Pharmacology
Team 437

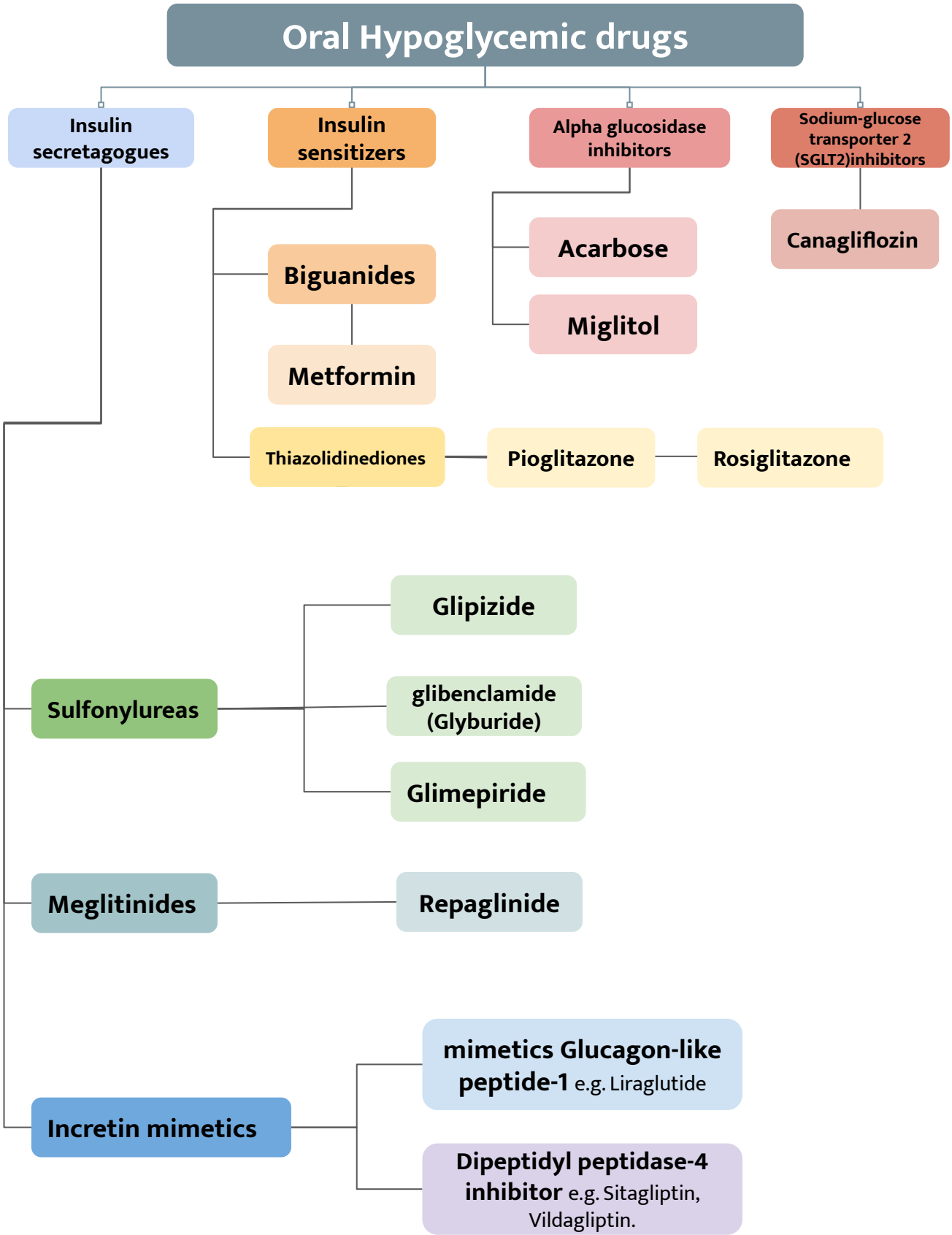
MED437
KING SAUD UNIVERSITY

Oral Hypoglycemic Drugs

Color index:
Important
Note
Extra

Editing File

Mind map


Oral Hypoglycemic drugs
Insulin secretagogues
Insulin sensitizers
Alpha glucosidase inhibitors
Sodium-glucose transporter 2 (SGLT2)inhibitors
Acarbose
Miglitol
Canagliflozin
Biguanides
Metformin
Thiazolidinediones
Pioglitazone
Rosiglitazone
Glipizide
Sulfonylureas
glibenclamide (Glyburide)
Glimepiride
Meglitinides
Repaglinide
mimetics Glucagon-like peptide-1 e.g. Liraglutide
Incretin mimetics
Dipeptidyl peptidase-4 inhibitor e.g. Sitagliptin, Vildagliptin.

