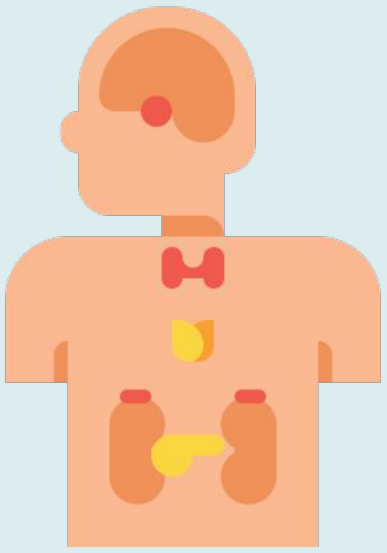


Pharmacology 439

MED439
KING SAUD UNIVERSITY

Endocrine Block

Pharmacology Team 439

Color index:

Main Text

Important

Dr's Notes

Female Slides

Male Slides

Extra

Revision

Endocrine Pharmacology

Summary

Editing file

Most likely SAQ

Least likely SAQ

Table of contents

Revision:

- The revision will include Dr. Ishfaq's lectures (not included in SAQ) & Dr. Hussain's lecture (IMPORTANT for SAQ).

- **Click here to check out Dr. Ishfaq's 439 Revision Notes**

- ***Based on previous years, not information from doctors**

Lecture (1): Growth hormone and pituitary adenomas pharmacology

Drug	M.O.A	Uses	ADRs
GH Deficiency			
GH agonist			
Sermorelin	Synthetic growth hormone releasing hormone (GHRH) from hypothalamus	**Defective hypothalamic releasing of GHRH** BUT normally functioning anterior pituitary somatotrophs.	-
Somatropin	Recombinant human growth hormone which is a 191-amino acid peptide, **identical** to the native form of hGH. (commonly used)	- Documented Growth failure in pediatric patients associated with **GH deficiency** and **Turner syndrome** - Wasting muscle - Idiopathic short stature. - Short bowel syndrome in patients who are also receiving specialized nutritional support.	- Hypothyroidism **- Leukemia** - Insulin resistance - Arthralgia - Increase in cytochrome P450 activity
Somatrem	Recombinant human growth hormone		
Mecasermin	**Recombinant IGF-1**	children with **severe IGF-1 deficiency** due to **mutations** in the GH receptor (**Laron dwarfism**) or development of **neutralizing antibodies against GH.**	**Hypoglycemia: can be avoided** by consumption of meal 20 min before or after the administration of drug.
GH Overproduction			
GH antagonist			
Octreotide	**Somatostatin analogues** Normally: ● Somatostatin physiologically inhibits GH secretion, but is rarely used clinically, since it has a very short half-life Octreotide: ● **Mainly Inhibit GH secretion.** ● Partially inhibits GH-induced IGF-1 generation. ● Reduce GHRH release.	**Treatment of acromegaly & gigantism**	- Significant GI disturbances. - Gallstones. **- Cardiac conduction abnormalities.**
Lanreotide			
Pegvisomant	**GH receptor antagonist:** A long-acting derivative of mutant GH that is able to cross-link GH receptors (bind to the receptor) but is incapable of inducing the conformational changes required for receptor activation.	**Treatment of acromegaly**	-
D2 receptor agonists			
Bromocriptine **(Only one safe in pregnancy)**	Selective activation of D2 receptors located on lactotroph cell surface (PRL-producing cells) → decrease adenylate cyclase activity → decreasing in cAMP level → **inhibition of prolactin (PRL) synthesis & release.**	★ **Prolactinoma** (pituitary adenoma with excess release of prolactin)	- GI intolerance - postural hypotension - Constipation - nasal stuffiness
Cabergoline **more effective than bromocriptine for tumor shrinkage**			
Pergolide Mesylate strong **vasospasm and uterotonic**			

Lecture (2,3): Hyper & Hypothyroidism

Drug	M.O.A	Uses	ADRs	C.I
Treatment of hyperthyroidism				
Thioamides				
Propylthiouracil (PTU) Protein binding: 80-90%	Inhibits synthesis of thyroid hormones by inhibiting the **peroxidase** enzyme. **PTU ONLY: blocks the conversion of T4 to T3 in peripheral tissues**	**-Drug Of choice in pregnancy** -Used for breastfeeding	-Skin reactions -Arthralgia -Gastric distress -anti-thyroid arthritis -Agranulocytosis (in patients with Graves' disease) **Immunoallergic hepatitis** with **PTU** -ANCA-positive vasculitis (rare)with **PTU** -Abnormal sense of taste or smell (rare) with **methimazole**	-
Methimazole(active metabolite) **Carbimazole** (prodrug) most of the drug is free		**Not used In pregnancy** nor breastfeeding		
Iodine\ Iodide				
1- Organic iodides: iopanoic acid or ipodate **2- Potassium iodide or lugol's solution**	-Inhibit thyroid hormone synthesis and release **-Block the peripheral conversion of T4 to T3** **-The effect is not sustained** (produce a temporary remission of symptoms)	**- Prior to thyroid surgery** - Following radioactive iodine therapy - Thyrotoxicosis	iodism Iodism symptoms: skin rash,hypersalivation, oral ulcers, metallic taste, bad breath.	-**Pregnancy** -Using it as single therapy
Radioactive Iodine (RAI)				
Radioactive Iodine (RAI)	-131I (iodine) 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.	- Hyperthyroidism mainly in old patients (above 40) - Graves' disease - Patients with toxic nodular goiter - Can be used as a diagnostic method	-High incidence of delayed hypothyroidism -Large doses have **cytotoxic actions** (necrosis of follicular cells followed by fibrosis) -May cause genetic damage -May cause leukemia & neoplasia	**Cross placenta & excreted in breast milk** (not safe in pregnancy)
β-blockers				
Propranolol **Atenolol** **Metoprolol**		Adjunctive therapy to relief the adrenergic symptoms of hyperthyroidism such as tremors, palpitation, heat intolerance and nervousness		Propranolol is contraindicated in asthmatic patients

