MEDICINE

432 Team

40 Parathyroid Disorders

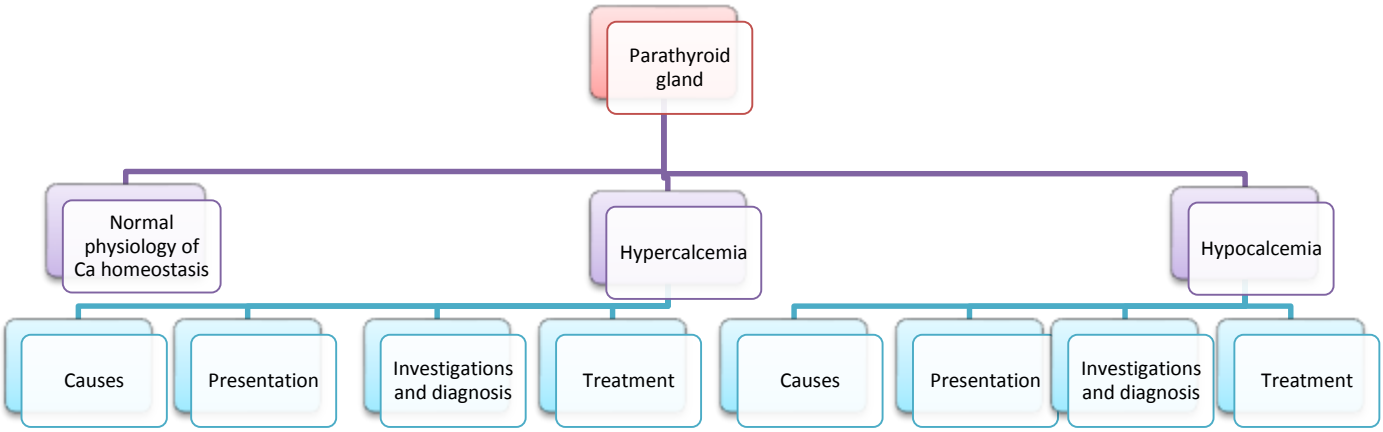
Done By:
Abdulmohsen Almeshari

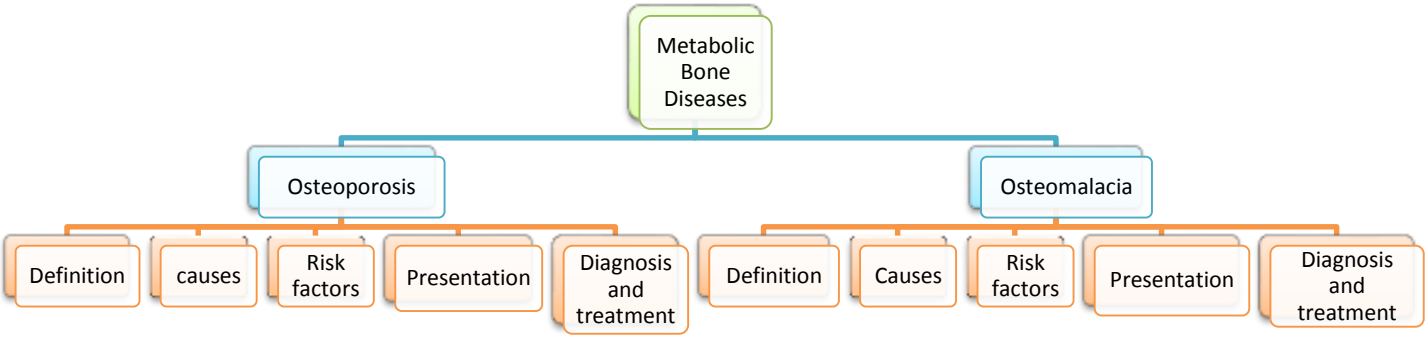
Reviewed By:
Zaina Alsawah

COLOR GUIDE: • Females' Notes • Males' Notes • Important • Additional

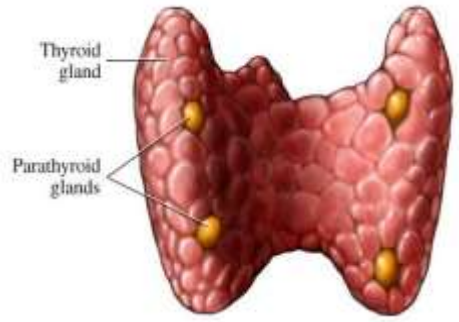
Objectives (not Given!)

