
بسم الله الرحمن الرحیم
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Pancreatic hormones and antidiabetic drugs

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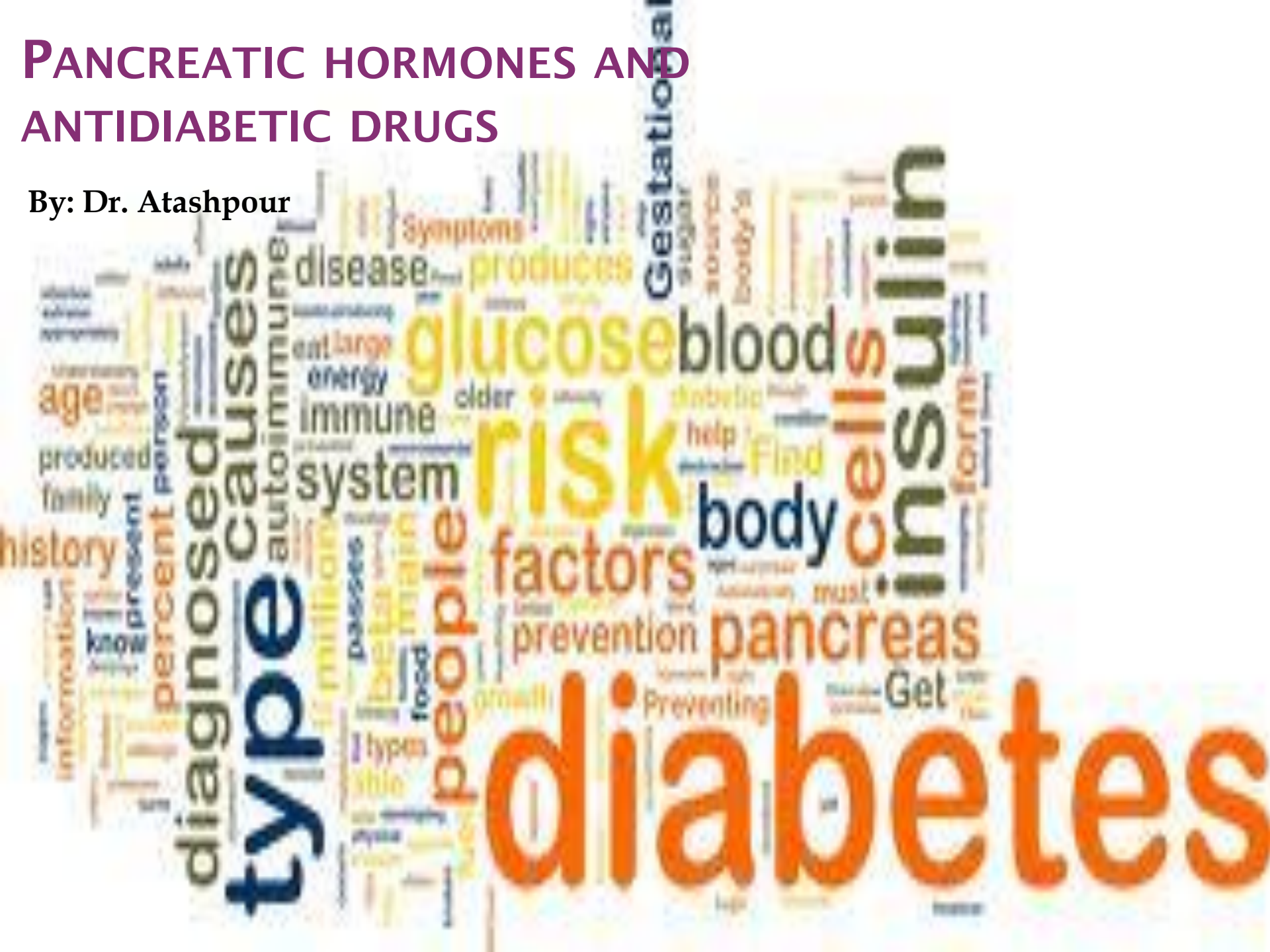


Cell Types	Approximate Percent of Islet Mass	Secretory Products
Alpha (A) cell	20	Glucagon, proglucagon
Beta (B) cell	75	Insulin, C-peptide, proinsulin, amylin
Delta (D) cell	3–5	Somatostatin
G cell	1	Gastrin
F cell (PP cell)[1]	1	Pancreatic polypeptide (PP)

Diabetes mellitus is defined as an elevated blood glucose associated with absent or inadequate pancreatic insulin secretion with or without concurrent impairment of insulin action :

Type 1(insulin-dependent diabetes)

Type 2 (non-insulin-dependent diabetes)

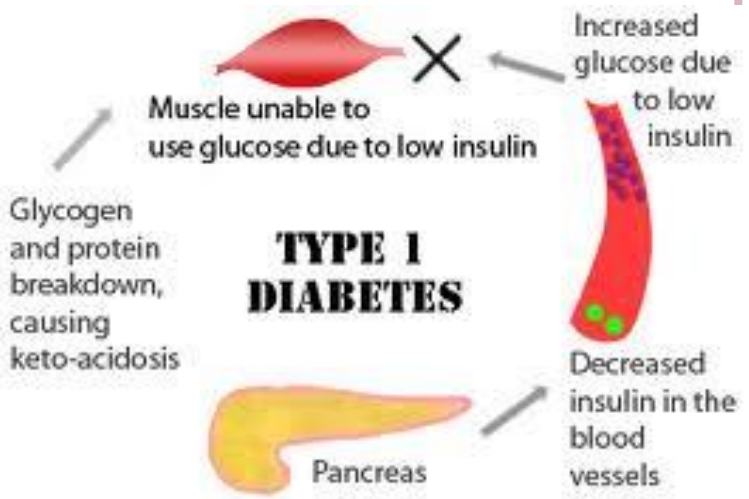
Type 3

Type 4 (gestational diabetes mellitus)

