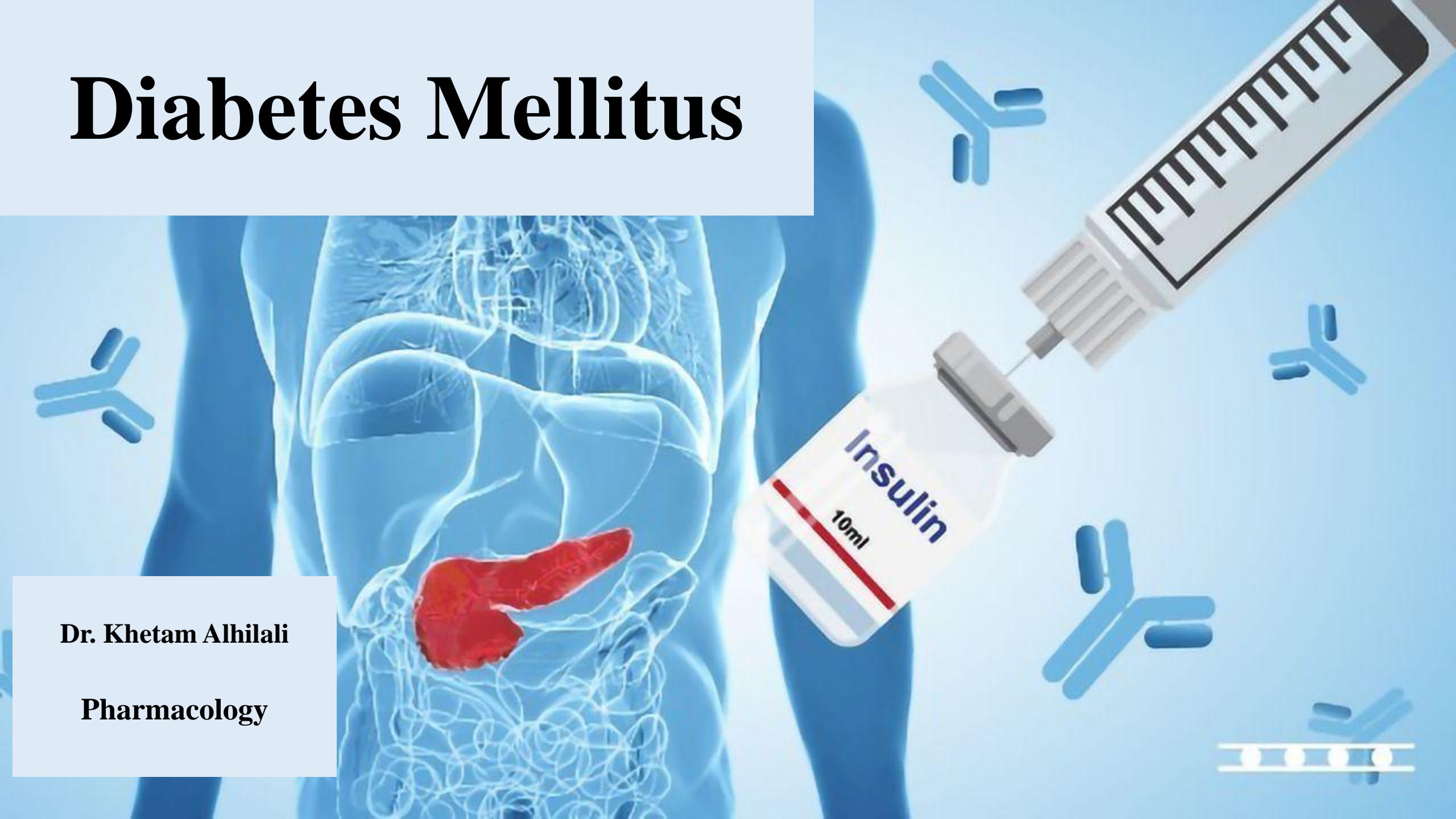


Diabetes Mellitus

Dr. Khetam Alhilali

Pharmacology



Diabetes Mellitus

- **Diabetes Mellitus (DM)**, commonly known as diabetes, is a metabolic disease that causes high blood sugar. The hormone insulin moves sugar from the blood into the cells to be stored or used for energy.
- With diabetes, the body either doesn't make enough insulin or can't effectively use the insulin it does make. This disease is characterized by high levels of blood glucose resulting from defects in insulin production, insulin action, or both.
- Untreated high blood sugar from diabetes can damage nerves, eyes, kidneys, and other organs.

Diabetes types

- **Type 1 diabetes (T1DM)** is an autoimmune disease. The immune system attacks and destroys cells in the pancreas, where insulin is made. It's unclear what causes this attack. About 10 percent of people with diabetes have this type.
- **Type 2 diabetes (T2DM)** occurs when your body becomes resistant to insulin, and sugar builds up in your blood.
- **Prediabetes (PM)** occurs when your blood sugar is higher than normal, but it's not high enough for a diagnosis of type 2 diabetes
- **Gestational diabetes (GDM)** is high blood sugar during pregnancy. Insulin-blocking hormones produced by the placenta cause this type of diabetes.

Diabetes Insipidus

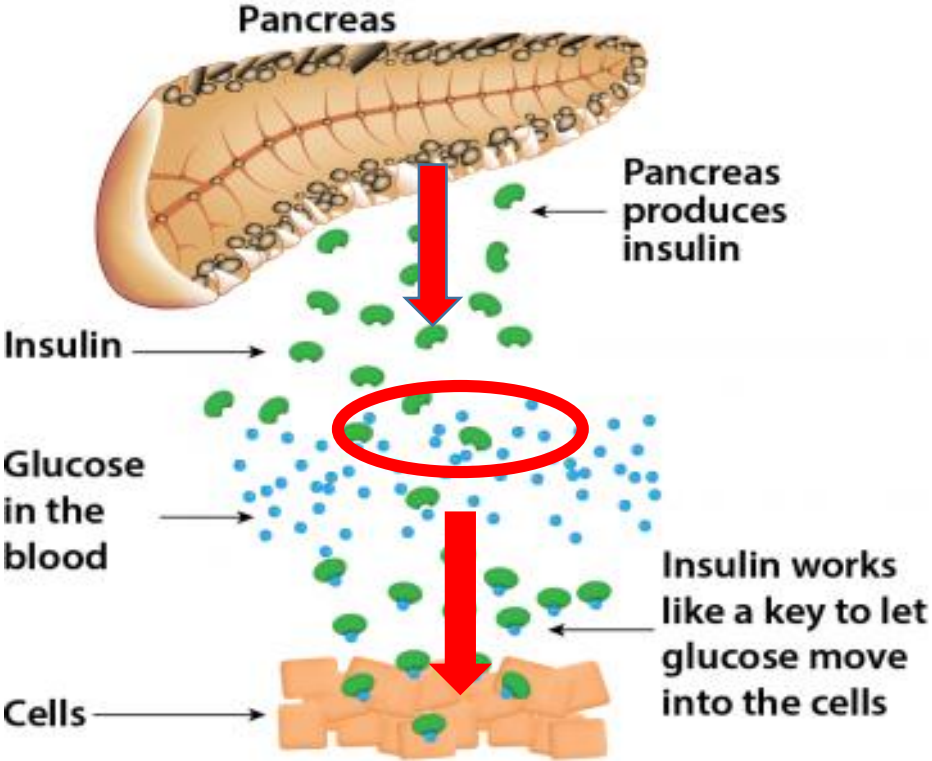
- A rare condition called diabetes insipidus is not related to diabetes mellitus, although it has a similar name. It's a different condition in which the kidneys remove too much fluid from your body.