Types of Diabetes Mellitus

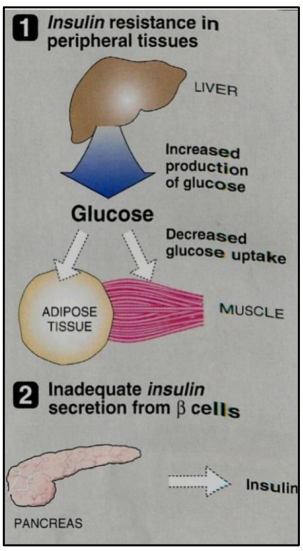
Diabetes

Type 1

Causes:
due to autoimmune or viral diseases

Type 2

Causes:*
Due to obesity, genetic factors.
Epidemiology:*
80-90% occurrence, over age 35, obesity is an important factor.

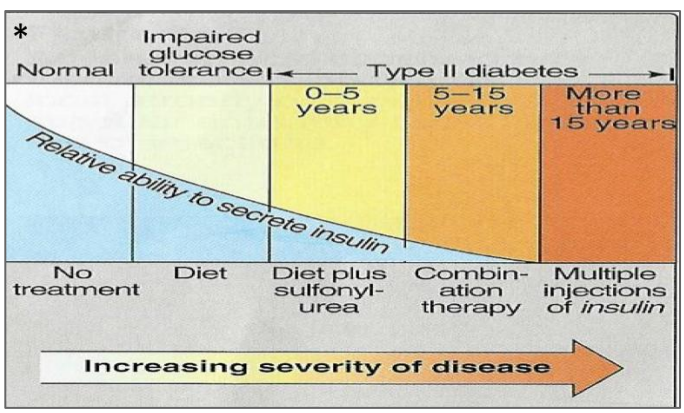


Patient with type II diabetes have two physiological defects:
I. Abnormal insulin secretion.
II.Resistance to insulin action in target tissues associated with decreased number of insulin receptors.

Treatment of Type II Diabetes *

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

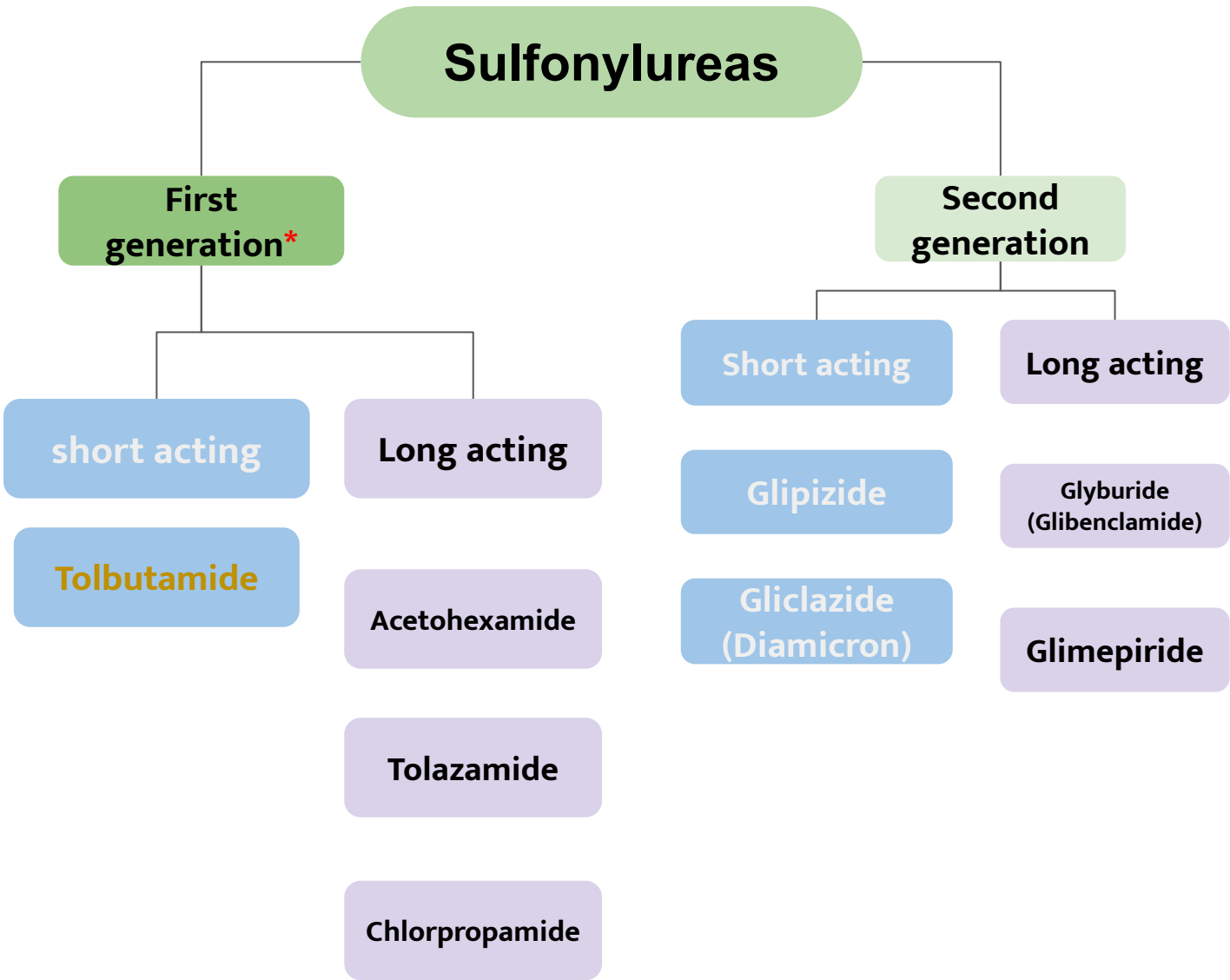
We use oral treatment if there is no improvement with the previous methods



