Pharmacology - ES

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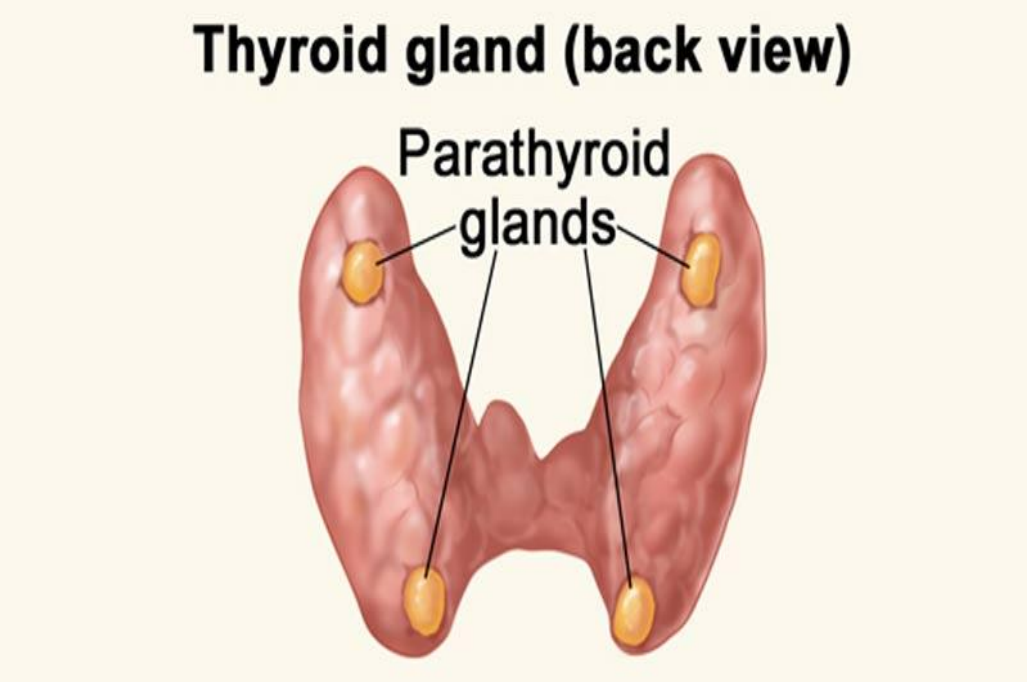
Parathyroid Hormone

- **The parathyroid glands are small endocrine glands in the neck of humans that produce parathyroid hormone**

- PTH is secreted from the parathyroid glands in response to a low plasma concentration of ionized (free) calcium (it's the main signal).
- PTH immediately causes the transfer of labile calcium stores from bone into the blood stream.
- PTH increases rates of dietary calcium absorption by the intestine indirectly via the vitamin D3 system activation of enterocyte activity.



CONT.

- Maintenance of **calcium**, **phosphate** and **magnesium** homeostasis is under the influence of two polypeptide hormones; p**arathyroid hormone(PTH)**, and **calcitonin (CT)**, as well as a sterol hormone, **1,25 dihydroxy cholecalciferol** ($1,25\ (OH)_2D_3$. Be aware that the maintenance is done mainly through PTH , calcitonin & 1.25 Vit D may help with that as well.

- These hormones regulate the flow of minerals in and out of the extracellular fluid compartments through their actions on **intestine, kidneys, and bones.**

CONT. (Pt 2)

The **PTH** acts **directly** on the bones and kidneys and **indirectly** on the intestine through its effect on the synthesis of 1,25 $(OH)_2D_3$. Its production is regulated by the concentration of serum ionized calcium. Lowering of the serum calcium levels works as a signal and will induce an increased rate of parathyroid hormone secretion

CALCITONIN

- Calcitonin release is normally stimulated by rising serum calcium levels and suppressed by hypocalcemia
- It opposes the work of PTH .
- Calcitonin is released by the "C" cells (parafollicular cells in the thyroid gland).
- It acts directly on the kidney and bones to restore the level of calcium to just below a normal set point which in turn inhibits secretion of the hormone.

Calcitonin is the physiological antagonist of PTH. The two hormones act in concert to maintain normal concentration of calcium ion in the extracellular fluid.

