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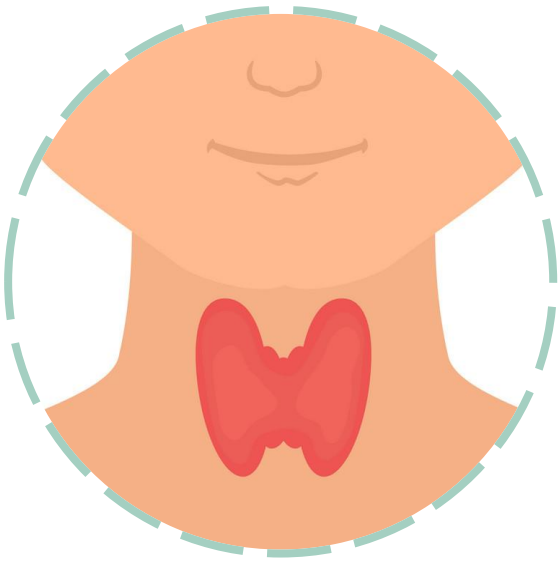
Mnemonic File



Endocrine Block

Pharmacology team 438

Oral Hypoglycemic Drugs

Objectives:

By the end of the lecture , you should know:

- Classify different categories of antidiabetic drugs.
- Identify mechanism of action, pharmacokinetics and pharmacodynamics of each class of antidiabetic drugs.
- Identify the clinical uses of antidiabetic drugs
- Know the side effects, contraindications of each class of antidiabetic drugs.

Color index:

Black : Main content
Red : Important
Blue: Males' slides only
Purple: Females' slides only
Grey: Extra info or explanation
Green : Dr. notes

Types of diabetes mellitus

Type II

Due to obesity & genetic factors

-80-90% occurrence

-Over age 35

VS

Type I

Due to autoimmune or viral diseases (the only treatment for insulin dependent diabetes is insulin injections)

Patients with Type II diabetes have two physiological defects:

1. Abnormal insulin secretion. (partial production of insulin)
2. Resistance to insulin action in target tissues associated with decreased number of insulin receptors.

Treatment of Type II Diabetes (NIDDM)[1]

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

Oral hypoglycemic drugs (Antidiabetic drugs)

1 Insulin secretagogues [2]:

1. **Sulfonylurea drugs.**
2. **Meglitinides.**
3. **Incretin mimetics.**

2 Insulin sensitizers [3]:

1. **Biguanides**
2. **Thiazolidinediones**

3 Agents that reduce carbohydrate absorption:

1. **Alpha glucosidase inhibitors**

4 Agents that reduce glucose renal reabsorption (Increase glucose excretion):

1. **Sodium/glucose cotransporter 2 (SGLT2) inhibitors**

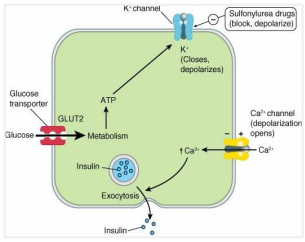
1. Type 2 diabetes is managed through a stepwise approach, starting with diet and exercise, followed by oral hypoglycemic drugs, then combination therapy if the patient is not responding to monotherapy of oral hypoglycemics, and finally in advanced severe cases insulin injections are used.
2. They increase the production of insulin
3. They increase the sensitivity of peripheral tissues to insulin.

Insulin secretagogues

- Are drugs which increase the amount of insulin secreted by the pancreas
- ★ Their action depends upon **functioning** pancreatic β-cells (Not for T1D)
- It includes: 1. Sulfonylureas 2. Meglitinides 3. Incretin mimetics

