Medicine
TEAM 437

MED437
KING SAUD UNIVERSITY

Parathyroid disorders

Objectives :

Not given

Done by :

Team leader: Salem Al-Ammari
Team members: - Mohammed Alswoaiegh - Abdullah Alzaid
- Shahad Aljebreen - Rinad Alghoraiby

Revised by :

Aseel Badukhon

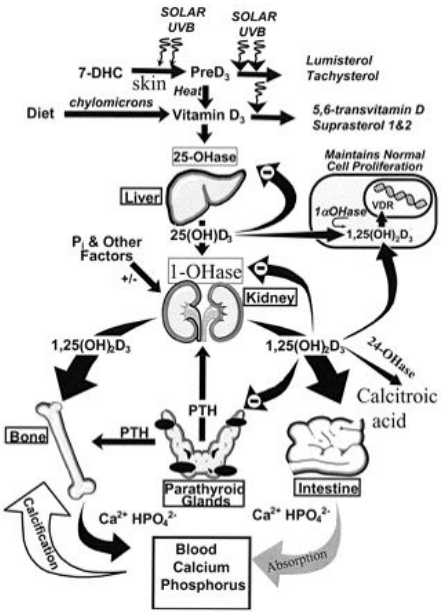
Resources :

Doctor's slides + Team 436
Lecturer: Prof. Riad Sulimani & Dr. Mona Fouda
Same as 436 slides: Yes

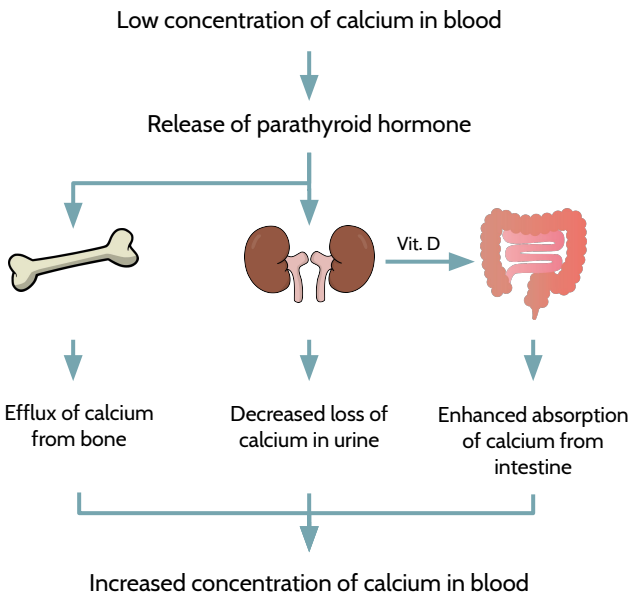
Calcium Metabolism

Physiology of calcium homeostasis

- PTH (parathyroid hormone) The most important factor
- Vitamin D
- Calcitonin (parafollicular cells “C cells” of thyroid gland): it opposes the effects of PTH by :
  - Inhibiting osteoclasts from breaking down bone
  - It inhibits CA reabsorption in renal tubular cells



Normal calcium range (2.1-2.5) which is a very narrow range.



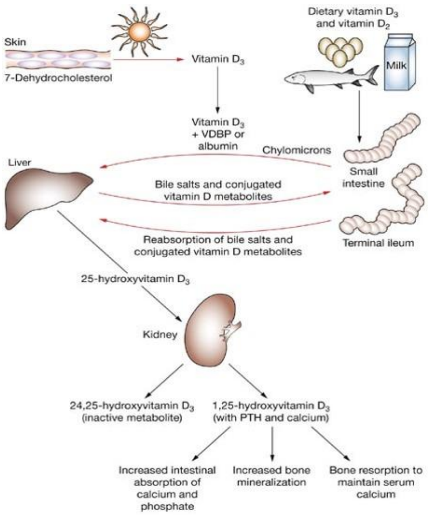
Vitamin D Metabolism

Best time for sun exposure in Riyadh:

Summer: 9 am - 10:30 & 2-3 pm

Winter: 10 am -2 pm

- 90% of vitamin D in our body comes from the skin by 7 dehydrocholesterol under UV sunlight at a particular angle, not from the diet, then metabolized and activated by the liver and kidneys.
- Direct exposure is required even the glass would prevent passage of ultraviolet.
- The appropriate time is between 10am to 3pm when ultraviolet rays are perpendicular to ground and has the ultimate impact.
- 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.
- It is called vitamin but it is steroid hormone “ it acts in the body like a hormone”.



