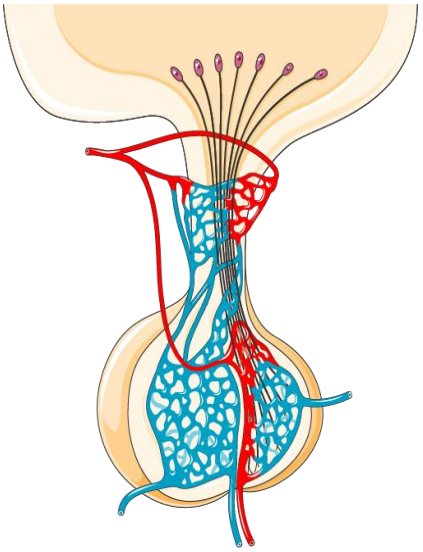
MEDICINE
KING SAUD UNIVERSITY

436 team
pharmacology



8,9: Oral Hypoglycemic Drugs

Objectives

1. Classify different categories of oral hypoglycemic drugs.
2. Identify mechanism of action, pharmacokinetics and pharmacodynamics of each class of oral hypoglycemic drugs.
3. Identify the clinical uses of oral hypoglycemic drugs
4. Know the side effects, contraindications of each class of oral hypoglycemic drugs.

Color index

- Extra information and further explanation
- **Important**
- **Doctors' notes**
- **Drugs names**
- **Mnemonics**

تمت المراجعة
شوق الأحمري & عبدالعزيز العنقري

Kindly check the editing file before studying this document

436 team pharmacology

تم بحمد الله

كل الشكر والتقدير لـ(أعضاء فريق علم الأدوية) المتميزين

لا تنسوهم من دعواتكم ♥

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- سعد الرشود
- عبدالرحمن الجريان
- عبدالرحمن الراشد
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- شوق الأحمري
- لمى التميمي
- ليلى مذكور
- لينا الوكيل
- لين التميمي
- منيال باوزير
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قادة فريق علم الأدوية :

- جومانا القحطاني - اللولو الصليهم - فارس النفيسة

Types of diabetes mellitus

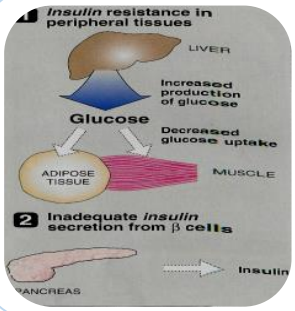
Type I diabetes

Causes: due to autoimmune or viral diseases

Type II diabetes

Causes: due to obesity, genetic factors.

Epidemiology: 80-90% occurrence , Over age 35, Obesity is an important factor.



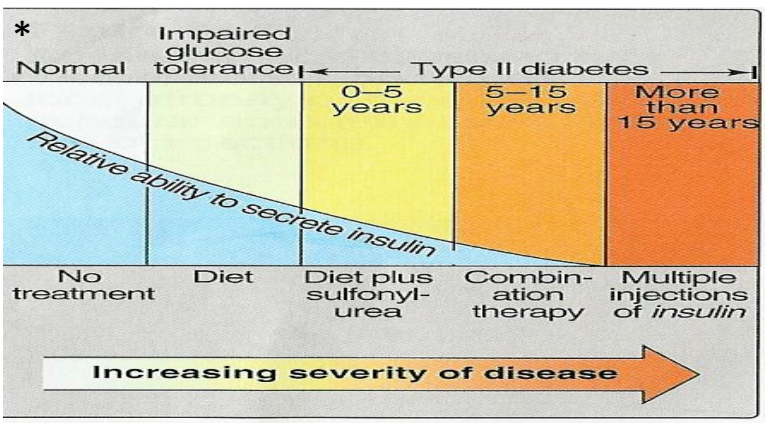
Patient with type II diabetes have two physiological defects:

