Endocrinology
L:3

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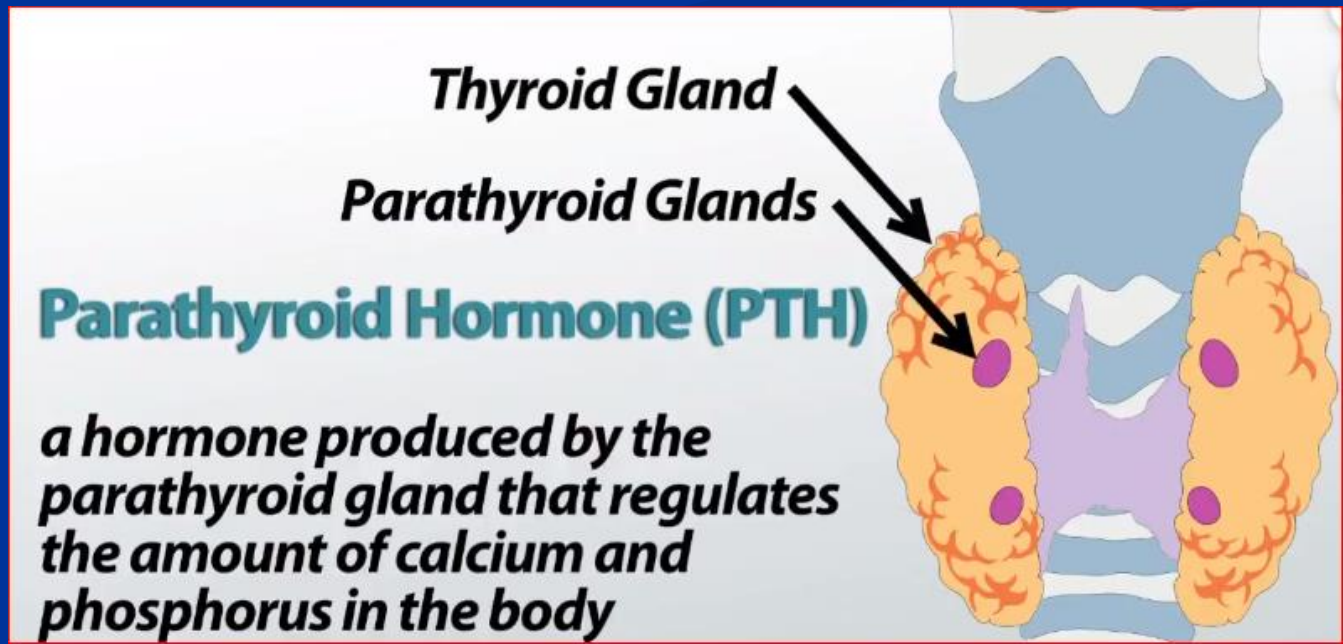
THE PARATHYROID GLANDS

- The four parathyroid glands lie behind the lobes of the thyroid. The parathyroid chief cells respond directly to changes in calcium concentrations via the calcium-sensing receptor located on the surface of parathyroid chief cells.
- PTH is a single-chain polypeptide of 84 amino acids that is secreted in response to a fall in **plasma ionised calcium concentration** .
- PTH has direct effects that promote **reabsorption of calcium from renal tubules and bone**. PTH also has indirect effects, mediated by **increasing renal conversion of 25-hydroxycholecalciferol** (i.e. 25-hydroxy-vitamin D) to the more potent **hormone 1,25-dihydroxycholecalciferol**, which results in increased **calcium absorption from food.**



Body Calcium 1200 g

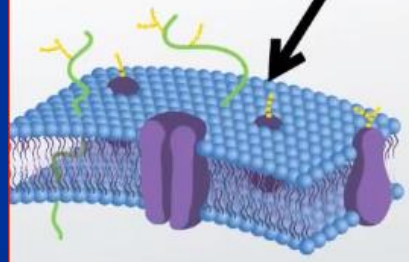
- **99%** of total body calcium is in bone.- Remain **1% !!!!???**
- **About 50%** of circulating calcium is bound to organic ions such as citrate or phosphate and to proteins.
- Total calcium measurements need to be corrected if the serum albumin is low, by adjusting the value for calcium upwards by 0.1 mmol/l (0.4 mg/dl) for each 5 g/l reduction in albumin below 40 g/l.
- Normal serum calcium concentration is 8.5 - 10.2 mg/dL (2.1- 2.5mmol/l)
- Possible critical values for total calcium are **< 6 mg/dL or >13 mg/dL**.
- Corrected calcium (mg/dL) = measured total Ca (mg/dL) + 0.8 (4.0 - serum albumin [g/dL])
- e.g s.Ca 6 mg/dl, s albumine 2g/dL)

