Parathyroid gland – metabolic bone disease

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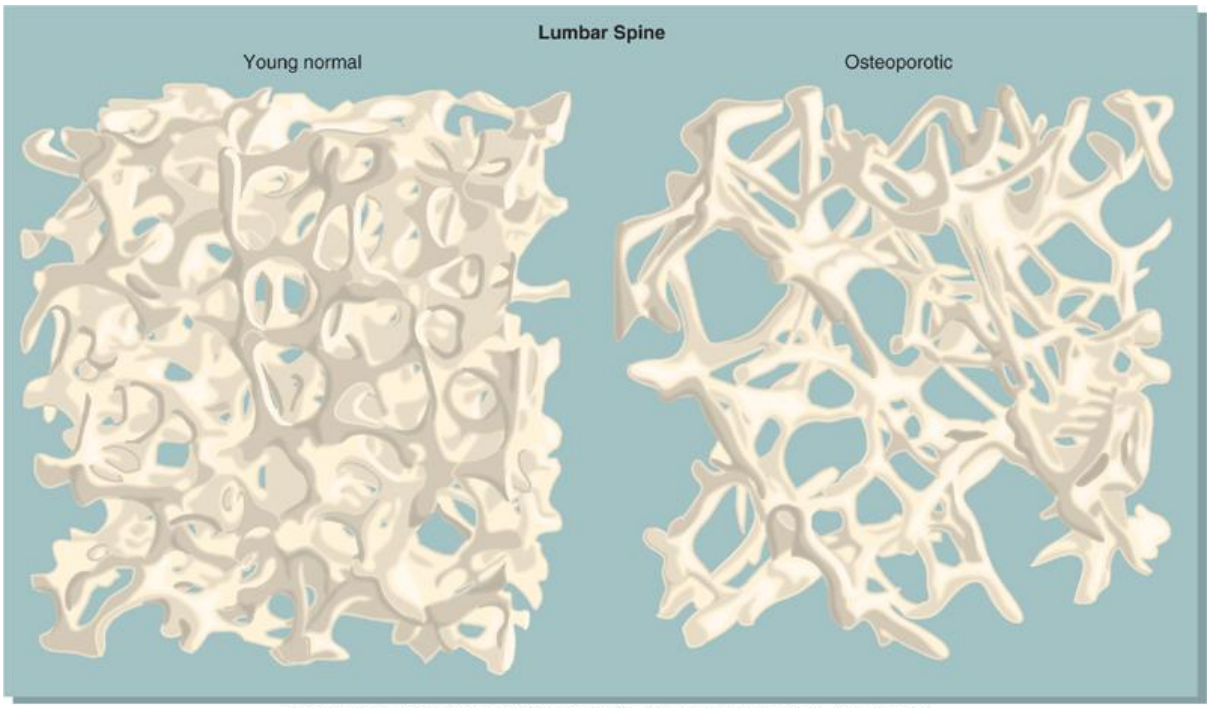
Medicine team 429

