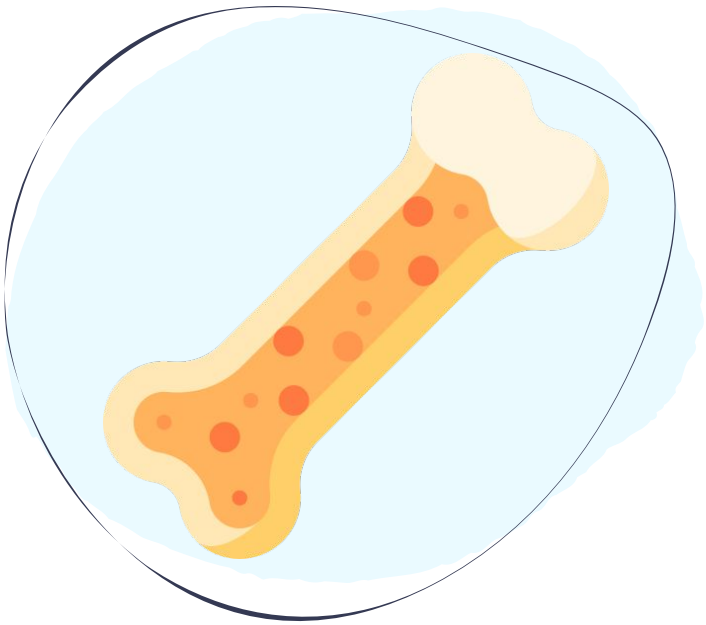
14

Orthopedic 441 Team

MED441 KING SAUD UNIVERSITY

Editing File



Metabolic Bone Disorders

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Color Index:

- Main Text
- Important
- 441 Notes
- Old Notes
- Extra

Objectives

- To be able to specify the symptoms and signs.
- Outline the assessment and appropriate investigation.
- Propose a limited differential diagnosis.
- Outline the principles of management of a patient with:
  - Osteoporosis.
  - Osteomalacia & Rickets.

Although there was 2 different doctors, the questions was from Dr. Hisham's slides, **BUT** this file will include both slides "mixed".

Resources

Rickets & Osteomalacia
By Osmosis

Osteoporosis
By Osmosis

Rickets
By Orthobullets

Osteomalacia
By Orthobullets

Osteoporosis & Osteopenia
By Orthobullets

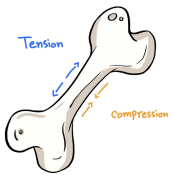
Bones

Outline

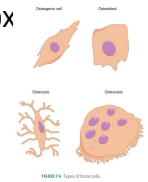
- Basic science "bone metabolism":
  - Metabolic pathways.
- Clinical features & Medications.
- Specific disorders: - Rickets/Osteomalacia. - Renal osteodystrophy. - Hypophosphatasia.
  - Osteogenesis imperfecta. - Osteoporosis.

Introduction

- Orthopedic surgeons have to deal with all types of bone (healthy or diseased), and that's why they have to know about bone metabolism, metabolic bone disorders needs a long term observation that's why it needs a specialized person.
- Bone functions:
  - Protect vital organs & structures.
  - Mechanical support for muscles & tendons[1] and act as lever arm for muscles.
  - Storage and regulation of calcium.
  - Hematopoiesis (bone marrow).
- There is a continuous activity in bone (bone resorption and bone formation as well as remodeling) not a concrete during all stages of life, that means bone is not only for protection and support but its contents play an important part in blood homeostasis, and many factors are involved in this process[2].
- Bone is a living tissue formed by bone matrix which consists of **40% organic** (connective tissue) mainly 'collagen type 1'[3] (responsible for tensile strength[4]) and **60% minerals**, mainly calcium hydroxyapatite, phosphorus, and traces of other minerals like zinc (provides compressive strength), so (collagen → tension | minerals (Ca^{2+}) → compression)[5].
- Bone Mass: Peak at 16-25 years, decreases by 0.3-0.5%/year after skeletal maturity, 2-3% decline/year in untreated post-menopausal women = osteoporosis, Improve/maintain bone mass by resistance medications, bone may become weak in certain conditions.



- All bones aren't straight, normally they're curved.
- Bone cells:
  - Osteoblasts "bone forming cells", its function:
    - Regulate osteoclasts (RANKL + OPG).
    - Produce non-mineralized bone matrix "collagen type 1" → calcium + phosphate = Hydrox
  - Osteoclasts "bone resorbing cells" "bone macrophage".
  - Osteocytes":
    - 90-95% of all cells in bone.
    - Originate from osteoblasts.
    - Function to maintain bone and cellular matrix.



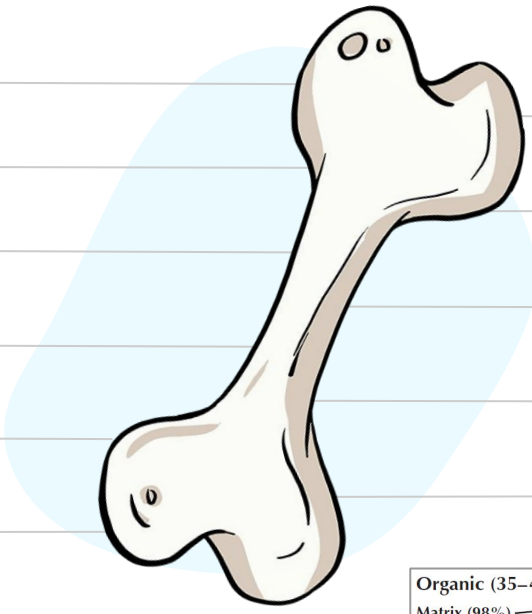
- Constant interplay between bone formation (Osteoblasts) and bone breakdown (Osteoclasts) → Bone remodeling, why remodel? Repair fatigue stresses from repeated micro-trauma.
- Signaling pathways "RANK-RANKL-OPG pathway":
  - Bone formation:
    - Stimulate osteoblasts + inhibit osteoclasts.
  - Bone resorption:
    - Activation of osteoclasts.
  - Osteoblasts produce:
    - RANKL → Bind RANK → Stimulates osteoclasts → Bone resorption.
    - Osteoprotegerin (OPG) → Competes with RANK → Limits osteoclast function → Less resorption.

1- Tendons can't work without bones.
2- While osteoblasts are forming new bones, osteoclasts are removing the dead or aged ones, this process accelerates with aging and when estrogen levels drop (e.g. menopause), the rate of formation decrease and the rate of loss increase (3% of bone mass will be lost yearly), the opposite happens in the childhood where bone formation is higher than resorption, any imbalance in this process will lead to disease.
3- There are other types but the majority of it in the bone are type 1.
4- Tensile strength is the measurement of the force required to pull something.
5- Minerals protect the bone from compressive forces (Push), while collagen protects the bone form tensile forces (Pull).

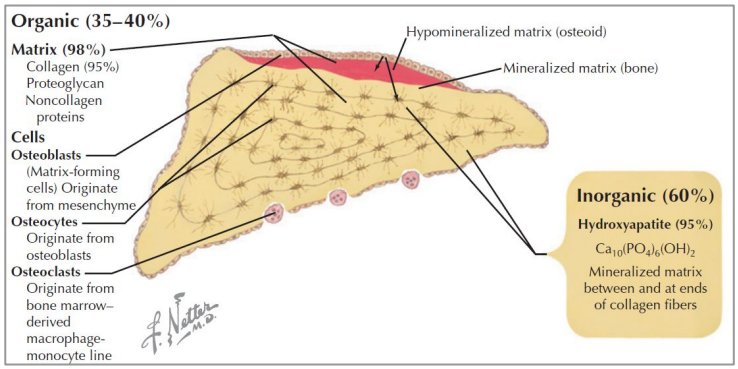
Bone Metabolism Factors

IMPORTANT

- Calcium
- Phosphorus
- Estrogen[1]
- Intestinal absorption[2]
- Renal excretion
- Sun exposure



- Parathyroid gland
- Thyroid gland
- Glucocorticoid hormones "steroids"
- Diet
- Vitamin D



Regulation of Bone Remodeling

Systemic

- PTH:
  - Bone resorption.
- Vitamin D - Calctriol – 1-25 Hydroxyvitamin D:
  - Increases bone mineralization.
- Calcitonin:
  - Limits bone resorption "inhibits osteoclasts".
- Sex hormones (Estrogen/Androgens):
  - Increase BMD "bone mineral density".
- Growth hormone:
  - Positive effect on bone formation.
- Thyroid Hormone:
  - Bone resorption.
- Corticosteroids:
  - Cause bone loss by decreasing bone formation "inhibit collagen synthesis and activate cell death for osteoblasts".

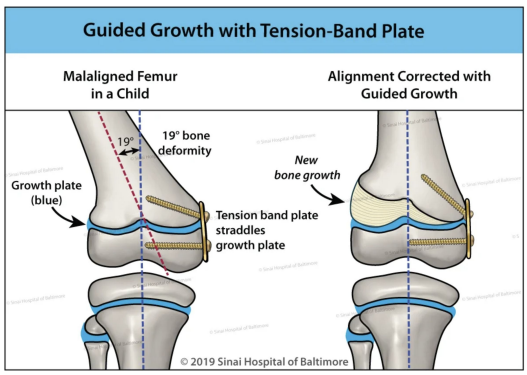
Local

- Pro-resorptive cytokines:
  - IL-1, IL-6, GM-CSF..
  - Stimulate osteoclasts → Bone resorption.
- Anti-resorptive cytokines:
  - IL-4, Interferon-B, Prostaglandin-E2.
  - Inhibit osteoclasts differentiation → Bone formation.
  - NSAIDs inhibit bone healing in rats.
- TGF-B:
  - Inhibits RANKL → Bone formation.
- BMP "bone morphogenetic proteins":
  - Promoted osteoblast differentiation → Bone formation.
  - Given intraoperatively to promote bone formation.

1- Sedentary lifestyle can lead to osteoporosis after menopause.
2- Patients with intestinal problems (such as celiac disease) have poor calcium absorption.

