"He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all." – William Osler

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MEDICINE
TEAMWORK

PARATHYROID DISORDERS

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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:

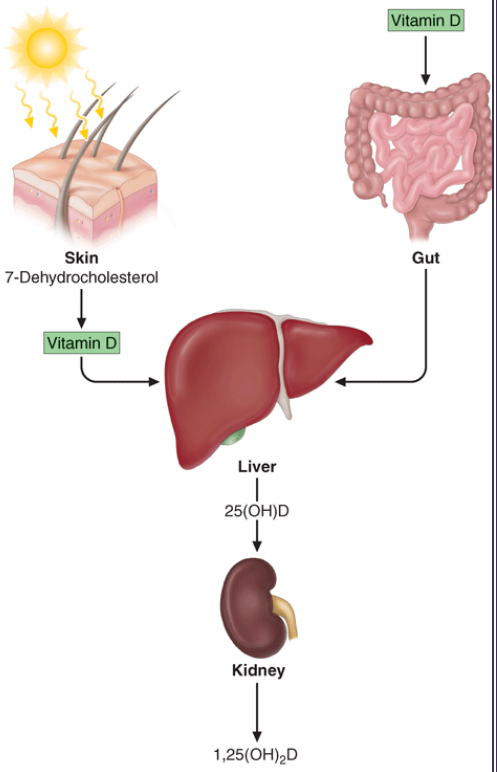
Vitamin D:

- Is a steroid hormone that is mostly related to keeping Ca2+ at hemostasis

Source:

A) External ingestion of Vit. D and

B) Photochemical cleavage of Cholecalciferol (vitamin D3) under effect of sunlight (UV)



Activation: regardless of the source Vit. D enters the circulation and is carried by Vit D binding protein to the liver.

- **The liver perfoms a hydroxylation reaction to form** 25-(OH) D. This reaction is not physiologically regulated, which causes the 25-(OH) D to be the most abundant form.
  - Is then carried to the kidney where it undergoes further hydroxylation to achieve it most potent form 1,25-dihydroxycholecalciferol (calcitriol OR 1,25-$(OH)_2D_3$)). 25-(OH) D previous form is only 1/1000 potent as calcitriol.
- Patients with ESRD (End Stage Renal Disease) should be given this form and not D3 because they cannot hydroxylize it

Actions:

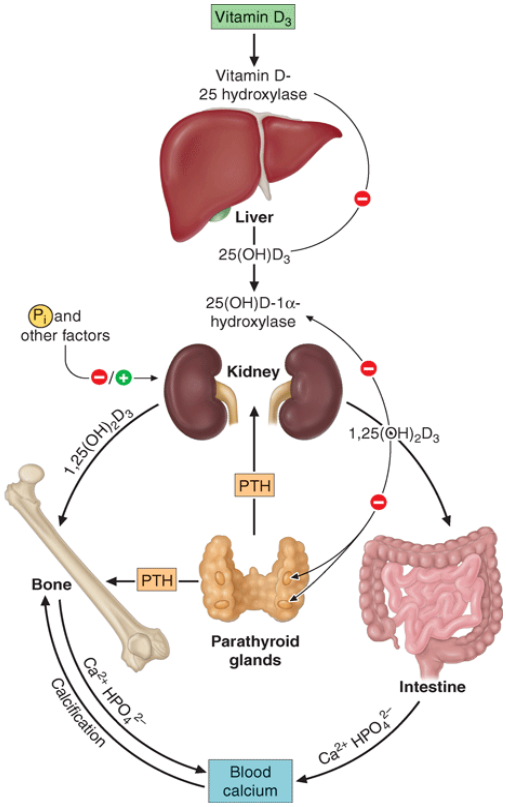
- Promotes absorption of calcium and phosphorus from the intestine **(main action)**
- Increases reabsorption of calcium and phosphorus by renal tubules (not physiologically significant)
- Increases bone mineralization: It seems that with physiologic doses that Vit D. promotes bone mineralization. However, this action's importance is debatable, but it seems the only role Vit D. has on mineralization is proving Ca2+ for deposition.