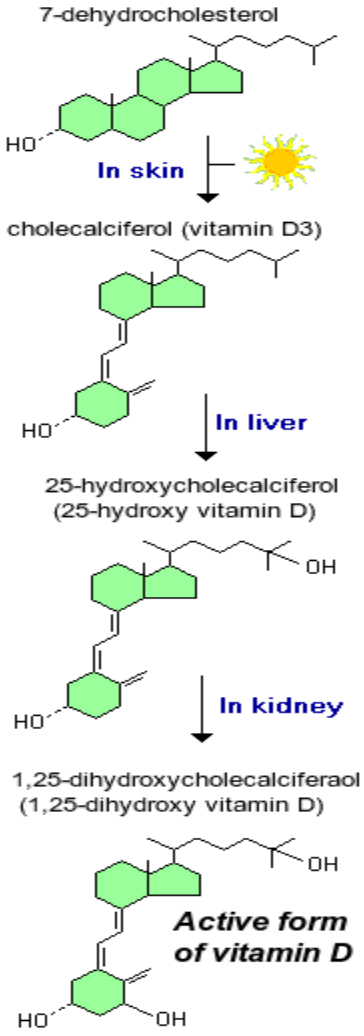


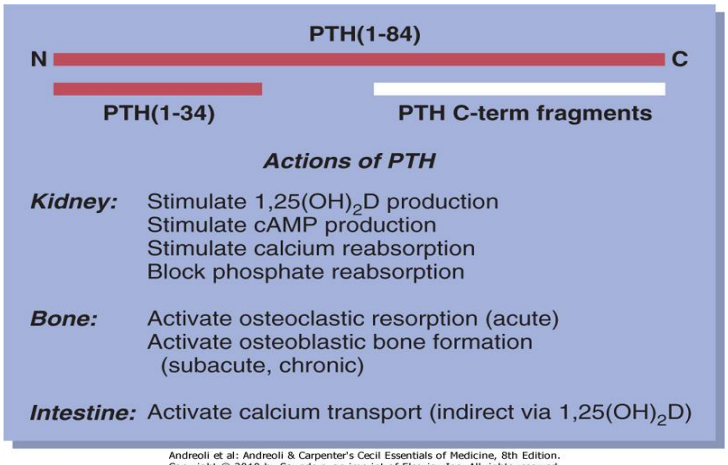
Contents:

Sources: 427 team, voice lecture, step up, kumar and andreoli's Cecil

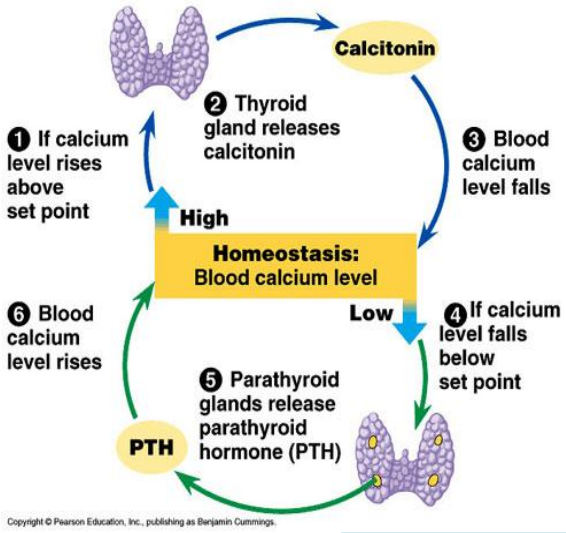
Normal physiology and biochemistry:

- Normal total calcium level in the blood is 8.5-10.5 mg/dl And is maintained by three principal hormones:
  - Vitamin D:
    - Vitamin D is considered a steroid hormone
    - Cholecalciferol (vitamin D3) is synthesized in the skin by sunlight (UV)
    - The biologically active form is:
      - 1,25-dihydroxycholecalciferol(calcitriol OR 1,25-$(OH)_2D_3$))
      - Produced by hydroxylation twice in the liver and kidney
      - The ***most potent form***
      - Patients with ESRD should be given this form and not D3 because they cannot hydroxylize it
    - Function:
      - Promotes absorption of calcium and phosphorus from the intestine
      - Increases reabsorption of calcium and phosphorus by renal tubules
      - Increases bone mineralization
    - Net effect is increase in plasma calcium and phosphorus
  - PTH
    - there are normally four parathyroid glands which are situated posterior to the thyroid
    - Secreted from the chief cells of the parathyroid glands.
    - PTH levels rise as serum ionized calcium falls
    - function:
      - increasing osteoclastic resorption of bone (occurring rapidly)
      - increasing intestinal absorption of calcium (a slow response)
      - increasing synthesis of 1,25-(OH)2D3 (Enhances hydroxylation in the kidney)
      - increasing renal tubular reabsorption of calcium
      - Increasing excretion of phosphate.
  - Calcitonin:
    - Produced by the parafollicular or C cells of the thyroid gland in response to hypercalcemia.
    - Works on lowering serum calcium





Andreoli et al: Andreoli & Carpenter's Cecil Essentials of Medicine, 8th Edition.



