Key words summary

These summaries **do not include the whole lecture**, we just wrote what we think it is important.

Good luck

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Editing file

★ **the drug of choice.** ⊗ **Inhibit\block**

« لو أن الناس كلما استصعبوا أمرًا تركوه؛ ما قام للناس دنيا ولا دين! »

عمر بن عبدالعزيز

Subclass	Drug	Indication	Comment
L1 | Drugs used Hyperthyrodism			
Thioanides Inhibit synthesis of thyroid hormones by inhibiting the peroxidase enzyme + PTU blocks the conversion of T4 to T3 in peripheral tissues	Propylthiouracil (PTU) Methimazole = Carbimazole (CMZ)	PTU: - Recommended in pregnancy. - Recommended in breast feeding. CMZ: shouldn't be given to preg. (teratogenic) & breast feeding.	P.K: PTU: 80-90% protein binding, CMZ: Most of the drug is free. ADRs: Both: Skin reactions, Agranulocytosis, PTU: ANCA +ve vasculitis.
Iodine • Inhibit thyroid hormone synthesis and release. • Block the peripheral conversion of T4 to T3. • The effect is not sustained.	Organic iodides: iopanoic acid or ipodate Potassium iodide	- Prior to thyroid surgery to decrease vascularity & size of the gland. - Following radio-active iodine therapy	C.I: shouldn't be used a single therapy. Pregnancy. Toxicity: Iodism symptoms.
Radioactive iodine (RAI) ^{131}I isotope (therapeutic effect due to emission of β rays) → Accumulates in the thyroid gland and destroys parenchymal cells, producing a long-term decrease in thyroid hormone levels.	^{131}I isotope	- Hyperthyroidism mainly in old patients. - Graves' disease. - Patients with toxic nodular goiter - As a diagnostic.	Disadvantages: - High incidence of delayed hypothyroidism. - Large doses have cytotoxic actions (necrosis of the follicular cells. - C.I: in pregnancy.
β blockers Adjunctive therapy to relief the adrenergic symptoms of hyperthyroidism such as tremor, palpitation, heat intolerance and nervousness. e.g. **Propranolol**, Atenolol , Metoprolol			C.I: Asthmatic patients in case of Propranolol
- During pregnancy	Before preg.: better to start w\ ^{131}I or subtotal thyroidectomy. During preg.: ★ PTU is the drug of choice.		
Management of hyperthyroidism due to Graves' disease	Sever	Mild-moderate	
	Radioiodine is preferred in adults.	Start w\ methimazole, if preg or lactating women → use PTU.	
L2 | Drugs used in hypothyrodism			
Levothyroxine (T4)	★ The drug of choice for replacement therapy in almost all cases of hypothyroidism.	P.K: stable, long T1\2. - Absorption is increased when given on empty stomach. ADRs: child: restlessness, insomnia, accelerated bone maturation. Adults: cardiac arrhythmia & other hyperthyroidism symptoms. C.I: old pts & pts w\ cardiac problems: start T4 w\ reduced dose.	
Liothyronine (T3)	- More potent & rapid action than levothyroixine. - Short T1\2 (not for routine replacement therapy.		
Liotrix	- Combination of synthetic T4 & T3 in a ratio 4:1 that attempt to mimic the natural hormonal secretion - High cost, lack of therapeutic rationale.		
Myxedema coma	★ Loading dose of **levothyroxine** I.V. - Liothyronine I.V → for rapid response but it may provoke cardiotoxicity. - Hydrocortisone → used in case of adrenal & pituitary insufficiency.		

