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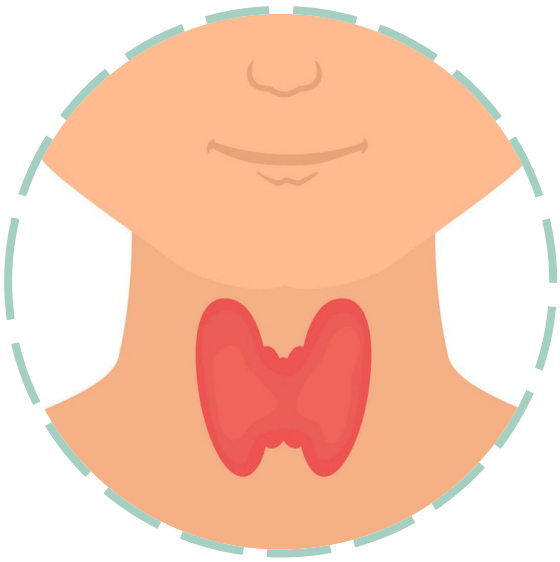

# Endocrine Block

Pharmacology team 438

# Summary


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**Table of contents:**

# Lecture(1): GH & Drugs used in Pituitary adenoma

| Drugs | MOA | Uses | ADRs |
|---|---|---|---|
| **GH agonists (Drugs Used in Case of GH Deficiency)** | | | |
| **Sermorelin** | Synthetic growth hormone releasing hormone (GHRH) | if a patient possesses **defective hypothalamic releasing of GHRH** BUT normally functioning anterior pituitary somatrophs | - |
| **Somatropin**<br>**Somatrem** | Recombinant human growth hormone | -Documented Growth failure in pediatric patients associated with **GH deficiency** and **Turner syndrome.**<br>-Idiopathic short stature.<br>-Wasting muscle in patients with AIDS.<br>-Short bowel syndrome in patients who are also receiving specialized nutritional support. | -**Leukemia.**<br>-Rapid growth of melanocytic lesions<br>-Hypothyroidism.<br>-Insulin resistance.<br>-Arthralgia.<br>-Enzyme inducers. |
| **Mecasermin** | Recombinant IGF-1 | for children with **severe IGF1 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 antagonists (Drugs Used in Case of GH Overproduction )** | | | |
| **Octreotide**<br>**Lanreotide** | **Somatostatin analogues:**<br>**-Mainly Inhibit GH secretion**<br>-Partially inhibits GH-induced IGF-1 generation.<br>-Reduce GHRH release. | - acromegaly & gigantism. | -Significant Gastrointestinal disturbances.<br>-Gallstones.<br>**-Cardiac conduction abnormalities.** |
| **Pegvisomant** | **GH receptor antagonist:**<br>**- cross-link GH receptor but is incapable of inducing the conformational changes** required for receptor activation | | - |
| **Dopamine D2 receptor Agonist** | | | |
| **Bromocriptine** (Safe in pregnancy: no uterotonic\ vasospastic effect)<br>**Cabergoline** (NOT safe in pregnancy) (More effective)<br>**Pergolide Mesylate** (Has strong vasospasm and uterotonic effects) | Selective activation of D2 receptors located on lactotroph cell surface (PRL-producing cells) →**inhibition of PRL synthesis & release.** | **- Prolactinoma ( they are the initial therapy )** | - GI intolerance, postural hypotension, constipation, **nasal stuffiness** |