VITAMIN D3 (CHOLECALCIFEROL)

Vitamin D3, through its active metabolite, 1,25- (OH)2D3, also plays an

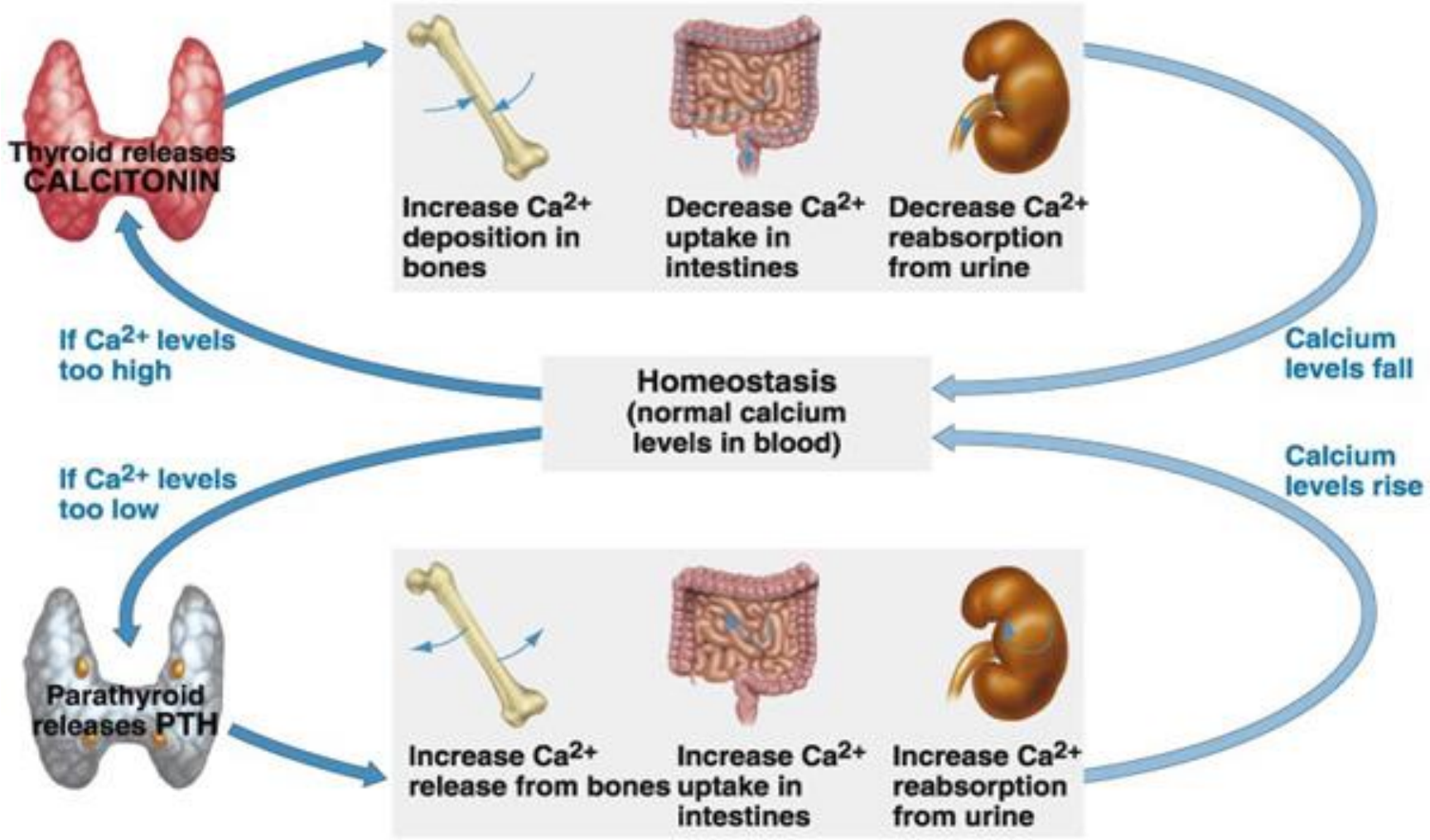
important role in maintaining calcium homeostasis by:

- **Enhancing intestinal calcium absorption** . In case a patient has calcium deficiency , the therapeutic course usually consist of pills of both calcium and vitamin D to enhance the absorption of calcium even more .

- **PTH-induced mobilization of calcium from bone.**

- c**alcium reabsorption in the kidney.**

- So, keep in mind that vitamin D is essential for keeping calcium levels within the normal and needed range



This figure summarises everything that had been said so far
Notice that when calcitonin decreases the concentration of calcium , the concentration reaches the normal but not less than that & when the parathyroid hormone increases the calcium concentration it is increased to the normal level not more than that.

CLINICAL USES OF PARATHYROID HORMONE, CALCITONIN, VITAMIN D, AND BISPHOSPHONATES

Hyperparathyroidism

- Primary hyperparathyroidism is due to **excessive production of PTH** by one or more of hyperfunctioning parathyroid glands. This leads to hypercalcemia which fails to inhibit the gland activity in the normal manner.
- The cause of primary hyperparathyroidism is **unknown**. A genetic factor may be involved in this uncontrolled PTH release. The clonal origin of most parathyroid adenomas suggests a defect at the level of the gene controlling the regulation and/or expression of parathyroid hormone.