Effect on:	bone	Kidney	Gut	Final effect
PTH	↑ resorption	↑Ca++reabsorption ↓phosphate reabsorption	Activates vitamin D	↑plasma calcium ↓plasma phosphate
Calcitonin	↓resorption	↓Ca++reabsorption ↓phosphate reabsorption	↓postprandial Ca++ absorption	↓plasma calcium ↓plasma phosphate
Vitamin D	↑ resorption	↑Ca++reabsorption ↓phosphate reabsorption	↑Ca++absorption ↑phosphate reabsorption	↑plasma calcium ↑plasma phosphate

Hypercalcemic states:

Causes:

- 1ry hyperparathyroidism:
  - General features:
    - Primary hyperparathyroidism is the ***most common cause of hypercalcemia***
    - Calcium is high in blood → high calcium in urine
    - Phosphorus is low.
    - PTH is high**.**
    - Calcium is depleted from bones so we have osteoporotic bones
  - Causes:
    - Adenoma ***80%*** of cases – one gland is involved
    - Hyperplasia 15-20% of cases – all glands are involved
    - Carcinoma less than 1% of cases
  - Diagnosis is made by:
    - high calcium, high PTH, and low phosphorus
    - other findings: hypercalciuria, urine cAMP is elevated
  - Treatment of choice is surgery:
    - ***Remove the adenoma***
    - If there is hyperplasia then remove ***3 and a half glands***
    - We do not do surgery if the patient is asymptomatic, unless he or she is:
      - Less than 50 years old
      - Organ damage is present on investigations
      - Very high calcium levels
  - Postoperative complications:
    - Post operative hypocalcaemia
    - Bone hunger syndrome
      - Bone takes all the calcium from the blood
      - Causes muscle spasm due to hypocalcaemia
- Kidney disease: Usually causes hypocalcaemia but sometimes secondary hyperparathyroidism due to vitamin D deficiency will cause hypercalcemia

- Secondary hyperparathyroidism
- Sarcoidosis: increases GI calcium intake
  - Almost all granulomatous disorders can lead to hypercalcemia
- Thyrotoxicosis (hypercalcemia due to increased metabolism)
- Adrenal insufficiency.
- Immobilization.
- Drugs
  - Thiazide diuretics
  - Lithium
  - Vitamin D intoxication – increased GI absorption
- Hypervitaminosis D & A
- ***MALIGNANCY IMP:***
  - Multiple myeloma:
    - Due to bone lysis
    - Release of osteoclast activating factors by myeloma cells
  - Lung cancer: releases PTH-like hormone
  - Metastatic cancer:
    - Breast cancer
    - Prostate
    - Kidney

Clinical features:

- Symptoms of hypercalcemia depend on the underlying cause of the disease, the time over which it develops (rapid increases in calcium cause more severe symptoms), and the overall physical health of the patient
- Severe elevations in calcium levels may cause coma.
- It causes the following
  - **Renal "stones"**: Nephrolithiasis, Dehydration, Nephrocalcinosis
  - "bones": Bone pain and aches ,Osteoporosis, Osteitis fibrosa cystica in hyperparathyroidism (subperiosteal resorption, bone cysts)⟶ Leads to pathological fractures
  - **Abdominal "moans"**: Pancreatitis, Peptic ulcer disease, Abdominal pain, Constipation, Weight loss and Nausea and vomiting
  - **Psychiatric "overtone"**: depression, fatigue, anorexia, sleep disturbance, mood disorder, lethargy
  - **Other**: gout, muscle weakness and pain, HTN, polydipsia, polyuria, arrhythmias, short QT interval on ECG, itching, vascular calcification, *Corneal calcification*
- Hypercalcemia of malignancy may lack many of the features commonly associated with hypercalcemia caused by hyperparathyroidism. In addition, the symptoms of elevated calcium level may overlap with the symptoms of the patient's malignancy

Treatment:

- You have to treat the cause.
  - Hydration with IV fluid and diuretics (furosamide; inhibits calcium resorption) should be the first step in management
  - Steroids IMP:
    - Sarcoidosis
    - multiple myeloma
    - lymphoma
    - hypervitaminosis- vitamin D intoxication
  - inhibit bone resorption in patients with osteoclastic disease(e.g. malignancies):

        - bisphosphonates
        - Calcitonin
        - anti-osteoclastic agent ➔ decreased bone resorption ➔ less calcium goes to the blood from bone
- haemodialysis for renal failure patients
- In primary hyperparathyroidism: surgery (mentioned earlier)

