DRUG TRETEMENT OF DM part 2

Semester IV

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Learning Outcomes

By the end of the 3 lecture, the students will be able to:

1. Describe the mechanism of action and side effects of sulphonylureas, metformin, acarbose, glitazones
2. Recognize side effects of sulphonylureas, metformin, acarbose, glitazones
3. Describe newer antidiabetic drugs.

Oral ant diabetic drugs

Sulfonylureas

- Classification:

First-generation compounds: chlorpropamide, tolbutamide

Second-generation compounds:

glibenclamide, gliclazide

Third-generation compounds:

glimepiride

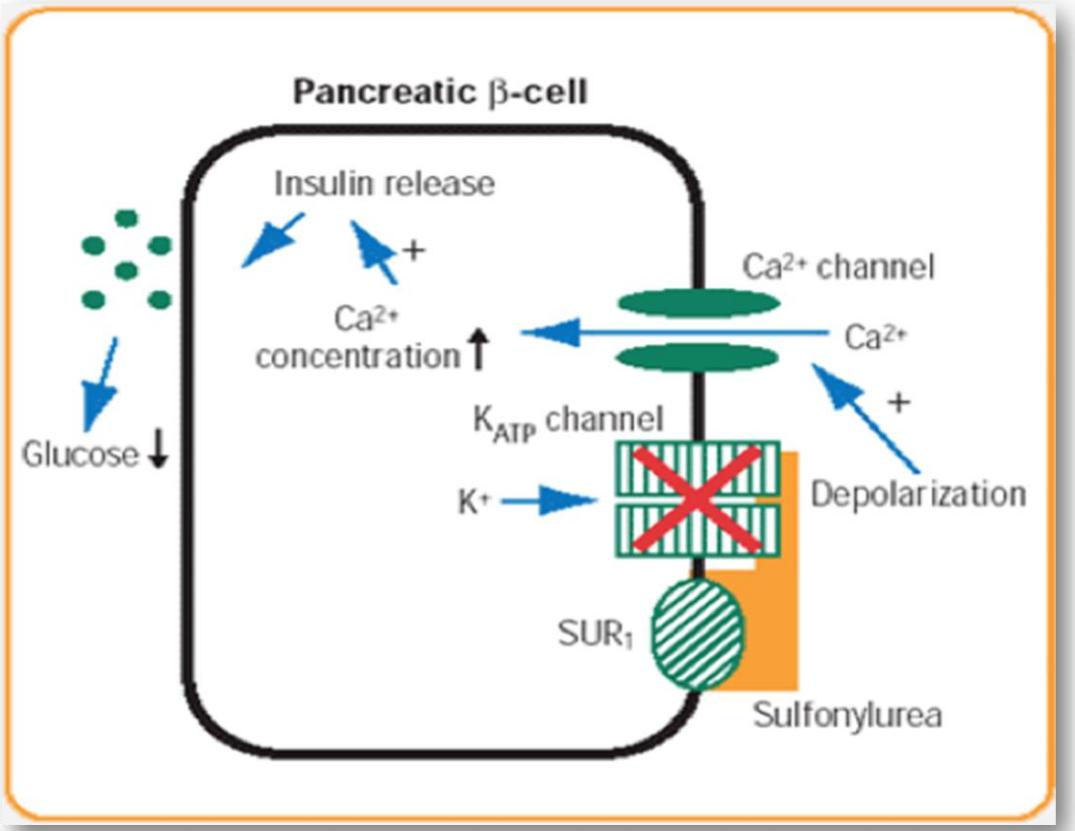
Pharmacokinetics:

- They are effectively absorbed from GIT.
- **Food** can reduce the absorption.
- **Plasma protein binding** is high (90 %).
- All sulfonylurea are metabolized by liver and excreted in urine.
- Sulfonylurea should be administered with caution to patients with either renal or hepatic insufficiency.

Mechanism of action:

- **↑ insulin secretion**

by pancreatic β cells. They block K+ channels in β- cells, leading to depolarization, increased Ca2+ entry via voltage-dependent calcium channels, and increased insulin secretion.



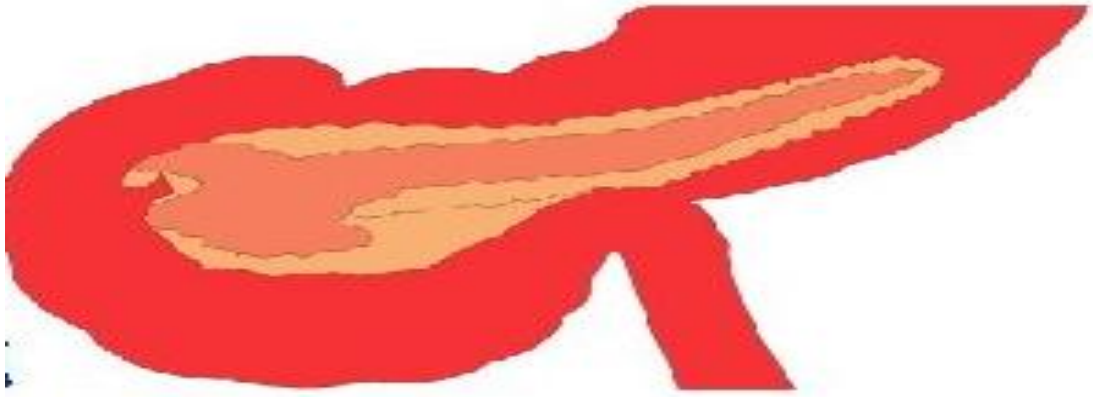
Therapeutic uses:

- Type 2 DM
- Given 30 minutes before food.

Adverse effects:

1- **Hypoglycemia:**

especially with long acting drugs or in elderly patients with hepatic or renal dysfunction.



2 - **Hepatotoxicity**.

3 - **Teratogenicity**.

4 - **Hypersensitivity reactions**.