Lecture (2,3): Hyper & Hypothyroidism

Drug	M.O.A	Uses	ADRs	C.I
Treatment of hypothyroidism				
subclass				
Levothyroxine (T4)	● A synthetic form of the thyroxine (T4) is the drug of choice for replacement therapy - Stable and has a long half life (7 days) - Administered once daily. - Restore normal thyroid levels within 2-3 weeks ●Major pathway of thyroid hormone metabolism is through sequential deiodination - 80% of circulating T3 is derived from peripheral T4 by monodeiodination - The liver is the major site of degradation for both T4 and T3 - 80% of the daily dose of T4 (levothyroxine) is deiodinated to yield equal amounts of T3 and rT3 (reverse T3,which is inactive)	Hypothyroidism regardless of etiology: Uses -Congenital -Pregnancy (drug of choice) -Hashimoto thyroiditis	ADRs in **OVERDOSE** ● **In children**: - Restlessness, insomnia - Accelerated bone maturation ADRs ● **In Adults**: **- Cardiac arrhythmias (Tachycardia, atrial fibrillation)** - Tremor, restlessness, headache - Heat intolerance - Muscle pain - Change in appetite, weight loss	In **old patients** and in patients with cardiac problems , treatment is started with reduced dosage
Liothyronine (T3)	- More potent (3-4 times) - rapid onset of action than levothyroxine -short half life			-**Not recommended for routine replacement therapy (requires multiple daily doses)** -Should be avoided in **Cardiac patients**
Liotrix	**Combination of synthetic T4 & T3 in a ratio 4:1 that attempt to mimic the natural hormonal secretion**		**The major limitations to this product are:** **Disadvantages** **- High cost** **- Lack of therapeutic rationale because 35% of T4 is peripherally converted to T3**	

Special Conditions of Hypo/Hyper thyroidism and their Management

Hyperthyroidism

Thyrotoxicosis during pregnancy:
Better to start therapy before pregnancy with ^{131}I or subtotal thyroidectomy to avoid acute exacerbation during pregnancy
During pregnancy:
Radioiodine is contraindicated - PTU is the drug of choice during pregnancy

Thyroid Storm:
a medical emergency of a sudden acute exacerbation of all the symptoms of thyrotoxicosis, presenting as a life-threatening syndrome.
- It should be treated in an ICU - Correct electrolyte abnormalities, treat cardiac arrhythmia & control hyperthermia by applying ice packs - Promptly administer antiadrenergic drugs (e.g. propranolol) - High-dose propylthiouracil (PTU) is preferred - Administer iodine compounds - Hydrocortisone to prevent shock - Rarely, plasmapheresis

Graves' Disease:
Mild/Moderate Hyperthyroidism: Start methimazole, 5–30 mg/day, (PTU preferred in pregnant women).
Relapse: Definitive radioiodine (Second course of anti thyroid
drug therapy in children) Remission: Monitor thyroid function every 12 mo indefinitely
Severe Hyperthyroidism: firstly radioiodine then once thyroid function is normalized give antithyroid drugs before surgery.

Hypothyroidism

Myxedema Coma
Life–threatening hypothyroidism
The treatment of choice is loading dose of levothyroxine intravenously 300-400µg initially followed by 50µg daily High Risk of Cardiac symptoms due to the high dose
I.V. liothyronine can be used for rapid response but it may provoke cardiotoxicity
I.V. hydrocortisone may be used in case of adrenal and pituitary insufficiency.

Hypothyroidism in Pregnancy
In pregnant hypothyroid patient 20-30% increase in thyroxine is required because of :
elevated maternal (TBG) induced by estrogen
early development of fetal brain which depends on maternal thyroxine.

Lecture (4): Treatment for Osteoporosis

Drug	M.O.A	Uses	ADRs	C.I
Antiresorptive				
Bisphosphonates Best drugs for osteoporosis				
Nitrogenous: Alendronate*,Ibandronate ,Risedronate, Zoledronate **&** **Non-Nitrogenous** Etidronate, Clodronate, Tiludronate	★ **1. Bind to calcium and concentrate in bones**, by resembling pyrophosphate bound to hydroxyapatite decreasing its solubility and make it more resistance to osteoclastic activity. **2. Prevent bone resorption by Inhibit osteoclast function.** **Block cholesterol synthesis** *Alendronate is **toxic to esophagus as oral preparation**	● **Osteoporosis**; secondary to menopause or long term glucocorticoids..etc ● Paget's Disease ● **Malignancy-associated hypercalcemia** ---------- ★ Should be taken in **upright position** and with a **large amount of water** to prevent esophagitis	● **GIT irritation:** nausea, vomiting, gastritis, **Esophagitis***, ulceration → Drinking large amount of water to prevent the risk of tablet from getting stuck in esophagus. ● Gastroesophageal reflux ± ulceration → Avoiding this by giving it on empty stomach and sitting while sitting in upright for 30 min. ● Flu like manifestation: fever, chills when given I.V. infusion ● **Osteonecrosis** of the mandible bone of jaw upon long use with IV infusion preparation usually after dental surgical procedures - If a **dental implant** or extraction is already planned, delay bisphosphonate therapy for a few months until the jaw heals completely ● **Atrial fibrillation** → more in women with **alen**dronate **and zole**dronate when taken as IV preperation	● Decreased renal function ● Peptic Ulcer ● Esophageal reflux
RANKL inhibitors				
Denosumab	★ **Blocks RANKL from interacting with RANK receptor** expressed on preosteoclast → ↓ osteoclastogenesis → no mature osteoclasts ● Binds also to mature osteoclasts → increase their apoptosis ● Net effect is decreasing bone resorption ● A fully humanized monoclonal antibody that **-mimics the activity of osteoprotegerin (OPG)**	● Extremely expensive treatment reserved **for patients who cant tolerate nor respond to bisphosphonates**	● Respiratory and urinary infections ● Eczema and skin rash ● Pancreatitis	● Patients with **hypocalcemia,** as denosumab decreases serum calcium concentration. ● Correct Ca and Vit D levels before starting the treatment

