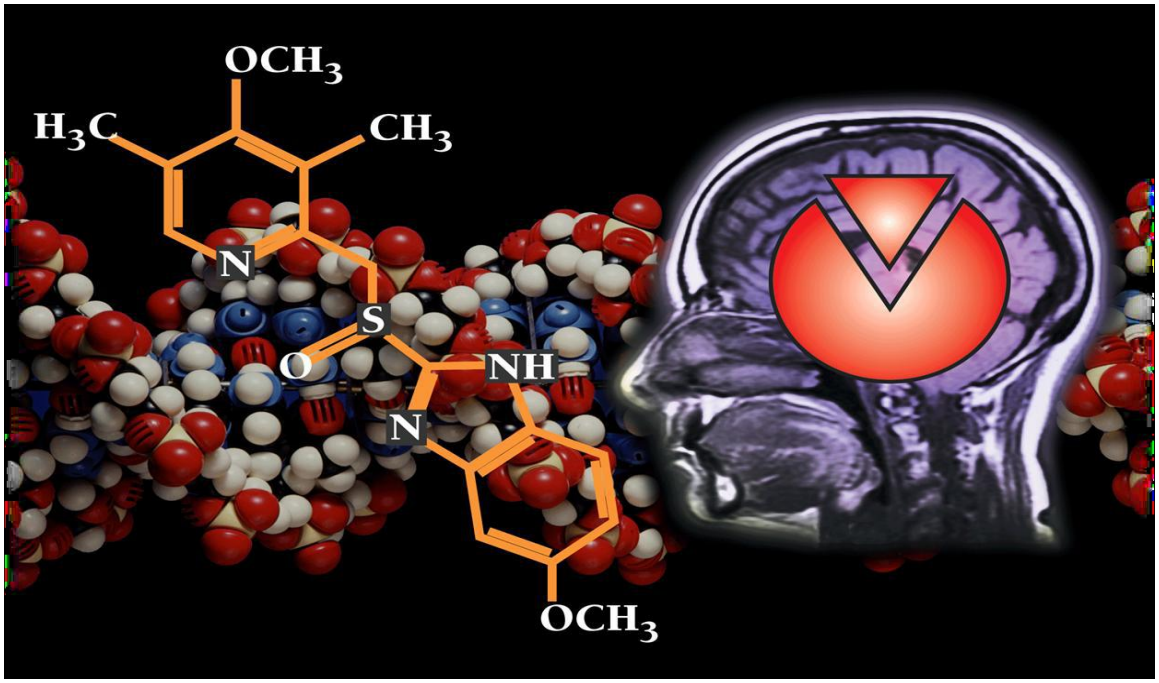
King Saud University
College Of Medicine
Pharmacology Team 430
Endocrine Block

Oral Hypoglycemics



Note: Texts in red are doctors' notes; Text in green are additional info or for illustration.

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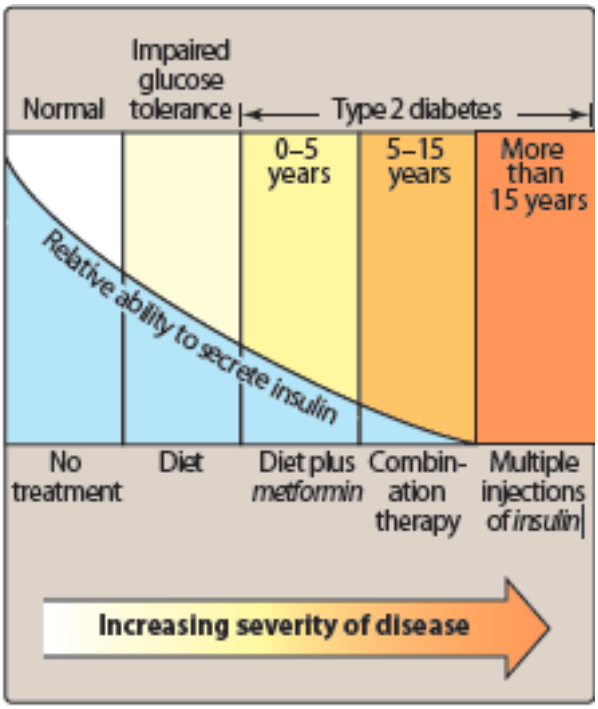
Introduction:

- **Type I** : is ***due to autoimmune or viral diseases***
- **Type II:** is influenced by genetic factors, obesity, aging and peripheral *insulin* resistance.