Hypocalcaemia

Causes:

- Hypoparathyroidism:
    - Most common cause of hypocalcaemia (some books say chronic kidney disease)
        - Causes:
            - Usually due to surgery on the thyroid or parathyroid gland
            - Autoimmune Hypoparathyroidism is rare and it is usually in the young.
            - Severe vitamin D deficiency.
    - Low serum calcium, high serum phosphate, low PTH, low urine cAMP
- Acute pancreatitis – due to calcium deposition
- hypomagnesaemia (magnesium is required for parathyroid gland function)
- pseudohypoparathryoidism:
    - autosomal recessive disease causing congenital end-organ resistance to PTH
    - PTH levels are high
    - Also characterized by short metacarpal bones and mental retardation
- Chronic kidney disease
- Malabsorption
- Blood transfusion with citrated blood (citrate binds calcium)

Clinical presentation:

- asymptomatic
- Rickets and Osteomalacia
- increased neuromuscular irritability:
    - numbness/tingling
    - Tetany (check page 10 for pictures) :
        - Hyperactive deep tendon reflexes
        - ***Chvostek's sign***: tapping on the facial nerve leads to contraction or twitching of the facial muscles
        - ***Trosseau's sign***: inflation of the sphygmomanometer cuff above systolic pressure for 3 minutes induces tetanic spasm of the fingers and wrist
- Chronic hypocalcaemia causes low calcium and high phosphorus this causes calcifications in:
    - The eye→ early cataracts
    - Basal ganglia→ Extrapyramidal symptoms: seizure and dementia
    - The heart's conduction system → heart block and prolonged Q-T interval and arrhythmias

Diagnosis:

- The clinical picture is often complete
- Investigations
    - Serum urine and creatinine : evaluate renal disease
    - PTH levels:
        - Low in Hypoparathyroidism

        - High in vitamin D deficiency and pseudohypoparathryoidism
    - Vitamin D levels, magnesium levels
    - **X-rays** of metacarpals

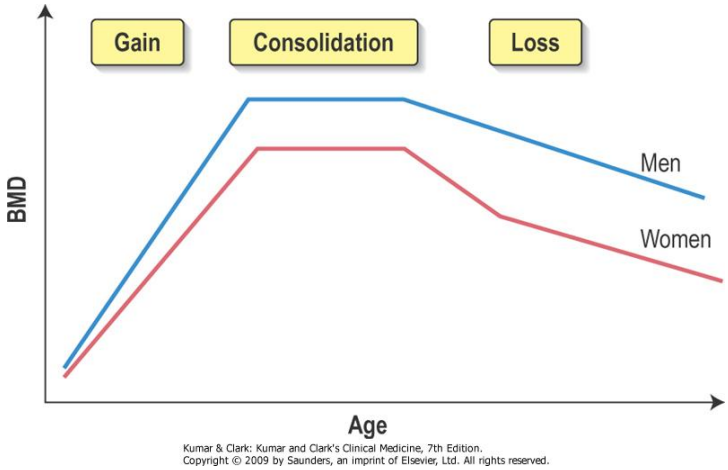
Treatment

- If symptomatic: give emergency IV calcium gluconate slowly and under ECG monitor, and add magnesium
- If patient is on digoxin this might cause cardiac arrest
- For long term management:
    - Oral calcium supplements (calcium carbonate)
    - Vitamin D supplements

Osteoporosis

General considerations:

- Defined as: a **decrease in bone mass or quality** that results in bone fragility and higher risk of fractures
- The World Health Organization (WHO) defines osteoporosis as a bone density of 2.5 standard deviations (SDs) below the young healthy adult.
- ***Morbidity and mortality in osteoporotic patients is related to fractures***
- They experience NO BONE PAIN
- Bone mass decreases with age, but will depend on the 'peak' mass attained in adult life and on the rate of loss in later life.



- Pathogenesis: Osteoporosis results from increased bone breakdown by osteoclasts and decreased bone formation by osteoblasts leading to loss of bone mass.