I. Abnormal insulin secretion.

II. Resistance to insulin action in target tissues associated with decreased number of insulin receptors.

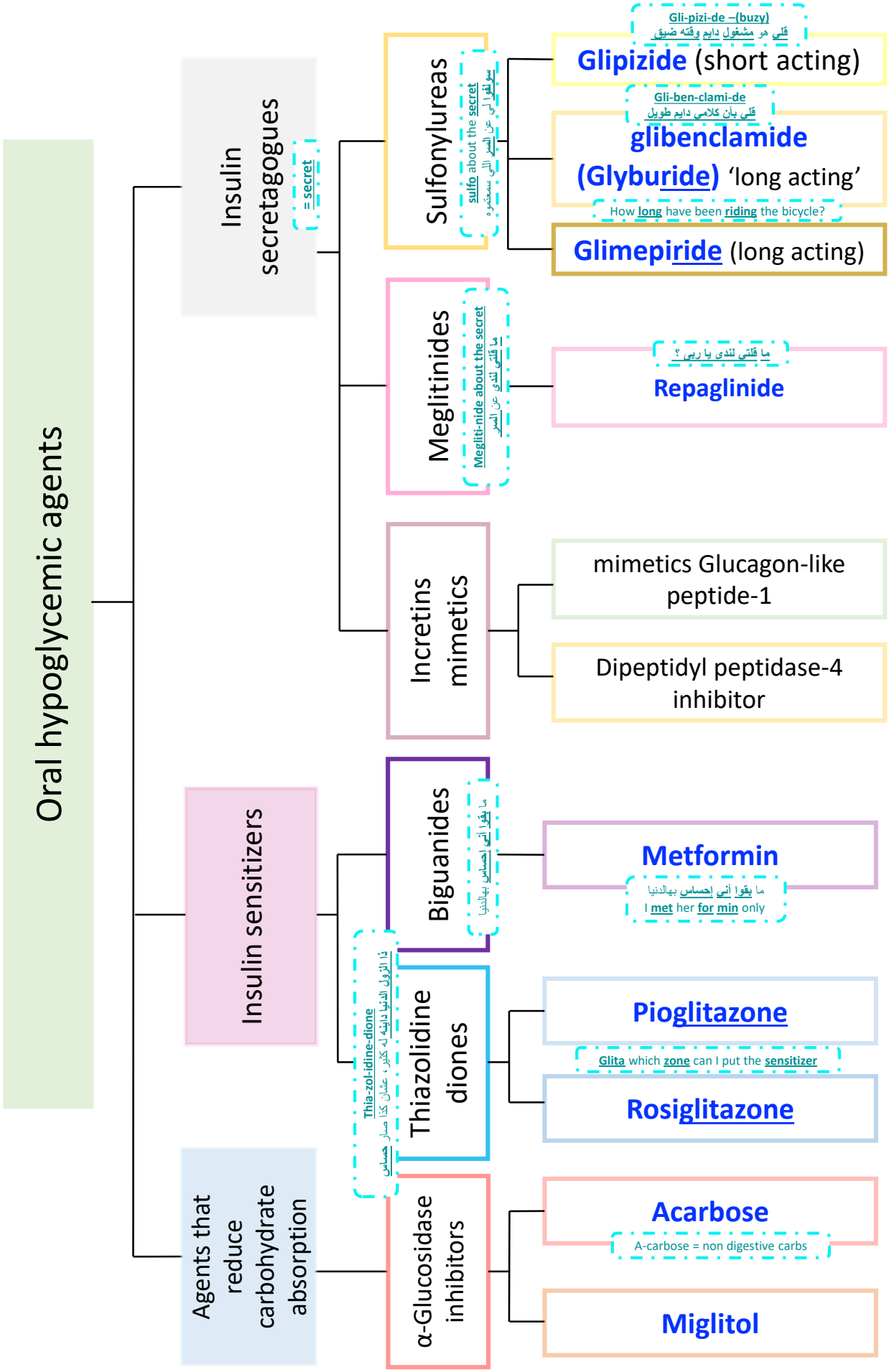
Treatment of Type II Diabetes (only female slides)

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



* يعني الشخص اللي عنده السكري النوع الثاني وما يتعامل مع المرض زين أبدا أعطيه أدوية وإذا ما صار فيه تحكم بالأدوية أو الأدوية ما فادته ممكن أصير أعطيه أنسولين

