Disorder of the parathyroid gland

Objectives:

- Not given

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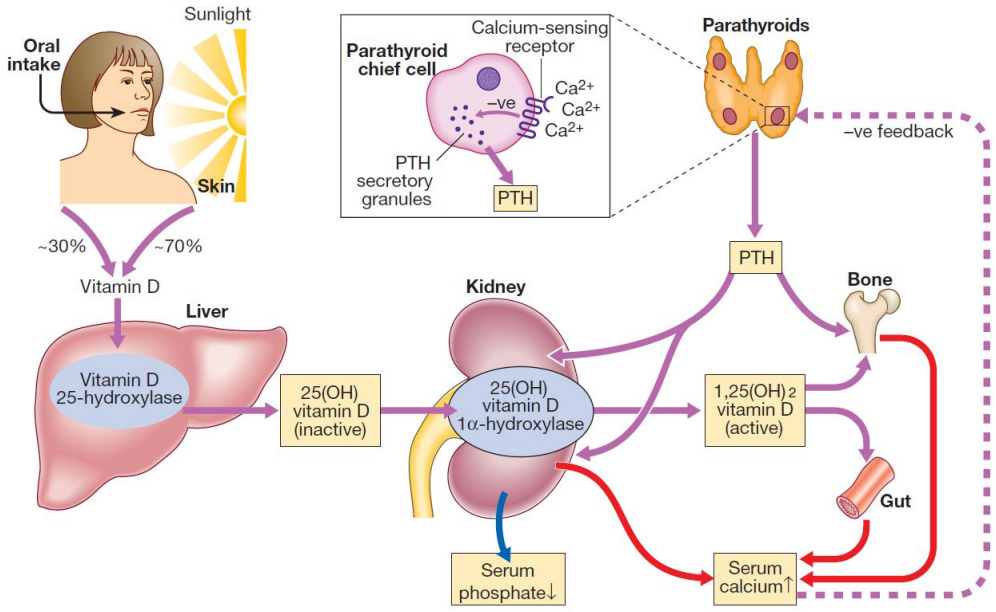
- Editing file
- Feedback

Special thanks to laila mathkour for her hard work 

Introduction



Another picture

★ Parathyroid glands are the 4 small glands behind the thyroid gland, they are important in the minerals homeostasis.
Calcium in the body can be either be bound or free:
1. most of it is bound to protein.
2. free active small amount ionized calcium (which is very important in regulation of hormones that we talk about it).
Calcium is important not only for the bone but also for the skeletal, cardiac muscle and neural functions. That is why any minimal change will trigger the response of the body hormones. Also, Ca has a very low physiological range (2.15 - 2. 55) mmol/l. So, it is a very narrow window which means any disturbance of this range will trigger the secretion of PTH and calcitonin.

★ The parathyroid chief cells respond directly to changes in calcium concentrations via a G-protein-coupled cell surface receptor (the calcium-sensing receptor) located on the cell surface.
When serum ionised calcium levels fall, PTH secretion rises. PTH acts on the renal tubules to promote reabsorption of calcium and reduce reabsorption of phosphate, and on the skeleton to increase osteoclastic bone resorption and bone formation. PTH also promotes conversion of 25-hydroxycholecalciferol to the active metabolite 1,25-dihydroxycholecalciferol; the 1,25- dihydroxycholecalciferol, in turn, enhances calcium absorption from the gut.

Calcium homeostasis is maintained by 3 hormones: PTH (main hormone), Calcitonin and Vitamin D. These hormones regulate the flow of minerals in and out of the extracellular fluid compartments through their actions on intestine, kidneys, and bones.		
Hormone	**I. Parathyroid hormone** The most important one	**II. Calcitonin,** Antagonist hormone for PTH.
Origin	Secreted from Parathyroid gland	Secreted by the parafollicular cells (C cells) of the **thyroid** gland
production	• It's released in response to hypocalcemia. • Its production is regulated by the concentration of serum ionized calcium. e.g. if we have low Ca because of vitamin D deficiency for example, PTH will increase and the calcitonin will decrease.	• It's released in response to small increases in plasma ionic calcium.
Effect	↑ plasma calcium concentration. ↓ plasma phosphate concentration	↓ plasma calcium concentration. ↑ plasma phosphate concentration
physiology	• The PTH acts directly on the bones and kidneys and indirectly on the intestine	• Calcitonin acts on the kidney and bones to restore the level of calcium to

	through its effect on the synthesis of 1,25 $(OH)_2 D_3$ (in the kidney) .	just below a normal set point which in turn inhibits secretion of the hormone. • Calcitonin is not that strong but it has the physiological antagonist of PTH by inhibiting osteoclasts from breaking down bone. • It inhibit Ca reabsorption in renal tubular cells

III. Vitamin D (sterol hormone) It is called vitamin but it is steroid hormone " it acts in the body like a hormone "

- 90% of vitamin D in our body comes from the skin by 7 dehydrocholesterol under UV sunlight, not from the diet, then metabolized and activated by the liver and kidneys.
- Vit D formation starts at the skin from direct sunshine then to the liver it become 25-dihydroxyvitamin D3. After that it goes to the kidneys which will form 1,25-dihydroxyvitamin D3 under the influence of PTH. **check this picture**
- Synthesized by the body or taken in food with help of PTH.
- Increases Renal and intestinal calcium and Phosphate absorption.
- Best time for sun exposure in Riyadh: Winter(10 am - 2 pm) - Summer (9 am - 10:30 & 2 - 3 pm)
- In the lab we measure the most abundant form of Vitamin D which is 25-hydroxyvitamin D. while the most potent (has the effect) form of Vitamin D is 1,25-dihydroxyvitamin D3.