Hypercalcemic States

- Old times. Hypercalcemia is diagnosed late when the patient experienced renal stones or osteoporosis. But, nowadays the majority are diagnosed early and incidentally because they will be asymptomatic.
- Comprehensive biochemistry panel measures all biochemical components within blood.

Parathyroid - related

- Primary hyperparathyroidism
  - Solitary adenomas
  - Multiple endocrine neoplasia
- Lithium therapy
- Familial hypocalciuric hypercalcemia, (autosomal dominant) (PTH IS NORMAL), mild hypercalcemia, hypercalciuria, Mg high normal or high

  "The kidneys reabsorb more calcium with known mechanism besides a strong family history"

Malignancy - related

- Increased PTHrp: commonest cause (BREAST CANCER)
- MULTIPLE MYELOMA: production of osteoclast activating factor
- LYMPHOMA and SARCOIDOSIS

  "Chronic granulomatous disease (non-caseating)" : 1,25 dihydroxyvitamin D
- PTH IS NORMAL in malignancy induced hypercalcemia

Malignancy induced hypercalcemia either by:

1. Bone metastasis causing more bone resorption
2. Release of osteoclast activating factor
3. PTHrP: PTH related protein

Q: **Which of the following agents behind hypercalcemic effect of lymphomea and sarcoidosis?**
A: 1,25 dihydroxyvitamin D

Vitamin D - related

- Vitamin D intoxication
- ↑ 1,25(OH)2D; sarcoidosis and other granulomatous diseases
- Idiopathic hypercalcemia of infancy

Associated with high bone turnover

- Hyperthyroidism
- Immobilization "Immobilization would increase calcium resorption"
- Thiazides "Thiazides increase renal calcium reabsorption"
- Vitamin A intoxication

Associated with renal failure

- Severe secondary hyperparathyroidism
- Aluminum intoxication
- Milk alkali syndrome

Adrenal Insufficiency

- A combination of increased calcium input into the extracellular space and reduced calcium removal by the kidney.
- The mechanisms responsible for the reduction in calcium removal were decreased glomerular filtration and increased tubular calcium reabsorption.

Primary 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. 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.
- A single adenoma occurs in about 80% of patients with primary hyperparathyroidism.
- 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:

- **Most common presentation is asymptomatic hypercalcemia**
- "Bones, stones, abdominal moans and psychic groans"
- The two major sites of potential complications are the bones and the kidneys.

Bone disease: osteoporosis and fractures, osteitis fibrosa cystica

Osteitis fibrosa cystica 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.

Neuromuscular: fatigue, lethargy, weakness

Neuropsychiatric: depressed mood, psychosis

Cardiovascular: hypertension, ventricular hypertrophy

Kidney: nephrocalcinosis, stones (ca oxalate)

Nowadays such complications are seen less commonly and around 20% of patients or less show such complications.

Other features include:

"peptic ulcer (late), pancreatitis, gout and pseudogout, anemia, constipation"

Diagnosis

- The presence of established hypercalcaemia in more than one serum measurement accompanied by elevated immunoreactive PTH is characteristic (iPTH).
- Serum phosphate is usually low but may be normal.
- Hypercalcemia is common and blood alkaline phosphatase (of bone origin) is raised.

- ↑ Calcium ↓ Phosphorus ↑ PTH

In normal circumstances, when you have Ca, you would have low PTH.

Other Diagnostic tests:

- Plain X-ray of hands can be diagnostic showing subperiosteal 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 gland(s):
  - Ultrasonography
  - MRI
  - CT
  - Thallium 201 – Tehcnichum99m scan (subtraction study)

Treatment of Hyperparathyroidism

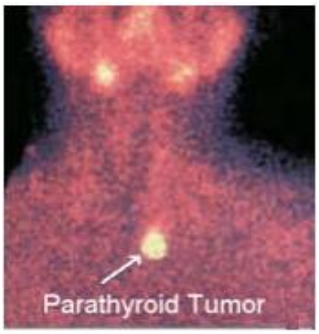
- In primary hyperparathyroidism: if patient is symptomatic (lithiasis, osteoporosis, pancreatitis) **surgery is indicated:**
  - bilateral neck exploration or
  - focused parathyroid exploration if adenoma is localized preoperatively
- Intraoperative PTH monitoring
- Endoscopic parathyroidectomy
- **Medical treatment:** cinacalcet (Calcimimetic agent): if patient is a high surgical risk