Mind Map



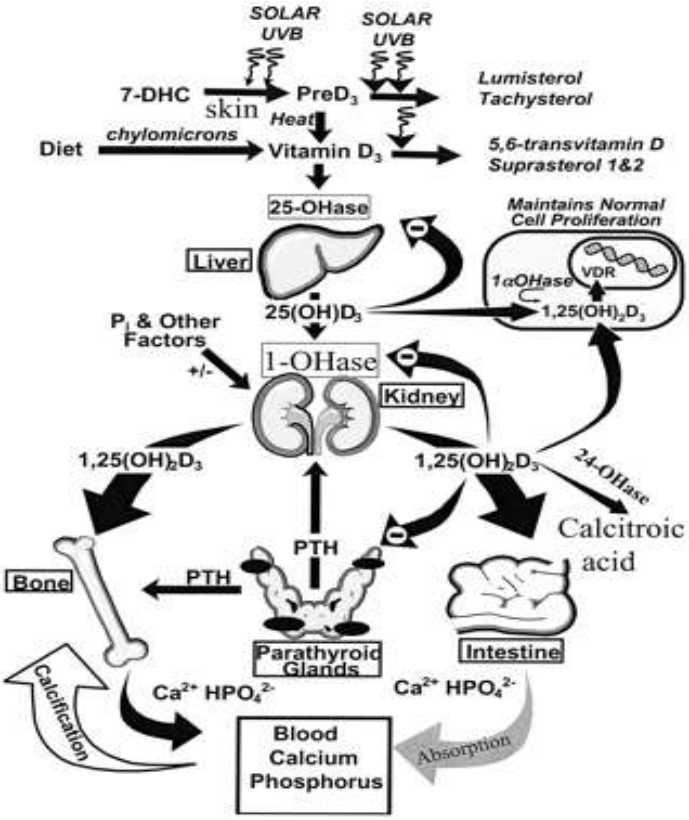


Let's review some basics!



The four parathyroid glands lie behind the lobes of the thyroid. From their name, parathyroid glands secrete the parathyroid hormone (PTH) in response to decreased blood level of Ca.

Calcium is very important to the normal function of:
Bones
Muscles
Nerve conduction



Vitamin D (Cholecalciferol) is provided in the diet and is produced in the skin from cholesterol. In the skin, 7-dehydrocholestrol is transformed into pre vitamin D3 and then into Vitamin D3 under the influence of ultra-violet beams. Vitamin D3 then travels in the blood till it reaches the liver where it gets its first hydroxylation and transforms into 25-hydroxycholecalciferol. Then, in the kidney, under the influence of PTH and other factors, this form will get another hydroxylation to produce: **1,25 dihydroxycholecalciferol**. This active form will then go to both, the intestine and bones. In the intestine, it will promote Ca absorption. In the bones, it works synergistically with PTH to stimulate osteoclast activity and bone resorption and thus, increasing overall Ca in the body.

The main stimulus for PTH secretion is *hypocalcemia*, while the main stimulus for Calcitonin secretion is *hypercalcemia.* Calcitonin is produced by the c cells in the Thyroid and its major role is to inhibit osteoclastic bone resorption. (Physiological antagonist of PTH)

25-hydroxycalciferol is the most abundant form of vitamin D and thus, it's the one measured when testing for vitamin D levels.

We usually give the inactive form of vit D (vit D3) as a supplement to patients in need. **But** if a patient has **renal failure**, we give him the activated form (1,25 dihydroxycholecalciferol).

Some drugs can interfere with the hydroxylation process that occurs in the liver. The most important of which is **Phenytoin**.