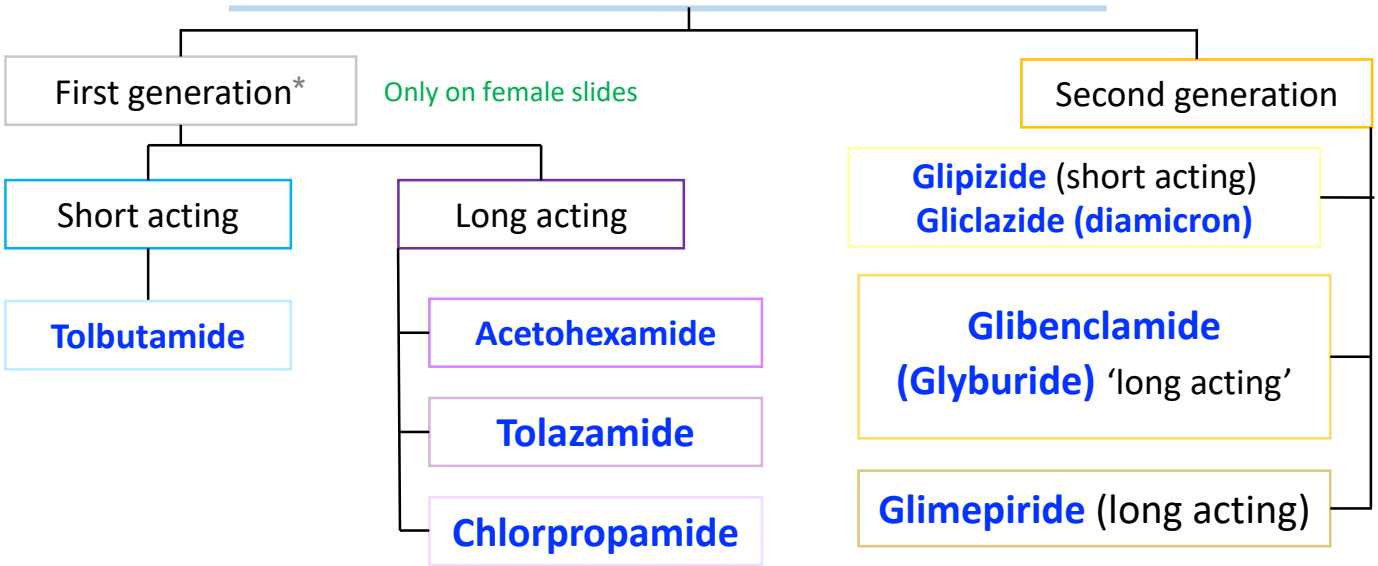
Oral hypoglycemic drugs



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

Sulfonylureas



Sulfonylureas

M.O.A

- Normally: ↑ Hyperglycemia → Blockade of ATP dependent K^+ channels → Opening of voltage-dependent Ca^{2+} 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)

Pharmacokinetics

Only female slides

- 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)

* Only in female slides، أسمح لكم تسحبون عليهم بناء على كلام بروف.حنان ☺

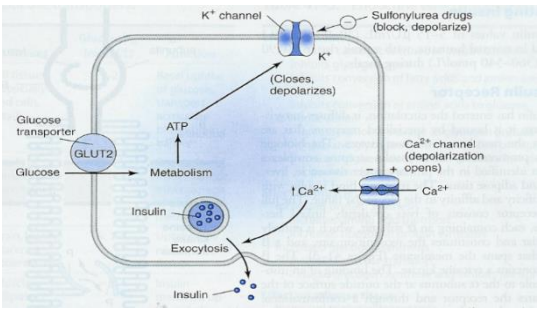
Sulfonylureas

Sulfonylureas	
Uses	Treatment of type II diabetes, as monotherapy or in combination with other antidiabetic drugs.
ADRs	• Hyperinsulinemia & Hypoglycemia: ✓ More common in long acting sulfonylureas. particularly (glyburide, and glimepiride) ✓ More in old age, hepatic or renal diseases. • Weight gain due to increase in appetite 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

