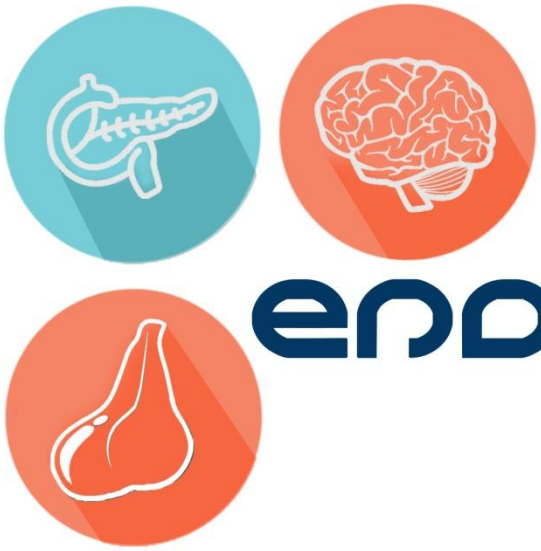

endocrine system

Pharmacology

Sheet Slide

number	5
Done by	Enas Ajarma
Correction	Abdullah AlZibdeh
Doctor	Suhail

ربّ اشرح لي صدري , ويسر لي أمري , واحلل عقدة من لساني , يفقهوا قولي

Students' questions about the last lecture :

- Due to the fact that carbemazole is a pro-drug which is converted into the active form inside the body , where is the actual site of conversion ? in the blood .

- Regarding the figure which correlates blood calcium level with PTH secretion (slide #4 of parathyroid) , be aware that the major regulator of PTH secretion is the free form of calcium (ionized calcium) not the bound calcium.

Calcitonin

The third hormone that is involved in calcium metabolism , but it has a minor role as compared to PTH & Vit. D . it is a peptide (32 a.a) synthesized in parafollicular cells of the thyroid gland , it is regulated by ionized calcium .

Hypercalcemia increases calcitonin synthesis & release , opposite to PTH , whereas Hypocalcemia results in a decrease in calcitonin .

Effects :

- Inhibits bone resorption ; because it inhibits the movement of calcium & phosphate from the bone .

- On kidney , it increases calcium & phosphate excretion or inhibits their reabsorption .
- On the intestine , it decreases calcium & phosphate absorption (questionable).
  The net effect is decrease calcium and phosphate.

May be more important in regulating bone remodeling than in Ca++ homeostasis: Evidence: Chronic excess of calcitonin does not produce hypocalcemia and removal of parafollicular cells does not cause hypercalcemia (PTH and Vitamin D3 regulation dominate).

	PTH	Vit. D	Calcitonin
$[Ca^{++}]$	↑	↑	↓
$[PO_4^{--}]$	↓	↑	↓

Disorders affecting the parathyroids :

♣ **Hyposecretion (hypoparathyroidism):**

➢ Causes:

- Thyroidectomy (most common cause): there is no way to remove the thyroid without removing them when they are located on its posterior surface.
- Idiopathic

- decrease sensitivity of target tissues to PTH (pseudohypoparathyroidism) ; the patient has normal blood

levels of PTH , but it has manifestations of hypoparathyroidism (calcium is low , and phosphate is high). This is completely different from desensitization. It could be due to complete absence of the receptor or any modification in its structure.

**(0-13 min)

- Symptoms of hypoparathyroidism:

Are those of hypocalcemia :

Parasthesia, tingling lips, fingers, and toes, carpopedal spasm, muscle cramps, tetanic contractions, convulsions (seizures) .

Bronchospasm, Depression, anxiety, abdominal pain and Cataract.

- Lab tests

- ↓ blood [Ca++]

- ↑ blood [PO4--] ;

in fact hyperphosphatemia has no clinical significance ,while hypophosphatemia has a clinical significance.

- ↓ urinary [cAMP] ;

cAMP is used to assist the function of parathyroids , so low levels mean hypoparathyroidism ,while high levels mean hyperparathyroidism

- ↓ urinary [PTH]

Secreted by active secretory mechanism.