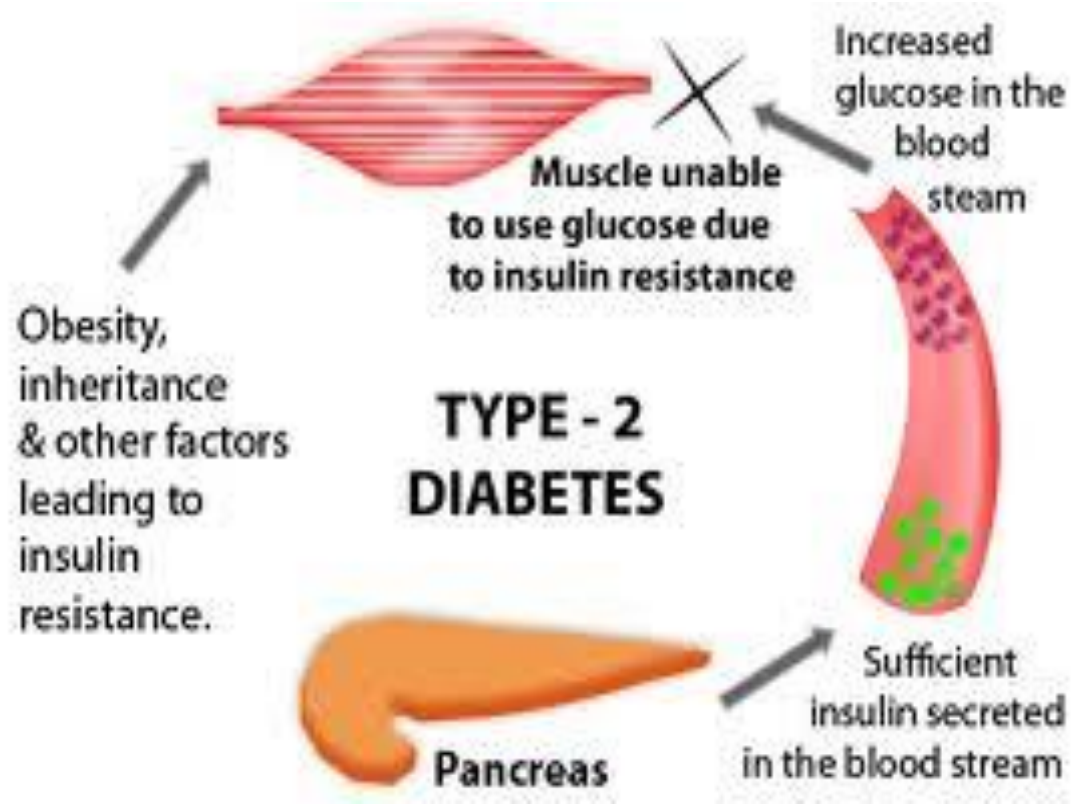
Type 1 Diabetes: What Is It?

type 1 occurs:

when the immune system attacks the insulin-producing beta cells in the pancreas.



Diabetic ketoacidosis : caused by insufficient or absent insulin and results from excess release of fatty acids and subsequent formation of toxic levels of ketoacids



Impaired insulin action:
Blood glucose rise
Increased free fatty acid flux and TG levels and low levels of HDL.
Ketoacidosis may occur as the result of stress such as infection or the use of medication that enhance resistance(glucocorticoids)
Nonketotic hyperosmolar coma(due to dehydration): blood glucose rise 6-20 times the normal range
Altered mental state
Lose consciousness

Insulin Secretion

Stimulant of insulin secretion:

Glucose

Other sugars (eg, mannose)

Certain amino acids(leucine, arginine)

Glucagon-like polypeptide-1(GLP-1)

Glucagon

Vagal activity

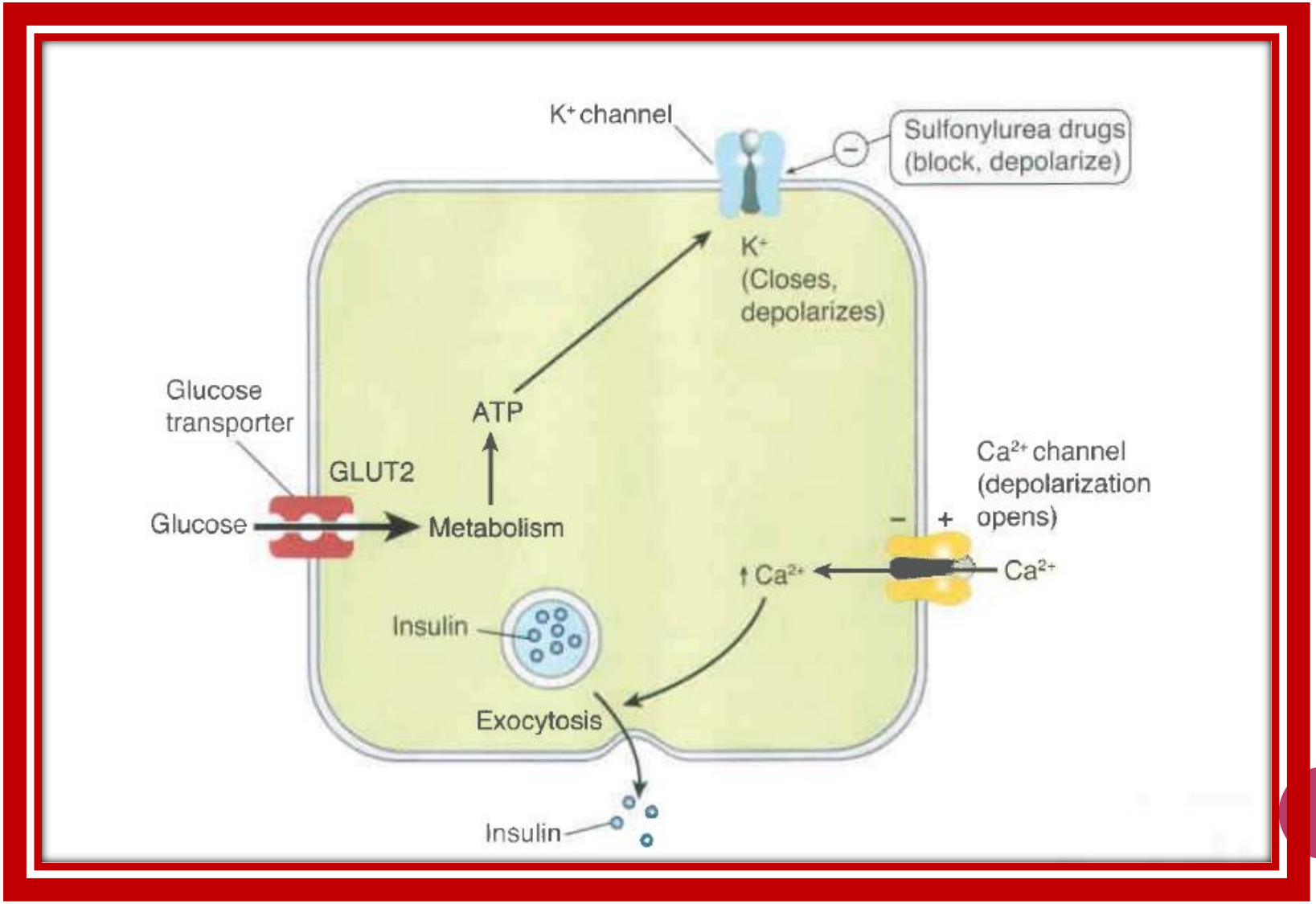
Inhibitory signal of insulin secretion:

Somatostatin

Leptin

Chronically elevated glucose and fatty acids levels

Insulin Secretion

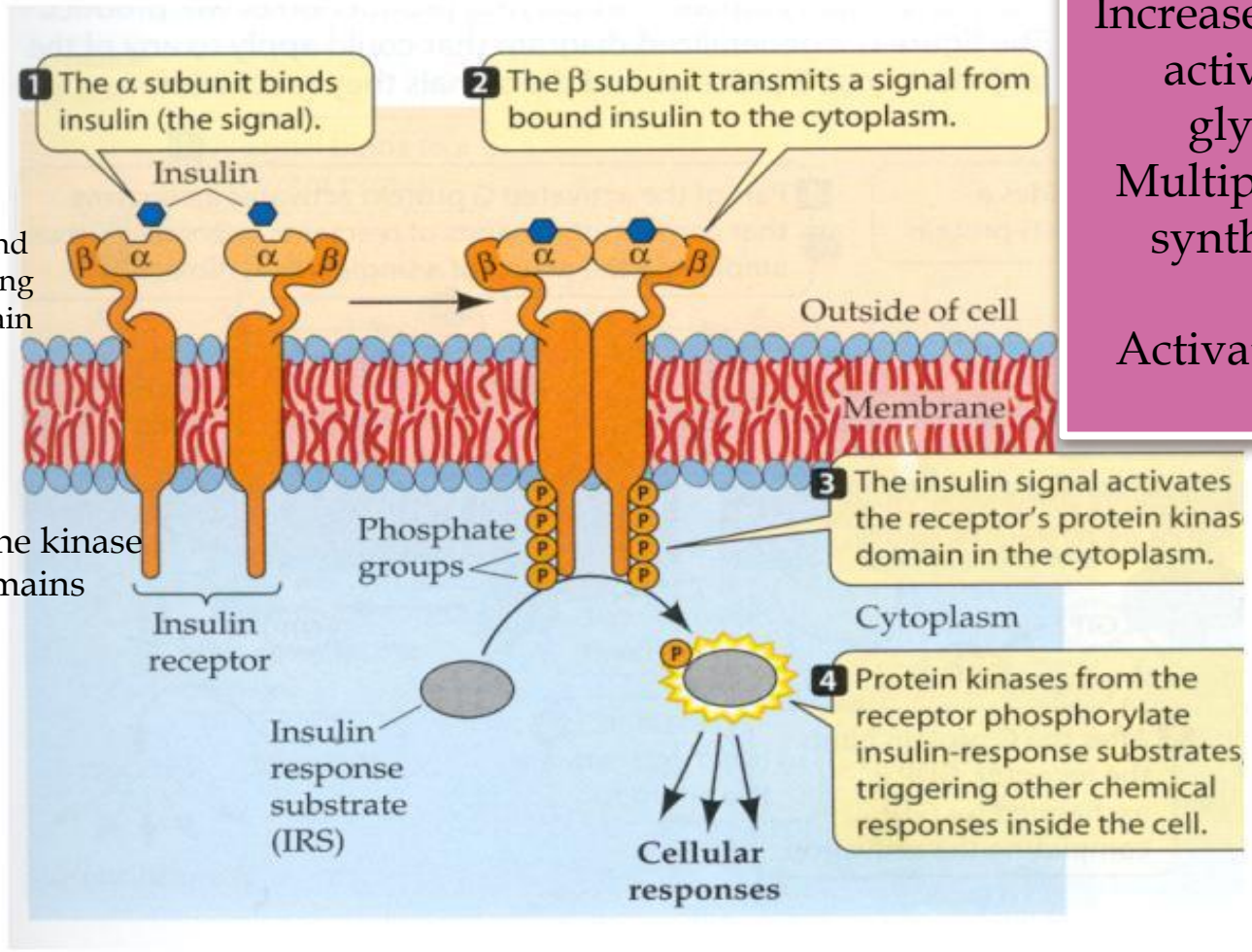


Insulin degradation

Liver(60%)
Kidney (35-40%)
Ratio reversed in insulin-treated diabetics receiving SC insulin injection

Basal insulin values: 5-15 μU/ml
During meals: 60-90μU/ml

Insulin Receptor



Translocation of glucose transporter esp. GLT4 to the cell membrane with a resultant increase in glucose uptake
Increased glucogen synthase activity and increased glycogen formation
Multiple effects on protein synthesis, lipolysis and lipogenesis
Activation of transcription factors

Glucocorticoids
Growth hormones

Transporter	Tissues	Glucose K_m (mmol/L)	Function
GLUT 1	All tissues, especially red cells, brain	1–2	Basal uptake of glucose; transport across the blood-brain barrier
GLUT 2	Beta cells of pancreas; liver, kidney; gut	15–20	Regulation of insulin release, other aspects of glucose homeostasis
GLUT 3	Brain, kidney, placenta, other tissues	< 1	Uptake into neurons, other tissues
GLUT 4	Muscle, adipose	≈ 5	Insulin-mediated uptake of glucose
GLUT 5	Gut, kidney	1–2	Absorption of fructose

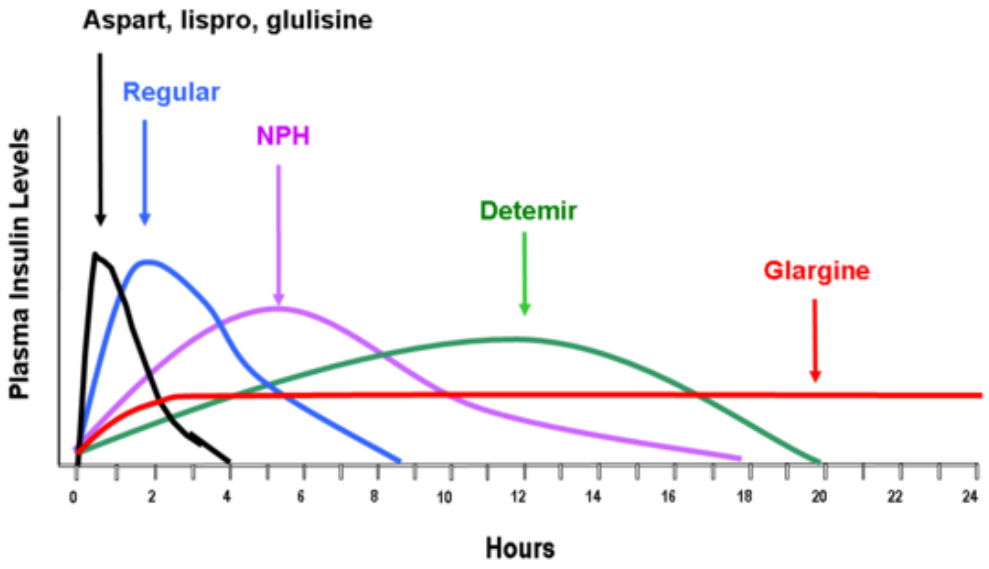
Insulin preparation

- Differences In the recombinant DNA production techniques
- Amino acid sequences
- Concentration
- Solubility
- Time of onset and duration of action

Preparation	Species Source	Concentration
Rapid-acting insulins		
Insulin Lispro, Humalog (Lilly)	Human analog	U100
Insulin Aspart, Novolog (Novo Nordisk)	Human analog	U100
Insulin Glulisine, Apidra (Aventis)	Human analog	U100
Short-acting insulins		
Regular Novolin R (Novo Nordisk)	Human	U100
Regular Humulin R (Lilly)	Human	U100, U500
Intermediate-acting insulins		
NPH Humulin N (Lilly)	Human	U100
NPH Novolin N (Novo Nordisk)	Human	U100
Premixed insulins		
Novolin 70 NPH/30 regular (Novo Nordisk)	Human	U100
Humulin 70 NPH/30 regular and 50/50 (Lilly)	Human	U100
50/50 NPL, Lispro (Lilly)	Human analog	U100
75/25 NPL, Lispro (Lilly)	Human analog	U100
70/30 NPA, Aspart (Novo Nordisk)	Human analog	U100
Long-acting insulins		
Insulin detemir, Levemir (Novo Nordisk)	Human analog	U100
Insulin glargine, Lantus (Aventis/Hoechst Marion Roussel)	Human analog	U100