- More potent than 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

[1] only male slides

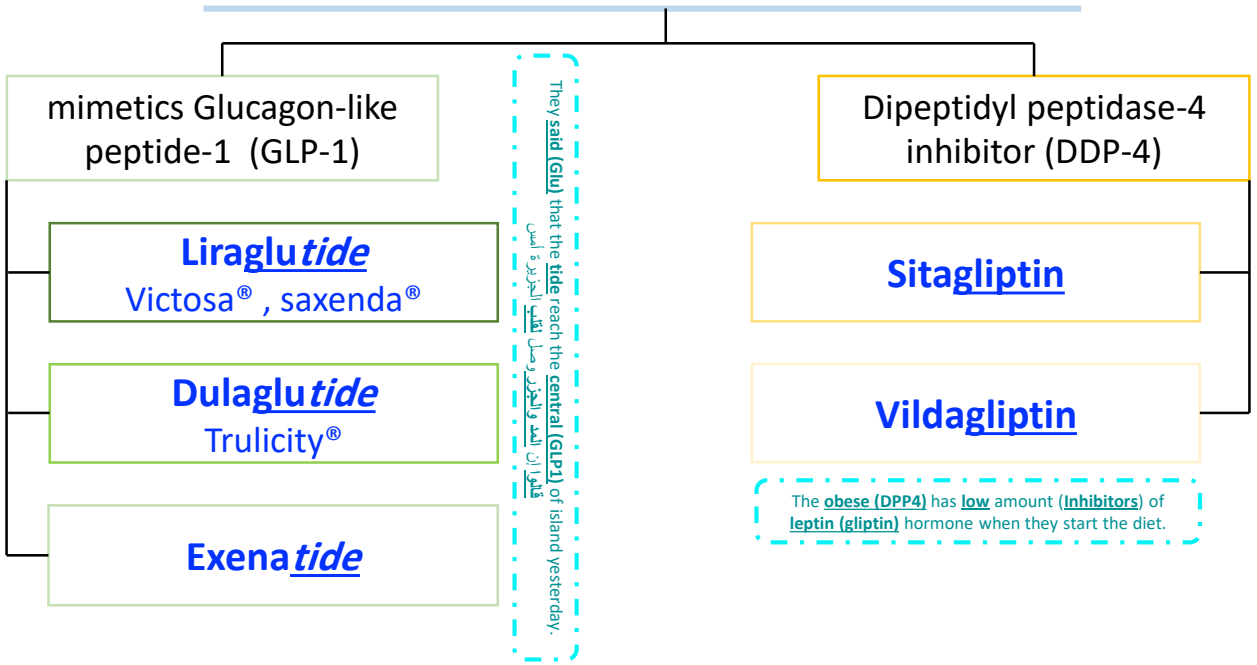
[2] only female slides

Meglitinides

Repaglinide

M.O.A	• Rapidly acting insulin secretagogues • Mechanism of action is identical to sulfonylureas.
P.K	• Orally, well absorbed. • Very fast onset of action, peak 1 h. • Short duration of action (4 h). • Metabolized in liver (be careful with liver diseased pt) and excreted in bile. **When the pt has renal disease we use meglitinides instead of sulfonylurea**. • Taken just before each meal (3 times/day) the dose should be skipped if the meal is missed. (only female slides)
indication	• Type II diabetes, as: monotherapy or in combination with other oral hypoglycemic drugs • As alternative to sulfonylureas in patients allergic to sulfur.
ADRs	Less incidence than sulfonylureas (only female slides) • Hypoglycemia[3] • Weight gain.

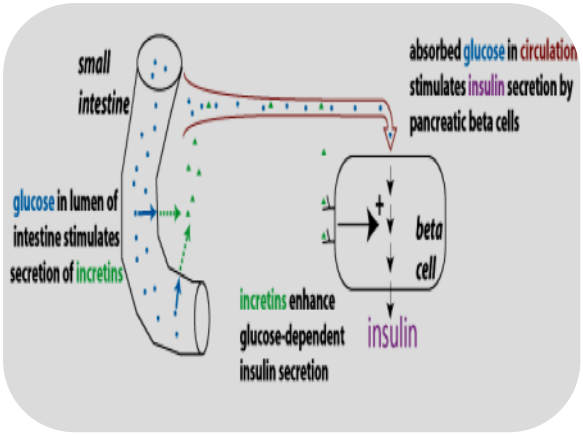
Incretins[4]



[3] The production of the incretins hormones depend on the presence of food that's why they have no risk of hypoglycemia. They are not used in type1 because it depends on functioning beta cells .

[4] New drug the only one that used s.c

Incretins



Incretins 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. Inhibit (it stimulates beta cells, so it is secretagogues) alpha cells &decrease glucagon secretion.