- ↓ urinary [Ca++]

- ↓ urinary [PO4--]

- Rx of hypoparathyroidism:

Drug of choice for chronic cases:

- Vitamin D: (remember: hyperphosphatemia has no clinical significance, while hypophosphatemia has a clinical significance.)
Calcifediol, Calcitriol, Ergocalciferol, α-Calcidol , Dihydrotachysterol.

NOTE1: cholicalciferol (inactive form of Vit.D3), it has to be activated first in the liver then in the kidney, but if you have a patient with impairment in the liver or the kidney, you should give him the final product of Vit.D which is **Calcitriol**.

NOTE2: administration of Vit.D will increase phosphate which is already high due to hypoparathyroidism , but as we said hyperphosphatemia has no clinical significance .

Drug of choice for acute cases:

very rare. In this case, we cannot wait for the PTH to move the calcium, so instead of giving PTH, we give:

- Ca++ supplement, Ca++ rich diet and Ca++ salts (chloride, gluconate, carbonate...)

NOTE : in general hypoparathyroid patients are best treated with Vit. D , but if they were specified as acute they should be treated by calcium supplements.

- Teriparatide (synthetic rPTH)

It is not effective in pseudoparahypothyroidism. It is recently approved in the management of osteoporosis; although

hyperparathyroidisim leads to osteoporosis, but they found that small doses could be effective by increasing bone formation
** (13-23min)

♣ **Hypersecretion (hyperparathyroidism):**

➢ Causes :

- 1º hyperparathyroidism (adenomas)
- 2º hyperparathyroidism: 2º to any cause of hypocalcaemia e.g. malabsorption syndrome, renal disease.
- 3º hyperparathyroidism Results from hyperplasia of the parathyroid glands and a loss of response to serum calcium levels; this disorder is most often seen in patients with chronic renal failure.

➢ Symptoms of hyperparathyroidism:

Are those of hypercalcemia:

Generalized weakness and fatigue, depression, bone pain, muscle pain (myalgias), decreased appetite, feelings of nausea and vomiting, constipation, polyuria, polydipsia, cognitive impairment, kidney stones (because of calcium secretion in the urine) and osteoporosis…

Hypercalcaemia also can result from other diseases (including some cancers, some cancer therapies, tuberculosis,..), and in such cases, the patient is vulnerable to kidney stones.

➢ Lab. Tests :

- ↑ blood [Ca++]
- ↓ blood [PO4--], considered as a problem and we have to replace with phosphate.
- ↑ urinary [cAMP]
- ↑ urinary [PTH]
- ↑ urinary [Ca++]
- ↑ urinary [PO4--]

Bone x-ray → bone decalcification

➢ Rx of hyperparathyroidism:

- Low Ca++ diet
- Na+ phosphate (to replace the decreased levels of phosphate)
- Steroids e.g. Prednisolone... ↓ Ca++ absorption from GIT
- Calcitonin
- Surgery (best Rx; remove the parathyroids and replace with Vit.D to treat hypoparathyroidism)
- **Cinacalcet** (calcimimetic (calcium like effect)); it has the same negative feedback effect on PTH secretion like calcium , but does not elevate calcium levels), (oral tab). It is used to treat patients with chronic kidney disease who are on dialysis & also used to treat patients with 1º & 2º hyperparatyroidism & cancer of parathyroid gland.

- Diuretics e.g. Furosemide (↑ Ca++ excretion)
- Plicamycin; inhibits bone resorption (anti-cancerous drug)
- Biophosphonates

Etidronate, Pamidronate… ↑ bone formation and ↓ bone resorption (also used in osteoporosis) .

Paget's disease

It is a rare bone disorder characterized by deminaralization of bone (loss of calcium in bone). This disease is characterized by disorganized bone formation, ↑ bone resorption, fractures, spinal cord injuries, deafness…

Rx:

- Salmon calcitonin (drug of choice), S.C, I.M
- Biophosphanates, orally

Etidronate, alendronate, residronate, pamidronate…

**(23-30 min)

Osteoporosis

➢ <u>Definitions:</u>

- **Osteoblasts:** Fibroblasts essential for bone formation and mineralization of bone matrix.
- **Osteoclasts:** Cells that break down bone and are responsible for bone resorption.
- **Bone matrix:** The intercellular substance of bone formed by osteoblasts, consisting of collagenous fibers, ground substance, and inorganic salts.