Lecture (4): Treatment for Osteoporosis

Drug	M.O.A	Uses	ADRs	C.I
Antiresorptive + Bone Anabolic Agents (Dual effect)				
Strontium **Triple mechanism** ● ↑ Osteoblast activity ● ↑ OPG in osteoblasts ● ↓ Osteoclast activity	**Dual MOA** **Effects on Osteoblasts:** 1. **Acts as an agonist on Ca Sensing Receptor [CaSR]** → enhances differentiation of preosteoblast to osteoblast → ↑ bone formation 2. **Stimulate the expression of OPG** → increase RANKL binding → ↓ osteoclastogenesis → ↓ bone resorption **Effects on Osteoclasts:** Acts as an agonist on CaSR → suppress differentiation of preosteoclast to osteoclast → ↑ osteoclast apoptosis → ↓ bone resorption	● Osteoporosis; secondary to menopause or glucocorticoids..etc ● Malignancy-associated hypercalcemia	● GIT irritation: nausea, vomiting, headache & eczema ● All resolve within the first 3 months	● Severe renal disease ● Hypersensitivity to the drug ● Risk of venous thromboembolism (can't give it to **immobilized** person) ● **Phenylketonuria** _____ **Interaction** ● Food containing milk (calcium) ± its products ● Antacids ● Oral Tetracycline and quinolones chelates it
Sex Hormones				
Estrogen	Estrogen in females **and** Androgens in males are essential for normal bone remodeling: ○ ↑ osteoclast apoptosis and Inhibit osteoblast apoptosis (protective effect on the bones) ○ ↑ release of growth factors from osteoblasts ○ ↓ number and depth of resorption cavities ○ ↓ release of inflammatory cytokines that helps to cause resorption	**Hysterectomy**: use estrogen only (if the uterus was removed already, it is safe to give estrogen only) ● If **uterus is present**: Estrogen + Progestin to protect the uterus ● Hormonal Replacement therapy **(HRT)**: menopausal symptoms ● **SERMs:** Menopause/Elderly	● Vaginal bleeding ● Risk for breast cancer ● Venous thromboembolism	
Androgen		Elderly men		
Selective Estrogen Receptor Modulators (SERMs)				
Raloxifene	● Anti-Estrogens that exhibits partial agonistic action ● Agonist in bones and Antagonist in female sex organs ● Works only on women especially post-menopausal women More organ selective compared to estradiol No carcinogenic effects like estrogen	Post menopausal women ●↑ bone density by (2%) and ↓ fracture risk by (30%) ● No stimulation of breasts nor endometrial tissue ● No need for progestin in women with a uterus ● ↓ LDL ● Good for women with a risk of uterine and breast cancer ● Lower risk for thromboembolism compared to estrogen	ADRS ● May ↑ hot flashes ● No effect on HDL	

Lecture (5): Calcium & Vit D disorders

Parathyroid Hormone For hypocalcemia

Definition	● PTH: A hormone that plays a critical role in controlling calcium , and phosphate balance. ● PTH is released from the parathyroid gland in response to low plasma Ca2+ level , its secretion is inversely related to [Ca2+]
Action	● **Bone**: Mobilization of Ca2+ and PO4 3- from bone. In response to hypocalcemia , PTH stimulates osteoclasts cells to↑the outward flux of calcium from bone to restore serum calcium level. Action ● **Kidney**: ↑ calcium active reabsorption and ↑formation of calcitriol which is the active form of vitamin D (by stimulating 1-α-hydroxylase enzyme in the kidney) ● **GIT**:↑absorption of calcium in the presence of permissive amount of Vit D, **The overall action of PTH is to ↑plasma Ca+2 levels in response to hypocalcemia**
Effects	★ **Daily**, **Intermittent** administration of recombinant human PTH, for 1 to 2 hours / day SC in the thigh (alternate thigh every day) leads to a net stimulation of bone formation for treatment of osteoporosis. You must have gaps in administration to avoid fractures ○ **Mechanism**:↑Osteoblast number/function→↑Bone formation→ ↑Bone mass/strength (Anabolic action) ● **Continuous or chronic exposure** elevated PTH leads to bone resorption and risk of fracture (as seen with primary or secondary hyperparathyroidism) ○ **Mechanism**: ↑Osteoclast →↑Bone resorption →↑Serum Ca2+ (more than bone formation)
Uses Hypocalcemia	● Treatment of severe osteoporosis ● Resistant cases failed to respond to other medications

Definition	Effects/P.K	Uses	ADRs/C.I
Teriparatide Toxic for bone marrow or Tumor			
Synthetic polypeptide form of PTH (PTH analogue). ● It belongs to a class of anti-osteoporosis drugs, the so-called "anabolic" agents (= stimulate bone formation).	**Given** once daily as subcutaneous injection ● As PTH ,the therapeutic effects of teriparatide depend upon the pattern of systemic exposure: -**Once daily administration** → stimulates new bone formation by preferential stimulation of osteoblastic activity over osteoclastic activity. -**Continuous administration**→ may be detrimental to the skeleton because bone resorption may be stimulated more than bone formation (↑ risk of fracture).	● Should not be used routinely due to **carcinogenic effects.** ● Use in severe osteoporosis or patients not responding to other drugs. ● For treatment of osteoporosis in people who have a risk of getting fracture (increase bone mass & strength) ● Good for postmenopausal osteoporosis. ● Note: **Patients receiving Teriparatide must have sufficient intake of vitamin D and calcium.** (In Hypocalcemia , there will be an exaggerated effect due to PTH release. So it's recommended that the patient complete a supplementation course first)	-● **Carcinogenic effect** (development of osteosarcoma) rare but serious limits use ● Diarrhea, heartburn, nausea ● Elevated serum calcium can occur in some cases leading to kidney stones. ● headache, leg cramps ● Orthostatic hypotension C.I: Should not be used by people with increased risk for bone tumors (osteosarcoma) including ● People with paget's disease of bone (can transform to malignant bone cancer). ● People who had radiation treatment involving bones (malignancy risk) ● Not recommended in children