Glinides: repaglinide & nateglinide

- They **increase insulin secretion**
  by the same mechanism like sulfonylureas .

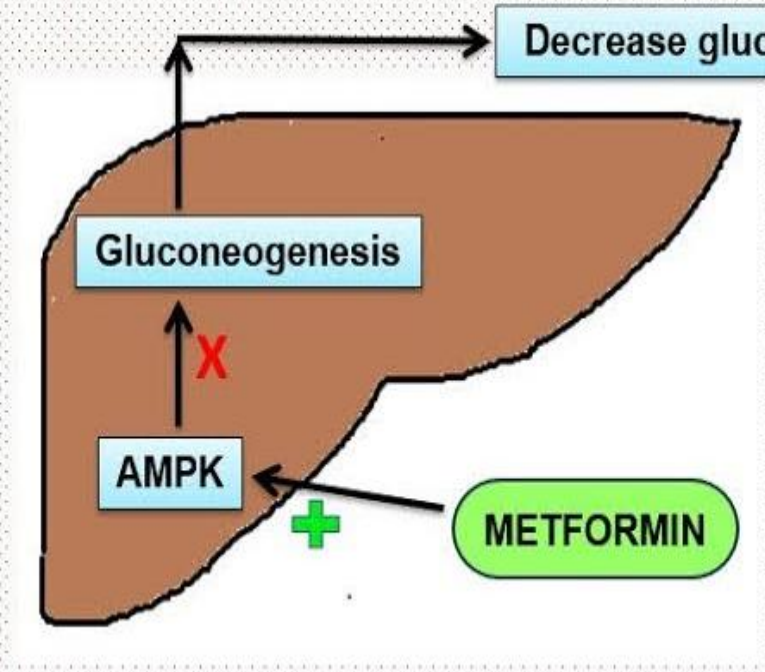
- **Fast onset** and **short duration**
  so; they are taken **orally** just *before meals*
  to control **postprandial hyperglycemia**.

- They **don't contain sulfur**,
  so they can be used in patients allergic to sulfonylureas.

Biguanides: metformin

- Metformin is the only drug available in this class
- Activates the enzyme AMP dependent protein kinase (AMPK)

PRIMARY ACTION



OTHER ACTIONS

- Increase glucose uptake
- Increase insulin sensitivity
- Increase fatty acid oxidation
- Decrease intestinal glucose absorption

★★ **METFORMIN DO NOT CAUSE THE RELEASE OF INSULIN FROM THE PANCREAS**

Pharmacokinetics:

- Metformin is well absorbed from small intestine.
- Does not bind to plasma proteins
- Half life is short.
- Excreted unchanged in **urine**.

Therapeutic uses:

- **Type 2 DM**

  either alone (in mild cases) or

  in combination with other drugs.

- **Obese patients**:

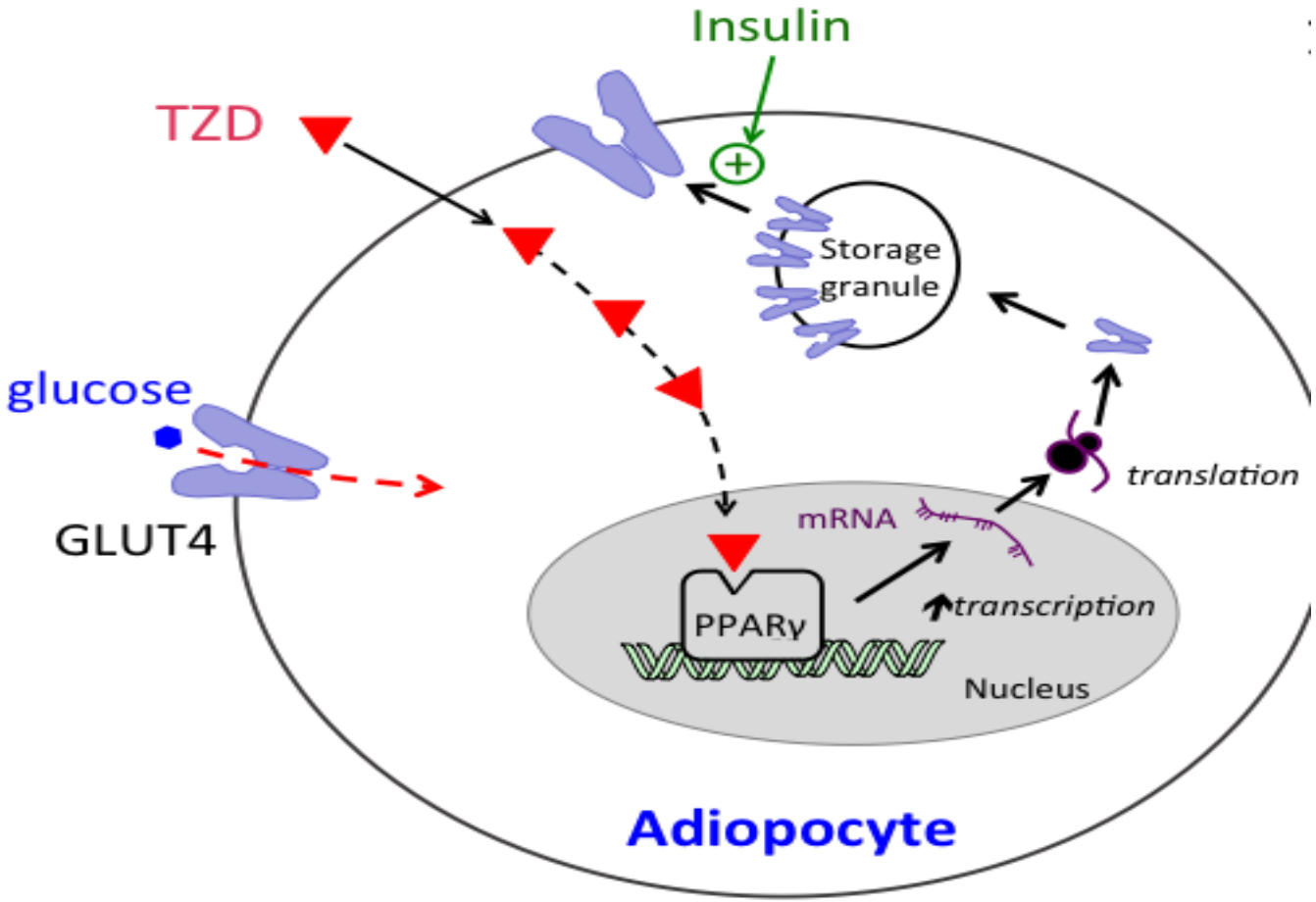
  to enhance weight loss in

Adverse effects:

- **GIT upset (the most common):**
  anorexia, vomiting, and diarrhea.
- **Lactic acidosis (the most important):**
  due to increased **anaerobic glycolysis**
  especially in patients with severe **renal**
  or **hepatic** diseases
  or cardiopulmonary dis.
- **Vitamin B12 deficiency**

Thiazolidinediones (TZD): Pioglitazone

- They act on **nuclear genes** called PPAR- γ present in muscles, adipose tissue, and liver cells **leading to:**
- ↑ number of glucose **transporters** →↑ glucose uptake.
- ↑ insulin receptor **sensitivity** (by about 60%).



Pioglitazone

- **Therapeutic uses:**

  in type 2 DM To improve insulin resistance.

- **Adverse effects:**

➢Hepatotoxicity

➢Salt and water retention leading to:

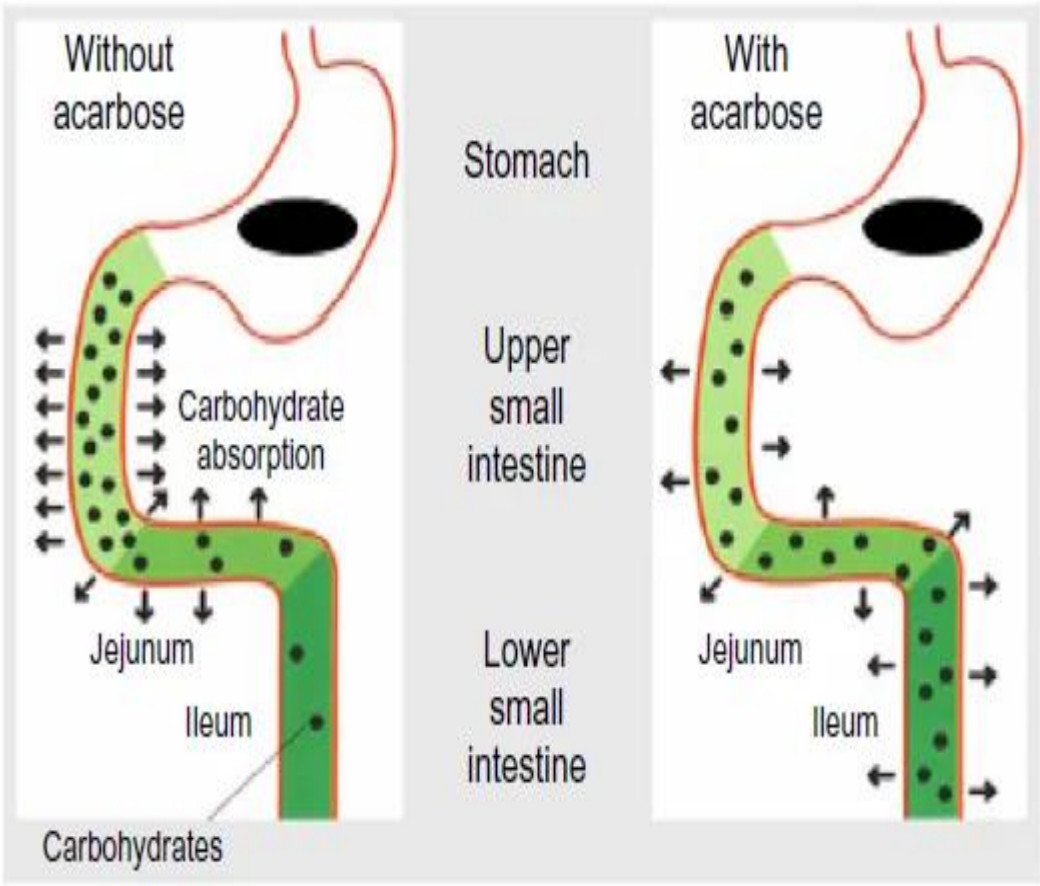
peripheral edema & weight gain.

(avoid in patients with CHF).

α-Glucosidase inhibitors: Acarbose

- They act by **competitive inhibition of intestinal *α-glucosidase enzyme*** → ↓ digestion & absorption of carbohydrates. (starch blockers)
- **GIT side effects** are common:

  Flatulence, diarrhea, abdominal pain.



Case Discussion/reflection

- According to the current recommendation of professional guidelines, the patient should be prescribed metformin therapy concurrently with dietary and lifestyle measures. This is based on the finding that metformin can delay progression of diabetes and prevent microvascular as well as macrovascular (heart attack, stroke) complications. Metformin does not increase circulating insulin, reduces insulin resistance, is unlikely to induce hypoglycaemia and may have a positive influence on pancreatic p cell health. Lack of serious toxicity over several decades of use of metformin is well established. No other antidiabetic drug has all these favourable features, and therefore, it is considered the first-choice drug. Metformin is particularly suitable for this patient who is overweight, because it can help weight reduction. A combination of antidiabetic drugs is not indicated at this stage. Another drug needs to be added only when the target blood glucose and HbA1 , levels are not attained by metformin alone.