Hyperparathyroidism watch 9:10mins

-Whenever we have a problem with Ca, PO or Mg, we always have to correlate it with PTH and vitamin D and do not base our differential diagnosis on one abnormal mineral, because they connect together.

★ Primary hyperparathyroidism: the most common disorder of the parathyroid

- Primary hyperparathyroidism is due to excessive production of PTH by one or more of hyperfunctioning parathyroid glands. The gland will become autonomously hyperactive and not under the normal control any more.
- This leads to hypercalcemia which fails to inhibit the gland activity in the normal manner. Normally, in hypercalcemia, the triggering normal physiological response should lower the calcium but this does not happen in autonomous functioning hyperpara.
- Most common cause of hypercalcemia in the outpatient setting.
- The cause of primary hyperparathyroidism is unknown. A genetic factor may be involved and it could be sporadic or familial.
- 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.
- The incidence of the disease increases dramatically after the age of 50 and it is 2 - 4 folds more common in women.

★ Causes:

- A **single adenoma** occurs in about 80% of patients with primary hyperparathyroidism[1].
- Four glands hyperplasia account for 15-20% of cases.
- A parathyroid carcinoma could be the etiology in a rare incidence of less than 1%.

★ Clinical Features:

- The two major sites of potential complications are the **bones and the kidneys.**
- Now a days such complications are seen less commonly and around 20% of patients or less show such complications.
- Usually the clinical features do not present early but if the patient takes a while to come to you, he might have these features, they are very non-classic, vague symptoms and that is why they are missed initially.
- Abnormality of Ca and PTH affect every organ in the human body including brain ,ovaries and testes not only bones. **Picture**

Most common presentation: is asymptomatic hypercalcemia	
kidneys	1. Nephrolithiasis (renal stones) 2. Nephrocalcinosis (diffuse deposition of calcium-phosphate complexes in the parenchyma)
Bones	1. Bone aches and pains. 2. Osteoporosis and fractures. 3. In skeleton a condition called osteitis fibrosa cystica[2] could occur with subperiosteal resorption of the distal phalanges**,** distal tapering of the clavicles, a **"salt and pepper" appearance of the skull** as well as bone cysts and brown tumors of the long bones. 4. Note: such overt bone disease even though typical of primary hyperparathyroidism is very rarely encountered.
Groans	1. Muscle pain and weakness 2. Peptic ulcer disease because of hypercalcemia causes gastric irritation. 3. Pancreatitis 4. Gout and pseudogout 5. Constipation
Psychiatric	1. Easy fatigability 2. Depression, psychosis. 3. Anorexia. 4. Sleep disturbances. 5. Anxiety, lethargy
Cardiovascular	1. Hypertension → ventricular hypertrophy. 2. Shortened QT interval
Others	3. Anemia 4. Weight loss 5. polydipsia 6. polyuria

[1] it can be multiple Adenoma, but the most common condition is a single adenoma so you have to know how to work it up.

[2] the classic old presentation, as PTH acts mainly on the osteoclasts to resolve bone so, when we have an excessive PTH all the time, what happen is this excessive release will cause lytic lesions and this is what we mean by cyst.

★ Diagnosis:

Now a days almost 90% of diagnosed cases in the developed countries are picked up by routine screening for calcium level using the new automated machines[3].

Lab tests	1. Ca is high (the presence of established hypercalcaemia in more than one serum measurement) 2. Elevated immunoreactive PTH is characteristic (iPTH). 3. Serum phosphate is usually low but may be normal. This is very important for differential diagnosis, because we will talk later about something called secondary hyperpara that is related to kidney disease and the phosphate will not be low. • Hypercalcemia is common and blood alkaline phosphatase (of bone origin) is raised.
Radiology (In the old days, before we had all of these radiological modalities, they used to say that the best localization is the hand of a good surgeon "they used to send the patient to a good surgeon to do exploratory surgery", but nowadays the radiograph will make the surgery easier, anesthesia shorter and the scar smaller)	Plain X-ray of hands can be diagnostic showing sub periosteal bone resorption usually on the radial surface of the distal phalanx with distal phalangeal tufting as well as cysts formation and generalized osteopenia.
	Preoperative localization of the abnormal parathyroid glands: • Ultrasonography • MRI • CT • Thallium ^{201} – Tehcnichum^{99m} scan (subtraction study)[4] • Sestamibi scan.

★ Treatment: it is mainly surgical treatment, most of the time we resect the gland and the patient will be fine, Ca and PTH will go back to normal and most of complications will go back to normal.

- ❑ A large proportion of patients have "biochemical" hyperparathyroidism but with prolonged follow up they progress to overt clinical presentation.
- ❑ Resection of the parathyroid lesion is curative with recurrences observed mainly in the multiple glandular disease.

- **Medical Treatment of the hypercalcaemia:** Before sending patient to the surgery if he is presented with high Ca, we have to lower it, because it is not safe for anesthesia and surgery, it can affect the cardiovascular stability of the patient, so what we do is we give him a lot of fluids .
- **In acute severe forms:** the mainstay of therapy is adequate hydration with saline and forced diuresis[5] by diuretics to increase the urinary excretion of calcium rapidly along with sodium and prevent its reabsorption by the renal tubules . Sometimes for whatever reason "for e.g: the patient is too old ,has a high risk of surgery or has comorbidities" we might not send him to surgery and we have to treat them medically.