# Lecture(2&3): Hyper and Hypothyroidism

| Drugs | MOA | Uses | ADRs | ADRs\C.I |
|---|---|---|---|---|
| **Hyperthyroidism** | | | | |
| **1) Thioamides (Antithyroid)** | | | | |
| **Propylthiouracil** (Mostly protein bind) (Less readily crosses placenta) | -**Both PTU and Methimazole:** Inhibits synthesis of thyroid hormones **by inhibiting the peroxidase enzyme.**<br>- **PTU ONLY**: blocks the conversion of $T_4$ to $T_3$ in peripheral tissues | **- Drug of choice in pregnancy**<br>**- Used for breastfeeding** | -Skin reactions<br>-Arthralgia<br>-Gastric distress and nausea<br>-anti-thyroid arthritis<br>**-Agranulocytosis (in patients with Graves disease)** | **Specific ADRs:**<br>**-Immunoallergic hepatitis**<br>-ANCA-positive vasculitis |
| **-Methimazole<br>-Carbimazole** (Free;not bound to plasma protein) (Cross placenta) | | **- Not used in pregnancy nor breastfeeding** | | **Specific ADRs:**<br>-Abnormal sense of taste or smell |
| **2) Iodide\Iodine (Have temporary effect)** | | | | |
| **1- Organic iodides:** iopanoic acid or ipodate<br>**2-Potassium iodide** or lugol's solution | - Inhibit thyroid hormone synthesis and release<br>**- Block the peripheral conversion of $T_4$ to $T_3$** | **-Prior to thyroid surgery**<br>-Following radioactive iodine therapy<br>-Thyrotoxicosis | - iodism | **C.I:**<br>-Pregnancy<br>-Using it as single therapy |
| **3) Radioactive Iodine (RAI)** | | | | |
| **RAI** (Crosses Placenta and excreted in milk) (Disadvantage: Large dose has cytotoxic effect, delayed hypothyroidism) | **-Accumulates in the thyroid gland and destroys parenchymal cells** | **- old patients (above 40)**<br>-Can be used as a diagnostic method | - | - |
| **4) Beta-Blockers** | | | | |
| **-Propranolol<br>-Atenolol<br>-Metoprolol** | - | **-Adjunctive therapy to relief the adrenergic symptoms of hyperthyroidism** | - | **C.I:**<br>-Propranolol in asthma |
| **Hypothyroidism** | | | | |
| **Levothyroxine (T4)** | **Advantages:**<br>-Stable, long T½<br>- once daily | **The drug of choice for replacement therapy** | If overdose:<br>- **Children**: restlessness , insomnia accelerated bone maturation<br>- **Adults**: **cardiac arrhythmia,** tremor, restlessness, headache,weight loss, heat intolerance, muscle pain | **C.I:**<br>-Old patients<br>-cardiac problems |
| **Liothyronine (T3)** | **Advantages:**<br>- Potent, rapid onset<br>**Disadvantages:**<br>- shortT½ | - | - | C.I: cardiac problems |
| **Liotrix** | Combo of T4.T3 **mimic the natural secretion** | | | |

# Lecture(4): Drug used in Osteoporosis

| Drugs | MOA | Uses | ADRs | C.I |
|---|---|---|---|---|
| **Antiresorptive** | | | | |
| **Bisphosphonates** | | | | |
| **Nitrogenous**<br>**-Alendronate**<br>**-Ibandronate**<br>**-Risedronate**<br>**-Zoledronate** | 1. **Bind to calcium** and concentrate in bones, **bound to hydroxyapatite decreasing its solubility** and make it more resistance to osteoclastic activity.<br><br>2. **Prevent bone resorption by Inhibit osteoclast function**<br>-Block steps in cholesterol synthetic pathway in osteoclast leading to apoptosis.<br>***In bones it is retained for months** | -Osteoporosis<br>-Paget's Disease<br>-Malignancy associated with hypercalcemia | **★Should be taken in upright position AND with a large amount of water to prevent esophagitis.**<br><br>-GIT irritation:N&V, gastritis, ulceration<br><br>-Gastroesophageal reflux ± ulceration<br><br>-Flu like manifestation.<br><br>-Atrial fibrillation (w\Alendronate and Zoledronate)<br><br>-Osteonecrosis of the of the mandible bone of jaw (**delay bisphosphonate therapy for a few months until the jaw heals completely**)<br><br>-Calcium and Vit D supplementation should be given **after a gap**, because it can inhibit their absorption | -Decreased renal function<br>-Peptic Ulcer<br>-Esophageal reflux |
| **Non-Nitrogenous**<br>**-Etidronate**<br>**-Clodronate**<br>**-Tiludronate** | | | | |
| **RANKL inhibitors** | | | | |
| **Denosumab** | Fully humanized monoclonal antibody that **mimics the activity of osteoprotegerin (OPG):**<br><br>-**Blocks RANKL from interacting with RANK receptor** expressed on preosteoclast→ ↓osteoclastogenesis → no mature osteoclasts<br><br>-Binds also to mature osteoclasts → increase their apoptosis | -**reserved for patients who cant tolerate nor respond to bisphosphonates** | -Respiratory and urinary infections<br>-Eczema and skin rash<br>-Pancreatitis | -Patients with **hypocalcemia** (denosumab decreases Ca leve) |