Hypercalcemia:

"Hypercalcaemia is one of the most common biochemical abnormalities and is often detected during routine biochemical analysis in asymptomatic patients" – Davidson's

Causes:

The main cause of hypercalcemia is **primary hyperparathyroidism (adenoma = 80% or hyperplastic glands = 20%)**. Other causes are listed in the table below:

Cause	Mechanism of hypercalcemia
Sarcoidosis	The granulomatous cells produce 1,25 dihydroxycholecaliferol.
Thyrotoxicosis	Not well understood, but the Dr mentioned that the whole body is working at increased rate.
Adrenal insufficiency	
Thiazides	Increases Ca reabsorption in the kidneys.
Hypervitaminosis D&A	Increased intake of vitamin D.
Immobilization	Increases bone turnover.
Malignancy (The most common malignancy that causes hypercalcemia is breast cancer. Multiple myeloma is the most common hematological malignancy that causes hypercalcemia)	Either by: I. Releasing substances that mimic PTH function. II. Invasion of the bone and releasing Ca into the blood.
Familial Hypocalciuric Hypercalcemia (FHH)	Inactive mutations in: I. Ca sensing receptors in the parathyroid glands. II. Ca receptors in the kidney (That mediate Ca reabsorption)

Remember!

Multiple myeloma patients' main presentation includes anemia & back pain.

Presentation:

The major impact of hypercalcemia is on bones (osteoporosis) and on kidneys (renal stones). Hypercalcemic patients typically present with "*bones, stones, abdominal groans, and psychic moans*"

Related signs & symptoms include: polyuria, polydipsia, fatigue, renal colic, lethargy, anorexia, nausea, dyspepsia, peptic ulceration, constipation, depression and impaired cognition. Hypertension is also a common feature.

In the skeleton, a condition called **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 (due to lytic lesions) as well as bone cysts and *brown tumors* of the long bones (areas of bone resorption). Such overt bone disease, even though typical of primary hyperparathyroidism, is very rarely encountered.

Investigations & diagnosis:

Note!

When a patient comes to you with renal stones, make sure you check their blood calcium levels. Identifying & eliminating the major cause that leads to the stones' formation is the first step in treating this patient. Removing the stone alone won't help.

As mentioned before, the main cause of hypercalcemia is *primary hyperparathyroidism*. **Lab tests** in this case will show:

- ↑ **(High) serum Ca levels**
- ↓ **(Low) serum phosphorus levels**
- ↑ **(High) PTH levels**

In cases of malignancies not associated with the parathyroid gland, PTH will be low.

1- The Glucocorticoid suppression test:

The hypercalcaemic of **non-parathyroid origin** e.g. vitamin D intoxication, sarcoidosis and lymphoproliferative syndromes generally respond to the administration of prednisolone in a dose of 40-6- mg daily for 10 days by a decrease in serum calcium level. On the other hand, the response is unusual in hypercalcaemia secondary to primary hyperparathyroidism and ectopic PTH production. A positive test result i.e. significant decrease in serum calcium (it's a suppression test) is a contraindication to neck exploration and signals the need for investigation for a non-parathyroid cause of hypercalcaemia.

2- Radiograph:

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.

3- **Other diagnostic tests**:

Pre-operative localization of the abnormal parathyroid gland(s):

- Ultrasonography
- MRI
- CT
- Thallium^{201} – Technichum^{99m} scan (Subtraction study)

Treatment:

> ***Note!***
> If there's a single adenoma, then we just remove it. But in case of 4 glands hyperplasia, 3.5 of the hyperplastic glands are removed and the rest of the hyperplastic gland can be transplanted to the forearm to allow further debulking at a later date.

- ✓ Remove the cause!
- ✓ Surgery (**In primary hyperparathyroidism**) ➔ Removal of the adenoma or 3 ½ of the hyperplastic glands. (the ultimate therapy)
- ✓ **Hydration / Diuretics**➔ Induce calciuresis (loop diuretics are given which will excrete Sodium and Calcium)
- ✓ **Bisphosphonates / Calcitonin** ➔ Work on ostecolcasts inhibition (Anti-resorptive)
- ✓ Mythramyxin ➔ Toxic antibiotic, which inhibits bone resorption and used in hematological and solid neoplasms causing hypercalcemia.
- ✓ Steroids ➔ Useful in multiple myeloma or other malignant neoplasms.
- ✓ Phosphate ➔ Oral phosphate can be used as an antihypercalcaemic agent and is commonly used as a temporary measure during diagnostic workup.
- ✓ Estrogen ➔ It also decreases bone resorption and can be given to postmenopausal women with primary hyperparathyroidism using medical therapy.

> ***Note!***
> **Secondary hyperparathyroidism** is an increase in PTH secretion, which is adaptive and unrelated to intrinsic disease of the parathyroid glands. This is due to chronic stimulation of the parathyroid glands by a chronic decrease in the ionic calcium level in the blood. Caused by Vit D deficiency. Lab findings: normal or low Ca level with high PTH.