[3] we detect it when the person does a certain lab test "ex: complete medical profile" then we find high Ca then we have to repeat it and then we start thinking if this is related to PTH or not . this is the classical presentation these days.

[4] Isotope material is taken up by the hyperfunctioning gland so, once you do it and after a certain time, you wait and you see that there is a one parathyroid gland that is still hyper functioning, the normal physiology of the human body will get rid of isotope material through the kidney and surgeons love that because they will open 2 cm on top of this gland. sometime we do it with ultrasonography or MRI because we prefer to do two radiological localization so, we do not rely on one test, we do two tests.

[5] lasix: its main action is in the loop of henle to cause excretion of Na and the Ca will go out with Na, we used to do it but we do not anymore, because it is not very effective and we use better agent.

Other agents :

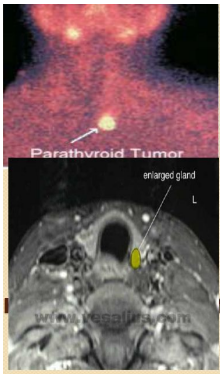
- **Calcitonin[6]:** inhibit osteoclast activity and prevent bone resorption.
- **Bisphosphonates[7]:** They are given intravenously or orally to prevent bone resorption.
- **Phosphate**: Oral phosphate can be used as an antihypercalcaemic agent and is commonly used as a temporary measure during diagnostic workup.
- **Estrogen:** It also decrease bone resorption and can be given to postmenopausal women with primary hyperparathyroidism using medical therapy.
- **Glucocostiroids[8]:** In hypercalcaemia associated the hematological malignant neoplasms.
- **Mythramycin:** A toxic antibiotics which inhibit bone resorption and is used in hematological and solid neoplasms causing hypercalcaemia.
- **Cinacalcet**: treatment for patients with primary hyperparathyroidism who are unwilling to have surgery or are medically unfit.

- **Surgical Treatment:**

❑ Surgical treatment should be considered in all cases with established diagnosis of primary hyperparathyroidism. bilateral neck exploration or focused parathyroid exploration if adenoma is localized preoperatively . (after the surgery the patient will go under hungry bone syndrome which will cause hypocalcemia)

❑ Indication for surgery: symptomatic patient (lithiasis, osteoporosis, pancreatitis) , or aged less than 50 , or Asymptomatic but with significant hypercalcaemia.

❑ 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.



★ **Differential diagnosis of hypercalcemia:** (very important to know the causes especially the red ones and to know that here the Ca is high while the PTH is NORMAL)

-Do not forget that there are other causes of high PTH and high Ca rather than primary hyperpara. Also, there is something called non-PTH hypercalcemia, once **Ca is high and PTH is normal** think of other causes.

Parathyroid - related	1. Primary hyperparathyroidism a. Solitary adenomas b. Multiple endocrine neoplasia **2. Lithium therapy** **3. Thyrotoxicosis** 4. Familial hypocalciuric hypercalcemia (PTH is normal)

[6] "acts against PTH" the problem with calcitonin that, it has what we call it idiosyncratic reaction. So, after 24 - 48 hours it can cause a reaction. So, we like to use calcitonin which inhibit the osteoclastic activity just before the surgery, because if we give it longer, it will give this reaction.

[7] Very similar to calcitonin, it suppress osteoclasts, but it take a long time. It does not act immediately, it takes weeks so we usually give it to the patient for a while.

[8] It has a very very limited role.

Vitamin D – related	1. Vitamin D intoxication 2. **Increase production of 1,25(OH)2D; sarcoidosis and other granulomatous diseases.** 3. Idiopathic hypercalcemia of infancy
Malignancy - related	1. Solid tumor with metastases **(breast cancer)** 2. Solid tumor with humoral mediation of hypercalcemia (lung and kidney) 3. Hematologic malignancies (multiple myeloma[9], **lymphoma**, leukemia) Note: PTH is normal in malignancy induced hypercalcemia
Associated with high bone turnover	1. Hyperthyroidism 2. Immobilization 3. **Thiazides** 4. **Increase Vitamin A intoxication**
Associated with Renal Failure:	1. Severe secondary hyperparathyroidism 2. Aluminum intoxication 3. Milk alkali syndrome 4. **Adrenal insufficiency** 5. **Thiazides diuretics**

★ Secondary hyperparathyroidism:

As we mentioned, when we have a high PTH, we always have to correlate it with Ca and PO, because if a high PTH is correlated with high Ca and low Phosphate → very classic primary hyperpara. But if high PTH is associated with normal Ca → secondary hyperpara.

- An increase in PTH secretion which is adaptive and unrelated to intrinsic disease of the parathyroid glands is called secondary hyperparathyroidism.
- This is due to chronic stimulation of the parathyroid glands by a chronic decrease in the ionic calcium level in the blood.
- Most common causes of secondary hyperpara: 1. CKD 2. vitamin D deficiency.
- In classic vitamin D deficiency: both Ca and PO will be low
- CKD: Ca might be normal or low but the PO will be high because there is a problem with kidney excretion of PO.

★ Tertiary hyperparathyroidism:

- After long standing secondary hyperparathyroidism.

Hypoparathyroidism watch 6mins. picture

Deficient secretion of PTH which manifests itself biochemically by ↓ Ca^{2+}(hypocalcaemia), ↑ PO^{4} hyperphosphatemia and diminished or absent circulating iPTH and clinically the symptoms of neuromuscular hyperactivity. In this case the 4 glands are not working because if 2 or 3 are abnormal, the remaining gland will compensate.