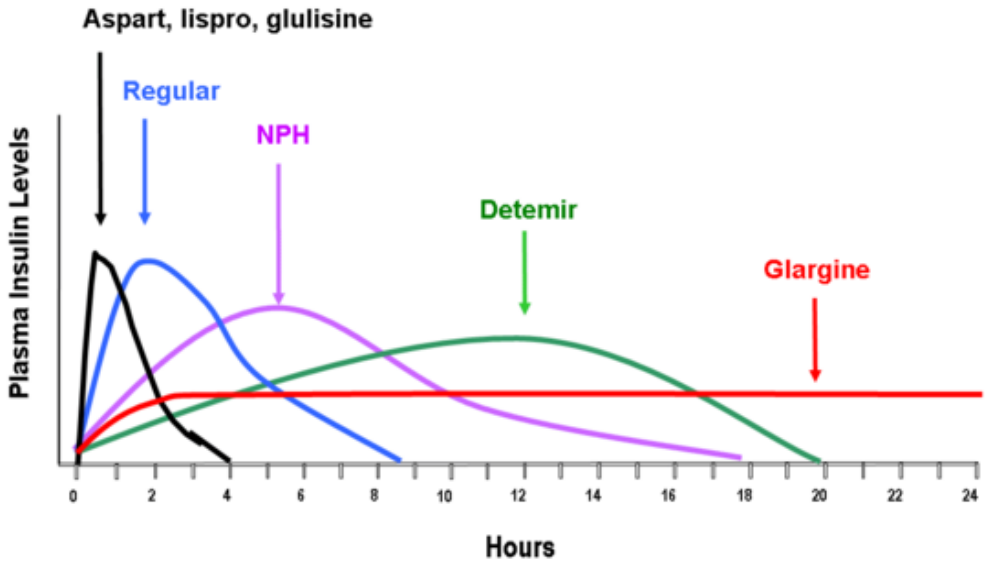
1- RAPID ACTING INSULIN

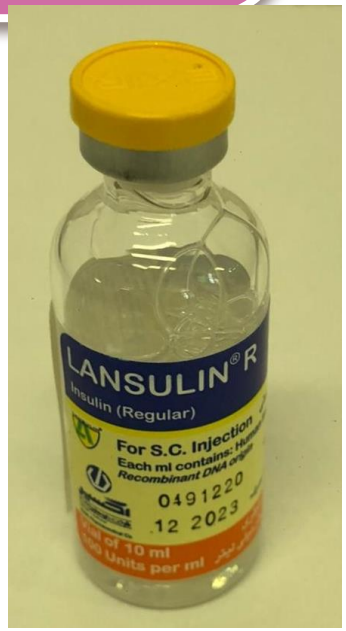
Insulin lispro, insulin aspart and insulin glulisine
4-5 hrs: decrease the risk of postmeal hypoglycemia
Preferred insulins for use in continuous SC insulin infusion device



2- SHORT ACTING INSULIN

Regular insulin
30min.2-3hrs,5-8hrs
IV(ketoacidosis) or SC
30-45 min before meal(if administered at mealtime, blood glucose rises faster than the insulin with resultant early postprandial hyperglycemia and an increased risk of late postprandial hypoglycemia

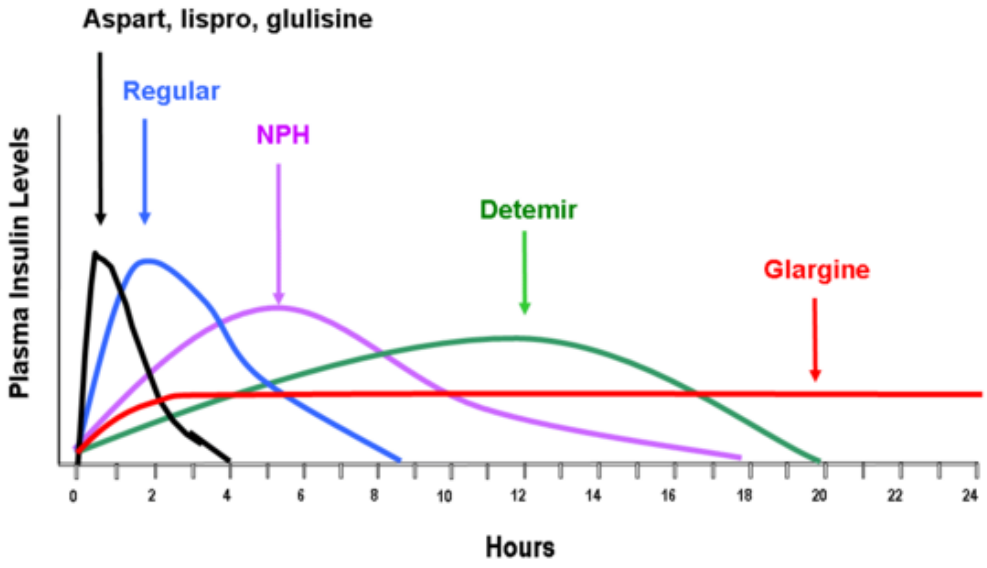




3- INTERMEDIATE-ACTING AND LONG-ACTING INSULIN

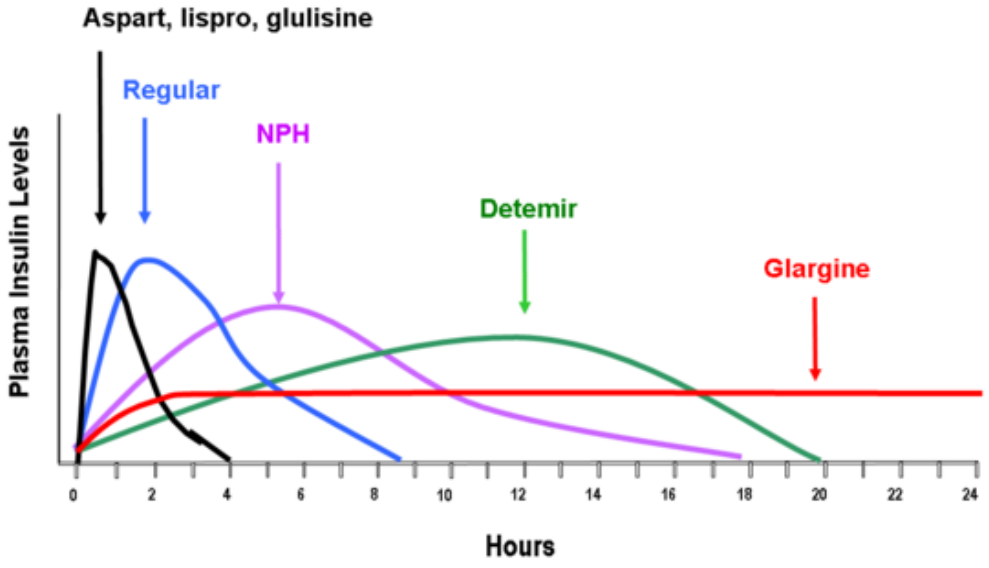
a. NPH(neutral protamine hagedorn or isophane) insulin:

- **Intermediate-acting**
- **Absorption and onset of action are delayed by insulin+ protamine**
- **Onset:2-5hrs, duration 4-12hrs**
- **+ regular, lispro, aspart or glulisine insulin and given 2-4times a day**
- **for insulin replacement**