- Corrected ca =6 +0.8(4-2)---6+0.8(2)===6+1.6====7.6

Ca

calcium

Phospholipids



P

phosphate

Calcium homeostasis

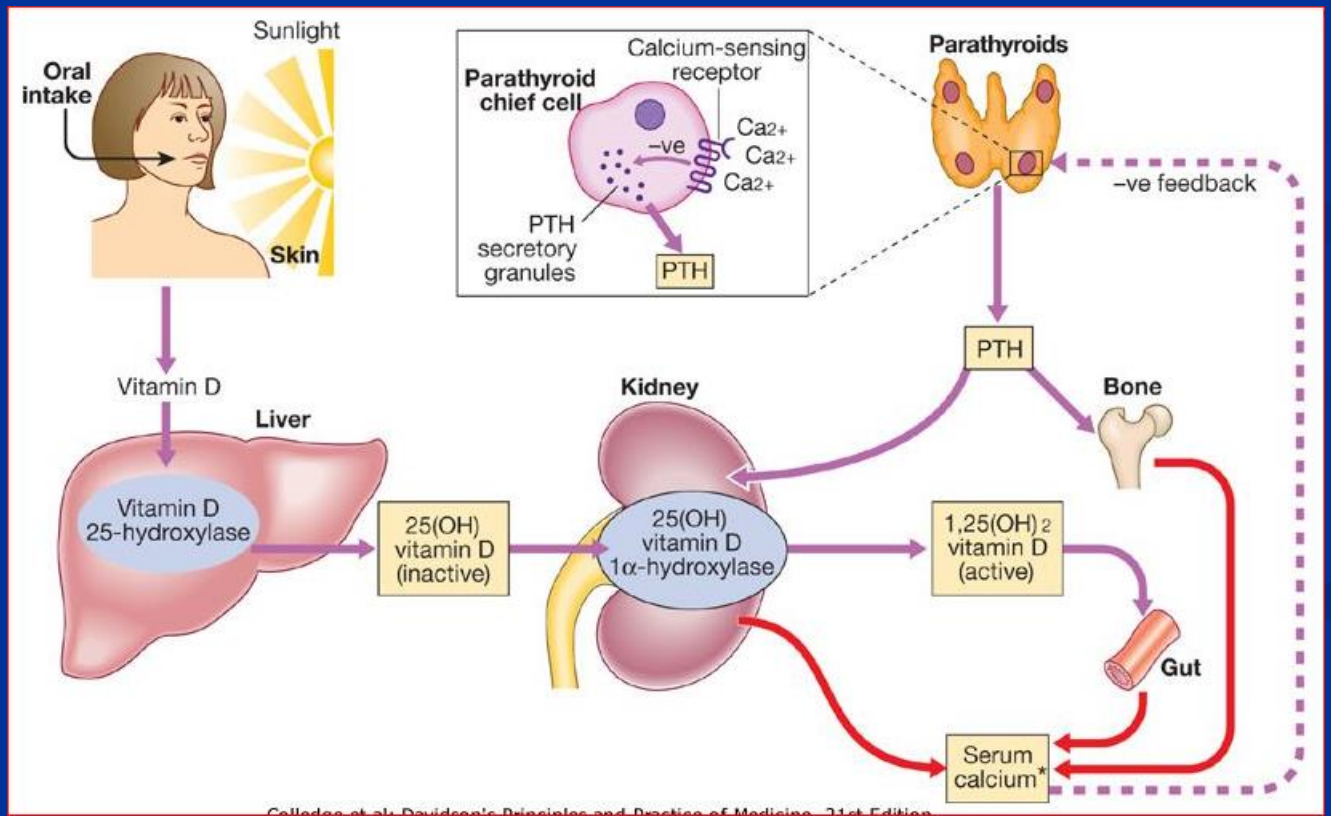
Interactions between PTH, vitamin D and calcium.

Calcium in serum exists as 50% ionised (Ca2+),

10% non-ionised or complexed with organic ions such as citrate and phosphate, and

40% protein-bound, mainly to albumin.

It is the ionized calcium concentration which regulates PTH production.