★ Hypocalcemia with Hypoparathyroidism causes:

1. **Surgical hypoparathyroidism:** (the commonest cause)
    a. Head and neck surgeries :
        i. thyroidectomy.
        ii. parathyroidectomy
        iii. Radical surgery for head and neck malignancies.

[9] Production of osteoclast activating factor.

b. After anterior neck exploration for thyroidectomy, abnormal parathyroid gland removal, excision of a neck lesion.

c. It could be due to the removal of the parathyroid glands or due to interruption of blood supply to the glands.(Ischemic damage "cutting the artery by mistake")
When the patient has a thyroid operation and the surgeon is not expert enough not to touch parathyroid gland , because there is fascia " a capsule " that surrounds the thyroid and the parathyroid is attached to it , he will cause hypopara. so most good surgeons will localize the parathyroid and will not remove it during thyroidectomy.

2. Idiopathic hypoparathyroidism:

-Now we know that idiopathic hypopara is an autoimmune disease and it can be associated with other autoimmune diseases. In this case we have to check for ABs and association with other diseases.

a. A form occurring at an early age (genetic origin) with autosomal recessive mode of transmission "multiple endocrine deficiency –autoimmune-candidiasis (MEDAC) syndrome"

b. Juvenile familial endocrinopathy

c. Hypoparathyroidism – Addison's disease – mucocutaneous candidiasis (HAM) syndrome, AKA Polyglandular autoimmune syndrome type 1.

d. Circulating antibodies for the parathyroid glands and the adrenals are frequently present.

e. Other associated disease:

i. Pernicious anemia

ii. Ovarian failure

iii. Autoimmune thyroiditis

iv. Diabetes mellitus

f. The late onset form occurs sporadically without circulating glandular autoantibodies.

3. Functional hypoparathyroidism

In patients who has chronic hypomagnesaemia of various causes. Magnesium is necessary for the PTH release from the glands and also for the peripheral action of the PTH.

Low magnesium levels → lead to increased urinary loss of calcium

It happens in the patient with malabsorption, so when Mg is low it will affect the parathyroid release of PTH, but this functional effect is temporary, once you correct the Mg, the gland goes back to normal (very rare).

★ Hypocalcemia without Hypoparathyroidism causes:

1. Vitamin D deficiency

a. Vitamin D and Calcium deficiency.

b. Vitamin D resistance (very rare)

c. Decreased intestinal absorption of vitamin D or calcium due to primary small bowel disease, short bowel syndrome, and post-gastrectomy syndrome

d. Drugs that cause rickets or osteomalacia: such as phenytoin, phenobarbital, cholestyramine, and laxativ. Anti-epileptic drugs: activate cytochrome p 450 in the liver which will clean many hormones in the body including vitamin D. So always in the history of a patient with vitamin D deficiency, make sure that medication history is complete.

2. **Chronic Renal Failure**
    a. The most common cause of hypocalcemia.
    b. The kidney converts 25 hydroxy-D to the more active 1,25 hydroxy-D → So Renal failure = Loss of vitamin D.
    c. Hyperphosphatemia in CKD lower Ca concentration.

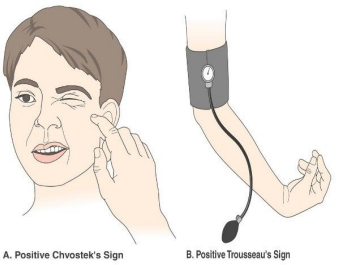
3. **Others** :
    a. Acute pancreatitis (quite common)
    b. Citrated blood in massive transfusion (not uncommon).
    c. Low plasma albumin, e.g. malnutrition, chronic liver disease.
    d. Pseudohypoparathyroidism (syndrome of end-organ resistance to PTH)
    e. Hyperphosphatemia: in phosphate therapy.

★ Clinical Features:

- **Neuromuscular:** (As you know, we need normal Ca for neuromuscular junction activity and low Ca will cause hyperactivity)
    - The rate of decrease in serum calcium is the major determinant for the development of neuromuscular complications[10] "sudden drop".
    - When nerves are exposed to low levels of calcium they show abnormal neuronal function which may include decrease threshold of excitation, repetitive response to a single stimulus and rarely continuous activity.
        - Parathesia
        - acyte tetany (post-surgical) OR chronic .
        - Hyperventilation
        - Adrenergic symptoms
        - Numbness
        - Convulsion (More common in young people and it can take the form of either generalized tetany followed by prolonged tonic spasms or the typical epileptiform seizures).

[10] Symptoms based on rate of decrease:
1. Acute: due to surgery (during few days) → increase in NM firing which manifested by tetany and the classic sign (carpopedal spasm " flexion of MCP and extension of PIP and DIP +/- involvement of wrist").
2. Chronic: numbness, tingling and GI symptoms.

- Signs of latent tetany:
  - Chevostek sign[11] watch 0:36 seconds
  - Trousseau sign[12] watch 0:44 seconds
  - Extrapyramidal signs **(due to basal ganglia calcification)**



- **Other clinical manifestation:** (Not very classic and we usually see it in the juvenile and pediatric hypopara)
  - Posterio -lenticular cataract
  - Cardiac manifestation: (dangerous)
    - Prolonged QT interval in the ECG
    - Resistance to digitalis
    - Hypotension
    - Refractory heart failure with cardiomegally can occur
  - Dental Manifestation: (in pediatric hypopara)
    - Abnormal enamel formation with delayed or absent dental eruption and defective dental root formation.
  - Malabsorption syndrome: (Ca is important for normal function of the gut)
    - Presumably secondary to decreased calcium level and may lead to steatorrhoea with long standing untreated disease. e.g. in celiac disease

★ Diagnosis:

In the absence of renal failure, the presence of:

1. hypocalcaemia. (diagnostic)
2. hyperphosphatemia.(diagnostic)
3. Undetectable serum iPTH **confirms** the diagnosis or it can be detectable if the assay is very sensitive.
4. Low urine cAMP.

