Calcium metabolism and the Parathyroid Glands

Calcium, osteoclasts and osteoblasts-essential to understand the function of parathyroid glands.

Calcium is an essential element for contraction of voluntary/smooth muscles, NT release, hormonal release, bone composition, acts as 2nd messenger

Calcium exists in bound form in blood and it is bound to albumin and phosphate

Only 10% of the calcium is free and is active and performs its physiological function.

An imbalance of Calcium can either result in:
- Hypercalcemia- well known symptoms including fatigue or weakness
- Hypocalcemia-tetany attacks

We have 3 normal factors/hormones which control normal blood calcium levels and they act on 3 different tissues:
1. PTH
2. Calcitonin-thyroid
3. Vitamin D

*These factors work in harmony to regulate Calcium levels.

*They all work on the kidneys, intestines and bones

→ Function on bone-controls osteoclastic and osteoblastic effects

→ Function on kidneys-controls excretion of Ca and Phosphate

→ Function on intestine-controls absorption of Ca and Phosphate

**To reduce any factor which has a high concentration in the blood you think of:

- Limit food intake(number 1 control),
- Increase metabolism of the substance,
- Increase excretion(kidney)[it is easy to "hit" this site with drugs
- Decrease absorption from the intestines.

Parathyroid Hormone (PTH)

- 83 a.a polypeptide, binds with specific membrane receptor, activates cAMP system
- Regulated by blood Ca level

Increased secretion with decrease levels of Ca

- Starts as a pre-precursor:
  PreproPTH(in the ER)-------→ProPTH(modifications in the Golgi)--------→PTH

-Hypercalcemia shows a decrease in PTH

-Phosphate plays a little role in controlling PTH synthesis and release.

Tremendous release of PTH when free calcium levels are below 3.5mg/dL and reduced secretion when blood Ca levels are above 5mg/dL.

Effects on the bone:

- The bone is the primary target of PTH

- Increases resorption-mobilization of Calcium from bone to blood (due to activated adynelate cyclase giving an increase in cAMP which activates resorption)
Effects on the intestine: **Indirect effect**, increases formation of Vitamin D → increase absorption of Ca and phosphate from intestines.

**Effect on kidneys:**
- Increases reabsorption of Ca and GREATLY increases release/excretion of phosphate
  - The amount of phosphate which is excreted is SO great, that it far exceeds the amount of phosphate absorbed by the intestine and that which has been removed from the bone.
  - This effect is mediated by cAMP, and cAMP levels in urine can be used as a diagnostic tool to assess the function of the parathyroid gland.
  - e.g.: in hyperparathyroidism → cAMP levels in the urine INCREASE and vice versa in cases of hypoparathyroidism.

**General actions of PTH:** Increase Ca blood levels, Decrease Phosphate blood levels

**Vitamin D**
- **Increased levels of PTH stimulates synthesis of Vitamin D**
- Vitamin D synthesis starts in the skin, yet Vitamin D is activated initially in the liver and final activation occurs in the kidney.
  - 7D-Cholesterol in the skin is exposed to Sun and UV light (recommended for at least 15-20 minutes daily)
    - (Vitamin D deficiency is very common nowadays, especially in the elderly, which may result in osteomalacia in adults and rickets in children)

**Synthesis of vitamin D:**

\[
\begin{align*}
7\text{- dehydrocholesterol} & \quad \text{Skin, UV light} \quad \rightarrow \quad \text{Cholecalciferol (D\textsubscript{3})} \\
\text{(Liver) 25(OH) Cholecalciferol} & \quad \rightarrow \quad \text{(Kidney) 1,25(OH)\textsubscript{2}} \\
\text{Cholecalciferol (Calcifediol; Calcidiol)} & \quad \rightarrow \quad \text{(Calcitoral, diet)} \\
\end{align*}
\]

- **Effect on the Bone:** Vitamin D increases bone resorption,
- **Effect on the intestine (primary target):** increases absorption of Ca and phosphate,
- **Effect on kidney:** increases reabsorption of BOTH Ca and Phosphate.

