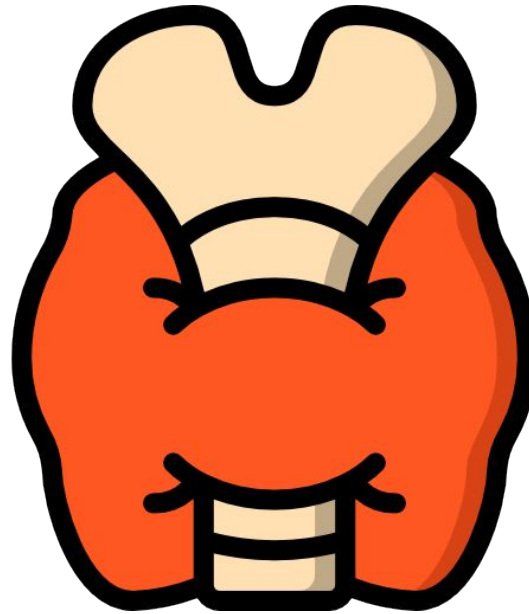


Lecture 49

Editing file



Parathyroid disorders

Objectives:

- ★ Understand the metabolism of Vitamin D
- ★ Know the disorders of Parathyroid glands
- ★ Define the Osteoporosis
- ★ Define the Osteomalacia
- ★ Understand Calcium and related hormones physiology
- ★ Understand hyperparathyroidism

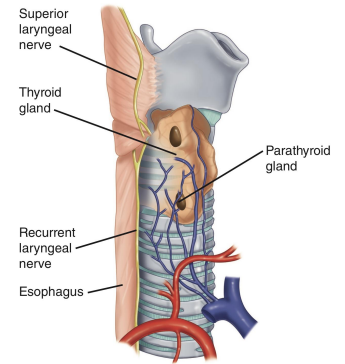
Color index:

Original text Females slides Males slides
Doctor's notes Text book Important Golden notes Extra

Review of the basics

◀ Anatomy of parathyroid glands

- The parathyroid glands are **four** small, pea-sized structures attached to the posterior aspect of the thyroid gland, external to the fibrous thyroid capsule
- The glands are anatomically separated into **two superior** and **two inferior** parathyroids.
- Both sets are supplied by the inferior thyroid arteries with venous drainage through the thyroid plexus of veins.



Lateral view of trachea, thyroid gland, and parathyroids.

◀ Calcium and phosphate homeostasis

- Calcium plays an important role in numerous physiologic processes, ranging from **muscle** contraction to **neuronal** impulse transmission and **bone** mineralization.
- Extracellular calcium concentrations are **tightly regulated** to protect against large fluctuations, it has a **very narrow range (2.1-2.5 mmol/l)**.
- Only 0.1% of total body calcium is found in the extracellular fluid (ECF). The vast majority of the remaining calcium, approximately 99%, is stored within bone
- **Recall from endocrine block:**
 - **40%** of serum calcium is **bound to plasma proteins** (Increase in pH leads to increased calcium affinity.
 - **10%** of serum calcium is **complexed with anions** such as phosphate and citrate.
 - **50%** serum calcium is in a free, **ionized** form. (Only this one is biologically active)
- Like calcium, a very small quantity (1%) of total body phosphate is found in the extracellular space; most phosphate is in bone.

◀ Hormones that regulate Ca and PO₄

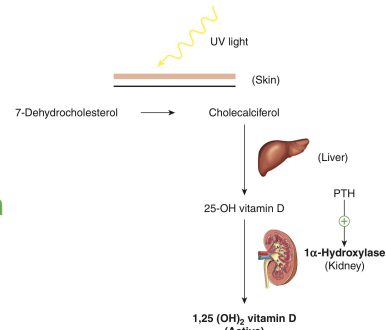
- These hormones regulate the flow of minerals in and out of the extracellular fluid compartments through their actions on intestine, kidneys, and bones.

| Hormone | Action |
|--|---|
| PTH (Polypeptide) | <ul style="list-style-type: none"> • Source: Chief cells of parathyroid • Action: The PTH acts directly on the bones and kidneys and indirectly on the intestine through its effect on the synthesis of 1,25 (OH)₂D₃, Increases serum Ca, decreases serum phosphate, increases urine phosphate, and increases 1,25-(OH)₂D₃ (calcitriol) production by activating 1α-hydroxylase in PCT • Regulation: <ul style="list-style-type: none"> ◦ Stimulate PTH secretion: Low Ca, High PO₄ or Low Mg (if Mg is severely low it will suppress PTH) ◦ Inhibit PTH secretion: The opposite |
| Vitamin D (Called vitamin but it is steroid hormone) | <ul style="list-style-type: none"> • Source: Skin of animals, including humans (Endogenous, 90%) or plants (Exogenous) • Action: Increase intestinal absorption of Ca²⁺ and PO₄, increases bone mineralization at low levels and increases bone resorption at higher levels. • Regulation: <ul style="list-style-type: none"> ◦ High PTH, Low Ca²⁺, Low PO₄ → Increases 1,25 - (OH)₂D₃ production. ◦ Also, 1,25 - (OH)₂D₃ feedback inhibits its own production. |
| Calcitonin (Polypeptide) | <ul style="list-style-type: none"> • Source: Parafollicular cells ("C" cells) of thyroid • Action: Decrease bone resorption by inhibiting osteoclasts (Opposes actions of PTH), it also inhibits Ca reabsorption in renal tubular cells, but in general it's not important in the normal Ca Homeostasis, may be used for treatment of hypercalcemia. • Regulation: Secretion stimulated by High Ca and inhibited by Low Ca |

◀ Vitamin D metabolism

- **How is Vitamin D formed?**

1. Specific wavelengths of UV light at a particular angle react with **7-dehydrocholesterol** to produce **vitamin D3 (Cholecalciferol)**.
2. Cholecalciferol is first hydroxylated in the liver to form **25-hydroxycholecalciferol**. This is the storage form of vitamin D. It is also the level **measured in clinical lab tests**.
3. In the kidney, 25-hydroxycholecalciferol undergoes a second hydroxylation reaction catalyzed by **1 α -hydroxylase**. The product of this reaction, **1,25-dihydroxycholecalciferol** [1,25-(OH)₂ vitamin D], **is the active form of vitamin D**, also referred to as calcitriol. **This is the form used in treating Vitamin D deficiency.**



- **Best time for sun exposure in Riyadh:**

- Summer: 9 am - 10:30 & 2-3 pm (ultraviolet rays are perpendicular to ground)
- Winter: 10 am - 2 pm

Note: The time is different from a country to another bc it depends on the angle of the UV light that hits our skin. The exposure to sunlight has to be direct (Not through window/glass)