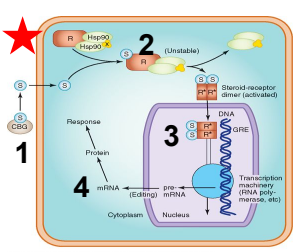
# Lecture(4): Drug used in Osteoporosis

| Drugs | MOA | Uses | ADRs |
|---|---|---|---|
| **Antiresorptive** | | | |
| **Sex Hormones** | | | |
| **Estrogen** | They are **essential for normal bone remodeling:**<br>-↑ osteoclast apoptosis and Inhibit osteoblast apoptosis<br>-↑ release of growth factors from osteoblasts<br>-↓ number and depth of resorption cavities<br>-↓ release of inflammatory cytokines causing resorption | -Hysterectomy: estrogen only<br>-If uterus is present: Estrogen + Progestin<br>-Hormonal Replacement therapy (HRT): menopausal symptoms<br>-SERMs: Menopause\ elderly | -Risk for breast cancer<br>-vaginal bleeding<br>-venous thromboembolism |
| **Androgen** | | -For elderly men only | |
| **Selective Estrogen Receptor Modulators (SERMs)** | | | |
| **Raloxifene** | -Antiestrogens that exhibit partial agonistic action<br>**-Acting as an agonist in bones and an antagonist in female sex organs**<br>-Works only on women especially post-menopausal women | **Advantages:**<br>- Increase bone density and decrease fracture risk<br>- No stimulation of breasts nor endometrial tissue<br>- No need for progestin in women with a uterus<br>- Decrease LDL<br>**- Good for women with a risk of uterine and breast cancer**<br>-Lower risk for thromboembolism compared to estrogen<br><br>**Disadvantages:**<br>- Hot flashes<br>-no effect on HDL | |
| **Antiresorptive + Bone Anabolic Agents (Dual effect)** | | | |
| **Strontium** | -**Effects on Osteoblasts:**<br>1. **Acts as an agonist on Ca Sensing Receptor [CaSR] → enhances** differentiation of preosteoblast to osteoblast .<br>2. **Stimulate the expression of OPG**<br><br>-**Effects on Osteoclasts:**<br>1. **Acts as an agonist on CaSR → suppress** differentiation of preosteoclast to osteoclast. | -Osteoporosis; secondary to menopause or glucocorticoids..etc<br>-Malignancy associated hypercalcemia | **ADR**:<br>-GIT irritation: N&V<br>-headache & eczema<br><br>**C.I:**<br>-Severe renal disease<br>-Risk of venous thromboembolism<br>-Hypersensitivity to the drug<br>**-Phenylketonuria** |

# Lecture(5): drugs used in calcium and Vit D disorder

| Drugs | MOA | Uses | ADRs |
|---|---|---|---|
| **Factors involved in Ca metabolism & bone remodeling** | | | |
| **Parathyroid Hormone (PTH)** | - released **in response to low Ca2+ level**<br>- **Increase plasma Ca2+ levels by**:<br>- **Bone**: stimulation of osteoclasts to ↑ outward flux of Ca2+ to restore serum calcium level<br>- **Kidney:** ↑ Ca2+ active reabsorption and ↑ formation of calcitriol<br>- **GIT:** ↑ reabsorption of Ca2+ | - Treatment of severe osteoporosis<br>- Resistant cases failed to respond to other medication<br>★ **Daily, intermittent** administration of recombinant human PTH → **net stimulation of bone formation for treatment of osteoporosis**<br>★ **Continuous** or chronic exposure to high serum PTH conc. (like in hyperparathyroidism ) → **bone resorption and risk of fractures** | – |
| **Teriparatide** | Synthetic polypeptide form of PTH (PTH analogue) same mechanism of action | - **Should not be used routinely due to carcinogenic effects**<br>- Severe osteoporosis or patients not responding to other drugs<br>- Osteoporosis in people who have risk of getting fracture<br>- Good for postmenopausal osteoporosis | **ADRs:**<br>- **Carcinogenic effect (osteosarcoma)**<br>- Elevated serum Ca2+ lead to kidney stones<br>- Diarrhea, heartburn, nausea<br>- headache, leg cramps<br>- **Orthostatic hypotension**<br>**C.I:**<br>Should not be used in people with ↑ risk for (osteosarcomas):<br>- People with paget's disease<br>- People who had radiation treatment involving bones<br>-**Not recommended in children** |
| **Calcitonin** | - Released in response to **rise plasma Ca2+ levels.**<br>- Causes **rapid fall in Ca2+** through:<br>- **Bone:**↓resorption by inhibiting osteoclast activity.<br>- **Kidney:** ↓ **reabsorption** of Ca2+ & PO4 | - Osteoporosis (major indication, alternative to other drugs)<br>- Hypercalcemia (short term treatment of hypercalcemia of malignancy)<br>-Paget's disease<br>- Has **Lower efficacy** compared to other drugs | - Nause<br>- Flushing of face & hands<br>- Nasal irritation<br>- Local inflammation at site of injection |
| **Vit D**<br>**(2 Forms:**<br>**- D3 cholecalciferol [skin]**<br>**-D2 Ergocalciferol [plant] )** | **- Increases plasma Ca2+ levels:**<br>- **Bone:** ↑ bone resorption<br>- **GIT:** ↑ Ca2+ absorption<br>- **Kidney**: ↑ reabsorption of Ca2+ | - Rickets and osteomalacia<br>-psoriasis<br>-Osteoporosis<br>-Cancer prevention (Prostate and colorectal ) | – |