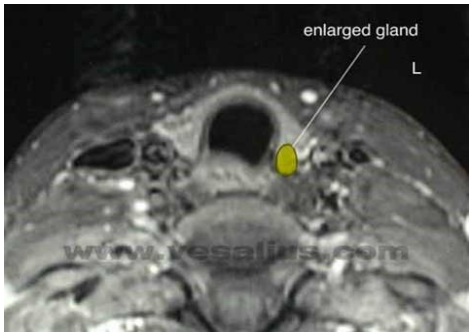
If the patient is elderly, has comorbidities and need to do the surgery. At this situation, you might give calcimimetic which resembles calcium and will reduce production of PTH.

Treatment of Hyperparathyroidism

- **Surgery of primary hyperparathyroidism:**
  - Preoperative localization: U/S, CT, MRI, sestamibi scan
  - Removal of adenoma If hyperplasia: subtotal (removal of 3 ½ of glands)

The remnant parathyroid gland can be positioned in the forearm instead of the original site which will be fibrotic and would superimpose the gland.





Do we treat hypercalcemia and asymptomatic patient?
1- See if the patient has any complications such as renal stone,osteoporosis and etc.
2- The younger the patient -> stronger the indication

Secondary Hyperparathyroidism

- Chronic renal disease causing hypocalcemia "The most important cause as the body loses the active conversion of vit D to the most biological active form of vit D that shows the majority of its effect"
- Severe vitamin D deficiency
- Malabsorption "Celiac disease"

Tertiary Hyperparathyroidism

- Tertiary Hyperparathyroidism occurs after long standing secondary hyperparathyroidism, such as CKD

Hypoparathyroidism

Causes:

- **Surgical hypoparathyroidism**
  - The commonest
  - After anterior neck exploration for thyroidectomy, abnormal parathyroid gland removal, excision of a neck lesion.
  - It could be due to the removal of the parathyroid glands or due to interruption of blood supply to the glands.
  - Two structures that are in danger in case of thyroidectomy are parathyroid glands and recurrent laryngeal nerves.

- **Idiopathic hypoparathyroidism**
  - A form occurring at an early age (genetic origin) with autosomal recessive mode of transmission "multiple endocrine deficiency autoimmune candidiasis (MEDAC) syndrome"
  - "Juvenile familial endocrinopathy"
  - "Polyglandular autoimmune syndrome Type 1 (AKA HAM syndrome)": In children and In this sequence
    (moniliasis "mucocutaneous candidiasis" → hypoparathyroidism → hypoadrenalism)
  - Circulating antibodies for the parathyroid glands and the adrenals are frequently present.
  - Other associated disease:
    - Pernicious anemia
    - Ovarian failure
    - Autoimmune thyroiditis
    - Diabetes mellitus
  - The late onset form occurs sporadically without circulating glandular autoantibodies.

- **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.
  - Severe diarrhea, malabsorption or other conditions that might cause hypomagnesemia. Magnesium is like the fuel for parathyroid glands.So, if you have a patient with hypocalcemia, you have to check or measure Mg in the blood.

Q: **Which of the following elements is important for parathyroid function?**
Zinc, Iron, Mg or Sodium
A: Mg

Hypoparathyroidism

- **Clinical presentations:**

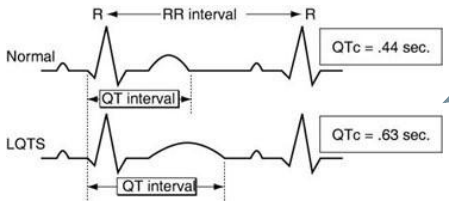
Tetany:
- if severe hypocalcemia
- post surgical

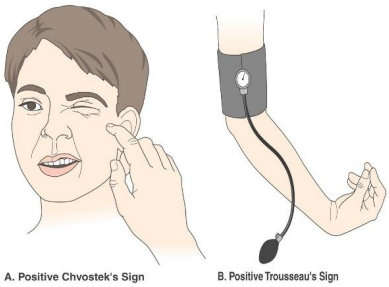
Eyes:
Cataract
Long standing hypocalcemia.