◀ Normal bone physiology

- **Bone has 3 major functions:**

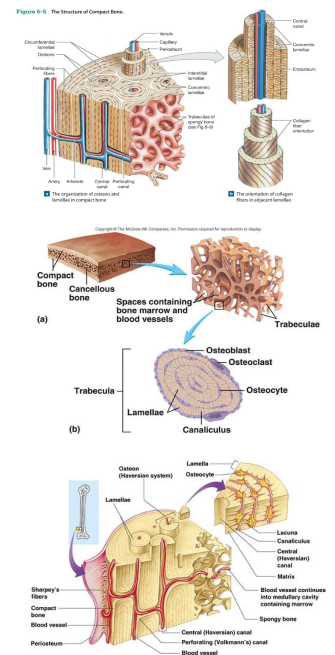
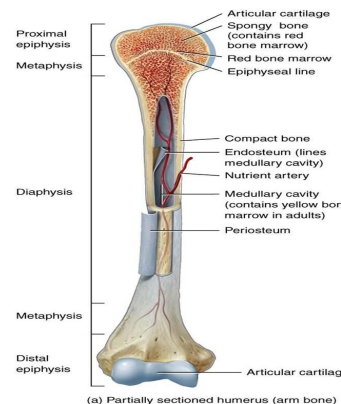
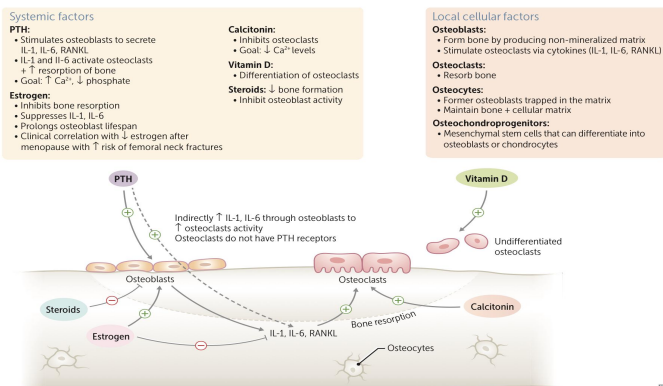
1. Provide *rigid support* to extremities and body cavities containing vital organs.
2. Provide *efficient levers* and sites of attachment of muscles which are all crucial to locomotion.
3. Provide a *large reservoir of ions* such as calcium, phosphorus, magnesium and sodium which are critical for life and can be mobilized when the external environment fails to provide them

- **There are 2 types of bone:**

1. **Cortical bone:** The compact bone of Haversian system such as in the shaft of long bones.
2. **Trabecular bone:** The lattice-like network of bone found in the vertebrae and the ends of long bones.

- The different pattern of bone loss affecting trabecular and cortical bone results in two different fracture syndrome. Defective cortical bone → Fractures of long bones. Defective trabecular bone → Vertebral or pelvic fractures.

- **Bone are highly active, the skeleton completely regenerate every 9 years.**



In the past, it was thought that osteocytes only function as precursors of osteoblasts, but now we know that they play an important role in the signaling process of osteoblasts and osteoclasts

Primary Hyperparathyroidism

Definition

- Primary hyperparathyroidism is due to **excessive production of PTH** by one or more of hyperfunctioning parathyroid glands. This leads to **hypercalcemia** which **fails to inhibit the gland** activity in the normal manner.

Etiology

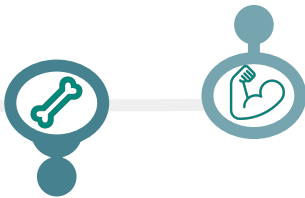
- The cause of primary hyperparathyroidism is unknown, **a genetic factor** may be involved.
- The clonal origin of most parathyroid adenomas suggests a defect at the level of the gene controlling the regulation and/or expression of parathyroid hormone.
- The incidence of the disease increases dramatically after the age of 50 and it is 2-4 folds more common in women.
- A single adenoma occurs in about 80%** of patients with primary hyperparathyroidism.
- Four glands hyperplasia account for 15-20%** of cases.
- A parathyroid carcinoma could be the etiology in a rare incidence of less than 1% **but should always be considered as a differential.**

Clinical features

- Classic presentation: Stones, Bones, Abdominal groans and Psychic moans**
- The most common presentation: Asymptomatic hypercalcemia**, nowadays almost **90%** of diagnosed cases in the developed countries are picked up by routine screening for calcium level using the new automated machines. **early on, patients usually present with very vague manifestations.**
- The two major sites of potential complications are the **bones and the kidneys**. Nowadays such complications are seen less commonly and around 20% of patients or less show such complications.

Neuromuscular

Fatigue, lethargy, weakness



Bone

Osteoporosis and fractures, osteitis fibrosa cystica*

Neuropsychiatric

Depressed mood, psychosis



Cardiovascular

Hypertension
(Mechanism is unclear),
ventricular hypertrophy



Kidney

Nephrocalcinosis (diffuse deposition of calcium- phosphate complexes in the parenchyma) and **Nephrolithiasis** (ca oxalate stones)



Other manifestations

peptic ulcer (late), pancreatitis, gout and pseudogout, anemia, constipation, **Corneal calcification** (sign of longstanding hyperCa)



★ ***Osteitis fibrosa cystica** (In advanced disease) is a **cystic bone spaces filled with brown fibrous tissue** (“brown tumor” consisting of osteoclasts and deposited hemosiderin from hemorrhages; causes bone pain).

- Osteitis fibrosa cystica could occur with subperiosteal resorption of the distal phalanges, distal tapering of the clavicles, a “salt and pepper” appearance of the skull as well as bone cysts and brown tumors of the long bones.

◀ DDX of hypercalcemia ★

Parathyroid-related

- **Primary hyperparathyroidism:**
 - Solitary adenomas
 - Multiple endocrine neoplasia
- **Lithium therapy**
- **Familial Hypocalciuric Hypercalcemia**
 - Autosomal dominant
 - Usually asymptomatic
 - **PTH is normal**
 - Mild hypercalcemia
 - Hypocalciuria
 - Mg high normal or high.

Vitamin D- related normal PTH levels

- **Vitamin D intoxication**
 - **↑ 1,25(OH)2D: Sarcoidosis and other granulomatous diseases**
 - **Idiopathic hypercalcemia of infancy**
- Note:** Sarcoidosis is a non-caseating chronic granulomatous disease

Malignancy-related

- **Increased PTHrp:** commonest cause (**BREAST CANCER**)
 - **MULTIPLE MYELOMA:** production of osteoclast activating factor
 - **Solid tumor with humoral mediation of hypercalcemia** (lung, kidney)
 - **↑ 1,25(OH)2D: Lymphoma**
 - **Leukemia**
- Note: **PTH is normal** in malignancy induced hypercalcemia

The condition demonstrates **increased renal reabsorption of calcium despite hypercalcaemia**. PTH levels are normal or slightly raised and **urinary calcium is low**. It is caused by loss of function **mutations** in the gene on the long arm of chromosome 3 encoding for the **calcium-ion-sensing G-protein coupled receptor in the kidney and parathyroid gland**. Parathyroid **surgery is not indicated** as the course appears benign. This diagnosis can be differentiated from hyperparathyroidism in an isolated case by the calcium creatinine ratio in blood and urine.