1) sulfonylureas

Prof.Hanan= memorize the highlighted drugs

Class	First generation (-amide)		Second generation (-ride/zide)	
Drug	-Acetohexamide -Tolazamide -Chlorpropamide	- Tolbutamide	- Glyburide (glibenclamide) - Glimepiride	- Gliclazide - Glipizide
	Long acting	Short acting	Long acting (-ride)	Short acting (-zide)
MOA	• ↑Hyperglycemia→Blockade of ATP dependent K+channels→ Opening of voltage-dependent Ca+ channels → ↑intracellular calcium in the beta cells → ↑Insulin release • Stimulate insulin release from functioning B cells by **blocking of ATP-sensitive K channels** which causes depolarization and **opening of voltage- dependent calcium channels,** which causes an increase in intracellular calcium in the beta cells, which stimulates insulin release. 			
P.K	• **Orally**, well absorbed. ★ 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.**[1] • Reach peak concentration after 2-4 hr • Duration of action is variable • Metabolized in liver			
	-		• More potent than first generation • Have longer duration of action. • Have fewer adverse effects & drug interactions. • Less frequency of administration.	
Uses	• Treatment of Type II diabetes monotherapy or in combination with other antidiabetic drugs [2]			
ADR	1. **Hyperinsulinemia & Hypoglycemia:** ○ More common in long acting sulfonylureas; particularly (glyburide, and glimepiride) ○ More in old age, hepatic or renal diseases. 2. **Weight gain due to increase in appetite** unless the diabetic diet and exercise program are followed. 3. **Allergy manifestation as they contain Sulfa.**			

	Glipizide	Glyburide (Glibenclamide)	Glimepiride
Absorption	Well reduced by food	Well	
Metabolism	Yes	Yes	
Duration of action	10 – 16 hrs, short	12 – 24 hrs, long	
Doses	Divided doses 30 min before meals	Single dose	
Excretion	Urine		

1. All hypoglycemic drugs are C.I during pregnancy, even if the patient was diagnosed with type 2 diabetes. The only treatment that is allowed during pregnancy is insulin.
2. Determined by measuring blood glucose level and the patient's response to the treatment

2) Meglitinides

Drug	Repaglinide (-glinide)
MOA	• **Rapidly** acting insulin secretagogues • Mechanism of action is identical to sulfonylureas (↑Hyperglycemia→**Blockade of ATP dependent K+channels→ Opening of voltage-dependent Ca+ channels** → ↑intracellular calcium in the beta cells → ↑Insulin release)
P.K	• **Orally**, well absorbed. ★ 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** [1]**.**
Uses	• Type II diabetes as a monotherapy or in combination with other oral hypoglycemic drugs ★ **As alternative to sulfonylureas (SU) in patients allergic to SU** and in elderly
ADR	• Less incidence than sulfonylureas [2]: ○ Hypoglycemia. ○ Weight gain.

3) Incretin mimetics

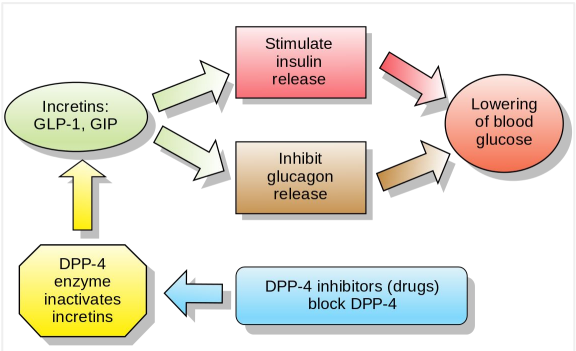
Incretins

➔ They are **GI hormones secreted from intestine** in response to food even before blood glucose level becomes elevated.

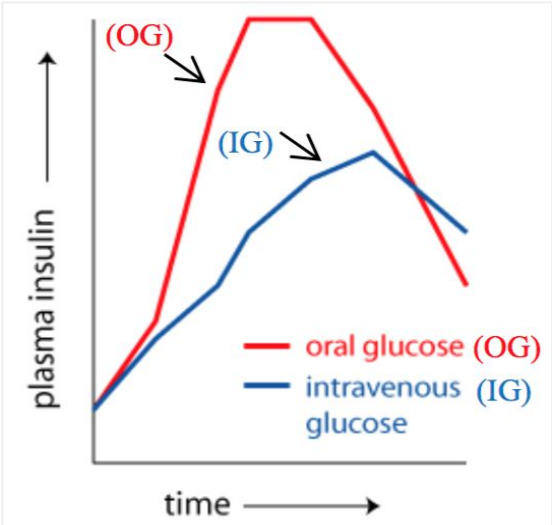
➔ They are carried through circulation to pancreatic beta cells.