CNS:
- (calcification of basal ganglia) causing extrapyramidal disorders
- numbness

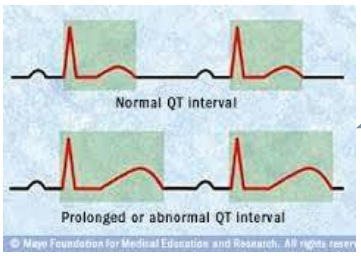
Cardiac:
prolonged QT interval
Can cause ventricular arrhythmia.
Q: What is the most classical sign of hypocalcemia in ECG?
A: Prolonged QT-interval

Signs:
- Trousseau sign "Inflate blood pressure cuff above the systolic pressure for up to three minutes.Positive if patient develops spasm of hand"
- Chvostek sign "by tapping the skin over the facial nerve about 2 cm anterior to the external auditory meatus Ipsilateral contraction of the facial muscles is a positive sign."




A. Positive Chvostek's Sign

B. Positive Trousseau's Sign



- ↓ Calcium ↑ Phosphorus ↓ PTH

Chronic Hypocalcemia

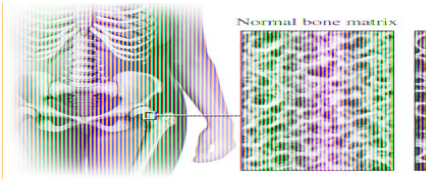
Major causes of chronic hypocalcemia other than hypoparathyroidism:

- Deficiency of vitamin D or calcium.
- Decreased intestinal absorption of vitamin D or calcium due to primary small bowel disease, short bowel syndrome, and postgastrectomy syndrome.
- Drugs that cause rickets or osteomalacia such as phenytoin, phenobarbital, cholestyramine, and laxative.
- Vitamin D dependent rickets:
  - 1-alpha-hydroxylase deficiency and hereditary resistance to to vitamin D
- States of tissue resistance to vitamin D
- Excessive intake of inorganic phosphate compounds
- Pseudohypoparathyroidism: Receptors defect
  - Type 1A autosomal dominant (resistance to PTH + somatic features)
  - Type 1B (isolated resistance, PTH IS HIGH)
- Severe hypomagnesemia
- Renal impairment

~ The ones highlighted cause hypocalcemia with high PTH !

Treatment of Hypocalcemia

- We don't give PTH because it is only injectable and expensive.
- Rather we give Calcium and Vit D
- Calcium: 1-2 gm daily
- Vitamin D analogs: calcitriol or alfacalcidol
- If severe and acute with tetany:
  give 10 cc of 10% calcium gluconate Intravenously slowly (careful in patients on digoxin)



Osteoporosis

Extra:
Introduction to Osteoporosis—Decreased Bone Matrix

Osteoporosis is the most common of all bone diseases in adults, especially in old age. It is different from osteomalacia and rickets because it results from diminished organic bone matrix rather than from poor bone calcification.

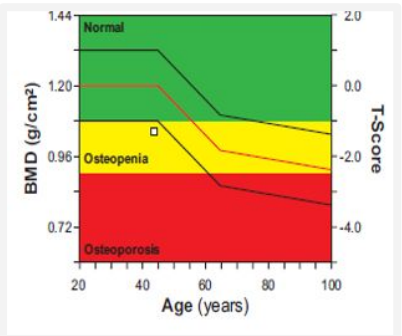
In persons with osteoporosis the osteoblastic activity in the bone is usually less than normal, and consequently the rate of bone osteoid deposition is depressed. Occasionally, however, as in hyperparathyroidism, the cause of the diminished bone is excess osteoclastic activity.