Associated with high bone turnover

- **Hyperthyroidism**
- **Immobilization (Esp. in ICU)**
- **Thiazides:** increase renal calcium reabsorption
- **Vitamin A intoxication**

Associated with renal failure

- **Severe secondary hyperparathyroidism**
- **Aluminum intoxication**
- **Milk alkali syndrome**

Adrenal Insufficiency

Medical treatment of Hypercalcemia (Females slides only)

In acute severe forms the mainstay of therapy is **adequate hydration** with saline and forced diuresis by **diuretics** to increase the urinary excretion of calcium rapidly along with sodium and prevent its reabsorption by the renal tubules.

Glucocorticoids

In hypercalcaemia associated the hematological malignant neoplasms

Calcitonin

Also inhibit osteoclast activity and prevent bone resorption

Phosphate

Oral phosphate can be used as an antihypercalcaemic agent and is commonly used as a temporary measure during diagnostic workup.

Mythramycin

A toxic antibiotics which inhibit bone resorption and is used in hematological and solid neoplasms causing hypercalcaemia.

Bisphosphonates

They are given intravenously or orally to prevent bone resorption.

Estrogen

It also decrease bone resorption and can be given to postmenopausal women with primary hyperparathyroidism using medical therapy

Emergency Box 19.2

Treatment of acute severe hypercalcaemia

Acute hypercalcaemia often presents with dehydration, nausea and vomiting, nocturia and polyuria, drowsiness and altered consciousness. The serum Ca^{2+} is over 3 mmol/L and sometimes as high as 5 mmol/L. While investigation of the cause is under way, immediate treatment is mandatory if the patient is seriously ill or if the Ca^{2+} is above 3.5 mmol/L.

- **Rehydrate** at least 4–6 L of 0.9% saline on day 1, and 3–4 L for several days thereafter. Central venous pressure (CVP) may need to be monitored to control the hydration rate.
- **Intravenous bisphosphonates** are the treatment of choice for hypercalcaemia of malignancy or of undiagnosed cause. Pamidronate is preferred (60–90 mg as an intravenous infusion in 0.9% saline or glucose over 2–4 hours or, if less urgent, over 2–4 days). Levels fall after 24–72 hours, lasting for approximately two weeks. Zoledronate is an alternative.
- **Prednisolone** (30–60 mg daily) is effective in some instances (e.g. in myeloma, sarcoidosis and vitamin D excess) but in most cases is ineffective.
- **Calcitonin** (200 units i.v. 6-hourly) has a short-lived action and is little used.
- **Oral phosphate** (sodium cellulose phosphate 5 g three times daily) produces diarrhoea.

◀ Diagnosis



Lab tests

- The presence of established **hypercalcaemia** in more than one serum measurement accompanied by elevated **immunoreactive PTH** is characteristic (**iPTH**).
- Serum phosphate is usually **low** but may be normal.
- Blood alkaline phosphatase (of bone origin) is raised.
- **Summary: ↑ Calcium, ↓ Phosphorus, ↑ PTH**; when this combination is present in an asymptomatic patient then further investigation is usually unnecessary.
- **Hypercloreaemic acidosis** (Often mild)
- **24-hour urinary calcium** or single calcium creatinine ratio should be measured in a young patient with modest elevation in calcium and PTH **to exclude familial hypocalciuric hypercalcaemia**
- **Protein electrophoresis/immunofixation:** to exclude myeloma
- **Hydrocortisone suppression test:** hydrocortisone 40 mg three times daily for 10 days leads to suppression of plasma calcium in sarcoidosis, vitamin D-mediated hypercalcaemia and some malignancies.

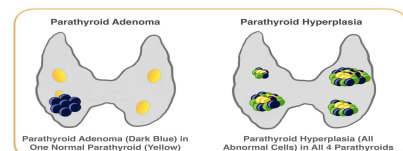
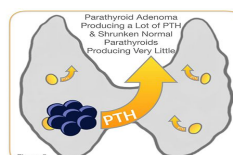
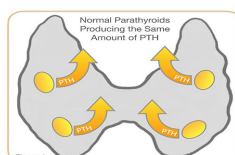


Imaging

- **Plain X-ray** of hands can be diagnostic showing subperiosteal bone resorption usually on the radial surface of the distal phalanx with distal phalangeal tufting as well as **cysts formation** and generalized **osteopenia**. **Abdominal X-ray may show stones**.
- **Preoperative localization of the abnormal parathyroid gland(s):**
 - Ultrasonography
 - MRI
 - CT: usually done after sestamibi scan for further localization of the adenoma
 - **Thallium 201 – Technetium 99m scan (subtraction study) and sestamibi scan** (85-95% sensitivity)

◀ Treatment

- ★ **Surgical treatment (Parathyroidectomy)** should be considered in all cases with established diagnosis of primary hyperparathyroidism.
 - while waiting for surgery, patient should be kept hydrated, sometimes given diuretics to increase calcium excretion.
- **If patient is symptomatic (lithiasis, osteoporosis, pancreatitis) surgery is indicated:**
 - Bilateral neck exploration
 - Or Focused parathyroid exploration if adenoma is localized preoperatively
- During surgery the surgeon identifies all four parathyroid glands (using biopsy if necessary) followed by:
 - The **removal of the enlarged parathyroid, not all the 4 glands** (In case of **adenoma**)
 - Or **3 1/2 glands** in case of multiple glandular **hyperplasia**. (You can easily live with half a parathyroid gland)
- Intraoperative PTH monitoring
- Endoscopic parathyroidectomy
- Minimal access surgery is used, and some centres measure PTH levels intra-operatively to ensure the adenoma has been removed.
- **Medical treatment:** cinacalcet (Calcimimetic agent) can be used if patient has high surgical risk e.g. **elderly and dialysis patients**



01

Secondary hyperparathyroidism:

- An increase in PTH secretion which is adaptive and unrelated to intrinsic disease of the parathyroid glands is called secondary hyperparathyroidism.
- Physiological compensatory hypertrophy of all parathyroids because of **chronic hypocalcaemia**.
- **Causes: chronic kidney disease (Most common)**, vitamin D deficiency or malabsorption
- **PTH** levels are **raised** but calcium levels are low or normal, and PTH falls to normal after correction of the cause of hypocalcaemia where this is possible.

02

Tertiary hyperparathyroidism:

- The development of **apparently autonomous parathyroid hyperplasia** after long-standing secondary hyperparathyroidism, **most often in renal failure**.
- **Plasma calcium and phosphate are both raised**, the latter often grossly so. (cf. 1ry hyperparathyroidism)
- Parathyroidectomy is necessary at this stage.

Summary of Hyperparathyroidism

| Type | Calcium | PTH | Vitamin D | Phosphate |
|-----------|---------|------|-----------|-------------|
| Primary | High | High | Normal | Low |
| Secondary | Low | High | Low | High or Low |
| Tertiary | High | High | Low | High |

An area for your notes

Hypoparathyroidism

Definition

- **Deficient secretion of PTH** which manifests itself biochemically by **hypocalcaemia**, **hyperphosphatemia diminished or absent circulating iPTH** and clinically the symptoms of neuromuscular **hyperactivity**.

Etiology

- **The most common causes are autoimmune or post-surgery** (Thyroidectomy)¹

1- Surgical hypoparathyroidism (The commonest):

- After anterior neck exploration for **thyroidectomy**, abnormal parathyroid gland removal², excision of a neck lesion.
- It could be due to the removal of the parathyroid glands or due to interruption of blood supply to the glands.