*only in girls slides

Insulin secretagogues

Insulin secretagogues: are drugs which increase the amount of **insulin** secreted by the pancreas. Because it increase the insulin release it can lead to **hypoglycemia** Their action depends upon functioning pancreatic β-cells, so we can't use it in type one



In males slides only second generation sulfonylureas were discussed

*only in girls slides

Sulfonylureas

M.O.A

- **Normally:** ↓ Hyperglycemia Blockade of ATP dependent K+ channels
  Opening of voltage-dependent Ca2+ channels ↓ intracellular calcium in the beta cells ↓ Insulin release (only female slides)
- **Sulfonylureas:** Stimulate insulin release from functioning **β 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.
  (Hence, not effective in totally insulin-deficient pts" type-1).
- Potentiation of insulin action on target tissues. (only male slides)
- Reduction of serum glucagon concentration. (only male slides)

P.K

- **Orally,** well absorbed.
- Reach peak concentration after 2-4 hr.
- All are **highly bound to plasma proteins.**
- Duration of action is variable.
- Second generation has longer duration than first generation, that's why 2nd generation are more favorable.
- **Metabolized in liver**, so any problem in the liver will increase the ADRs.
- **Excreted in urine (elderly and renal disease**, in risk of increase ADRs even with small dose).
- **Cross placenta**, stimulate fetal **β-cells** to release insulin → fetal hypoglycemia at birth.
  (pregnant lady should not use any OHA instead we should give her regular insulin).

In male slides there is only one table for P.K Which will be in the next slide

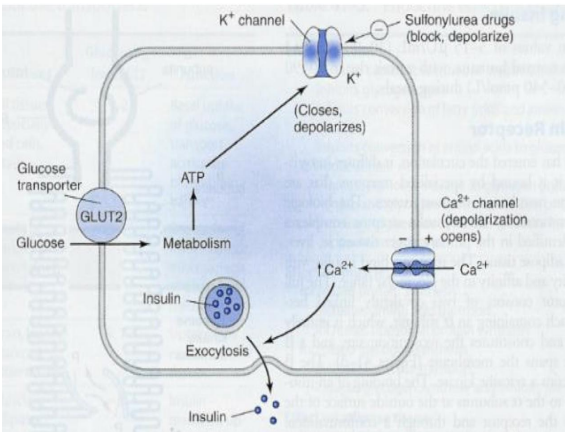
Uses

- Treatment of type II diabetes, as monotherapy or in combination with other Use antidiabetic drugs.not in type I because there is no beta cells

ADR

A- Hyperinsulinemia & Hypoglycemia:
1- More common in long acting sulfonylureas. particularly (glyburide and glimepiride)
2- More in old age, hepatic or renal diseases.
B- Weight gain due to increase in appetite due to high insulin unless the diabetic diet and exercise program are followed.

