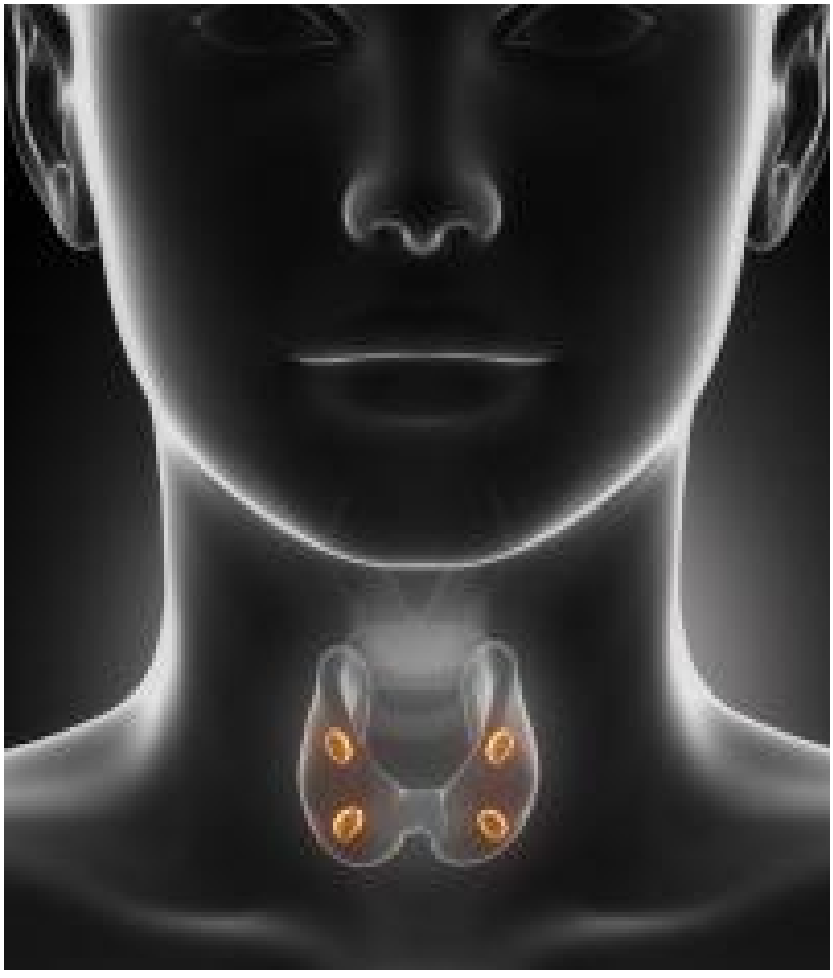
ENDOCRINE BLOCK



PARATHYROID GLAND & Ca^{+2} METABOLISM

Correction File

2-year-old woman presents to her physician with a month-long history of vague abdominal pain, constipation, and nausea and vomiting. She also has experienced diffuse bone pain over the past month, which she attributed to "just getting old." Physical examination reveals diffuse abdominal tenderness. Relevant laboratory findings are as follows:
Sodium: 140 mEq/L Calcium: 12.3 mg/dL Chloride: 110 mEq/L Bicarbonate: 26 mEq/L
Potassium: 4.0 mEq/L .. Phosphate: 2.0 mg/dL Blood urea nitrogen/creatine: 20:1.2 mg/dL

What is the most laboratory finding is strking ? Hypercalcemia

Mention the diffrential diagnissis of this case ?
1- Hyperparathyrodism **2-** Melignancy **3-** Intoxification to vitamin D
4- Paget's disease **5-** Alkail syndrome

What is the most common cause of hypercalcemia ?
In outpatients→ hyperparathyrodism / in inpatients→ melignancy

How is calcium regulated in the body?
1-Parathyroid hormone (PTH) stimulates osteoclasts to resorb calcium from bone; ↑calcium reabsorption in the distal convoluted tubules of the kidney; ↑production of 1,25-(OH)2 vitamin D by the kidney; & ↓ renal reabsorption of phosphate.
2-Vitamin D promotes calcium reabsorption from bone and the small intestine.
3-Calcitonin inhibits osteoclast activity, thereby ↓reabsorption of calcium from bone. In normal calcium homeostasis, calcitonin is likely not as significant.