Q1

Treatment of DK include the following except:

A. Regular insulin.
B. Normal sodium.
C. KCL.
D. Sulphonylurea.

Q2

Sulphonylureas act by:

a) Reducing the absorption of carbohydrate from the gut

b) Increasing the uptake of glucose in peripheral tissues

c) Reducing the hepatic gluconeogenesis

d) Stimulating the beta islet cells of pancreas to produce insulin

True or False: Sulphonylureas are effective in totally insulin deficient patients. This consideration is:

- a) True
- b) False

Q3

Thiazolidinediones act by:

a) Diminishing insulin resistance by increasing glucose uptake and metabolism in muscle and adipose tissues

b) Reducing the absorption of carbohydrate from the gut

c) Stimulating the beta islet cells of pancreas to produce insulin

d) Stimulating the hepatic gluconeogenesis

Q4.

Alpha-glucosidase inhibitors act by:

a) Diminishing insulin resistance by increasing glucose uptake and metabolism in muscle and adipose tissues

b) Competitive inhibiting of intestinal alpha-ghucosidases and modulating the postprandial digestion and absorption of starch and disaccharides

c) Reducing the absorption of carbohydrate from the gut

d) Stimulating the beta islet cells of pancreas to produce insulin

Q5

- **Which of the following drugs is most likely to cause hypoglycemia when used in the treatment of type 2 diabetes?**

A. Acarbose

B. Glibenclamide

C. Metformine

D. Rosiglitazone

Q6.

Which one of the following drugs promotes the release of endogenous insulin?

A. Acarbose

B. Pioglitazone

C. Glimpride

D. Metformin

Q7.

The combination of metformin and ethanol increases the risk of which of the following?

A. Serious hepatotoxicity
B. Excessive weight gain
C. Hypoglycemia
D. Lactic acidosis

Q8.

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. Repaglinide

C. Glipizide

D. Pioglitazone

Q9.

The PPAR-γ receptor that is activated by thiazolidinediones increases tissue sensitivity to insulin by which of the following mechanisms?

A. Activating adenylyl cyclase and increasing the intracellular concentration of cAMP

B. Inactivating a cellular inhibitor of the GLUT2 glucose transporter

C. Inhibiting acid glucosidase, a key enzyme in glycogen breakdown pathways

D. Regulating transcription of genes involved in glucose utilization

Q10

A 55 years old obese lady discovered to have random blood glucose 260 mg/dl during screening at 100 million health and her fasting blood glucose later was 160 mg/dl. She was told that she has type 2 DM. What is the next step?

A. Just follow up

B. Metformin should be started

C. She can be given a small dose sulphonyl urea

D. Pioglitazone is given to improve insulin resistance

E. Long acting insulin at bed time

Q11

- **The release of insulin from pancreatic beta cells would most likely be stimulated by which of the following?**

(A) Clonidine

(B) Norepinephrine

(C) Diazoxide

(D) Glipizide

Q12

- **To supplement other oral type 2 diabetes medication, a patient is prescribed a drug to inhibit the intestinal absorption of carbohydrates. What would be an appropriate drug?**

(A) Metformin

(B) Acarbose

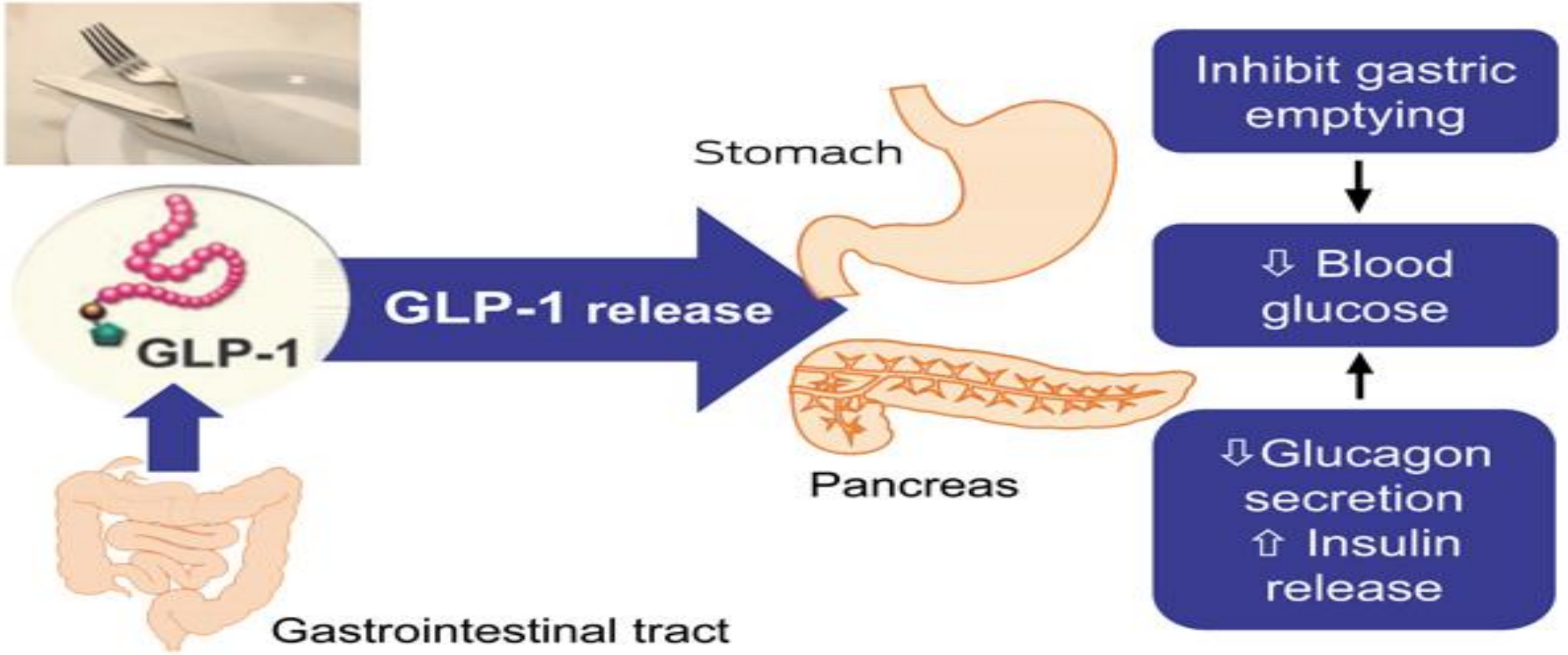
(C) Repaglinide

(D) Pioglitazone

Newer antidiabetic drugs

Glucagon-like peptide-1 (GLP-1)

is released from the gut in response to oral glucose.