Medical Treatment of the hypercalcemia

- In **acute severe** forms the main stay of therapy is adequate **hydration** with **saline** and forced diuresis by **diuretics** to increase the urinary excretion of calcium rapidly along with sodium to prevent its (calcium) reabsorption by the renal tubules.

<<Extra info>>
Diuretics, are medications designed to increase the amount of water and salt expelled from the body as urine.

Other agents

- **Glucocorticoids**
  - In hypercalcemia associated the **hematological malignant neoplasms.**
- **Mithramycin**
  - A toxic antibiotics which inhibit bone resorption and is used in **hematological and solid neoplasms** causing hypercalcemia.

Other agents, CONT.

- **Calcitonin**
  - Also inhibit osteoclast activity and prevent bone resorption. (To create balance)
- **Bisphosphonates**
  - They are given intravenously or orally to prevent bone resorption and decrease calcium concentration in the blood.
- **Phosphate**
  - Oral phosphate can be used as an anti-hypercalcemic agent and is commonly used as a temporary measure during **diagnostic** workup.
- **Estrogen**
  - It also decrease bone resorption and can be given to **postmenopausal women** with primary hyperparathyroidism related to increasing calcium levels using medical therapy

Surgery

- Surgical treatment should be considered in all cases (especially if it was a case of a malignancy related to the parathyroid) with established diagnosis of primary hyperparathyroidism.
- During surgery the surgeon identifies all four parathyroid glands (using biopsy if necessary) followed by the removal of enlarged parathyroid or 3 ½ glands in multiple glandular disease. The patient is left with half a gland

Hypoparathyroidism

- **Deficient secretion of PTH** which manifests itself biochemically by **hypocalcemia, hyperphosphatemia** (Ca & Phosphate levels are the opposite, when this increases the other decreases & vice versa) , diminished or absent circulating **iPTH** (intact PTH) and clinically the symptoms of neuromuscular hyperactivity.

Hypoparathyroidism

Treatment:

- The mainstay of treatment is a combination of **oral calcium** with pharmacological doses of **vitamin D** or its potent analogues. Phosphate restriction in diet may also be useful with or without aluminum hydroxide gel to lower serum phosphate level. Hyperphosphatemia is related to hypocalcaemia So increasing the phosphate concentration means we will have a decreased level of calcium .

Osteoporosis

- **Postmenopausal osteoporosis** is the **most common** form of osteoporosis. In perimenopausal women, the greatest amount of bone density is lost during the first 5 year after onset of menopause
- **Women going through menopause at a particularly early age are especially at risk for developing osteoporosis.**

<<Extra info>> Postmenopausal osteoporosis develops after menopause, when estrogen levels drop, and lack of Estrogen reduces the suppression of RANKL expression by bone lining cells, leading to increased osteoclastic bone resorption

Treatment

Take some prophylactic regimen at the onset of menopause such as

- estrogen replacement therapy (ERT),
- calcium supplementation
- D3.
- However, the benefits of ERT, including increased bone density, decreased risk of colon cancer, and decreased vaginal atrophy , must be weighed against the slightly **increased risk of breast cancer**, endometrial cancer, stroke, and deep vein thrombosis. So, if we were dealing with a patient whose first degree relative had a breast cancer , It is advised not to include the oestrogen replacement therapy in the regimen , Vitamin D and calcium supplementation will be enough .
- ERT appropriate combinations with a progestin negate such risk

Paget's Disease

- Paget's disease is an uncommon disorder of bone characterized by **mixed** lytic and sclerotic bone changes.
- These individuals have areas of increased bone resorption and other areas of abnormal new bone formation.
- The abnormal bone formation can result in **pain**, **deformity**, and **fracture of affected bones**.

Treatment

- The **bisphosphonates** and **calcitonin** are most commonly used in the treatment of this disease.
- the bisphosphonates are given in a cyclic pattern to treat Paget's disease (The purpose of using a cyclic pattern in giving the treatment is to give the bone the ability to grow in a normal way) . **Because Long-term continuous use of bisphosphonates can be associated with the induction of osteomalacia through a direct impairment of new bone formation.**

Renal Osteodystrophy

- Patients with **chronic renal failure** develop **hyperphosphatemia**, **hypocalcemia**.
- The secondary hyperparathyroidism (because PTH will be released to solve the hypocalcemia) is due to hyperphosphatemia and decreased 1, 25-(OH)D2 formation.

Treatment

- Oral or **intravenous 1,25-(OH)2 D3** (calcitriol) therapy (to treat hypocalcemia) along with **oral phosphate-binding agents** (to treat hyperphosphatemia) and **calcium supplementation.**