Lecture (5): Calcium & Vit D disorders

Vitamin D

Definition	• Vitamin D is a steroid hormone that is intimately involved in the regulation of plasma calcium levels.
Forms	• **Cholecalciferol (Vitamin D3)**: found in the skin. ○ Vitamin D3 is usually for vitamin D-fortified milk & foods. It's also available in drug combination product. • **Ergocalciferol (Vitamin D2)**: found in the plants. ○ Vitamin D2 is the prescription form of vitamin D It's also used as food additive (milk + egg yolk, & fish oil) Forms • **Both:** Vit D2 and Vit D3 have equal biological activities. ○ both travel to the liver and then convert to their active form in the kidneys. • **Calcifediol** is the major circulating form and principle storage form of vitamin D • **Calcitriol** is the active form of Vit D.
Metabolism	1. **Sunshine** (UV light): Cholecalciferol (D3) is generated in the skin from 7-dehydrocholesterol by the action of ultraviolet radiation (sunshine). 2. **The Liver**: The initial transformation of (Vit D3) & Vit D2 occurs in liver to (Calcifediol) the main storage form of Vit D in our body. 3. **In the kidney**: parathyroid hormone stimulates the formation of the active form of vitamin D (calcitriol /1,25 Dihydroxycholecalciferol) by α hydroxylase.
Effects Net effect is increasing Ca^{2+} levels	• **Bone**: Activation of osteoblast cells (↑ resorption ⟶ ↑ Ca in the blood ⟶ stimulate osteoblast activity). • **Kidney**: Increased reabsorption of Ca2+ & PO4. • **GIT**: Increased absorption of Ca2+ from the intestine. • Decreases the production of PTH by the parathyroid glands (Vit D⟶ increase Ca⟶ decrease in PTH). • **The overall effect of vitamin D is to increase plasma Ca+2 concentrations**.

Definition	Effects/P.K	Uses	ADRs/C.I
Calcitonin For hypercalcemia			
• **Produced by** the parafollicular cells (C cells) of the thyroid gland. • It is released when there is an elevated level of Ca+2 in the blood. • Calcitonin does **not** appear to be critical for the regulation of calcium homeostasis even if thyroid gland is removed.	• **Route of administration**: S.C , Nasal spray. • **Bone**: Decrease bone resorption by inhibiting osteoclast activity. • **Kidney**: Decreases reabsorption of Ca+2 & PO4, thus increasing their excretion. The major effect of calcitonin administration is a rapid fall in Ca+2	• Osteoporosis (major indication of calcitonin; alternative to other drugs) (by inhibition of osteoclasts⟶ ↓bone loss). • Hypercalcemia (short-term treatment of hypercalcemia of malignancy), or in Pagets disease.	-• Nausea • Local inflammation (at site of Injection) • Flushing of face & hands • Nasal irritation (nasal spray)

Lecture (6): Corticosteroids

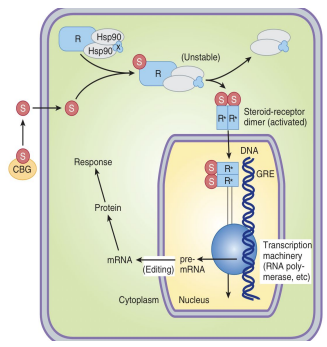
Corticosteroids Agonists

Glucocorticoids

Drug	**Natural: cortisol** **Synthetic form: hydrocortisone**	**Synthetic Glucocorticoids** **1.Prednisone** **and its active metabolite prednisolone** **2. Dexamethasone** **3.Budesonide** **4.Beclomethasone**

M.O.A

- Corticosteroid (S) is present in the blood bound to the **corticosteroid binding globulin (CBG)** (CBG) and enters the cell as the free molecule.
- The **intracellular** receptor (R) is bound to the stabilizing proteins, including **heat shock protein 90 (Hsp90)** (Hsp90) and several others (X).
- When the complex binds a molecule of steroid, the Hsp90 and associated molecules are released
- The steroid receptor complex **enters the nucleus** as a dimer, binds to the **glucocorticoid response element (GRE) on the gene**, and regulates gene transcription by **RNA polymerase 2** and associated transcription factors.
- The resulting mRNA is edited and exported to the cytoplasm for the production of protein that brings about the **final hormone response**.



Uses

Adrenal Disorders

Addison's disease (chronic adrenocortical insufficiency).

Acute adrenal insufficiency associated with life threatening shock, infections or trauma

Congenital adrenal hyperplasia (in which synthesis of abnormal forms of corticosteroids are stimulated by ACTH).