Exenatide :

- **is a synthetic GLP-1 analog**
- **Mechanism of action:**

1. They ↑ insulin secretion and ↓ glucagon secretion.
2. They slow gastric emptying and ↓ appetite.

- **Therapeutic uses:**

Type 2 DM: given by injection (s.c.)

used either alone or in combination.

- **Major adverse effects:**

nausea, vomiting

Acute pancreatitis is a risk.

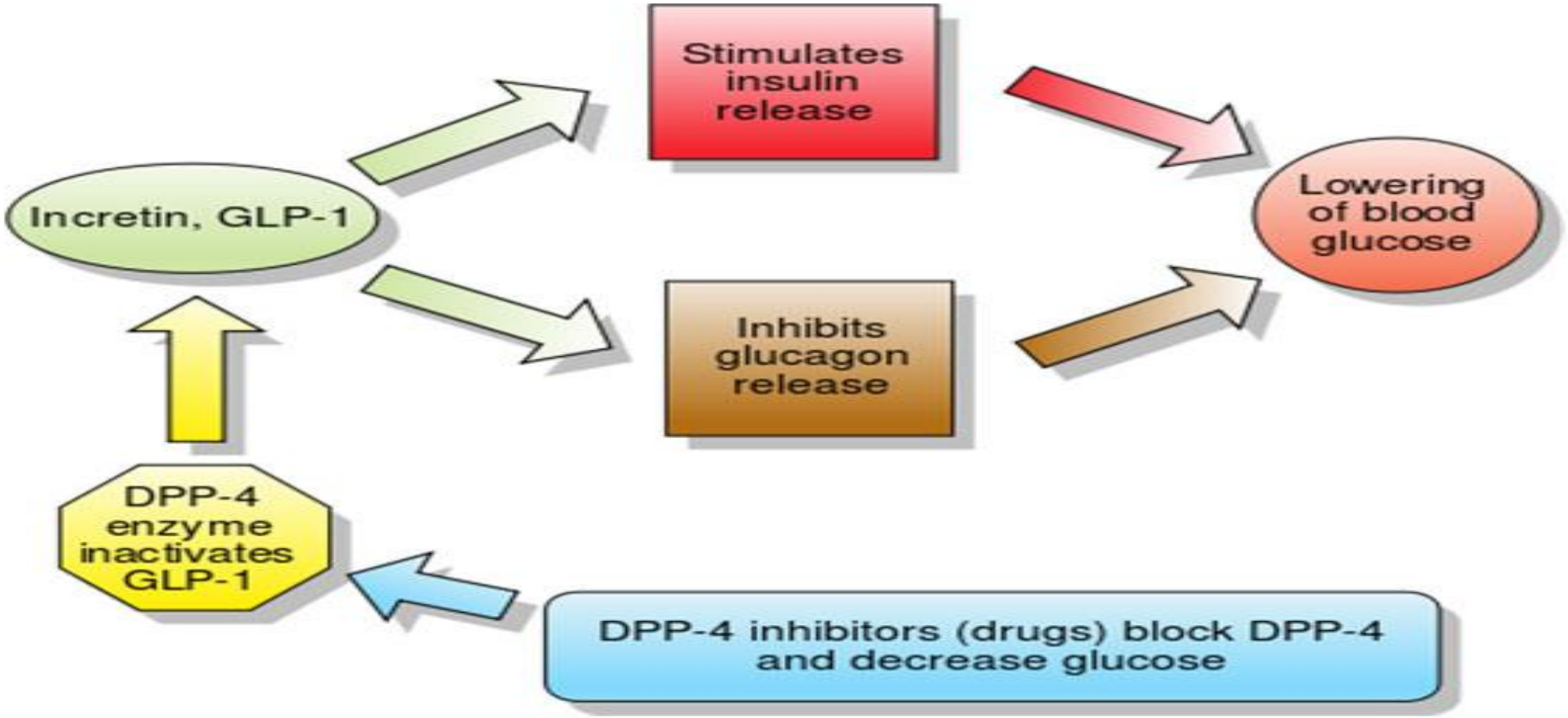
Liraglutide:

- longer-acting GLP- 1 agonist due to its tight binding to plasma proteins extends t½ to > 12 hours and duration of action to > 24 hours.
- Injected s.c. once daily.
- Use of liraglutide lead to weight loss and it is approved for use in obesity.

Dulaglutide:

- is a very long acting GLP-1 receptor agonists which need to be injected once weekly.

Dipeptidyl peptidase 4 inhibitors (Gliptins):



Sitagliptin

➢**Mechanism of action:**

inhibits dipeptidyl peptidase 4 (DPP-4),

the enzyme responsible for the proteolysis of the incretins (GLP-1).