Subclass	Drug	Indication	Comment
L3 | Drugs used in Osteoporosis			
Bisphosphonates - Structurally similar to pyrophosphate (preventing its action by ⊗ the enzymes responsible for utilizing it. - stick to calcium → concentrate in bones, bound to hydroxyapatite decreasing its solubility and making it more resistant to osteoclastic activity. - Block steps in cholesterol synthetic pathway.	Nitrogenous: **Alendronate[1], Ibandronate[2], Risedronate[3], Zoledronate[4]** → must be given on an **empty** stomach / or infused IV + with a full glass of water.	- ★ Osteoporosis, 2ndry to menopause, glucocorticoids. - Paget's disease. - Malignancy + hyperCa^{2+} C.I: - ↓ renal function. Peptic ulcer\esophageal reflux	ADRs: - Gastro-esophageal reflux. - osteo-necrosis of the jaw (after dental surgical procedures) - Atrial fibrillation w\ **1** & **4**. Dosing: - Give it in upright position. - Separate 4h before giving Ca, Mg, Al containing drugs.
RANKL Inhibitors - binds to RANKL, expressed by osteoblast → ⊗ RANKL from interacting with RANK expressed on preosteoclasts - binds also to mature osteoclast promote its apoptosis. → ↓ **bone resorption**	**Denosumab** → Fully human human monoclonal antibody.	Taken S.C. \ 6 months ADRs: - Infections: urinary & respiratory - Eczema & skin rash. - Constipation & cataract. - Joint pain. C.I: pts w\ hypocalcemia.	
Strontium Dual action: 1- on osteoblast: agonist for Ca sensing R (CaSR) → enhances differentiation of preoteoblast to osteoblast → ↑ bone formation. 2- On osteoclast: agonist for CaSR → ⊗ differentiation of preosteoclast to osteoclast → ↑ osteoclast apoptosis → ↓ bone resorption	**Strontium ranelate** (orally)	- Osteoporosis, 2ndry to menopause,glucocorticoids - Malignancy + hyperCa^{2+} ADRs: - GIT irritation → resolved in 1st three months. Interactions: food: milk & its products, Antacids, P.O tetracycline & quinolones.	C.I: - Sever renal disease. - Hypersensitivity to storntium. - ↑ risk of venous thromboembolism. - In phenylketonuria.
Estrogen & Androgen ↑ Osteoclast apoptosis & inhibit osteoblast apoptosis. ↑ Release of growth factors from osteoblasts ↓ Release of inflammatory cytokines causing resorption	1- hysterectomy → use estrogen only. 2- uterus is present → estrogen + progestins. 3- hormonal replacement therapy → menopausal symptoms. 4- SERMs (e.g. Raloxifene) → menopausal & elderly. 5- Androgen → for elderly men.		ADRs: As a HRT (estrogen): - Vaginal bleeding. - Risk of breast cancer. - Venous thromboembolism.
SERM (Raloxifene) Antiestrogens that exhibit partial **agonistic** action; acting as an agonist in bone & an **antagonist** in some female sex organs. - Its action only on bones & CVS.	Advantages: - ↑ bone density & ↓ fracture risk - No stimulation of breast or endometrial tissue - No need for progestin in women with uterus - ↓ LDL & ↓ risk of thromboembolism compared to estrogen & Good for women with risk of uterine and breast cancer.		Disadvantages: - May ↑ hot flushes. - No effect on HDL.
L4 | Drugs used in calcium & vitamin D disorders			
PTH & Teriparatide Enhances intestinal Ca2+ absorption in the presence of permissive amounts of vitamin D. Response to PTH: 1- **Dialy intermittent**: stimulate bone formation. 2- **Continuous (chronic) exposure:** bone resorption. **Both are taken S.C.**	**Teriparatide** (PTH analogue) Uses: - Osteoporosis in people have a risk of getting fracture. - Sever osteoporosis. - Resistance cases fail to response to other medications. ADRs: Carcinogenic effect (osteosarcoma) & postural hypotension & kidney stones. C.I: ↑ risk of osteosarcoma, paget's disease, children.		
Calcitonin (S.C., Nasal spray or solution) - Released when there is ↑ Ca^{2+} level - ↓ Ca $^{2+}$ level In plasma - Protects against hypercalcemia caused by milk-alkali syndrome (↑ Ca^{2+}) & thiazide use (↓ Ca $^{2+}$) Uses: hypercalcemia, osteoporosis, paget's disease	**Vit.D** - In the kidney → PTH stimulate the formation of **active form calcitriol (1,25-dihydoxycholecalciferol) by 1alpha-hydroxylase**. (calcidiol, 25-hydroxycholecalciferol): an inactive form of vit.D Uses: Rickets & osteomalacia, psoriasis, cancer prevention.		

L5 | Pharmacology of corticosteroids

Effects of steroids:

Metabolic effects
- ↑ Glucose
- ↑ Insulin → lipolysis (cortisol) & lipogenesis (insulin).
→ occurs when the pt is treated w\ 100mg of hydrocortisone longer than 2 wks.

Catabolic effects
- On muscle protein.
- C.T, fat, skin wasting.
- On bones

Immune effects
- ↓ IL secretion.
- ⊗ phospholipase A2 & ⊗ prostaglandins synthesis.

Others
- Cortisol is required for normal renal excretion of H_2O load
- Stimulate gastric acid secretion.

Cortisol (hydrocortisone)
- Major natural glucocorticoid.
- Peaks in the morning trough midnight.
- Metabolized in the liver & has **short duration of action**.
- Diffuse poorly across normal skin & mucous mem.

ADRs:
- Salt retaining effect → hypertension.

Synthetic glucocorticoids
* Prednisone (prednisolone), Dexamethasone & Triamcinolone →
- Longer T1\2 & duration of action. Low salt retaining effect. Better penetration for topical activity.

* Beclomethasone & Budsonide → used in asthma. Rapidly penetrate airway mucosa. Very short T1\2 after entering the blood = ↓ systemic effects.

ADRs of both natural & synthetic glucocorticoids:
- Cushing syndrome (in high dose). - Myopathy & muscle wasting. - Adrenal suppression
- Osteoporosis. - Impaired wound healing. - Peptic ulcer. - Acute psychosis, depression.
- Hypertension. - Growth suppression.

Mineralocorticoids
Aldosterone is very important in the regulation of blood volume & blood pressure.