Hypocalcemia:

Causes:

- **Hypoparathyroidism**
  - Post Surgery: After anterior neck exploration for thyroidectomy, abnormal parathyroid gland removal, or 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.
  - Functional hypoparathyroidism: In patients who have chronic hypomagnesaemia of various causes. Mg is necessary for the PTH release from the glands. (Here, the gland is normal. The only problem is with the decreased levels of magnesium)
  - Idiopathic:
    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.

- Pseudohypoparathyroidism (Tissue resistance to PTH)
- **Vitamin D deficiency**
- **Chronic renal failure** (most common – Kumar)
- Alkalosis

Presentation:

A. **Neuromuscular**

I. Tetany: **Trousseau's and Chvostek's signs** as well as extrapyramidal signs (as a result of basal ganglia calcification)
II. Parasthesia
III. Hyperventilation
IV. Convulsions
V. Adrenergic symptoms

Note!

Sometimes, if Trousseau's sign wasn't obvious, and you were suspecting hypocalcemia, you can induce the appearance of the sign by inflating the sphygmomanometer above the systolic pressure. The patient will complain of numbness and pain starting in his index finger. Immediately deflate the sphygmomanometer after you see this reaction.

Note!

Extrapyramidal signs include:
Resting tremor
Shuffling gait
Masked facies
Cogwheel rigidity

B. **Other clinical manifestations**

I. Cardiac: Prolonged **QT** interval (Very dangerous as it may cause **ventricular fibrillation**)
II. Eye: **Cataract** formation
III. **Dental** manifestiation (absent dental eruption & defective dental root formation).
IV. **Malabsorption** syndrome: presumably secondary to decreased calcium levels and may lead to steatorrhea with long standing untreated disease.

Investigations & diagnosis: (no need for imaging, imaging is only done for hyperfunctioning glands)

In hypoparathyroidism, the following lab results will appear:

- ↓ **(Low) serum Ca levels**
- ↑ **(High) serum phosphorus levels** (absorption of Ca in the kidneys is associated with loss of phosphate, and vice versa. That is why their levels are usually opposed)
- ↓ **(Low) PTH levels** (low in hypoparathyroidismi, high in other causes) kumar

Treatment:

- ✓ Calcium and vitamin D supplements. (As well as phosphate restriction in diet)
- ✓ In cases of emergency (severe tetany): Slow injection of 10 cc of 10% of calcium gluconate with ECG monitoring.
- ✓ IV magnesium in case of hypomagnesemia
- ✓ In cases of Hungry bone syndrome: (patients with hyperparathyroidism and severe bone disease who undergo successful parathyroidectomy, hypocalcaemia may be severe): Parenteral calcium infusion with later supplementation of oral calcium and vitamin D.

Osteoporosis:

"Osteoporosis is by far the **most common bone disease**. It is characterized by reduced bone mineral density (BMD) with an increased risk of fracture, and increases markedly with age. The condition affects up to 30% of women and 12% of men at some time during their life." – Davidson's.

Causes:

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

Steroids & Osteoporosis

Use of steroids will eventually lead to osteoporosis by several mechanisms. These include: renal Ca loss, inhibition of intestinal Ca absorption, and increasing osteoclast activity and inhibiting osteoblast activity. They usually affect the axial bones (40%) more than others.
So, we advise patients who take steroids to take the least possible dose in the morning of every other day along with Ca & vit D suppliments.

Risk Factors:

These include: female gender, early menopause, hyperthyroidism, hyperparathyroidism, inflammatory bowel disease, malabsorption and chronic liver disease.

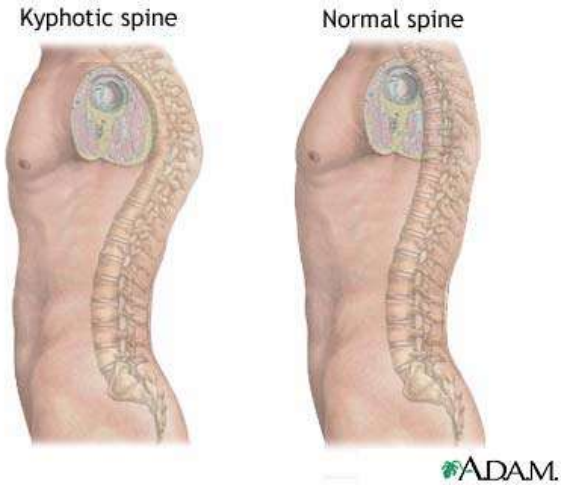
Presentation:

	Type 1	Type 2
Age	51-75	>70
Sex ratio (F:M)	6:1	2:1
Type of bone loss	Mainly trabecular	Trabecular and cortical
Rate of bone loss	Accelerated	Not accelerated
Fracture sites	Distal radius and vertebrae	Vertebrae, hips, pelvis, proximal humerus
Parathyroid function	Decreased	Increased
Ca absorption	Decreased	Decreased
Metabolism of 25(OH)2D to 1,25(OH)2d	Decreased	Decreased
Main causes	Factors related to menopause	Factors related to aging

Patients are usually asymptomatic until it causes fractures. Pain without fractures is **not** a symptom of Osteoporosis. In well established osteoporosis, dorsal kyphosis *(look at the picture below)* and loss of height occurs.

Note! (From Davidson's)

The most common sites for fractures in osteoporosis are:
- The forearm (Colles fracture)
- The spine (vertebral fractures causing back pain, height loss, and kyphosis)
- Femur (Hip fracture)



Types of osteoporosis:

Type 1"Post Menopausal Osteoporosis": Usually affects woman within 15 years of menopause, causes fractures in trabecular bone. E.g. Distal radius (Colle's fracture), and vertebrae (crush and wedge fractures)

Type 2 "senile osteoporosis": Usually affects individuals over the age of 70, causes fractures of both Cortical & Trabecular bone. E.g. Femur neck fractures.

Investigations & diagnosis:

X-rays of skeleton do not show a decrease in osseous density until at least 30% of bone mass has been lost.

Methods to assess bone mass: SPA (single photon absorptiometry), DPA (dual photon absorptiometry) ,CT, DEXA (the best method).

Dual-energy x-ray absorptiometry (DEXA) is a device used to measure the bone mineral density (BMD) (It measures it by the ability of the tissue to absorb the photons emitted from the radionuclide source or the X-ray tube). Pictures are usually taken from the lumbar spine or femoral neck. (Sometimes, we take the pictures from the distal 1/3 of the forearm). It compares the results of the patient to the values of a normal person. A standard deviation of **more than -2.5** is diagnostic of *osteoporosis*. Values between -1.0 and -2.5 indicate osteopenia, while values above -1.0 are regarded as normal.

Treatment:

- ✓ Prevention through public awareness
- ✓ Adequate calcium and vitamin D supplements
- ✓ Bisphophonates: reduces bone breakdown
- ✓ Raloxifene: a selective estrogen receptor modulator, which is useful in post-menopausal patients.
- ✓ Hormone replacement therapy (HRT)

Osteomalacia & rickets:

"Osteomalacia is defective mineralization of newly formed bone matrix or osteoid. Rickets is defective mineralization at the epiphyseal growth plate and is found in association with osteomalacia in children." – Kumar & Clark's

Causes:

- Vitamin D deficiency (**commonest cause**)
- Ca deficiency
- Phosphate deficiency
- Systemic acidosis
- Liver disease / Renal disease
- Malabsorption (Celiac disease) ➔ Test for anti-gliadin antibodies.
- Hereditary forms
- Intestinal and gastric surgery: **Bariatric surgery**
- Drugs: anti epileptic drugs

Presentation:

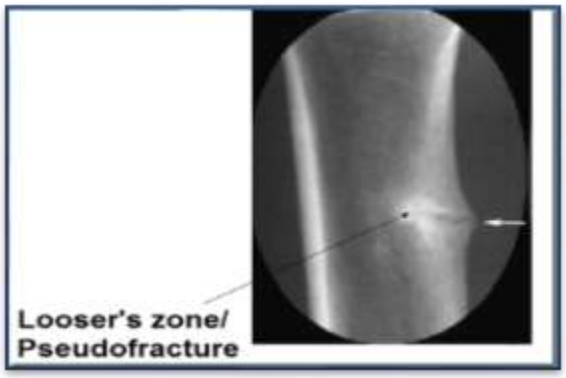
- "Manifestations of **rickets** in children include enlargement of epiphyses at the lower end of the radius and swelling of the costochondral junctions ('rickety rosary')" – Davidson's. This will lead to bone pain, reduction in growth and bowing of the long bones.
- In osteomalacia, 2/3 of the patients are asymptomatic. It's almost always an incidental radiological finding. The rest may present with large skull, frontal bossing, bowing of legs, muscle weakness, erythema, deafness and bone **pain**. Muscle weakness and bone pain lead to *waddling gait* (https://www.youtube.com/watch?v=R4dI4nrsVd8). Further progression may lead to fractures. These include: Vertebral crush, tibia, or femur fractures. Healing is rapid.