# Lecture(6): Glucocorticoids

| Drugs | MOA | Uses | ADRs |
|---|---|---|---|
| **Corticosteroid Agonists** | | | |
| **Glucocorticoid**<br>**Cortisol** (Hydrocortisone)<br>-Short duration<br>- Poorly diffuse<br>-little mineralocorticoid effect ( causes hypertension) | 1-in the blood they **bound to the corticosteroid binding globulin (CBG)**<br><br>2- The intracellular receptor is bound to the **stabilizing proteins** (Hsp90) and several others (X). **When a molecule of steroid binds to the receptor, the Hsp90 and others are released.**<br><br>3- The Steroid – receptor complex enters the nucleus, **binds to the glucocorticoid response element (GRE)** on the gene, and regulates gene transcription by RNA polymerase 2.<br><br>4- The resulting mRNA is edited and exported to the cytoplasm for the production of protein that brings the final hormone response.<br><br>  <br> | ***Adrenal Disorder:**<br>**1. Addison's disease**<br>**2. Acute adrenal insufficiency**<br>**3. Congenital adrenal hyperplasia**<br><br>***Non- adrenal Disorder:**<br>**1. Allergic reactions.**<br>**-Beclomethasone & budesonide use in asthma** and other condition in which good surface activity on mucous membrane or skin(systemic effect and toxicity are reduced)<br>**2. Collagen vascular disorder**<br>**3. Organ transplants**<br>**4. GI disorders**<br>**5. Hematologic disorders**<br>**6. Infections**<br>**7. Neurologic disorders**<br>**8. Pulmonary diseases**<br>**9. Thyroid diseases**<br>**10. Renal disorders**<br>**11. Miscellaneous** | **Toxicity**<br>**(when gevin in high doses > than 100 mg daily for > than 2 weeks) :**<br>1. **Cushing's syndrome**<br>2. Increased growth of fine hair on face, thighs & trunk, myopathy, muscle wasting,<br>thinning of skin<br>, **Diabetes Mellitus**<br>3.**Osteoporosis** & aseptic necrosis of the hip<br>4. **Wound healing is impaired**<br>5. Peptic ulcer<br>6. Acute psychosis, depression<br>7. Subcapsular cataracts<br>8. **Growth suppression**<br>9. **Hypertension**<br>10. Adrenal suppression |
| **Synthetic Glucocorticoids:**<br>- Prednisone (active metabolite Prednisolone)<br>-Dexamethasone<br>-Beclomethasone<br>-Budesonide<br><br>-Longer duration<br>-Longer half life<br>-Better penetration<br>-reduced mineralocorticoid effect | | | |
| **Mineralocorticoid**<br>**- Aldosterone**<br>**- Fludrocortisone**<br>-Promote Na reabsorption and K excretion<br>-Aldosterone has little glucocorticoid activity and short half life | | - Fludrocortisone is favored for **replacement therapy** after adrenalectomy<br><br>- other conditions in which mineralocorticoid therapy is needed. | - |