Type 1 diabetes (T1D)

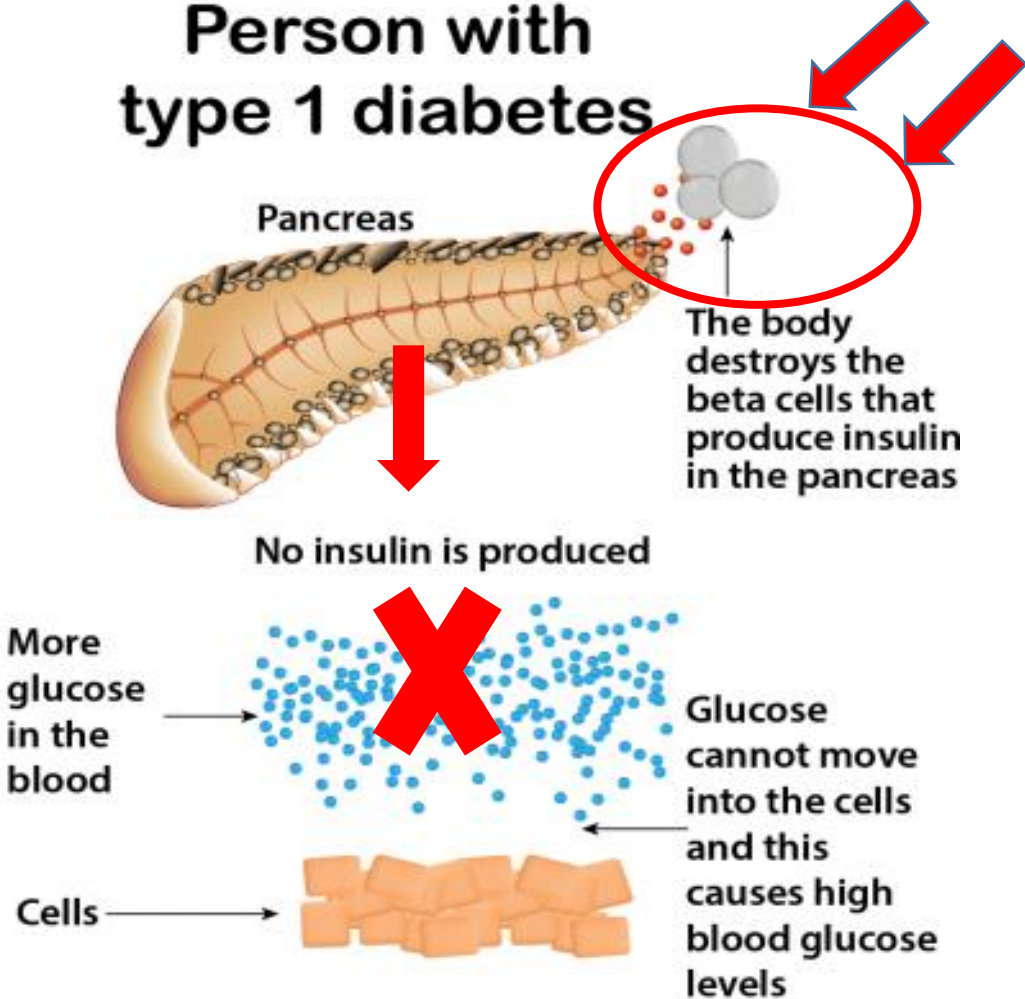
- Type 1 diabetes can and does occur at any age, but is more commonly diagnosed in younger people. It is less common than type 2 diabetes, with only 10-15% of all people with diabetes having type 1.
- In type 1 diabetes, the pancreas cannot produce enough insulin because **the cells that actually make the insulin have been destroyed by the body's own immune system.** The insulin has to be replaced in another way, which is why, if you have type 1 diabetes, you must have insulin injections every day.

Type 1 diabetes

Person without diabetes



Person with type 1 diabetes



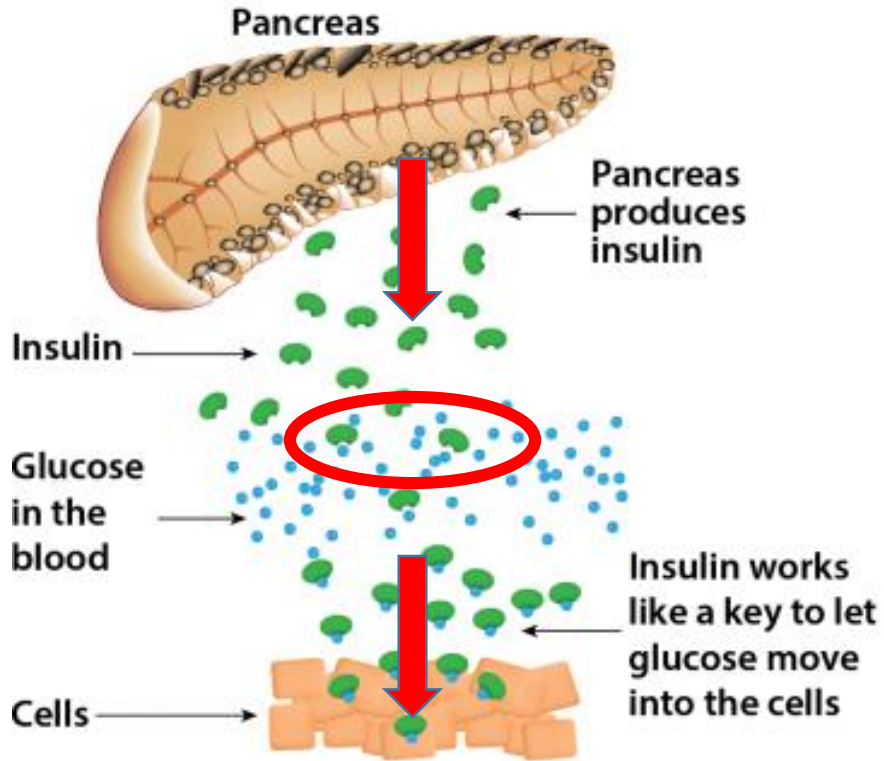
In type 1 diabetes, the pancreas stops making insulin.