Mechanical Forces

- Wolff's Law:
  - Bone remodels in response to mechanical stress.
  - Osteocytes detect mechanical load → Bone formation/hypertrophy.
  - Clinically: Weight bearing + resistance training → Increase BMD.
- Heuter-Volkmann Law:
  - Mechanical forces influence longitudinal growth.
  - Compression → Inhibits longitudinal growth.
  - Distraction → Accelerates longitudinal growth.
  - Clinically: Guided-Growth.

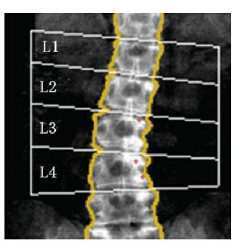


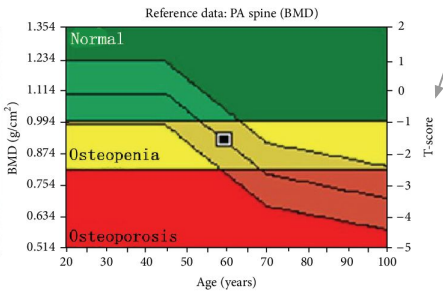
Bone Strength

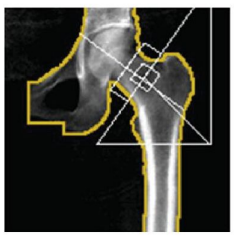
- Affected by **mechanical stress** which means exercise and weight bearing (strengthening the bone) "Wolff's law".
- One of the most important factors which affect bone strength is the exercise, it helps in overcome osteoporitic problems, so any metabolic disease management must include special **workout exercises** with special equipments.
- Gets reduced with menopause and advancing age, and bed ridden patients.
- Reduced bone density on X-rays is called **Osteopenia**.
- Osteopenia is also a term used to describe a degree of reduced bone density, which if advanced becomes **Osteoporosis** (can be diagnosed **only by DEXA**).

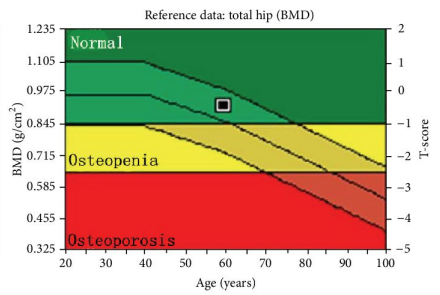
Bone Density

- Bone density is diagnosed at current time by a test done at radiology department called: **DEXA scan** (**D**ual **E**nergy **X**-ray **A**bsorptiometry)[1], which is measured radiation absorption (more absorption → more density), they do it in three areas (vertebrae, wrist "distal of radius", and neck of femur) these bones get affected first and might get fractured easily (we need to protect them).
- However, increased bone density **does not** always mean increased bone strength, as sometimes in **Brittle bone disease** "osteogenesis imperfecta" (which is a dense bone) is not a strong bone but fragile bone which may break easily.
- The measurement of bone density will be expressed as a T score (see image).



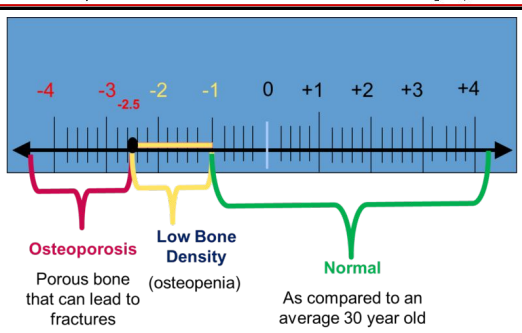




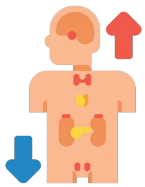


WHO criteria for diagnosing osteoporosis using bone density measurements

Classification	T-score
Normal	-1.0 or greater
Osteopenia	Between -1.0 and -2.5
Osteoporosis [2]	-2.5 or less
Severe Osteoporosis	-2.5 or less with a fragility fracture



1- It's very important to learn how to read the graph, you may be asked to do so.
2- If you suspect osteoporosis in the exam, you should choose the -2.5 or less, NEVER 2.5, FOCUS ON THE MINUS –.



Hormonal Regulations

Plasma levels | **Calcitonin** | **Parathyroid hormone**

Plasma Levels

! There are normal plasma levels in osteoporosis.

- **Calcium**: 2.2-2.6 mmol/l
- **Phosphorus**: 0.9-1.3 mmol/l
  - ➔ Both absorbed by intestine and secreted by kidney in urine.
- **Alkaline phosphatase**: 30-180 units/l (normal in osteoporosis, unless if there's complication like a fracture)
  - ➔ Is elevated in bone increased activity like during growth or in metabolic bone disease or destruction, use it as a clue, it's not specific so can't tell you the diagnosis (indicator of bone metabolism).
- **Vitamin D**: 70-150 nmol/l (promotes Ca^{2+} absorption from kidney and intestines).

Calcitonin

! Not used in treatment due to its side effects.

- Secreted by **C cells** of thyroid gland.
- Its secretion is regulated by serum calcium.
- Its action is to cause inhibition of bone resorption and increasing calcium excretion by this it causes lowering of serum calcium.
  - ➔ Inhibit reabsorption from kidney & intestine and trying to bring it back to the bone, used to be given as supplement but not anymore because of its side effects.

Parathyroid Hormone

IMPORTANT

- Production levels are related to serum calcium levels, PTH secretion is increased when serum calcium is low **($\downarrow Ca^{2+} \rightarrow \uparrow PTH$)**.
- **Action of PTH**:
  1. Increases calcium levels in the blood by increasing its release from bone (osteoclastic activity).
  2. Increases intestinal absorption by activating vitamin D.
  3. Increases reabsorption from the kidney and increases the excretion of phosphorus.
- If the parathyroid hormone is high due to a body demand, that's mean calcium is low we need to increase it, how? From the bone (readily available) so basically you will sacrifice the bone for the seek of heart, brain & vital organs. So, it works as a storage for calcium.

Hyperparathyroidism		
Primary	Secondary[1]	**Tertiary**[2,3] IMPORTANT
Adenoma of the gland.	Low Ca^{2+} (e.g. renal failure).	Prolonged or sustained stimulation = hyperactive nodule or hyperplasia. "when secondary hyperplasia leads to autonomous overactivity"

1- Partial resistance to PTH action leads to parathyroid gland hyperplasia and increased PTH secretion, often in patients with renal failure and osteomalacia (due to low or low normal serum calcium levels).
2- Irreversible clonal outgrowth of parathyroid glands, usually in long-standing inadequately treated chronic renal failure on dialysis.
3- It happened after long standing hyperparathyroidism, you treated the cause like adenoma, but the PTH hormone continues to be secreted.

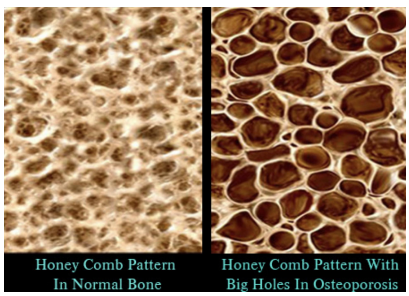
Metabolic Bone Disease

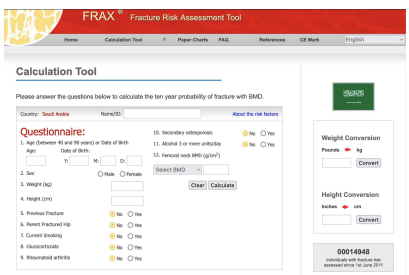
Introduction

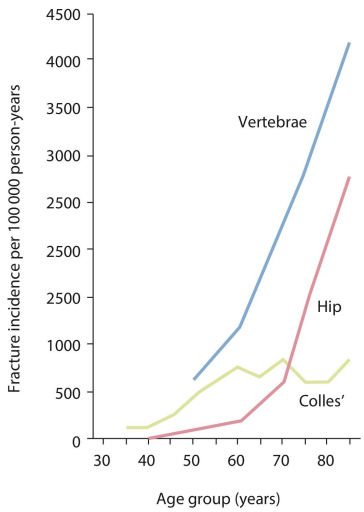
- Pathology in shape, strength, and structure of bone, resulting from altered bone homeostasis, examples:
  - Rickets. - Hypophosphatasia. - Osteogenesis Imperfecta. - Fibrous Dysplasia.
  - Osteomalacia. - Osteoporosis. - Hyper-PTH.
- General clinical features:
  - Electrolyte disturbances. - Fractures (pathological/low-energy).
  - Bone deformity. - Abnormal gait. - Short stature

Osteoporosis + Osteopenia 1

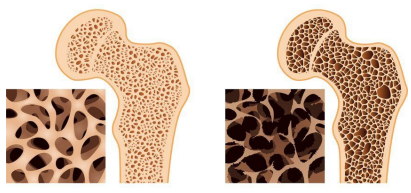
- Decreased bone mass:
  - Decreased total amount of bone/unit volume ⟶ Reduced density (but each unit volume is normal).
- Normal mineralization unlike osteomalacia (the unit volume is reduced).
- Is it important?
  - 200 million people affected yearly, mainly post-menopause and age-related.
  - 1.5 million osteoporotic fractures/year (700k vertebra, 300 hip, 200k wrist).
- **Diagnosis:**
  - Postmenopausal women/men with a T-score of ≤ −2.5 SD bone mineral density (BMD) measured through dual-energy X-ray absorptiometry (DEXA) at minimum of two sites: femoral neck, lumbar spine, or distal radius (in case scanning cannot be done at the hip or spine) is considered to have osteoporosis (this is a diagnostic and not a therapeutic threshold).
  - Presence of low-trauma (fragility) fracture (hip, spine, distal radius, proximal humerus) irrespective of BMD readings.
  - Osteopenia (T-score −1.0 to −2.5) on DEXA scan and high FRAX score based on country-specific threshold.
  - Osteopenia or low bone mass is not a separate disease entity and should be used for epidemiologic purpose only.
- FRAX (Fracture Risk Assessment Tool):
  - For fracture probability, Saudi Arabian FRAX model should be used for citizens, use other country-specific FRAX models for expatriates based on country of birth.
  - FRAX can be calculated without DEXA at baseline:
    - High-risk patients (see below for risk stratification) should be treated.
    - Intermediate risk, BMD should be measured using DEXA and FRAX recalculated with DEXA readings added.
  - Peripheral scanning using ultrasound may be used for screening but not for diagnosing osteoporosis.