| Drugs | MOA | Uses |
|---|---|---|
| **Corticoids Antagonist** | | |
| **1) Receptor Antagonist** | | |
| **Spironolactone** | -**mineralocorticoid antagonist** & K-sparing diuretic | Treatment of primary aldosteronism **(Conn's syndrome)** |
| **Mifepristone** | -A competitive inhibitor of **glucocorticoid receptors** | -Treatment of **Cushing's syndrome** |
| **2) Synthetic Inhibitors** | | |
| **Ketoconazole ( Anti Fungal )** | -It inhibits the cytochrome p450 enzymes necessary for the synthesis of all steroids | -used to reduce steroid level in: **Adrenal cancer**, hirsutism, breast cancer, prostate cancer |

# Lecture(7): Uses of insulin in DM

| Drugs | Characteristics | Uses | ADRs | Advantages |
|---|---|---|---|---|
| **Insulin sources: recombinant human analogue** | | | | |
| **Ultra-short acting insulins (Monomeric) e.g. Lispro, aspart, glulisine** | | | | |
| **Insulin *lispro***<br>**Insulin *aspart***<br><br>**Onset: 15mins**<br>**Duration: 4hrs** | Clear solutions at neutral pH.<br>• S.C. (5 -15 min before meal) & **I.V. in emergency situations** | -external insulin pump<br>(doesn't clog the pump)<br>-control postprandial hyperglycemia (s.c.)<br>-**emergency diabetic ketoacidosis (i.v).** | We R Laughing<br>Ha Ha Ha<br><br>**Weight gain** (due to anabolic effects of insulin)<br><br>**Insulin resistance**<br><br>**Lipodystrophy** (a buildup of fatty tissue) at the injection sites.<br><br>**Hypersensitivity**<br><br>**Hypoglycemia (Most important)**<br><br>**Hypokalemia** | **Advantage:**<br><br>Rapid onset of action.<br>-Duration of action is no longer than 3-4 hrs *regardless of the dose*:<br>**-Decreased risk of hyperinsulinemia (thus less hypoglycemia risk).** |
| **Short acting insulins (Hexameric) e.g. Humulin R, Novolin R** | | | | |
| **Humulin R**<br>**Novolin R**<br>**(Regular insulin)**<br><br>**Onset: 30mins**<br>**Duration: 8hrs** | Soluble crystalline zinc insulin.<br>Clear solutions at neutral pH.<br>• S.C. & **I.V. in emergency situations** | -Control postprandial hyperglycemia (s.c.) & **emergency diabetic ketoacidosis (i.v.)**<br>-Can be used in **pregnancy.** | | - |
| **intermediate acting insulins e.g. NPH, Lente** | | | | |
| **Isophane (NPH) insulin**<br>Neutral Protamine Hagedorn insulin *in phosphate buffer*<br><br>**Onset: 1hr**<br>**Duration: 16hrs** | Turbid suspension at neutral pH.<br>• Given S.C., **not I.V** | Can **not** be used in ketoacidosis or emergency | | **Insulin Mixtures:**<br>1- NPH\ R insulin<br>2- NPL + NPA<br><br>**Advantage:**<br><br>Have two peaks<br>(reduce the use of injections for the diabetic patients and provide a basal level of insulin during the day) |
| **Lente insulin**<br>**(Humulin L, Novolin L)**<br><br>**Onset: 1hr**<br>**Duration: 16hrs** | Turbid suspension at neutral pH.<br>• Given S.C., **not I.V**<br>**Mixture of :**<br>-30% semilente insulin **(amorphous precipitate of zinc insulin *in acetate buffer*)**<br>-70% ultralente insulin **(poorly soluble crystal of zinc insulin)** | | | - |

