D, 25-hydroxyvitamin D3 [25(OH)D3], to the active moiety 1,25-dihydroxyvitamin D3 [1,25(OH)2D3], which in turn will enhance intestinal calcium, and to a lesser extent phosphate reabsorption.
  - The net effect of the mobilization of calcium from bone, the increased absorption of calcium from the gut and the increased reabsorption of renal calcium is to restore the ECF calcium to normal and to inhibit further production of PTH and 1,25(OH)2D3.

- The opposite sequence of events ie diminished PTH and 1,25(OH)2D3 secretion occurs when the ECF calcium is raised above the normal range and the effect of suppressing the release of these hormones diminishes skeletal calcium release, intestinal calcium absorption and renal calcium reabsorption and restore the elevated ECF calcium to normal.

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DISORDERS OF PARATHYROID FUNCTION

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Syndromes

- **Hyperparathyroidism:** Excessive PTH secretion is known as hyperparathyroidism, and is often the result of a benign parathyroid tumor (primary hyperparathyroidism) that loses its sensitivity to circulating calcium levels. In chronic renal failure secondary hyperparathyroidism can result.

- **Hypoparathyroidism:** Insufficient PTH secretion is known as hypoparathyroidism, and is commonly caused by surgical misadventure (e.g., inadvertent removal during routine thyroid surgery), autoimmune disorder, or inborn errors of metabolism.
Hypoparathyroidism

- Deficient secretion of PTH is characterized clinically by:
  - symptoms of neuromuscular hyperactivity and
  - biochemically by:
    - hypocalcemia,
    - hyperphosphatemia,
    - and diminished to absent circulating iPTH.
Etiology:

1. **Surgical hypoparathyroidism:**
   - Most common type.
   - After any surgical procedure including thyroidectomy, removal of abnormal parathyroid glands, and excision of malignant neck lesions.

2. **Idiopathic hypoparathyroidism:**
   - is a broad category of disorders undoubtedly with more than one cause.
   - 2 subcategories:
     - occurring at an early age
     - occurring late in life.
• **Congenital absence** of the glands (as in DiGeorge's syndrome).
• Early age are of genetic origin, with an **autosomal recessive** mode of transmission.
• This type of hypoparathyroidism is "multiple endocrine deficiency-autoimmune-candidiasis (MEDAC) syndrome" or "juvenile familial endocrinopathy" or "hypoparathyroidism-Addison's disease-mucocutaneous candidiasis (HAM) syndrome"
• Circulating **autoantibodies** specific for parathyroid and adrenal tissue are frequently present.
• The late-onset form of idiopathic hypoparathyroidism occurs sporadically without circulating glandular autoantibodies.

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3. **Functional hypoparathyroidism:**
   - Occurs in patients who have undergone long periods of hypomagnesemia.
   - Selective defects in gastrointestinal magnesium absorption, generalized gastrointestinal malabsorption, or alcoholism.
   - Since magnesium is required for PTH release from the glands.
   - Hypocalcemia is also present.
   - Treatment with magnesium salts is followed within minutes by an increase in serum iPTH.

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Pathology:

1. Decrease bone resorption;
2. Decreased renal phosphate excretion, increased serum phosphate, decreased, 1,25(OH)2D3, and decreased intestinal absorption of calcium; and
3. Increased renal excretion of calcium for the prevailing serum concentration of calcium. There is hypocalcemia and usually hyperphosphatemia, if dietary phosphate intake has been normal. Urinary calcium is usually low unless eucalcemia has been restored with treatment. Hypocalcemia and alkalosis (due to decreased bicarbonate excretion), if sufficiently severe, cause increased neuromuscular excitability with consequent tetany and, rarely convulsions.

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Clinical Features:

A. Neuromuscular Manifestations:
   • Complications are most likely to occur within 1-2 days after parathyroidectomy, when serum calcium decreased acutely.
   1. Paresthesias – Numbness and tingling may occur abound the mount, in the tips of the fingers, and sometimes in the feet.
   2. Tetany – An attack of tetany usually begins with prodromal paresthesias and is followed by spasms of the muscles of the extremities and face. The hands, forearms, and, less commonly, the feet become contorted in a characteristic way. First, the thumb is strongly adducted, followed by flexion of the metacarpophalangeal joints.
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3. **Hyperventilation** – patients may hyperventilate and secrete increased amounts of epinephrine. Hyperventilation causes hypocapnia and alkalosis, which in turn worsen hypocalcemia by causing increased binding of ionic calcium to plasma proteins.

4. **Adrenergic symptoms** – Increased epinephrine secretion produces further anxiety, tachycardia, sweating, and peripheral and circumoral pallor.

5. **Convulsions** – Patients with hypoparathyroidism may have convulsions.
6. **Signs of latent tetany** – Chvostek's sign is elicited by tapping the facial nerve just anterior to the ear lobe. The response ranges from twitching of the lip at the corner of the mouth to twitching of all of the facial muscles on the stimulated side.