Type 2 diabetes

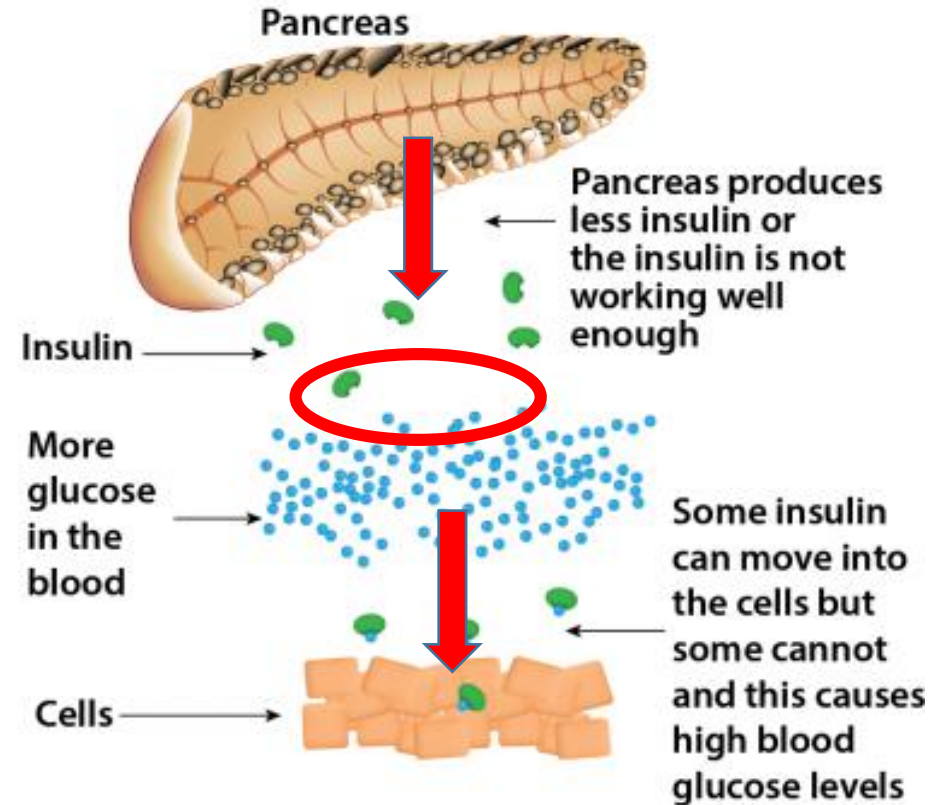
- Type 2 diabetes is the most common form of diabetes, affecting 85–90% of all people with diabetes. It usually occurs in adults, but younger people and even children are now developing this type of diabetes.
- Unlike someone with type 1 diabetes, **with type 2 diabetes the body still produces insulin, but it is not produced in the amount the body needs and it does not work effectively**

Type 2 diabetes

Person without diabetes



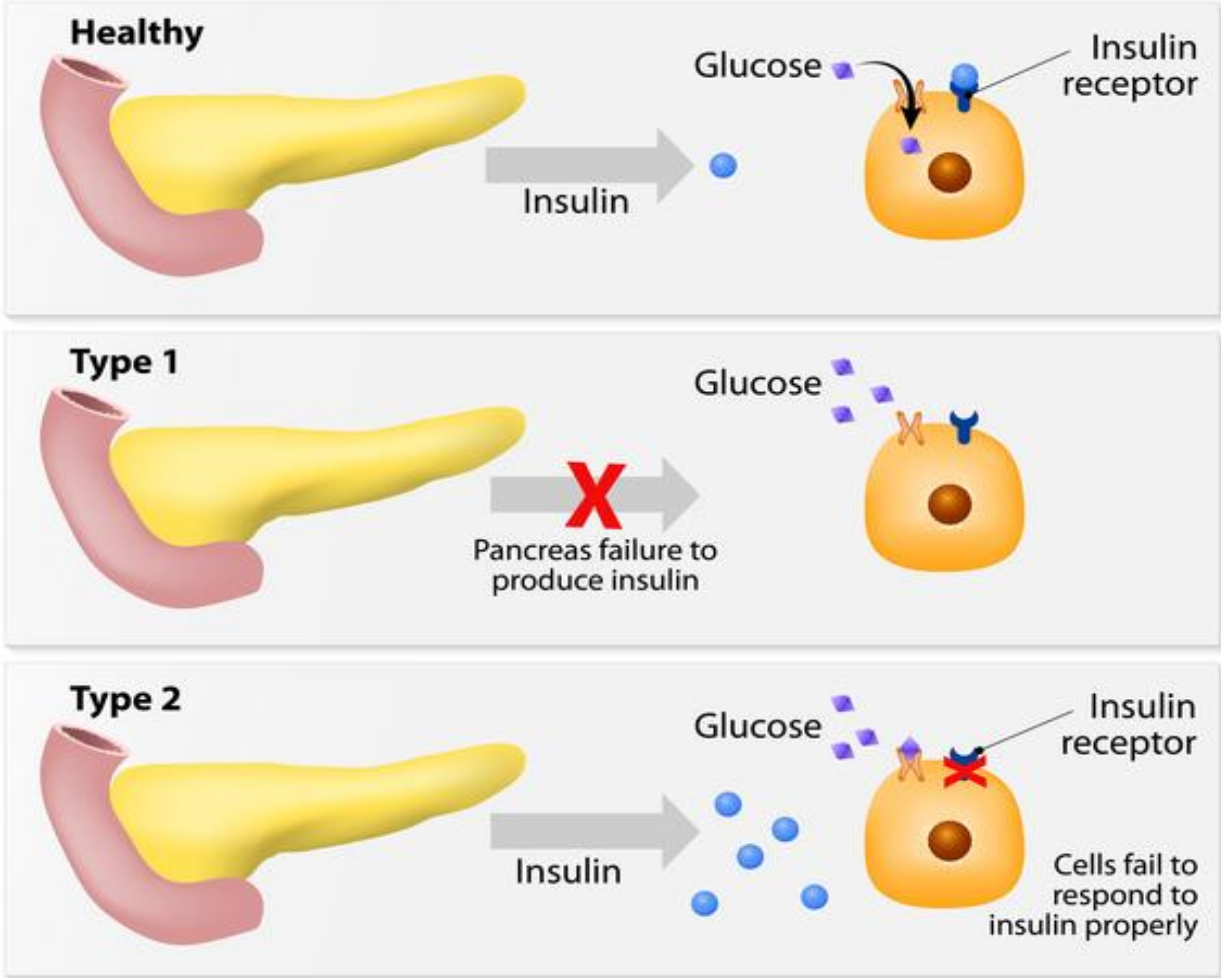
Person with type 2 diabetes



In type 2 diabetes, the pancreas makes some insulin but it's not working as well as it used to.

Compare between Type 1 and type 2 diabetes

DIABETES MELLITUS



What are the symptoms of diabetes

- Sometimes the symptoms of diabetes are so mild that it might go unnoticeable. Following are the diabetes symptoms.
- Often urination (polyuria)
- Very thirsty (polydipsia) and hungry all the time (polyphagia), even after following a diet chart.
- Blurry Vision
- Extreme tiredness
- Cuts/bruises longer to get healed than normal
- Numbness, tingling pain in hands and legs
- Weight loss is also a diabetes symptom. Even after taking a proper diet, the weight reduces, it might be because of diabetes type 1.

Diabetes Treatments

- There are a number of treatments available to help the patient manage and treat his diabetes. Everyone is different, so treatment will vary depending on the individual needs.

□-A. **Non pharmacological treatment.**

□-B. **pharmacological treatment.**

- For type 1 diabetes, you'll need to use **insulin** to treat diabetes. The patients take the insulin by injection or by using a pump.
- For Type 2 diabetes, the patient may have to use **insulin or tablets**, though might initially be able to treat their diabetes by eating well and moving more.