# Lecture(7): Uses of insulin in DM

| Drugs | Characteristics | Uses | ADRs | Advantages |
|---|---|---|---|---|
| **Insulin sources: recombinant human analogue** | | | | |
| **Long acting insulins e.g. insulin glargine (lantus), insulin detemir (Levemir)** | | | | |
| **Insulin glargine (lantus)**<br><br>**Onset: 2hrs**<br>**Duration: 24hrs** | -Clear solution **BUT** forms precipitate (hexamer) at injection site.<br>- Shouldn't be mixed w\other insulins in the same syringe.<br>• Given S.C. only, **not I.V** | Can **not** be used in ketoacidosis or emergency | **-Weight gain**<br>**-Insulin resistance**<br>**-Lipodystrophy**<br>**-Hypersensitivity**<br>**-Hypoglycemia**<br>**-Hypokalemia** | **Advantage:**<br>-Constant circulating insulin **(peak-less profile)** over **24 hr**<br>**-Produce flat prolonged hypoglycemic effect.**<br>-*reduced risk of nocturnal hypoglycemia* → Safer than NPH & Lente insulins. |

## Dosing Consideration:

-Blood glucose **monitoring** is required in all patients receiving insulin.
-**Rotate injection** sites within the same region.
-Insulin should be **stored in refrigerator** and **warm up to room temp before use.**

# Lecture(8): Management of DKA and Hypoglycemia

## 1) Diabetic Ketoacidosis "DKA"

- Emergency condition develops as a result of **insulin deficiency**
- **Symptoms: Ketotic breath (fruity w\acetone smell )** polyuria and thirst, tachycardia, Kussmaul–Kien respiration, Nausea, vomiting, abdominal pain, Mental status changes (confusion, coma)

### Treatment:

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

## 2) 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:**
  - **Autonomic:**
    - ↑**sympathetic**: tachycardia, palpitation, sweating, anxiety, tremor.
    - ↑**parasympathetic**: nausea, vomiting.
  - **Neurological:**
    - **coma** due to low glucose delivery to the brain
    - headache, visual disturbance, slurred speech, dizziness, tremors, mental confusion, convulsions

### Treatment:

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

# Lecture(9&10): Oral Hypoglycemic Drugs

## Treatment of Type II Diabetes (NIDDM)

1. Proper dietary management.
2. Increase physical activity.
3. Caloric restriction and weight loss are IMP in obese diabetic patients.
4. Oral antidiabetic drugs.

## Oral hypoglycemic drugs(Antidiabetic drugs ):

**1- Insulin sensitizers :** Biguanides, Thiazolidinediones
**2- Insulin secretagogues:** Sulfonylurea, Meglitinides, Incretin mimetics.
**3- Agents that reduce carbohydrate absorption:** Alpha glucosidase inhibitors
**4- Agents that reduce glucose renal reabsorption:** Sodium/glucose cotransporter 2 (SGLT2) inhibitors

| Drugs | MOA | Uses | ADRs | C.I |
|---|---|---|---|---|
| **Insulin sensitizers** | | | | |
| **Biguanides** | | | | |
| **- Metformin** | - Reduces insulin resistance.<br>**- Increases sensitivity of liver, muscle & adipose tissues to insulin & increase peripheral glucose utilization (tissue glycolysis).**<br>- Inhibits hepatic (gluconeogenesis).<br>- Impairs glucose absorption from GIT.<br>**- Improve lipid profile : ↓LDL, ↓ VLDL , ↑HDL** | **- In patients with type 2 diabetes who are obese (first-line therapy)**.<br>- Treatment of Type 2 diabetes monotherapy or in combination with other antidiabetic drugs. | **- GIT disturbances:** metallic taste, N&V, diarrhea (**should be taken with meals + started at a low dose** to avoid intestinal side effects then increase gradually)<br>**- Lactic acidosis** (renal\ pulmonary insufficiency, liver diseases, alcoholism, Heart failure, cardiogenic\septic shock)<br>**- In long term use:** Interference with **vitamin B12** absorption | - Renal disease<br>- Liver disease<br>-Cardiopulmonary dysfunction<br>- Pregnancy<br>- Alcoholism<br>**Advantages:**<br>**-No risk of hypoglycemia**<br>**- No weight gain**<br>**- prominent lipid-lowering effect** |
| **Thiazolidinediones** | | | | |
| **- Pioglitazone**<br>**- Rosiglitazone** | - Activate peroxisome proliferator-activated receptor-Gamma **(PPAR-Gamma)**<br>- Increase sensitivity of target tissues to insulin.<br>- Increase glucose uptake and utilization in muscle and adipose tissue | - Type II diabetes with insulin resistance.<br>- Used either alone or in combination with sulfonylurea, biguanides or insulin.<br>**- No risk of hypoglycemia when used alone** | - Hepatotoxicity (monitor liver function test)<br>**- Fluid retention (Edema)**<br>**- Congestive heart failure**<br>- Failure of estrogen-containing oral contraceptives.<br>- Mild weight gain | |