➢**Therapeutic uses:**

Type 2 DM: given **orally**

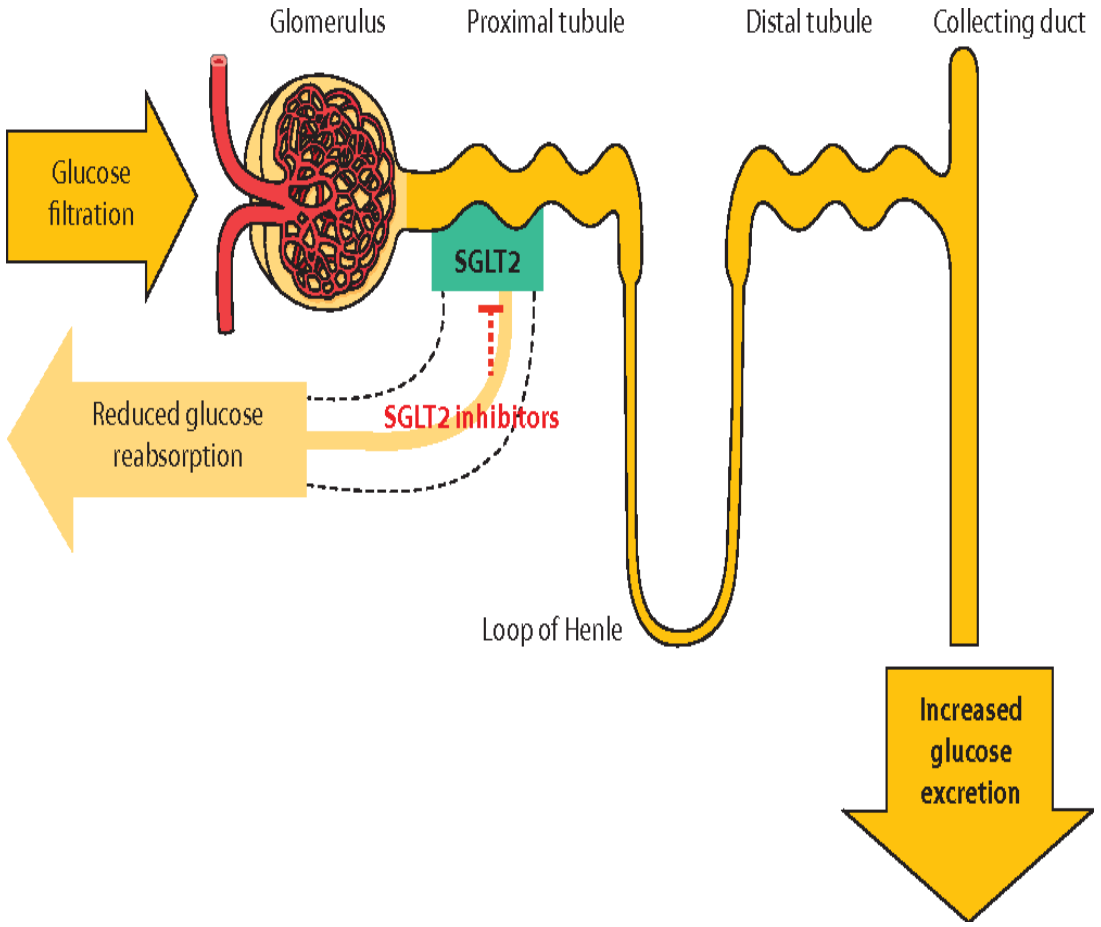
Used alone or in combination with **metformin**.

➢**Side effects:**

headache and nausea.

Sodium-glucose cotransporter-2 (SGLT2) inhibitors

- Practically all the glucose filtered at the glomerulus is reabsorbed in the proximal tubules.
- The major transporter which accomplishes this is SGLT-2
- Its inhibition induces glucosuria and lowers blood glucose in type 2 DM, as well as causes weight loss.



Dapagliflozin

- These SGLT-2 inhibitors are approved for use in type 2 DM patients.
- After once daily dosing, they produce round-the-clock glucosuria and lower blood glucose levels.
- Used alone or in combination with other antidiabetic drugs, they reduce HbA1c levels by 0.5-1.0%, but do not cause hypoglycaemia.
- Can predispose lo urinary tract infections and increased urinary frequency.
- They are contraindicated in patients with renal insufficiency.
- SGLT-2 inhibitors **reduce the risk of hospitalizations for heart failure by ~30% and often decrease the risk of cardiovascular death**.

Treatment of diabetic complications

Hypoglycemic coma

- **Causes:**

1. Large dose of insulin or sulfonylurea.
2. Missed meal while taking insulin or sulfonylureas.

- **Treatment:**

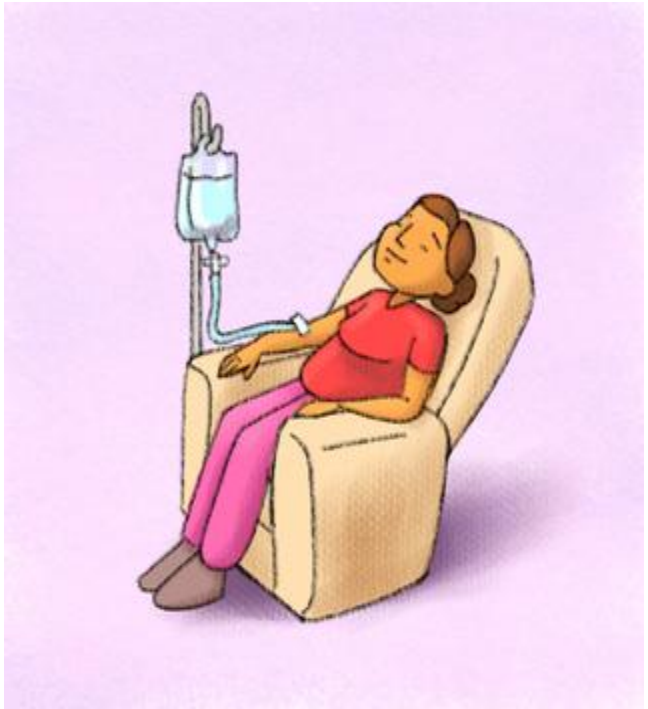
1. If the patient is conscious or semiconscious → give him sugar solution.
2. If the patient is in deep coma:

   (1) i.v. glucose

   (2) Glucagon i.m.