If The patient is found to have elevated PTH & normal creatine. How does this help explain her clinical presentation?
The patient has primary hyperparathyroidism (as evidenced by high PTH, high calcium, and normal renal function)

Causes Of Hyperparathyrodism		
Primary	**Secondary**	**Tertiary**
(80%) due to a PTH-producing parathyroid adenoma that is not responsive to normal feedback regulation.	Elevated production of PTH in response to ↓calcium levels (as in renal failure)	Autonomous hyperparathyroidism in the setting of long- standing secondary hyperparathyroidism (end- stage renal failure).

Mention other signs and symptoms that can be found in this patient ?
Painful bones, renal stones (nephrolithiasis), abdominal groans (abdominal pain, nausea, vomiting, and anorexia), psychic moans (changes in mental status, concentration, and mood), and fatigue overtones.

What is the appropriate treatment for acute, severe forms of this condition?
Hydration. If the electrolyte abnormality persists, a loop diuretic can be used (to increase calcium excretion). If needed, calcitonin and bisphosphonates can also be prescribed.

What is the most appropriate long-term treatment for this patient?
Parathyroidectomy. Surgery for primary hyperparathyroidism has cure rates of 96%–98%.

65-year-old woman presents to the emergency department with sharp pain in her lower back after lifting some heavy objects while moving into a new home. The pain radiates to the anterior abdomen and is exacerbated by sitting and moving. On physical examination, she appears kyphotic with a "dowager hump." A plain film radiograph reveals multiple vertebral compression fractures.

What underlying condition contributed to these fractures?

Osteoporosis. This disease is characterized by reduced bone mass with microarchitectural disruption, porosity, and skeletal fragility. Osteoporosis is difficult to diagnose, as a fracture is often the first clinical manifestation.

What two factors contribute most to this condition?

The majority of postmenopausal women with osteoporosis have bone loss related to age and/or estrogen deficiency

Mention the mechansim how does the estrogen prevent osteoporosis ?

Estrogen naturally suppresses cytokines (such as interleukin-1 and -6) and receptor activator of nuclear κ-B ligand (RANKL,) which both increase osteoclast activity. RANKL interacts with RANK to promote development and function of osteoclasts. Denosumab is the first osteoporosis treatment that acts by blocking RANK-RANKL binding.

What secondary factors increase the risk of this condition?

1- Physical inactivity.
2-Calcium and vitamin D deficiency.
3-Prolonged glucocorticoid therapy.
4-Hyperparathyroidism.
5-Hyperthyroidism.

What tests and/or imaging tools can be used to test bone density?

Dual-energy x-ray absorptiometry (DEXA) scans are used to compare bone density to an age-matched reference population. Density more than two standard deviations below the expected range confirms the diagnosis.

What are the appropriate treatments for this condition?

1- The mainstay of treatment and prevention of osteoporosis is bisphosphonates such as alendronate and risedronate. This is in addition to continuation of both calcium and vitamin D supplementation. These agents act by decreasing osteoclastic bone resorption. One of the side effects of bisphosphonates is esophagitis; thus, patients are instructed to take it with water and while standing or sitting upright (and remain so for at least 30 minutes).
2-Raloxifene, a selective estrogen receptor modulator is also used in refractory cases.
3- Intermittent administration of recombinant parathyroid hormone has also shown to be effective.