★ **Incretins regulate blood glucose by (MAO):**
- ◆ Increase insulin secretion
- ◆ Decrease glucagon secretion

➔ **Incritine includes:**
- ◆ **GLP-1 (glucagon-like peptide-1)**
- ◆ **GIP (gastric inhibitory peptide)**
- ◆ Both are inactivated by **dipeptidyl peptidase-4 (DPP-4)**



- A comparison between the the amount of insulin secretion in response to Oral and I.V glucose.
- It shows that oral glucose induces insulin secretion more than I.V glucose due to the action of **incretins**



1. To avoid hypoglycemia.
2. Because they have shorter duration of action.

Types of Incretin mimetics

GLP-1 agonists (-glutide)

- **Dulaglutide** (Trulicity[1])
- **Liraglutide**
  - Victoza [1], the lower dose for diabetes
  - Saxenda [1], the higher dose for obesity
- **Exenatide**
  - Byetta, immediate-release given S.C. twice daily
  - Bydureon, extended-release given once weekly
- **Semaglutide** (Rybelsus[1]) the first **oral** GLP-1

DPP- 4 inhibitors (-gliptin)

- **Sitagliptin** (Januvia[1])
- **vildagliptin**
- **Linagliptin**

Class	GLP-1 agonists (-glutide)	DPP- 4 inhibitors (-gliptin)
Drugs	**Liraglutide (Victoza, Saxenda)**	**Sitagliptin (Januvia)**
MOA	• Binds to GLP-1 receptors & stimulates insulin secretion from β cells • It also reduces glucagon secretion by inhibiting a cells of the pancreas ★ It decreases appetite and **inhibits body weight gain**	• Inhibit DPP-4 enzyme and leads to an increase in incretin hormones (GLP-1) level. This results in an increase in insulin secretion & decrease in glucagon secretion
P.K	• given **s.c.** once/day (single- dose prefilled disposable pens) • The maximum dose of Victoza is 1.8mg [2]	• given orally • given once daily • half life = 8– 14 h
Uses	• **Saxenda**: As a treatment for adults who are obese or **overweight with at least one weight-related comorbid condition** (e.g. hypertension, type 2 diabetes mellitus, or dyslipidemia). • Used together with diet and exercise to treat type 2 diabetes and in patients who are not controlled with other oral antidiabetics.	• Type II DM as an adjunct to diet & exercise as a monotherapy or in combination with other antidiabetic drugs
ADR	• Nausea,vomiting and diarrhea (most common) • Hypoglycemia when combined with sulfonylureas or insulin (not alone) • Loss of appetite • Pancreatitis (rare)	• Nausea, abdominal pain, diarrhea • Nasopharyngitis • Headache
C.I	Not used in type 1 diabetes	-

1. Trade name
2. to avoid the dose side effects, you give partial doses (e.g. starting at 0.6) and gradually increasing it (0.8, 1.2, etc) but the maximum is 1.8

Insulin sensitizers[1]

Drugs that increase the sensitivity of peripheral target organs to insulin

- **Biguanides** E.g. Metformin
- **Thiazolidinediones** E.g Pioglitazone

1) Biguanides

Drug	Metformin
MOA	• 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
P.K	• **Orally** • Not bound to serum protein, t 1/2: 3 hours. • Not metabolized, excreted unchanged in urine
Advantages	★ **No risk of hypoglycemia**[2] • No weight gain • has prominent lipid-lowering activity[3] • Inexpensive
Uses	★ **In patients with type 2 diabetes who are obese** because it promotes modest weight reduction **(first-line therapy)**. • Type 2 diabetes as monotherapy or in combination with other antidiabetics.

ADR	• **GIT disturbances**[4]**:**
	  ○ Metallic taste in the mouth, nausea, vomiting, diarrhea
	  ○ Metformin **should be taken with meals** and **should be started at a low dose** to avoid intestinal side effects then increase gradually.
	★ **Lactic acidosis**[5] **(very rare):**
	  ○ Serious lactic acid accumulation usually occurs only in the presence of predisposing conditions:
	  ■ Renal insufficiency
	  ■ Severe liver disease
	  ■ Alcohol abuse[6]
	  ■ Heart failure[7]
	  ■ Pulmonary insufficiency[7]
	  ■ Cardiogenic or septic shock[7]
	• **In long term use:** Interference with **vitamin B12** absorption[8].