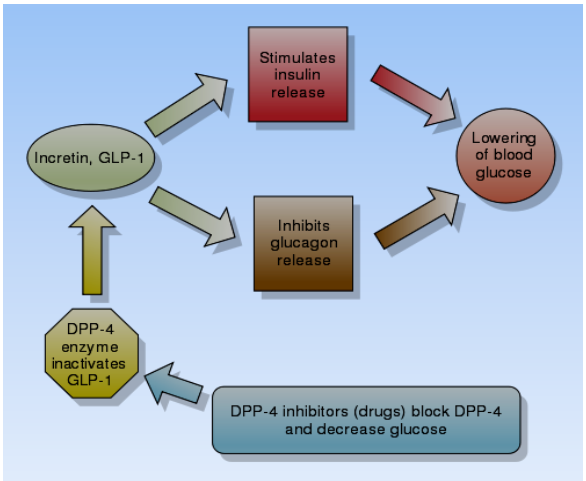
Incretins regulate blood glucose by (only female slides)

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

Types of Incretin hormones

1. GLP-1 (glucagon-like peptide-1)
2. GIP (gastric inhibitory peptide) 'only female slides'

Both are inactivated by dipeptidyl peptidase-4 (DPP-4).



When we eat - just when the food reach the intestine- Incretin (glucagon-like peptide-1) will be secreted, which stimulates insulin secretion, for sure that will decrease glucose in the blood, to inhibit the release of incretin there is enzyme called Dipeptidyl peptidase-4 will inactivate glucagon-like peptide-1 (GLP-1)

Incretins

	Incretins mimetics (GLP-1 agonists) **Liraglutide**	Dipeptidyl peptidase-4 inhibitor (DPP- 4 inhibitors) **Sitagliptin** januvia®
M.O.A	• Binds to GLP-1 receptors & stimulates insulin secretion from β cells. • It also reduces glucagon secretion by inhibiting alpha cells of the pancreas. Lira on diet =tide • It decreases appetite and inhibits body weight gain. عكس المجموعات اللي قبل(only female slides)	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.
P.K	Incretins = Injection **Given s.c. once/week** (single- dose pre-filled disposable pens)	• Is given orally. Drink lepton • Is given once daily. (bc it has high half life = 8– 14 h)
indication	• 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. (NOT USE AS MONOTHERPY, unless the patient on diet or exercising)
C.I	Not used in type 1 diabetes.	
ADRs	Nausea & vomiting and diarrhea (most common). Hypoglycemia when combined with sulfonylureas or insulin. (but alone does not cause hypoglycemia) **Pancreatitis** (rare)+ Loss of appitite Arrythmia (only male slides)	Nausea. Abdominal pain, diarrhea. Nasopharyngitis (Runny nose) Headache (only female slides) Joint and muscle pain (male slides)

Biguanides

Insulin sensitizers: Are drugs which increase the sensitivity of peripheral target organs to insulin[5]. (only female slides)

Metformin	
M.O.A	• Reduces insulin resistance, but does not stimulate insulin release. • 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. • **Decrease the appetites (helpful in obese patients)** • Improve lipid profile : ↓ LDL, ↓ VLDL , ↑ HDL (only female slides)
Pharmacokinetics	• Orally. • NOT bound to serum protein, so low t ½: 3 hours. • NOT metabolized, so excreted unchanged in urine
indication	• In patients with type 2 diabetes who are **obese** because it promotes modest weight reduction **(first-line therapy).** • Type II diabetes as monotherapy or in combination with other antidiabetics.
Advantages	• **No risk of hypoglycemia** • **No weight gain** (anorexia) • has prominent lipid-lowering activity • Inexpensive
C.I	• **Renal disease.** • Liver disease.. • Cardiopulmonary dysfunction. (lung disease + heart failure) • Pregnancy • Alcoholism

[5] Because it doesn't effect the insulin secretion it doesn't cause hypoglycemia

Biguanides

Metformin

ADRs

- GIT disturbances: 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. (it will go after a while, if not we should switch to another medications)*
- **Lactic acidosis** (very rare 1:30,000): Serious lactic acid accumulation usually occurs only in the presence of a predisposing conditions (**Renal insufficiency**, Severe liver disease , Alcohol abuse, Heart failure, Pulmonary insufficiency , Cardiogenic or septic shock)*
- Interference with vitamin B_{12} absorption (long term use).

Thiazolidinediones (glitazones)

Pioglitazone & Rosiglitazone (Rosiglitazone not used any more bc of its cardiac effects)

M.O.A

- Activate peroxisome proliferator-activated receptor-γ **(PPAR-γ)** 'female slides'

Glita any zone ? P-PAR! قلتي لي أي منطقة تعيش ؟ بالير !