- **Definition:**
  Low bone mass with micro-architectural disruption resulting in fracture from minimal trauma
- Generally patients are asymptomatic. It is impossible that osteoporosis can cause pain, the pain is secondary to bone fractures, osteoarthritis or others.
- Hip fractures are bad, 20% patients with hip fracture die within the year. Besides, she/he might lose self-esteem and develop depression.
- **Causes:**

Menopause	Old age
Calcium and vitamin D deficiency	Use of steroids
Estrogen deficiency in women and androgen deficiency in men	

- **Exclude secondary causes especially in younger individuals and men:**
  - Hyperparathyroidism (primary or secondary)
  - Vitamin D inadequacy
  - Malabsorption state (e.g. celiac disease, IBD, short gut syndrome)
  - Hypercalciuria
  - Hyperthyroidism
  - Chronic lung disease
  - Malignancy (e.g. myeloma, bony metastasis)
  - Rheumatoid arthritis
  - Hepatic insufficiency
- **Diagnosis:**
  - Dual-energy x-ray absorptiometry (DEXA) measuring bone mineral density (BMD) and comparing it to BMD of a healthy woman
  - More than -2.5 SD below average: osteoporosis
  - It measures bone mass by the ability of the tissue to absorb the photons emitted from the radionuclide source or the X-ray tube.
  - DEXA is what we use to diagnose osteoporosis. Other methods are not used anymore for osteoporosis diagnosing.

Bone density scanner

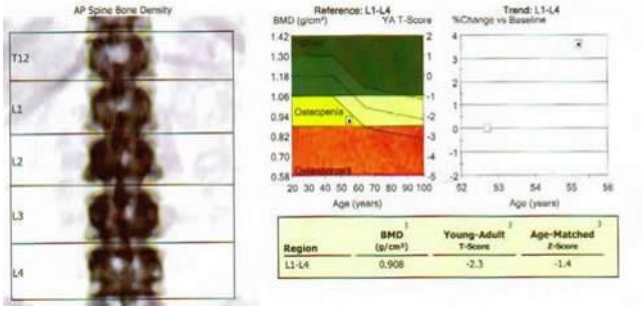


- Lumbar spine.
  "L1 to L4"
- Femoral neck

If there is osteoporosis in one site, the patient will be labeled as osteoporotic

Osteoporosis

- Bones density cannot be measured by an absolute number. To diagnose osteoporosis, you have to compare a patient's bone density with the bone density of her or his age group.
- **WHO osteoporosis criteria 1994:** definition based on BMD:
  - **Normal:** greater than or equal to – 1 SD
  - **Osteopenia:** BMD which lies between – 1 and – 2.5 SD
    Osteopenic patients are given only Calcium and Vit D supplements only, No need for osteoporotic treatment.
  - **Osteoporosis:** less than or equal to – 2.5 SD
  - **Severe osteoporosis:** osteoporosis with 1 or more fragility fractures



Q: Which BMD results indicate Osteopenia?
A- greater than or equal to -1 SD
B- BMD which lies between -1 and -2.5 SD
C- less than or equal to -2.5 SD
D- 1 or more fragility fractures
A: B

- **Treatment:**
  - Prevention
  - Public awareness
  - Adequate calcium and vitamin D supplements
  - Bisphosphonates: reducing bone breakdown
  - Denosumab: reduces bone break down
  - Teriparatide: anabolic "In case of severe osteoporosis that causes multiple fractures. We will give teriparatide intermittently not continuously which is PTH"

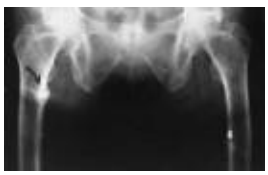
- **Effects:**
  - Steroids for several days causes bone loss more on axial bones (40 %) than on peripheral bones (20%)
  - Muscle weakness
  - Prednisolone more than 5 mg /day for long time

- **Management:**
  - Use smallest possible dose
  - Shortest possible duration
  - Physical activity
  - Calcium and vitamin D
  - Pharmacologic treatment: bisphosphonates, ? PTH

Osteomalacia

- **Definition:**
  - Reduced mineralization of bone
  - Rickets occurs in growing bone "In children. This would be permanent."
  - A mineralization problem due to inadequate conc. of Ca, P or vit D, Fracture will happen by very minor trauma.
  - Osteomalacia means in adults, Rickets means in children.