**Trousseau's sign** – should be sought with a sphygmomanometer cuff. The cuff is inflated to above systolic blood pressure for at least 2 minutes while the hand is observed carefully. A positive response consists of the development of typical carpal spasm, with relaxation occurring 5-10 seconds after the cuff is deflated.

7. **Extrapyramidal signs** – classic Parkinsonism.
B. Other Clinical Manifestations:

1. Posterior lenticular cataract.
2. Cardiac manifestations.
3. Dental manifestations.
Diagnosis:

Measurement of:

A. Serum calcium.
B. Serum phosphours.
C. Serum iPTH.

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**Treatment:**

A. Therapeutic Difficulties:
   - Theoretically, the most appropriate therapy for hypoparathyroidism would be physiologic replacement of PTH.
   - Parenterally high cost.

B. Emergency Measures for Tetany:
   - Intravenous calcium.
   - This aim is to prevent laryngeal stridor and convulsions.

C. Severe Hypocalcemia ("Hungry Bone" Syndrome):
   - As much as 10g of elemental calcium administered intravenously by infusion over 24 hours may be required to increase serum calcium above 7.5 mg/dl.

D. Severe Hypoparathyroidism:
     - Errocalciferol (vitamin D2).
     - Calcium.

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Complications:

- Hypercalcemia.
- Hypercalciuria.

Prognosis:

- Long-term restoration of serum calcium to normal or nearly normal ranges usually results in improvement in most manifestations of surgical and idiopathic hypoparathyroidism.

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PSEUdoHYPOparathyroidism & PSEUdoPSEUDOHypoParathyroidism

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PSEUDOHYPOPARATHYROIDISM & PSEUDOPSEUDOHYPO-PARATHYROIDISM

• Rare familial disorder characterized by target tissue resistance to PTH, hypocalcemia, increased parathyroid gland function, and a variety of congenital defects in the growth and development of the skeleton, including short stature and short metacarpal and metatarsal bones.
• Patients with pseudopseudohypoparathyroidism have the developmental defects without the biochemical abnormalities of pseudohypoparathyroidism.

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• There are also patients with pseudohypo-parathyroidism who have target tissue resistance to the hormone but no developmental abnormalities, and others with developmental abnormalities who experience spontaneous cure of biochemical abnormalities.
• There are even patients who have developmental abnormalities and clinical hypoparathyroidism in the face of typical osteitis fibrosa cystica.
• This syndrome is known as pseudohyphyperparathyroidism.

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Etiology:

- Cannot be ascribed to a single underlying biochemical defect.

- It is likely that defects in any one of a number of limiting steps, from receptor binding of the hormone to final expression of the cellular action of PTH, could be involved.
Genetic Basis of Pseudohypoparathyroidism:

- Pseudohypoparathyroidism is inherited.

- The 2:1 female:male ratio of occurrence suggests an X-linked dominant mechanism.

- Several cases of male-to-male transmission of the developmental defects have been recorded.
Incidence:

• Rare.

Pathologic Physiology:

• The biochemical findings in patients with surgical or idiopathic hypoparathyroidism.
Clinical Features:

• Most of the symptoms and signs of pseudohypoparathyroidism are the same as those of surgical hypoparathyroidism and idiopathic hypoparathyroidism and are due almost entirely to chronic hypocalcemia.

• Certain unique developmental features.
  • Mentally retarded, short and stocky, and obese with rounded faces.
  • Many have one or more short metacarpal or metatarsal bones.
  • There may be delayed dentition, defective enamel, and absence of teeth.

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Diagnosis:

• The diagnosis of pseudohypoparathyroidism is likely when the developmental abnormalities described above are present.

• Serum calcium and phosphorus are normal in such a patient.

Treatment:

• Identical to that for hypoparathyroidism.

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Hyperparathyroidism

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Hyperparathyroidism

- Elevation of PTH
  - Primary
  - Secondary
PRIMARY HYPERPARATHYROIDISM

• Primary hyperparathyroidism represents an overlapping group of syndromes that are caused by excessive, secretion of PTH by one or more hyperfunctioning parathyroid glands.

• Hypercalcemia fails to inhibit gland activity in the normal manner.

• Nephrolithiasis, osteitis fibrosa cystica, and soft tissue calcification is rare today.

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Etiology:

• Genetic factor may be involved.
• Autosomal dominant trait.
• Thyroid carcinoma.

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Incidence:

- The incidence of primary hyperparathyroidism increases dramatically in both men and women after age 50; it is 2-4 times more common in women.
- The age-adjusted incidence was estimated to be 42 per 100,000.
- Patients over 40 years of age have revealed as many as 1/1000 to 1/200 patients with the disease.

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A. Parathyroid Glands:

- Hyperplastic, adenomatous, or malignant.
- ------("adenoma") occurs in about 80% of patients with hyperparathyroidism and multiple-gland involvement ("hyperplasia") in about 20%.
- Less than 2% of hyperfunctioning glands are malignant.
- Familial primary hyperparathyroidism and the hyperparathyroidism associated with multiple endocrine neoplasia almost always involve multiple glands.
- Abnormal parathyroid glands usually weigh 0.2 – 2g (27-75 mg is normal) and have a characteristic yellow-red color and "bulging" appearance in situ.