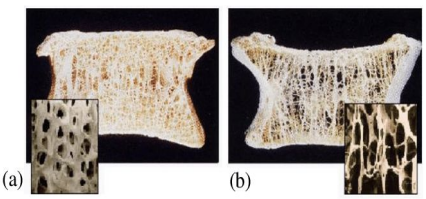




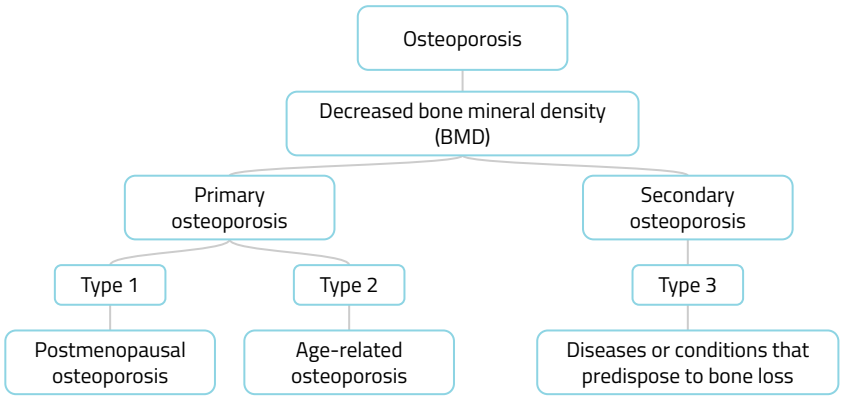


The incidence of fractures of the vertebrae, hip and wrist rises progressively after the menopause.





Osteoporosis Types



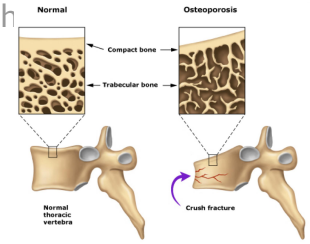
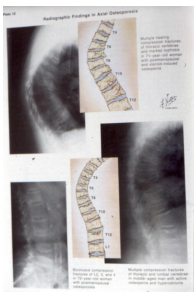
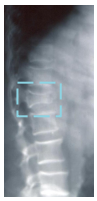
Primary Osteoporosis

Type	Postmenopausal	Senile
Description	• Due to rapid decline in estrogen level. • This results in increased osteoclastic activity. • Normal bone loss usually 0.3% per year (varies between people). • Post-menopausal bone loss 3% per year (10x folds than normal).	• Usually by 7th to 8th decades there is steady loss of at least 0.5% per year. • It is part of physiological manifestation of aging.
Risk Factors	• Race (Caucasian "white ladies"). • Hereditary. • Body build (thin people). • Early menopause. • Smoking, alcohol intake, drug abuse. • Low calcium intake. • Inactivity "chronic lack of exercise".	• Male menopause (decreased testosterone). • Dietary: Less calcium and vitamin D and protein. • Muscle weakness. • **Reduced activity** (exercise is the best way to delay osteoporosis in men).
Clinical Features	• Osteoporosis is a silent disease (asymptomatic until complications happen). • Osteoporosis is serious due to possible complications, mainly fractures. - **Most common** site (vertebra), **2nd** most common (distal radius), **most serious** (hip). • The best way to treat osteoporosis is to prevent it in the first place. • Osteoporosis does not cause pain usually "painless unless it causes fractures". • Osteoporosis causes gradual increase in dorsal kyphosis. • Osteoporosis leads to loss of height due to collapsed vertebrae "shorter back". • **Osteoporosis is not osteoarthritis**, but the two conditions may co-exist.	

Secondary Osteoporosis

It happens most of the time in young patients e.g. 45 years old, causes include:

- **Drug induced: Steroids** (especially in young people), alcohol, smoking, phenytoin, heparin, immunosuppressives.
- Hyperparathyroidism, hyperthyroidism, Cushing's syndrome, gonadal disorders, malabsorption, malnutrition, osteogenesis imperfecta.
- **Chronic diseases:** RA, renal failure, tuberculosis, ankylosing spondylitis, COPD.
- **Malignancy:** Multiple myeloma, leukemia, metastasis.

Kyphosis and Height Loss "Dowager's hump"	• With osteoporosis the anterior part of the vertebra narrows which leads to kypho… …oss of h…    
Osteoporotic Fractures "Fragility Fractures"	• They are pathological fractures. • **Most common** is **vertebral** osteoporotic compression fracture (OVC fractures), they present with **back pain**. • Vertebral micro-fractures occur unnoticed (dull ache). • **Most serious** is **hip** fractures (high mortality rate). • Also common is wrist fractures (**Colles' fracture** "distal radius"). • We must observe the hip & the vertebrae.  
Disuse Osteoporosis	• State of bone loss due to local skeletal unloading or systemic immobilization. • Occurs locally adjacent to immobilised bone or joint. • May be generalised in in bed-ridden patients or ICU patients. • Awareness of and attempts for prevention are helpful (by moving the limb).

General Management

Nutrition Counseling	**1**	Improve calcium intake
	2	Increasing vitamin D intake
Physical Activity Counseling	**3**	Weight-bearing and muscle strengthening exercise
	4	Fall prevention education
Lifestyle Counseling	**5**	Smoke cessation
	6	Limiting excessive alcohol intake
Pharmacotherapy	**7**	Pharmacotherapy
Testing	**8**	Testing bone mineral density: DXA (Dual Energy X-Ray Absorptiometry)
Communication	**9**	Physician referral letter to repot the patient's fragility fracture, risk factors, and recommendations for treatment
	10	Patient education letter to explain bone health risk factors and recommendations for treatment

- Indication: Based on DEXA scan "–2.5 or less"& FRAX score.

Management

Drug Therapy

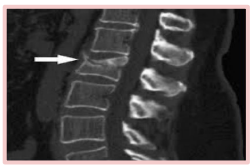
- Estrogen has a definite therapeutic effect and was used extensively as HRT but cannot be recommended now (**not used anymore**) due to serious possible side effects (such as tumors and CV risks).
- Adequate intake of calcium and vitamin D is mandatory (prior to and with treatment).
- Drugs which inhibit osteoclast activities:
  - E.g. Oral **Bisphosphonates as first line of treatment** for most patients like sodium alendronate *(FOSAMAX, BONVIVA)*.
- Drugs that enhance osteoblast activities: Bone stimulating agents like strontium *(PROTELOS)*, teriparatide *(FORTEO)*.
  - The problem in this type of medication is the risk of malignancy.
- Denosumab, zoledronic acid, teriparatide, and romosozumab are other alternative 1st line therapies for specific groups of patients and when bisphosphonates are not feasible, contraindicated or failed.
- Every treatment option has recommended duration for use, after which the patient should be assessed for the need to continue treatment or go through drug holiday, a drug holiday is not feasible with denosumab because of the increased risk of vertebral fractures after stopping treatment, so another agent should be prescribed if denosumab is discontinued.

Exercise

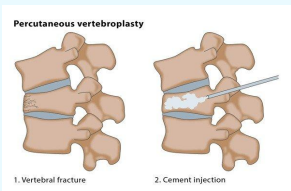
- Resistive exercises.
- Weight bearing exercises e.g. Walking.
- Exercise should be intelligent to avoid injury which may lead to fracture.

Management of Fractures

- Use of load shearing (brace) implants in fracture internal fixation instead of plating.
- Plates = load bearing "all pressure on it" | Screws "IM nail" (preferred)= load sharing "some pressure on it and some on bone".
- Pain relief.
- Prevention of further fractures and instability.
- Vertebroplasty and kyphoplasty.

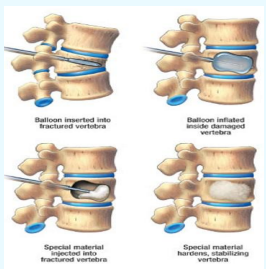


Vertebroplasty



- It's the injection of bone cement into the collapsed vertebra through pedicles.
- The injection is done under X-ray control (image intensifier) by experienced orthopedi or interventional radiologist.
- It results in immediate pain relief.
- It helps to prevent further OVF "osteoporotic vertebral fracture".
- Possible complication is leakage of cement into spinal canal (nerve injury) or venous blood (cement PE), burns around the tissue.

Kyphoplasty



- Used more than vertebroplasty.
- It's the injection of bone cement into the collapsed vertebra **AFTER inflating a balloon** "ballon then cement" in it to correct collapse and make a void (empty space) into which cement is injected.
- It is possible that some correction of kyphosis is achieved.
- It is safer because cement is injected into a safe void (low leakage risk).

Practically, refer to Endocrinology or Fracture Liaison Service.

Prevention of Osteoporosis

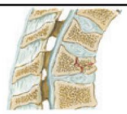
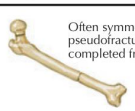
- Prevention of osteoporosis should start from **childhood** (especially girls).
- Healthy diet, adequate sunshine, regular **exercise**, avoidance of smoking or alcohol, caution in steroid use.
- At some time in the past there was a recommendation of HRT (Hormone Replacement Therapy) for postmenopausal women and men, **but now this is discontinued**.