★ Treatment: we give him oral medication (Ca + vitamin D). Unfortunately, we can not give them PTH.. you might read in other resource that there is synthetic PTH but it is not available in our country.

- **The mainstay of treatment is a combination of:**
  i. Oral calcium
  ii. pharmacological doses of active form of vitamin D or its potent analogues (calcitriol or alfacalcidol). We give them active vitamin D, because we do not have PTH to activate alpha 1 hydroxylase which is responsible for the conversion from inactive to active form.
  iii. Phosphate restriction in diet may also be useful with or without aluminum hydroxide gel to lower serum phosphate level especially in case of CKD.

[11] we ask the patient to open his mouth, then we tap on the facial nerve → tingling of the mouth angle due to excitability.

[12] We inflate the sphygmometer and we Waite → decrease blood supply and spasm.

- **Emergency Treatment for hypocalcemic tetany:**

  Calcium (IV calcium gluconate) should be given parenterally[13] only in case of symptomatic and present of neural irritability till adequate serum calcium level is obtained and then vitamin D supplementation with oral calcium should be initiated.

★ Pseudo-hypoparathysoidism and Pseudo-pseudo-hypoparathyroidism:

- A rare familial disorders with target tissue resistance to PTH.
- There is hypocalcaemia, hyperphosphataemia, with increased parathyroid gland function.
- There is also a variety of congenital defects in the growth and development of skeleton including:
  - Short stature
  - Short metacarpal and metatarsal bones
- In pseudo pseudo hypoparathyroidism they have the developmental defects without the biochemical abnormalities.
- The diagnosis is established when low serum calcium level with hyperphosphatemia is associated with increased serum iPTH as well as diminished nephrogenous CAMP and phosphature response to PTH administration.

Metabolic bone diseases

★ Bone types:

1. **Cortical Bone[14]:** The compact bone of Haversian systems such as in the shaft of long bones.
2. **Trabecular Bone[15]:** The lattice – like network of bone found in the vertebrae and the ends of long bones.

- The difference pattern of bone loss affecting trabecular and cortical bone results in two different fracture syndrome.
- Disorders in which cortical bone is defective or scanty lead to fractures of long bones whereas disorders in which trabecular bone is defective or scanty lead to vertebral fractures and also may help in fractures of lone bones because of the loss of reinforcement.
- Bone is resorbed and formed continuously throughout life and these important processes are dependent upon three major types of bone cells.
  a. **Osteoblasts:** The bone forming cells which are actively involved in the synthesis of the matrix component of bone (primarily collagen) and probably facilitate the movement of minerals ions between extracellular fluids and bone surfaces.
  b. **Osteocytes[16]:** The are believed to act as a cellular syncytium that permits translocation of mineral in and out of regions of bone removed from surfaces, as well as signaling between different bone cells.
  c. **Osteoclasts:** The bone resorption cells.

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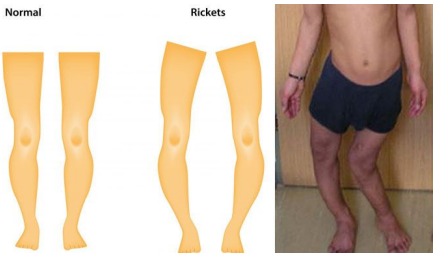
[13] administration of calcium gluconate should be very slow because if it's fast it can cause cardiac arrest
[14] cortical bones get deficient as we get old (60s and 70s)
[15] we talk about trabecular bone mainly in immediate postmenopausal period.
[16] in past we thought that it is a silent precursor of osteoblast. Now, we know it is the Maestro of The Orchestra, it has a dendritic process that send signals to osteoblasts and osteoclasts as a response to any minor trauma or change in volume.

★ Bone functions:

- Provide rigid support to extremities and body cavities containing vital organs.
- Provide efficient levers and sites of attachment of muscles which are all crucial to locomotion.
- Provide a large reservoir of ions such as calcium, phosphorus, magnesium and sodium which are critical for life and can be mobilized when the external environment fails to provide them.

★ Osteomalacia:

Failure of organic matrix (osteoid) of bone to **mineralize** normally.[17]



A number of factors are critical for normal bone mineralization. An absence or a defect in any one of them may lead to soft bones, produces:

- rickets during bone growth in children because of bone deformity which is not present in adults because the skeleton is formed and instead of that they may present with neuromuscular symptoms.
- osteomalacia following epiphyseal closure in adults.

★ Causes:

The most common biochemical causes are a decrease in the product of concentrations of calcium and phosphate in the extracellular fluid so that the supply of minerals to bone forming surfaces is inadequate.

1. Vitamin D deficiency because of:	
A. Inadequate sunlight exposure without dietary supplementation	• House- or institution bound people. • Atmosphere smog. • Long term residence in far northern & far southern latitudes. • Excessive covering of body with clothing.
B. Gastrointestinal diseases that interrupts the normal enterohepatic recycling of vit. D & its metabolites, resulting in their fecal loss. (common)	• Chronic steatorrhea (pancreatic) • Malabsorption (gluten-sensitive enteropathy) • Surgical resection of large parts of intestine. • Formation of biliary fistulas.
C. Impaired synthesis of 1,25(OH)2D3 by the kidney. the most common cause is vitamin D deficiency and because we are not exposed to the sun, we have a huge problem with vitamin D particularly in our	• Nephron loss, as occurs in chronic kidney disease • Functional impairment of 1,25(OH)2D3 hydroxylase (eg. In hypoparathyroidism) • Congenital absence of 1,25(OH)2D3 hydroxylase (vit. D-dependency rickets type I).