HYPERCALCAEMIA

Hypercalcaemia: is one of the most common biochemical abnormalities and is often detected during routine biochemical analysis in asymptomatic patients.

- It can present with chronic symptoms, and occasionally patients present as an acute emergency with severe hypercalcaemia and dehydration
- **CAUSES OF HYPERCALCAEMIA:**
- With normal or elevated (i.e. inappropriate) PTH levels -
- Primary or tertiary hyperparathyroidism
- -Lithium-induced hyperparathyroidism
- Familial hypocalciuric hypercalcaemia
- With low (i.e. suppressed) PTH levels: Malignancy (e.g. lung, breast, renal, ovarian, colonic and thyroid carcinoma, lymphoma, multiple myeloma)
- Elevated 1,25(OH)2 vitamin D (e.g. vitamin D intoxication,
- Sarcoidosis, HIV, Thyrotoxicosis
- Paget's disease with immobilisation
- Milk-alkali syndrome
- Thiazide diuretics
- Glucocorticoid deficiency

HYPERCALCAEMIA Cont.

- **Primary hyperparathyroidism and malignant hypercalcaemia** are by far the most common causes.
- Familial hypocalciuric hypercalcaemia **(FHH**) is a rare but important. This autosomal **dominant disorder** is caused by an inactivating mutation in the **calcium-sensing** receptor, which reduces the ability of the parathyroid gland to 'sense' ionised calcium concentrations. As a result, **higher** than normal calcium levels are required to suppress PTH secretion.
- Marginal elevations in serum calcium levels are typically observed in affected individuals, with PTH concentrations that are 'inappropriately' at the upper end of the normal range, or even slightly elevated.
- In addition, a reduced sensitivity of calcium-sensing receptors in the kidney tubules leads to increased **calcium reabsorption** and **hypocalciuria**. An individual with FHH is almost always asymptomatic and without complications, but may end up having an unnecessary (and ineffective) parathyroidectomy if misdiagnosed as having primary hyperparathyroidism.
- Lithium may also cause hyperparathyroidism by reducing the sensitivity of the calcium-sensing receptor

HYPERCALCAEMIA: Clinical assessment

- **Symptoms and signs** of hypercalcaemia include polyuria and polydipsia, renal colic, lethargy, anorexia, nausea, dyspepsia and peptic ulceration, constipation, depression, drowsiness and impaired cognition.
- Patients with malignant hypercalcaemia can have a rapid onset of symptoms and may have clinical features that help to **localise the tumor .**
- Patients with primary hyperparathyroidism may have a chronic, non-specific history. Their symptoms are described by the adage **'bones, stones and abdominal groans'**. However, about **50%** of patients with primary hyperparathyroidism are asymptomatic.
- Patients present with renal calculi (**5%** of first stone formers and **15%** of recurrent stone formers have primary hyperparathyroidism).
- Hypertension is common in hyperparathyroidism.
- Parathyroid tumors are almost **never palpable**.
- A family history of hypercalcaemia raises the possibility of **FHH or MEN**

Hyper Ca :Investigations

Low plasma phosphate and **elevated alkaline phosphatase** support a diagnosis of primary hyperparathyroidism or malignancy.

High plasma **phosphate** and **alkaline phosphatase** accompanied **by renal impairment** suggest **tertiary hyperparathyroidism**.

-The most discriminant investigation is the measurement of **PTH** using a specific immunoradiometric assay.

-If PTH is normal or elevated and urinary calcium is elevated, then hyperparathyroidism is confirmed.

- Low urine calcium excretion indicates **FHH**

- **SECODARY HYPERPARATHYRODISM?????**

TREATMENT OF SEVERE HYPERCALCAEMIA

- **Rehydration** with normal saline : To replace as much as a 4-6 l deficit. May need monitoring with central venous pressure in old age or renal impairment.
- Bisphosphonates: e.g. disodium pamidronate 90 mg i.v. over 4 hours

Causes a fall in calcium which is maximal at 2-3 days and lasts a few weeks. Additional rapid therapy may be required in very ill patients

- Forced diuresis with saline and furosemide
- Glucocorticoids, e.g. prednisolone 40 mg daily
- Calcitonin
- Haemodialysis
- Treat the cause