Comparison

IMPORTANT

	Osteomalacia	Osteoporosis
Onset	Any age	Postmenopausal, old age
illness	ill	Not ill (unless complications)
Symptoms	Generalized chronic ache	Asymptomatic until fractures
Muscles	Weak	Normal
X-ray	Looser zones	Nil (late X-ray changes)
ALP	Increased	Normal
PO_4	Decreased	Normal

Comparison of Osteoporosis and Osteomalacia

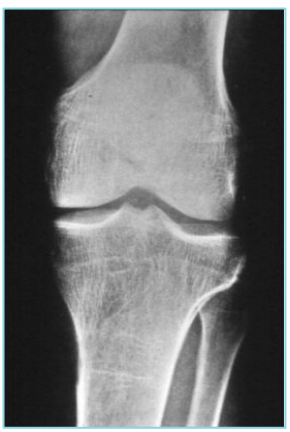
	Osteoporosis	Osteomalacia
Definition	Unmineralized matrix; Mineralized matrix; Normal	Unmineralized matrix; Mineralized matrix; Bone mass decreased, mineralization normal	Unmineralized matrix; Mineralized matrix; Bone mass variable, mineralization decreased
Age at onset	 Generally elderly, postmenopause	 Any age
Etiology	Endocrine abnormality, age, idiopathic, inactivity, disuse, alcoholism, calcium deficiency	Vitamin D deficiency, abnormality of vitamin D pathway, hypophosphatemic syndromes, renal tubular acidosis, hypophosphatasia
Symptomatology	 Pain referable to fracture site	 Generalized bone pain
Signs	Tenderness at fracture site	Tenderness at fracture site and generalized tenderness
Radiographic features	 Axial predominance	 Often symmetric, pseudofractures, or completed fractures; Appendicular predominance
Laboratory findings Serum Ca^{++}	Normal	Low or normal (high in hypophosphatasia)
Serum P_i	Normal $Ca^{++} \times P_i$ >30	Low or normal $Ca^{++} \times P_i$ >30 if albumin normal (high in renal osteodystrophy)
Alkaline phosphatase	Normal	Elevated, except in hypophosphatasia
Urinary Ca^{++}	High or normal	Normal or low (high in hypophosphatasia)
Bone biopsy	Tetracycline labels normal	Tetracycline labels abnormal

Osteoporosis
Reduced amount of bone

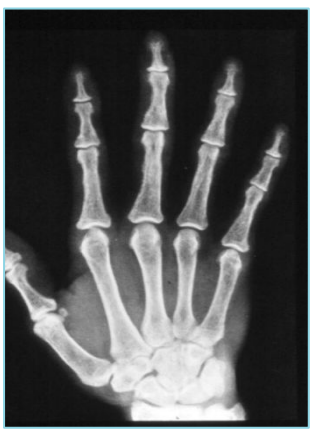
OsteoMalacia
Normal amount of bone, but reduced **M**ineralization of normal osteoid

Hyperparathyroidism 2

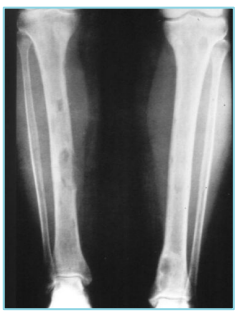
Hyperparathyroidism	
• Excessive PTH secretion: Primary, secondary or tertiary. • Leads to increased bone resorption, subperiosteal erosions, osteitis manifested by fibrous replacement of bone. • Significant feature is **hypercalcemia** "renal stones, constipation". • In severe cases: Osteitis fibrosa cystica and formation of brown tumors.	
X-ray Changes	• Generalized decrease in bone density. • Sub-periosteal bone resorption (scalloping of metacarpals and phalanges "hands mainly"). • Brown tumors (empty bone areas with bleeding caused by bone reuptake, not a true tumor). • Chondrocalcinosis "calcification of the cartilage around joints" (wrist, knee, shoulder).
Management	By management of the cause: • Primary hyperparathyroidism due to neoplasm (adenoma or carcinoma) by excision. • Secondary hyperparathyroidism by correcting the cause of hypocalcemia. • Tertiary hyperparathyroidism by excision of hyperactive (autonomous) nodule. • Extreme care should be applied after surgery to avoid **hypocalcemia** due to hungry bones syndrome "severe resistant hypocalcemia". - One of the very important things you must pay attention to, it needs a lot of monitoring, the moment you correct hyperparathyroidism (1st 48 hours is critical), the bone might absorb a lot of calcium leading to severe hypocalcemia, that might lead to cardiac problems (cardiac arrest) or convulsions, if that happens it is very difficult to correct the hypocalcaemia.

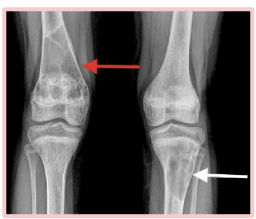


Early erosions

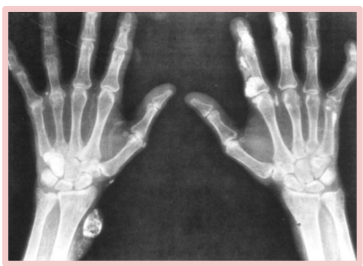


Scalloped distal phalanges





Brown tumors



Chondrocalcinosis

TABLE 3

Lab Comparison

Hyperparathyroidism	Calcium	PTH	Vitamin D	Phosphate
Primary	↑	↑→	↑	↓
Secondary	↓→	↑	↓	↑ or ↓
Tertiary	↑	↑↑	↓	↑

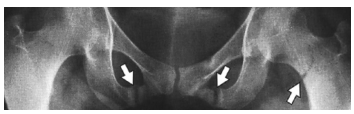
Key: ↑Elevated, ↓decreased, →normal.

Rickets & Osteomalacia 3

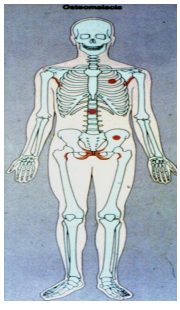
	Rickets	Osteomalacia
	Different expressions of the same disease, which is: Inadequate mineralization.	
Pathology	• Failure of mineralization of cartilage and osteoid tissue. • Decreases longitudinal bone growth and weakness mechanical properties of tubular bone. • Qualitative defect (osteoporosis is a quantitative defect).	
Onset	• Prior to skeletal maturity (open growth plates) in **children**.	• After skeletal maturity (closure of growth plates) in **adults**.
Affected Site	• Areas of endochondral growth (e.g. proximal humerus and proximal femur).	• **All** skeleton is incompletely calcified (slowly progressive).
Biochemistry	• Hypocalcemia (always check Ca^{2+}, PO_4, vitamin D and ALP levels). • Hypocalciuria. • High alkaline phosphatase. Low Ca^{2+}, low PO_4, high ALP	
Causes	• Calcium deficiency (diet, malabsorption). • Hypophosphatemia (to deposit calcium you need phosphate). • **Defect in vitamin D** metabolism: Nutritional "vegan", underexposure to sunlight, intestinal malabsorption "celiac disease", liver & kidney diseases.	

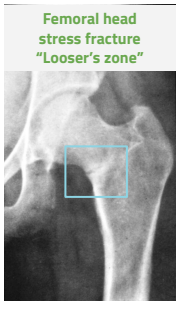
Osteomalacia

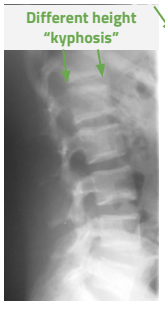
Description	• Metabolic bone disorder in adults.
Clinical Features (The difference here is that the growth is stopped in Adults unlike children so no growth-related symptoms here)	• Bone pain **mainly backache**, muscle weakness, fatigue. • Reduced bone density. • Vertebral changes: **Biconcave vertebrae**, vertebral collapse (shortening), kyphosis, scoliosis. • Stress fractures "late": **Looser's zones** in scapula , ribs, pelvis, proximal femur.
Management	**Medical:**
	• Both "vitamin D + calcium" + lifestyle modification + exercise + sun exposure.
	Surgical:
	• Fracture management. • Correct deformity if needed "the **residual** deformities only (**after treatment**)".

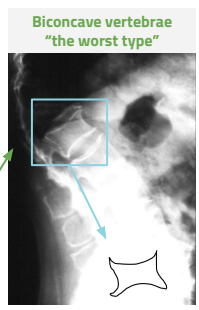


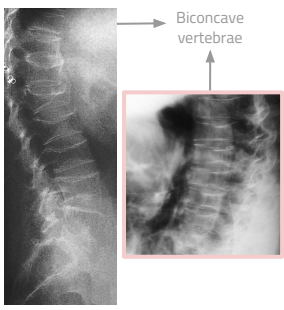
Looser's zones in the pubic rami and left femoral neck











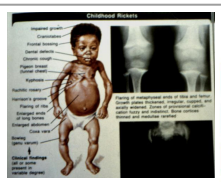
Rickets

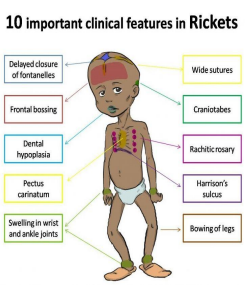
Diagnosis

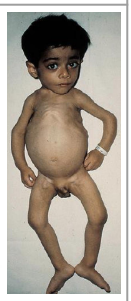
- Based on: Clinical features, radiographs (X-ray), labs, +/- genetics.

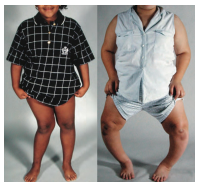
Clinical Features

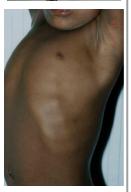
(The growth plate got affected, many symptoms due to that)



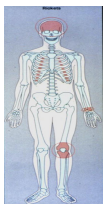






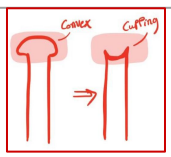


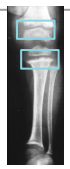
- Depends on age of onset.
- Infants:
  - Generalized muscle weakness.
  - Lethargy, irritability.
  - Hypotonia.
  - Delayed closure of skull fontanelles.
  - **Craniotabes**: Softening of skull bones.
- Child is restless, babies cry without obvious reason.
- **Failure to thrive**.
- Limb deformities, mostly "lower limbs":
  - Bowing: Genu varum "early".
  - Genu valgum "late".
- Bone pain, coxa vara, difficulty walking.
- Joint thickening "hypertrophy" of ankles, and especially around **wrists** and **knees**.
  - Wrist is the most important X-ray to confirm the diagnosis.
- Ligamentous laxity.
- Enlargement of costal cartilage: **Rachitic rosary**.
- Pigeon chest deformity "pectus carinatum", harrison's sulcus.
- In severe cases with **very low calcium**: Tetany or convulsions.