[17] they develop pseudofracture

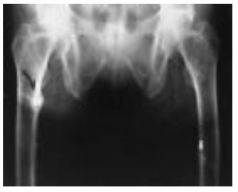
region because it is too sunny, so, people avoid sun and our lifestyle changed.	• Suppression of 1,25(OH)2D3 production by endogenously produced substance (cancer).
D. Target cell resistance to 1,25(OH)2D3 e.g. absent, or diminished number of 1,25(OH)2D3 receptors, as in vit.D-dependency rickets type II.	
2. Phosphate deficiency because of:	
A. Dietary:	• Low intake of phosphate. • Excessive ingestion of aluminum hydroxide.
B. Impaired renal tubular reabsorption of phosphate:	• X-linked hypophosphataemia. • Adult-onset hypophosphataemia. • Other acquired & hereditary renal tubular disorders associated with renal phosphate loss (Fanconi's sydnrome, Wilson's disease). • Tumor-associated hypophosphataemia
C. Systemic Acidosis because of:	• Chronic renal failure • Distal renal tubular acidosis • Ureterosigmoidoscopy • Chronic acetazolamide & ammonium chloride administration
D. Drug induced Osteomalacia.	• Antiepileptic drugs.

★ Clinical presentation:

- The clinical manifestations of osteomalacia in adults usually go unrecognized because of the non-specific skeletal pain and muscular weakness and erythema (two third of patients are asymptomatic).
- Proximal muscle weakness and pain are the common symptoms.
- Incidental radiological findings.
- Unexplained high Alkaline phosphatase.
- Deafness
- Only when the disease is extensive, deformities occur: large skull, frontal bossing, bowing of legs.
- fractures tendency: ribs, vertebral crush fractures, tibia or femur. healing is rapid.
- Clinically patients with osteomalacia have a characteristic waddling gait, that is due to the proximal muscle weakness and to the pain and discomfort during movements of the limbs.
- Some patients have severe muscular hypotonia and paradoxically brisk deep tendon reflexes.

★ Diagnosis:

Patients with osteomalacia go through three phases of development characterized by unique changes in the serum concentration of calcium, phosphate, PTH and vit D3 levels and the radiographically assessed bone lesions.

Lab tests	• Low serum vitamin D • Phosphate and calcium: may be normal or low. • High serum ALP • High PTH explanation: ★ The underlying defect leading to these changes is the decrease in the production of $1,25(OH)_2D3$ which is due to diminished availability of the major circulating metabolites of vit D 25(OH) D3. ★ The decreased 1,25(OH)2D3 results in decreased intestinal calcium absorption, decreased bone resorption, hypocalcaemia, increased PTH secretion and hypophosphatemia. ★ The resulting decreased CaxPho. Product in serum is insufficient for the normal mineralization of bone and the osteomalacic process is initiated. ★ The increased PTH secretion and hypophosphatemia occur at the expense of osseous demineralization caused by hyperparathyroidism.
Radiology	★ X-ray: Subperiosteal resorption, looser's zones (pathognomonic) ★ Bone scan. 

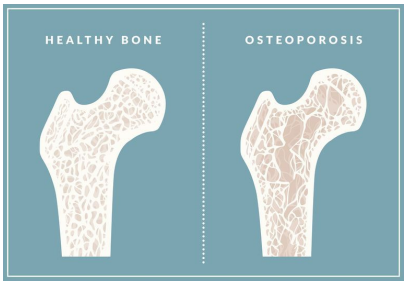
★ Treatment: we decide what is the dose Biochemically and hormonally, when we give vitamin D things will go back to normal, but radiologically it will take longer, it may takes months or years for the bones to become normal.

- Correcting underlying cause.
- Patients with osteomalacia due to simple dietary deficiency of vit D or lack of exposure to sunlight will respond well to small daily doses of vit D, calcium and sun exposure.
- Administration of oral doses of ergocalciferol(D2) or cholecalciferol (D3)(2000 IU daily) for several months will heal the bone disease and restores biochemical and hormonal values to normal in most cases.
- It is important to administer calcium to provide adequate calcium for bone mineralization (1-2 gm of elemental calcium daily).
- Serum ALP and PTH decrease slowly over several weeks but improvement in radiological appearances may take several months.
- Other forms of osteomalacia may need different preparations and doses of treatment e.g., osteomalacia secondary to malabsorption may require huge doses of vit D (200,000 IU orally) because of the poor absorption of the drug or even I.V./I.M. vit D (40,000-80,000 IU).

★ Osteoporosis:

Decrease in bone mass and strength associated with an increased tendency to fractures from minimal trauma.

It is a silent thief because it progresses without you realizing till at a certain age, the presentation will be a bone fracture. The problem is not the bone mass itself but the complications such as fractures.



Type I: Post Menopausal	Type II: Senile
Fractures of bones composed mainly of Trabecular bone. e.g: Distal Radius → Colle's fracture Vertebra → Crush & Wedge fractures	Fractures of bones composed of both cortical & Trabecular bone. e.g: Hip → Femure neck fracture
Usually affects woman within 15 years of menopause.	Usually affects individuals over the age of 70 years.