C.I	• Renal disease • Liver disease • Cardiopulmonary dysfunction • Pregnancy • Alcoholism

1: **first line therapy** afterlife style modifications.
2: only happens with insulin secretagogues, because they ONLY increase the sensitivity and won't increase insulin secretion.
3: very beneficial as most diabetic patients have abnormal lipid profile, these drugs are even used by some obese patients to decrease obesity and correct lipid profile without the risk of hypoglycemia.
4: particularly at the beginning of the therapy, ask patient to tolerate GIT disturbances as they will **subside** in a few weeks
5: due to their glycolytic action
6: because alcohol itself increases glycolysis
7: due to low oxygen delivery to tissues. Tissues start depending more on glycolysis so patient already has high glycolysis.
8: later on in the therapy when B_{12} absorption is affected it is recommended to give the patient supplements.

2) Thiazolidinediones

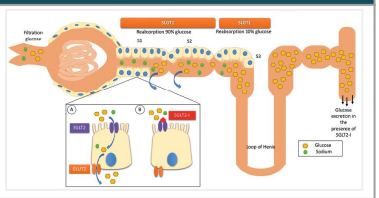
Drug	Pioglitazone & Rosiglitazone (-glitazone)
MOA	• Activate peroxisome proliferator-activated receptor-Gamma **(PPAR-Gamma[1])** • Increase sensitivity of target tissues to insulin. • Increase glucose uptake and utilization in muscle and adipose tissue
P.K	• **Orally** (once daily dose). • Highly bound to plasma albumins (99%) • Slow onset of activity • Half life 3-4 h[2] • Metabolized in the liver • Excreted in bile and urine
Uses	• Type II diabetes with insulin resistance. • Used either alone or in combination with sulfonylurea, biguanides or insulin. ★ No risk of hypoglycemia when used alone
ADR	• Hepatotoxicity (monitor liver function tests for 1st year of therapy). ★ Fluid retention (Edema) ★ Congestive heart failure[3] • Mild weight gain • Failure of estrogen-containing oral contraceptives[4]

α-Glucosidase inhibitors

Drug	Acarbose	Miglitol
MOA	• 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).	
P.K	• No hypoglycemia if used alone • Given orally, not absorbed[5] and taken just before meals.	-
Uses	★ Are effective alone in the earliest stages **of impaired glucose tolerance[6]** • Are not recommended alone as therapy for moderate to severe hyperglycemia[7] ○ Most useful in combination with other oral hypoglycemic drugs or with insulin.	
ADR	• GIT: **Flatulence, bloating,** diarrhea, abdominal pain.	
C.I	• Irritable bowel syndrome. • Inflammatory bowel disorders. • Intestinal obstruction	

1: present in peripheral tissue, increase the tissues' insulin sensitivity.
2: only given once daily despite short half life because even though its plasma level decreases, its effect (configurations changes) that it does to the receptor are long lasting.
3: not given to cardiac patients. 4: drug-drug interaction
5:advantage as its effect is in the GIT. 6: pre-diabetes
7: not given alone if patient is proven to be diabetic

Sodium-glucose transporter 2 inhibitors

Drug	Canagliflozin, Dapagliflozin, Empagliflozin (-gliflozin)
MOA	• Inhibits SGLT2 in the kidneys→inhibits glucose and Na reabsorption→ this allows excess glucose to be excreted in the urine→ this will reduce blood sugar levels. 
Uses	• Used with diet and exercise to control high blood sugar in patients with type 2 diabetes. • To **reduce risk of major adverse cardiovascular events**[1] in adults with type 2 diabetes and established cardiovascular disease.
ADR	★ Urinary tract infections. ★ Yeast infections[2](vagina or penis) • Increased urination and dry mouth. • Thirst • Itching (vagina or penis) • Fatigue