Treatment

Non pharmacological treatment

- ❖ Healthy eating
- ❖ Regular exercise
- ❖ Weight loss
- ❖ Blood sugar monitoring
- ❖ Diabetes Self-management Education
- ❖ Medical Nutrition Therapy
- ❖ Physical Activity
- ❖ Smoking Cessation
- ❖ Immunization
- ❖ Psychological Issues

Possibly, diabetes medication or insulin therapy

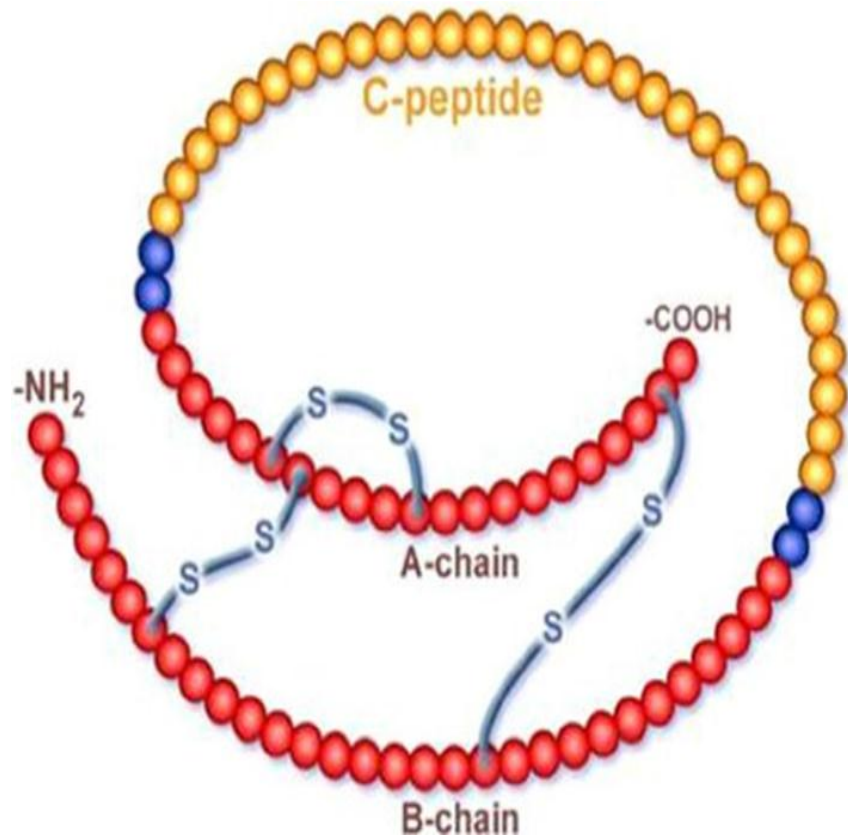
Insulin

- Insulin is a polypeptide hormone produced by pancreatic islet β cells that is primarily responsible for regulation of blood glucose and storage of carbohydrates and lipids.
- Type 1 diabetes is due to inadequate production of insulin caused by destruction and loss of insulin producing pancreatic islet β cells.
- Type 2 diabetes is due to relative insulin resistance. It is considered to be the main anabolic hormone of the body.

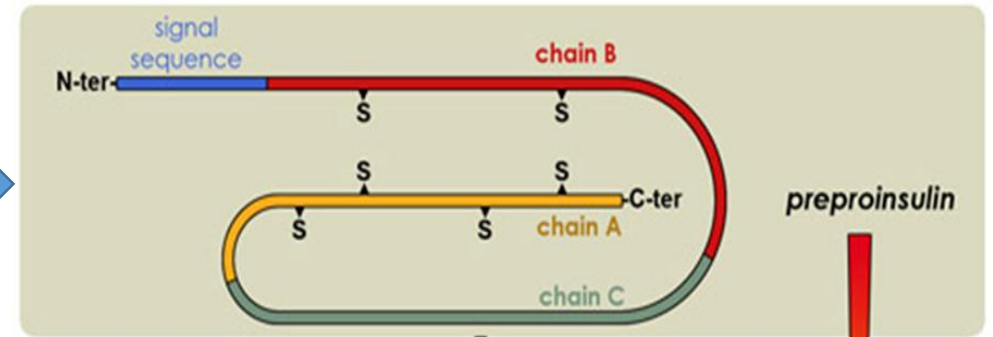
Insulin Structure

- Synthesized as part of proinsulin(86AA) and then excised by enzymes, releasing **functional insulin (51 AA)** and **C peptide (31 AA)**.
- Insulin is a polypeptide hormone of 51 amino acids.(MW-6000)
- Composed of 2 polypeptide
- Chains A (21 AA)
- Chain B (30 AA)
- Held together by disulfide bonds.