2- Functional hypoparathyroidism:

- In patients who have **chronic hypomagnesaemia** of various causes.
- Magnesium is necessary for the PTH release from the glands and also for the peripheral action of the PTH.
- **Severe diarrhea, malabsorption or other conditions that might cause hypomagnesemia.**
- Magnesium is like the fuel for parathyroid glands. So, if you have a patient with hypocalcemia, you have to check or check Mg.

3- Idiopathic hypoparathyroidism:

- A form occurring at an early age (genetic origin) with **autosomal recessive mode** of transmission "**multiple endocrine deficiency autoimmune-candidiasis (MEDAC) syndrome**"
- "**Juvenile familial endocrinopathy**"
- "**Polyglandular autoimmune syndrome Type 1 (AKA "Hypoparathyroidism – Addison's disease – mucocutaneous candidiasis (HAM) syndrome")**": In children (2-4y/o) and In this sequence (moniliasis "**mucocutaneous candidiasis**" → **hypoparathyroidism** → **hypoadrenalism**)
- Circulating antibodies for the parathyroid glands and the adrenals are frequently present.
- **Associated disease:**
 - Pernicious anemia
 - Ovarian failure
 - Autoimmune thyroiditis
 - Diabetes mellitus
- The late onset form occurs sporadically without circulating glandular autoantibodies

1- A good surgeon should be aware and take caution of the recurrent laryngeal and parathyroid gland when performing thyroid surgery
 2- The major danger after operation is hypocalcaemia, which is more common in patients who have significant bone disease and/or vitamin D deficiency– the 'hungry bone' syndrome. Pre-treat such patients, with alfacalcidol 2 µg daily from 2 days preoperatively for 10–14 days, and routine vitamin D replacement (preferably without calcium) is always indicated if deficiency is diagnosed.

Clinical Presentation of Hypoparathyroidism



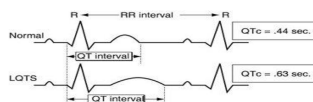
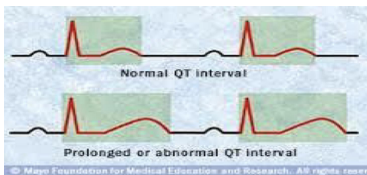
Neuromuscular

- The **rate of decrease in serum calcium is the major determinant** for the development of neuromuscular complications.
- When nerves are exposed to low levels of calcium they show abnormal neuronal function which may include decrease threshold of excitation, repetitive response to a single stimulus and rarely continuous activity
- Paresthesia and numbness around mouth, hands and feet and **laryngeal stridor**
- **Tetany (if severe acute hypocalcemia, usually post-surgical)**
- Hyperventilation and **carpopedal spasm** (Adduction of thumb and hyperextension of the fingers)
- Adrenergic symptoms
- Convulsion (More common in young people and it can take the form of either generalized tetany followed by prolonged tonic spasms or the typical epileptiform seizures)
- **Signs of latent tetany :**
 - **Chevostek sign:** Contraction of facial muscles on tapping on zygomatic arch
 - **Trousseau sign:** Carpopedal spasm when inflating sphygmomanometer 20 mmHg above systolic BP
- ★ Extrapyramidal signs (due to basal ganglia calcification): **Parkinsonism usually occur in old individuals, if a young pt presented with Parkinsonism suspect hypocalcemia**



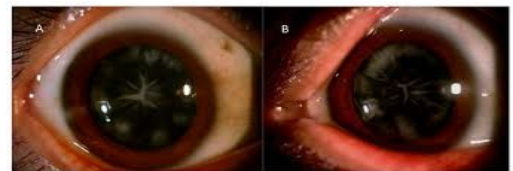
Cardiac manifestation

- **Prolonged QT interval** in the ECG
- Resistance to digitalis
- Hypotension
- Refractory heart failure with cardiomegaly can occur



Eyes

- **Postero-lenticular cataract** in long standing hypocalcemia **due to deposition of calcium phosphate.**



Dental manifestation

- **Abnormal enamel formation** with delayed or absent dental eruption and defective dental root formation



Malabsorption syndrome

- Presumably secondary to decreased calcium level and may lead to **steatorrhea** with long standing untreated disease. **low calcium also decreases magnesium absorption → further aggravate hypocalcemia**

◀ DDX of hypocalcemia with high PTH

- 1 **Deficiency of vitamin D (commonest cause) or calcium.**
- 2 **Severe hypomagnesemia** (Here there will be **LOW** PTH)
- 3 **Renal impairment (chronic renal failure → High phosphate)**
- 4 **Excessive intake of inorganic phosphate compounds**
- 5 **States of tissue resistance to vitamin D**
- 6 **Vitamin D dependent rickets:** 1-alpha-hydroxylase deficiency and hereditary resistance to to vitamin D
- 7 **Malabsorption** Decreased intestinal absorption of vitamin D or calcium due to primary small bowel disease, short bowel syndrome, postgastrectomy syndrome and **acute pancreatitis**
- 8 **Drugs that cause rickets or osteomalacia such as phenytoin, phenobarbital, cholestyramine, and laxative**
- 9 **Pseudohypoparathyroidism (Resistance to PTH)¹**
 - Type 1A autosomal dominant (resistance to PTH + somatic features)
 - Type 1B (isolated resistance, PTH IS HIGH)

◀ Diagnosis

- In the **absence of renal failure** the **presence of hypocalcaemia with hyperphosphatemia** is virtually diagnostic of hypoparathyroidism.
- **Undetectable serum iPTH confirms the diagnosis** or it can be detectable if the assay is very sensitive.
- Parathyroid antibodies: Present in idiopathic hypoparathyroidism

◀ Treatment

Acute and severe with tetany (emergency)

- Give 10 cc of 10% **calcium gluconate parenterally** slowly and under ECG monitoring (careful in patients on digoxin)
- After obtaining adequate serum calcium level, vitamin D supplementation with oral calcium should be initiated.

Chronic hypocalcemia

- The mainstay of treatment is a combination of oral **calcium (1-2gm daily)** with pharmacological doses of **vitamin D (Calcitriol or alfacalcidol)** or its potent analogues.
- Phosphate restriction in diet may also be useful with or without aluminum hydroxide gel to lower serum phosphate level. **always give active vitamin D because low PTH leads to decreased conversion of vitamin D to its active form at the kidney level.**

Note: Can we give PTH? Not really, because it's only injectable and expensive, it also has a short half life, so you will need multiple injections to maintain a normal Ca level.

1- PTH will be high but ineffective, it will lead to hypocalcemia and hyperphosphatemia. Associated with Albright hereditary osteodystrophy (may have **shortened fourth and fifth metatarsal or metacarpal bones** and short stature). Pseudo-pseudohypoparathyroidism describes the phenotypic defects but without any abnormalities of calcium metabolism.

