بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pharmacology | FINAL 8

Insulin and Oral Hypoglycemic Drugs pt.3

Written by : Bushra Masalha
Layan Abuhaweleh
Bushra Al-daboubi
NST memberah

Reviewed by : Sereen Samara

Insulin and Oral Hypoglycemic Drugs

Insulin Sensitizers

Thiazolidinediones or glitazones

- Insulin is required for their action, but do not promote its secretion.

- Two members of the class are

1. pioglitazone
2. Rosiglitazone

MOA: They are target the peroxisome proliferator activated receptor (PPARγ): a nuclear hormone receptor >>>> regulate fat and glucose metabolism >>>> increased insulin sensitivity in adipose tissue, liver, and skeletal muscle.

Thiazolidinediones (chemical name rare use it) / **Glitazones** :
Pioglitazone and Rosiglitazone
are oral Hypoglycaemic sensitisers that have similar responses to Metformin but not similar mechanism
Used in : Type 2 DM , PCOS
MOA : work on intracellular receptor (PPAR gamma- one of its isoforms, in the future you might come across alpha which is used to treat patients with lipid imbalance)
it is a transcription factor, it regulates transcription (synthesis of RNA of many genes)- increase or decrease synthesis.

Extra clarifying not included just for understanding mechanism :
It increases mRNA for glucose transporter protein-so increase glucose transport to liver and skeletal muscle.
Decrease lipolysis - decrease FFA - decrease low grade inflammation (one of the causes of insulin resistance)- enhance insulin sensitivity and decrease resistance.

Insulin Sensitizers

Thiazolidinediones or glitazones

- LDL is not affected by pioglitazone, whereas LDL has increased with rosiglitazone (cardiovascular toxicity and also due to water retension). HDL increases with both drugs.

- The TZDs lead to redistribution of fat from visceral to subcutaneous tissues >>>> **weight gain**.

Why metformin is more preferable than glitazones?

Glitazones drugs increase weight (causes weight gain)

1. The level of Leptin will be decreased which causes an increase in appetite. (inverse relationship)
2. Redistribution of the fat (not the main cause according to the doctor)

Glitazones drugs are cardiotoxic

It is **contraindicated** for MI patients

****important ; All drugs that treat DM protect cardiac muscles except Glitazones**

So when we use these drugs??

but should be aware if patient has myocardial infarction

If metformin **DOESN'T benefit** the patient

If the patient **has allergies** from metformin

Insulin Sensitizers

Thiazolidinediones or glitazones

- The glitazones are recommended as a second-line alternative for patients who fail or have contraindications to metformin therapy.

- Both drugs are absorbed well from GIT
- It is recommended that these agents NOT be used in nursing mothers.
- The relief of insulin resistance causes ovulation to resume in premenopausal women with polycystic ovary syndrome.

- Women taking oral contraceptives and TZDs may become pregnant (WHY?!) because TZDs have been shown to reduce plasma concentrations of the estrogen-containing contraceptives.

Insulin Sensitizers

Thiazolidinediones or glitazones

- Adverse effects:
- Very few cases of liver toxicity Rare
- Weight increase. Important
- Osteopenia and increased fracture risk. Rare
- Increased risk of myocardial infarction and death. Important

α-Glucosidase Inhibitors

Drug Members:

1. Acarbose
2. Miglitol

- Used for the treatment of patients with Type 2 diabetes.
- Are taken at the beginning of meals. (WHY?!) They act by delaying the digestion of carbohydrates, thereby resulting in lower postprandial glucose levels.
- Mechanism of action:

3. Reversible inhibiting α-glucosidase in the intestinal brush border. (This enzyme is responsible for the hydrolysis of oligosaccharides to glucose)
4. Inhibits pancreatic α-amylase. (WHAT is **α-amylase?)**

Acarbose

Acarbose is an **oral hypoglycemic drug** belonging to the **alpha-glucosidase inhibitor** family. It is the most important and commonly used drug of this group, particularly in Jordan. It is mainly used in **Type 2 Diabetes Mellitus (DM2)** as an **adjunctive therapy**, rather than as a primary treatment. It is usually administered together with drugs such as **metformin or sulfonylureas**.

Mechanism of Action

Alpha-glucosidase is an enzyme present in the gastrointestinal tract that breaks down **glucose polymers and complex carbohydrates into their monomers**. Since carbohydrates can only be absorbed from the gastrointestinal tract in their **monomer forms**, inhibition of this enzyme decreases carbohydrate digestion and consequently decreases glucose absorption.

Acarbose inhibits alpha-glucosidase, causing glucose polymers to remain undigested and therefore reducing the absorption of **dietary glucose** from the gastrointestinal tract. As a result, **postprandial blood glucose levels decrease**.