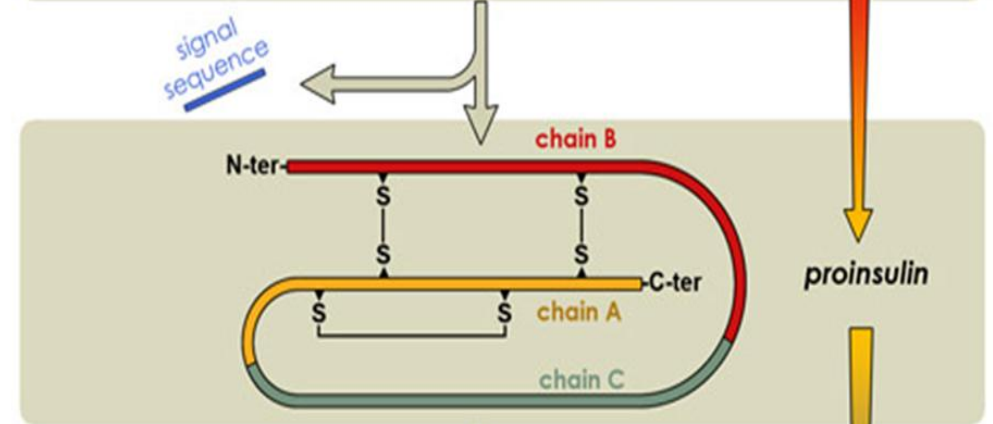
Insulin Synthesis



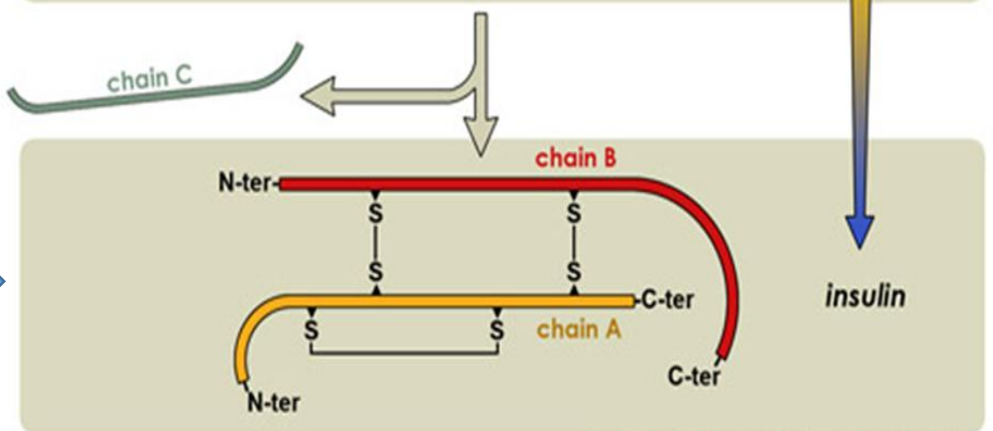
Beta Cells Synthesize
pre-proinsulin



cleaved by enzymes →
proinsulin



cleaved again →
insulin



©2004 Beta Cell Biology Consortium

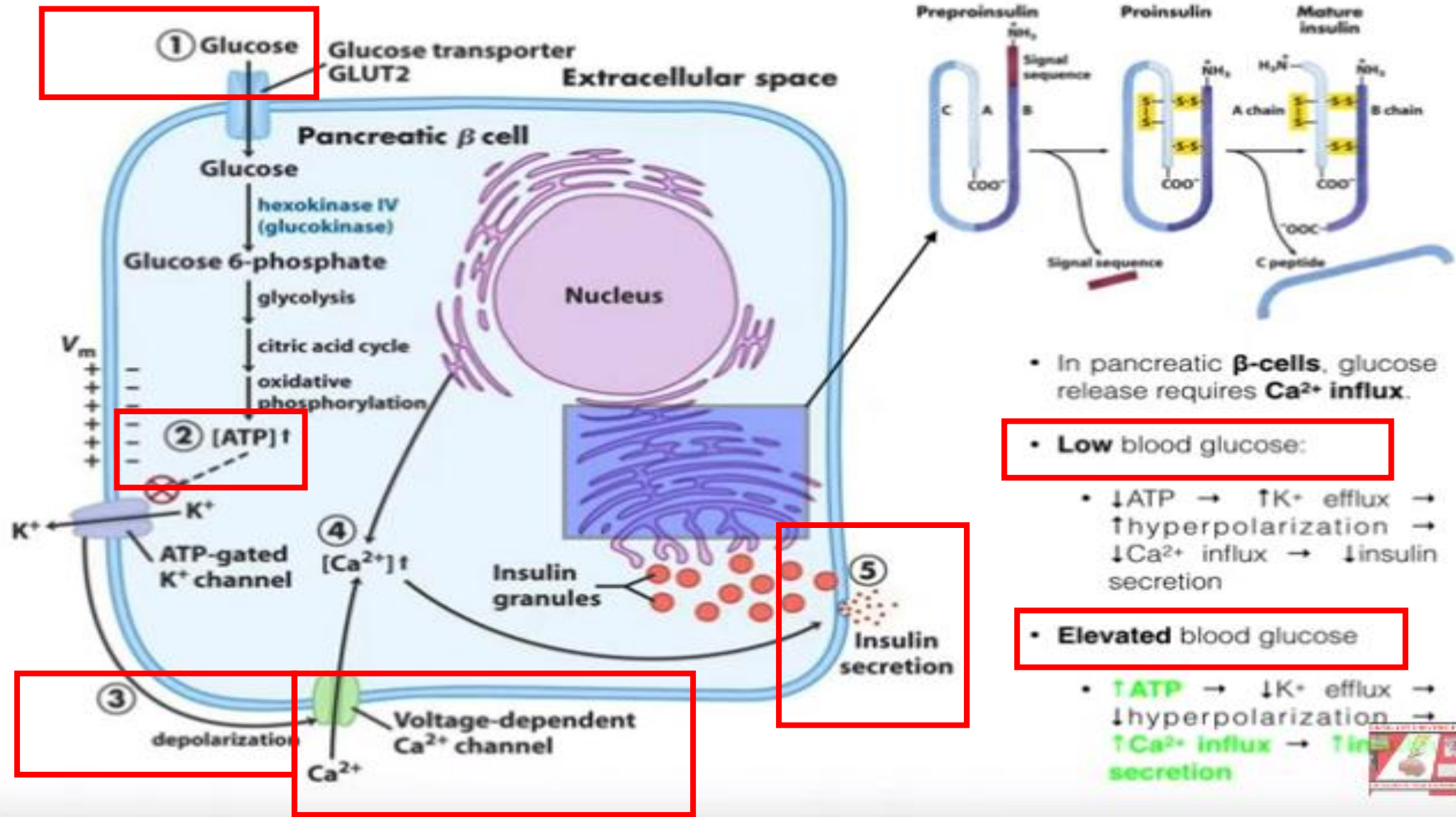
Insulin

- ❖ **Insulin** is released when there is a stimulus (high blood glucose) and exerts its function.
- **Insulin** has half life of 6 mins.
- **Insulin** is degraded by enzyme insulinase present in the liver and kidneys
- ❖ **C- peptide**
 - **C-peptide** is essential for proper folding of insulin
 - **C-peptide** has longer half life compared to insulin.
 - So quantity of C- peptide in the serum indicator of amount of insulin production and secretion

Insulin Synthesis and Regulation of Insulin Secretion

- **Insulin** synthesis is stimulated by glucose or feeding and decreased by fasting.
- **Threshold** of glucose- stimulated insulin secretion is 100 mg/dl.
- **Glucose** rapidly increase the translation of the insulin mRNA and slowly increases transcription of the insulin gene.
- **No insulin** is produced when plasma glucose below 50 mg/dl
- **Half-maximal insulin** response occurs at 150 mg/dl
- **A maximum insulin** response occurs at 300 mg/dl
- ❖ **Insulin secretion is biphasic:**
 - **Upon glucose stimulation– an initial burst of secretion (5-15 min.)**
 - **Then a second phase of gradual increment that lasts as long as blood glucose is high**

Pancreatic β -cell Glucose Detection & Insulin Release



- In pancreatic β -cells, glucose release requires **Ca^{2+} influx**.

- **Low blood glucose:**

- \downarrow ATP \rightarrow \uparrow K^+ efflux \rightarrow hyperpolarization \rightarrow \downarrow Ca^{2+} influx \rightarrow \downarrow insulin secretion

- **Elevated blood glucose**

- \uparrow ATP \rightarrow \downarrow K^+ efflux \rightarrow hyperpolarization \rightarrow \uparrow Ca^{2+} influx \rightarrow \uparrow insulin secretion