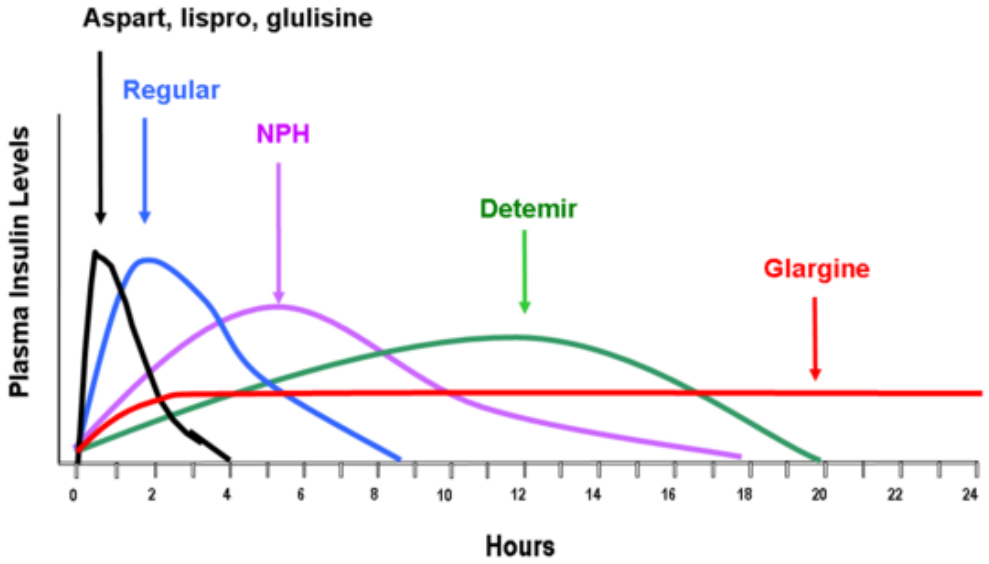
3- INTERMEDIATE-ACTING AND LONG-ACTING INSULIN

a. **Insulin glargine:**
   - **Soluble, peakless, long-acting insulin analog**
   - **Provide reproducible Background insulin replacement**
   - **Soluble in an acidic solution but precipitates in the more neutral body pH after SC injection. Insulin molecules slowly dissolve away from the crystalline depot and provide a low, continuous level of circulating insulin**
   - **Slow onset(1-1.5 hrs), max effect after 4-6hrs, duration 11-24hrs**
   - **Should not be mixed with other insulins**



3- INTERMEDIATE-ACTING AND LONG-ACTING INSULIN

a. **Insulin detemir:**
   - **Long acting insulin analog**
   - **Prolong availability of the injected analog by increasing self-aggregation in SC tissue and reversible albumin binding**
   - **Less hypoglycemia than NPH insulin**
   - **Onset:1-2hrs, duration more than 24hrs**



3-MIXTURES OF INSULINS

Because intermediate-acting NPH insulins require several hours to reach adequate therapeutic levels, their use usually requires supplements of rapid- or short-acting insulin before meals
For convenience, these are often mixed together in the same syringe before injection.
Lispro, aspart and glulisine+ NPH: just before injection
NPL(neutral protamine lispro) or NPA(neutral protamine aspart)+ lispro or aspart insulin: premixed formulation

Insulin Delivery Systems

- Portable pen injector

Insulin (Regular)	INJECTION	100 IU/ml	PARENTERAL	
Insulin Aspart	INJECTION, SUSPENSION	100 IU/ml	PARENTERAL	30% soluble Insulin Aspart + 70% Insulin Aspart crystallised with Protamine
Insulin Aspart	INJECTION, SOLUTION	100 IU/ml	PARENTERAL	
Insulin Biphasic Isophane	INJECTION, SUSPENSION	100 IU/ml	PARENTERAL	(Isophane Insulin 75% + Insulin Regular 25%)
Insulin Biphasic Isophane	INJECTION	100 IU/ml	PARENTERAL	Isophane Insulin 70% + Insulin Reg 30%
Insulin Detemir	INJECTION, SOLUTION	100 IU/ml	PARENTERAL	
Insulin Glargine	INJECTION	100 IU/ml	PARENTERAL	
Insulin Glargine	INJECTION	300 IU/ml	PARENTERAL	
Insulin Glulisin	INJECTION, SOLUTION	100 IU/ml	PARENTERAL	
Insulin Isophane	INJECTION	100 IU/ml	PARENTERAL	
Insulin Lispro	INJECTION, SOLUTION	100 IU/ml	PARENTERAL	
Insulin Biphasic Lispro	INJECTION, SUSPENSION	100 IU/ml	PARENTERAL	Insulin Lispro 25% + Insulin Lispro Protamine 75%
Insulin Biphasic Lispro	INJECTION, SUSPENSION	100 IU/ml	PARENTERAL	Insulin Lispro 50% + Insulin Lispro Protamine 50%
Insulin Zinc	INJECTION	100 IU/ml	PARENTERAL	

Generally, the total daily insulin requirement in units is equal to the weight in pounds divided by four, or 0.55 times the person's weight in kilograms. Approximately half the total daily insulin dose covers the background or basal insulin requirements, and the remainder covers meal and snack requirement and high blood sugar corrections. This is an approximate calculation and has to be individualized. Examples of reduced insulin requirement include newly diagnosed persons and those with ongoing endogenous insulin production, longstanding diabetes with insulin sensitivity, significant renal insufficiency, or other endocrine deficiencies. Increased insulin requirements typically occur with obesity, during adolescence, during the latter trimesters of pregnancy, and in individuals with type 2 diabetes.

Insulin Treatment of Special Circumstances

- A. Diabetic ketoacidosis
  - Caused by inadequate or absent insulin replacement, mostly in type I diabetes
  - Typically occurs in newly diagnosed type I patients/ those who have experienced interrupted insulin replacement/ rarely in Type 2 diabetes who have concurrent stressful conditions such as sepsis or pancreatitis or on high dose of steroid therapy
  - Sign & symptoms: nausea, vomiting, abdominal pain, change in mental status, elevated blood and urinary ketones and glucose
  - Treatment: aggressive IV hydration(normal saline), insulin therapy(regular insulin, IV), maintenance of potassium and other electrolyte levels

Insulin Treatment of Special Circumstances

- B. Hyperosmolar Hyperglycemic Syndrome
  - Type 2 diabetes and is characterized by profound hyperglycemia and dehydration
  - Inadequate oral hydration esp. in elderly patients, with other illnesses, the use of medication that elevates the blood sugar or cause dehydration such as phenytoin, steroids, diuretics and beta blockers
  - Diagnostic hallmarks: declining mental status and even seizure, as plasma glucose > 600mg/dl, calculated serum osmolality> 320 mmol/L.
  - Treatment: aggressive rehydration and restoration of glucose and electrolyte homeostasis, low dose insulin may be required

COMPLICATION OF INSULIN THERAPY

a. Hypoglycemia

- Most common complication of insulin therapy
- May result from inadequate carbohydrate consumption, unusual physical exertion, and too large a dose of insulin
- Cause signs of autonomic hyperactivity_ **sympathetic(** tachycardia, palpitation, sweating, tremulousness) & **parasympathetic**(nausea, hunger)- may progress to convulsion and coma if untreated

COMPLICATION OF INSULIN THERAPY

a. Hypoglycemia

Treatment:

- Glucose administration: simple sugar or glucose(in liquid form)
- Mild hypoglycemia in patient who is conscious and able to swallow: dextrose tablets, glucose gel, or any sugar-containing beverage or food
- In sever hypoglycemia with unconsciousness: IV infusion of 20-50mL of 50% glucose solution during 2-3 min/ IM or SC injection of Glucagon (15min)
- Honey or syrup can be inserted onto the buccal pouch

- **Glucagon** As HCl INJECTION, POWDER 1 mg PARENTERAL

COMPLICATION OF INSULIN THERAPY

Hypertrophy at Injection Sites

- Hypertrophy of SC fatty tissue if injected repeatedly at the same site. However, this may be corrected by avoiding the specific injection site or by liposuction

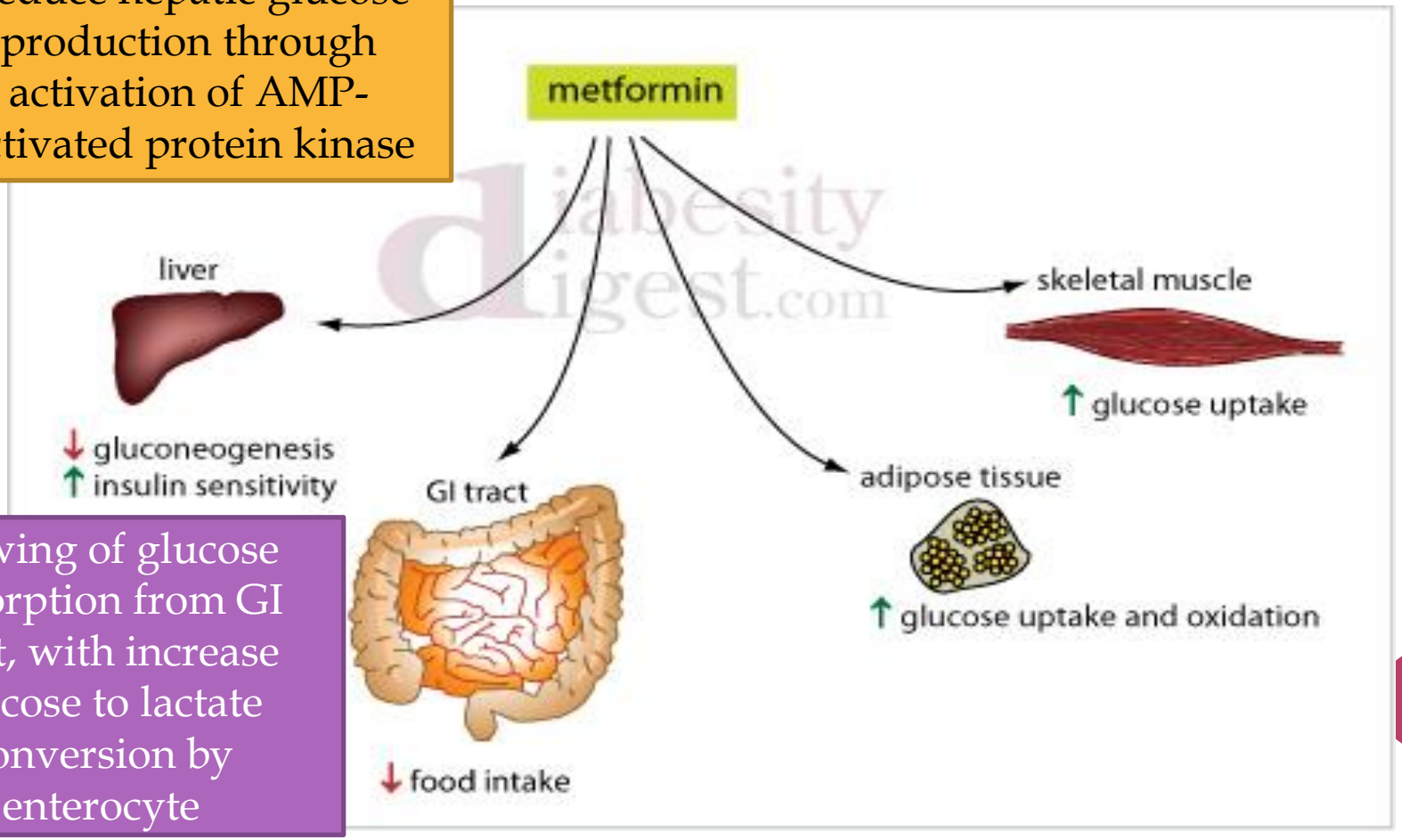

Oral Antidiabetic
Agents

Increase insulin secretion	Decrease hepatic glucose production	Reduce insulin resistance	Slow the digestion and absorption of starch and disaccharides	Increase insulin release Decrease glucagon secretion	Decrease post-meal glucose levels and reduce appetite
Insulin secretagogues: Sulfonyureas, Meglitinides	Biguanides	Thiazolidinediones	α–glucosidase inhibitors	Incretin-based therapies	Amylin analog

BIGUANIDES

- Metfromin
- Phenformin: lactic acidosis

Reduce hepatic glucose production through activation of AMP-activated protein kinase



Slowing of glucose absorption from GI tract, with increase glucose to lactate conversion by enterocyte

BIGUANIDES

- Metfromin
- Phenformin: lactic acidosis

Reduce hepatic glucose
p
ac

Biguanide blood glucose-lowering action does not depend on functioning pancreatic beta cells
Less fasting hyperglycemia as well as lower postprandial hyperglycemia after biguanids
Hypoglycemia rare

Slow
abso
trac
glu
co
enterocyte

Biguanides

- Half-life: 1.5-3
- Not bound to plasma proteins
- Not metabolized
- Excreted as active compound by the kidneys
- Block gluconeogenesis: impair hepatic metabolism of lactic acid
- Renal insufficiency biguanides accumulate and increase the risk of lactic acidosis

First line therapy for type 2 diabetes esp. in obese patients (does not increase weight or provoke hypoglycemia)

Decrease the risk of macrovascular and microvascular disease

Metfromin + insulin secretagogues or thiazolindinediones

Prevention of type 2 diabetes

With meals(max: 2.5g)

Metformin	TABLET	1000 mg	ORAL	
Metformin	TABLET, EXTENDED RELEASE	1000 mg	ORAL	
Metformin	TABLET, EXTENDED RELEASE	750 mg	OR	
Metformin	TABLET, EXTENDED RELEASE	500 mg	OR	
Metformin	TABLET	500 mg	ORAL	
Metformin	TABLET	850 mg	ORAL	
Metformin	SOLUTION	500 mg/5ml	ORAL	
Metformin+Glibenclamide	TABLET		ORAL	Metformin HCl 500 mg+ Glibenclamide 2.5 mg
Metformin+Glibenclamide	TABLET		ORAL	Metformin HCl 500 mg+ Glibenclamide 5 mg
Metformin+Glibenclamide	TABLET		ORAL	Metformin HCl 1000 mg+ Glibenclamide 5 mg
Metformin+Pioglitazone	TABLET		ORAL	Metformin HCL 500 mg + Pioglitazone 15 mg

500 mg POq12hr or 850 mg PO qDay with meals. Increase dose in increments of 500 mg/week or 850 mg q2weeks on basis of glycemic control and tolerability
Maintenance: 1500-2550 mg/day PO divided q8-12 hr with meals
Not exceed 2550 mg/day. ER: not exceed 2g/day