Osteoporosis

“The silent thief”



Introduction

- **Decrease in bone mass¹** and **strength** with micro-architectural disruption resulting in fracture² from minimal trauma
- Generally patients are asymptomatic until fractures occur
- It is **impossible that osteoporosis cause pain**, the pain is secondary to bone fractures, osteoarthritis or others.
- **The first manifestation of reduced bone mass is usually a wrist fracture** or a vertebral crush fracture caused by a small amount of force which produces severe localized pain.
- Subsequent **vertebral fractures³** may contribute to **chronic back pain**.
- In well established osteoporosis, **dorsal Kyphosis** and **loss of height** occurs. (‘Widow’s stoop’)
- **Hip fractures with its fatal complications** also occur commonly as osteoporosis become more severe.

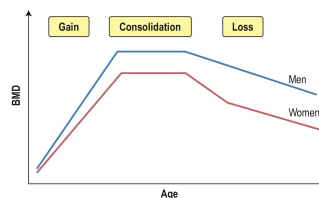


Figure 11.37 Lifetime changes in bone mineral density (BMD). Peak bone mass is achieved between 20 and 30 years of age (gain), and consolidated up to around the age of 40 years. Then, age-related bone loss occurs in both men and women, with an accelerated loss in women starting around the time of menopause which lasts between 5 and 10 years.

Types of osteoporosis

| | Type 1 osteoporosis (Post-menopausal) | Type 2 osteoporosis (Senile) |
|--------------------------|--|---|
| Age | Usually affects woman within 15 years of menopause | >70y/o of both genders |
| Type of bone loss | Mainly trabecular | Trabecular and cortical |
| Rate of bone loss | Accelerated | Not accelerated |
| Fracture sites | Distal radius (Colle’s fracture ⁴), vertebra (Crush and wedge fractures) | Hip ⁵ and femur neck fractures |

Note: Age related bone loss particularly trabecular bone in the spine begins in women before menopause

- **Other causes:** Ca and Vitamin D deficiency, Estrogen deficiency in women, androgen deficiency in men and **the use of steroids** (Those treated for myasthenia gravis, SLE etc.)
- **Exclude secondary causes especially in younger individuals and men:**
 - Hyperparathyroidism (1ry/2ndary), Vitamin D inadequacy
 - Malabsorption state (e.g. celiac disease, inflammatory bowel disease, short gut syndrome)
 - Hypercalciuria, hyperthyroidism, chronic lung disease and rheumatoid arthritis
 - Malignancy (e.g. myeloma, bony metastasis) and hepatic insufficiency

1- Mineralization is **not affected**

2- Fractures increase morbidity and mortality; so the goal is to prevent them

3- Sudden onset of severe pain in the spine, often radiating around to the front, suggests vertebral crush fracture.

4- Colles’ fractures typically follow a fall on an outstretched arm.

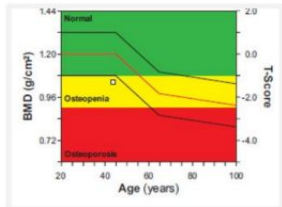
5- Due to mainly cortical bone loss

Osteoporosis cont.

◀ Diagnosis

- **ALP and PTH are within normal range** in patients with osteoporosis due to sex hormones deficiency and aging.
- **X-rays of skeleton do not show** a decrease in osseous density **until at least 30% of bone mass has been lost.**
- **Available bone assessment methods:**
 1. Single-Photon absorptiometry (SPA)
 2. Dual-Photon absorptiometry (DPA)
 3. Computed Tomography (CT)
 4. **Dual-Energy X-ray Absorptiometry (DEXA) (Gold standard)**
 - Measures bone mineral density (BMD, aka T-score) usually of the lumbar spine and proximal femur and comparing it to BMD of a healthy woman, **very sensitive to bone mass reduction but cannot tell you the cause (osteomalacia or osteoporosis)**
 - **More than -2.5 SD below average → osteoporosis**
- Measure bone mass by **the ability of the tissue to absorb the photons** emitted from the radionuclide source or the X-ray tube.

Bone density scanner



Scan:

- Lumbar spine "L1 to L4"
 - Femoral neck
- If there is osteoporosis in one site, the patient will be labeled as osteoporotic

Table 11.24 Indications for DXA scanning

| |
|--|
| <ul style="list-style-type: none"> • Radiographic osteopenia • Previous fragility fracture (in those aged <75 years) • Glucocorticoid therapy (in those aged <65 years) • Body mass index below 19 (kg/m²) • Maternal history of hip fracture • BMD-dependent risk factors in Table 11.23 <p>In patients presenting with height loss and/or kyphosis, lateral thoracic spine X-ray should be the initial investigation.</p> |
|--|

★ WHO osteoporosis criteria 1994, definition based on BMD:

| | |
|----------------------------|---|
| Normal | Greater than or equal to - 1 SD |
| Osteopenia | Between - 1 and - 2.5 SD |
| Osteoporosis | Less than or equal to - 2.5 SD |
| Severe osteoporosis | Osteoporosis with 1 or more fragility fractures |

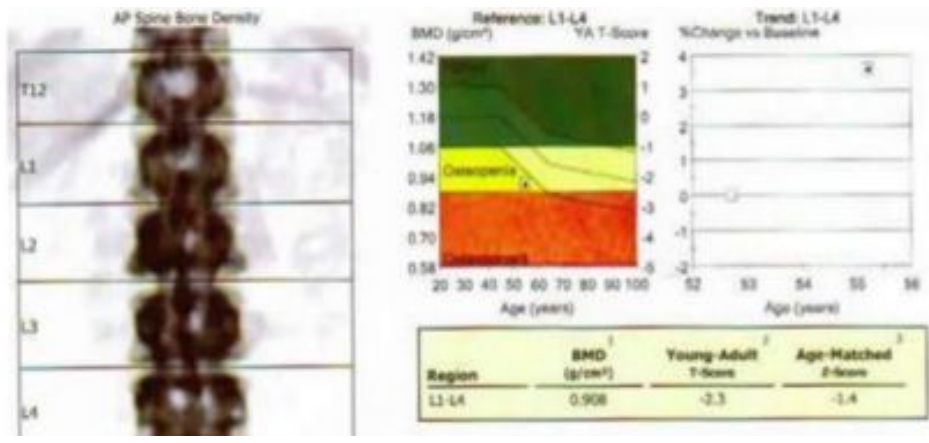


Table 11.23 Risk factors for fragility fractures

| BMD-dependent | BMD-independent |
|--|--------------------------------|
| Female sex | Increasing age |
| Caucasian/Asian | Previous fragility fracture |
| Gastrointestinal disease | Family history of hip fracture |
| Hypogonadism | Low body mass index |
| Immobilization | Smoking |
| Chronic liver disease | Excess alcohol use |
| Chronic kidney disease | Glucocorticoid therapy |
| Low dietary calcium intake | High bone turnover |
| Vitamin D insufficiency | Increased risk of falling |
| Chronic obstructive pulmonary disease | Rheumatoid arthritis |
| Drugs | |
| Heparin | |
| Calcineurin inhibitors, e.g. ciclosporin | |
| Anticoagulants | |
| Thiazolidinediones | |
| Aromatase inhibitors | |
| Anti-androgens | |
| GnRH analogues | |
| Proton pump inhibitors | |
| ?Selective serotonin reuptake inhibitors | |
| Endocrine disease | |
| Cushing's syndrome | |
| Hyperthyroidism | |
| Hyperparathyroidism | |
| Other diseases | |
| Diabetes mellitus | |
| Mastocytosis | |
| Multiple myeloma | |
| Osteogenesis imperfecta | |

Management

- It is appropriate to begin to **look for risk factors that predispose a person to osteoporosis** and develop a rational prevention program tailored to person's risk before the menopause. e.g., **Women with thin light frame**, history of low calcium intake, decreased physical activity, high alcohol or caffeine consumption, smoking, family history of osteoporosis, history of prior menstrual disturbances or history of drug like antiepileptics or steroids are all high risk groups and in the presence of one or more of such risk factors measurement of BMD provides further information to the risk of fractures.
- Strategy: Prevent Osteoporosis**, detect and treat early to decrease further progression and limit disability and provide rehabilitation as well as raising public awareness.