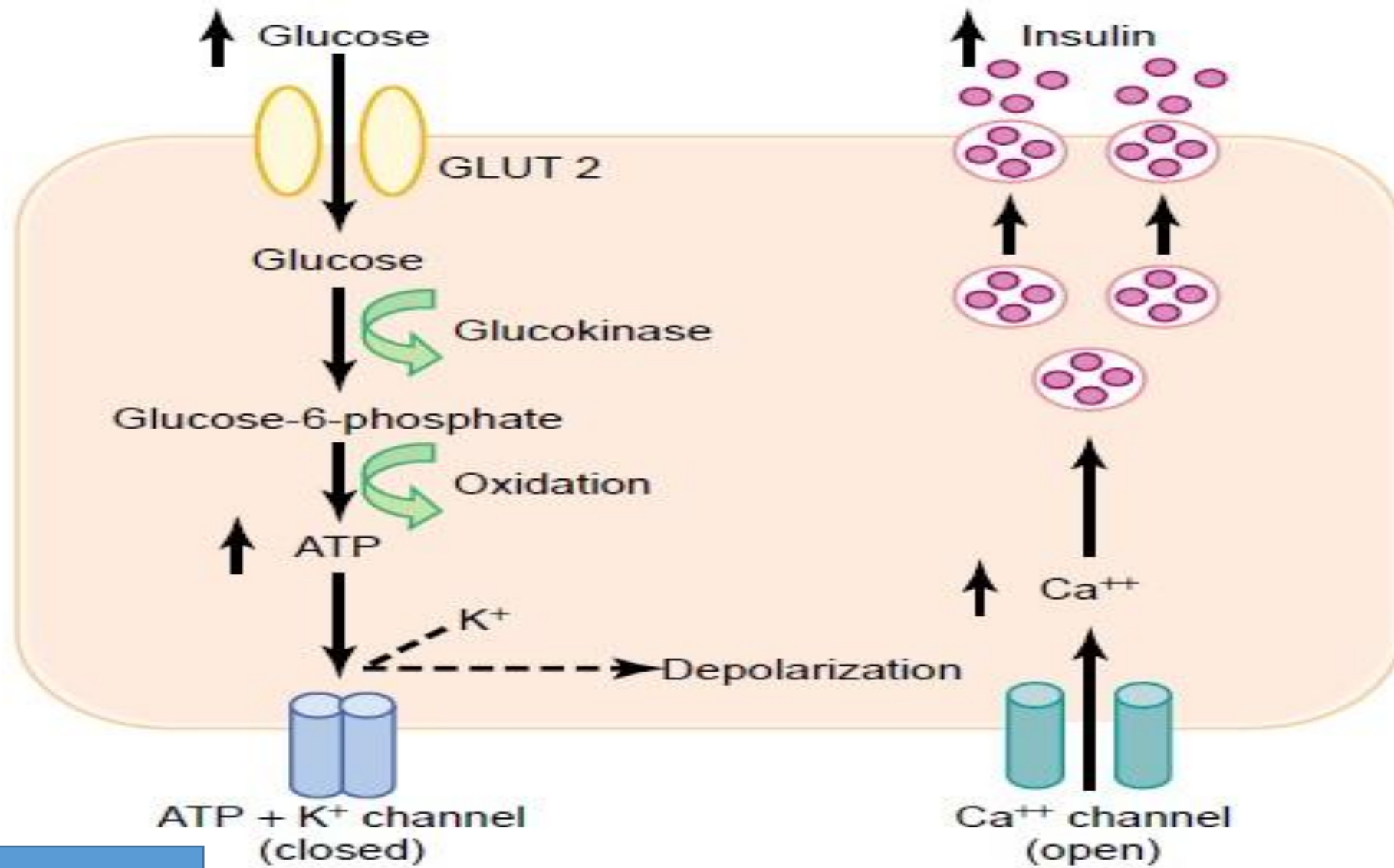


The Mechanism of Insulin Release by Pancreatic β -cells

Mechanisms of Insulin Secretion

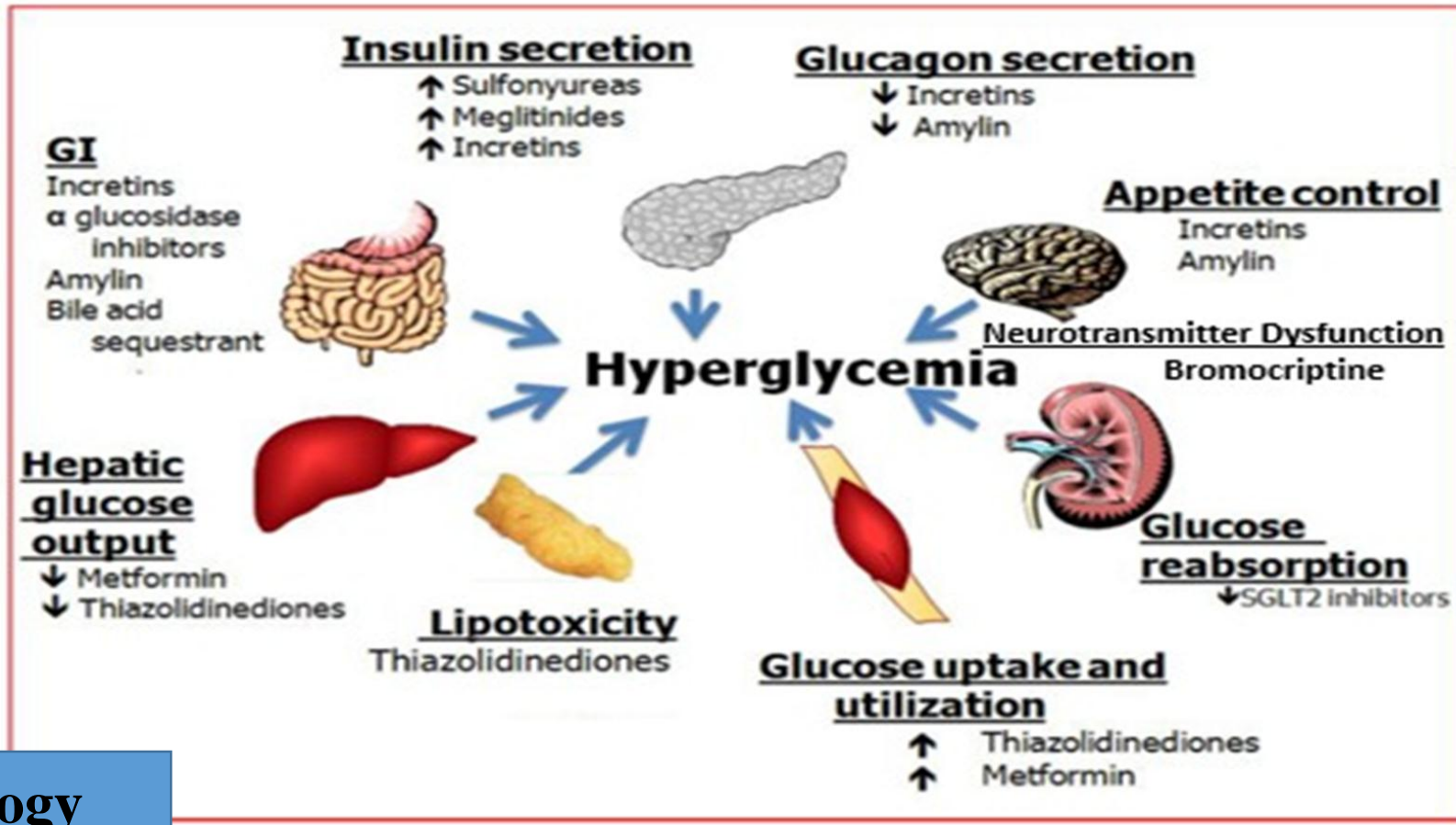
- **The pancreatic beta cells** in response to increased blood glucose concentration
- The beta cells have a large number of **glucose transporters (GLUT-2)** that permit a rate of glucose influx
- glucose is phosphorylated to **glucose-6-phosphate** by glucokinase.
- The glucose-6-phosphate is subsequently oxidized to form adenosine triphosphate (**ATP**), which inhibits the ATP-sensitive **potassium channels** of the cell.
- Closure of the potassium channels depolarizes the cell membrane, thereby opening voltage-gated **calcium channels**, which are sensitive to changes in membrane voltage. This produces an influx of calcium that stimulates fusion of the **docked insulin-containing vesicles** with the cell membrane and secretion of insulin into the extracellular fluid by exocytosis.

Mechanisms of Insulin Secretion



B. Pharmacological treatment Insulin, Medicines, & Other Diabetes Treatments

- Type 1 DM → Insulin
- Type 2 DM → Insulin and other medicines



Sites of Action of
Pharmacological
Therapies

B. Pharmacological therapy /1. Insulin

❖ Usual Adult Dose for Diabetes Type 1

Note: Regular human insulin is available in 2 concentrations: 100 units of insulin per mL (U-100) and 500 units of insulin per mL (U-500)

-Total daily insulin requirements are generally between 0.5 to 1 unit/kg/day

❖ Usual Adult Dose for Diabetes Type 2

-Initial doses are often in the range of 4 to 6 units or 0.1 units/kg or 10% of basal insulin dose

-Use HbA1c values to guide therapy; consult current guidelines for optimal target ranges

The different types of insulin

Types of Insulin and How They Work

Insulin type	How fast it starts to work (onset)	When it peaks	How long it lasts (duration)
<input type="checkbox"/> Rapid-acting	About 15 minutes after injection	1 hour	2 to 4 hours
<input type="checkbox"/> Short-acting, also called regular	Within 30 minutes after injection	2 to 3 hours	3 to 6 hours
<input type="checkbox"/> Intermediate-acting	2 to 4 hours after injection	4 to 12 hours	12 to 18 hours
<input type="checkbox"/> Long-acting	Several hours after injection	Does not peak	24 hours; some last longer

B. Pharmacological therapy / 2. Type 2 Non Insulin Therapies

❖ **Goals Of Diabetes Treatment.**

- To keep the blood sugar as normal as possible without serious high or low blood sugars
- To prevent tissue damage caused by too much sugar in the blood stream

❖ **Normal ranges for blood sugar.**

- People who don't have diabetes or pre-diabetes keep their blood sugars between 60 - 100 mg/dl overnight and before meals, and less than 140 mg/dl after meals. Although the ultimate goal of diabetes management is to return the blood sugar to the natural or non-diabetic level, this may be difficult without excessive low blood sugars or hypoglycemia.