- Increase glucose uptake and utilization in muscle and adipose tissue (PPAR-γ receptors modulate the expression of the genes involved in lipid and glucose metabolism).
- Increase sensitivity of target tissues to insulin.

P.K

- Orally (once daily dose).
- Highly bound to plasma albumins (99%).
- Slow onset of activity.
- Half life 3-4 h.
- Metabolized in liver.
- Excreted in bile and urine (64%).

indication

- Type II diabetes with insulin resistance.
- Used either alone or combined with sulfonylurea, biguanides or insulin.
- **No risk of hypoglycemia when used alone.**

Thia-zol-idine-dione

ذا الزول الدنيا داينه له كثير ، عشان كذا صار حساس وقلبه ما عاد صار يتحمل أي شيء

ADRs

- Hepatotoxicity (liver function tests for 1st year of therapy).
- **Precipitate congestive heart failure**, which lead to Fluid retention (edema), so mild weight gain.
- Failure of estrogen-containing oral contraceptives. (only female slides)

* الكلام الكثير (الشرح) موجود فقط في سلايدز البنات ☺

α -Glucosidase inhibitors

Acarbose & Miglitol

M.O.A

- Reversible inhibitors of **intestinal α-glucosidases** in intestinal brush border cells that are responsible for carbohydrate digestion (degradation of oligosaccharides to monosaccharides).
- Decrease carbohydrate digestion and glucose absorption in small intestine **(lower postprandial glucose level).**

Pharmacokinetics

Acarbose:

- Given orally.
- Not absorbed (poorly absorbed).
- Excreted in feces and urine.
- Taken just before meals.
- No hypoglycemia if used alone.

indication[6]

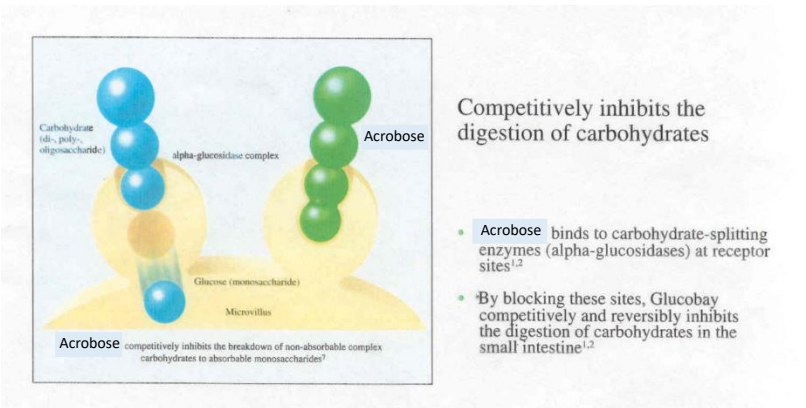
- Are effective alone in the earliest stages of **impaired glucose tolerance.** Use with **prediabetes** patients
- Are not recommended alone as therapy for moderate to severe hyperglycemia.
- Are most useful in combination with other oral hypoglycemic drugs or with insulin.

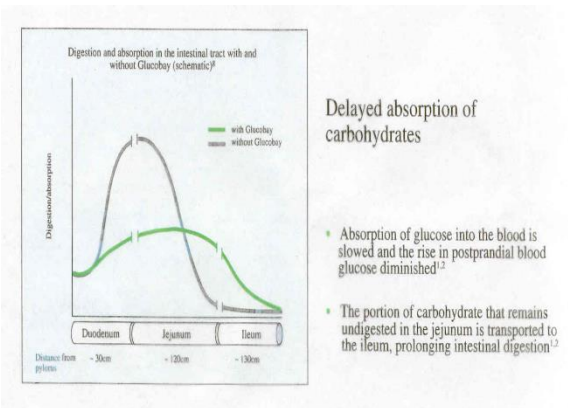
C.I[6]

- Irritable bowel syndrome.
- Inflammatory bowel disorders.
- Intestinal obstruction.

ADRs

GIT side effects: Flatulence, bloating, diarrhea, abdominal pain.