Organs involved in calcium metabolism : Skeleton, GIT and kidney

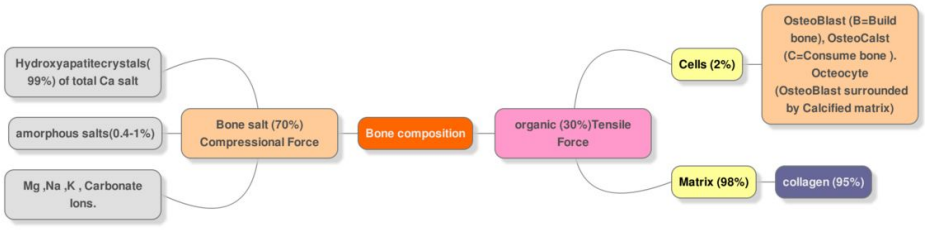
Protein-bound calcium:
• Most of this calcium is bound to albumin & much smaller fraction is bound to globulin
•Binding of calcium to albumin is pH-dependent
•Acute respiratory alkalosis increases calcium binding to protein thereby ⬇ ionized Ca level

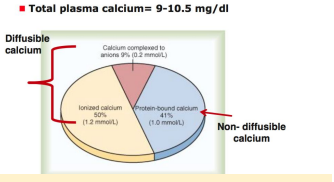
Calcium ions in ECF and cellular fluids is essential in :-
Neuromuscular excitibility , hormonal secretion, enzymatic regulation, blood coagulation and 2nd messenger

Phosphorous is an essential mineral necessary: for ATP and cAMP second messenger systems
- Phosphate plasma concentration is around 4 mg/dL.
- **Forms:** Ionized (diffusible) around 50% of total
- un-ionized (non-diffusible) and protein- bound (50%)
- Calcium is tightly regulated with Phosphorous in the body.

Functions of phosphorus : -cellular metabolism -source of cellular energy -as a part of membranes.

Mention the site of absorbtion of GIT ?
1- Duodenum : active transport 2-small instenine ; concentration gradient

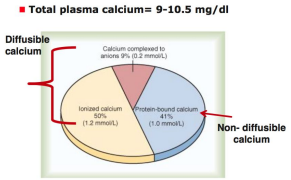




Tetany < 9-10.5 > Renal stones

REGULATION OF PLASMA CALCIUM AND PHOSPHATE CONCENTRATIONS
- **non**hormonal Mechanisms Can Rapidly Buffer Small Changes in Plasma Concentrations of Free Calcium
- Hormonal Mechanisms Provide High-Capacity, Long-Term Regulation of Plasma Ca & Phosphate Concentration

Amorphous salts:
- A type of exchangeable calcium
- Play role in rapid regulation of ionized Ca^{+2} level in ECF
- always in equilibrium with Ca^{+2} in ECF



Hormones involved in calcium metabolism : PTH, calcitonin, Vit D and PTH related peptide.
Formation of Vitamin D : see slide (biochemistry)
Function: ⬆ Ca Blood Level How ?
1.Intestinal tract. Has a potent effect to ⬆ calcium & phosphate absorption
2.Renal: ⬆ Renal calcium and Phosphate absorption
3.Bone : Bone absorption.
4- stimulates differentiation of immune cells.

Effects of Vitamin D on Bone & Its Relation to Parathyroid Hormone Activity.
-Vitamin D in smaller quantities :
- promotes bone calcification (by ↑ calcium and phosphate absorption from the intestine and enhances the mineralization of bone.
- The administration of extreme quantities of vitamin D causes absorption of bone:
* by facilitating PTH action on bones. * number & activity of esteoclasts.

How to Control Vit D: 1- low Ca^{+2} ions 2- prolactin 3- PTH All stimulate renal 1,alpha hydroxylase.

Parathyroid hormone: from parathyroid glands, stimulated by hypocalcaemia.
Function : ⬆ plasma Ca and ⬇PO in blood.

Mechanism: acts via 2nd messenger mechanism utilizing cAMP

Act on bone resorption → release Ca (slow effect)	**Act on kidney** reabsorbtion of Ca & excretion of PO(rapid effect)	**Act on intestine**
- Activation of osteoclasts - Depression of osteoblastic activity - Stimulates the formation of new osteoclasts	1. ⬇ phosphate reabsorption from the proximal convoluted tubules (phosphaturic action). A- ⬆Phosphate excretion in the urine B- ⬇ plasma phosphate conc. 2. ⬆ Ca^{+2} & Mg ions reabsorption from the distal convoluted tubules, collection ducts and ascending loop of Henle. 3. ⬆ Formation of 1,25 vit D3 in the kidney. stimulate formation of 1-alpha hydroxylase enzyme.	⬆ absorption of calcium and phosphate indirectly through stimulating formation of 1,25 – $(OH)_2$-D_3 in kidney