An important point is that acarbose only affects the absorption of **glucose obtained from the diet**. It has **no significant effect on endogenous glucose metabolism or insulin secretion**. Therefore, it does not directly affect:

- **Gluconeogenesis**
- **Glycogenolysis**
- **Glycogenesis**
- **Insulin secretion**

Acarbose is administered **at the beginning of meals**, because its action is directed toward the digestion and absorption of carbohydrates obtained from food.

α-Glucosidase Inhibitors

- Acarbose is poorly absorbed.
- Miglitol is very well absorbed but has no systemic effects.

- The major side effects are:

1. Flatulence, diarrhea, and abdominal cramping. (WHY?!)
2. Patients with inflammatory bowel disease, colonic ulceration, or intestinal obstruction should not use these drugs.

Absorption and Adverse Effects

Acarbose is **poorly absorbed** from the gastrointestinal tract. Consequently, both the drug and the undigested carbohydrates remain within the GI tract.

The presence of undigested carbohydrates in the intestine leads to **gastrointestinal disturbances**, which are the most common and important adverse effects reported by patients.

Because Acarbose can **aggravate gastrointestinal symptoms,** it is not used in patients with inflammatory bowel diseases, as it may worsen their symptoms.

Why Is Acarbose Mainly Used in Type 2 Diabetes?

Acarbose is primarily useful in **Type 2 Diabetes Mellitus**, where dietary carbohydrate intake and impaired glucose handling contribute significantly to hyperglycemia. By reducing the absorption of dietary carbohydrates, acarbose can provide additional glycemic control.

In contrast, the fundamental problem in **Type 1 Diabetes Mellitus** is **insulin deficiency**. Therefore, insulin replacement is the main and most effective treatment.

Acarbose is **not absolutely contraindicated in Type 1 diabetes**, but it provides **negligible clinical benefit** in these patients. Even when administered together with insulin at different times (to lower the risk of hypoglycaemic shock) , its therapeutic effect is limited. Therefore, it is generally not clinically useful for managing Type 1 diabetes.

Incretin Hormones

First, let us go back to **physiology and biochemistry** to remember what incretin hormones are and how they work.

When we eat food, incretin hormones are released from the gastrointestinal tract. Their overall function is to limit the sharp postprandial elevation in blood glucose.

Incretins exert three major effects:

1. **Increase insulin secretion**, but in a controlled manner.
2. **Decrease glucagon secretion.**
3. **Delay gastric emptying**, which increases the sensation of fullness and therefore decreases appetite.

These actions occur through activation of the **GLP-1 receptor**.

We previously discussed similar effects when studying **amylin**.

Amylin is secreted from the pancreas and:

- decreases glucagon secretion;
- delays gastric emptying.

Its analogue, **pramlintide**, can be administered together with insulin as an adjunctive drug.

Therefore, **incretin and amylin are similar because both decrease glucagon secretion and delay gastric emptying. However, they differ in their effects on insulin secretion,** as incretin increases insulin secretion.

Delayed gastric emptying → increased feeling of fullness → decreased appetite.
In addition, food remains in the stomach for a longer period, and the transfer of glucose-containing gastric contents from the stomach to the intestine occurs more slowly.
Therefore:
Slower transfer of glucose to the intestine → slower glucose absorption → slower elevation of blood glucose.

Why Do Incretin-Based Drugs Have a Lower Risk of Hypoglycemia?
Incretins **increase insulin secretion in a glucose-dependent manner**, meaning that their insulin-stimulating effect decreases as blood glucose levels fall. Therefore, incretin-based drugs have a **lower risk of hypoglycemia** compared with insulin and sulfonylureas.
(Incretins → glucose-dependent insulin secretion; Sulfonylureas → glucose-independent insulin secretion; Exogenous insulin → glucose-independent glucose-lowering effect.)

Incretins are important hormones in the regulation of blood glucose.
In general, greater incretin activity contributes to lower postprandial blood glucose levels.
This raises an important therapeutic question:
Why do we not enhance the incretin pathway in patients with type 2 diabetes mellitus?
This is exactly the principle behind the next two important groups of antidiabetic drugs.

Incretin Mimetics

- Oral glucose results in a higher secretion of insulin than occurs when an equal load of glucose is given intravenously.
- This effect is referred to as the (incretin effect) and is apparently reduced in Type 2 diabetes.

Exenatide

incretin analogue produced through biotechnology, providing a pharmacological alternative to endogenous incretin. It acts as a **GLP-1 (glucagon-like peptide-1) receptor agonist**, activating the same receptor through which endogenous GLP-1 (natural incretin hormone) exerts its effects.
However, **exenatide has a relatively short duration of action**.

- Is an incretin mimetic.