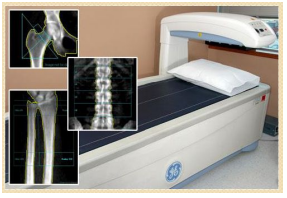
★ Causes:

- Menopause, Old age.
- Calcium and vitamin D deficiency
- Estrogen deficiency in women and androgen deficiency in men
- Use of steroids:
  - Steroids for several days causes bone loss more on axial bones (40 %) than on peripheral bones (20%).
  - Muscle weakness
  - Prednisolone more than 5 mg /day for long time.
- Exclude secondary causes especially in younger individuals and men, Common secondary causes of bone loss:
  - hyperparathyroidism
  - vitamin D deficiency
  - malabsorption state(e.g.:celiac disease,IBD,short gut syndrome)
  - Hypercalciuria
  - Hyperthyroidism
  - Chronic lung disease (COPD)
  - Malignancy
  - Rheumatoid arthritis
  - Hepatic insufficiency

★ Clinical Features:

- It is usually an asymptomatic disease until fractures occur. The first manifestation of reduced bone mass is usually a wrist fracture or a vertebral crush fracture caused by a small amount of force which produces severe localized pain.
- Subsequent vertebral fractures may contribute to chronic back pain.
- In well established osteoporosis dorsal Kyphosis and loss of height occurs.
- Hip fractures with its fatal complications also occur commonly as osteoporosis becomes more severe.

★ Diagnosis:

Lab tests	ALP and PTH are within normal in patients with osteoporosis due to sex hormones deficiency and aging.
radiology	X-rays of skeleton do not show a decrease in osseous density until at least 30% of bone mass has been lost.
	Assessment of bone mass available methods:  • Single-Photon absorptiometry (SPA) • Dual-Photon absorptiometry (DPA) • Computed Tomography (CT) • Dual-Energy X-ray Absorptiometry (DEXA).[18] This is the most accurate test in measuring bone mineral density (BMD): it measures the bone density of the lumbar spine and proximal femur and compare it to BMD of a healthy woman. -Measure bone mass by the ability of the tissue to absorb the photons emitted from the radionuclide source or the X-ray tube. -Age related bone loss particularly trabecular bone in the spine begins in women before menopause. It is appropriate to begin to look for risk factors that predispose a person to osteoporosis and develop a rational prevention program tailored to person's risk before the menopause. e.g., Women with thin light frame, history of low calcium intake, decreased physical activity, high alcohol or caffeine consumption, smoking, family history of osteoporosis, history of prior menstrual disturbances or history of drug like antiepileptics or steroids are all high risk groups

[18] This is what you need to know, and what we rely on these days. it is a simple x Ray machine, the patient lies flat and it detects how much x Ray beam is absorbed by the bone mass and reflected in the plate. So, the less bone you have, the less Ray absorption, more details in the next page.
-DEXA test results will be in the form of two scores:
- T score: This number shows the amount of bone you have compared with a young adult of the same gender with peak bone mass.
- A score of -1 and above is considered normal.

A score between -1.1 and -2.4 is classified as osteopenia (low bone mass). A score of -2.5 and below is defined as osteoporosis.
- Z score: This number reflects the amount of bone you have compared with other people in your age group and of the same size and gender.

	and in the presence of one or more of such risk factors measurement of BMD provides further information to the risk of fractures.

WHO Osteoporosis criteria 1994: (Definition based on BMD):

- Normal: BMD within 1 SD (T score above -1).
- Osteopenia: BMD which lies between 1 and 2.5 SD " below young normal adult.
- Osteoporosis: more than or equal to 2.5 SD " below young normal adult ".
- Severe osteoporosis: osteoporosis + with 1 or more fragility fractures

★ Management:

- **Prevention:**
  - Public awareness
  - Adequate calcium and vitamin D supplements
  - Physical activity
  - Detect and treat early to decrease further progression
  - Limit disability and provide rehabilitation
- **Treatment:**

First line of treatment:

- Bisphosphonates → reducing bone breakdown.
- Denosumab: reduces bone break down.
- Teriparatide: anabolic.
- More explanation in the table: just read it

Target group	Aim	Method of treatment
The Adolescent Female	Peak bone mass attainment	1. Adequate calcium intake of 1200 mgm/day is recommended. 2. Adequate sun exposure or vit D supplementation to ensure adequate level. 3. A reasonable exercise program is recommended. 4. Genetic influence on peak bone mass attainment.
The Premenopausal Female	Maintenance of bone mass	1. Adequate calcium intake; 1000-1500 mgm/day disease. 2. Adequate sun exposure or vit D supplementation 3. A reasonable exercise program is recommended, but not to the point of amenorrhea. 4. Avoidance of osteopenia-producing conditions/medications/lifestyles: a. Smoking & excessive alcohol intake, excessive caffeine/protein intake. b. Amenorrhea/oligomenorrhea. c. Cortisone, excessive thyroid hormone replacement (?), loop diuretics, prolonged heparin exposure.