Treatment of diabetic ketoacidosis

- **Fluids:**
  isotonic saline solution i.v. immediately.
- **Regular insulin:**
  i.v infusion (0.1 unit/kg/hr). switch to s.c. insulin when the patient is biochemically stable.
- **Potassium:** is given according to K+ level.
- **Bicarbonate (HCO3):** only in severe acidosis.
- Treatment of precipitating factors e.g. **antibiotics for infection**.



Q1. Sitagliptin acts by:

a) Reducing the absorption of carbohydrate from the gut

b) Increasing the uptake of glucose in peripheral tissues

c) Reducing the hepatic gluconeogenesis

d) Inhibits dipeptidyl peptidase 4 (DPP-4)

Q2. One the main advantages of Liraglutide over exenatide is that

A. It is longer in duration.
B. It is a synthetic amylin analogue.
C. It increases glucagon secretion.
D. It is used instead of insulin in type 1 diabetes

Q3. Dapagliflusin acts by:

a) Reducing the absorption of carbohydrate from the gut

b) Inhibits sodium-glucose cotransporter-2 (SGLT2)

c) Reducing the hepatic gluconeogenesis

d) Inhibits dipeptidyl peptidase 4 (DPP-4)

Q4. What is the first step in the management of diabetic ketoacidosis?

a. To provide fluids intravenously

b. To provide insulin

c. To provide bicarbonate

d. To initiate insulin and fluids simultaneously

Q5. In a patient with type 2 diabetes, which drug mimics the action of incretins to augment glucose-dependent insulin secretion?

(A) Acarbose

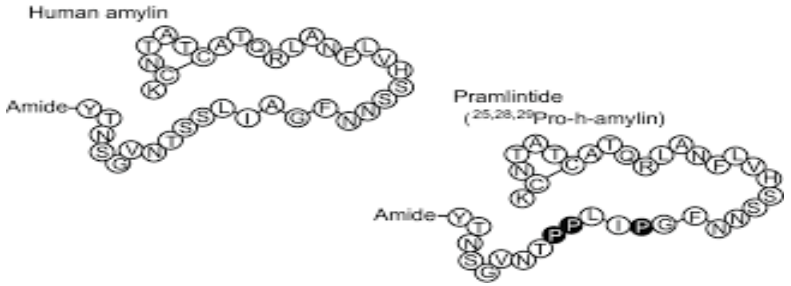
(B) Glucagon

(C) Exenatide

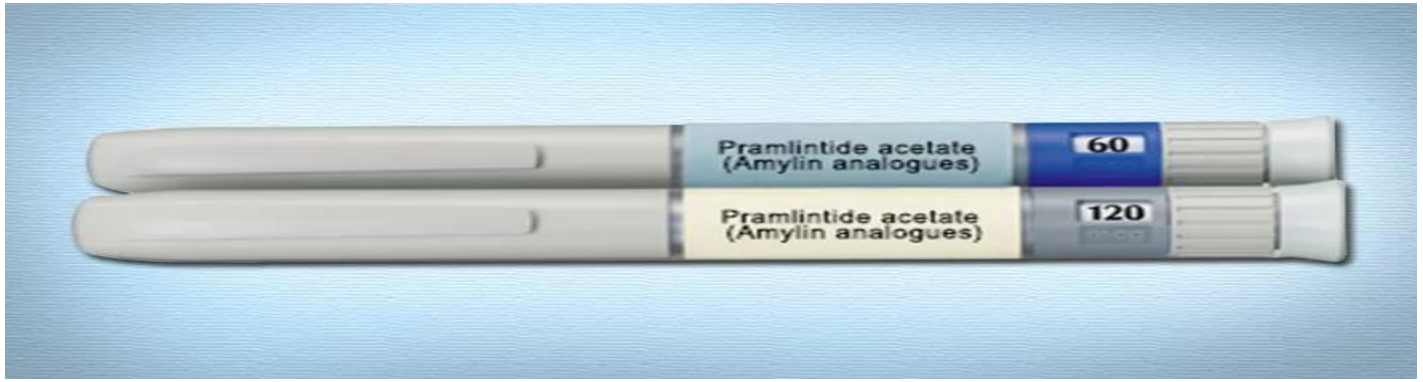
(D) Metformin

Nice to know

Amylin analogue: Pramlintide



- Amylin is produced by pancreatic beta cells and is stored in the same granules as insulin. As such it is secreted along with insulin. acts in the brain to reduce glucagon secretion from alpha cells.
- Pramlintide is a synthetic amylin analogue which is used to with insulin injection when insulin alone fails to control postprandial glycemic peak.
- Hypo glycaemia is the most important adverse effect.



Q4. Pramlintide is

A. a synthetic amylin analogue
B. a synthetic GLP-1 analogue
C. Sodium-glucose cotransporter-2 (SGLT2) inhibitor
D. An Alpha-glucosidase inhibitor

GLUCAGON

- It is secreted by the alpha cells of the islets of Langerhans and commercially produced now by recombinant DNA technology.
- Uses

I. Hypoglycaemia Use of glucagon to counteract insulin/ oral hypoglycaemic drug induced hypoglycaemia is only an appropriate measure for the emergency, and must be followed by oral glucose/sugar given repeatedly till the blood glucose level stabilizes.