Mechanisms of Insulin Release:
Glucose enter β cells and then phosphorylation start to produce ATP , ATP will go close K channel which will depolarize the cells, this will open Ca channel → Ca move insulin vesicles to the membrane → exocytosis
sulfonylureas blocks K channel → no depolarization → no opening of Ca channel → no insulin release



Second generation sulfonylureas: 'female slides'

- more potent than the first generation.
- Have longer duration of action.
- Less frequency of administration.
- Have fewer adverse effects and drug interactions.

	Glipizide	Glyburide (Glibenclamide)	Glimepiride
Absorption	Well, reduced by food	Well	Well
Metabolism	Yes	Yes	Yes
Metabolites[1]	Inactive	Moderate activity	Moderate activity
Duration of action	10 – 16 hrs (short)	12 – 24 hrs long	12 – 24 hrs long
Half-life[1]	2 – 4 hrs	Less than 3 hrs	5 - 9 hrs
Dose[2]	Divided doses 30 min before meals	Single dose	Single dose
Excretion	Urine	Urine	Urine

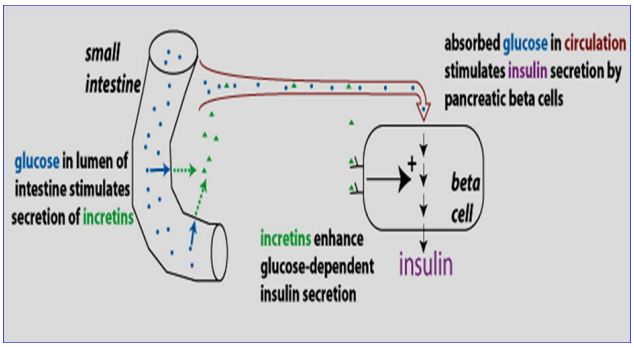
Meglitinides e.g. Repaglinide faster onset and shorter duration than Sulfonylureas	
M.O.A	• **Rapidly** acting insulin secretagogues. • Insulin secretagogue as sulfonylureas.
P.K	• Orally, well absorbed. • Very fast onset of action, peak 1 h. • short duration of action (4 h). • **Metabolized in the liver & excreted in bile.** (When the patient has **renal disease or with old age** we use meglitinides instead of sulfonylurea. • Taken just before each meal 'postprandial hyperglycemia' (3 times/day) **the dose should be skipped if the meal is missed**. 'female slides'
Uses	• **Type II diabetes**(monotherapy or in combination with other antidiabetics). • **Patients allergic to sulfonylurea.**
ADR	Less incidence than sulfonylureas. 'female slides' • Hypoglycemia • Weight gain.

Incretin mimetics

Incretins are GI hormones secreted in response to food, carried through circulation to the βcells to stimulate insulin secretion & inhibit a cells & decrease glucagon secretion.

Incretins regulate blood glucose by:

1. **Increase insulin secretion.**
2. **Decrease glucagon secretion.**



Main Incretin hormone:

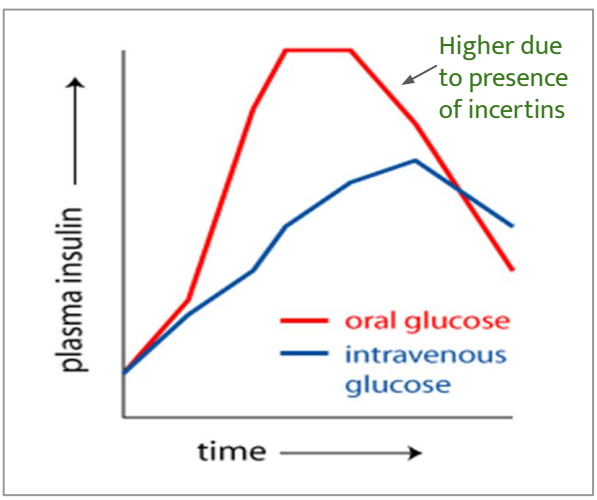
- GIP (Gastric inhibitory peptides.)
- **GLP-1 (glucagon-like peptide-1)**
- **GLP-1 agonists,** e.g. Liraglutide(Victoza, Saxenda)^{R}
  Dulaglutide(Trulicity)^{R}, Exenatide