Type II diabetes patients have two physiological defects:

A. **Abnormal insulin secretion.**
B. **Resistance to insulin action in target tissues associated with decreased number of insulin receptors.**

- In type 2 diabetes, the pancreas retains some β-cell function, but variable *insulin* secretion is insufficient to maintain glucose homeostasis.
- After years, the β cells become exhausted and dysfunctional, this is when overt diabetes happens.
- Diabetes has a great number of complications that may cause serious cardiac, renal, and nervous complications.
- Goal of treatment: The goal in treating type 2 diabetes is to maintain blood glucose concentrations within normal limits and to prevent the development of long-term complications of the disease.



Drugs used for treatment of Type-2 diabetes (hypoglycemic):

A. Insulin secretagogues:

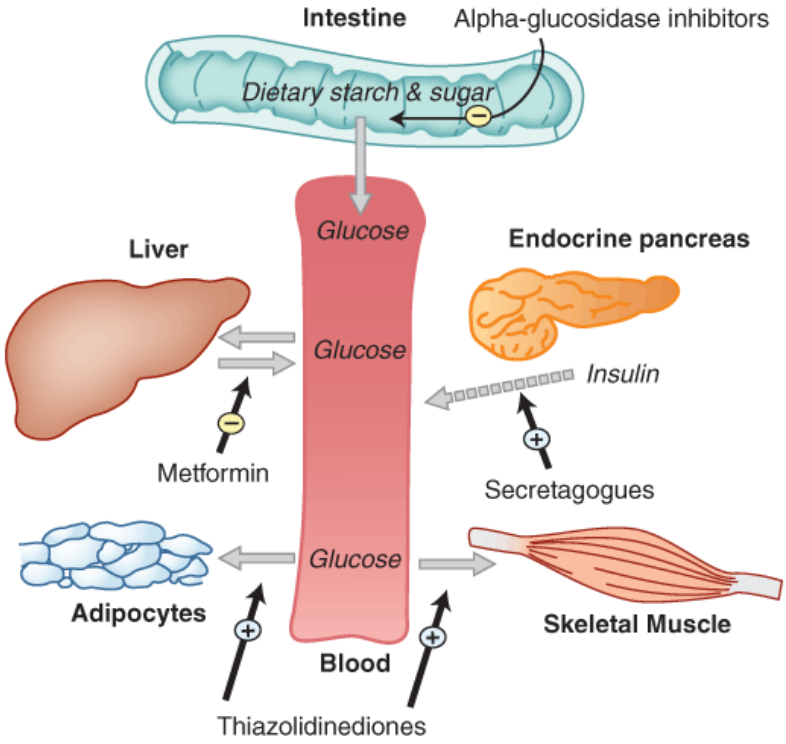
1. Sulfonylurea drugs
2. Meglitinide analogues

B. Insulin sensitizers

1. Biguanides
2. Thiazolidinediones

C. Others drugs:

1. Alpha glucosidase inhibitors
2. Dipeptidyl peptidase-4(DPP-4) inhibitors



A)Insulin secretagogues:

- Are drugs which increase the amount of insulin secreted by the pancreas.
- For insulin secretagogues to function a patient must have at least 30% of his β-cells functioning. This explains why they can't be used with type I Diabetes (β cells destroyed by autoimmune process)
- Include:
  1. **Sulfonylureas**
  2. **Meglitinides**

1-Sulfonylureas:

First generation sulfonylureas:

The most important and safest First generation sulfonylurea is **Tolbutamide** (tole-BYOO-ta-mide). It is safe for old diabetic patients or patients with renal impairment (because it has a short duration of action with **inactive metabolites**)

A disadvantage to first generation sulfonylureas have a number of interactions with different drugs (decrease it's metabolism) and rarely cause prolonged hypoglycemia.