Box 11.18 Management of osteoporosis: summary

Treatment is guided by risk of fracture, not BMD alone. If intermediate risk from clinical factors, request DXA scan (see: www.shef.ac.uk/FRAX or other risk calculator until familiar with assessments). Do not underestimate the risk from steroids or previous fracture.

Many guidelines (e.g. NICE) recommend bisphosphonate as first-line drugs in most cases. Other options include:

- strontium ranelate or denosumab:
 - in young (to defer bisphosphonate use)
 - new fracture on a bisphosphonate or a fall in BMD or bisphosphonate use for 5–10 years
- teriparatide if multiple vertebral fractures or high risk
 - i.v. zoledronate after hip fracture

BMD monitoring is required in:

- selected high-risk cases
- low-risk cases not treated

1 The Adolescent Female (Peak bone mass attainment)

- Peak bone mass: the highest bone mass a person reach in their life, usually in their early 20s.
- Adequate calcium intake of 1200 mg/day is recommended, to maximize peak bone mass
- Adequate sun exposure or vit D supplementation to ensure adequate level.
- A reasonable exercise program is recommended.
- Genetic influence on peak bone mass attainment.

2 The Premenopausal Female (Maintenance of bone mass)

- Adequate calcium intake; 1000-1500 mg/day disease.
- Adequate sun exposure or vit D supplementation
- A reasonable exercise program is recommended, but not to the point of amenorrhea.
- Avoidance of osteopenia-producing conditions/medications/lifestyles:
 - Smoking & excessive alcohol intake, excessive caffeine/protein intake.
 - Amenorrhea/oligomenorrhea → make sure the menstrual cycle is regular
 - Cortisone, excessive thyroid hormone replacement (?), loop diuretics, prolonged heparin exposure.

3 The Immediately Postmenopausal Female (Prevention of bone mass loss)

- Consideration of estrogen replacement therapy
- If intact uterus, consideration of medroxyprogesterone
- Other modalities of therapy:
 - Bisphosphonates, SERMS (Selective estrogen receptor modulators) e.g., Evista, Livial,
 - Protelos (strontium ranelate) → old drug, Forteo (Teripratide) or Prolia (Denosumab) → the only bone building drugs (anabolic)
 - all of these cannot be used for life (only for 5-10 yrs), hence why we try to delay them as much as possible

4 The elderly postmenopausal female with low bone mass but no compression fractures (Prevention of bone mass loss & restoration of bone mass previously lost)

Skipped by Dr

- Adequate calcium intake: 1000-1500 mg/day and Adequate supply of vit D (1000-2000IU)
- A reasonable exercise program with physical therapy instruction in paraspinous muscle group strengthening exercise.
- Avoidance of osteopenia-producing conditions/medications/lifestyles:
 - Smoking & excessive alcohol intake, excessive caffeine/protein intake.
 - Cortisone, excessive thyroid hormone replacement (?)
- Other modalities: Same as NO. 3 above

Osteoporosis cont.

Management cont.

Skipped by Dr

5

The male or female with corticosteroid induced osteopenia (Prevention of bone mass loss & restoration of bone mass previously lost)

- Steroids for several days causes bone loss more on axial bones (40 %) than on peripheral bones (20%). Steroids may also cause Muscle weakness
- Prednisolone more than 5 mg /day for long time may lead to osteopenia → osteoporosis
- Bone mass measurement if possible to identify bone mass loss
- Shortest duration and Lowest possible dose of corticosteroids: ? Deflazacort
- A program of reasonable calcium intake (1000- 1500 mg daily, depending upon urinary calcium), exercise, & avoidance of other osteopenia-producing situations is indicated.
- Adequate intake of vit D (1000-2000 IU)
- **Other modalities of therapy:**
 - Estrogen (Females), testosterone (males)
 - Bisphosphonates (Reduces bone breakdown), ?PTH (Teriparatide, **in case of severe osteoporosis that causes multiple fractures. Teriparatide should be given intermittently not continuously**)
 - Forteo

6

The elderly (age>62) post menopausal female with fractures (spine &/hip) (Prevention of further fractures.)

| Intervention | Vertebral fracture | Non-vertebral fracture | Hip fracture |
|--------------------|--------------------|------------------------|----------------|
| Alendronate | + | + | + |
| Etidronate | + | ND | ND |
| Ibandronate | + | + ^a | ND |
| Raloxifene | + | ND | ND |
| Risedronate | + | + | + |
| Strontium ranelate | + | + | + ^a |
| Zoledronate | + | + | + |
| Denosumab | + | + | + |
| Teriparatide | + | + | ND |
| PTH (1-84) | + | ND | ND |

^aDemonstrated only in high-risk subgroup. ND, not demonstrated.

Summary of osteoporosis management from Kumar

Prevention and treatment

- New vertebral fractures require bed rest for 1–2 weeks and strong analgesia, muscle relaxants (e.g. diazepam 2 mg three times daily), or intravenous pamidronate (single dose 60–90 mg) are also given for pain relief.
- Non-spinal fractures are treated by conventional orthopaedic means.
- **Daily intakes of 800–1000 mg of calcium and 400–800 IU of vitamin D are recommended, throughout life.**

Pharmacological intervention

Bisphosphonates e.g. alendronate, risedronate, zoledronate

- Are **first-line treatment** in most patients with osteoporosis.
- They inhibit bone resorption through inhibition of osteoclast activity, increase bone mass at the hip and spine, and most have been shown to reduce fracture incidence.
- Oral bisphosphonates should be taken in the fasting state with a **large drink of water**, while the patient is **standing or sitting upright**. The patient should subsequently remain upright and avoid food and drink for at least 30 min. Generally well tolerated but may be associated with upper gastrointestinal side-effects such as **oesophagitis**, particularly if the dosing instructions are not closely followed.
- Osteonecrosis of the jaw is rarely seen following high dose i.v. nitrogen-containing bisphosphonate in patients who have malignant disease

Summary of osteoporosis management from Kumar cont.

Strontium ranelate (2 g daily)

- Is a useful **alternative to oral bisphosphonates** particularly in the frail elderly who have difficulty in complying with the dosage regimen. Its mechanism of action is uncertain.