1. Improves glucose-dependent insulin secretion
2. Slows gastric emptying time
3. Decreases food intake
4. Decreases postprandial glucagon secretion
5. Promotes β-cell proliferation.

Should ne administrated before meal

- Consequently, weight gain and postprandial hyperglycemia are reduced, and HbA1c levels decline.

Exenatide

- Is polypeptide >>> administered subcutaneously NOT orally

- Similar to pramlintide, the main adverse effects consist of:
- Nausea, vomiting, and diarrhea.(GIT side effects)

Semaglutide (Ozempic)

Ozempic (semaglutide) is an incretin analogue, and a **GLP-1 receptor agonist** used in the management of **type 2 diabetes mellitus**. When administered, semaglutide binds to and activates GLP-1 receptors, leading to **increased glucose-dependent insulin secretion, decreased glucagon secretion, and delayed gastric emptying**.

Delayed gastric emptying causes food to remain in the stomach for a longer period, thereby **increasing satiety and decreasing appetite**, which can ultimately contribute to **weight loss**.

Clinically, **semaglutide is often preferred over short-acting exenatide** because it has a **longer duration of action**. Depending on the specific formulation, longer-acting GLP-1 receptor agonists require less frequent administration (once a week), which may **improve patient compliance**.

Because semaglutide can produce significant weight loss, it is also used for **weight management**, including in individuals without diabetes mellitus. Its effects on gastric emptying and the gastrointestinal tract may cause **GI disturbances**, such as discomfort, while the associated increased satiety and decreased appetite contribute to its weight-loss effect.

The doctor mentioned **two observed cases of sudden death following the use of Ozempic (semaglutide) for weight loss** in individuals who did not have type 2 diabetes mellitus. In one case, sudden death occurred approximately **one week** after use, while in the other, it occurred approximately **one month** later. According to the doctor, both individuals had obtained the Ozempic injections from **Egypt**, raising additional questions regarding the source of the injections.
However, these observations **do not establish a causal relationship between semaglutide and sudden death**. They represent individual clinical observations in which a temporal association was noticed.
Important: Correlation or temporal association does not imply causation.
Therefore, based on the doctor's statement, these two cases should **not be presented as scientific evidence that Ozempic causes sudden death**. They were mentioned as personal clinical observations that raised concern and may warrant further investigation, but **causation has not been established**.

A possible question is:
Do patients with type 2 diabetes mellitus who use these drugs have an increased risk of sudden death?
Currently, there is **no established evidence that GLP-1-based therapies increase the risk of sudden death in patients with type 2 diabetes mellitus**. In fact, GLP-1 receptor agonists are highly effective and are widely used in the management of these patients.
Incretin-based therapy includes two main approaches:

- **Incretin analogues / GLP-1 receptor agonists**, which mimic the action of endogenous incretin.
- **DPP-4 inhibitors**, which inhibit **dipeptidyl peptidase-4 (DPP-4)**, the enzyme responsible for breaking down incretin hormones.

The mechanism and clinical importance of **DPP-4 inhibitors** will be discussed in the next slide.

Dipeptidyl Peptidase-IV Inhibitors (DPP-IV)

usually end with the suffix **"-gliptin"**

Sitagliptin **commonly used**

- Orally inhibits the enzyme DPP-IV!!!

What is **DPP-IV?**

- Is responsible for the inactivation of incretin hormones, such as glucagon-like peptide-1 (GLP-1)
- Sitagliptin prevents incretin hormone inactivation >>> results in:

1. Increased insulin release in response to meals
2. Reduction in inappropriate secretion of glucagon.

Why is the risk of hypoglycemia low with sitagliptin?
Sitagliptin has a **low risk of hypoglycemia** because its effect on insulin secretion is **glucose-dependent.** Therefore, as blood glucose levels fall, the incretin-mediated stimulation of insulin secretion also decreases, preventing a sharp decline in blood glucose.

Dipeptidyl Peptidase-IV Inhibitors

Sitagliptin

- Is well absorbed after oral administration.

- The majority of sitagliptin is excreted unchanged in the urine>>>>>> Dosage adjustments are recommended for patients with renal dysfunction.

The most common adverse effects being:

1. Nasopharyngitis
2. Headache

- Rates of hypoglycemia is very low.

For example, if **sitagliptin** and a **sulfonylurea** are compared, both can increase insulin secretion; however, the **risk of hypoglycemia is higher with sulfonylureas**. Sulfonylureas can stimulate insulin secretion **independently of the blood glucose level**, potentially producing a greater insulin response even when blood glucose is low. In contrast, sitagliptin enhances insulin secretion in a **glucose-dependent manner**, so its insulin-stimulating effect decreases as blood glucose falls. Therefore, sitagliptin has a **lower risk of hypoglycemia**.
Clinically, **metformin has a very low risk of hypoglycemia when used as monotherapy**, because it does not directly stimulate insulin secretion.