Drug and drug properties	**Tolbutamid short-acting** we have to memorize this drug only as example of first generation drugs-	Acetohexamide intermediate-acting	Tolazamide intermediate-acting	Chlorpropamide long- acting
Absorption	Well	Well	Slow	Well
Metabolism	Yes	Yes	Yes	Yes
Metabolites	Inactive	Active	Active	Inactive
Half-life	4 - 5 hrs	6 – 8 hrs	7 hrs	24 – 40 hrs
Duration of action	Short (6 – 8 hrs)	Intermediate (12 – 20 hrs)	Intermediate (12 – 18 hrs)	Long (20 – 60 hrs)
Excretion	Urine	Urine	Urine	Urine

Second-generation sulfonylureas:

- More potent (single dose)
- Have fewer adverse effects
- Have fewer drug interactions
- Have a longer duration
- Contraindicated in **hepatic impairment or renal insufficiency.**

  With liver impairment, it might metabolize these drugs into active metabolites. This especially happens with **Glyburide.**

	Glipizide	Glibenclamide (Glyburide) (GLYE-byoor-ide)	Glimepiride
Absorption	Well reduced by food	Well	Well
Metabolism	Yes	Yes	Yes
Metabolites	Inactive	Inactive	Inactive
Half-life	2 – 4 hrs	Less than 3 hrs	5 - 9 hrs
Duration of	10 – 16 hrs	12 – 24 hrs	12 – 24 hrs
Action	short	long	long
Doses	Divided doses 30 min before meals	Single dose	Single dose 1 mg
Excretion	Urine	Urine	Urine

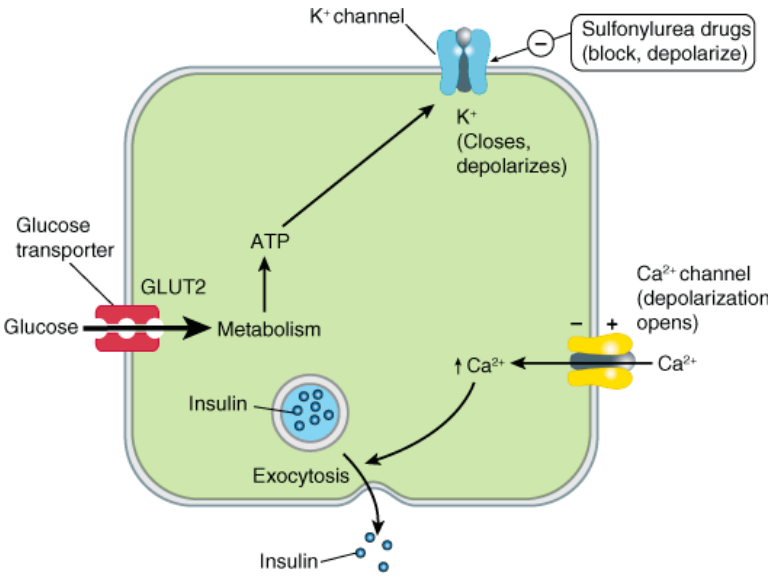
Mechanism of action of Sulfonylureas:

Stimulate insulin release from functioning B cells by **blocking of ATP-sensitive K channels resulting** in depolarization and calcium influx (Hence, not effective in totally insulin-deficient pts" type-1).

Pharmacokinetics:

- Orally, well absorbed. (All oral hypoglycemics are taken orally)
- Reach peak concentration after 2-4 hr.
- All are highly bound to plasma proteins.
- Duration of action is variable (depends on which drug and which generation)
- Second generation has longer duration than first generation.
- Metabolized in liver
- Excreted in urine (This may cause a problem in elderly (decreased number of functional nephrons) or patients with renal impairment)
- Cross placenta, stimulate fetal B cells to release insulin → hypoglycemia at birth.

  Note: In case of pregnancy, regular insulin is used.



Uses:

Type II diabetes: **monotherapy** or **in combination** with other antidiabetic drugs.

Adverse effects:

1. Hyperinsulinemia & Hypoglycemia: more in elderly and patients with renal disease.
2. Weight gain due to increase in appetite

Edema can also happen.

2-Meglitinide analogues:

e.g. **Repaglinide** (re-PAG-lin-ide)

Mechanism of Action:

- Are rapidly acting insulin secretagogues
- These drugs also work on the ATP sensitive K+ channels by binding to some active sites shared with sulfonylurea drugs and to another unique binding site.

Pharmkokinteics of Meglitinide analogues:

- Orally, well absorbed.
- Very fast onset of action, peak 1 h.