Investigations & diagnosis:

- Renal function, serum calcium, phosphate, alkaline phosphatase, vitamin D and PTH levels should be measured.

  ↓(Low) serum Ca levels
  ↓(Low) serum vitamin D
  ↓(Low) PO4 levels
  ↑(High) PTH levels
  ↑(High) serum alkaline phosphatase

- In rickets, "X-rays will show widening of the growth plate with a cupped and ragged metaphysis". – Danish
- In osteomalacia, X-rays will show typical pseudo-fractures (**Looser's zones**) in the ribs, long bones & pelvis. "Looser's zones are linear areas of low density (less white) surrounded by sclerotic borders". – Danish
- Bone biopsy (usually not required), can be used to confirm the diagnosis.



Treatment

- ✓ Correcting underlying cause
- ✓ Calcium & Vitamin D supplements (**Vit D replacement is the cornerstone of treatment**)
- ✓ In hypophosphatemic rickets the treatment is with phosphate supplement with vit D to prevent hypocalcemia and secondary hyperparathyroidism.
- ✓ Sun exposure

Summary

The PTH is secreted from the parathyroid gland in response to low calcium level in the blood, its function is to increase Ca level by:

1. Bone resorption.
2. Increases Ca reabsorption from kidneys.
3. Increases synthesis of Vit D in the kidneys witch absorbs Ca from the intestine.

Hypercalcaemia is most commonly caused by primary hyperthyroidism (single adenoma in 80% of the cases).

Clinical features of hyperparathyroidism include: stones(kidney stones), moans(depression), groans (abdominal pain).

Osteitis fibrosa cystica: a skeleton disorder caused by hyperparathyroidism which induces osteoclastic activity. It is characterized by: "salt and pepper" appearance of the skull, brown tumors (lytic bone lesions), subperiosteal resorption of distal phalanges.

Hyperparathyroidism is diagnosed by: high PTH, high Ca, low PO4.

It is treated by: 1. Medically (in acute cases): by hydration and loop diuretics

2. Surgically: by resection of the parathyroid lesion.

Hypocalcaemia: most common cause is due to low PTH after parathyroidectomy.

Presentation: 1. With symptoms of neuromuscular hyperactivity: Tetany (chvostek's sign, trousseau sign, extrapyramidal signs), Parasthesia, hyperventilation.

2. Other manifestations include: cataract, Ventricular fibrillation, prolonged QT, malabsorption.

Hypoparathyroidsm is diagnosed by: low PTH, low Ca, high PO4

Treated by: Oral Ca and vit D

Osteoporosis: most common bone disease, patients are asymptomatic until it causes fractures (especially in the femur, forearm and spine). Diagnosed by DEXA scan.

There are 2 types of osteoporosis:

a. postmenopausal → fractures in trabecular bone
b. senile → fractures in cortical bone

Osteomalacia: defective mineralization of bones in adults, while rickets: is defective mineralization in children. They're both caused by Vit D deficiency.

Manifestations in children: Bowing of long bones, reduction of growth, bone pain.

Manifestations in adults: could be asymptomatic, or can have symptoms like: large skull, frontal bossing, bone pain, waddling gait.