Denosumab (fully human monoclonal antibody to RANKL)

- Administered as a single subcutaneous injection every 6 months.
- Fracture risk reduction is equivalent to bisphosphonates.
- In addition to promoting osteoclastogenesis, RANKL has a role in the immune system and denosumab has been associated with **exacerbations of eczema** and a small increase in severe cases of **cellulitis**.

Raloxifene (60 mg daily), a selective oestrogen-receptor modulator (SERM)

- Activates oestrogen receptors on bone while **having no stimulatory effect on endometrium (cf: hormone replacement therapy [HRT])**.
- It has been shown to reduce BMD loss at spine and hip, though fracture rates are reduced only in the spine.
- Side-effects are leg cramps, flushing, increased risk of thromboembolism (similar to HRT) and stroke.

Recombinant human parathyroid hormone peptide 1–34 (teriparatide) and recombinant human parathyroid hormone 1–84

- **Anabolic agents** that stimulate bone formation.
- They are indicated for **severe cases of osteoporosis** or in women who are intolerant of, or fail to respond to other therapies. A side-effect is **transient hypercalcaemia**.
- Non-osteoporotic bone diseases such as **osteomalacia should be excluded** prior to treatment. Neither agent should be used in people with skeletal metastases or osteosarcoma.

Oestrogen therapy

- Because of adverse effects on breast cancer and cardiovascular disease risk, HRT is a second-line option for osteoporosis except in early postmenopausal women at high fracture risk who also have perimenopausal symptoms.

Testosterone

- Given to men with biochemical evidence of hypogonadism.

Glucocorticoid-induced osteoporosis

- Individuals requiring continuous oral glucocorticoid therapy for 3 months or more (at any dose) should be assessed for co-existing risk factors (age, previous fracture, hormone status).
- Postmenopausal women, men aged over 50 years and any individuals who have sustained a fragility fracture should receive treatment **without waiting for DXA scanning**.
- For these individuals, **bisphosphonates and teriparatide are the approved agents**. Calcium and vitamin D supplementation should also be given.

Osteomalacia

Definition

- **Failure of organic matrix (osteoid) of bone to mineralize** normally. A number of factors are critical for normal bone mineralization. An absence or a defect in any one of them may lead to osteomalacia, **the most common biochemical causes are a decrease in the product of concentrations of calcium and phosphate** in the extracellular fluid so that the supply of minerals to bone forming surfaces is inadequate.
- **Called rickets** if it occurs in children (during bone growing)

Etiology

1- Vitamin D deficiency (Most common cause)

| Inadequate sunlight ¹ exposure without dietary supplementation. | Gastrointestinal diseases that interrupts the normal enterohepatic recycling of vit. D & its metabolites, resulting in their fecal loss. |
|--|--|
| <ul style="list-style-type: none"> ● House- or institution bound people. ● Atmosphere smog. ● Long term residence in far northern & far southern latitudes. ● Excessive covering of body with clothing. | <ul style="list-style-type: none"> ● Chronic steatorrhea (pancreatic) ● Malabsorption (gluten-sensitive enteropathy) ● Surgical resection of large parts of intestine. ● Bariatric surgery ● Formation of biliary fistulas. |
| Impaired synthesis of 1,25(OH)2D3 by the kidney. | Target cell resistance to 1,25(OH)2D3 |
| <ul style="list-style-type: none"> ● Nephron loss, as occurs in chronic kidney disease ● Functional impairment of 1,25(OH)2D3 hydroxylase (eg. In hypoparathyroidism) ● Congenital absence of 1,25(OH)2D3 hydroxylase (vit. D-dependency rickets type I). ● Suppression of 1,25(OH)2D3 production by endogenously produced substance (cancer). | <ul style="list-style-type: none"> ● e.g. absent, or diminished number of 1,25(OH)2D3 receptors, as in vit.D-dependency rickets type II. ● extremely rare |

2- Phosphate deficiency

Skipped by Dr

| Dietary | Impaired renal tubular reabsorption of PO ₄ |
|--|---|
| <ul style="list-style-type: none"> ● Low intake of phosphate. ● Excessive ingestion of aluminum hydroxide. | <ul style="list-style-type: none"> ● X-linked hypophosphataemia. ● Adult-onset hypophosphataemia. ● Other acquired & hereditary renal tubular disorders associated with renal phosphate loss (Fanconi's syndrome, Wilson's disease). ● Tumor-associated hypophosphataemia |

3- Systemic acidosis

Skipped by Dr

- Chronic renal failure, Distal renal tubular acidosis
- Ureterosigmoidostomy, Chronic acetazolamide & ammonium chloride administration

Other causes:

- Drug induced Osteomalacia (Anti-epileptic drugs), liver disease and Ca deficiency

¹: which normally provides 90% of vitamin D, while the other 10% is from the diet.

Clinical features

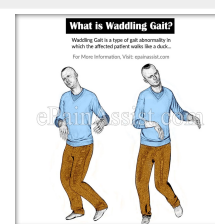
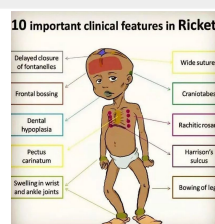
- Two thirds of patients are **asymptomatic**, incidental radiological finding, unexplained high alk phosph.
- Large skull, frontal bossing, **bowing of legs** (Permanent, will not resolve with treatment), deafness, erythema, bony tenderness
- **Fracture tendency:** vertebral crush fractures, tibia or femur. Healing is rapid.
- The clinical manifestations of osteomalacia in **adults usually go unrecognized because of the non-specific skeletal pain and muscular weakness**. Only when the disease is extensive, deformities occur with fractures of ribs, vertebrae and long bones.
- Clinically patients with osteomalacia have a characteristic **waddling gait**, that is due to the **proximal muscle weakness** and to the pain and discomfort during movements of the limbs.
- Some patients have severe muscular hypotonia and paradoxically brisk deep tendon reflexes.

Diagnosis



Lab tests

- Patients with osteomalacia go through phases of developments characterized by unique changes in the serum concentration of calcium, phosphate, PTH and vit D3 levels and the radio graphically assessed bone lesions.
- The underlying defect leading to these changes is the **decrease in the production of 1,25(OH)2D3** which is due to diminished availability of the major circulating metabolites of vit D 25OHD3.
- **The decreased 1,25(OH)2D3 results in decreased intestinal calcium absorption, decreased bone resorption, hypocalcaemia, increased PTH secretion as an adaptive response and hypophosphataemia**
- The **decreased Ca x Pho**. Product in serum is insufficient for the normal mineralization of bone and the osteomalacic process is initiated. There will also be high alkaline phosphatase.
- The increased PTH secretion and hypophosphataemia occur at the expense of osseous demineralization caused by hyperparathyroidism.