Non-adrenal Disorders

Allergic reactions: due to their immunosuppressive effect
(e.g. bronchial asthma, angioneurotic edema,drug reactions, urticaria, allergic rhinitis):
-Beclomethasone & budesonide have been developed for use in asthma and other condition in which good surface activity on mucous membrane or skin is needed and systemic effects are to be avoided.
-Rapidly penetrate the airway mucosa but have very short half lives after they enter the blood, so that systemic effects and toxicity are greatly reduced. (advantage)

Collagen vascular disorders: (e.g rheumatoid arthritis, systemic lupus erythematosus, giant cell arteritis, polymyositis, mixed connective tissue syndrome)

Organ transplants (prevention & treatment of rejection – immunosuppression)

GI disorders (e.g inflammatory bowel disease)

Hematologic disorders (leukemia, multiple myeloma, acquired hemolytic anemia, acute allergic purpura>

Infections (acute respiratory distress syndrome (associated with high immune response), sepsis)

Neurologic disorders (to minimize cerebral edema after brain surgery, multiple sclerosis).
Dr: write it please: **(Dexamethasone** is mostly used in neurological disorders due to its long duration of action and low salt-retaining activity**)**

Pulmonary diseases (e.g. aspiration pneumonia, bronchial asthma, sarcoidosis)

★**Thyroid diseases** (autoimmune diseases: malignant exophthalmos, subacute thyroiditis)

Renal disorders (nephrotic syndrome) / **Miscellaneous** (hypercalcaemia, mountain/motion sickness)

ADRs

Toxicity

- Cushing's syndrome like effect (iatrogenic, by higher doses > than 100 mg hydrocortisone daily for > than 2 weeks characterized by moon shape face & buffalo hump).
- Increased growth of fine hair on face, thighs & trunk
- Myopathy, muscle wasting, thinning of skin
- Diabetes Mellitus - Osteoporosis & aseptic necrosis of the hip wound healing is impaired
- Wound healing is impaired - Peptic ulcer (↑GI acidity)
- Acute psychosis, depression - Subcapsular cataract
- Growth suppression - Hypertension
- Adrenal suppression

Lecture (6): Corticosteroids

Corticosteroids Agonists

Mineralocorticoids

Drug	Aldosterone	Fludrocortisone
M.O.A	Same as that of glucocorticoids **mineralocorticoids response element**	
P.K	• The major natural mineralocorticoid in human • Aldosterone has short half life & little glucocorticoid activity.	
Uses	• **Fludrocortisone** is favored for replacement therapy **after adrenalectomy** (removal of adrenal cortex) & in other conditions in which mineralocorticoid therapy is needed.	
P.D	• Aldosterone is the **main salt-retaining hormone**, promotes Na Reabsorption, K excretion, in the distal convoluted tubule & thus it is very important in the regulation of blood volume & blood pressure. • Its secretion is regulated by ACTH & by the renin-angiotensin system.	

Corticosteroids Antagonists

1) Receptor Antagonists

Drug	Spironolactone	Mifepristone
M.O.A	• **Mineralocorticoid antagonist** & **K-sparing diuretic** • Antagonists of aldosterone at its receptor.	**Competitive** inhibitor of glucocorticoid receptors
Uses	Treatment of primary aldosteronism (Conn's syndrome).	Treatment of Cushing's syndrome

2) Synthetic Inhibitors

Drug	Ketoconazole (Anti Fungal)
M.O.A	• In low doses it acts as an **antifungal** • In high doses it blocks the synthesis of mineralocorticoids. • Inhibits cytochrome p450 enzymes necessary for synthesis of all steroid
Uses	Number of conditions in which reduced steroid level are desirable such as: • Adrenal cancer, when surgical therapy is impractical or unsuccessful because of metastasis. • Hirsutism • Breast cancer • Prostate cancer

Methods for minimizing corticosteroid toxicity

- Local application (e.g; aerosol for asthma)
- Alternate day therapy (to reduce pituitary suppression)
- Tapering the dose soon after achieving a therapeutic response.
- To avoid adrenal insufficiency in patient who have had long term therapy, additional stress doses may need to be given during serious illness or before major surgery.

Lecture (7): Use of insulin in treatment of diabetes

Insulin

Mechanism of action

1. Insulin binds to tyrosine kinase
2. Phosphorylation of **IRS-1** and **IRS-2** (insulin receptor substrate)
3. → binding and activating other kinases (e.g., PI3-K) or bind to adaptor proteins (e.g. growth factor receptor-binding protein 2) that translates insulin signal to a guanine nucleotide-releasing factor that ultimately activates the GTP binding protein RAS and the MAPK system.

Interaction with Receptor

Results in multiple effects including:

- **Translocation** of glucose transporters (**GLUT**) to cell membrane with resulting **increase in blood glucose uptake**
- Glycogen synthase activity and **increased glycogen formation**
- **Effects on protein synthesis**
- **Lipogenesis**

Effects of insulin

Carbohydrate Metabolism

REMEMBER insulin function is anabolic

- ↑ Glucose uptake & utilization by peripheral tissues (Translocation of glucose transporters (GLUT-4) to cell membrane)
- ↑ Glycogen synthesis (glycogen synthase)
- ↑ Conversion of carbohydrate to fats.
- ↓ Gluconeogenesis.
- ↓ Glycogenolysis (liver)
- ↑ Glycolysis (muscle).

Fat Metabolism

- **Liver:**
- ↑ Lipogenesis.
- ↓ Lipolysis.
- Inhibits conversion of fatty acids to keto acids.
- **Adipose Tissue:**
- ↑ Triglycerides storage.
- ↑ Fatty acids synthesis.
- ↓ Lipolysis

Protein Metabolism

- **Liver:**
- ↓ protein catabolism.
- **Muscle:**
- ↑ amino acids uptake.
- ↑ protein synthesis
- ↑ glycogen synthesis (glycogenesis).

potassium

- ↑ potassium uptake into cells.

Pharmacokinetics

Routes of administrations of exogenous insulin

Can not be given orally **why?** because its a protein and it will be digested (destruction by PH)

- Insulin syringes (**S.C.**, arms, abdomen, thighs).
- Portable pen injector (pre-filled).
- Continuous S.C. infusion (insulin pump):
  - 1- More convenient
  - 2- Eliminate multiple daily injection
  - 3 -Programmed to deliver basal rate of insulin.
- **Intravenously IV** (in a hyperglycemic emergency)
- Inhaled aerosols, transdermal, intranasal (**Under Clinical Trials**).