[6] only female slides

summary

Subclass	Sulfonurea 1st generation				Sulfonylurea 2nd Generation			Meglitinides
Drug	Tolbutamide	Acetohexamide	Tolazamide	Chlorpropamide	Glipizide	Glyburide	Glimepiride	Repaglinide
MOA	Insulin secretagogues: Blocking of ATP sensitive K channels→depolarization →opening of voltage dependent calcium channels → increase in intracellular calcium in the beta cells → stimulate insulin release							
Indication	***Diabetes Mellitus T2***							Type II diabetes (monotherapy or in combination) Alternative to sulfonylureas in patients allergic to sulfur.
ADRS	• Weight gain. • Hyperinsulinemia • Hypoglycemia (with long acting)							Less incidence than sulfonylureas: • Hypoglycemia. • Weight gain.
Contraindicat	Pregnancy	• Elderly • Renal disease (especially long acting) . • Pregnancy						-
Notes	• Orally, well absorbed. • Highly bound to plasma proteins. • Metabolized in liver • Excreted in urine				• More potent. • Longer duration of action. • Less frequency of administration. • Fewer drug interactions. • Absorption reduced by food • (Glipizide).			• Very fastonset of action (peak 1h). • Excreted in bile • Taken just before each meal • Sulfa free.

summary

Incretins

	mimetics Glucagon-like peptide-1: Dulaglutide Liraglutide Exenatide	Dipeptidyl peptidase-4 inhibitor: Sitagliptin vildagliptin
Drug		
MOA	Binds to GLP-1 receptors & stimulates insulin secretion from β cells. It also reduces glucagon secretion by inhibiting alpha cells of the pancreas. It decreases appetite and inhibits body weight gain	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
Indic.	As a treatment for adults who are obese or overweight with at least one weight-related comorbid condition.	Type II DM as an adjunct to diet & exercise as a monotherapy or in combination with other antidiabetic drugs
ADRS	Nausea & vomiting (most common). Hypoglycemia when combined with sulfonylureas or insulin. Pancreatitis (rare) Lose of appetite , arrythmia	Nausea. Abdominal pain. Diarrhea.

Thiazolidinediones (Pioglitazone & Rosiglitazone)

M.O.A	Increase glucose uptake and utilization in muscle and adipose tissue Increase sensitivity of target tissues to insulin.
Indic.	Type II diabetes with insulin resistance. Used either alone or combined.
ADRs	Hepatotoxicity Congestive heart failure, Fluid retention (edema), weight gain. Failure of estrogen-containing oral contraceptives.

a -Glucosidase inhibitors(Acarbose & Miglitol)

M.O.A	Reversible inhibitors of intestinal a-glucosidases in intestinal brush border cells that are responsible for carbohydrate digestion.
Indic.	Are most useful in combination with other oral hypoglycemic drugs or with insulin. Taken before meals
C.I	Irritable bowel syndrome. Inflammatory bowel disorders. Intestinal obstruction.
ADRs	GIT side effects: Flatulence, bloating, diarrhea, abdominal pain. No hypoglycemia if used alone

Biguanides (Metformin)

M.O.A	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.
Indications	In patients with type 2 diabetes who are obese because it promotes modest weight reduction (first-line therapy). Type II diabetes as monotherapy or in combination with other antidiabetics.
C.I	Renal disease. Liver disease.. Cardiopulmonary dysfunction. Pregnancy Alcoholism
ADRs	• GIT disturbances: Metallic taste in the mouth, nausea, vomiting, diarrhea. • Lactic acidosis (very rare) • vitamin B12 deficiency

MCQs

Q1: Which one of the following oral hypoglycemic drugs can be used in case of diabetic patient with renal disease ?

A. Glyburide. B. Repaglinide. C. Metformin. D. Glimepiride.

Q2: 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.

Q3: Which one of the following hypoglycemic drugs can be used in patient with type 1 diabetes ?

A. glibenclamide. B. Repaglinide. C. Miglitol. D. Dulaglutide.

Q4: 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+ channels.

Q5: 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.

Q6: Which one of the following hypoglycemic drugs would be least likely to cause hypoglycemia ?

A. Glimepiride. B. Glyburide. C . Repaglinide. D. Dulaglutide.

Q7: which one of the following hypoglycemic drugs is taken pre-prandial ?

A. Acarbose. B. Rebaglilinde. C. Metformin. D. All of them.

Q8: Which one of the following hypoglycemic drugs is taken by injection once a wake rather than orally ?

A. Liraglutide. B. Sitagliptin. C . Repaglinide. D. Both A & B .

Q9: Both Liraglutide and Extenatide are anti-diabetic by acting as :

A. GIP agonist. B. GLP-1 agonist. C. GLP-1 antagonist. D. DPP-4 inhibitors. E. Both B & D.

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.