INCRETIN-BASED THERAPIES IN TYPE 2 DIABETES MELLITUS

1) DPP-IV INHIBITORS ("-gliptin") SITAGLIPTIN

MECHANISM OF ACTION

- DPP-IV (dipeptidyl peptidase-IV) is an enzyme that inactivates incretin hormones (e.g., GLP-1).
- Sitagliptin orally inhibits DPP-IV → prevents incretin inactivation → increases endogenous GLP-1 levels.

↑ Active incretins (GLP-1)

- **Pancreas (β-cells)**: ↑ Insulin secretion (glucose-dependent)
- **Pancreatic α-cells**: ↓ Glucagon secretion (from α-cells)

↓ Blood glucose

PHARMACOKINETICS

- Well absorbed after oral administration.
- Majority excreted unchanged in urine. Dose adjustment recommended in renal dysfunction.

ADVERSE EFFECTS

- Nasopharyngitis
- Headache

- Very low risk of hypoglycemia.

CLINICAL USES

- Type 2 diabetes mellitus (as monotherapy or in combination with other agents).
- Suitable when low risk of hypoglycemia and weight neutrality are desired.

2) INCRETIN MIMETICS (GLP-1 RECEPTOR AGONISTS) EXENATIDE

MECHANISM OF ACTION (GLP-1 RECEPTOR AGONIST)

Exenatide mimics GLP-1

- **Pancreas (β-cells)**: ↑ Insulin secretion (glucose-dependent)
- **Stomach**: Slows gastric emptying
- **Central appetite**: ↓ Food intake
- **Pancreatic α-cells**: ↓ Postprandial glucagon secretion

β-cell proliferation

↓ Postprandial hyperglycemia
↓ Weight gain
↓ HbA1c levels

PHARMACOKINETICS

- Exenatide is a polypeptide → NOT given orally.
- Administered subcutaneously.
- Should be administered before meal.

ADVERSE EFFECTS

Mainly gastrointestinal side effects:

- Nausea
- Vomiting
- Diarrhea

CLINICAL USES

- Type 2 diabetes mellitus (as add-on to diet, exercise, and other medications).
- Beneficial in overweight/obese patients due to weight loss effect.

WHY RISK OF HYPOGLYCEMIA IS LOW (with both classes)

Their actions are glucose-dependent: insulin secretion ↑ when glucose is high and decreases when glucose is low.

COMPARISON SUMMARY

Feature	DPP-IV Inhibitors (Sitagliptin)	Incretin Mimetics (Exenatide)
Mechanism	↑ Endogenous incretin (GLP-1) by inhibiting DPP-IV enzyme	Direct GLP-1 receptor agonist (mimics incretin)
Route	Oral	Subcutaneous injection
Effect on insulin	↑ Glucose-dependent insulin secretion	↑↑ Glucose-dependent insulin secretion (stronger)
Effect on glucagon	↓ Inappropriate glucagon secretion	↓ Postprandial glucagon secretion
Effect on gastric emptying	Minimal	Slows gastric emptying
Effect on weight	Weight neutral	Weight loss
Risk of hypoglycemia	Very low	Low (when not combined with insulin or sulfonylurea)
Common adverse effects	Nasopharyngitis, headache	Nausea, vomiting, diarrhea

OVERALL BENEFITS (Both classes)

- ✓ Lower HbA1c
- ✓ Low risk of hypoglycemia
- ✓ Do not cause weight gain (Exenatide causes weight loss)
- ✓ Cardiovascular benefit with several GLP-1 RAs (e.g., exenatide, liraglutide, semaglutide)

OVERALL USE IN TYPE 2 DIABETES

- Improve glycemic control (↓ fasting and postprandial glucose, ↓ HbA1c)
- Favorable weight effect (weight neutral with DPP-IV inhibitors; weight loss with GLP-1 RAs)
- Low risk of hypoglycemia (especially as monotherapy or with metformin)
- Useful with lifestyle modification (diet, exercise, and other medications)

⭐ Metformin has the lowest risk of hypoglycemic shock among oral antidiabetic drugs when used as monotherapy.

Under normal conditions, glucose is filtered through the nephron and then **reabsorbed back into the blood by the SGLT2 transporter**.
Therefore, normally:
Filtered glucose → SGLT2-mediated reabsorption → glucose returns to the blood
If glucose is reabsorbed back into the circulation, it contributes to the blood glucose level.
So, what can we do therapeutically?
We can **inhibit this transporter**.
SGLT2 inhibitor → ↓ glucose reabsorption → glucose remains in the tubular fluid → glucose is excreted in the urine.
Therefore:
↑ glucose in urine → ↓ glucose in blood
An easy way to remember it:
What increases in the urine decreases in the blood, and vice versa.