PTH:

- Secreted from the chief cells of the parathyroid glands. PTH is the principle hormone responsible for immediate changes in ionized Ca2+ levels, and that to increase Ca2+ to normal ranges.

Actions:

- Increases osteoclastic resorption of bone to free Ca2+ (occurring rapidly)
- Increases synthesis of 1,25-(OH)2D3 (Enhances hydroxylation in the kidney), and increases intestinal absorption of calcium (indirect effect)
- Increases renal tubular reabsorption of calcium and increases excretion of phosphate. Note that with resorption of Ca2+, phosphate is also released from bone, but the act of increased phosphate excretion gives a net negative balance of phosphate.



Biosynthesis, secretion, metabolism, and regulation:

- PTH is a preformed peptide hormone that is released in minutes after cellular cleavage. **If low levels of Ca2+ continue PTH transcription rates increase, and the gland enlarges to provide more PTH.**
- Magnesium is important for proper PTH secretion, as its deficiency causes functional hyperparathyroidism.
- It is metabolized by the kidney, liver and peripheral tissues.
- PTH secretion increases in response to low Ca2+ and vice versa.

Calcitonin:

- Is a hypocalcaemic peptide that is produced by the **parafollicular or C cells of the thyroid gland**
- **Calcitonin antagonizes the actions of PTH**, but is of limited physiologic importance in normal humans.
- It has some pharmacologic role in treatment of diseases like: Paget disease, osteoporosis, and hypercalcemia of malignancy.
- It acts on the kidney and bones to restore the level of calcium to just below a normal set point which in turn inhibits secretion of the hormone.

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

These hormones regulate the flow of minerals in and out of the extracellular fluid compartments through their actions on **intestine, kidneys, and bones.**

Hypercalcemic states:

- Primary hyperparathyroidism:
- Primary hyperparathyroidism is due to excessive production of PTH by one or more of hyperfunctioning parathyroid glands.
- This leads to hyprcalcemia 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.

General features:

- Primary hyperparathyroidism is the ***most common cause of hypercalcemia***
- Calcium is high in blood → high calcium in urine
- Phosphorus is usually low, but can be normal especially in cases of Chronic Kidney Disease.
- PTH is high.
- Calcium is depleted from bones so we have osteoporotic bones

Secondary hyperparathyroidism :
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

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
- Serum phosphate is usually low but may be normal. Hypercalcaemia is common and blood alkaline phosphatase (of bone origin) and the urinary hydroxyproline concentrations are commonly elevated when the bones are involved. Nephrogenous CAMP is elevated in about 80% of patients but the test is rarely used because of technical difficulties
- The Glucocortisoid suppression test:
  - 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 is a contraindication to neck exploration and signals the need for investigation for a non-parathyroid cause of the hypercalcaemia.
- Radiograph:
    - Plain X-ray of hands can be diagnostic showing subperiosteal bone resorption usually on the radial surfacy of the distal phalanx with distal phalangeal tufting as well as cysts formation and generalzed osteopenia.
- Pre-operative localization of the abnormal
    - Ultrasonography
    - MRI
    - CT
    - Thallium ^{201} – Tehcnichum^{99m} scan (subtraction study)

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: this is due to increased synthesis of 1,25(OH)2D by macrophaes and other cells of the granulamatous tissue. Almost all granulomatous disorders can lead to hypercalcemia
- Thyrotoxicosis: due to increased bone turnover, where bone resorption is more than bone deposition.
- Adrenal insufficiency.
- Immobilization: this again happens because of increased bone turnover. This happens more with children, especially those who are paraplegic or quadraplegic. In adults this only happens when someone has an underlying bone disease.
- Drugs
    - Thiazide diuretics
    - Lithium
    - Vitamin D intoxication – increased GI absorption
- Hypervitaminosis D & A
- Metabolic disturbance e.g. hypomagnesia, pancreatitis, gout or pseudogout
- ***MALIGNANCY IMP:*** this is a common finding in cancer patients, and can be due to thee process: 1) solid tumor elaboration of PTHrP, PTH related peptide, (like in lung or renal cancers) which cause bone resorbtion and hypercalcemia. 2) Direct bone involvement of blood tumors like Lymphoma, and Multiple Myeloma that release osteoclastic activating factors. 3) Metastatic Cancer (breast, prostate, and kidney). These patients usually present with symptoms relating to their cancer, rather than the hypercalcemia itself.