Insulin degradation

- Basal level of endogenous insulin is **5-15 µU/ml**
- Half life of circulating insulin is 3-5 min.
- 60% liver & 40% kidney (**endogenous** insulin)
- 60% kidney & 40% liver (**exogenous** insulin)

Complications

1. **Hypoglycemia**
2. Hypersensitivity Reactions
3. **Lipodystrophy** (a buildup of fatty tissue) at the injection sites.
4. Weight gain (Due to anabolic effects of insulin)
5. Insulin resistance
6. Hypokalemia

Lecture (7): Use of insulin in treatment of diabetes

Drug	Characteristics	P.k	Uses
Ultra short acting insulin			
Insulin **Lispro** (Humalog®), insulin **Aspart** (Novolog®)		• **Clear solutions** at neutral pH. IV • Do not aggregate or form dimers or hexamers **(monomeric analogue)** • Fast onset of action **(5-15 min)** • Short duration of action **(3-5 h)** • S.C. (5 -15 min before meal). • Reach peak level 30-90 min after injection. • 3 times/dayMimic the prandial mealtime insulin release. • **I.V in emergency.** in case of diabetic ketoacidosis (DKA)	• Preferred for external insulin pump • Used to control postprandial hyperglycemia (S.C.) and **emergency** (best) **diabetic ketoacidosis (I.V)** (clear solution)
short acting insulin			
Humulin (Regular insulin)		• Soluble crystalline zinc insulin. • **Clear** solutions at neutral pH • Forms hexamers • Onset of action **30-45 min** (s.c.) • Duration **6-8 h** (longer) • **I.V. in emergency situations** • Peak 2-4 h • 2-3 times/day	• Control postprandial hyperglycemia (S.C.) & **emergency diabetic ketoacidosis (I.V)** ★ **Can be used in pregnancy** (DOC, even in T2DM)
Intermediate acting insulins			
Isophane (NPH) insulin	• NPH, is a Neutral Protamine Hagedorn insulin in phosphate buffer. • NPH insulin is combination of protamine & crystalline zinc insulin (1:6 molecules) proteolysis release insulin.	• Turbid suspension at neutral pH • Given S.C. only, **not I.V Can't** be used in ketoacidosis or emergency • Onset of action **1-2 h** • Duration of action **13-18 h** • Peak serum level 5-7 h	**Insulin Mixtures:** 1. NPH/regular insulin: 75/25, 70/30, 50/50 . 2. (NP**L** = NPH/**L**ispro) (NP**A** = NPH/**A**spart), NPL & NPA have the same duration as NPH, have two peaks.
Lente insulin (Humulin L, Novolin L)	• Mixture of: - 30% semilente insulin **(amorphous precipitate of zinc insulin in acetate buffer)** - 70% ultralente insulin **(poorly soluble crystal of zinc insulin)** • **Turbid suspension** at neutral pH. • Given S.C., **Not intravenously (I.V)**	• Delayed onset of action (1-3 h). • Peak serum level 4-8 h. • Duration of action 13-20 h. • Lente and NPH insulins are equivalent in activity. • Lente is **not** used in diabetic ketoacidosis or emergency.	
Long acting insulins			
Insulin glargine (lantus®) **Advantages over intermediate- acting insulins:** Constant circulating insulin over 24 hr, with no peak (peak-less profile). Produce flat prolonged hypoglycemic effect. Reduced risk of nocturnal hypoglycemia → Safer than NPH & Lente insulins.	• Clear solution **BUT forms precipitate (hexamer)** at injection site due to PH. • Slow onset of action 2 hr • Absorbed less rapidly than NPH & Lente insulin • Given S.C. only, **Not intravenously** • **Should not be mixed** with other insulins in the same syringe.	• Maximum effect after 4-5 h • **Prolonged duration of action (24 h)** • Once daily. Produce broad plasma concentration plateau **(low continuous insulin level)** • Glargine must be used in regimens with rapid or short acting insulins	

Lecture (8): Diabetic ketoacidosis & Hypoglycemia

Diabetic Ketoacidosis

- It is a serious acute emergency situation that requires admission to hospital with a risk of death.
- It develops as a result of **insulin deficiency**
- It is a characteristic feature of **type I diabetes** but may occur with type II especially during stress.

Symptoms: Ketotic breath (fruity w\acetone smell)

Treatment of diabetic ketoacidosis

Rehydration	Insulin (short acting)	Potassium therapy	Bicarbonate therapy
- To restore blood volume and perfusion of tissues. - Infusion of isotonic saline (0.9% sodium chloride) lactated Ringer solution	- **Regular insulin**, should be administered by means of **continuous I.V infusion in small doses** through an infusion pump (0.1 U/kg/h). - Insulin stops lipolysis and promotes degradation of ketone bodies.	- potassium replacement must be initiated, added to infusion fluid to correct serum potassium concentration	- For correction of metabolic acidosis - bicarbonate therapy should be used **only if the arterial pH < 7.0 after 1 hour of hydration**

Hypoglycemia

Blood sugar of less than 70 mg/dl is considered hypoglycemia
Is a **life threatening disorder** that occurs when blood glucose level becomes < 50 mg/dl
Caused by: Overdose of insulin or oral hypoglycemic drugs , Missed or delayed meal, Excessive physical exercise.
Symptoms:
1-Autonomic:
↑sympathetic: tachycardia, palpitation, sweating, anxiety, tremor.
↑parasympathetic: nausea, vomiting.
2-Neurological:
-coma due to low glucose delivery to the brain
-headache, visual disturbance, slurred speech, dizziness, tremors, mental confusion, convulsions

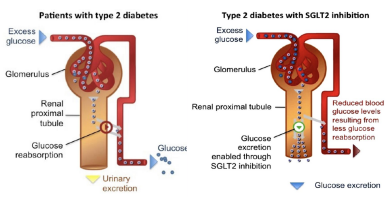
Treatment of hypoglycemia

Drug	P.K	Uses	ADRs
Glucagon	- Glucagon (1 mg S.C or I.M) - 20-50 ml of 50% glucose solution I.V infusion.	**Unconscious** patient	Risk of possible phlebitis
Sugar	Sugar containing beverage or food (30 g orally).	**Conscious** patient	