HYPERPARATHYROIDISM

It is customary to distinguish three categories of hyperparathyroidism,

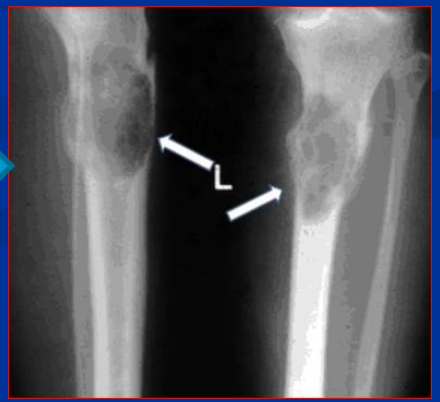
- **primary hyperparathyroidism:** there is autonomous secretion of PTH, usually by a single parathyroid adenoma varying in size from a few millimetres to several centimetres in diameter.
- **Secondary hyperparathyroidism :** is present when there is increased PTH secretion to compensate for prolonged hypocalcaemia and is associated with hyperplasia of all parathyroid tissue. Its effect is to restore serum calcium levels at the expense of the stores of calcium in bone.
- **Tertiary hyperparathyroidism**: a very small proportion of cases of secondary hyperparathyroidism, continuous stimulation of the parathyroids results in adenoma formation and autonomous PTH secretion. .

HYPERPARATHYROIDISM

- Primary hyperparathyroidism is the most common of the parathyroid disorders
- It is two to three times more common in women than men and 90% of patients are over 50 years of age.
- Hyperparathyroid bone disease is now rare due to earlier diagnosis and treatment.
- Osteitis fibrosa cystica results from increased bone resorption by osteoclasts with fibrous replacement in the lacunae. This may present as bone pain and tenderness, fracture and deformity.
- **Chondrocalcinosis** is due to deposition of calcium pyrophosphate crystals within articular cartilage. It typically affects the menisci at the knees and can result in secondary degenerative arthritis or predispose to attacks of **acute pseudogout**
- There are characteristic changes on plain X-rays.In the early stages there is demineralisation, with subperiosteal erosions and terminal resorption in the phalanges . A 'pepper-pot' appearance may be seen on lateral X-rays of the skull. ..
- Reduced bone mineral density is now the most common skeletal manifestation of hyperparathyroidism by DEXA scanning(dual-energy X-ray absorptiometry).
- In over 90% of patients an experienced surgeon will locate the adenoma without difficulty.

Multiple tiny well defined radiolucencies seen in Hyperparathyroidism

x-ray: extensive osteolytic lesion in proximal end of tibia
(Osteitis fibrosa cystica)



Management of Hyperparathyroidism

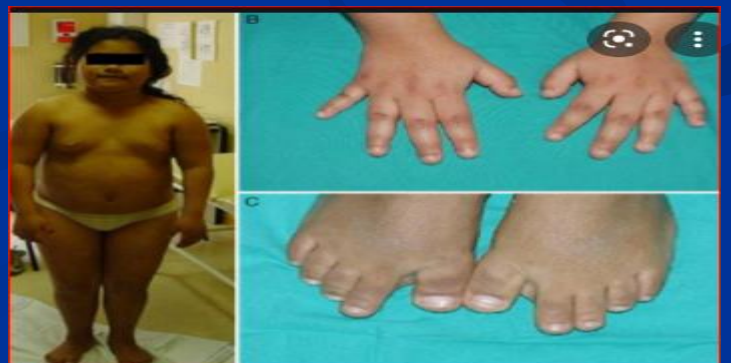
- Hypercalcaemia in patients with primary hyperparathyroidism responds less well to glucocorticoids and bisphosphonates than in those with malignancy.
- Urgent neck surgery is occasionally required, but strenuous attempts should be made to replace fluid deficits and lower the serum calcium concentration
- Surgery is indicated for young patients < 50 years) and those with clear-cut symptoms or documented complications such as peptic ulceration, renal stones, renal impairment or osteopenia.
- Large number of patients have only vague symptoms or are asymptomatic. They can be reviewed every 6-12 months and should be encouraged to maintain a high oral fluid intake to avoid renal stones
- Drugs that enhance the sensitivity of the calcium-sensing receptor (calcimimetics)e.g. –**Cinacalcet-** are being developed and, in the future, may offer an alternative to surgery in hyperparathyroidism