**Net result of Vitamin D:** Increase in both Ca and Phosphate levels in the blood
Calcitonin
- Produces an opposite effect to Vitamin D and PTH
- It is synthesized and secreted from the Parafollicular cells of the thyroid gland.
- Major regulator of Calcitonin release is blood calcium levels.
  - Hypercalcemia: increases Calcitonin release and reduces blood calcium and phosphate levels
  - Hypocalcemia: decreases Calcitonin release and there is an increase in calcium levels from other mechanisms (that were mentioned earlier).

Effects on bone: decreases bone resorption, prevents movement of Ca and Phosphate from bone to blood.
On kidney: increases excretion of Ca and phosphate
On intestine: decreases absorption of Ca and phosphate.

The net effect of Calcitonin on Ca homeostasis is not as important as the roles of PTH and Vitamin D.

**Chronic excess of Calcitonin doesn't produce severe hypocalcemia, and complete removal of the parafollicular cells doesn't lead to fatal/life-threatening hypercalcemia.

The effects of PTH, Vitamin D and Calcitonin are summarized in the table below:

<table>
<thead>
<tr>
<th></th>
<th>PTH</th>
<th>Vitamin D</th>
<th>Calcitonin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium Conc.</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Phosphate Conc.</td>
<td>↓</td>
<td>↑</td>
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Disorders of the Parathyroid Gland:

1. **Hypoparathyroidism (hyposecretion of PTH)**
   - #1 cause: thyroidectomy (removal of the thyroid)
   - Many surgeons prefer to perform subtotal thyroidectomy in which only part of the thyroid (the affected part) is removed.
     - In this way, at least one of the parathyroid glands can be spared. Remember, a part of the thyroid gland tissue will still be present because the parathyroid gland can either be adhered (sticking) on the thyroid gland or embedded within the thyroid's substance.
     - This means there is no way in which you can remove the thyroid without removing the parathyroid glands.
   - Surgical removal of the thyroid is recommended especially in cases of hyperthyroidism or thyroid cancer even though Iodine 131 therapy will not affect the parathyroid glands. Surgical removal will allow the patient to return to a euthyroid state.
   - The disadvantages of keeping a small amount of thyroid tissue with the parathyroid gland is that there is a possibility for this tissue to grow again or become malignant.
   - In total thyroidectomy (where both the thyroid and all the parathyroid glands are removed) the patient will suffer from both hypothyroidism and hypoparathyroidism.
     - To treat hypothyroidism give patient thyroid replacement therapy.
     - To treat hypoparathyroidism, give the patient increased supplements of Ca and Vitamin D and PTH itself.
   - **Idiopathic causes** (unknown etiology)
- **Pseudohypoparathyroidism**: the target cells are insensitive to PTH (but PTH levels are still normal)

Symptoms of hypoparathyroidism include: Symptoms of hypocalcemia (parasthesia, tingling of lips, ***convulsions/seizures, bronchospasms, depression, cataracts.***

***The parathyroid gland should always be assessed in patients with frequent tetanic attacks and seizures (this is the most common and diagnostic symptom for hypoparathyroidism)***

**Lab. Tests (hypoparathyroidism):**

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
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<tbody>
<tr>
<td>↓ blood [Ca^{++}]</td>
<td></td>
</tr>
<tr>
<td>↑ blood [PO_{4}^{--}]</td>
<td></td>
</tr>
<tr>
<td>↓ urinary [cAMP]</td>
<td></td>
</tr>
<tr>
<td>↓ urinary [PTH]</td>
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</table>

**Treatment:**

- **Drug of Choice (1st line drug)** = **VITAMIN D!!** (since it produces similar effects of PTH; elevates Ca blood levels)
- Many dosage forms available; solutions, multivitamin tablets. Recommended dosage in Vitamin D deficiency is at least 50 I.U. (international units). Large doses are needed.
- Use of human recombinant PTH
- Ca supplements and Calcium-rich diet
- Calcium salts (fluoride, gluconate, carbonate)-these are oral effective drugs and usually given in cases of ACUTE HYPOPARATHYROIDISM only. (Calcium salts give immediate effects rather than Vitamin D which needs to work on all three tissues [kidney, bone, intestine] to increase blood Ca levels). But acute attacks of hypoparathyroidism is uncommon.
- Teriparatide (a synthetic recombinant PTH)-recently approved in the management of osteoporosis.