Calcitonin hormone: from thyroid (parafollicular or C cells), stimulated by hypercalcaemia.
other causes of secretion : Estrogen,gastrin, glucagon,secretin , CCK, and B-adrenergic stimulation
Function: ⬇Ca^{+2} in blood very rapidly through (opposite effect to PTH)
On bones : ⬆ Ca^{+2} depostion of bone and Inhibt bone resbsorbtion
On kidneys : ⬇Ca^{+2} reabsorbtion & ⬆ Ca^{+2} excretion in addtion to phosphate.

Abnormalities

RICKETS (In children):- Normal formation of the collagen matrix BUT Incomplete mineralization (poor calcification) → ↓Soft Bones→ bone deformity. It is caused by lack of Vit-D → lack Ca^{+2} & PO in ECF & tetany
Sex linked gene on the X chromosome.
Treatment of Rickets:
supplying adequate calcium and phosphate in the diet and, administering large amounts of vitamin D.

Tetany in Rickets
Early Stage :
- no tetany
- (PTH stimulate osteoclastic absorption of bone)
- ECF Ca level is normal

When the bones finally become exhausted of Ca → Ca level falls rapidly.
blood level of Ca falls below 7 mg/dl
→ signs of tetany: (positive Chvostek's sign)
→Death: tetanic respiratory spasm

OSTEOMALACIA (In adult) :- Demineralization (poor calcification) of preexisting bones→ More Susceptibility to Fracture. caused by severe deficiencies of Vit-d & Ca as a result of steatorrhea.
Renal rickets : is caused of prolonged renal disease which will effect the enzyme a-hydrxylase

Osteoporosis:- reduction in bone mass. Most affected: vertebral compression & hip fracture. Post-menopausal women > men lose bone mass (1ry osteoporosis). it is the most common of all bone disease.. it effect Both the bone salt & organic matrix.
2ry Osteoporosis :-Risk Factors:-Cushing's syndrome, Long term glucocorticoids therapy, Hyperparathyroidism ,Hyperthyroidism Vit D disorders ,Certain malignancies.

the cause of the diminished bone:
- the osteoblastic activity in the bone is usually < normal so the rate of bone osteoid deposition is depressed.
- excess osteoclastic activity.

causes of osteoporose :
(1) lack of physical stress (2) malnutrition
(3) lack of vitamin C
(4) postmenopausal lack of estrogen
(5) old age (6) Cushing's syndrome

Hyperparathyrodism

Primary	Secondary
❖ Hyperclacemia ❖ Hypophosphatemia ❖ Multiple bone cysts ❖ Broken bone ❖ ⬆ Alkaline phosphate	due Ca++ ⬇ in ECF causes : 1- ⬇calcium diet 2-Pregnancy 3- Lactation 4-Ricktes 5- Osteomalcia 6- Chronic renal failure

Manifestations

•CNS depressed •Peripheral nervous system depressed •muscle weakness
•Constipation •Abdominal pain •Peptic ulcer
•Decrease appetite •Depressed relaxation of the heart during systole.
•Calcium containing stones in kidney
•Parathyroid poisoning: Precipitation of calcium in soft tissues occur when Ca2+ > 17mg/dl death

Hypoparathyroidism (rare)

causes - Injury to the parathyroid glands (surgery). -Autoimmune.
symptoms (due to hypocalcaemia)
• Tingling in the lips, fingers, and toes
• Muscle cramps & pain in the face, hands, legs, & feet
• Malformations of the teeth, including weakened tooth enamel.
• Loss of memory
• Dry hair, brittle nails, & dry, coarse skin
• Cataracts on the eyes
•Headaches
Signs of Hypoparathyroidism
• Tetany can be overt or latent
• Chvostek's sign: (Positive) Tapping the facial nerve as it emerge from the parotid gland in front of the ear causes contraction of facial muscles.
• Trousseau's sign (Positive) Arresting (stopping) blood flow to the forearm for few minutes (e.g., by sphygmomanometer) causes flexion at the wrist, thumb and metacarpophalangeal joints.
• Delayed cardiac repolarization with prolongation of the QT interval
• Paresthesia
Treatment: Calcium carbonate and vitamin D supplements

Pseudohypoparathyroidism:-(have normal parathyroid gland but failed to response to PTH and PTH injection.