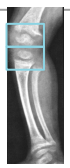
UL: Away from elbow (distal radius & proximal humerus "deltoid hide it").
LL: Around the knee.

X-ray Changes

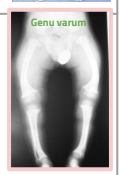




Growth plate widening and thickening

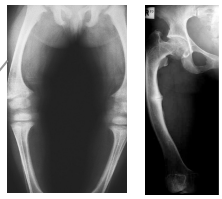


Metaphyseal cupping



Long bone deformities

- Growth plate (physeal) widening & thickening.
- **Metaphyseal cupping**.
- Long bone deformities.
- Fraying of metaphysis (Indistinct borders).
- Decreased bone density.
- Looser's zones, pseudofracture on the compression side of bone.
- Rachitic rosary: Prominence of rib heads at the osteochondral junction.
- Genu varum/valgum.
- Codfish vertebrae.
- Cat back: Dorsal kyphosis.



Classical nutritional rickets, showing the well-marked physes, the flared metaphyses and the bowing deformities of the lower limb bones

Management

Medical:

- Adequate vitamin D replacement.
- Sun exposure.
- Calcitriol (1-25 vitamin D).
- Phosphate replacement.
- Calcium.
- Burosomab.
- Check if there's no systemic illness "treat the cause".

Very Imp MCQ:
7 y/o with genu valgum of angle 20° has difficulty standing and tripping "X-Ray pic" what will you do to him?
- 1st: Treat him with medication until you normalize every thing, and then see if there are deformity left then correct it "vit D then corrective osteotomy if needed".

Surgical:

- Case by case to **correct residual deformities** (post rachitic) by corrective osteotomy.
  - Don't perform surgery immediately because the bone is still growing, after 18-24 months of treatment.
- Treat fractures.

Child with abdominal symptoms + rickets features → Refer to pediatrician

Rickets Types

Vitamin D Resistant Rickets	• **Most common heritable form** (XLD, AR, AD). • **Inability of renal tubules to absorb phosphate**. • Also known as: **Familial hypophosphatemic rickets**.
Nutritional	• Dietary. • Celiac disease or hepatic disease • **Rickets of prematurity**: - Premature infants in NICU. - TPN, hepatobiliary disease, diuretic therapy, etc.. • **Drug-induced rickets** "Anti-epileptics in children": - **Child + Seizure disorder on medication + frequent fractures**.
Vitamin D Dependent	• Type 1: Inability to hydroxylate. • Type 2: Receptor insensitivity.
Renal Osteodystrophy	• Definition: - Biochemical + skeletal manifestation of CKD or ESRD. • Pathophysiology: - Damaged kidney → Inability to excrete PO_4 → Hyperphosphatemia. • Orthopedic issues: - SCFE "slipped capital femoral epiphysis, discussed in pediatric hip lecture". - AVN "avascular necrosis". - Bowing of long bones.
Hypophosphatasia	• Inherited disorder resulting in rickets-like features. • Main pathology is decreased or lack of alkaline phosphatase (ALP).

Table 42-1 Biochemical Abnormalities in Rickets

	Biochemical Abnormality					
Type of Rickets	**Calcium**	**Phosphate**	**Alkaline Phosphatase**	**PTH**	**25-(OH) vitamin D**	**1,25-$(OH)_2$ vitamin D**
Nutritional	NI	NI↓	↑	↑	↓↓	↓
Vitamin D–resistant (XLH, RTA, Fanconi, oncogenic)	NI	↓	↑	NI	NI	NI
Vitamin D–dependent type I (inability to hydroxylate)	↓	↓	↑	↑	↑↑	↓↓
Vitamin D–dependent type II (receptor insensitivity)	↓	↓	↑	↑	NI↑↑	↑↑↑↑
Renal osteodystrophy	NI↓	↑	↑	↑↑	NI	↓↓

Osteogenesis Imperfecta (Brittle Bone Disease)

Definition

- Genetic connective tissue disorder affecting the formation of type 1 collagen.
- COL1A1, COL1A2.

Pathology

- Type 1 collagen is reduced in quantity.
- Some have a quality issue with mutant collagen.
- Weaker bones.

Types

Sillence classification:

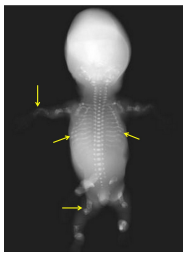
- Type 1: Mild form.
- Type 2: Lethal form.
- Type 3: Severe deforming form.
- Type 4, 5, others: Variable features.

Clinical Features

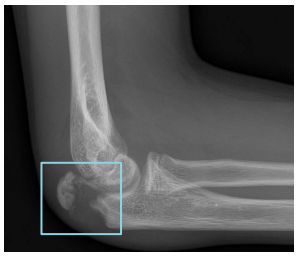
Orthopedic:

- **Multiple fractures + increased bone fragility**:
  - **Olecranon apophyseal avulsion fractures** in children are pathognomonic for OI.
  - Might be 1st sign of disease, especially milder forms.
- Bowing.
- Short stature.
- Kyphoscoliosis.
- Basilar invagination.
- Ligamentous laxity.
- Radial head dislocation.
- Coxa vara.

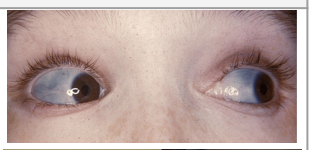
Full body X-ray of a neonate demonstrates multiple rib fractures, right femur fracture and right forearm fractures (yellow arrows).

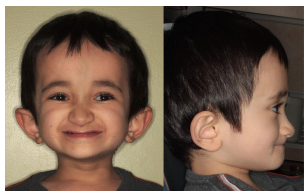


Olecranon fracture



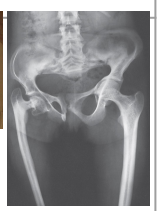
Non-Orthopedic:





- Blue sclera.
- Dentinogenesis imperfecta.
- Hearing loss.
- Bleeding tendency.
- Triangular facies.
- Low set ears.
- Hyper-metabolism (risk of malignant hyperthermia).
- Cardiovascular: Mitral prolapse, aortic regurgitation.

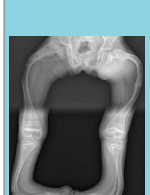
X-ray Changes

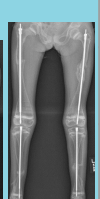


- Generalized osteopenia/demineralization of bone
- Frequent fractures:
  - Multiple fractures at different stages of healing.
  - More than 3 rib fractures in a child → Rule out osteogenesis imperfecta.
  - Delayed skull ossification and **Wormian bones**:
    - Wormian bone is extra skull bones occurring within a suture (skull joint).

Management

"Medical + Surgical combined"





Medical:

- Bisphosphonates.

Surgical:

- Indicated in type 3, type 4 and deforming types of osteogenesis imperfecta.
- Long bone telescoping rodding as soon as the child starts pulling to stand.

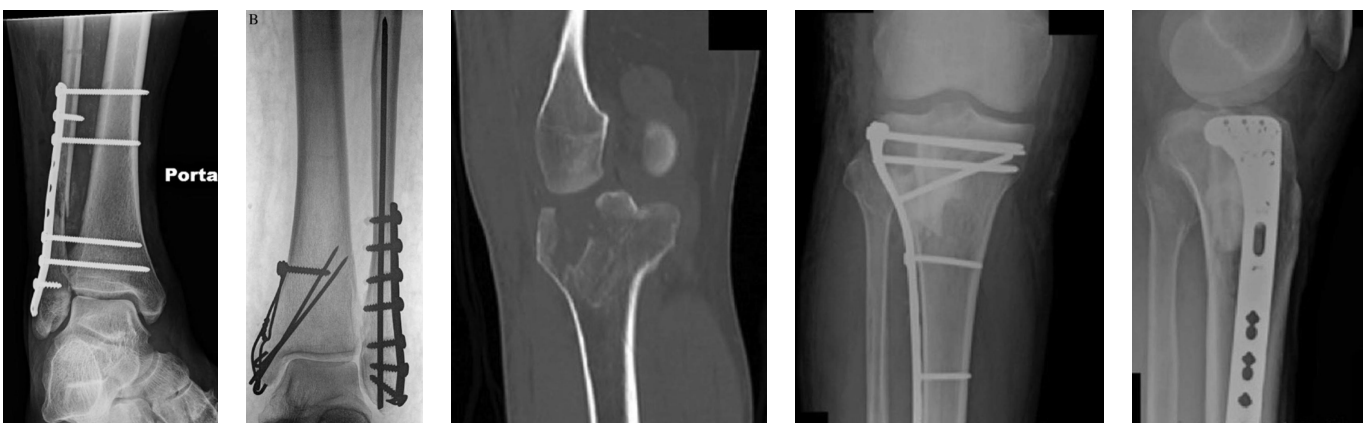
Medications and Bone Metabolism

Table 1. Impact of Medications on Bone Homeostasis

Medication	Mechanism of Action	Effects on Bone
Diphosphonates[19]	Inhibit osteoclast differentiation and function and promote apoptosis	Inhibit resorption and improve BMD
Denosumab[19]	Anti-RANKL antibody	Inhibit resorption and improve BMD
Parathyroid hormone (PTH; teriparatide)[16,29,30]	Promote osteoblast RANKL secretion	Stimulate resorption and may promote fracture healing
NSAIDs[31]	Inhibition of COX-1 and COX-2 enzymes and decrease PGE_2	Impaired bone healing, clinical effect likely duration dependent
Methotrexate (MTX)[19]	Inhibits osteoblast proliferation at high doses	Neutral at low doses used for rheumatologic disease; decreases bone formation at higher doses
Antiepileptics[19]	Effect on the CYP-450 pathway adversely affects the vitamin D-PTH-calcitonin axis	May cause rickets and osteomalacia
Statins[19]	Increase osteoblast BMP-2 release and decrease osteoclast differentiation	Improve BMD
Corticosteroids[32]	Initiate proapoptotic pathways in osteoblasts	Diminish osteogenesis

Surgical Treatment in Metabolic Bone Disease

Principles + Techniques	
Protect the Entire Bone Segment if Possible	• Use intramedullary implants, if possible, nails better than plates.
Promote Weight Bearing ASAP	• Load-sharing implants (nails) better than load bearing (plates).
Augment Fixation (Don't rely on poor biology)	• Use cement. • Use bone substitutes. • Purchase more bone.