Fludrocortisone
- It is favored for replacement therapy after adrenalectomy & other conditions in which mineralo. is needed.
- Has long duration of action (compared with aldosterone)

Corticosteroid antagonist: A- ⊗ Receptor B- ⊗ Synthesis.

A- ⊗ Receptor (1- Spironolactone & Eplerenone. 2- Mifepristone)

1- Spi + Epl → Mineralocorticoid antagonist & K-sparing diuretic. Used to treat 1ry aldosteronism.

2- Mifep. → competitive inhibitor of glucocorticoid receptors & progesterone receptors

B- ⊗Synthesis (Ketoconazole)

MOA: inhibits cyt-p450 → reduce steroid level

Uses: Adrenal carcinoma, Hirstuism, breast & prostate cancer.

L6 | Uses of insulin in diabetes

Insulin
Its R present mainly in muscle, adipose tissue & liver.

1- **Ultra-short**: Lispro, Aspart, Glulisine.
2- **Short-Regular insulin**: (Humulin R, Novolin R)
3- **Intermediate**: NPH (Isophane), Lente (Humulin L, Novolin L)
4- **Longe**: Glargine (Lantus), Detemir (Levemir).

- All are taken S.C.
- 1 & 2 can be taken I.V (ER Diabetic ketoacidosis (DKA))

Ultra-short
- Clear solution at neutral pH. & Monomeric analogue.
- Given before each meal → ~ 3 times\day.
- Onset: **5-15 min** & duration: **3-5 hrs**.
- Preferred for external insulin pump (Lispro does not form hexamers)

Short-Regular insulin
- Clear solution at neutral pH + soluble crystalline zinc insulin. & Hexameric analogue.
- Given before each meal → ~ 3 times\day.
- Onset: **30-45 min**. & Duration: **6-8 hrs**.
- Can be used in pregnancy.

Intermediate acting

NPH (Isophane)
- Turbid, can't be used in DKA
- Onset: **1-2 h**.
- Duration: **13-18h**.

Insulin mixture: have the same duration as NPH & 2 peaks.

Lente
- 30% semilente, 70% ultralente.
- Turbid, can't be used in DKA.
- onset: **1-3h**.
- Duration: **13-20h**.

Long acting
- Clear, but forms precipitate at injection site.
- Slow onset of action (2h). Duration: **24h** → Once daily.
- Should not be mixed with other insulins in the same syringe.
- Max. effect after 4-5h.
- Must be used in regimens w\ rapid or short acting insulins.
- Peakless (no peak)
- Has reduced risk of hypoglycemia.

Complications: Hpoglycemia, lipodystrophy, weight gain, insulin resistance, hypokalemia.

L7 | Management of diabetic ketoacidosis & hypoglycemia

❖ Lines of treatment of diabetic ketoacidosis

1- Dehydration → give fluid therapy rehydration → restore blood V & perfusion of tissues.	**2- Hyperglycemia** → give insulin therapy (short acting insulin) → Regular insulin **I.V** → insulin stops lipolysis & promotes degradation of ketone bodies.	**3- Electrolyte deficits** → give K^+ therapy → correct serum K^+ conc.	**4- Ketoacidosis** → give Bicarbonate therapy (only if the arterial pH <7.0 after 1h of hydration) → correction of metabolic acidosis.

❖ Management of Hypoglycemia

If the patient is conscious: - Sugar containing beverage or food (30g **orally**)	**If the patient is unconscious**: A- Glucagon (1mg S.C or I.M). B- 20-50 ml of 50% glucose solution I.V infusion (risk of phlebitis.

L8 & 9 | Oral Hypoglycemics

Class	Mechanism	Site of action	Comments & Main advantages	Main side effects
Sulfonylureas Stimulate insulin release from functioning* B cells by ⊗ of ATP-sensitive K channels	Stimulates **insulin secretion**	Pancreatic beta cells	• Effective • Inexpensive	• **Hypoglycemia** • Weight gain
Meglitinides **Repaglinide** MOA same as Sulfo, **Rapidly** acting Insulin secretagogue		Pancreatic beta cells	Sulfa free	•**Hypoglycemia** •Weight gain
Biguanides **Metformin** ↑ the sensitivity of target organs to insulin & ↑ peripheral glucose utilization	Decreases **insulin resistance**	Liver	• mild weight loss • No hypoglycemia	• GIT symptoms, • Lactic acidosis • Metallic taste
Thiazolidinediones **Pioglitazone** Activate (PPAR-γ) nuclear receptors in muscles. liver and adipose tissue.		Fat, muscle	orally No hypoglycemia	**Hepatoxicity** Edema, mild **weight gain**
α-Glucosidase inhibitors **Acarbose**	Inhibits **α-glucosidase**	GI tract	orally Low risk	•GI symptoms, flatulence
Incretins mimetics **Dulaglutide** GLP-1 agonists	Increase incretin	GI tract	Once/week, **s.c.**	Nausea & vomiting
DPP-4 inhibitors **Sitagliptin**	Inhibit incretin breakdown	GI tract	orally	Nausea & abdominal pain