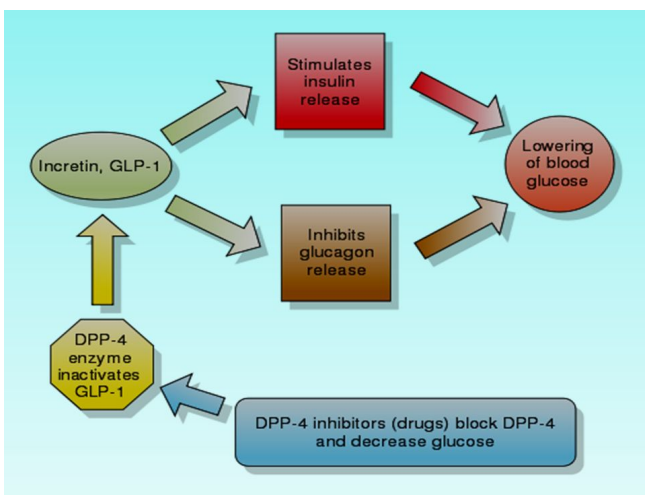
Taken by **injection**

- **Inactivated by dipeptidyl peptidase-4 (DPP-4) enzyme.**
  DPP-4 Inhibitors:

e.g. Sitagliptin, Vildagliptin.

Therefore it will increase incretin





GLP-1 agonists (Incretin mimetics)

e.g. Liraglutide

M.O.A	-**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 'female slides'
P.K	• **is glucagon-like peptide-1 (GLP-1) agonist**. • given s.c. once/week (single- dose prefilled disposable pens). • Used together with diet and exercise to treat type 2 diabetes and in patients who are not controlled with other oral antidiabetics. • **Not used in type 1 diabetes.** • As a treatment for adults who are obese and has one of these (e.g. hypertension, type 2 diabetes mellitus, or dyslipidemia).
ADR	• Nausea,vomiting and diarrhea(most common). • Hypoglycemia when combined with sulfonylureas or insulin. • Loss of appetite.'male slides' • Pancreatitis(rare). • Arrhythmia.'male slides'

Dipeptidyl peptidase-4 (DPP- 4) inhibitors

e.g. **Vildagliptin** ,**Sitagliptin**(Januvia)^{R}

P.K	• Orally • Half life 8-14 h
M.O.A	**Inhibit DPP-4 enzyme** and leads to an **increase in incretin hormones level.** This results in an **increase in insulin secretion & decrease in glucagon secretion.**
Uses	**Type 2 DM** as an adjunct to diet & exercise as a monotherapy or in combination with other antidiabetics.
ADR	• **Nausea, abdominal pain, diarrhea.** • Runny nose. 'male slides' • Joint and muscle pain. 'male slides' • Nasopharyngitis and headache 'female slides'

Insulin sensitizers

Biguanides

e.g. Metformin
more in **liver and peripheral**

Thiazolidinediones

e.g. pioglitazone
More in **muscle** and **adipose tissue**

Metformin

M.O.A	• Reduces insulin resistance 'female slides' • Does not stimulate insulin release. • Increases liver,muscle & adipose tissues sensitivity to insulin & increase **peripheral** glucose utilization (tissue glycolysis) • Inhibits hepatic glucose production (gluconeogenesis). • Impairs glucose absorption from GIT. • Decrease the appetites (helpful in obese patients) • **Improve lipid profile:decrease LDL,VLDL and increase HDL** 'female slides'
P.K	• Orally. • Not bound to serum protein. t ½ 3 hours. • Not metabolized.so excreted unchanged in urine
Uses	• **Obese patients with type II** diabetes because it promotes modest weight reduction (first-line therapy). • **type II Monotherapy** or in combination with other antidiabetics.
Advantages	**No risk of hypoglycemia** when used alone No weight gain (anorexia) has prominent lipid-lowering activity* Inexpensive*
ADR	• **Metallic taste in the mouth** • **GIT disturbances:** nausea, vomiting, diarrhea should be taken with meals and should be started at a low dose 'details only in female slides' • **Lactic acidosis (very rare)** predisposing factors(Renal insufficiency, Severe liver disease , Alcohol abuse, Heart failure, Pulmonary insufficiency , Cardiogenic or septic shock)'details only in female slides' • **Vitamin B12 deficiency (Long term use) .**
Contraindications	• Renal impairment. Impaired excretion • Liver impairment. Impaired metabolism • Lung disease • Alcoholism. They already have increased glycolysis • Heart failure