- **Causes:**
  - Vitamin D deficiency (commonest cause)
  - Ca deficiency
  - Phosphate deficiency
  - Liver disease
  - Renal disease
  - Malabsorption (Celiac disease)
  - Hereditary forms
  - (Intestinal and gastric surgery): bariatric surgery "Is a very important cause nowadays. Can be overcomed by Vit D supplements."
  - Drugs: anti epileptic drugs "Might interfere with Vit D hydroxylation in the liver."
- **Clinical Presentation:**
  - Two thirds of patients are asymptomatic
  - Incidental radiological finding
  - Unexplained high alk phosph
  - Large skull, frontal bossing, bowing of legs, deafness, erythema, bony tenderness
  - Fracture tendency: vertebral crush fractures, tibia or femur (Healing is rapid)
  - Bony aches and pains
  - Muscle weakness
  - Waddling gait, that is due to the proximal muscle weakness and to the pain and discomfort during movements of the limbs.
  - Some have severe muscular hypotonia and paradoxically brisk deep tendon reflexes
- **LAB:.**
  - Ca level
  - Po4 level
  - Alk phosph "clue"
  - PTH
  - Vitamin D level
- ↓ serum vitamin D ↑ serum alkaline phosphatase ↑ PTH
- **Radiology:**
  - X-ray: growing bones vs mature bones, Subperiosteal resorption, looser's zones (pathognomonic)
  - Bone scan



Incomplete fractures. Pseudofractures

- **Treatment:**
  - Calcium and vitamin D supplements
  - Sun exposure
  - Results of treatment is usually very good.
  - Correcting underlying cause "Such as celiac disease that might affect Vit D intestinal absorption. So, correct the cause."

Paget's Disease

Paget's Disease, also known as osteitis deformans, is a thickening and weakening of the bone. This is a metabolic bone disease which involves the destruction and regrowth of new bone that results in deformity.

The Stages:

1. The first is the hyper vascular or osteolytic phase
2. The second phase is the intermediate phase.
3. The final stage of the disease is the quiescent stage.

Paget's disease of bone interferes with your body's normal recycling process, in which new bone tissue gradually replaces old bone tissue. Over time, the disease can cause affected bones to become fragile and misshapen. Paget's disease of bone most commonly occurs in the pelvis, skull, spine and legs.

Causes:

The cause of Paget's disease of bone is unknown. combination of environmental and genetic factors contributes to the disease. Several genes appear to be linked to getting the disease.

Risk factors:

- Age. older than 40 .
- Sex. Men more than women.
- National origin. Paget's disease of bone is more common in England, Scotland, central Europe and Greece — as well as countries settled by European immigrants. It's uncommon in Scandinavia and Asia.
- Family history. If you have a relative who has Paget's disease of bone,

Symptoms:

This disease causes your body to generate new bone faster than normal, the rapid remodeling produces bone that's softer and weaker than normal bone, which can lead to bone pain, deformities and fractures. might affect only one or two areas of your body or might be widespread.

Your signs and symptoms, if any, will depend on the affected part of your body :

- Pelvis. cause hip pain.
- Skull. overgrowth of bone in the skull can cause hearing loss or headaches.
- Spine. nerve roots can become compressed. This can cause pain, tingling and numbness in an arm or leg.
- Leg. causing you to become bow legged. Enlarged and misshapen bones in your legs can put extra stress on nearby joints, which may cause osteoarthritis in your knee or hip.

Complications :

Paget's disease of bone progresses slowly. Possible complications include:

- Fractures and deformities.
- Osteoarthritis.
- Neurologic problems.
- Heart failure.
- Bone cancer.

Paget's Disease

Diagnosis:

1. Imaging tests:
   Bone changes can be revealed by: X-rays, Bone scan.
2. Lab tests:
   People usually have elevated levels of alkaline phosphatase in their blood, which can be revealed by a blood test.

Treatment :

If the disease is active -indicated by an elevated alkaline phosphatase level -and is affecting high-risk sites in your body, such as your skull or spine, your doctor might recommend treatment to prevent complications, even if you don't have symptoms.

Medications : Osteoporosis drugs (bisphosphonates) are the most common treatment for Paget's disease of bone.

Examples include:

- Alendronate (Fosamax)
- Ibandronate (Boniva)
- Pamidronate (Aredia)
- Risedronate (Actonel)
- Zoledronic acid (Zometa, Reclast)

If you can't tolerate bisphosphonates, might prescribe calcitonin (Miacalcin), a naturally occurring hormone involved in calcium regulation and bone metabolism.

Surgery:

In rare cases, surgery might be required to:

- Help fractures heal
- Replace joints damaged by severe arthritis
- Realign deformed bones
- Reduce pressure on nerves

Paget's disease of bone often causes the body to produce too many blood vessels in the affected bones, increasing the risk of serious blood loss during an operation.