Causes/risk factors:

- ***Old age***
- Estrogen depletion:
    - ***Menopause*** – a major risk factor because estrogen is protective to bone
    - History of athletic amenorrhea, eating disorders, oligomenorrhea
    - Early menopause
- Female gender: women have a lower peak bone mass and smaller vertebral end plates
- Calcium and vitamin D deficiency
- hypogonadism
- Decreased peak bone mass
- Smoking/alcohol
- Drugs
    - Heparin
    - Use of steroids (decrease GI absorption of Ca, increase osteoclastic activity)
        - Major impact on axial bone IMP
    - Anticonvulsants (Phenytoin, Phenobarbitone) IMP

Classification:

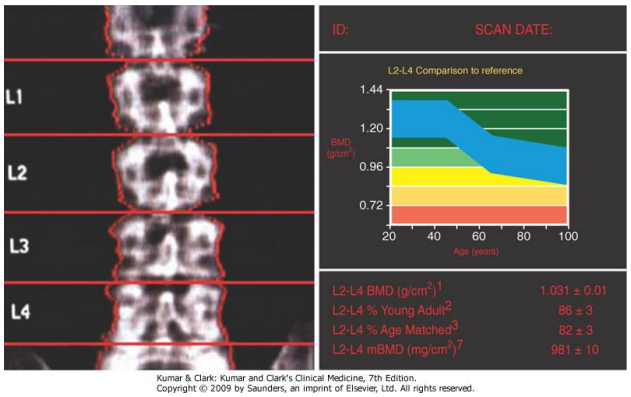
- Type1: (postmenopause)
  - Fractures of bones composed mainly of Trabecular bone
  - Usually affects woman within 15 years of menopause
  - Colles and vertebral fractures are common
- Type2: (senile)
  - Usually affects individual over age of 70 years (old age)
  - Fractures of bones composed of both cortical & Trabecular bone
  - Fractures of the femur's neck and pelvic bones are common

Clinical features:

- Osteoporosis is considered a ***silent*** disease until fractures occur and that will cause severe pain. But before that patients don't have any pain.
- Fractures:
  - **Fracture is the only cause of symptoms in osteoporosis**
  - Vertebral bodies:
    - Vertebral body compression fracture are the most common type of fracture
    - Result in severe pain and deformities including kyphosis and lordosis
    - Severe back pain after minor trauma and restricted movement
  - Colles fracture: fracture of the distal radius – due to fall on an outstretched arm
  - hip fractures: have the most serious consequences by far, with a mortality rate of more than 20% within the first year

Diagnosis is by Dual energy X-ray Absorptiometry (DXA) scan IMP

- gold standard
- very precise for measuring bone density
- measuring bone mineral density (BMD) and comparing it to BMD of a healthy 30 year old individual
- Results can be:
  - Normal
  - Osteopenia: 1-2.5 standard deviations below average
  - Osteoporosis: 2.5 standard deviations below average



Treatment

- Inhibit resorption
  - Bisphosphonates
    - Decrease osteoclastic activity via binding to hydroxyapetitie
    - Reduce risk of fracture
    - ADRs: include oesophageal disease irritation and ulceration
  - Calcium supplements
  - Vitamin D supplements
  - Calcitonin – found in nasal spray
- Weight baring exercise to stimulate bone formation
- Prevention
    - Public awareness measures
  - Reduce modifiable risk factors
  - Hormone replacement therapy

- Raloxifene: Selective estrogen receptor modulators
- Calcium supplementation
- Prevent injuries

Osteomalacia/Rickets

General considerations:

- **Inadequate mineralization of bone matrix (osteoid).**
- Rickets (in children) and Osteomalacia (in adults)
- They are usually caused by a defect in vitamin D availability or metabolism.