Estrogens: -

stimulate osteoblast -inhibit osteoclast -enhance PTH secretion so → ⬇ Ca loss from bone.
Pregnant women needs more Ca, bone turn over ⬆: osteoporosis (hip bone). During lactation 280-800mg of Ca lost in milk / day, so mother compensate by :
1- intestinal absorption 2- bone resorption 3- renal excretion of Ca

68-year-old woman Presents to the emergency department with right wrist pain, swelling, and displacement following a fall on the stairs at home .Past medical history showed previous fractures and has been treated with corticosteroid .

How can further fractures be prevented?
By Replacing what is missing (Ca supplements, Vit D, Na fluoride.)

What are the appropriate treatments for this condition?

- The mainstay of treatment and prevention of osteoporosis is bisphosphonates (such as alendronate and risedronate) in addition to continuation of both calcium and vitamin D supplementation.
- Raloxifene, a selective estrogen receptor modulator is also used in refractory cases.
- Intermittent administration of recombinant parathyroid hormone has also shown to be effective.

so generally the drugs that can be used in treatment of osteoporosis:

<table>
<tr><th colspan="2">Anti-resorptive Agents</th><th>Bone Anabolic Agents</th></tr>
<tr><td>Bisphosphonates</td><td>Androgen Analoges</td><td rowspan="2">Teriparatide</td></tr>
<tr><td>Rankl Inhibitors</td><td>Estrogen Analoge</td></tr>
<tr><td>Calcitonin</td><td>Selective Estrogen Receptor Modulators</td><td rowspan="2">Strontium</td></tr>
<tr><td colspan="3">STRONTIUM (dual action)</td></tr>
</table>

Since Bisphosphonates are the most commonly used treatment of osteoprosis , what is their MOA ?
Analogs to pyrophosphate which is a natural inhibtor of mineralization → thereby inhibiting activation of enzymes that utilize it in the cholestrol synthetic pathway within osteoclast → inhibiting osteoclast function → prevent bone resorption

What are the other indications ?

- Paget's Disease
- Malignancy- associated hypercalcaemia

When should we consider options other than alendronate, (and other bisphosphonates) ?
if the patient has Peptic ulcer , esophageal reflux or Decreased renal function .

How can we avoid the Gastro-esophageal reflux and ulcerations associated with the use of bisphosphonates ?
By taking the dose with large amount of water on empty stomach while sitting in upright

What could be the other ADRs in case of admenstring Bisphosphonates by IV ?

- Flue like manifestations upon IV infusion
- Osteo-necrosis of the mandible > jaw and usually after dental surgical procedures → due to activation of matrix metalloproteinase that cause lysis.
- Atrial fibrillation > women with alendronate & zolidronate

How to prevent the previous ADRs ?
we start first with I.V drugs than we switch to the Oral preparations.

What is the mechanism of action of DENOSUMAB ?

it mimics the activity of osteoprotegrin by binding to RANKL (ligand) expressed by osteoblasts → inhibits it from interacting with RANK (the osteoclast cell-surface receptor) expressed on preosteoclasts → ↓ osteoclastogenesis → prevent bone resorption .

What are the situations in which denosumab should be avoided ?

- patients with hypocalcemia.
- TB patients

What should be done prior to administration of DENOSUMAB in patient with hypercalemia ?

Correcting Ca & Vit D levels before starting denosumab .

What are the main ADRs of RANKL inhibtors ?

urinary & respiratory infections , Eczema & skin rash , Constipation , Cataract and Joint pains

Elderly female came with sever osteoporosis what is the best treatment can be used and how does it work ?