1) B
2) D
3) C
4) B
5) B
6) D
7) D
8) A
9) B
10) D

* Biguanides & GLP-1 agonist → weight loss
Sulfonylureas & Meglitinides & Thiazolidinediones → weight gain

MCQs

Q11: 37 years old male who is obese and has diagnosed as prediabetes. His blood glucose and lipid is significantly high. He failed to loss his weight with diet and exercise. Which one of the following drugs is first line of treatment in his case?

A. Sitagliptin. B. Metformin. C . Repaglinide. D. Both A & C .

Q12: A 32 years old male who is diabetic. He did not tell his doctor that he drinks alcohol almost daily. The doctor prescribed metformin for him. Which one of the following adverse effect could be seen in this patient ?

A. pancreatitis. B. urinary tract infections. C. Liver cirrhosis. D. Lactic acidosis.

Q13: 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. Sitagliptin . B. Glyburide. C. Repaglinide. D. Pioglitazone.

Q14: 21 years old female, her family have history of diabetes type2. She did oral glucose tolerance test. And the result was 156mg/dl which mean she is a prediabetes. Which one of the following can be used alone in this early stage to control her blood glucose level ?

A. Dulaglutide. B. Rebaglilinde. C. Acarbose. D. All of them.

Q15: 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. Glinide—increases insulin sensitivity.
C. Sulfonylurea—increases insulin secretion.
D. Thiazolidinedione—decreases hepatic gluconeogenesis.

Q16: 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 should not be combined with sulfonylureas or insulin.
D. Weight gain is a common adverse effect.

***The TZDs (pioglitazone and rosiglitazone) can cause fluid retention and lead to a worsening of heart failure. They should be used with caution and dose reduction, if at all, in patients with heart failure. glyburide, repaglinide, and sitagliptin do not have precautions for use in heart failure patients.**

11) B
12) D
13) D
14) C
15) C
16) B

MCQs

Q17: Which one of the following hypoglycemic drugs is preferable to be used in diabetic patient who is obese or hypertensive or even with high lipid profile ?

A. Liraglutide. B. Metformin. C . Repaglinide**.** D. Both A & B .

Q18: Which of the following is the most appropriate initial oral agent for management of type 2 diabetes in patients with no other comorbid conditions ? *

A. Glipizide. B. Insulin. C. Metformin. D. Pioglitazone.

Q19: Which one of the following anti-diabetic drug may interference with vitamin B12 absorption if it use for long term ?

A. Liraglutide. B. Metformin. C . Repaglinide. D. glibenclamide.

Q20: 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. Glyburide. B. Saxagliptin. C. Metformin. D. Both A & C.

Q21: Which of the following diabetes medications is most appropriately paired with an adverse effect associated with its use?

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

Q22: Sulfonylureas are class of oral diabetes drugs which excreted mainly by kidney in urine. Which one of these drugs has the least risk to develop hypoglycemia in patient with renal insufficiency ?***

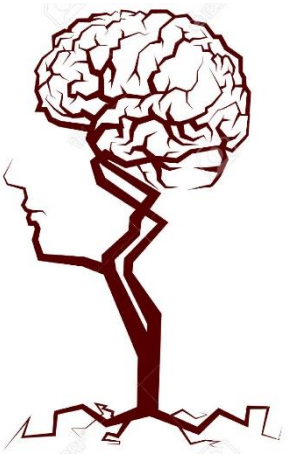
A. glibenclamide. B. Glimepiride. C. Glipizide. D. Glyburide.

* This question was taken from Lippincott's study questions, and I think when they said no other comorbid condition , they refer to Renal disease, Liver disease., Cardiopulmonary dysfunction and Heart failure where the risk of lactic acidosis is increased with them .

** Metformin should not be used in patients with kidney disease due to the possibility of lactic acidosis.

*** This point was mentioned by Dr.alhummayyd , the table in slide 6 shows that the Glipizide is only drugs which get inactivated into inactive Metabolites . So even if the patient has renal disease there will not be as serous as others drugs.

17) D
18) C
19) B
20) C
21) D
22) C



إِنَّ فِي ذَٰلِكَ لَآيَاتٍ لِّقَوْمٍ يَتَفَكَّرُونَ ﴿٣﴾

قادة فريق علم الأدوية :

- جومانا القحطاني - اللولو الصليهم
- فارس النفيسة

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شوق الأحمري

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