SGLT2 inhibitors are considered among the antidiabetic drugs with important **cardioprotective effects**.
Therefore, if a patient with **diabetes mellitus** has a **cardiac complication** or a significant cardiac problem, an SGLT2 inhibitor may be a preferred option.
Diabetes mellitus + cardiac complications → consider/prefer an SGLT2 inhibitor.

SGLT2 inhibitors

- Sodium–glucose cotransporter 2 inhibitors

Drugs members: commonly end with the suffix: **“-gliflozin”**

1. Canagliflozin
2. Dapagliflozin

- Drugs for type 2 diabetes.

MOA:

The sodium–glucose cotransporter 2 (SGLT2) is responsible for reabsorbing filtered glucose in the tubular lumen of the kidney. By inhibiting SGLT2, these agents decrease reabsorption of glucose, increase urinary glucose excretion, and lower blood glucose.

Why Do SGLT2 Inhibitors Act as Diuretics?

These drugs behave as **diuretics** because glucose has an **osmotic property**.
When glucose remains in the renal tubules and is excreted in the urine, it **draws water with it**.
Therefore:
SGLT2 inhibition → glucosuria → water follows glucose → ↑ urine formation
This is called **osmotic diuresis**.

Why Does the Patient Urinate More Frequently?

The increased amount of urine eventually reaches the **bladder**.
As more urine accumulates in the bladder:
↑ urine volume in the bladder → ↑ bladder filling → increased urge to urinate
Therefore, patients taking SGLT2 inhibitors may experience **increased frequency of urination**.
So the complete idea is:
Glucose is excreted → glucose pulls water with it → more urine is produced → bladder fills more rapidly → patient urinates more frequently.

Effect on Blood Glucose

The primary antidiabetic effect of these drugs is produced by **eliminating glucose through the urine**.
Therefore, they lower blood glucose **without requiring insulin secretion as their primary mechanism**.
In simple terms:
Instead of returning glucose to the blood, we allow the kidney to remove it in the urine.

SGLT2 inhibitors may affect electrolytes, but this effect is generally weak.
So do not make the electrolyte disturbance the major feature of this drug class.

Why Are SGLT2 Inhibitors Cardioprotective?
One explanation is related to their **diuretic effect**.
SGLT2 inhibitors increase glucose excretion in the urine, which causes **osmotic diuresis**. As urine output increases, circulating blood volume decreases.
Therefore:
↑ Urine output → ↓ blood volume → ↓ cardiac workload → reduced stress on the heart
This contributes to their cardioprotective effect.
However, according to the notes, the cardiovascular benefit is **not explained only by diuresis or glucose excretion**.
There is also a **direct cardioprotective effect**. The notes mention that SGLT2 inhibitors may act directly on the heart, **improve mitochondrial function, and protect cardiac cells against free-radical-related damage**.
This effect is described as being **opposite to glitazones**, which may promote fluid retention and can therefore worsen cardiac problems in susceptible patients.
So the important idea is:
SGLT2 inhibitors have both indirect and direct cardioprotective effects.
Indirect:
SGLT2 inhibition → osmotic diuresis → ↓ blood volume → ↓ cardiac workload.
Direct:
Cardiac effects that are **independent of glucose removal from the blood**, including effects on mitochondrial function and protection from oxidative/free-radical damage, as stated in the notes.

SGLT2 inhibitors

- Inhibition of SGLT2 also decreases reabsorption of sodium and causes osmotic diuresis >>>> reduce systolic blood pressure.
- However, they are not indicated for the treatment of hypertension!!!!!

Adverse effects:

- The most common adverse effects with SGLT2 inhibitors are :
- Female genital mycotic infections (vulvovaginal candidiasis)
- Urinary tract infections.

SGLT2 Inhibitors – Adverse Effects

Why Do SGLT2 Inhibitors Increase the Risk of Infection?

Because SGLT2 inhibitors prevent renal glucose reabsorption, **glucose remains in the urine (glucosuria).**

When urine contains a higher concentration of glucose, it provides a favorable environment for the growth of microorganisms, including bacteria such as **E. coli and Staphylococci**, as well as fungi.

Therefore:

SGLT2 inhibition → ↑ urinary glucose → enhanced microbial growth → ↑ risk of urinary and genital infections

Important Adverse Effects

For this reason, SGLT2 inhibitors can increase the risk of:

- **Urinary tract infections (UTIs)**
- **Mycotic (fungal) infections**

How Does a UTI Develop?

The notes describe UTI development as requiring several contributing factors:

Glucose in the urine + entry of microorganisms + favorable conditions for microbial growth → urinary tract infection

However, remember that SGLT2 inhibitors also cause **increased urination**.