Thiazolidinediones E.g: Pioglitazone

M.O.A	➢ Activate peroxisome proliferator-activated receptor-(PPAR-Gamma) 'female slides' ➢ **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%) (unlike metformin) • Slow onset of activity • Half life 3-4 h • Metabolized in the liver • Excreted in urine 64% & bile
Uses	• **Type II diabetes with insulin resistance.** • Used either alone or in combination with other antidiabetics. • **No risk of hypoglycemia when used alone**
ADR	• **Hepatotoxicity** (liver function tests for 1st year of therapy). • Fluid retention (Edema). • **Precipitate congestive heart failure** • **Mild weight gain.** • Failure of estrogen-containing oral contraceptives. (only female slides)

α-Glucosidase inhibitors

E.g. Acarbose, Miglitol

M.O.A	❖ **Reversible inhibitors of intestinal alpha- glucosidases** responsible for degradation of oligosaccharides to monosaccharides. (Competitively) ❖ **Decrease carbohydrate digestion and absorption in small intestine.**
P.K **(Acarbose)**	• **Decrease postprandial hyperglycemia. And No hypoglycemia.** • Given orally, poorly absorbed , And Taken just before meals. • Metabolized by intestinal bacteria. • Excreted in **stool** and **urine** 'in male slides only '
Uses 'female slides'	• Are effective alone in the earliest stages of impaired glucose tolerance. Use with prediabetes patients • Are not recommended alone as therapy for moderate to severe hyperglycemia • Are most useful in combination with other oral hypoglycemic drugs or with insulin.
ADR	• **GIT: Flatulence**, diarrhea, abdominal pain.
C.I 'female slides'	• Irritable bowel syndrome.**(IBS)** • Inflammatory bowel disorders. **(IBD)** • Intestinal obstruction.

Sodium-glucose transporter 2 (SGLT2) inhibitors

E.g. Canagliflozin (Invokana)

M.O.A	❖ **Inhibits SGLT2 in the kidneys**. 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.**
ADR	• **Urinary tract infections.** Due to the presence of sugar in urinary tract • Increased urination and dry mouth. • Thirst. • **Yeast infections**(vagina or penis). • Itching(vagina or penis). • Fatigue.

Summary

GROUP	Alpha-Glucosidase inhibitors	Sodium-glucose transporter 2 (SGLT2) inhibitors
Drugs	Acarbose, Miglitol	Canagliflozin
M.O.A	-Reversible inhibitors of intestinal -glucosidases **-Decrease carbohydrate digestion and absorption in small intestine.** -Decrease postprandial hyperglycemia.	Inhibits SGLT2 in the kidneys. This **allows excess glucose to be excreted in the urine.** This will reduce blood sugar levels.
Site of action	**GI tract**	**Kidney**
Main advantages	**Low risk**	**-**
ADRs	-**GIT: Flatulence**, diarrhea, abdominal pain. -No hypoglycemia when used alone.	**-Urinary tract infection.** **-Increased urination and dry mouth.** **-Thirst.** **-Yeast infections(vagina or penis).** **- Itching(vagina or penis).** **-Fatigue.**

Summary

GROUP	Insulin secretagogues			
SUB-GROUP	Sulfonylureas	Meglitinides	Incretin mimetics)	
Drugs	Gliclazide,Glipizide, Glyburide,Glimepiride	Repaglinide	GLP-1 agonists (Liraglutide)	DPP- 4 (Sitagliptin)
M.O.A	**Stimulate insulin** release from functioning B cells by blocking of ATP-sensitive K channels resulting in depolarization and calcium influx.		Binds to GLP-1 receptors stimulates insulin secretion from β cells. It also reduces glucagon secretion by inhibiting alpha cells.	Inhibit DPP-4 enzyme and Inhibit incretin breakdown
Site of action	**Pancreatic beta cells**	**Pancreatic beta cells**	**GI tract**	**GI tract**
Main advantages	• **Effective** • **Inexpensive**	**Sulfa free**	**Once/week, s.c.**	**orally**
Uses	Type 2 DM.	-Type 2 DM. -Patients allergic to sulfonylurea.	Used together with diet and exercise to treat type 2 diabetes and in patients who are not controlled with other oral antidiabetics.	Type 2 DM as an adjunct to diet & exercise as a monotherapy or in combination with other antidiabetics.
ADRs	**-Hypoglycemia.** **-Weight gain.**		**-Nausea,vomiting and diarrhea.** -Loss of appetite. -Arrhythmia. -Pancreatitis(rare).	**-Nausea, abdominal** pain, diarrhea. -Runny nose. -Joint and muscle pain.