  Because of its rapid onset, repaglinide is indicated for use in controlling postprandial glucose levels.

- Short duration of action (4 h).
- Metabolized in the liver & excreted in bile.

Uses of Meglitinide:

- Type II diabetes: monotherapy or combined with other antidiabetic drugs.
- Patients allergic to sulfur or sulfonylurea

ADRs of meglitinide:

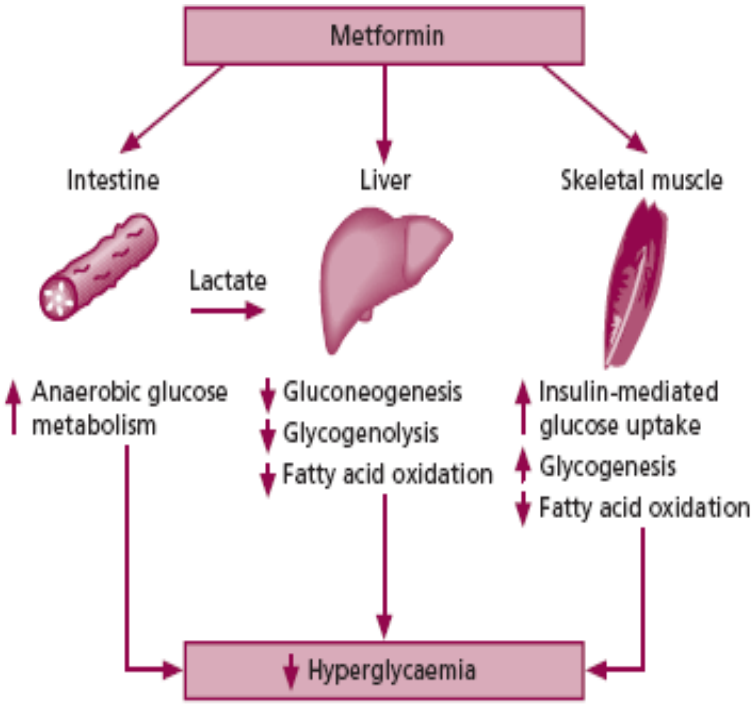
- Less incidence than sulfonylureas
- Hypoglycemia:
- Because this drug is used for postprandial glucose levels, hypoglycemia is especially a risk if a meal is delayed or skipped or contains inadequate carbohydrate.
- We don't use it with sulfonylurea to avoid the hypoglycemia
- Weight gain. (any drug that increase **insulin level will cause weight gain**)

B)Insulin sensitizers:

1-Biguanides e.g. Metformin

Mechanism of Action:

- **It increases glucose uptake and use by target tissues, thereby decreasing *insulin* resistance (insulin sensitizing effect)**
- Inhibits gluconeogenesis. Excess glucose produced by the liver is a major source of high blood glucose in type 2 diabetes, accounting for the high blood glucose on waking in the morning.
- Does not stimulate insulin release, which decreases the risk of developing hypoglycemia.
- Impairs glucose absorption from GIT (this is a minor effect compared to the previous)
- **blood glucose-lowering action does not depend on functioning pancreatic beta cells**
- Reduces plasma glucagon level: ↓LDL&VLDL, ↑ HDL



Pharmacokinetics of metformin:

- Orally.
- NOT bound to serum protein.
- NOT metabolized.
- t ½ 3 hours.
- Excreted unchanged in urine

Uses of metformin:

- Obese patients with type II diabetes (First-line therapy)
- Monotherapy or in combination.

Advantages:

- No risk of **hyperinsulinemia** or **hypoglycemia**
- **No weight gain.** There might even be weight loss because of loss of appetite (anorexia).

Adverse effects of metformin:

- Metallic taste in the mouth
- GIT disturbances: nausea, vomiting, diarrhea. The previous two side effects are dose-related, tend to occur at the onset of therapy, and are often transient.
- Lactic acidosis. Metformin **favors anaerobic** glycolysis, which finally yields lactic acid, causing acidosis. This is an important side effect because lactic acidosis is potentially fatal.
- Long term use interferes with vitamin B_{12} absorption.