This increased urinary flow can cause some **dilution of urinary glucose** and more frequent emptying of the bladder.

So, although glucosuria provides a favorable environment for microorganisms, frequent urination may provide some flushing of the urinary tract.

The important clinical point remains:

SGLT2 inhibitors increase glucosuria, which increases susceptibility to urinary and particularly genital infections.

Why Are Females More Susceptible to UTIs?

Females generally have a **higher susceptibility to UTIs** because their anatomical structure facilitates the **ascending entry of microorganisms into the urinary tract**.

Therefore:

Female urinary anatomy → easier entry/ascending spread of microorganisms → ↑ susceptibility to UTI

This is a general anatomical predisposition and is **not specific to SGLT2 inhibitors**.

Very Important: SGLT2 Inhibitors and Type 1 Diabetes Mellitus

❌ SGLT2 inhibitors should not be routinely used for Type 1 Diabetes Mellitus.

Why?

Because patients with **type 1 diabetes mellitus already have a tendency to develop ketoacidosis** due to severe insulin deficiency.

Why Is Type 1 DM Predisposed to Ketoacidosis?

In type 1 diabetes mellitus, there is **absolute or severe insulin deficiency**.

Therefore, glucose cannot be adequately utilized by insulin-dependent tissues.

The body consequently shifts toward the utilization of **fatty acids** as an alternative energy source.

So:

↓ **Insulin**

→ ↓ glucose utilization by insulin-dependent tissues

→ ↑ mobilization and utilization of fatty acids

→ ↑ ketone-body production

→ **ketoacidosis**

The **adipose tissue** provides the fatty acids that contribute to this process.

Easy memory line

No insulin → cannot adequately use glucose → use fat → produce ketones → ketoacidosis.

Why Are SGLT2 Inhibitors Particularly Concerning in Type 1 DM?
SGLT2 inhibitors themselves can **increase the risk of ketoacidosis**.
This is particularly important because:
Type 2 DM
Ketoacidosis is **not usually the major baseline metabolic tendency**.
Type 1 DM
The patient is **already predisposed to ketoacidosis** because of severe insulin deficiency.
Therefore:
Type 1 DM already predisposes to ketoacidosis + SGLT2 inhibitors can further increase the risk of ketoacidosis → clinically important risk.

SGLT2 INHIBITORS
(Sodium–glucose cotransporter 2 inhibitors)

1) WHAT ARE THEY?

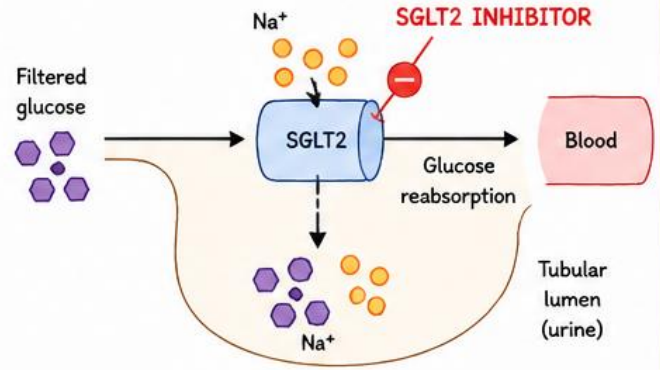
- Sodium–glucose cotransporter 2 inhibitors.
- Drugs for type 2 diabetes mellitus.

2) DRUGS (EXAMPLES)

- Canagliflozin
- Dapagliflozin

3) MECHANISM OF ACTION (MOA)

In the proximal convoluted tubule (PCT)
SGLT2 normally reabsorbs ~90% of filtered glucose along with sodium (Na^+).



Inhibition of SGLT2 → ↓ reabsorption of glucose and Na^+
→ ↑ urinary glucose excretion (glucosuria)
→ ↓ blood glucose

ADDITIONAL EFFECT

↓ Na^+ reabsorption
→ osmotic diuresis (natriuresis + glucosuria)
→ ↓ intravascular volume
→ ↓ systolic blood pressure.

NOT indicated for the treatment of hypertension.

4) ADVERSE EFFECTS

Most common adverse effects:

- Female genital mycotic infections (vulvovaginal candidiasis)
- Urinary tract infections

Other possible adverse effects:

- Increased urination (polyuria)
- Volume depletion, dehydration, dizziness, hypotension
- Genital pruritus
- (Rare) euglycemic diabetic ketoacidosis, especially in insulin-deficient states

5) CLINICAL USE

- Approved for treatment of type 2 diabetes mellitus to improve glycemic control.
- Can be used as monotherapy (when metformin not appropriate) or in combination with other antidiabetic agents.