Important Notes

Dr. Hisham Alsanawi's Notes:

Bone metabolism:

- **Calcium & Phosphorus** are important factors controlling metabolism.
- **Bone strength** is affected by **mechanical stress** = **Exercise** is important.
- **Osteoporosis** only diagnosed with **DEXA** "-2.5 or less".
- Production of **PTH** is related to serum **calcium** level.
- **Tertiary** hyperparathyroidism: **Prolonged** sustained stimulation.

Rickets & Osteomalacia:

- **X-ray** findings of Rickets: - **Growth plate widening** and thickening - Metaphyseal **cupping** - **Long bones deformity**.
- **First start with vitamin D & calcium replacement, don't do surgery for the deformities at first, after treatment only you can correct the residual deformities by corrective osteotomy.**

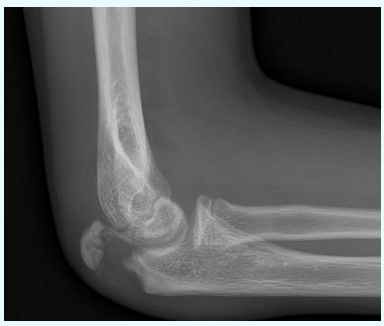
Osteoporosis:

- Primary **senile** osteoporosis important risk factor is **reduced activity**.
- The best & first line treatment is bisphosphonates

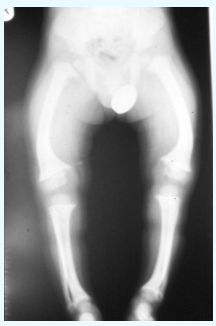
Important to differentiate between osteomalacia and osteoporosis by the table in the team last slide, but generally **ALP & PO4 are normal in osteoporosis**.

Dr. Abdullah Addar's Notes:

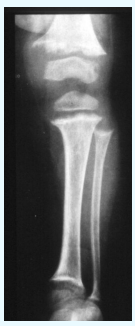
- Patient present with S&S of rickets and have **epilepsy** -> **Drug-induced rickets**.
- **Avulsion of olecranon apophyseal fracture** is pathognomonic for **Osteogenesis imperfecta** in children.
- **Osteogenesis imperfecta** -> **Surgery** (to protect the entire segment) & **medical** (bisphosphonates).
- Patient presented with **hypocalcemia**, **abdominal pain** and S&S of **rickets**, what to do next? - Investigate for **celiac disease**.



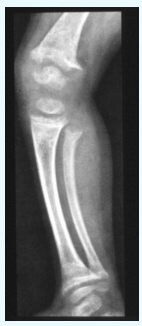
Olceranon apophyseal fracture



Long bone deformities



Growth plate widening



Metaphyseal cupping

EXTRA

Metabolic Bone Disease

- see 2010 Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis for details

Osteoporosis

Definition

- a condition characterized by decreased bone mass and microarchitectural deterioration with a consequent increase in bone fragility and susceptibility to fracture
- BMD is measured at hip and lumbar spine, BMD T-score ≤-2.5 is indicative of osteoporosis
- osteopenia (low bone mass): BMD with T-score between –1.0 and –2.5

ETIOLOGY AND PATHOPHYSIOLOGY

Secondary Osteoporosis

- gastrointestinal diseases
  - gastrectomy
  - malabsorption (e.g. celiac disease, IBD, bariatric surgery)
  - chronic liver disease
  - eating disorder
  - poor nutrition
- bone marrow disorders
  - multiple myeloma
  - lymphoma
  - leukemia
- endocrinopathies
  - Cushing's syndrome
  - hyperparathyroidism
  - hyperthyroidism
  - premature menopause
  - DM
  - hypogonadism
- malignancy
  - secondary to chemotherapy
  - myeloma
- rheumatologic disorders
  - rheumatoid arthritis
  - SLE
  - ankylosing spondylitis
- drugs and chemotherapy
  - corticosteroid therapy
  - anti-epileptic drugs
  - chronic heparin therapy
  - androgen deprivation therapy
  - aromatase inhibitors
- renal disease
- immobilization
- COPD (due to disease, tobacco, and glucocorticoid use)

Clinical Features

- commonly asymptomatic
- height loss due to collapsed vertebrae
- fractures: most commonly in hip, vertebrae, humerus, and wrist (see Figure 22, E49)
  - fragility fractures: fracture with fall from standing height or less (does not include fractures of fingers and toes)
  - Dowager's hump: collapse fracture of vertebral bodies in mid-dorsal region
  - x-ray: vertebral compression fractures (described as wedge fractures, require a minimum of 20% height loss), "codfishing" sign (weakening of subchondral plates and expansion of intervertebral discs)
- pain, especially backache, associated with fractures

Approach to Osteoporosis

1. assess risk factors for osteoporosis on Hx and physical
2. decide if patient requires BMD testing with dual-energy x-ray absorptiometry (DEXA): men and women ≥65 yr (or younger if presence of risk factors, see Table 32, E48)
3. initial investigations
   - all patients with osteoporosis: calcium corrected for albumin, CBC, creatinine, ALP, TSH
   - also consider serum and urine protein electrophoresis if vertebral fractures, celiac workup, and 24 h urinary Ca^{2+} excretion to rule out additional secondary causes
   - 25-OH-vitamin D level should only be measured after 3-4 mo of adequate supplementation and should not be repeated if an optimal level ≥75 nmol/L is achieved
   - lateral thoracic and lumbar x-ray if clinical evidence of vertebral fracture (or in individuals at moderate risk of fracture to help decide if they require medical therapy)
4. assess 10-yr fracture risk by combining BMD result and risk factors
   1). WHO Fracture Risk Assessment Tool (FRAX)
   2. Canadian Association of Radiologists and Osteoporosis Canada Risk Assessment Tool (CAROC)
      - approach to management guided by 10-yr risk stratification into low, medium, and high-risk
5. for all patients being assessed for osteoporosis, encourage appropriate lifestyle changes (see Table 33, E48)

Corticosteroid Therapy is a Common Cause of Secondary Osteoporosis
Individuals receiving ≥7.5 mg of prednisone daily for over 3 mo should be assessed for bone-sparing therapy
Mechanism: increased resorption + decreased formation + increased urinary calcium loss + decreased intestinal calcium absorption + decreased sex steroid production

Calcium plus Vitamin D Supplementation and Risk of Fractures
Osteoporosis Int 2015;27:367-376
Purpose: To review trials of vitamin D and calcium therapy for reducing fracture risk in osteoporosis.
Study: Systematic review searching 2011-2015, inclusive, identified 8 RCTs totaling 30970 participants. RCTs reviewed included healthy adults and ambulatory older adults with medical conditions (excluding cancer). Vitamin D and calcium combination therapy was compared to placebo.
Results: Analysis of RCT data revealed that calcium plus vitamin D supplementation produced a statistically significant reduction in risk of total fractures (0.85; CI:0.73-0.98) and in hip fractures (0.70; CI:0.56-0.87). Subgroup analysis was significant for community dwelling or institutionalized patients.
Conclusions: Systematic analysis suggests that vitamin D and calcium therapy significantly decreases fracture risk. This study did not specifically look at individuals with osteoporosis. However, it still supports that vitamin D and calcium should continue to be used as preventive treatment for individuals at increased risk of fractures.

Vitamin D and Calcium for the Prevention of Fracture: A Systematic Review and Meta-analysis
JAMA Netw Open 2019;2:e1917789
Purpose: To investigate if fracture risk is associated with supplementation with vitamin D alone or vitamin D in combination with calcium.
Study Selection: Observational studies with ≥200 fracture cases and RCTs with ≥500 participants that reported ≥10 incident fractures.
Results: Vitamin D supplementation alone was not associated with a reduced risk of any fracture or hip fracture (RR, 1.14; 95% CI, 0.98-1.32). However, combined supplementation with vitamin D (400-800 IU daily) and calcium (1000-1200 mg daily) was associated with a 6% reduction in fracture risk (RR, 0.94; 95% CI, 0.89-0.99) and a 16% reduction of hip fracture risk (RR, 0.84; 95% CI, 0.72-0.97).
Conclusion: Vitamin D alone was not associated with reduced fracture risk but daily supplementation with a combination of vitamin D and calcium was.