Lecture (9,10): Oral Hypoglycemic drugs

Drug	M.O.A	Uses	ADRs	C.I / P.K
1) Insulin Secretagogues				
1) Sulfonylureas				
First generation (short acting) — **Tolbutamide** Second generation (long acting) — **Glyburide**, **Glimepiride** Second generation (short acting) — **Gliclazide**, **Glipizide**	stimulate insulin release from functioning β cells seen in all insulin by **blocking of ATP-sensitive K channels**	Treatment of Type 2 diabetes monotherapy or in combination with other antidiabetic drugs	- **Hyperinsulinemia & Hypoglycemia:** ● More common in long acting sulfonylureas; particularly (glyburide, glimepiride). ● More in old age, hepatic or \ renal disease. - **Weight gain** due to increase in appetite.	**P.K:** - Orally. ★ All are highly bound to plasma proteins. - Excreted in urine (**caution: elderly and renal disease**). ★ Cross placenta, stimulate fetal β-cells to release insulin → fetal hypoglycemia at birth.
2) Meglitinides				
Repaglinide	stimulate insulin release from functioning β cells seen in all insulin by **blocking of ATP-sensitive K channels**	- Type 2 diabetes as a monotherapy or in combination with other oral hypoglycemic drugs. ★ **As alternative to sulfonylureas in patients allergic to them (SU).**	Less incidence than sulfonylureas: (due to their shorter DOA) ● Hypoglycemia. ● Weight gain.	**P.K:** - Very fast onset of action, peak 1 h. - Short duration of action (4 h). - Metabolized in liver and excreted in bile. - Taken just before each meal (3 times/day). The dose should be skipped if the meal is missed.
3) Incretin mimetics				
GLP-1 agonists — **Liraglutide**	- Binds to GLP-1 receptors and **stimulates** insulin secretion from β cells). - **Reduces** glucagon secretion, by inhibiting α cells of the pancreas. - Decreases appetite and **inhibits** body weight gain.	- Saxenda®: treatment of obesity in adults who are overweight with at least one weight-related **comorbid condition** (e.g. HTN, T2DM, or dyslipidemia). - Together with diet and exercise to treat: ○ Type 2 diabetes. ○ Patients who are not controlled with other oral antidiabetics.	- Nausea, vomiting and diarrhea (**most common**) - **Hypo**glycemia when combined with *Sulfonylureas* or *insulin* (as an additive in diabetes type 1) (not alone). - Pancreatitis (rare).	**C.I:** Not used in type 1 diabetes. **P.K:** ★ Given **S.C.** once/day.
DPP-4 inhibitors "Gliptins" — **Sitagliptin**	**Inhibit DPP-4 enzyme** and leads to an increase in incretin hormones (GLP-1) level.	Type 2 DM as an adjunct to diet & exercise as a monotherapy or In combination with other antidiabetic drugs.	- Nausea, abdominal pain, diarrhea. ★ **Nasopharyngitis**. - Headache.	**P.K:** Given orally/once daily.

Lecture (9,10): Oral Hypoglycemic drugs

Drug	M.O.A IMPORTANT	Uses	ADRs	C.I / P.K
2) Insulin sensitizers				
1) Biguanides				
★ **Metformin** The DR Mentioned the drug multiple times	If asked "in one sentence" you can say any one, if not mention everything - **Reduces** insulin resistance. - **Increases** sensitivity of liver, muscle & adipose tissues to insulin. - **Increase** peripheral glucose utilization (tissue glycolysis). - **Inhibits** hepatic glucose production (gluconeogenesis) - **Impairs** glucose absorption from GIT. - **Improve lipid profile:** ↓ LDL, ↓ VLDL , ↑HDL	● In patients with type 2 diabetes who are obese, because it promotes modest weight reduction **(first-line therapy** in general**)** (obese + blood glucose not that high). ● Type 2 diabetes as **monotherapy** or in **combination** with other antidiabetics (insulin secretagogue). **Advantages:** why it's first line - No risk of hypoglycemia. - No weight gain.	- **GIT disturbances**: ● Metallic taste in the mouth, nausea, vomiting, diarrhea. ★ **Lactic acidosis predisposing conditions:** ● Renal insufficiency. ● Severe liver disease. ● Alcohol abuse. ● Heart failure, Pulmonary insufficiency, Cardiogenic or septic shock. - **In long term use:** ● Interference with vitamin B12 absorption.	- Renal disease. - Liver disease. - Alcoholism. - Cardiopulmonary dysfunction. - Pregnancy.
2) Thiazolidinediones				
Pioglitazone **Rosiglitazone**	**Activate peroxisome proliferator-activated receptor-γ (PPAR-γ)** → Increase sensitivity of target tissues to insulin → **Increase glucose uptake and utilization** in muscle and adipose tissue.	- Type 2 diabetes with insulin resistance (with obesity). - Used either alone or in combination with sulfonylurea, biguanides or insulin. ★ No risk of hypoglycemia when used alone.	- Hepatotoxicity. ★ Fluid retention (Edema). ★ Congestive heart failure. - Mild weight gain. - Failure of estrogen-containing oral contraceptives.	-
3) α-Glucosidase inhibitors				
Acarbose **Miglitol**	- Reversible **inhibitors of intestinal α-glucosidases** in intestinal brush border cells that are responsible for carbohydrate digestion. - **Decrease carbohydrate digestion** and glucose absorption in small intestine (lower postprandial glucose level).	- Effective alone in the earliest stages of **impaired glucose tolerance**. - Most useful in combination with other oral hypoglycemic drugs or with insulin. - Not recommended alone as therapy for moderate to severe hyperglycemia	GIT: Flatulence, bloating, diarrhea, abdominal pain	- Irritable bowel syndrome (IBS). - Inflammatory bowel disorders (IBD). -Intestinal obstruction.
4) Sodium-glucose transporter 2 inhibitors				*Female slides only (except picture)
Canagliflozin **Dapagliflozin** **Empagliflozin** المعلومات بالصور كافية	**Inhibits SGLT2** in the kidney, allows excess glucose to be excreted in the urine → reduce blood sugar levels. 	- With diet and exercise to control high blood sugar in patients with type 2 diabetes. - To **reduce risk of major adverse cardiovascular events** in adults with T2DM and established cardiovascular disease.	★ Urinary tract infections. - Increased urination and dry mouth. - Thirst. ★ Yeast infections (vagina or penis). - Itching (vagina or penis). - Fatigue.	-