Lifestyle and home remedies:

- Prevent falls.
- Be sure your diet includes adequate levels of calcium and vitamin D, which helps bones absorb calcium.
- Exercise regularly.

Summary

	Primary Hyperparathyroidism	Secondary Hyperparathyroidism	Hypoparathyroidism	Pseudohypoparathysoidism (rare)	Osteomalacia	Osteoporosis
Causes	1- Single adenoma 2- Four glands hyperplasia 3- parathyroid carcinoma (rare)	chronic decrease in the ionic calcium level in the blood (Most common is Vit.D deficiency)	1- Surgical hypoparathyroidism (the most common cause) 2- Idiopathic hypoparathyroidism 3- Functional hypoparathyroidism	familial disorders with target tissue resistance to PTH.	1- Vitamin D deficiency 2- Phosphate deficiency 3- Systemic Acidosis 4- Drug induced Osteomalacia	1- Menopause 2- Old age 3- Ca and Vit. D deficiency 4- Estrogen deficiency in women and androgen deficiency in men 5-Use of steroids 6- other secondary causes
Clinical Features	Kidney related (nephrolithiasis, nephrolithiasis) Bones related (osteitis fibrosa cystica) Others (muscle weakness, easy fatigability, peptic ulcer, pancreatitis, hypertension, gout, pseudogout, anemia and depression)		Neuromuscular (Paresthesia, tetany, hyperventilation, adrenergic symptoms, convulsion) Others (Posterio -lenticular cataract, cardiac manifestation, dental manifestation, malabsorption syndrome)		Waddling gait. Muscular hypotonia. Brisk deep tendon reflexes.	Asymptomatic until fractures occur.
Diagnosis	Lab tests: Calcium (high) PTH (high) Phosphorus (low) The Glucocortisoid suppression test Plain X-ray: subperiosteal bone resorption. cysts formation. generalized osteopenia.	Calcium (low) PTH (high)	serum calcium (Low) serum phosphate (High) Serum PTH (Very low) urine cAMP (Low)	serum calcium (Low). serum phosphate (High). PTH (High). diminished nephrogenous CAMP and phosphature response to PTH administration.	1,25(OH)2D3 (Low) Ca (Low) PTH (High) PO4 (Low)	DXA
Management	Resection of the parathyroid lesion. Acute sever form: saline anddiuretics Others: Glucocostiroids, Mythramycin, Calcitonin, Bisphosphonates, Phosphate, Estrogen		Oral Ca with pharmacological vit.D. PO4 restriction in diet. Emergency (Tetany): Ca parenterally till adequate serum Ca is obtained then vit.D and oral Ca		Vit.D and Ca	Pharmacological: Bisphosphonate, Denosumab, severe cases IV Teriparatide Other: Adequate calcium and vitamin D supplement, Physical activity.

Questions

1.Which one of the following can cause hypercalcemia?
a.Cushing disease
b.Hypothyroidism
c.Loop diuretics
d.Thiazide

2.Which one is favourable Site of calcification in hypoparathyroidism?
A.Cerebellum
B.Basal ganglia
C.Optic chiasm
D.Brain stem

3. A 23-year-old man presented to the ER with right hip fracture, which happened after jogging. Lab results: PTH (high), Ca (high), vitamin D (normal), phosphorus (low), ALP (...). X-Ray of both hips and legs revealed large cystic areas, one of which involving the right femur neck.Which of the following is most likely the diagnosis?
A.Bone metastasis from an unknown primary
B.Primary hyperparathyroidism with brown tumors
C.Severe vitamin D deficiency with secondary hyperparathyroidism
D.Unknown diagnosis of chronic renal failure with renal osteodystrophy

4. A 21-year-old woman complains of urinary frequency, nocturia, constipation and polydipsia. Her symptoms started 2 weeks ago and prior to this she would urinate twice a day and never at night. She has also noticed general malaise and some pain in her left flank. A urine dipstick is normal. The most appropriate investigation is:
A.Serum phosphate
B.Serum calcium
C.Parathyroid hormone
D.Plasma glucose

5. 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 diuretics

Answers
1.D
2.B
3.B
4.B
5.C