  - The question is, if PTH INCREASES bone resorption, how can it treat osteoporosis?
  - A: Low doses of PTH can be used in the management of osteoporosis. This is known as the paradoxical effect.
  *Hyperparathyroidism may be a cause of osteoporosis*

**2. Hyperparathyroidism (hypersecretion):**

It can either be:

a. **Primary**: e.g. adenomas effecting the cells that secrete PTH
b. **Secondary**: Hyperparathyroidism is a secondary disease to any cause of hypocalcemia (remember Ca is the main regulator of PTH!!!).

  - What may cause hypocalcemia?
    - **#1 cause: Malabsorption syndrome**

Management of 2ndary hyperparathyroidism is quite simple, treat the cause of hypocalcemia.

c. **Tertiary**: Caused by hyperplasia of the parathyroid gland. There is a loss of response to blood calcium levels. That means that Ca levels NO LONGER control the synthesis and release of PTH and PTH is released in LARGE amounts.

  - This is usually seen in patients with chronic renal failure.

**Manifestations (similar to those seen in hypercalcemia):**

#1 Manifestation= **Generalized weakness and fatigue.**
-Other manifestations include: depression, bone and muscle pain, depressed appetite, nausea, vomiting, constipation, polyuria, polydipsia, some degree of osteoporosis and frequent formation of kidney/renal stones. (*Formation of kidney stones is due to the high demand on the kidney to excrete the excess Calcium in the blood (compensatory mechanism). The stones are not necessarily a deposition of both Ca and phosphate.

**Lab. Tests (hyperparathyroidism):**

- ↑ blood [Ca$$^{++}$$]
- ↓ blood [PO$$^{4-}$$]
- ↑ urinary [cAMP]
- ↑ urinary [PTH]** **compensatory mechanism
- ↑ urinary [Ca$$^{++}$$]**
- ↑ urinary [PO$$^{4-}$$]

**Bone x-ray → bone decalcification**

**Treatment:**

- Low calcium diet (decreasing intake, the simplest of all the treatments)
- Sodium phosphate: to replenish the lost phosphate. Phosphate is very important in the function of many enzymes.
- Steroids: e.g. Prednisolone and synthetic analogs of glucocorticoids decreases absorption of Ca from the kidneys. (increases Ca excretion)
- Calcitomin
  - The best treatment, is surgical removal of the parathyroid gland and administering Vitamin D supplements.
  - Calcimimetic drugs (orally effective).
  - Controls/inhibits synthesis and release of PTH without effecting Ca blood levels and resulting in dangerous hypercalcemia.
  - Used in the treatment of Primary and Secondary hyperparathyroidism and also some parathyroid cancers.

**Other drugs used to treat Hypercalcemia (FOR YOUR INFORMATION)**

- Diuretics e.g. Furosemide (↑ Ca$$^{++}$$ excretion)
- Plicamycin: Used in treatment of testicular cancer
  - Used to treat hypercalcemia associated with cancer, and can be used as an anticancerous therapy
- Biophosphonate (effective Orally):
  - Highly effective drugs that are used in the management of osteoporosis. Increase bone formation and decrease bone resorption.

**Paget's Disease:**

- Rare bone disorder, characterized by DEMINERALIZATION (loss of minerals from bones)
  - Can lead to bone deformities and disorganization, increased bone resorption, fractures, spinal cord injuries and even deafness (bones in the ear; incus, malleus and stapes are damaged)

**Treatment includes:** Salmon calcitonin (drug of choice, given IM and SC) [even better than human recombinant calcitonin].

Because this disease is characterized by demineralization, Biophosphonates can be used orally