Contraindications of metformin:

- Pregnancy.
- Renal disease. In patients with renal insufficiency, biguanides accumulate and thereby increase the risk of lactic acidosis (a dose-related complication)
- Liver disease. As a consequence of metformin's blockade of gluconeogenesis, the drug may impair the hepatic metabolism of lactic acid.
- Alcoholism.
- Conditions predisposing to hypoxia: cardiopulmonary dysfunction because of an increased risk of lactic acidosis induced by biguanide drugs

2-Insulin sensitizers - Thiazolidinediones (glitazones):

- E.g. **Pioglitazone** [pye-oh-GLI-ta-zone]

Mechanism of action of Pioglitazone:

- **Activate peroxisome proliferator-activated receptor -γ (PPAR-γ).** Regulates transcription of genes involoved in glucose utilization
- **Increase sensitivity** of target tissues **to insulin.**
- Increase glucose uptake and utilization in muscle and adipose tissue.

Pharmacokinetics of action of Pioglitazone:

- Orally (once daily dose).
- Highly bound to plasma albumins (99%)
- Slow onset of activity because it acts by expression of genes involved in lipid & glucose metabolism and insulin transduction.
- Half life 3-4 h
- Metabolized in the liver, Excreted in urine 64% & bile

Uses of Pioglitazone:

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

Adverse Effects of Pioglitazone:

- Hepatotoxicity (liver function tests for 1st year of therapy).

Other Thiazolidinediones have been withdrawn because of lethal hepatotoxicity.

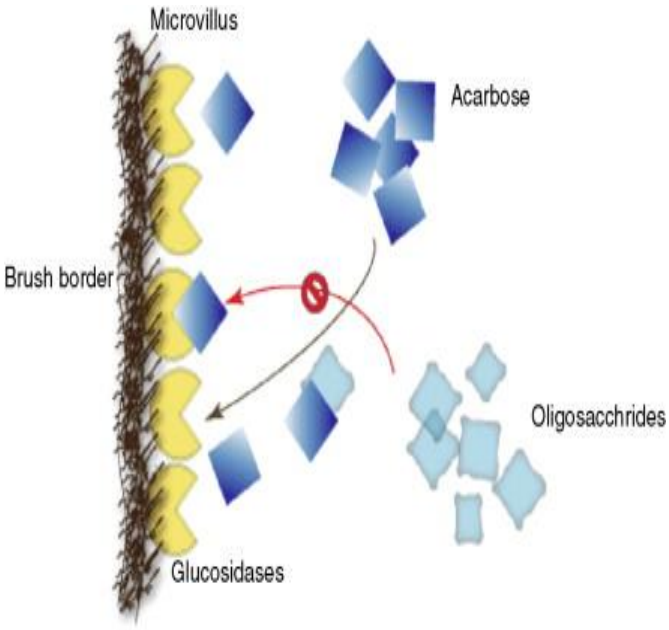
- Fluid retention (Edema).
- Precipitate congestive heart failure
- Mild weight gain.

C- Other drugs:

1-α- Glucosidase inhibitors:

E.g. Acarbose [AY-car-bose]

- Reversible inhibitors of **intestinal α-glucosidases** in intestinal brush border responsible for degradation of oligosaccharides to monosaccharides.
- decrease carbohydrate digestion and absorption in small intestine.
- Decrease **postprandial hyperglycemia.**
- Taken just before meals.
- **No hypoglycemia** if used alone.
- Ascarbose delays the absorption of carbohydrates, but don't inhibit it.
- Patients being treated with this drug are required to take glucose (monosaccharide) rather normal table sugar (a disaccharide)



Pharmcokinetics Acarbose

- Given orally, poorly absorbed.
- Metabolized by intestinal bacteria.
- Excreted in stool and urine (some of the drug's metabolites are absorbed and then excreted in urine)

Adverse effects of α-glucosidase inhibitors:

- GIT: Flatulence, diarrhea, abdominal pain.
- No hypoglycemia if used alone.

2-Incretin mimetics:

- Incretins are GI hormones secreted in response to food even before blood glucose level becomes elevated.
- Increase insulin secretion & decrease in glucagon secretion *(regulate blood glucose).*

Explanation: Oral glucose results in a higher secretion of insulin than occurs when an equal load of glucose is given IV. This effect is referred to as the "incretin effect" and is markedly reduced in type 2 diabetes. The incretin effect occurs because the gut releases incretin hormones, notably GLP-1 and glucosedependent insulinotropic polypeptide, in response to a meal. Incretin hormones are responsible for 60 to 70 percent of postprandial insulin

Incretins include:

- GLP-1 (glucagon-like peptide-1)
- GIP (gastric inhibitory peptide)
- Both are inactivated by dipeptidyl peptidase-4 (DPP-4).