The severity of the clinical manifestations – especially the degree of hypercalcemia – is generally proportionate.

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B. **Bone:**
- Analysis of bone biopsies shows the effects of excess PTH on bone.
- Increased bone resorption surfaces, increased numbers of osteoclasts, osteocytic osteolysis, and, in moderate to severe cases, marrow fibrosis.

C. **Kidney:**
- About 20-30% of patients have nephrolithiasis, which is frequently complicated by pyelonephritis.
- Gross nephrocalcinosis or calcification of the renal papillae is unusual.
D. **Other Organs:**
   - Calcification of other organs such as stomach, lung, and heart and blood vessels has been observed in patients with hyperparathyroid crisis (serum calcium > 15 mg/dl).

E. **Muscle:**
   - Myopathy is relatively common in primary hyperparathyroidism, and muscle biopsy may show neuropathic atrophy of both type I and type II muscle fibers. These histologic changes parallel clinical, neurologic, and neuromuscular dysfunction.

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Pathologic Physiology:

A. **Hypercalcemia:**
   - Because the excess PTH stimulates the transport of calcium into the blood from the intestinal and renal tubular lumina as well as from bone.
   - Many patients have decreased renal tubular reabsorption of phosphate, hyperphosphaturia, and hypophosphatemia.

B. **Calcium in Soft Tissues:**
   - Deposition of calcium in soft tissues occurs because the normal solubility product of Ca\(^{2+}\) x PO\(^{4-}\) in serum (approximately 40) is exceeded.
   - This may cause joint pain due to calcific tendinitis and chondrocalcinosis.

C. **Vitamin D Deficiency:**
   - Adaptive mechanism is the development of vitamin D deficiency which may render patients with even severe hyperparathyroidism eucalcemic or nearly so.
D. **Increased Degradation of PTH.**
   • A final adaptive mechanism may be a hypercalcemia-induced increase in the degradation of biologically active forms of PTH peripherally (eg, in the liver and possibly the kidney) and in parathyroid tissue itself.

E. **Hyperchloremic Acidosis:**
   • Patients with primary hyperparathyroidism generally have mild to moderate hyperchloremic acidosis. This is due chiefly to excess PTH, which decreases the urinary concentration of hydrogen ion and increases urinary bicarbonate excretion.

F. **Increased Urinary cAMP:**
   • Urinary cAMP is increased in as many as 80% of patients with primary hyperparathyroidism.

G. **Osteitis Fibrosa Cystica:**
Clinical Features:

A. Symptoms:

1. Hypercalcemia and associated hypercalciuria.

2. Osteitis fibrosa cystica:
   
   • Diffuse bone pain.

   • Pathologic fracture through a bone cyst.
B. Signs:

- Most patients show no signs of the disorder.
- Neurologic abnormalities are nonspecific and include impaired mental functions, mental depression, psychosis, hypoactive deep tendon reflexes, joint hyperextensibility, sensory loss for perception of pain and vibration, proximal muscle weakness, abnormal tongue movements, lingual atrophy, ataxic gain, and abnormally strong (hard) fingernails.
- Soft tissue calcification.
- Enlarged glands.
- Bone tenderness and deformities.

C. X-Ray Findings
Secondary hyperparathyroidism

- Disease outside of the parathyroid gland leads to excessive secretion of parathyroid hormone.
  - A common cause of this disorder is kidney disease - if the kidneys are unable to reabsorb calcium, blood calcium levels will fall, stimulating continual secretion of parathyroid hormone to maintain normal calcium levels in blood.
  - Secondary hyperparathyroidism can also result from inadequate nutrition - for example, diets that are deficient in calcium or vitamin D, or which contain excessive phosphorus (e.g. all meat diets for carnivores).

A prominent effect of secondary hyperparathyroidism is decalcification of bone, leading to pathologic fractures or "rubber bones".
Vitamin D deficiency 
$[25(OH)D < 20 \text{ ng/mL}]$

Intestinal calcium absorption

Ionized $\text{Ca}^{2+}$

Detection of low $\text{Ca}^{2+}$
$\text{Ca}^{2+}$-receptor in parathyroid glands

$\text{PTH}$

Secondary Hyperparathyroidism
Differential Diagnosis of Hypercalcemia

Due to increased serum PTH:
- Primary and "tertiary" hyperparathyroidism
- Some nonhematologic malignant diseases

Not due to increased serum PTH:
- Drug-induced hypercalcemia (thiazides, furosemide, vitamin D, calcium, vitamin A, lithium).
- Granulomatous diseases (sarcoidosis, tuberculosis, beryliosis).
- Genetic diseases (familial hypocalciuric hypercalcemia)
- Immobilization
- "Idiopathic" hypercalcemia.
- Some nonhematologic malignant diseases
- Malignant hematologic diseases
- Nonparathyroid endocrine diseases (Addison's disease, hyper- and hypothyroidism).

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