Summary

GROUP	Insulin sensitizers	
SUB- GROUP	Biguanides	Thiazolidinediones
Drugs	Metformin	pioglitazone
M.O.A	**Increases** liver,muscle & adipose tissues **sensitivity to insulin** & increase peripheral glucose utilization.	**-Increase sensitivity** of target tissues to **insulin.** -Increase glucose uptake and utilization in muscle and adipose tissue.
Site of action	**Liver**	**Fat, muscle**
Uses	Type 2 DM with insulin resistant as monotherapy or in combination with other antidiabetics.	
Advantages	• **mild weight loss** • **No hypoglycemia**	•**No hypoglycemia**
ADRs	**-Metallic taste in the mouth.** **- GIT disturbances.** **-Lactic acidosis(rare).** -Vitamin B12 deficiency.	-**Hepatotoxicity** (liver function tests for 1st year of therapy). **-Fluid retention (Edema).** -Precipitate congestive heart failure. **-Mild weight gain.**
C.I	-Renal impairment. -Liver impairment. - Lung disease. -Alcoholism. -Heart failure.	-

MCQs

1-Which of the following is a long acting sulfonylurea?
A- gliclazide B- glipizide
C-glyburide D- metformin

2- which of the following sulfonylurea has an INACTIVE metabolite
A- glipizide B- glyburide
C-glimepiride

3- Which of the following is a use of meglitinide?
A- type I diabetes B- type II diabetes
C- patients allergic to sulfonylurea D- B&C

4- inhibition of DPP-4 leads to:
A- increase incretin levels B- decrease incretin level
C-increase glucagon secretion D- none of the above

5- Which of the following is a mechanism of action of metformin
A- stimulation of insulin release
B- Increases liver,muscle & adipose tissues sensitivity to insulin
C-stimulate gluconeogenesis
D- stimulate glucose absorption from GIT

6- Both Liraglutide and Exenatide are anti-diabetic by acting as :
A- GIP agonist. B- GLP-1 agonist.
C- GLP-1 antagonist D- DPP-4 inhibitors.

7- which of the following is an adverse effect of Alpha-Glucosidase inhibitors?
A- metallic taste B- lactic acidosis
C-congestive heart failure D- flatulence

8-All of the following hypoglycemic drugs can be used as treatment for both type 1&2 diabetes , EXCEPT
A- Acarbose B- Pioglitazone
C Metformin D- Liraglutide

9- Sulfonylureas and Meglitinides act as insulin secretagogues mainly by which one of the following mechanism:
A- Opening the ATP dependent K+ channels.
B- Blocking the ATP dependent K+ channels.
C Opening the voltage-dependent Ca2+ channels.
D- Blocking the voltage-dependent Ca2+ channel.

10- 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. Which one of the following drugs can be safe to be used in his case ??
A- glibenclamide B-Repaglinide
C- Glipizide D-Glyburide

11- Which one of the following hypoglycemic drugs is taken by injection once a wake rather than orally ?
A-Liraglutide B- Sitagliptin
C-Repaglinide D- None of the above

12- Q10: Which of the following drugs for diabetes would be LEAST likely to cause weight gain?
A-Metformin B- Liraglutide
C-Pioglitazone D-Both A & B

Answers
1-C
2-A
3-D
4-A
5-B
6-B
7-D
8-D
0-B
10-B
11-A
12-D

SAQ

1-what is the main mechanism of action of sulfonylureas?
Block ATP-sensitive K channel2

2-Numerate 3 adverse effect of sulfonylureas?
1- Hypoglycemia.
2- Hyperinsulinemia.
3- Weight gain.

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Thanks for those who worked on the lectures :

Mohammed Alomar
Maan Shukr
Abdullah Alzahrani
Abdulrahman ALaujan

Notes by

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References:

✓ Doctors' slides and notes

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