HYPOCALCAEMIA

- The most common cause of hypocalcaemia is a low serum albumin with normal ionised calcium concentration. Conversely, ionised calcium may be low in the face of normal total serum calcium if the serum is alkalotic-for example, as a result of hyperventilation.
- Magnesium depletion should also be considered as a possible contributing factor, particularly in patients with malabsorption, on diuretic therapy or with a history of **alcoexcesshol**.
- The most common cause of **hypoparathyroidism** is damage to the parathyroid glands (or their blood supply) during **thyroid surgery**, although this complication is only permanent in **1%** of thyroidectomies. Transient hypocalcaemia develops in **10%** of patients 12-**36** hours following **subtotal thyroidectomy** for Graves' disease. Rarely, **hypoparathyroidism** can occur as a result of **infiltration** of the glands, e.g. in **haemochromatosis** and **Wilson's** disease.
- There are a number of rare **inherited forms of hypoparathyroidism**. One form is associated with autoimmune polyendocrine syndrome type 1 (**Chronic mucocutaneous candidiasis ,hypoparathyroidism , Addison's disease and dystrophy (skin, dental enamel, and nails).**
  DiGeorge syndrome **(heart defects, an impaired immune system and developmental delays).**

HYPOCALCAEMIA cont.

- **Autosomal dominant hypoparathyroidism** is the mirror image of familial hypocalciuric hypercalcaemia (FHH); an activating mutation in the calcium-sensing receptor results in hypocalcaemia, PTH concentrations that are 'inappropriately' low and hypercalciuria.
- **Pseudohypoparathyroidism** there is tissue resistance to the effects of PTH, such that PTH concentrations are markedly elevated. The features include short stature, short 4th metacarpals and metatarsals, rounded face, obesity , subcutaneous calcification and mentally retarded
- '**pseudo-pseudohypoparathyroidism**' is used to describe patients with these clinical features in whom serum calcium and PTH concentrations are normal.



Hypocalcemia :clinical assessment

- **Tetany** occurs in all syndromes in which ionised calcium concentrations are low. Additional features are specific to different etiologies
- -**Low ionised calcium** concentrations cause increased excitability of peripheral nerves. In the absence of alkalosis, tetany usually occurs in adults only if total serum calcium is < 2.0 mmol/l **(8 mg/dl)**. **Children** are more sensitive than adults .
- In children, a characteristic triad of **carpopedal** spasm, **stridor** and **convulsions** occurs,.
- The hands in carpal spasm adopt a characteristic position. The metacarpophalangeal joints are flexed, the interphalangeal joints of the fingers and thumb are extended, and there is opposition of the **thumb.**
- **Trousseau's sign** is carpopedal spasm that results from hypocalemia , such as that induced by pressure applied to the upper arm from an in- flated sphygmomanometer cuff more than the systolic blood pressure is followed by carpal spasm within 3 minutes
- Stridor is caused by spasm of the **glottis**.
- Adults complain of **tingling** in the hands and feet and around the mouth. The **Chvostek sign** (twitching of facial muscles in response to tapping over the area of the facial nerve

- Less often there is painful **carpopedal** spasm, while stridor and fits are **rare**

Hypocalcemia :clinical assessment . Cont.

- Hypocalcaemia causes papilloedema and prolongation of the ECG QT interval, which may predispose to ventricular arrhythmias.
- Prolonged hypocalcaemia and hyperphosphataemia (as in hypoparathyroidism) may cause calcification of the basal ganglia, grand mal epilepsy, psychosis and cataracts.
- Hypocalcaemia associated with hypophosphataemia, as in vitamin D deficiency, causes rickets in children and osteomalacia in adults

Management of hypocalcemia

- -To control tetany, alkalosis can be reversed acutely if arterial **PCO2** is increased by rebreathing expired air in a paper bag or administering 5% CO2 in oxygen.
- **Injection of 20 ml of a 10% solution of calcium gluconate** slowly into a vein will raise the serum calcium concentration immediately. An intramuscular injection of 10 ml may also be given to obtain a more prolonged effect.
- In severe cases of alkalotic tetany, intravenous **calcium gluconate** often relieves the spasm, while specific treatment of the alkalosis,
- Intravenous **magnesium** is required to correct the hypocalcaemia associated with hypomagnesaemia .
- **Persistent hypoparathyroidism and pseudohypo-parathyroidism** are treated with oral calcium salts and vitamin D analogues, either 1α-hydroxycholecalciferol (alfacalcidol) or 1,25-dihydroxycholecalciferol (calcitriol). This therapy needs careful monitoring because of the risks of iatrogenic hypercalcaemia, hypercalciuria and nephrocalcinosis