Imaging

- **X-ray:** growing bones vs mature bones, Subperiosteal resorption, looser's zones (pathognomonic)



Incomplete pseudofractures

Treatment

- Patients with osteomalacia due to simple dietary deficiency of vit D or lack of exposure to sunlight will **respond well to small daily doses of vit D, calcium and sun exposure**.
- Administration of oral doses of ergocalciferol(D2) or cholecalciferol (D3)(2000 IU daily) for several months will heal the bone disease and restores biochemical and hormonal values to normal in most cases.
- 1,25(OH)2D3 (**active form** (calcitriol)) has also been successful in the treatment of simple osteomalacia, **but not usually used**
- It is important to administer calcium to provide adequate calcium for bone mineralization (1-2 gm of elemental calcium daily).
- Serum ALP and PTH decrease slowly over several weeks but improvement in **radiological appearances may take several months**.
- Other forms of osteomalacia may need different preparations and doses of treatment e.g., osteomalacia secondary to malabsorption may require huge doses of vit D (200,000 IU orally) because of the poor absorption of the drug or even I.V./I.M. vit D (40,000-80,000 IU).

Summary

Primary hyperparathyroidism

- Most cases (80%) are caused by a single hyperfunctioning adenoma, with the rest (15%) resulting from parathyroid hyperplasia and, rarely (5%), parathyroid carcinoma.
- Hypercalcemia is associated with “stones, bones, moans, groans, and psychiatric overtones.”
- HyperCa treatment: Administer IV Fluids (first-line) and calcitonin. Add bisphosphonates if malignancy.

Secondary hyperparathyroidism

- Physiological compensatory hypertrophy of all parathyroids because of chronic hypocalcaemia.
- Causes: chronic kidney disease (Most common), vitamin D deficiency or malabsorption
- PTH levels are raised but calcium levels are low or normal, and PTH falls to normal after correction of the cause of hypocalcaemia where this is possible.

Tertiary hyperparathyroidism

- The development of apparently autonomous parathyroid hyperplasia after long-standing secondary hyperparathyroidism, most often in renal failure.
- Plasma calcium and phosphate are both raised, the latter often grossly so. (cf. 1ry hyperparathyroidism)
- Parathyroidectomy is necessary at this stage.

Osteoporosis

- A common metabolic bone disease characterized by low bone mass. It most often affects thin postmenopausal women with risk doubling after 65 years of age. Men are also at risk for osteoporosis, but the diagnosis is often overlooked.
- Commonly asymptomatic until fractures occur.
- Exam may reveal hip fractures, vertebral compression fractures (loss of height and progressive thoracic kyphosis), and/or distal radius fractures (Colles fracture) following minimal trauma
- Diagnostic test: DEXA (Osteoporosis: Bone mineral density (T-score) is 2.5 standard deviations (SDs) less than normal. Osteopenia: T-score between 1 and 2.5 SDs below normal.)
- Lifestyle modifications: Adequate calcium and vitamin D intake (supplementation can be used for prevention), smoking cessation, avoiding heavy alcohol use, and weight-bearing exercises.
- Best initial treatment: Bisphosphonates (eg, alendronate, risedronate, ibandronate, zoledronic acid) are used in the treatment of osteoporosis, not osteopenia.

Summary of Hyperparathyroidism

| Type | Calcium | PTH | Vitamin D | Phosphate |
|-----------|---------|------|-----------|-----------|
| Primary | High | High | Normal | Low |
| Secondary | Low | High | Low | High/Low |
| Tertiary | High | High | Low | High |

| | Type 1 osteoporosis (Post-menopausal) | Type 2 osteoporosis (Senile) |
|----------------|--|------------------------------|
| Age | Usually affects woman within 15 years of menopause | >70y/o |
| Type | Mainly trabecular | Trabecular and cortical |
| Rate | Accelerated | Not accelerated |
| Fracture sites | Distal radius (Colle's fracture), vertebra (Crush and wedge fractures) | Hip and femur neck fractures |

Lecture Quiz

Q1: A 65-year-old female is recently diagnosed with a compression fracture of the second lumbar vertebra. She was diagnosed with osteoporosis 3 years ago with T-score of -2.6 on bone densitometry. Her mother and sister were both treated for breast cancer. Her medical history includes hypertension and a deep venous thrombosis. Current medications include lisinopril, omeprazole, calcium, and vitamin D. Physical examination is normal except for midline tenderness over the lower back. In addition to continuing calcium and vitamin D and advising weight bearing exercise, which of the following is the most appropriate management for this patient's osteoporosis?

- A- Alendronate
- B- Calcitonin
- C- Raloxifene
- D- Estradiol
- E- No additional treatment

Q2: A 54-year-old woman presents to her GP complaining of a change in her breathing sound. She first noticed numbness, particularly in her fingers and toes, three months ago but attributed this to the cold weather. Her partner now reports hearing a high pitched, harsh sound while she is sleeping. Her BMI is 27. While measuring blood pressure, you notice the patient's wrist flexing. The most likely diagnosis is?

- A- Obstructive sleep apnoea
- B- Hypocalcaemia
- C- DiGeorge syndrome
- D- Guillain-Barré syndrome

Q3: A 70-year-old woman with a history of vertebral crush fractures presents to the osteoporosis outpatient clinic. Which of the following investigations is most useful to assess the extent of her osteoporosis?

- A- Spinal x-rays
- B- MRI scan
- C- Full blood count, bone and liver biochemistry blood tests
- D- Vitamin D levels
- E- DEXA scan

Q4: A 58-year-old postmenopausal woman presents to your office on suggestion from an urologist. She has passed three kidney stones in the past 3 years. She is taking no medications. Her basic laboratory work shows the following:
Na: 139 mEq/L K: 4.2 mEq/L HCO₃ : 25 mEq/L Cl: 101 mEq/L

BUN: 19 mg/dL Creatinine: 1.1 mg/dL Ca: 11.2 mg/dL

A repeat calcium level is 11.4 mg/dL; Po₄ is 2.3 mmol/L (normal above 2.5). Which of the following tests will confirm the most likely diagnosis?

- A. Serum ionized calcium
- B. Thyroid function profile
- C. Intact parathormone (iPTH) level
- D. Liver function tests
- E. 24-hour urine calcium

Q5: A 46-year-old woman comes to the physician for a routine health examination. She was last seen by a physician 3 years ago. She has been healthy aside from occasional mild flank pain. Her only medication is a multivitamin. Her blood pressure is 154/90 mm Hg. Physical examination shows no abnormalities. Serum studies show:

Sodium: 141 mEq/L Potassium: 3.7 mEq/L Calcium: 11.3 mg/dL Phosphorus: 2.3 mg/dL

Urea nitrogen: 15 mg/dL Creatinine: 0.9 mg/dL Albumin: 3.6 g/dL

Subsequent serum studies show a repeat calcium of 11.2 mg/dL, parathyroid hormone concentration of 890 pg/mL, and 25-hydroxyvitamin D of 48 ng/mL (N = 25–80). Her 24-hour urine calcium excretion is elevated. An abdominal ultrasound shows several small calculi in bilateral kidneys. Further testing shows normal bone mineral density. Which of the following is the most appropriate next step in management?

- A. Refer to surgery for parathyroidectomy
- B. Perform percutaneous nephrolithotomy
- C. Order CT scan of the chest and abdomen
- D. Begin cinacalcet therapy

THANKS!!

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*Send us your feedback:
We are all ears!*