Causes:

- Vitamin D deficiency
  - ***Most common cause***
    - Inadequate sunlight exposure without dietary supplementation
    - Gastrointestinal: diseases that interrupts vitamin D absorption like gastric surgery
    - Kidney: Impaired synthesis of 1,25(OH)2D3 by the kidney like in chronic renal failure
    - Liver: primary biliary cirrhosis
- Phosphate deficiency:
  - Low intake of phosphate
  - Impaired renal tubular reabsorption of phosphate
- Calcium deficiency
- Drugs: ***antiepileptics*** interfere with liver hydroxylation like phenytoin MCQ

Clinical features:

- Bony aches and pains (including dental pain) **Unlike osteoporosis**
- Muscle weakness.
- Pathological fractures
- brisk deep tendon reflexes
- waddling gait

Laboratory investigations:

- ***Increased serum alkaline phosphatase***, indicating increased osteoblast activity IMP
- Low serum vitamin D, low phosphate and low calcium depending on the deficiency
- High PTH

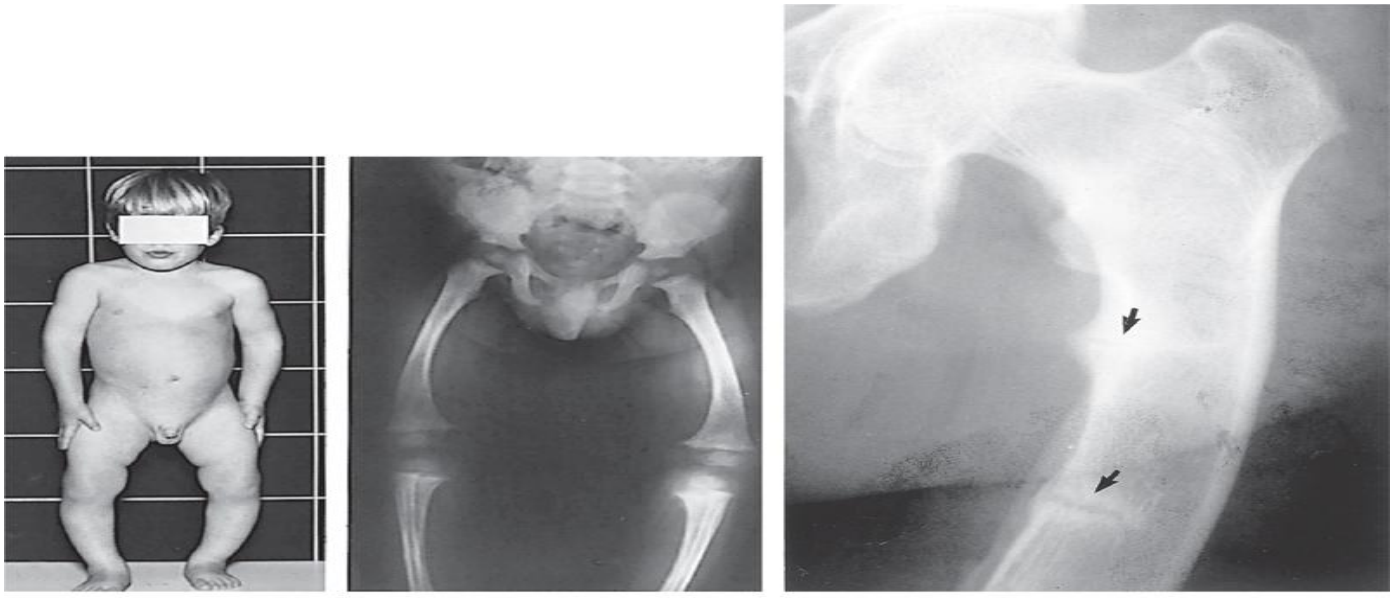
X-Ray

- Defective mineralization, especially in the pelvis, long bones and ribs
- Pseudo fractures or 'Looser's zones' - linear areas of low density surrounded by sclerotic borders.

Treatment

- Good prognosis that responds to treatment
- Vitamin D replacement:
  - ergocalciferol(D2) or Cholecalciferol (D3)
  - 1,25(OH)2D3 (calcitriol) in patients with kidney disease
- Calcium supplements
- Sun exposure

- In hypophosphataemic rickets the treatment is with phosphate supplement



A B C

a) A typical example of rickets. Note the bowing of the femurs and tibiae
b) epiphyses are open, mottled, and overgrown
c) Looser zones or pseudo fractures characteristic of Osteomalacia or rickets

The doctor stopped with the lecture here

Paget's disease

General considerations:

- Osteitis deformans or Paget's disease is a focal disorder of bone remodelling.
- most affected individuals are **asymptomatic**
- Pathogenesis:
  - The initial event of excessive resorption is followed by a compensatory increase in new bone formation, increased local bone blood flow and fibrous tissue in adjacent bone marrow.
  - Ultimately, formation exceeds resorption but the new bone is structurally abnormal

Clinical presentation:

- Most (60-80%) patients with radiologically identified Paget's disease are asymptomatic
  - Incidental radiological finding
  - an asymptomatic elevation of serum alkaline phosphatise
- symptoms include:
  - bone pain
  - joint pain when an involved bone is close to a joint
  - deformities

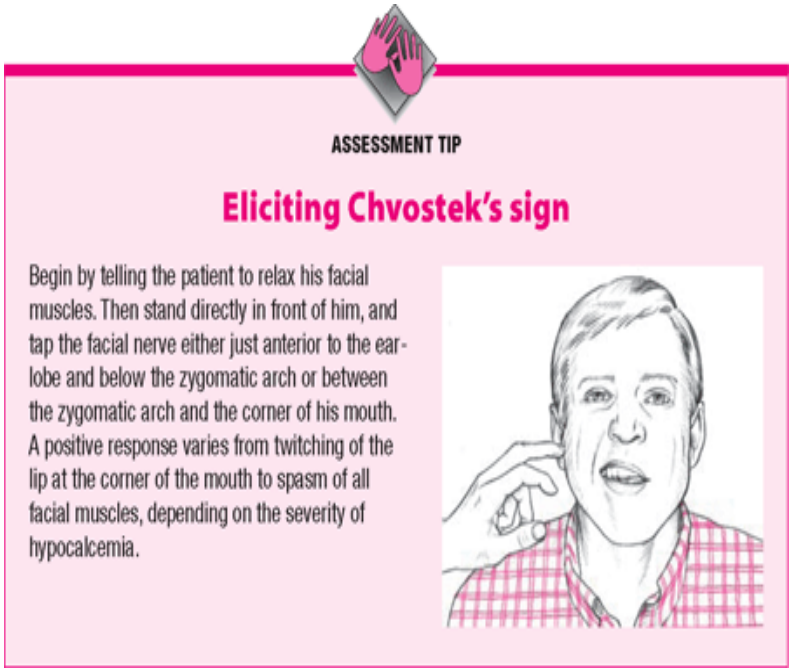
        - Tibia: bowed
        - Skull: large skull and frontal bossing
    - Fracture tendency: vertebral crush fractures, tibia or femur. Healing is rapid
    - Erythema, bony tenderness.
    - osteogenic sarcoma in pagetic bone
- Complications:
    - Deafness due to 8th nerve compression
    - increased bone blood flow (myocardial hypertrophy and high-output cardiac failure)
    - pathological fractures

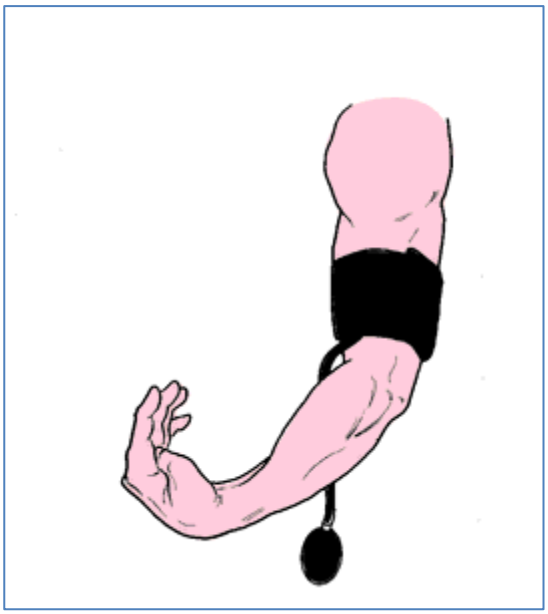
Laboratory:

- Increased serum alkaline phosphatase with normal serum calcium and phosphate
- Isotope bone scans show the extent of skeletal involvement
- Urinary hydroxyproline excretion is increased
- X-ray: areas of osteosclerosis mixed with osteolytic lesions

Treatment:

- Calcitonin.
- Bisphphosphonates.
- Plicamycin (rarely used).





Trosseau's sign