II. Glucagon may be used to stimulate the heart in beta adrenergic blocker treated patients.

- The hormone that is secreted by the alpha cells of the pancreas that raises blood glucose when levels are low is:

A. glucagon
B. epiniphrine
C. insulin
D. cortisol

- Insulin promotes all but which of the following:

A. **lipolysis**
B. lipogenesis
C. protein synthesis
D. glucose entry into cells

- Which of the following tissues requires insulin for glucose entry into cells:

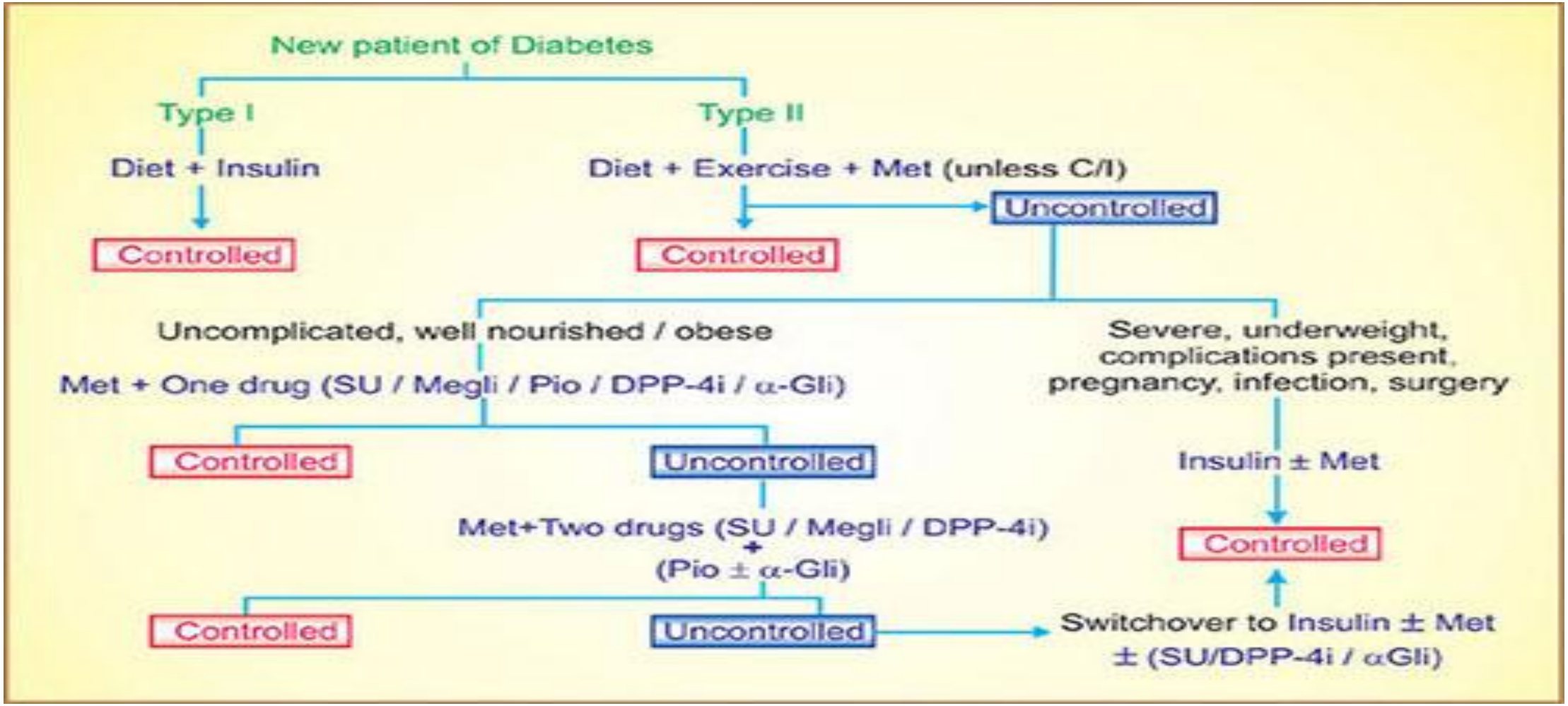
A. muscle

B. liver

C. kidney tissue

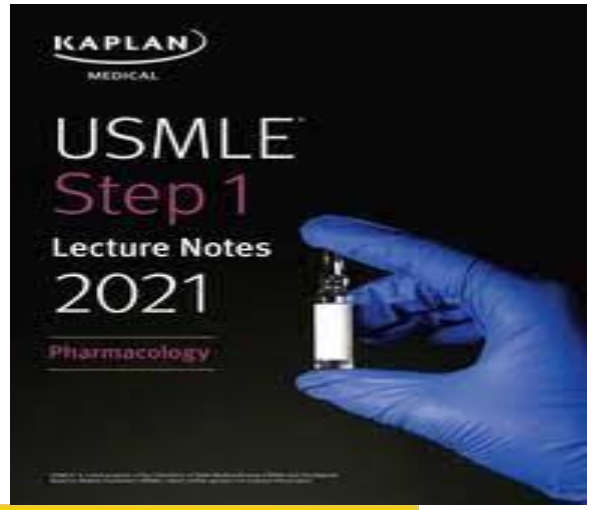
D. nervous tissue

Simplified flow chart of management approaches in diabetes mellitus (nice to know)

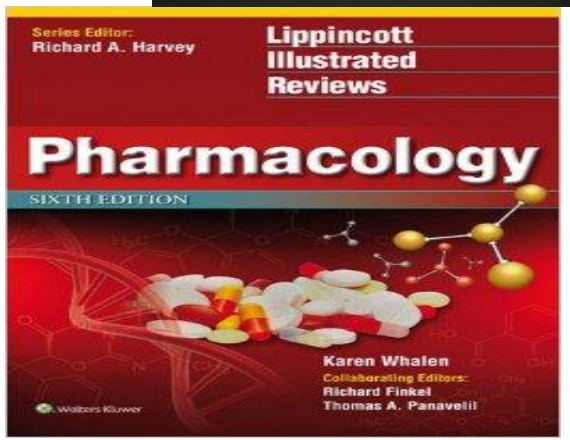


References or further readings

1) **Kaplan USMLE STEP1, lecture notes Pharmacology latest edition.**



2) **Lippincott's illustrated review: Pharmacology, latest edition**

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