STRONTIUM , it has both anabolic & antiresor-ptive effects resulting in a rebalance in favor of bone formation.

what are the Interactions of this drug and what should be done to avoid them ?

- Food specially containing milk+ its products
- Antacids
- Oral tetracycline & quinolones

Therefore, 2 hrs spacing for precautions

in which situation it should be contraindicated ?

- In severe renal disease.
- In hypersensitivity to it
- In increased risk of thromboembolism & MI
- In phenylketonuria

51-year-old woman presents to the clinic because her periods have become irregular and this irregularity began about 3 years ago. She complains of hot flashes that occur a few times and she was admitted to hospital six months ago after fracturing her hip bone .

What are the appropriate treatments for this condition?

Hormone Replacement Therapy (HRT)

Explain the options of treatment wither this female undergo hysterectomy or not ?

Estrogen In fertile period if hysterectomy OR Estrogen with progestins if uterus is present.

What could be a better option of treatment if the patient is elderly male and has osteoporosis ?

Androgen and we can also use Selective Estrogen Receptor Modulators

What could be used as a preventive therapy of osteoporosis and its complications ?

Selective Estrogen Receptor Modulators . EX (RALOXIFENE) ,
it may ↑ risk of thromboembolic events and ↑ hot flushes .

What are the principal factors involved in calcium metabolism and bone remodeling?
1- Parathyroid hormone (PTH) 2- Teriparatide. 3- Vitamin D. 4- Calcitonin.

What are the target tissue of vit D and calcium?
1- Bone (Absorption and resorption) 2- Kidney (reabsorption) 3- Intestine (calcium absorption).
* Parathyroid hormone response to low plasma calcium level.

What are the effects of PTH?
Effects on bone: mobilization of calcium & phosphate from bone in response to hypocalcemia.
Effects on kidney: 1- ↑ calcium reabsorption.
2- ↑ formation of calcitriol (active form of vit D).
Effects on GIT: ↑ absorption of calcium.

Response to PTH:
1- intermittent administration of PTH for 1 to 2 hours/day lead to net stimulation of bone formation.
2- continuous exposure to elevated PTH leads to bone resorption & risk of fracture.

What are the clinical uses of PTH?
- Treatment of severe osteoporosis.
- Resistancecases failed to response to other medications.

Teriparatide: It is Synthetic polypeptide form of PTH (PTH analogue).
Also it is given once daily by subcutaneous injection.

What are the therapeutic uses of Teriparatide?
1- should not be used routinely ue to carcinogenic effects. 2- Use in severs osteoporosis or with patient who is not responding to other drugs. 3- For treatment of osteoporosis in people who have a risk of getting fracture.
4- Good for postmenopausal osteoporosis.

What are the Adverse effects of Teriparatide?
1- Carcinogenic effect (osteosarcoma). 2- Diarrhea, heart burn, nausea. 3- Headache, leg cramps.
4- Hypotension when standing. 5- ↑serum calcium which can lead to kidney stones.

What are the contraindications of Teriparatide?
1- Should not be used by people with increased risk for bone tumors (osteosarcoma) including:
- people with agets disease of bone.
- People who had radiation treatment involving bones.
- Children not recommneded.

Mention the therapeutic use of vit D?
1-Rickets 2- Osteoporosis 3- Psoriasis 4- Cancer prevention (prostate and colorectal)

What are the effects of Vitamin D?
In bone: Activation of osteoblast cells.
In kidney: ↑ reabsorption of Calcium and phosphat.
In GIT: ↑absorption of calcium.
* Calcitonin is produced by parafollicular cells (C cells) of thyroid gland. it relesed when there is an ↑ of calcium in the blood.
Mention the clinical uses, routes of adminstration and adverse effects ?
Clinical uses : Osteoporosis and Hypercalcemia,Paget disease, Milk-alkail syndrome and reduce calcium excertion
Route of administration: subcutaneous, nasal spray & solution (calcitonin salmon).
Adverse effects: Nausea, flushing of face & hand, nasal irritation & local inflammation at site of injection.