The Immediately Postmenopausal Female	Prevention of bone mass loss	Consideration of estrogen replacement therapy If intact uterus, consideration of medroxyprogesterone Other modalities of therapy: 1. Bisphosphonates 2. SERMS (Selective estrogen receptor modulators) e.g., Evista, Livial 3. Protelos (strontium ranelate) 4. Forteo (Teripratide) 5. Prolia (Denosumab)
The elderly postmenopausal female with low bone mass but no compression fractures	Prevention of bone mass loss & restoration of bone mass previously lost	1. Adequate calcium intake: 1000-1500 mg/day 2. Adequate supply of vit D (1000-2000IU) 3. A reasonable exercise program with physical therapy instruction in paraspinous muscle group strengthening exercise. 4. Avoidance of osteopenia-producing conditions/medications/lifestyles: a. Smoking & excessive alcohol intake, excessive caffeine/protein intake. b. Cortisone, excessive thyroid hormone replacement 5. Other modalities of therapy: a. Bisphosphonates b. SERMS (Selective estrogen receptor modulators) e.g., Evista, Livial c. Protelos (strontium ranelate) d. Forteo (Teripratide) e. Prolia (Denosumab)
The elderly (age>62) postmenopausal female with fractures (spine & hip)	Prevention of further fractures	-
The male or female with corticosteroid induced osteopenia	Prevention of bone mass loss & restoration of bone mass previously lost	1. Bone mass measurement if possible to identify bone mass loss 2. Lowest possible dose of corticosteroids: ? Deflazacort 3. A program of reasonable calcium intake (1000-1500 mgm daily, depending upon urinary calcium), exercise, & avoidance of other osteopenia-producing situations is indicated. 4. Adequate intake of vit D (1000-2000 IU) 5. Other modalities of therapy a. Estrogen (Females), testosterone (males) b. Bisphosphonates c. Forteo

Summary

Disorders of the Parathyroid Function

1-primary Hyperparathyroidism
Causes:
-single adenoma
-4 glands hyperplasia
-parathyroid carcinoma

Clinical Features:
-nephrolithiasis
-nephrocalcinosis.
-osteitis fibrosa cystica
-peptic ulcer
-Pancreatitis - ↑ BP

Diagnosis:
↑ PTH, ↑ Ca, ↓ or normal PO4, ↑ ALP, X-ray(hands)→bone resorption or cystic formation, US, MRI, nuclear(subtraction study)→(pre-operative localization)

Treatment:
Resection of parathyroid lesion,
Other: Mythramycin, Calcitonin, Bisphosphonates (for ↑ Ca)

2-secondery Hyperparathyroidism
(↑ PTH, ↓ Ca)

Causes:
- ↓ vitD or Ca
- ↓ intestinal absorption of vitD or Ca
-Drugs.
- ↑ intake phosphate.
-renal failure

4-Pseudohypoparathysoidism
familial disorders with target tissue resistance to PTH.

Diagnosis:
↓ Ca, ↑ PO4, ↑ PTH

Clinical Features:
congenital defects in the growth of skeleton:
• Short statue
• Short metacarpal and metatarsal bones

3-Hypoparathyroidism
Causes:
-Surgical hypoparathyroidism
-autoimmune
-hypomagnesaemia

Clinical Features:
-Neuromuscular (Tetany)
-Cataract
-Cardiac: (↑ QT, ↓ BP)
-Dental
-Malabsorption (steatorrhoea)

Diagnosis:
↓ PTH, ↓ Ca, ↑ PO4

Treatment:
oral Ca + pharmacological vitD
PO4 restriction in diet

*Emergency: Tetany
Ca parenterally till adequate serum Ca level is obtained
then vitD + oral Ca

METABOLIC BONE DISEASES

1-Osteomalacia
(Failure of organic matrix of bone to mineralize normally)

Etiology:
-Vitamin D deficiency
-Phosphate deficiency
-Systemic Acidosis
-Drug induced

Findings:
- ↓ 1,25(OH)2D3
- ↓ Ca
- ↑ PTH
- ↓ PO4

Clinical Features:
-waddling gait
-deep tendon reflexes.

Treatment:
vit D and calcium.

2-Osteoporosis
(Decrease in bone mass and strength associated with an increased tendency to fractures)

Types:
1- Type **I** (Post Menopausal)
Trabecular bone Fractures.
2-Type **II** (Senile)
cortical & Trabecular bone Fractures.

Findings: normal ALP + PTH
-X-rays do not show a decrease in density until 30% of bone mass has been lost.

Clinical Features:
-asymptomatic until fractures occur. (wrist, vertebral, hip fracture) - loss of height.

Treatment:
-calcium intake -sun exposure or vit D
-reasonable exercise program
-Avoidance of osteopenia-producing condition.
-estrogen replacement therapy (Postmenopausal)
-Testosterone therapy (male)
- Other (Denosumab, Bisphosphonates)

Questions

Q1) Which one of the following cause hypercalcemia?

A. Furosemide
B. Hyperthyroidism
C. Chronic liver disease
D. Pseudohypoparathyroidism

Q2) Which one of the following cause hypercalcemia?

A. Cushing syndrome
B. Hypothyroidism
C. Thiazide diuretics
D. Loop diuretics

Q3) Which one is favorable Site of calcification in hypoparathyroidism?

A. Cerebellum
B. Basal ganglia
C. Optic chiasm
D. Brain stem

Q4) Which one of the following can cause hypocalcemia?

A. Cushion disease
B. Hypothyroid
C. Loop diuretics
D. Thiazides

Q5)A 45 years old patient with a history of recurrent kidney stones.
Investigations: Calcium level: High , Parathyroid hormone level: High
Which one of the following is the next step for management ?
A. Observation
B. Hydration
C. Parathyroidectomy
D. Thiazide diuretic

Q6) Which one of the following ECG changes is likely to be found in case of hypocalcemia?

A. Peaked T wave
B. U wave
C. Depressed P-R interval
D. Prolonged Q T interval

Ans: B , C , B , C , C , D