- **Bone resorption:** A process by which osteoclasts break down bone and release minerals resulting in transfer of Ca++ from bone to blood

- **Bone turnover=Bone remodeling:** Removal of old bone and its replacement by new bone. Bone is constantly being remodeled throughout adult life and in general, the processes of bone resorption and formation are "coupled" so that there is no net change in bone mass. During growth osteoblast activity is more than that of osteoclsts (bone formation) but in diseases such as osteoporosis bone resorption is greater than bone formation, leading to a net decrease in bone mass .

- Definition of osteoporosis:

A reduction in bone mass per unit volume leading to fractures particularly the spine, distal radius and proximal femur. It is often known as " the silent thief "because bone loss occurs without symptoms.

- Etiology:

- Hormone deficiencies Estrogen deficiency in ♀'s; androgen deficiency in ♂'s

Postmenopausal osteoporosis is the most common form of osteoporosis, especially for those who have menopause at early stages such as at 35 years old. The greatest amount of bone density is lost during the first 5 years after the onset of menopause (start therapy early).

Androgens are anabolic steroids needed for protein synthesis, in contrast to glucocorticoids, which are catabolic.

- Thyrotoxicosis
- Hyperparathyroidism
- Alcohol consumption
- Smoking
- Low Ca++ diet
- Malabsorption syndrome
- Drug-induced osteoporosis:

Glucocorticoids (Cushing's syndrome) ,GnRH agonists (used for prostate cancer in old males), Anticonvulsants and Heparin.

➢ <u>Osteoporosis risk factors:</u>

- Female, menopause (early menopause → high incidence)
- Family history of osteoporosis
- Limited physical activity
- Low Ca++ diet
- Low vit. D diet or limited exposure to sunlight
- Caffeine consumption
- Smoking
- Alcohol intake

- Chronic use of glucocorticoids or anticonvulsants

➢ Diagnosis of osteoporosis: -

- No symptoms in early stage

Symptoms are Fractures of vertebrae, hips, or wrist Low back pain Neck pain...

- lab. Tests X-ray, bone mineral density (BMD; densitometry; also used to evaluate the progress with therapy), blood biochemistry, bone biopsy if necessary.

➢ Treatment of osteoporosis:

Good outcome if started early. Late osteoporosis or patients with fracture 2º to osteoporosis although they resist Rx but therapy could limit further fractures.

Effective drugs:

- Estrogen + progesterone (small doses of estrogen after menopause protect against MI and osteoporosis , but estrogen could lead to uterine cancer , so to avoid this we add progesterone to ↓ incidence of uterine cancer. Also estrogen increases the synthesis of clotting factors which increases incidence of thromboembolic phenomena).

- Androgen therapy

- Selective estrogen receptor modulators (SERM) e.g. **Raloxifene** (has estrogenic effects on bone & anti- estrogenic actions on the uterus and breast).

- Vit. D + Ca++

- Biophpsphanates :Etidronate, Alendronate…

- Calcitonin (intranasal)

- Small dose of fluoride (slow release sodium fluoride), increases bone formation.

- Synthetic rPTH (Teriparatide), recently approved by FDA in the management of osteoporosis

- Denosumab (given SC every 6 months) An inhibitor to Receptor activator of nuclear factor kappa-B ligand (RANKL) recently approved for use in postmenaupausal osteoporosis, drug-induced bone loss and in bone metastasis. RANKL is a protein present on osteoblasts and activates activity of osteoclasts leads to osteoporosis.
This drug is associated with many side effects: Hypocalcaemia, serious infections-skin, bladder, heart=endocarditis, high blood cholesterol levels, pain in jaws and back...

➢ <u>Postmenopausal osteoporosis Rx or prophylaxis:</u>

- Estrogen + alendronate + Ca++& vit. D + intranasal calcitonin
- Raloxifene + alendronate + Ca++& vit. D + calcitonin
- Estrogen + progesterone
- Raloxifene + alendronate
- Teriparatide (rPTH) (S.C)
- Denosumab

The treatment depends on the response, the tolerance of the patient to the side effects of the drug, and the compliance.
** (30-47 min)

“MEDICINE IS ONLY FOR THOSE WHO CANNOT IMAGINE DOING ANYTHING ELSE “

BEST OF LUCK!