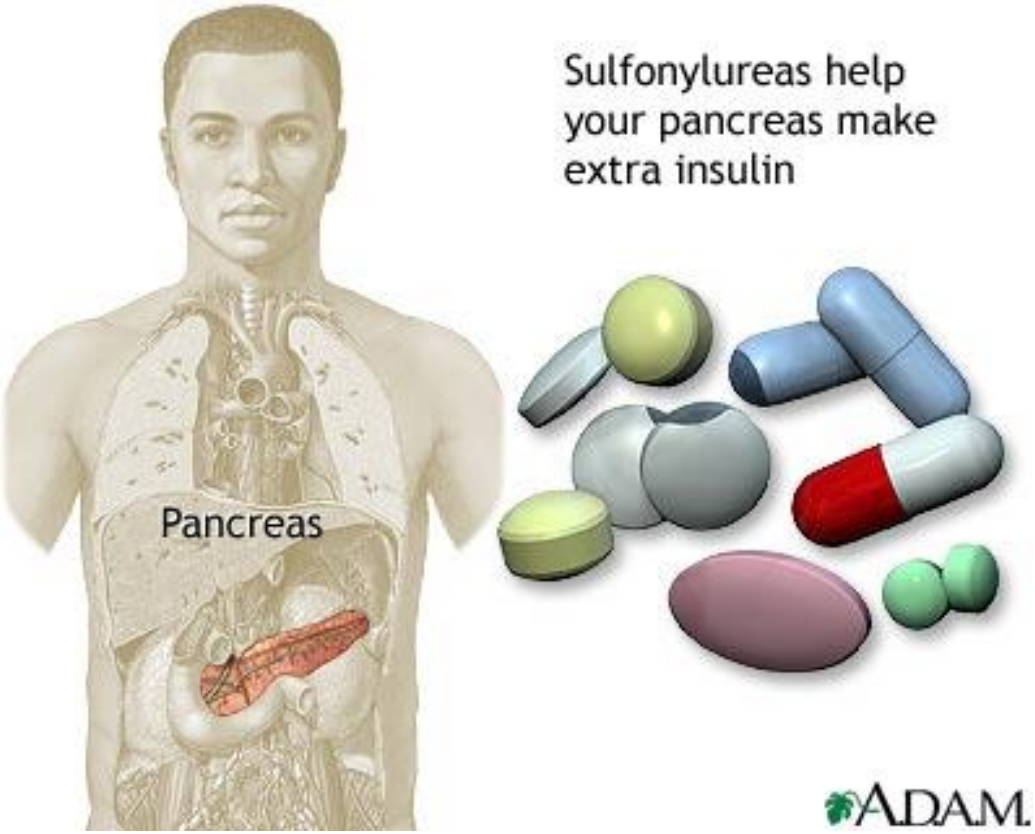
Biguanides

- ADVERSE EFFECT:
  - GI (anorexia, nausea, vomiting, abdominal discomfort, diarrhea)
  - Reduced absorption of vitamin B12 in long term therapy
  - Lactic acidosis: in absence of hypoxia or renal insufficiency less common with metformin than with phenformin therapy
  - No hypoglycemia

Contraindicated in patients with: Renal disease, alcoholism, hepatic disease, or condition predisposing to tissue anoxia(eg, chronic cardiopulmonary dysfunction)

Insulin secretagogues

SULFONYLUREAS

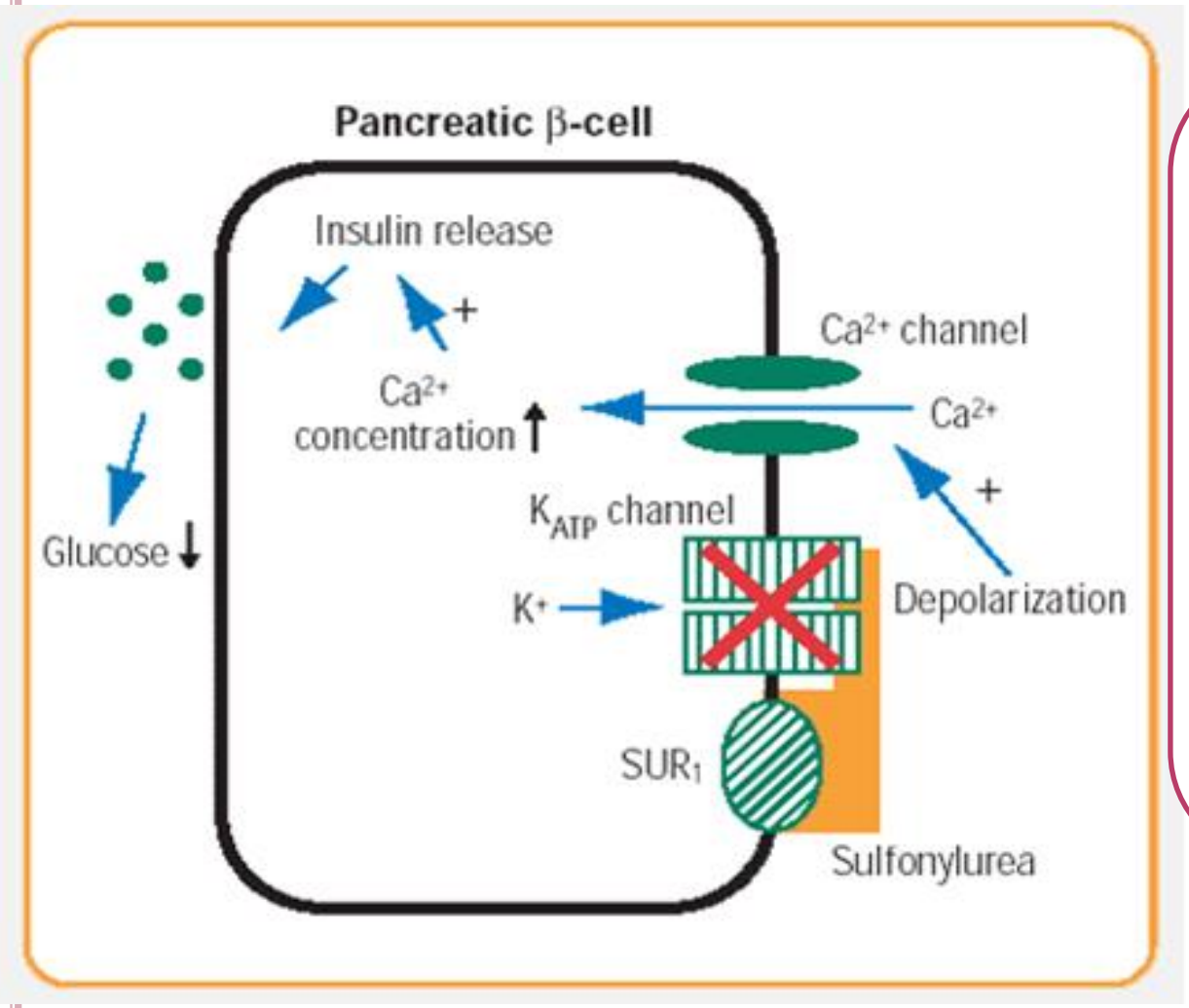


Increase insulin release

Reduction of serum glucagon level

Closure of potassium channels

Sulfonylureas mechanism of action



Long-term administration reduces serum glucagon levels(contribute to the hypoglycemic effect of the drugs)
Indirect inhibition due to enhanced release of both insulin and somatostatin, which inhibit alpha cell secretion