Summary from Dr. slides

Class \ Drug	Mechanism	Site of Action	Main Advantages	Main ADRs
Sulfonylureas **E.g Gliclazide**	Stimulates insulin secretion	Pancreatic beta-cells	- Effective - Inexpensive	- Hypoglycemia - Weight gain
Meglitinides **E.g Repaglinide**			- Sulfa free	
Biguanides **E.g Metformin**	Decrease insulin resistance	Liver	- Mild weight loss - No hypoglycemia	- GI symptoms - Lactic Acidosis - Metallic taste
Thiazolidinediones **E.g Pioglitazone**		Fat, muscle	- No hypoglycemia	- Hepatotoxicity - Edema - Mild weight gain
Incretins mimetics **E.g Dulaglutide**	Increase incretin	GI tract	- S.C once a day	-N&V
DPP-4 inhibitors **E.g Sitagliptin**	Inhibit incretin breakdown		- Orally	- N & abdominal pain
a-Glucosidase **E.g Acarbose**	Decrease glucose absorption in small intestine		- Low risk	- GI symptoms, flatulence
SGLT-2 inhibitors **E.g Dapagliflozin, Canagliflozin**	Inhibit renal SGLT-2	Kidney	- Orally - Reduced Na (CV benefits)	- Genital yeast - UTI - Increased Urination

1: used in patients with cardiac problems due to its effect on sodium excretion.
2: e.g.: candidiasis.

Quiz

MCQ

Q1- Which of the following classes of oral diabetes drugs is paired most appropriately with its primary mechanism of action?

A. DPP-4 inhibitor—inhibits breakdown of complex carbohydrates.
B. Sulfonylurea—increases insulin secretion.
C. Thiazolidinedione—decreases hepatic gluconeogenesis.

Q2- Which of the following statements is characteristic of metformin?

A. Metformin is inappropriate for initial management of type 2 diabetes.
B. Metformin decreases hepatic glucose production.
C. Metformin undergoes significant metabolism via the cytochrome P450 system.
D. Metformin should not be combined with sulfonylureas or insulin.
E. Weight gain is a common adverse effect.

Q3- A 64-year-old woman with a history of type 2 diabetes is diagnosed with heart failure. Which of the following medications would be a poor choice for controlling her diabetes?

A. Glyburide. B. Nateglinide. C. Pioglitazone. D. Sitagliptin.

Q4- KD is a 69-year-old male with type 2 diabetes and advanced chronic kidney disease. Which of the following diabetes medications is contraindicated in this patient?

A. Glipizide. B. Metformin. C. Liraglutide. D.Tolbutamide

Q5- Which of the following drugs for diabetes would be LEAST likely to cause weight gain?

A. Glimepiride. B. Liraglutide. C. Pioglitazone. D. Repaglinide.

Q6- Which of the following diabetes medications is most appropriately paired with an adverse effect associated with its use?

A. Canagliflozin—lactic acidosis. B. Metformin—urinary tract infections.
C. Repaglinide—heart failure. D. Liraglutide—pancreatitis.

SAQ

- 48-years-old male who is obese and he failed to loss his weight with diet and exercises , his blood glucose and lipid is significantly high and has diagnosed with type 2 DM.

Q1- Which drug is the first line of treatment in his case?
Q2- What is the M.O.A of that drug?
Q3- If the patient drinks alcohol almost daily and he did not tell his doctor that , what is the adverse effect that could be seen in this patient after taking the drug in q1?

Q4- Newly patient who was prediabetes, he is diagnosed now with type 2 diabetes. The medical history relieves that he can not tolerance Sulfasalazine or sulfamethoxazole. What is the drug that can be safe to be used in his case ?

Q5- 45-years-old female with type 2 diabetes, she has history of IBD "Crohn's disease", what is the drug that contraindicated in this case?

Answers:

MCQ

Q1	B
Q2	B
Q3	C
Q4	B
Q5	B
Q6	D

SAQ

Q1	Metformin
Q2	Increases liver,muscle & adipose tissues sensitivity to insulin & increase peripheral glucose utilization (tissue glycolysis)
Q3	Lactic acidosis
Q4	Repaglinide
Q5	α-Glucosidase inhibitors E.g. Acarbose, Miglitol

pharmacology

Team 438

Thank you for all your love and support.

Good luck future doctors!

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