Where we can find both vitamin D2 and D3 and how we get it?

Ergocalciferol (vitamin D2) found in plants while Cholecalciferol (vitamin D3) found in animal tissue, vitamin D3 is synthesized in the skin by the sunlight while vitamin D2 is derived from ergosterol in lower animal and plants.

vitamin D metabolism

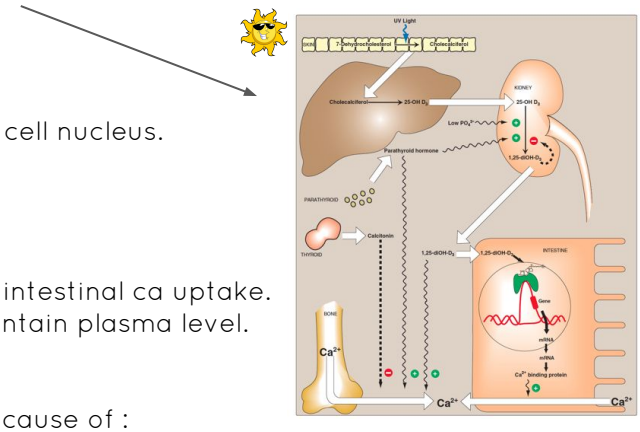
1- in skin Cholecalciferol (vitamin D3) is derived from 7-dehydrocholesterol by the sunlight.

2- In liver vitamin D3 is converted to 25-hydroxycholecalciferol (calcidiol) by the enzyme 25-hydroxylase.

3- In kidneys the 1-a-hydroxylase enzyme converts 25-hydroxycholeclciferol to 1,25-dihydroxycholecalciferol (active).

4- Active vitamin D is transported in blood by gc-globulin protein.

5-In the intestine -Vit D binds to intracellular receptor protiens so the receptor complex inracts with Target DNA in cell nucleus . it stimulates the synthesis of calcium binding protien for instenal uptake



What are vitamin D action?

it action typical of steroid hormones:
1- it binds to intracellilar receptor proteins.
2- The receptor complex interacts with target DNA in cell nucleus.
3- then stimulates or represses gene expression.

Write three functions of vitamin D?

1- Regulates plasma level of ca and phosphate.
2- stimulates synthesis of calcium-binding protein for intestinal ca uptake.
3- Mobilizes calcium and phosphate from bone to maintain plasma level.

What are the types and causes of rickets?

1- Nutritional rickets causes is vitamin D deficiency because of :
1- poor nutrition 2- insufficient exposure to sunlight 3- renal osteodystrophy. 4- hypoparathyroidism.
2- Inherited rickets causes:
1- vitamin D-dependent rickets (type 1 and 2) which is rare due to genetic disorders.
2- vitamin D deficiency because of genetic defects in: - Vitamin D synthesis - Vitamin D receptor.

Osteoporosis is reduction in bone mass per unit volume. Post-menopausal women lose more mass than men (primary osteoporosis). bone matrix composition is normal but it is reduced. increase fragility of bone and susceptibility to fractures.

What are the biomarkers of osteoporosis?

Bone formation markers:
1-Osteocalcin
2- bone-specific alkaline phosphatase.
3- P1NP (procollagen type-1 amino teminal propeptid

Bone resorption markers: 1- CTX-1 (carboxy-terminal cross-linked telopeptides of type-1 collagen).

What are the prevention of osteoporosis?

1- Good diet and exercise prevent osteoporosis
2- Hormone replacement therapy in menopause may prevent osteoporosis.

How to diagnose secondary osteoporosis ?

By Biochemical tests (while are not enough in Primary)

THANK YOU FOR CHECKING OUR TEAM..

DONE BY :

- Mohammed Almahmoud
- Khaleel ALHendas
- Futoon ALMutairi
- Omar alayed

Reviewed By :

- Sarah Alsalman
- Abdulrahman Alkaff

'The doctor said I need more calcium in my diet, so I'm switching from dark chocolate to milk chocolate.'