Clinical Signs of Fractures or Osteoporosis
- Height loss >3 cm (Sn 92%)
- Weight <51 kg (Sp 97%)
- Kyphosis (Sp 92%)
- Tooth count <20 (Sp 92%)
- Grip strength
- Armspan-height difference >5 cm (Sp 76%)
- Wall-occiput distance >4 cm (Sp 92%)
- Rib-pelvis distance ≤2 finger breadth (Sn 88%)

Online Clinical Tools
CAROC
www.osteoporosis.ca/multimedia/pdf/CAROC.pdf
FRAX
www.shef.ac.uk/FRAX/tool.aspx

EXTRA

Table 31. Indications for BMD Testing

Older Adults (age ≥50 yr)	Younger Adults (age <50 yr)
All women and men age ≥65 yr Menopausal women, and men 50-64 yr with clinical risk factors for fracture: Fragility fracture after age 40 Prolonged glucocorticoid use Other high-risk medication use (aromatase inhibitors, androgen deprivation therapy) Parental hip fracture Vertebral fracture or osteopenia identified on x-ray Current smoking High alcohol intake Low body weight (<60 kg) or major weight loss (>10% of weight at age 25 yr) Rheumatoid arthritis Other disorders strongly associated with osteoporosis: primary hyperparathyroidism, T1DM, osteogenesis imperfecta, uncontrolled hyperthyroidism, hypogonadism or premature menopause (<45 yr), Cushing's disease, chronic malnutrition or malabsorption, chronic liver disease, COPD, and chronic inflammatory conditions (e.g. inflammatory bowel disease)	Fragility fracture: Prolonged use of glucocorticoids Use of other high-risk medications (aromatase inhibitors, androgen deprivation therapy, anticonvulsants) Hypogonadism or premature menopause Malabsorption syndrome Primary hyperparathyroidism Other disorders strongly associated with rapid bone loss and/or fracture

Prevention - Hip

Alendronate	0.61 RR (0.42-0.90)
Risedronate	0.73 RR (0.58-0.92)
Denosumab	0.56 RR (0.35-0.90)
Teriparatide	0.64 RR (0.25-1.68)
Romosozumab	0.44 RR (0.24-0.79)

Prevention - Nonvertebral

Alendronate	0.84 RR (0.74-0.94)
Risedronate	0.78 RR (0.68-0.89)
Denosumab	0.80 RR (0.67-0.96)
Teriparatide	0.62 RR (0.47-0.80)
Romosozumab	0.67 RR (0.53-0.86)

Prevention - Vertebral

Alendronate	0.57 RR (0.45-0.71)
Risedronate	0.61 RR (0.48-0.78)
Denosumab	0.32 RR (0.22-0.45)
Teriparatide	0.27 RR (0.19-0.38)
Romosozumab	0.33 RR (0.22-0.49)

Table 32. Osteoporosis Risk Stratification

Low-Risk 10 yr fracture risk <10%	Unlikely to benefit from pharmacotherapy; encourage lifestyle changes Reassess risk in 5 yr
Medium-Risk 10 yr fracture risk 10-20%	Discuss patient preference for management and consider additional risk factors Factors that warrant consideration for pharmacotherapy: Additional vertebral fracture(s) identified on vertebral fracture assessment (VFA) or lateral spine x-ray Previous wrist fracture in individuals ≥65 yr or with T-score ≤–2.5 Lumbar spine T-score much lower than femoral neck T-score Rapid bone loss Men receiving androgen-deprivation therapy for prostate cancer Women receiving aromatase-inhibitor therapy for breast cancer Long-term or repeated systemic glucocorticoid use (oral or parenteral) that does not meet the conventional criteria for recent prolonged systemic glucocorticoid use Recurrent falls (defined as falling 2 or more times in the past 12 mo) Other disorders strongly associated with osteoporosis Repeat BMD and reassess risk every 1-3 yr initially
High-Risk 10 yr fracture risk >20%; OR Prior fragility fracture of hip or spine; OR More than one fragility fracture	Start pharmacotherapy (need to consider patient preference)

Factors Necessary for Mineralization

- Quantitatively and qualitatively normal osteoid formation
- Normal concentration of calcium and phosphate in ECF
- Adequate bioactivity of ALP
- Normal pH at site of calcification
- Absence of inhibitors of calcification

Treatment of Osteoporosis

Table 33. Treatment of Osteoporosis in Women and Men

Treatment for Both Men and Women	
Lifestyle	Diet: elemental calcium 1000-1200 mg/d; vitamin D 1000 IU/d Exercise: 3x30 min weight-bearing exercises, balance exercise, and aerobic exercise/wk Cessation of smoking, reduce caffeine intake Stop/avoid osteoporosis-inducing medications
Drug Therapy	
Bisphosphonate: inhibitors of osteoclasts	1st line in prevention of hip, nonvertebral, and vertebral fractures (Grade A): alendronate (PO), risedronate (PO), zoledronic acid (IV)
RANKL Inhibitors	Denosumab: 1st line in prevention of hip, nonvertebral, vertebral fractures (Grade A) *Denosumab should not be abruptly stopped/administration delayed. Increased risk of multiple vertebral fractures due to increased bone turnover on discontinuation. Used as an alternative initial treatment in postmenopausal women with osteoporosis who are at high risk for osteoporitic fractures.
Parathyroid Hormone Analogue	Teriparatide: 18-24 mo duration, followed by long-term anti-resorptive therapy with bisphosphonate or RANKL inhibitor
Sclerostin Inhibitors	Romosozumab: 12 mo duration
Treatment Specific to Post-Menopausal Women	
SERM (selective estrogen-receptor modulator): agonistic effect on bone but antagonistic effect on uterus and breast	Raloxifene: 1st line in prevention of vertebral fractures (Grade A) Advantages: prevents osteoporotic fractures (Grade A to B evidence), improves lipid profile, decreased breast cancer risk Disadvantages: increased risk of DVT/PE, stroke mortality, hot flashes, leg cramps
HRT: combined estrogen + progesterone (see Gynaecology, GY37)	Indicated for vasomotor symptoms of menopause For most women, risks > benefits Combined estrogen/progestin prevents hip, vertebral, total fractures Increased risks of breast cancer, cardiovascular events, and DVT/PE

Effect of High-Dose Vitamin D Supplementation on Volumetric Bone Density and Bone Strength: A Randomized Clinical Trial
JAMA 2019;322:736-45
Purpose: To investigate the effects of vitamin D supplementation on volumetric BMD and strength.
Methods: 311 healthy adults (ages 55-70) without osteoporosis, with baseline concentrations of 25-hydroxyvitamin D of 30-125 nmol/L, were randomized to receive daily doses of 400 IU, 4000 IU, or 10000 IU vitamin D3 for 3 years. For participants with calcium dietary intake <1200 mg/d, supplementation was provided. Primary Outcome: Total volumetric BMD at radius and tibia.
Results: Compared with the 400 IU group, radial volumetric BMD was significantly lower for the 4000 IU group (-3.9 mg HA/cm3; 95% confidence interval (CI), -6.5 to -1.3) and 10000 IU group (-7.5 mg HA/cm3; 95% CI, -10.1 to -5.0) with mean % change of -1.2% (400 IU), -2.4% (4000 IU), and -3.5% (10000 IU). Compared with the 400 IU group, tibial volumetric BMD differences were -1.8 mg HA/cm3 (95% CI, -3.7 to 0.1) (4000 IU) and -4.1 mg HA/cm3 (95% CI, -6.0 to -2.2) (10000 IU), with mean % change values of -0.4% (400 IU), -1.0% (4000 IU), and -1.7% (10000 IU).
Conclusion: In healthy adults, supplementation with daily 4000 IU or 10000 IU vitamin D for 3 years was associated with lower radial BMD compared with 400 IU. 10000 IU was associated with lower tibial BMD. There were no apparent benefits of high-dose vitamin D supplementation for bone health.

EXTRA

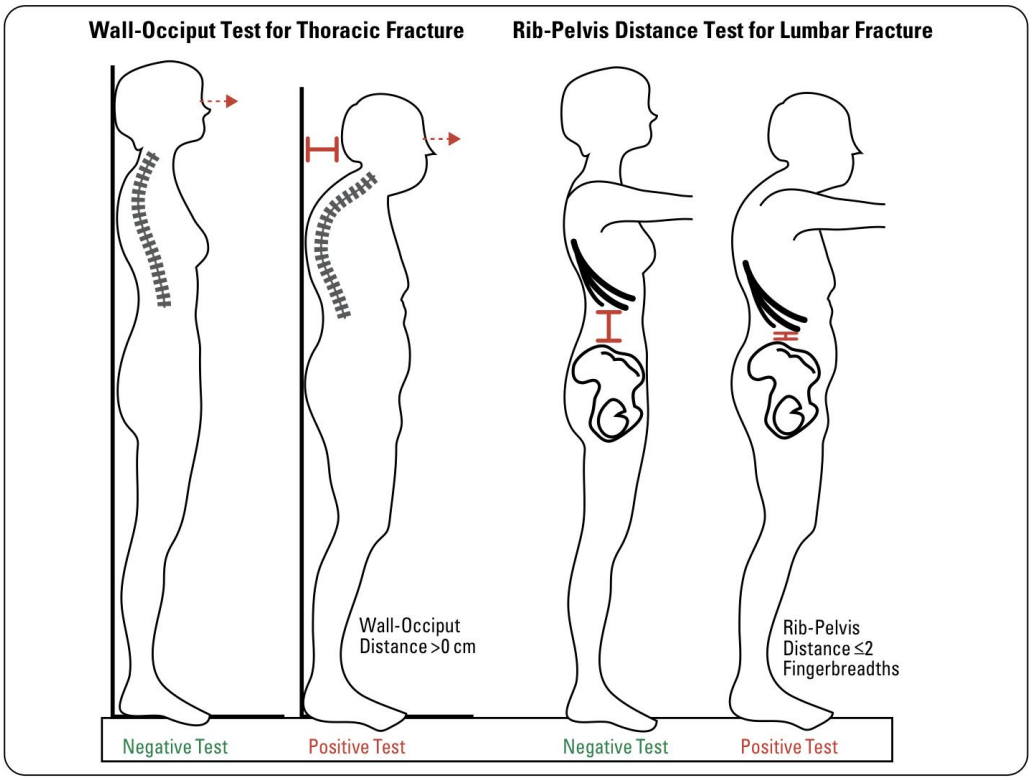


Figure 22. Physical examination test for vertebral fractures

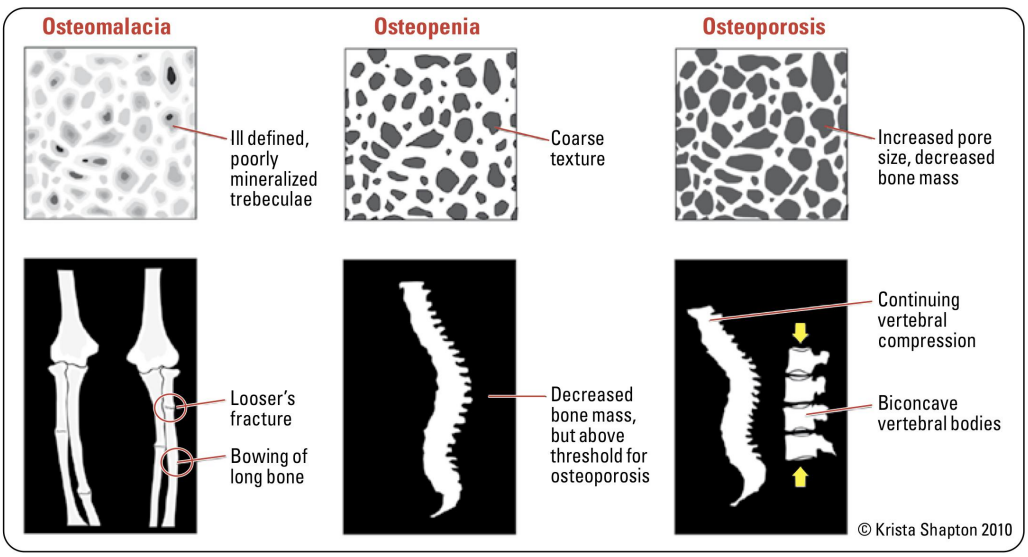


Figure 42. Osteomalacia, osteopenia, and osteoporosis

Disorders Strongly Associated with Osteoporosis Include:
Primary hyperparathyroidism, T1DM, osteogenesis imperfecta, uncontrolled hyperthyroidism, hypogonadism or premature menopause (<45 yr), Cushing's disease, chronic malnutrition or malabsorption, chronic liver disease, COPD, and chronic inflammatory conditions (e.g. IBD)