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.

Presentation:

- Half or more of patients with hyperparathyroidism are asymptomatic and stay years without knowing they have the disease.

The two major sites of potential complications are the **bones and the kidneys.**

- **Renal "stones"**: **1)** Nephrolithiasis: presentation of stones (pain, obstruction, infection, and loss of renal function), **2)** Dehydration, **3)** Nephrocalcinosis (deposition of calcium in the renal parenchyma)
- **"Bones":** Bone pain and aches, reduced bone density and Osteoporosis, **Osteitis fibrosa cystica** in hyperparathyroidism (subperiosteal resorption, bone cysts)→ Leads to pathological fractures.
- **Abdominal "moans"**: Abdominal pain, Constipation, Nausea and vomiting, Pancreatitis, Peptic ulcer disease.
- **Psychiatric "overtone"**: depression, fatigue, anorexia, sleep disturbance, mood disorder, lethargy.
- **Neuromuscular involvement:** include proximal muscle weakness, easy fatigability, and atrophy of muscles and may be so striking as to suggest a primary neuromuscular disorder. The distinguishing feature is the complete regression of neuromuscular disease after correction of the hyperparathyroidism.
- **Other**: *Corneal calcification,* short QT interval on ECG, and sever cases: arrhythmias.

- 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 → They are given intravenously or orally to prevent bone resorption.
    - Calcitonin → Also inhibit osteoclast activity and prevent bone resorption
    - Anti-osteoclastic agent ➔ decreased bone resorption ➔ less calcium goes to the blood from bone
    - Phosphate → Oral phosphate can be used as an antihypercalcaemic agent and is commonly used as a temporary measure during diagnostic workup.
    - Glucocostiroids → 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.
    - Estrogen → It also decrease bone resorption and can be given to postmenopausal women with primary hyperparathyroidism using medical therapy
- Hemodialysis for renal failure patients
- Prevent its reabsorption by the renal tubules.
- In primary hyperparathyroidism: surgery (mentioned earlier)

Major causes of chronic hypocalcemia other than hypoparathyroidism

- Dietary deficiency of vitamin D or calcium
- Decreased intestinal absorption of vitamin D or calcium due to primary small bowel disease, short bowel syndrome, and post-gastrectomy syndrome.
- Drugs that cause rickets or osteomalacia such as phenytoin, phenobarbital, cholestyramine, and laxative.

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, but these are usually accompanied with other autoimmune diseases with maybe other familial autoimmune diseases.
      - Severe vitamin D deficiency.
  - Low serum calcium, high serum phosphate, low PTH, low urine cAMP

- Hypomagnesaemia. Intracellular magnesium is necessary for PTH secretion and function. So this only happens with Sever hypomagnesmia, enough to cause depletion in intracellular levels. This maybe seen in alcoholics and malnourished patients.
- 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: this is usually seen with other sysmptoms of malabsoption of Anemia, etc)
- Hypocalcaemia can happen transiently in cases like: Acute pancreatitis, Blood transfusion with citrated blood (citrate binds calcium)

Major causes of chronic hypocalcemia other than parathyroprival hypoparathyroidism

- States of tissue resistance to vitamin D
- Excessive intake of inorganic phosphate compunds
- Psudohypoparathyroidism
- Severe hypomagnesemia
- Chronic renal failure

Clinical presentation:

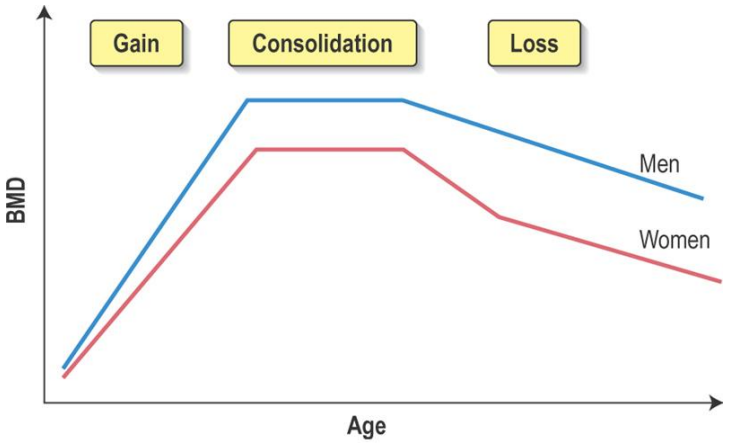
- Chronic hypocalcaemia is usually symptomatic and should be treated, and symptoms include:
  - Increased neuromuscular irritability: when the ECF levels of Ca2+ decrease, there is increase in neuronal membrane permeability, which eases the formation of action potentials.
  - Hyperactive deep tendon reflexes
  - Numbness/tingling
  - Muscle spasms: (check page 10 for pictures) :
    - *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. This is called the carpopedal spasm, see last page.
    - *In sever cases*: laryngeal spams and convulsions
- Chronic hypocalcaemia causes low calcium and high phosphorus this causes calcifications in:
  - The eye→ early cataracts
  - Basal ganglia
  - The heart's conduction system → heart block and prolonged Q-T interval and arrhythmias
- Rickets and Osteomalacia

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 (PHP)
  - Vitamin D levels, magnesium levels
  - Urinary Cyclic AMP response to exogenous PTH is used to evaluate a suspected case of PHP
  - **X-rays** of metacarpals

Treatment

- If symptomatic: give emergency IV calcium gluconate slowly and under ECG monitor, and add magnesium
- Monitor closely with patients who are on digoxin because acute therapy might cause cardiac arrest
- For long term management:
  - Oral calcium supplements (calcium carbonate)
  - Vitamin D supplements



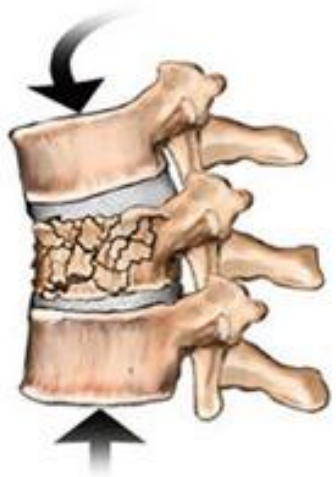
Osteoporosis

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.
- Osteoporosis should not be confused with Osteopenia: decreased calcification or density of bone rather decreased bone mass.
- Morbidity in osteoporotic patients is related to fractures
- 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 (vertebra are 65% trabecular) 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 (Femur neck is almost 75% cortical bone) and pelvic bones are common

Types of Bones: cancellous bone, also called trabecular bone or spongy bone is the light, porous bone enclosing numerous large spaces that give a honeycombed or spongy appearance, that is filled with marrow. Cancellous or trabecular bone provide support and flexibility without the weight of compact bone. It is found in most areas of bone that are not subject to great mechanical stress. Compact bone covers all bone surfaces and gives more strength for weight bearing, and muscle attachment. The two bone types differ in the amount of solid material in them.

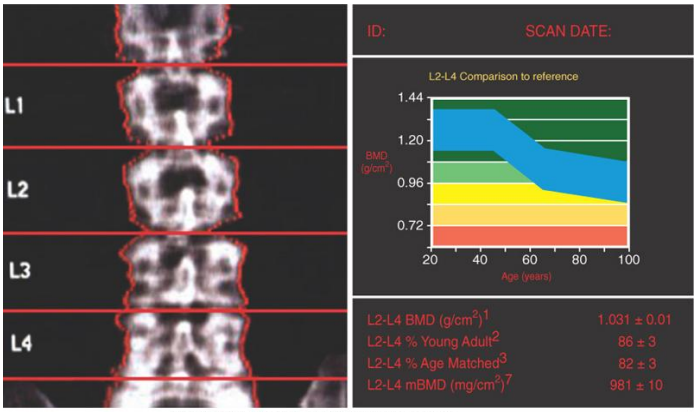
Clinical features:

- 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



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Treatment

- Prevention:
  - Public awareness measures to increase screening rates and other preventative measures
  - Reduce modifiable risk factors: smoking cessation, decrease body weight, increase activity, etc..
  - Prevent injuries
  - Calcium supplements
  - Vitamin D supplements
  - Weight baring exercise to stimulate bone formation
- Drug Therapy to Inhibit resorption
  - Bisphosphonates
    - Decrease osteoclastic activity via binding to hydroxyapetitie
    - Reduce risk of fracture
  - ADRs: include oesophageal disease irritation and ulceration
  - Calcitonin – found in nasal spray
  - Hormone replacement therapy
  - Raloxifene: Selective estrogen receptor modulators

Osteomalacia/Rickets

General considerations:

Osteomalacia: A disease characterized by gradual softening and bending of the bones with varying severity of pain; softening and bending occurs because the bones contain osteoid tissue that has failed to calcify.

- **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 (in descending frequency):

- Bony pains and tenderness (including dental pain) **Unlike osteoporosis** usually in the lower spine, pelvis, and lower extremities, where fractures have taken place, and may be associated with tenderness to palpation. The pain is characterized as dull and aching and is aggravated by activity and weight bearing.
- Muscle weakness.
- Pathological fractures
- Difficulty walking and waddling gait. Waddling gait: (Myopathic gait) is a form of gait abnormality. The "waddling" (walking with short steps and a clumsy swaying motion) is due to the weakness of the proximal muscles of the pelvic girdle. You can watch an informative video about it here: http://goo.gl/yA4FT
- Brisk deep tendon reflexes

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

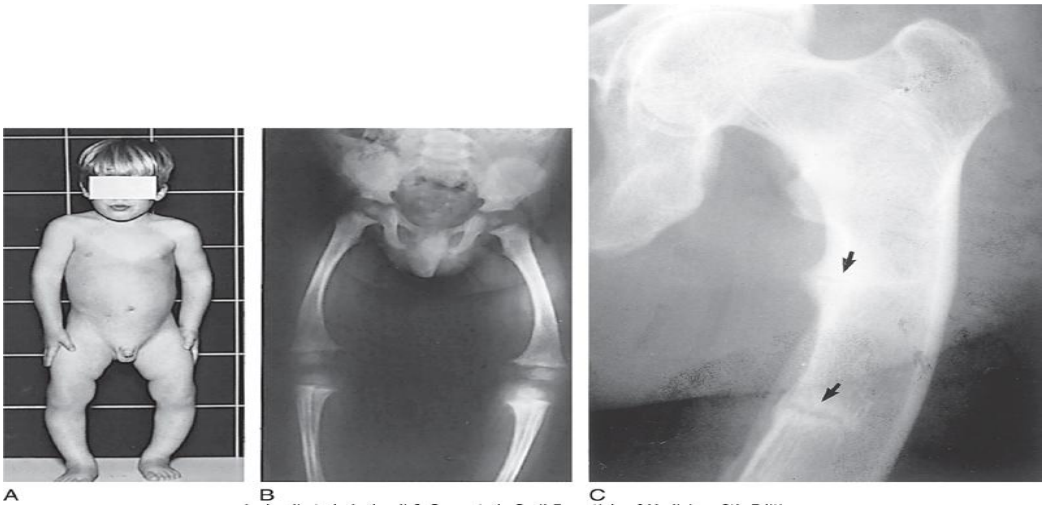
- Defective mineralization, especially in the pelvis, long bones and ribs.
- Pseudo fractures or 'Looser's zones' - linear areas of low density surrounded by sclerotic borders.

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

Pseudohypoparathysoidism and Pseudopseudohypoparathyroidism

- A rare familial disorder 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 statue
    - Short metacarpal and metatarsal bones
- In pseudopseudohypoparathyroidism they have the developmental defects without the biochemical abnormalities
- The diagnosis is established when low serum calcium level with hyperphosphataemia is associated with increased serum iPTH as well as diminished nephrogenous CAMP and phosphature response to PTH administration



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, but Paget disease was in last year's teamwork.