Particularly useful in patients with:

- ✓ High cardiovascular risk or established cardiovascular disease
- ✓ Heart failure
- ✓ Chronic kidney disease (some agents and dosing depends on eGFR)

6) BENEFITS

- ↓ Lowers blood glucose (through glucosuria)
- ↓ Lowers systolic blood pressure (mild)
- ↓ Causes modest weight loss
- ★ Cardioprotective: ↓ risk of major adverse cardiovascular events, ↓ heart failure hospitalization
- ★ Renoprotective: Slows progression of chronic kidney disease

7) KEY POINTS TO REMEMBER

- ★ Mechanism is independent of insulin.
- ★ Works by increasing urinary loss of glucose and sodium.
- ★ Causes osmotic diuresis → lowers systolic blood pressure but is NOT an antihypertensive drug.
- ★ Watch for genital mycotic infections and UTIs.
- ★ Risk of euglycemic ketoacidosis (rare but important).

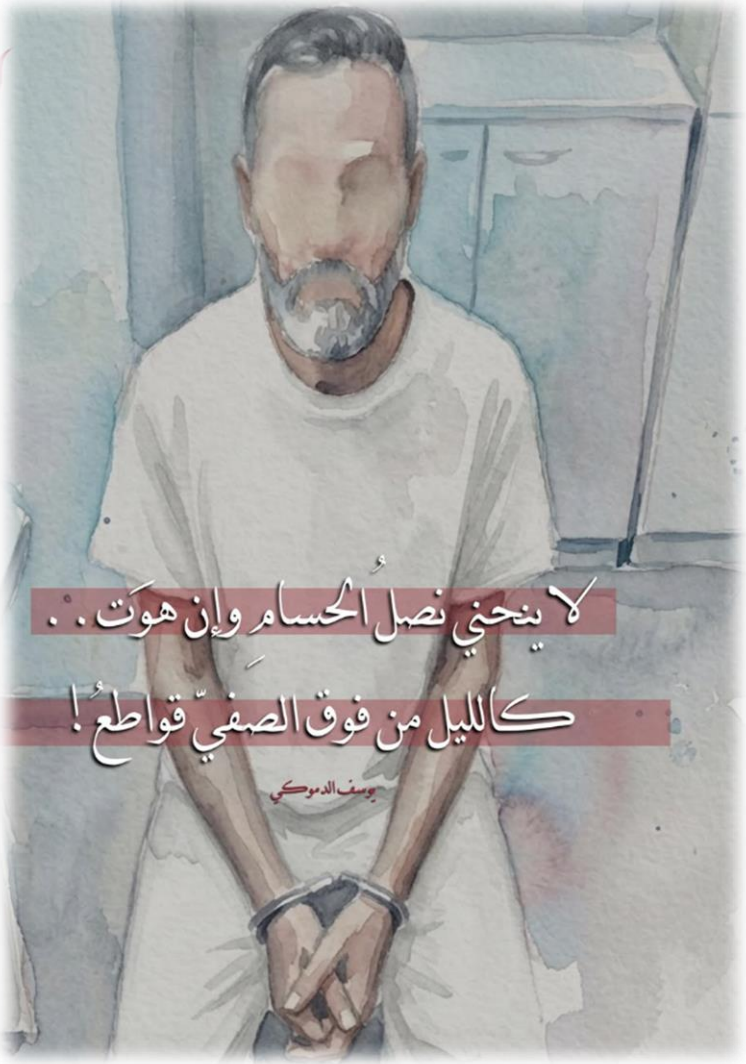
8) CONTRAINDICATIONS / PRECAUTIONS

- History of recurrent genital mycotic infections
- Severe renal impairment (agent/dose dependent)
- Risk of volume depletion
- Avoid in type 1 diabetes (risk of ketoacidosis)

SUMMARY: SGLT2 inhibitors block renal glucose and sodium reabsorption in the proximal tubule → glucosuria + natriuresis → ↓ blood glucose, ↓ blood pressure, weight loss, and cardio-renal protection, with main adverse effects being genital mycotic infections and urinary tract infections.

Additional Resources:

رسالة من الفريق العلمي:



مَعَ الطَّيَّةِ الأَخِيرَةِ مِنْ أَوْرَاقِ فَرِيقِنَا العِلْمِيِّ لِهَذَا الفَصْلِ الصَّيْفِيِّ، وَرَغْمَ مَا يَسْكُنُ قُلُوبَنَا جَمِيعاً مِنْ امْتِنَانٍ عَمِيقٍ وَتَقْدِيرٍ كَبِيرٍ لِكُلِّ مَنْ بَذَلَ وَقَدَّمَ -وَلَوْ بِقَدْرِ حَرْفٍ وَاحِدٍ -لِيَنْفَعَ بِهِ غَيْرَهُ، إِلاَّ أَنَّنَا لَمْ نَجِدْ فِي خِتَامِ هَذَا المَلَفِّ شَيْئاً أَبْلَغَ، وَلاَ أَوْجَبَ، وَلاَ أَقْرَبَ إِلَى جَوْهَرِ مَا نَسْعَى إِلَيْهِ، مِنْ أَنْ نَقِفَ وَإِيَّاكُمْ عِنْدَ المَعْنَى الأَسْمَى لِهَذِهِ المِهْنَةِ..