Sugar Test

- A glycosylated hemoglobin test measures the amount of glucose (sugar) in the blood. The test is often called **A1c**, or sometimes **HbA1c**. It's a simple blood test used to:
- Detect prediabetes - high sugar levels that can lead to diabetes, heart disease and stroke.
- **Random blood sugar test.** Blood sugar values are expressed in milligrams of sugar per deciliter (mg/dL) or millimoles of sugar per liter (mmol/L) of blood. Regardless of when you last ate, a level of 200 mg/dL (11.1 mmol/L) or higher suggests diabetes, especially if you also have signs and symptoms of diabetes, such as frequent urination and extreme thirst.
- **Fasting blood sugar test.** A blood sample is taken after an overnight fast. Results are interpreted as follows:
 - **Less than 100 mg/dL (5.6 mmol/L) is normal.**
 - **100 to 125 mg/dL (5.6 to 6.9 mmol/L) is diagnosed as prediabetes.**
 - **126 mg/dL (7 mmol/L) or higher on two separate tests is diagnosed as diabetes.**
- **(What does HbA1c mean?** HbA1c is what's known as glycated haemoglobin. This is something that's made when the glucose (sugar) in your body sticks to your red blood cells. Your body can't use the sugar properly, so more of it sticks to your blood cells and builds up in your blood. Red blood cells are active for around 2-3 months, which is why the reading is taken quarterly.)

Pharmacological therapy /Type 2 Non Insulin Therapies / **Medications**

- 1. Metformin**
- 2. Insulin releasing pills (secretagogues)**
- 3. Thiazolidinediones (glitazones)**
- 4. Starch blockers**
- 5. Incretin based therapies**
- 6. Amylin analogs**
- 7. SGLT2 inhibitors**

1. BIGUANIDES

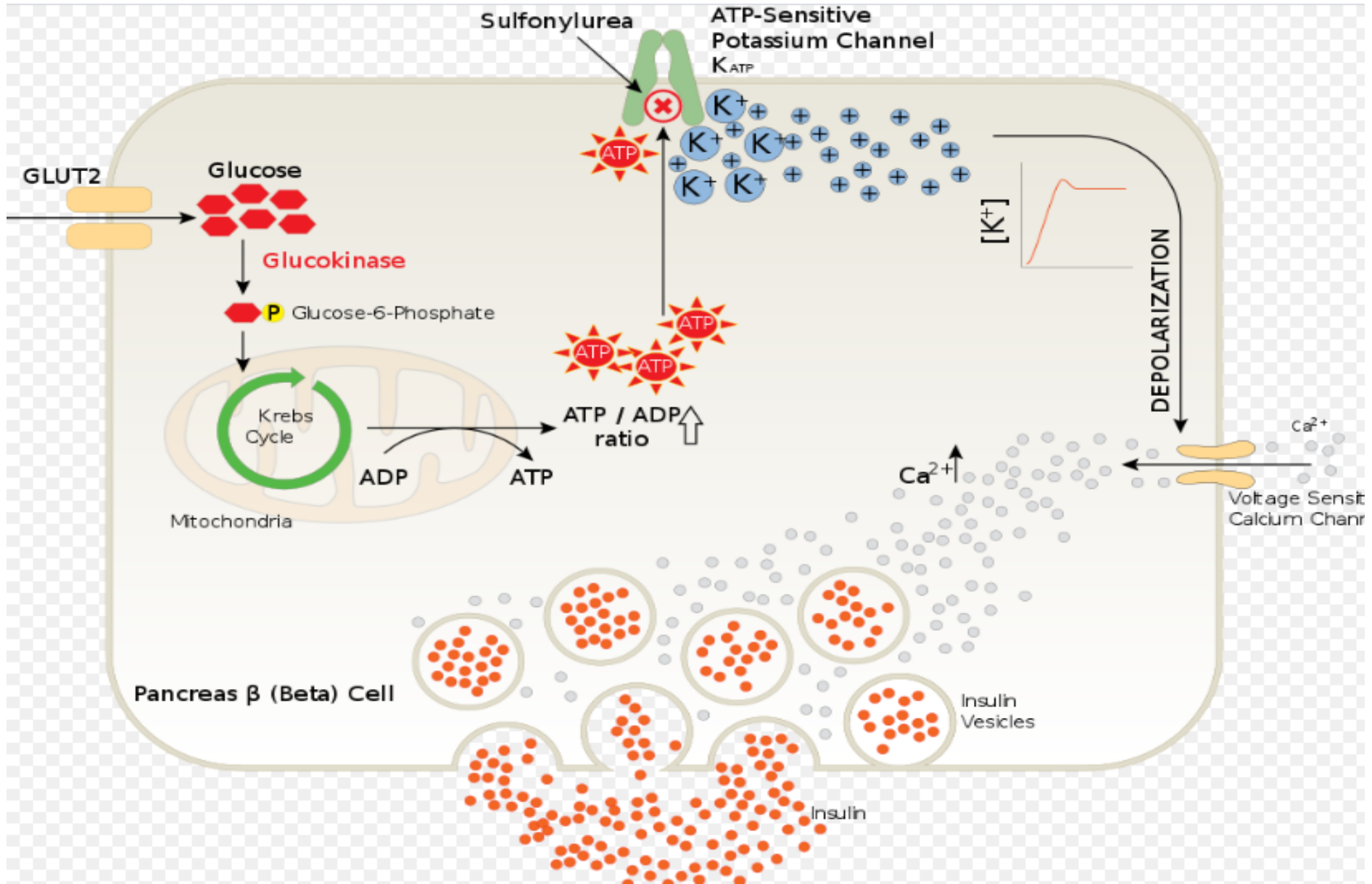
- **BIGUANIDES**: decreases glucose release from liver; decreases intestinal absorption of glucose; improves insulin sensitivity (increases glucose uptake and utilization).
- **Metformin (Glucophage®)** Initial: 500 mg twice daily or 850 mg once daily
- SE: Gastrointestinal symptoms (diarrhea, nausea, upset stomach),
- metallic taste

2. Insulin Releasing Pills (Secretagogues)

- **Sulfonylureas** The sulfonylureas (SFUs) were among the first oral medicines available to treat type 2 diabetes
- **Glinides** Another type of insulin releasing medicine (Secretagogues) are the Glinides (repaglinide and nateglinide).