Lecture (9,10): Oral Hypoglycemic drugs (Revision)

Notes:

- SAQ:

1. Drugs names and their classes

- **You're not required to know the spelling of all the drugs, just learn the spelling of one drug from each class and recognize the rest**
- **All the classes are important, do not skip anyone (dr focused on insulin Secretagogues and sensitizers)**

Name oral hypoglycemic drugs and their classes? (If asked about insulin releasing mention: Sulfonylureas, Meglitinides, or incretin mimetics)

1. **Class**: Sulfonylureas, **Drug**: any drug from the 2nd generation e.g. Glimepiride.
2. **Class**: Biguanides, **Drug**: Metformin

2. MOA

Mention the MOA? (*The doctor asked specifically about metformin MOA)

1. **Glimepiride**: stimulate insulin release from functioning β cells seen in all insulin by blocking of ATP-sensitive K channels
2. **Metformin***: "unless we asked to write the MOA 'in one sentence (you can write one of the 7 MOAs)' you'll need to write a detailed answer"

1- Reduces insulin resistance.

2- Increases sensitivity of liver, muscle & adipose tissues to insulin.

3- Increase peripheral glucose utilization (tissue glycolysis).

4- Inhibits hepatic glucose production (gluconeogenesis)

5- Impairs glucose absorption from GIT.

6- Improve lipid profile: ↓ LDL, ↓ VLDL , ↑HDL

3. **Acarbose or Miglitol:** Reversible inhibitors of intestinal α-glucosidases. "one sentence is enough"

- MCQs:

1. You'll have scenario based questions (Drugs, classes, MOA (also important for SAQ))
2. Make sure you differentiate between the two groups: Insulin Secretagogues & Insulin sensitizers

What is the main difference? Secretagogues: secretion, sensitizers: increase sensitivity

★ A patient with T2DM was initially prescribed Glimepiride but it failed to reduce his hyperglycemia. Would you prescribe (as a combination) another insulin Secretagogue (same class) or an Insulin sensitizer (diff class) and why?

Give insulin sensitizer. to avoid double effect of both drugs acting by the same MOA (we want a drug that has an additive effect with a different MOA. So **Combining drugs from the same class is ineffective**

3. What is the drug of choice in T2DM and why?

Generally **Metformin** is the DOC because: No risk of hypoglycemia or weight gain and inexpensive

(It promotes modest weight reduction, Improve lipid profile)

3. Regarding the side effects

★ A patient with T2DM developed hypoglycemia after taking a hypoglycemic drug, which drug caused this? (the options will be clear)

A. Sulfonylurea (Glyburide) B. Metformin

Lecture (9,10): Oral Hypoglycemic drugs (Revision)

Questions are from the students to the Dr

Q&A:

Q1: Are sulfonylureas contraindicated in pregnancy (since they cross the placenta)?

- They’re not. To treat gestational diabetes the drug needs to cross the placenta but it’ll have a minimal effect on the baby
- 2nd generation Sulfonylureas لو جبت لكم سؤال بالاختبار عن سكر الحمل تقدرون تختارون من ال

Q2: Do all insulin releasing drugs cause hypoglycemia?

- **Not all insulin releasing drugs cause hypoglycemia,** if the drug was taken at a certain time and in a certain amount and caused a significant increase in insulin (Hyperinsulinemia) it will cause hypoglycemia

Q3: What is the second line in the treatment of T2DM?

- Depends on the case(treatment protocols differs from one patient to another). But instead of changing the drug you can use combinations to reduce the ADRs
  e.g. Sulfonylureas cause Weight gain so they can be combined with a drug that increase the energy expenditure like Metformin

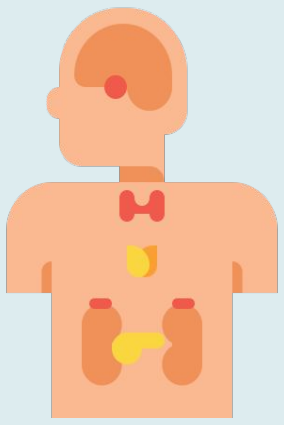
Q4: in the case of heart failure, should I choose Thiazolidinediones or metformin?

- Change the class, you can give Sulfonylureas

Q5: will the diabetic neuropathy be reversed after the treatment with hypoglycemics (after controlling the diabetes)?

- No, controlling the DM is not enough, you’ll need to treat the complications

Feedback Form



Endocrine Block

Pharmacology Team 439

Leaders

Banan AlQady Ghada AlOthman Nawaf Alshahrani

Members

- Arwa alqahtani
- Budoor Almubarak
- Ghada Alabdi
- Hamad Almosa
- Raghad Albarrak
- Saad Aldohaim
- Shuaa Kudary

- Special Thanks to Homoud Algadheb

اللهم ارحم مي بابعير و نجود المطيري و اغفر لهن، اللهم آنس وحدتهن، وآنسهنّ في وحشتهن، وآنسهنّ في غربتهن ، اللهم أنزلهن منزلاً منزلاً مباركًا وأنت خير المنزلين، وأنزلهن منازل الشهداء والصديقين، وحسن أولئك رفيقاً.