فَفِي زَمَنٍ تُخْتَبَرُ فِيهِ المَبَادِئُ وَتُعَادُ صِيَاغَةُ الإِنْسَانِيَّةِ عَلَى مَحَكِّ الأَلَمِ، يَقِفُ الطَّبِيبُ لَيْسَ جَسَداً يُدَاوِي الجِرَاحَ فَحَسْبُ، بَلْ ثَبَاتاً يَبْعَثُ الحَيَاةَ فِي المَعَانِي المَيِّتَةِ .وَإِنَّنَا -كَمَنْ نَخْطُو خُطُوَاتِنَا الأُولَى فِي هَذَا الطَّرِيقِ -نَنْظُرُ إِلَى قَامَةٍ عَالِيَةٍ كَالدُّكْتُورِ **حُسَام أَبُو صَفِيَّة**، لاَ كَشَخْصٍ يَمُرُّ فِي ذَاكِرَةِ الأَيَّامِ، بَلْ كَمُحَدِّدٍ أَخْلاَقِيٍّ وَبُصْلَةٍ حَيَّةٍ لِكُلِّ مَنْ حَمَلَ سَمَّاعَةً أَوْ خَطَّ حَرْفاً فِي عُلُومِ المِشْرَطِ وَالدَّوَاءِ.

إِنَّ مَا يَعِيشُهُ هَذَا الرَّجُلُ الصَّامِدُ، وَمَا يُكَابِدُهُ مِنْ أُسْرٍ وَظُلْمٍ بَعْدَمَا أَبَى أَنْ يَتْرُكَ مَرْضَاهُ أَوْ يَتَخَلَّى عَنْ مِحْرَابِهِ الإِنْسَانِيِّ، هُوَ الدَّرْسُ الأَشَدُّ بَلاَغَةً الَّذِي لَمْ تَحْوِهِ المَعَاجِمُ وَلَمْ تَسَعْهُ المُمَارَسَاتُ الأَكَادِيمِيَّةُ .لَقَدْ عَلَّمَنَا أَنَّ الطَّبِيبَ حِينَمَا يُقْسِمُ، فَإِنَّهُ لاَ يَعِدُ بِالشِّفَاءِ فَقَطْ، بَلْ يَعِدُ بِالبَقَاءِ، وَبِأَنْ يَكُونَ الجِدَارَ الأَخِيرَ الَّذِي يَتَّكِئُ عَلَيْهِ الخَائِفُونَ.

نَحْنُ لاَ نَنْظُرُ إِلَى مَحَطَّاتِ الاعْتِقَالِ وَالسَّجْنِ وَالإِعْيَاءِ كَنِهَايَةٍ لِلْقِصَّةِ، بَلْ كَشَاهِدٍ حَيٍّ عَلَى أَنَّ الحَقَّ حِينَمَا يَلْتَحِفُ بِالرَّحْمَةِ يَكُونُ أَقْوَى مِنَ القَسْوَةِ، وَأَنَّ حُرِّيَّةَ الرُّوحِ لاَ تُقَيَّدُ بِالأَغْلاَلِ .إِنَّنَا نَرَى فِيهِ المِهَنِيَّةَ فِي أَبْهَى صُوَرِهَا، وَالنُّورَ الَّذِي يُصِرُّ أَنْ يَنْبَعِثَ مِنْ صَمْتِ الزَّنَازِينِ لِيُضِيءَ بَصَائِرَنَا.
نَسْأَلُ اللهَ العَلِيَّ القَدِيرَ أَنْ يُعَجِّلَ بِفَرَجِهِ وَفَكِّ أَسْرِهِ، وَأَنْ يُعِيدَهُ سَالِماً مُعَافَىً إِلَى مَيْدَانِهِ الَّذِي اشْتَاقَ لِلَمَسَاتِهِ ..وَأَنْ يَجْعَلَنَا جَمِيعاً عَلَى ذَاتِ الأَثَرِ؛ أَطِبَّاءَ شُرَفَاءَ، يَحْمِلُونَ الإِنْسَانِيَّةَ عَقِيدَةً، وَيَقِفُونَ فِي وَجْهِ العَتَمَةِ جُنُوداً لِلأَمَلِ أَيْنَمَا حَلُّوا.

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			