# Lecture(9&10): Oral Hypoglycemic Drugs

| Drugs | MOA | Uses | ADRs | C.I |
|---|---|---|---|---|
| **Insulin secretagogues** | | | | |
| **Sulfonylurea drugs** | | | | |
| 1st generation:<br>-**Tolbutamide**<br>**(Short acting)**<br>**-Acetohexamide**<br>**(Long acting)** | Blockade of ATP dependent K+channels→ Opening of voltage-dependent Ca+ channels → ↑intracellular calcium in the beta cells → ↑Insulin release | Treatment of Type 2 diabetes as monotherapy or in combination with other antidiabetic drugs | **- Weight gain due to increase in appetite**<br>**-Hyperinsulinemia & Hypoglycemia:** More common in long acting sulfonylureas; particularly (glyburide, and glimepiride)<br>- **Allergy** | - |
| 2nd generation:<br>**- Gliclazide**<br>**- Glipizide**<br>**(Short acting)**<br>**- Glyburide (glibenclamide)**<br>**- Glimepiride**<br>**(Long acting )** | | | | **characteristics :**<br>-More potent than first generation<br>-Have longer duration of action.<br>-Have fewer adverse effects & drug interactions. |
| **Meglitinides** | | | | |
| **- Repaglinide**<br>**(Dose should be skipped if the meal missed)** | **- Rapidly** acting insulin secretagogues<br>- Mechanism of action is identical to sulfonylureas | **As alternative to sulfonylureas (SU) in patients allergic to SU** and in elderly | - Hypoglycemia.<br>- Weight gain.<br>(Less incidence than sulfonylureas) | - |
| **Incretin mimetics** | | | | |
| GLP-1 agonists:<br>**- Liraglutide (Victoza, Saxenda)** | - Binds to GLP-1 receptors & **stimulates insulin secretion** from β cells<br>- It also **reduces glucagon secretion** by inhibiting alpha cells of the pancreas<br>- It decreases appetite and **inhibits body weight gain** | **Saxenda**: As a treatment **overweight adults with at least one weight-related comorbid condition**<br>- Type II DM as an adjunct to diet & exercise as a monotherapy or in combination with other antidiabetic drugs | - N&V and diarrhea (most common)<br>- Hypoglycemia when combined with sulfonylureas or insulin (not alone)<br>- Pancreatitis (rare) | Not used in type 1 diabetes |
| DPP- 4 inhibitors:<br>**- Sitagliptin** | Inhibit DPP-4 enzyme and leads to an increase in incretin hormones (GLP-1) level | | - Nausea, abdominal pain, diarrhea<br>- Nasopharyngitis<br>- Headache | - |

# Lecture(9&10): Oral Hypoglycemic Drugs

| Drugs | MOA | Uses | ADRs | C.I |
|---|---|---|---|---|
| **α-Glucosidase inhibitors** | | | | |
| **- Acarbose**<br>**- Miglitol** | - Reversible inhibitors of **intestinal α-glucosidases** in intestinal brush border cells **that are responsible for carbohydrate digestion.**<br>- Decrease carbohydrate digestion and glucose absorption in small intestine **(lower postprandial glucose level).** | -Are effective alone in the earliest stages **of impaired glucose tolerance** (pre-diabetes) | - GIT: **Flatulence, bloating,** diarrhea, abdominal pain. | - Irritable bowel syndrome.<br>- Inflammatory bowel disorders.<br>- Intestinal obstruction |
| **Sodium-glucose transporter 2 inhibitors** | | | | |
| **- Canagliflozin**<br>**- Dapagliflozin**<br>**- Empagliflozin** | Inhibits SGLT2 in the kidneys→inhibits glucose and Na reabsorption→ excess glucose excretion→ reduce blood sugar levels. | - To **reduce risk of major adverse cardiovascular events** in adults with type 2 diabetes and established cardiovascular disease. | **- Urinary tract infections.**<br>**- Yeast infections (vagina or penis)**<br>- Increased urination and dry mouth.<br>-thirst<br>-itching<br>-fatigue | - |