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

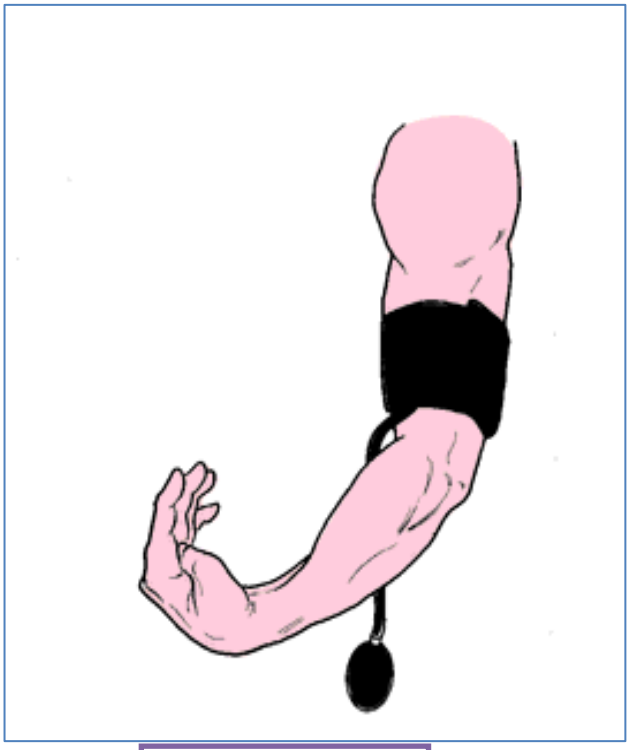
Laboratory:

- 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

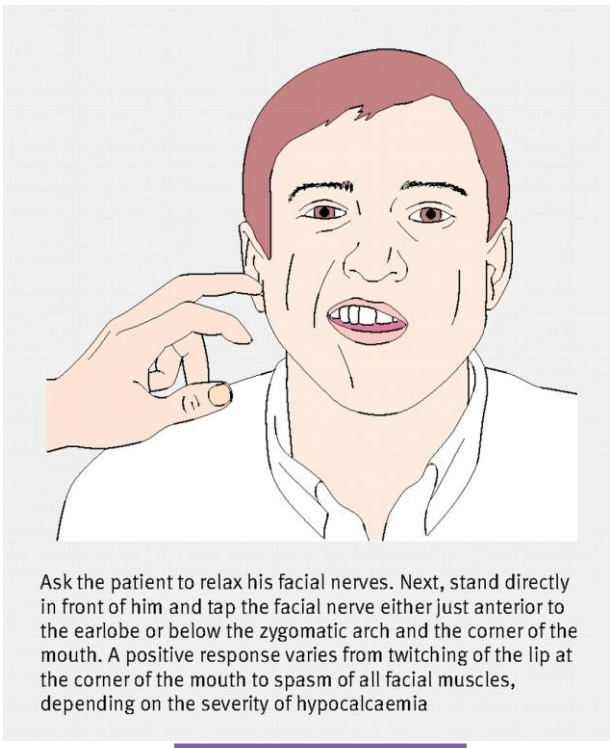
Treatment:

- Calcitonin.
- Bisphphosphonates.

- Plicamycin (rarely used).



Trosseau's sign



Chvostek's sign

Carpopedal spasm

References:

1. Harrison's principles of internal medicine. 18th ed. New York: McGraw-Hill; 2012.
2. Vitamin D: Production, Metabolism, and Mechanisms of Action - Chapter 3 - D. Bikle .
3. Stedman's Medical dictionary. Baltimore: Williams & Wilkins; 1995 - Stedman TL.
4. Pathophysiology of disease: an introduction to clinical medicine. New York: McGraw-Hill Medical; 2010 - McPhee SJ, Hammer GD.
5. Textbook of medical physiology. Philadelphia: Elsevier Saunders; 2006 - Guyton AC, Hall JE.