Incretin mimetics:

Exenatide [EX-e-nah-tide]

- is a glucagon-like peptide-1 (GLP-1) agonist.
- **given s.c.** This is a polypeptide. Polypeptides are quickly inactivated if they are taken orally because of protein breaking peptides in the GIT, and thus should be taken S.C
- Used as adjunctive therapy in patients with type 2 diabetes

3-Dipeptidyl peptidase-4 (DPP- 4) inhibitors:

E.g. Sitagliptin

Mechanism of action:

- Inhibit **DPP-4 enzyme** and leads to an increase in incretin hormones level (*gastrointestinal hormone secreted in response to food*).
- This results in an increase in insulin secretion & decrease in glucagon secretion.
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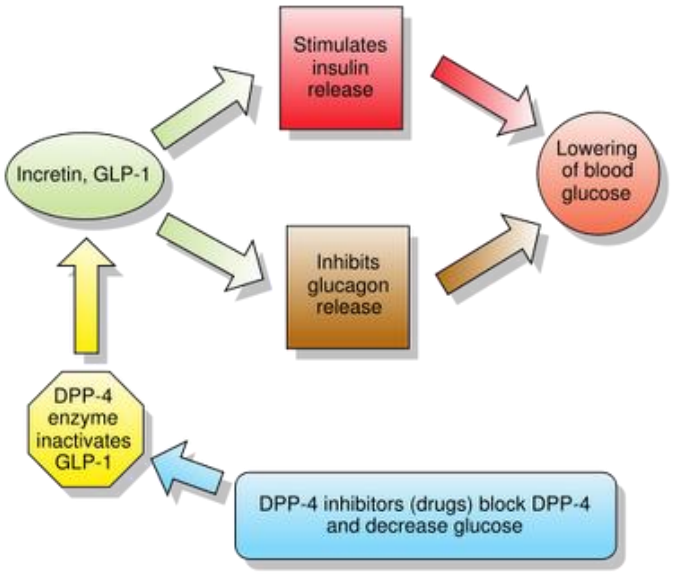

Pharmacokinetics:

- Orally
- Given once daily
- Half life 8-14 h
- Dose is reduced in patients with renal impairment

Uses of Sitagliptin:

Type 2 DM as an adjunct to diet & exercise as a monotherapy or in combination with other antidiabetic drugs.

Adverse effects:

Nausea, abdominal pain, diarrhea ,

Nasopharyngitis

Summary

- **1-Insulin secretagogues:** are drugs which increase the amount of **insulin secreted** by the pancreas. (Depend on functioning β cells, and thus are not effective in type I Diabetes)
- **Insulin secretagogues** include both **Sulfonylureas** and **Meglitinides,** and they both act on stimulating insulin release by **blocking of ATP-sensitive K channels**
- **Sulfonylureas** have variable durations of action with **second generation** having longer durations.
- Both generations are **metabolized in the liver** and **excreted in the Kidney.** This is of concern with elderly and patients with renal impairment.
- These drugs may also pass the placenta and cause fetal hypoglycemia, so regular insulin is used instead.
- **Tolbutamide** is the most used sulfonylurea because it is safe for old diabetic patients or patients with renal impairment (because it has a short duration of action with inactive metabolites).
- **Second generation sulfonylureas** (e.g. **Glibenclamide/ Glyburide**) are Contraindicated in hepatic impairment or renal insufficiency.
- sulfonylureas are used in Type II diabetes as **monotherapy** or in combination with other antidiabetic drugs.
- **ADRs:** hyperinsulemia, hypoglycemia, and weight gain.
- **Repaglinide (a Meglitinide analogues)** is also an acting insulin secretagogues that is used to control postprandial glucose levels and is used as monotherapy in managing diabetes type 2 or when patients are allergic to sulfur or sulfonylurea.
- **Metformin's (a biguanide)** main actions are increases glucose uptake and use by target tissues (insulin sensitization) and Inhibiting gluconeogenesis. **Insulin** has to be in certain amounts for it to give an effect.
- **Metformin** is excreated unchanged in the urine
- **It is used in obese patients as monotherapy** or combined therapy.
- **ADRs :** include: metallic taste, GIT disturbances (most common), and **increased rate of lactic acidosis (lethal).**
- **Contraindications**: 1) Pregnancy 2) Renal disease (excretion toxicity) 3) Liver disease 4) Alcoholism. 5) Conditions predisposing to hypoxia: cardiopulmonary dysfunction because of an increased risk of lactic acidosis induced by biguanide drugs
- **Thiazolidinediones (glitazones):** E.g. **Pioglitazone** are insulin sensitizers that are used as monotherapy or combined with other drugs, but have the adverse effects of hepatotoxicity and predisposition to congestive heart failure.
- **α- Glucosidase inhibitors: are** Reversible inhibitors of **intestinal α-glucosidases** in intestinal brush border responsible for degradation of oligosaccharides to monosaccharides and are poorly absorbed and mostly is excreated in stool. The unabsorbed sugars maybe fermented by insteinal bacteria to cause flatulence, diharreha, and abdominal pain.
- **Incretins** are GI hormones secreted in response to food even before blood glucose level becomes elevated. They are deactivated by dipeptidyl peptidase-4 (DPP-4).
- **Exenatide** [an incretin memtic given s.c. (Polypeptide)] is used as adjunctive therapy in patients with type 2 diabetes
- Sitagliptin Inhibit **DPP-4 enzyme** (enzyme responsible for incretin breakdown) and leads to an increase in incretin hormones level (*gastrointestinal hormone secreted in response to food*) → increase in insulin secretion & decrease in glucagon secretion.
- Sitagliptin is used in Type 2 DM as an adjunct to diet & exercise as a monotherapy or in combination with other antidiabetic drugs.
- **It's Adverse effects include:** GIT disturbance and Nasopharyngitis

Important strategy in choosing the appropriate drug:

- **Prone diabetic**→ insulin sensitizer (metformin)
- **Diabetic** →

1. First choice is drug sensitizer
2. Second is Combination (drug sensitizer –metformin-+ drug secretagogue – sulfonylureas -)
3. Insulin –if not controlled-

1-A 50-year-old woman has just been diagnosed withtype 2 diabetes and given a prescription for metformin.

Which of the following statements is characteristic of this medication?

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.

2-Which of the following classes of glucose-lowering agents has the ability to reduce insulin resistance?

A. α-glucosidase inhibitors.
B. DPP-IV inhibitors.
C. Meglitinides.
D. Sulfonylureas.
E. Thiazolidinediones.

3-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. Exenatide.
B. Glyburide.
C. Nateglinide.
D. Pioglitazone
E. Sitagliptin.

4-Which of the following drugs promotes the release of endogenous insulin?

A. Acarbose
B. Glipizide
C. Metformin
D. Miglitol
E. Pioglitazone

5-Which of the following is an important effect of insulin?

A. Incresed conversion of amino acids into glucose
B. Increased gluconeogenesis
C. Increased glucose transport into cells
D. Inhibition of of lipoprotein lipase
E. Stimulation of glycogenolysis

6-A 54 yr old obese patient with type 2 diabetes has a history of alcoholism. In this patient , metformin should either be avoided or used with extreme caution because the combination of metformin and ethanol increases the risk of which of the following?

A. A disulfiram-like reaction
B. Excessive weight gain
C. Hypoglycemia
D. Lactic Acidosis
E. Severe hepatotoxcity

7-Which of the following drugs is taken during the first part of a meal for the purpose of delaying the absorption of dietary carbohydrates?

A. Acarbose
B. Exenatide
C. Glipizide
D. Pioglitazone
E. Repaglinide

8- The PPAR-γ receptor is activated by thiazolidinediones increase tissue sensitivity to isulin by which of the following mechanisms?

A. Activating adenylyl cyclase and increasing the intracellular concentration of cAMP
B. Regulates transcription of genes involoved in glucose utilization
C. Inhibit acid glucosidase, a key enzyme in glycogen breakdown pathway
D. Stimulate the activity of tyrosine kinase that phosphorylates the isulin recptor .

Answer key: 1-B, 2-E, 3-D, 4-B, 5-C, 6-D, 7-A, 8- B