Approach to Hypocalcemia and Hypercalcemia

Hypocalcemia	Hypercalcemia
DIFFERENTIAL DIAGNOSIS	
PTH ABNORMALITIES (PO4 ") • HYPOPARATHYROIDISM surgery, irradiation, autoim mune, congenital, infiltrative, DiGeorge's syndrome • FUNCTIONAL HYPOPARATHYROIDISM Mg deficiency • PTH RESISTANCE pseudohypoparathyroidism **VITAMIN D ABNORMALITIES (PO4 #)** ○ VITAMIN D DEFICIENCY nutritional, malabsorption ○ ALTERED VITAMIN D METABOLISM cirrhosis, chronic renal failure, anticonvulsant ○ VITAMIN D RESISTANCE **DRUGS**: phosphates (hyperphosphatemia), calci tonin, bisphosphonates, plicamycin, loop diuretics **ACUTE CAUSES** acute pancreatitis, rhabdomyo lysis, tumor lysis, large transfusions of citrate containing blood products, toxic shock syndrome	**HYPERPARATHYROIDISM:** (most common cause among outpatients) parathyroid adenoma, parathyroid hyperplasia, parathyroid carcinoma (rare) **MALIGNANCY:** (most common cause among inpatients) lung, breast, prostate, renal, thyroid, GI,melanoma, sarcoma, multiple myeloma, lymphoma, leukemia **GRANULOMATOUS DISEASE:** TB, sarcoidosis, lymphoma **ENDOCRINE:** Addison's, hyperthyroidism,acromegaly **DRUGS:** vitamin D toxicity, thiazide, lithium, tamoxifen **NUTRITIONAL:** calcium supplement, vitamin D,vitamin A, milk alkali syndrome. **OTHERS:** immobility, Zollinger Ellison syndrome, familial hypocalciuric hypercalcemia, acute renal failure.
CLINICAL FEATURES	
HISTORY: tetany, stridor (laryngospasm), seizures,confusion, weakness, past medical history (thyroid surgery), medications (loop diuretics, bisphosphonates, calcitonin, anticonvulsants) **PHYSICAL:** hypotension, Trousseau's sign, Chvostek's sign, carpal/pedal spasm, weakness	**SYMPTOMS:** GI abdominal pain from constipation, pancreatitis, or peptic ulcer disease (moans), N&V MSK bony pain (groans) RENAL calculi (stones), polyuria CNS delirium (psychiatric overtone)
INVESTIGATIONS	
BASIC: LABS Ca, albumin, Mg, PO4, PTH, ALP, 25OH D3, 1,25(OH)2D3, lytes, urea, creatinine **SPECIAL:** ECG may show prolonged QT interval	**BASIC:** LABS Ca, albumin, Mg, PO4, PTH,ALP, 1,25(OH)2D3, lytes, urea, creatinine SPECIAL **MALIGNANCY WORKUP** consider PTHrP, serum protein electrophoresis. **HYPERPARATHYROIDISM WORKUP** consider U/S neck/thyroid and Tc sestamibi parathyroid scan, ECG may show shortened QT interval

MANAGEMENT	
SYMPTOM CONTROL: if severe symptoms, Ca gluconate 1 2 amps IV push then run a calcium drip 0.5 1.5 mg/kg/h, and MgSO4 2 g IV over 2 h. If mild symptoms, CaCO3 1 2 g PO TID, calcitriol (1,25(OH)2D3) 0.25 1 mg daily **TREAT UNDERLYING CAUSE**	**SYMPTOM CONTROL**: NS 200 500 mL/h IV _ furosemide 20 40 mg IV TID PRN. If Ca is 3.0 mmol/L [12 mg/dL] or more give bisphos-phonates (pamidronate 60 90 mg in 500 mL NS IV over 4 h or zoledronate 4 mg in 50 mL NS IV over 15 min). **TREAT UNDERLYING CAUSE**

Questions

1. A 58-year-old postmenopausal female presents to your office on suggestion from an urologist. She has passed 3 kidney stones within the past 3 years. She is taking no medications. Her basic laboratory work shows the following:
Na: 139 mEq/L
K: 4.2 mEq/L
HCO3: 25 mEq/L
Cl: 101 mEq/L
BUN: 19 mg/dL
Creatinine: 1.1 mg/dL
Ca: 11.2 mg/dL (normal: 2.2–2.6mmol/L – Kumar)
A repeat calcium level is 11.4 mg/dL; PO4 is 2.3 mmol/L (normal above 2.5). Which of the following tests will confirm the most likely diagnosis?

a. Serum ionized calcium
b. Thyroid function profile
c. Intact parathyroid hormone (iPTH) level
d. Liver function tests
e. 24-hour urine calcium

432 Medicine Team Leaders

Raghad Al Mutlaq & Abdulrahman Al Zahrani

For mistakes or feedback: *medicine341@gmail.com*

Answers:

1st Question: C