10 Yr Fracture Risk Assessment
FRAX (WHO Fracture Risk Assessment Tool) and CAROC (Canadian Association of Radiologists and Osteoporosis Canada) have been validated in the Canadian Population
FRAX and CAROC are available online from: https://www.osteoporosis.ca/health-care-professionals/clinical-tools-and-resources/

How Much Calcium Do We Need?

Age	Amount /day
4-8	1000 mg
9-18	1300 mg
19-50	1000 mg
>50	1200 mg

Calcium Content of Common Foods
1 cup milk = 300 mg
¾ cup yogurt = 332 mg
½ can salmon with bones = 240 mg
½ cup cooked broccoli = 33 mg
1 medium orange = 50 mg

Vitamin D Content in Food
- Milk fortified with vitamin D_3 contains 100 IU per 250 mL glass
- Foods such as margarine, eggs, chicken livers, salmon, sardines, herring, mackerel, swordfish, and fish oils (halibut and cod liver oils) all contain small amounts; supplementation is necessary to obtain adequate levels as dietary intake has minimal impact
- Most multivitamins provide 400 IU of vitamin D_3

EXTRA

Osteomalacia and Rickets

Definition
- osteopenia with disordered calcification leading to a higher proportion of osteoid (unmineralized) tissue prior to epiphyseal closure: rickets (in childhood), osteomalacia (in adulthood)

Etiology and Pathophysiology

Vitamin D Deficiency
- deficient uptake or absorption
  - nutritional deficiency
  - malabsorption: post-gastrectomy, small bowel disease (e.g. celiac sprue), pancreatic insufficiency
- defective 25-hydroxylation
  - liver disease
  - anticonvulsant therapy (phenytoin, carbamazepine, phenobarbital)
- loss of vitamin D binding protein
  - nephrotic syndrome
- decreased 1-α-25 hydroxylation
  - hypoparathyroidism
- renal failure

Mineralization Defect
- abnormal matrix
  - osteogenesis imperfecta
- enzyme deficiency
  - hypophosphatasia (inadequate ALP bioactivity)
- presence of calcification inhibitors
  - aluminum, high dose fluoride, anticonvulsants

Calcium Deficiency
- deficient uptake or absorption
  - nutritional deficiency
  - malabsorption
- hypercalciuria (in combination with renal phosphate wasting)

Hypophosphatemia
- gastrointestinal: poor nutritional intake, chronic diarrhea, excessive phosphate binders
- renal phosphate wasting
  - tumour-induced osteomalacia
  - Fanconi syndrome
  - X-linked/autosomal dominant/recessive hypophosphatemic rickets

Matrix Abnormalities
- type IV osteogenesis imperfecta
- fibrogenesis imperfecta ossium
- axial osteomalacia

Table 34. Clinical Features of Rickets and Osteomalacia

Rickets	Osteomalacia
Skeletal pain and deformities, bow-legged	Not as severe
Fracture susceptibility	Diffuse skeletal pain
Weakness and hypotonia	Bone tenderness
Disturbed growth	Fractures
Ricketic rosary (prominent costochondral junctions)	Gait disturbances (waddling)
Harrison's groove (indentation of lower ribs)	Proximal muscle weakness
Hypocalcemia	Hypotonia

Investigations

Table 35. Laboratory Findings in Osteomalacia and Rickets

Disorder	Serum Phosphate	Serum Calcium	Serum ALP	Other Features
Vitamin D Deficiency	Decreased	Decreased to normal	Increased	Decreased calcitriol
Hypophosphatemia	Decreased	Normal	Increased	
Proximal Renal Tubular Acidosis	Decreased	Normal	Normal	Associated with hyperchloremic metabolic acidosis
Conditions Associated with Abnormal Matrix Formation	Normal	Normal	Normal	

- radiologic findings
  - pseudofractures, fissures, narrow radiolucent lines – thought to be healed stress fractures or the result of erosion by arterial pulsation
  - loss of distinctness of vertebral body trabeculae; concavity of the vertebral bodies
  - changes due to secondary hyperparathyroidism: subperiosteal resorption of the phalanges, bone cysts, resorption of the distal ends of long bones
  - others: bowing of tibia, coxa profundus hip deformity
- bone biopsy: usually not necessary but considered the gold standard for diagnosis

Treatment
- definitive treatment depends on the underlying cause
- vitamin D supplementation
- PO_4^{3-} supplements if low serum PO_4^{3-}, Ca^{2+} supplements for isolated calcium deficiency
- bicarbonate if chronic metabolic acidosis

KDIGO 2017 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease

Kidney Inter Suppl 2017;7(1):1-60

Recommendations for Metabolic Bone Disease (MBD) in Chronic Kidney Disease (CKD)

Screening
- In CKD patients with evidence of CKD-MBD and/or risk factors for osteoporosis, perform BMD testing to assess fracture risk if results will impact treatment decisions
- In patients with CKD-BMD, it is reasonable to perform a bone biopsy if knowledge of the type of renal osteodystrophy will impact treatment decisions

Management
- Treatment of CKD-MBD should be based on serial assessments of PO_4^{3-}, Ca^{2+}, and PTH levels, considered together
- Suggest lowering elevated PO_4^{3-} levels towards the normal range
- Avoid hyperglycemia in adult patients and maintain serum Ca^{2+} in age-appropriate normal range in children

EXTRA

Renal Osteodystrophy

Definition

- changes to mineral metabolism and bone structure secondary to CKD
- represents a mixture of four types of bone disease:
  - osteomalacia: low bone turnover combined with increased unmineralized bone (osteoid)
  - adynamic bone disease: low bone turnover due to excessive suppression of parathyroid gland
  - osteitis fibrosa cystica: increased bone turnover due to secondary hyperparathyroidism
  - mixed uremic osteodystrophy: both high and low bone turnover, characterized by marrow fibrosis and increased osteoids
- metastatic calcification secondary to hyperphosphatemia may occur

Pathophysiology

- metabolic bone disease secondary to chronic renal failure
- combination of hyperphosphatemia (inhibits $1,25(OH)_2$ vitamin D synthesis) and loss of renal mass (reduced 1-α-hydroxylase)

Clinical Features

- soft tissue calcifications, necrotic skin lesions if vessels involved
- osteodystrophy, generalized bone pain, and fractures
- pruritus
- neuromuscular irritability and tetany may occur (with low serum calcium)
- radiologic features of osteitis fibrosa cystica, osteomalacia, osteosclerosis, osteoporosis

Investigations

- serum Ca^{2+} corrected for albumin, PO_4^{3-}, PTH, ALP, ± imaging (x-ray, BMD), ± bone biopsy (gold standard; only done if results inform treatment)

Treatment

- prevention
- maintenance of normal serum Ca^{2+} and PO_4^{3-} by restricting PO_4^{3-} intake to 1 g once daily
- Ca^{2+} supplements; PO_4^{3-} binding agents (calcium carbonate, aluminum hydroxide)
- activated vitamin D (calcitriol) with close monitoring to avoid hypercalcemia and metastatic calcification
- bisphosphates and denosumab are not often used for treatment (can worsen the adynamic components of renal osteodystrophy); bone biopsy may indicate if there are signs of increased bone turnover amenable to bisphosphonates

Quiz

Q1: Which of the following is a sign of rickets on an X ray?

- A: Gunstock deformity
- B: Kyphoscoliosis
- C: Metaphyseal cupping
- D: Bone marrow expansion

Q2: A 45-year-old osteoporotic lady presented for check up. She smokes 10 cigarettes per day and reached menopause at the age of 41, Her mother had a hip fracture at the age of 61. Which of the following is the major risk factor for her to develop osteoporosis?

- A: Smoking
- B: Early menopause
- C: Family history of osteoporosis
- D: Low calcium intake

Q3: An 82-year-old woman presented with back pain. There was no history of trauma, fever or weight loss. Physical examination showed mild thoraco-lumbar kyphosis but no tenderness. Neurologic examination is normal. X ray showed a compression fracture. What is the next step?

- A: Start anti-osteoporotic medication
- B: Admission and bed rest
- C: Open reduction and internal fixation (ORIF)
- D: 6 weeks of halo femoral traction

4: Which of the following is the most common site of clinical and radiological findings in established diagnosis of rickets?

- A: Cranium
- B: Lower limb
- C: Upper limb
- D: Thoracic cage

1:C 2:B 3:A 4:B

Quiz

SAQs

441 & 439 & 438:

1. Name 2 factors mentioned in the lecture that control bone metabolism you think are the most important ones? And explain why for each point.?
   - Page 4

2. Sketch a tibia (bone) demonstrating two rickets radiographic findings labeled in the sketch.
   - Page 14

Done by

Abdulrahman Alroqi

Special Thanks

Khalid Alqahtani
Abdullah Alomran

وفّقكم الله