Sulfonylureas

- **Sulfonylureas** are a group of medicines used in the management of Type 2 diabetes.
- Stimulating insulin release from the Beta cells of the pancreas.
- Their action is dependent upon the presence of functioning Beta cells, therefore, sulfonylureas do not work in people with type 1 diabetes.
- **Mechanism of action:** Sulfonylureas **stimulate insulin release by blocking ATP sensitive potassium channels in the Beta cells**, reducing potassium permeability. This causes depolarization of the cell and increases calcium entry, increasing insulin secretion.
- Rapidly lowering blood sugar
- But run the risk of causing hypoglycemia.



Pharmacology

Sulfonylurea generations

❑ **First generation sulfonylureas**

- Chlorpropamide (Diabinese) and tolbutamide (Orinase).

❑ **Second generation sulfonylureas**

- Glipizide (Glucotrol and Glucotrol XL), glyburide (Diabeta, Micronase, and Glynase PresTab), and glimepiride (Amaryl).

Sulfonylurea (1st generation)

❑ Tolbutamide (Orinase®)

- Initial: 1000-2000 mg daily
- Range: 250-3000 mg
- SE: hypoglycemia and weight gain
- Preferred SFU for elderly

Sulfonylurea (1st generation)

❑ Chlorpropamide (Diabinese)

- Adult Dosage: Initially 250mg daily. Elderly: initially 100-125mg daily. Titrate dose. Take with breakfast. Max 750mg daily.
- Administer 30 minutes before meal to improve absorption

❑ Contraindications

- Type I diabetes
- Diabetes ketoacidosis
- Hypersensitivity, sulfa allergy
- Severe renal impairment

Sulfonylurea (2nd generation)

□ Glipizide

- Include (Glucotrol® and Glucotrol XL®)
- Initial: 5 mg daily
- SE: hypoglycemia, weight gain

□ Glyburide (Micronase®, DiaBeta®).

- Initial: 2.5-5 mg daily
- Dose: Taken once or twice daily
- SE: hypoglycemia, weight gain

Sulfonylurea (2nd generation)

- Glimepiride (Amaryl®).
- Initial: 1-2 mg daily
- Range: 1-8 mg.
- Dose: Taken once daily

- SE: hypoglycemia, weight gain
- Need to take only once daily

3. Insulin Sensitizers //THIAZOLIDINEDIONES

□ **THIAZOLIDINEDIONES (Glitazones or TZDs): decrease insulin resistance in the body (muscle and fat tissues)**

❖ **Pioglitazone (Actos®) Pioglitazone (preferred over Rosiglitazone).**

- Initial: 15-30 mg daily. Range: 15-45 mg / once daily.

❖ **Rosiglitazone (Avandia®).**

- Initial: 4 mg daily. Range: 4-8 mg. Once or twice daily.

- **SE. of Pioglitazone and Rosiglitazone)**

- Anemia, swelling (edema) from fluid retention, weight gain, macular edema (in eye), bone loss and fractures in women

- May cause or worsen heart failure.

- Cannot use if have liver problems or severe heart failure.

- Requires liver monitoring.

4. STARCH BLOCKERS / ALPHA-GLUCOSIDASE INHIBITORS

❑ ALPHA-GLUCOSIDASE INHIBITORS: STARCH BLOCKERS

- Delay digestion and absorption of carbohydrates

❖ Acarbose (Precose®)

- Initial: 25 mg three times daily
- Range: 75-300 mg
- SE: flatulence

5. Incretin Based Treatments

- When the patient have type 2 diabetes, the blood sugar may be too high after a meal, even if patient eat very little carbohydrate (CHO). This, in part, is due to **glucagon** levels staying too high after meals.
- ((Glucagon, made by islet cells (alpha cells) in the pancreas, controls the production of glucose and another fuel, ketones, in the liver. Glucagon is released overnight and between meals and is important in maintaining the body's sugar and fuel balance. It signals the liver to break down its starch or glycogen stores and helps to form new glucose units and ketone units from other substances. It also promotes the breakdown of fat in fat cells.))
- ❖ The incretin based medicines are available in two families of medicines:
 - DPP-4 Inhibitors
 - GLP-1 analogs.

5.1 The dipeptidyl peptidase (DPP)–4 inhibitors

- **Inhibitors of dipeptidyl peptidase 4 (DPP-4 inhibitors)** are a class of oral hypoglycemics that block the enzyme dipeptidyl peptidase-4 (DPP-4). They can be used to treat diabetes mellitus type 2.
- increase insulin secretion, reduce glucose release from liver after meals
 - Sitagliptin (Januvia®). 100 mg daily / Range: 25-100 mg daily.
 - Linagliptin (Tradjenta®) 5 mg daily.
 - SE: runny nose, upper respiratory infection, rare severe allergic reactions (swelling of tongue, throat, face or body; severe rash)
 - No weight gain; Lower doses used if kidney problems

5.2 Glucagon-like peptide-1 (GLP-1)

□ GLP-1 ANALOGS:

- increase insulin secretion,
- reduce glucose release from liver after meals,
- delay food emptying from stomach and promote satiety and it used in T2DM
- **Exenatide (Byetta®) / 5 mcg SQ twice daily** (Subcutaneous (SQ or Sub-Q) injection means the injection is given in the fatty tissue, just under the skin)
- **Liraglutide (Victoza®) / 0.6 mg SQ once daily**
- **SE:** nausea, headache, hypoglycemia (when used with insulin secretagogues). Rare reports of sudden pancreatitis (inflammation of pancreas). May cause mild weight loss

6. Amylin Analog Treatment

- **((Amylin))** is released along with insulin from beta cells. It decreases glucagon levels, slows the rate at which food empties from your stomach, and makes your brain feel that you have eaten a full and satisfying meal. A fall in glucagon decreases the liver's glucose production.
- **Pramlintide** is an injected medicine for people with type 1 and type 2 diabetes that helps control blood sugar levels after eating.
- **Type 1 Diabetes** / 15 mcg SC immediately prior to major meals.
- **Type 2 Diabetes** / 60 mcg SC immediately prior to major meals

7. Sodium-glucose co-transporter (SGLT2) inhibitors

- ❑ **SGLT2 inhibitors:** increase glucose excretion in the urine
 - sodium-glucose co-transporter (SGLT)2 is responsible for >80% of proximal tubule glucose reabsorption
 - ❖ **Canagliflozin (Invokana®) 100-300 mg daily.**
 - ❖ **Dapagliflozin (Farxiga®) 5 - 10mg daily.**
 - ❖ **Empagliflozin (Jardiance®) 10 - 25 mg / daily**
 - SE: increased urination or urgency, lower blood pressure,
 - dizziness, genital yeast infections, urinary tract infections
 - increase in blood potassium; rare severe allergic reactions
 - (swelling of tongue, throat, face or body; severe rash)
 - Cannot use if have kidney problems

Diabetes and oral health

- People with diabetes have a higher risk of tooth and gum problems.
- Gum disease is more common and more severe in people with suboptimal blood glucose levels.
- With increased blood glucose levels, people living with diabetes may have more glucose in their saliva and very dry mouths. These conditions allow dental plaque to build up on teeth, which leads to tooth decay and cavities.
- Oral thrush (candidiasis) is a fungal infection. It is caused by an overgrowth of the yeast, caused by diabetes such as high glucose in saliva, poor resistance to infection and dry mouth (low saliva levels) can contribute to oral thrush.

A dark, possibly black, bowl is filled with smooth, white, rounded pebbles. Several white daisies with bright yellow centers are scattered among the pebbles. In the center of the bowl, a large, smooth, white stone is prominently displayed. The words "Thank You" are written in a black, elegant, cursive font across the surface of this large stone.

*Thank
You*