2ND-GENERATION SULFONYLUREAS

Glyburide

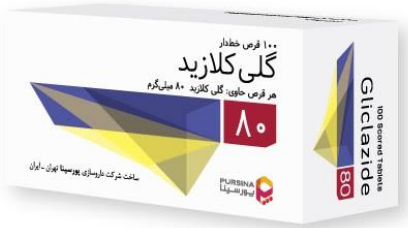
- Initial: 2.5-5 mg PO qDay
- Maintenance: 1.25-20 mg PO qDay or q12hr
- Not to exceed 20 mg/day
- Consider administering q12hr for doses >10 mg/day

- Metabolized in liver into products with very low hypoglycemic activity
- Hypoglycemia, + ethanol ingestion: flushing(rarely)
- Contraindicated in hepatic impairment and renal insufficiency

	5 mg	ORAL	Type 2 Diabetes Mellitus

2ND-GENERATION SULFONYLUREAS

Gliclazide



- Extensively metabolized in the liver. Less than 1% of the orally administered dose appears unchanged in the urine.
- Metabolites and conjugates are eliminated primarily by the kidneys (60-70%) and also in the feces (10-20%).
- Half-life: 10.4 hours. Duration of action is 10-24 hours.
- Total daily: 40-320mg. The dose should be adjusted according to the individual's response, commencing with 40-80mg daily and increasing until adequate control is achieved.
- A single dose should not exceed 160mg. When higher doses are required, gliclazide should be taken twice daily and according to the main meals of the day.

Gliclazide	**TABLET, EXTENDED RELEASE**	**30 mg**	**ORAL**	**Type 2 Diabetes Mellitus**
Gliclazide	TABLET, EXTENDED RELEASE	60 mg	ORAL	Type 2 Diabetes Mellitus
Gliclazide	TABLET	80 mg	ORAL	Type 2 Diabetes Mellitus

Glimepiride

- Hypoglycemia, + ethanol ingestion: flushing(rarely)
- Dose adjustment in hepatic impairment and renal insufficiency
- Initial: 1-2 mg PO qAM after breakfast or with first meal; may increase dose by 1-2 mg every 1-2 weeks; not to exceed 8 mg/day
- Use in monotherapy or, if glycemic response to glimepiride is inadequate at maximum dose, with insulin or metformin

Glimepiride	TABLET	1 mg	ORAL	Type 2 Diabetes Mellitus
Glimepiride	TABLET	2 mg	ORAL	Type 2 Diabetes Mellitus
Glimepiride	TABLET	3 mg	ORAL	Type 2 Diabetes Mellitus
Glimepiride	TABLET	4 mg	ORAL	Type 2 Diabetes Mellitus

MEGLITINIDE: REPAGLINIDE:

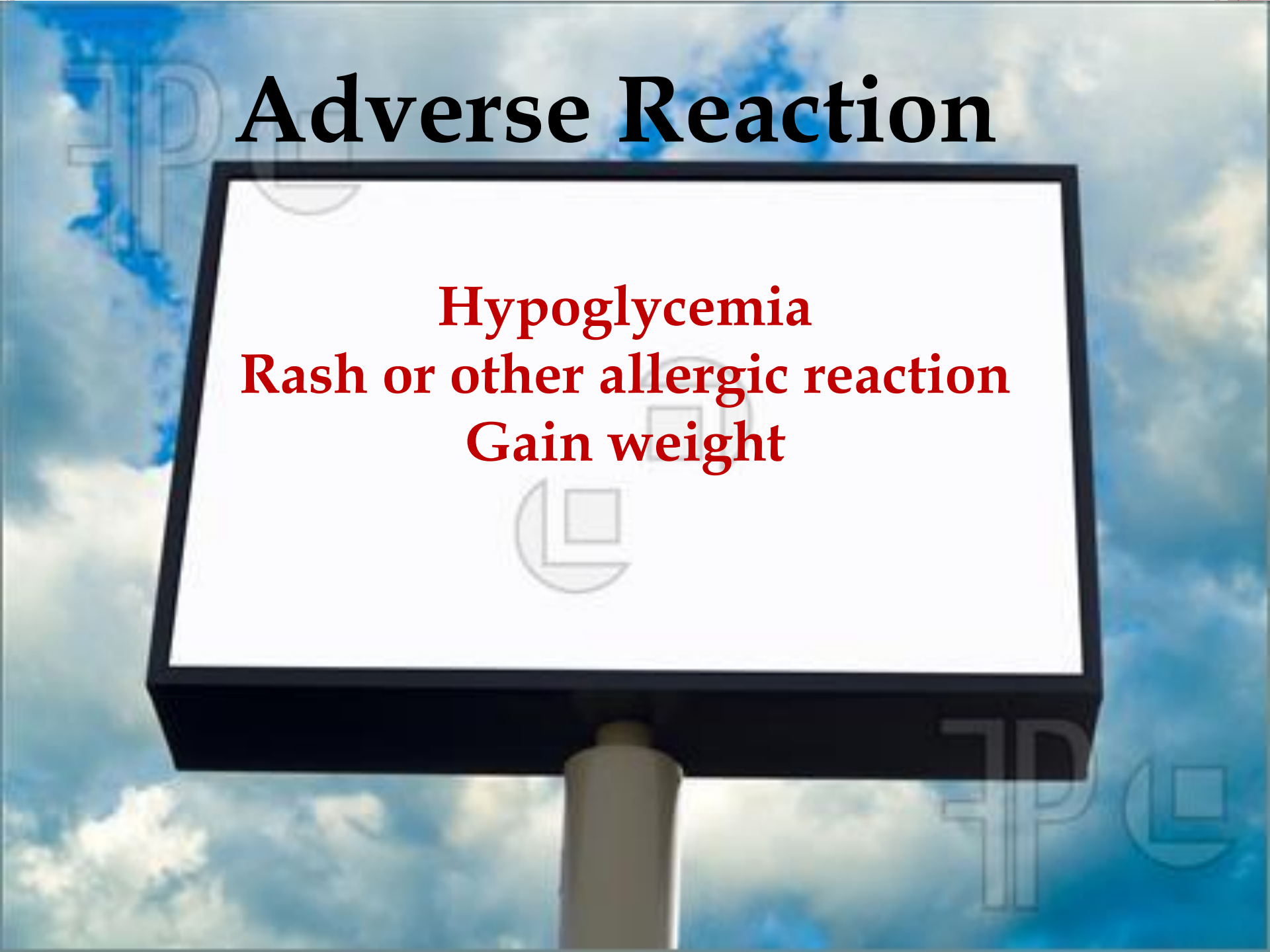
- Modulate beta-cell insulin release by regulating potassium efflux through the potassium channels
- Fast onset of action with peak effect within 1hr after ingestion, duration of action 4-7hrs
- Metabolized by CYP3A4
- Use in controlling postprandial glucose excursion(just before each meal)
- Hypoglycemia is a risk if the meal is delayed or skipped or contain inadequate carbohydrate
- Use cautiously in individuals with renal and hepatic impairment
- Monotherapy or + biguanides
- There is no sulfur in its structure, so it can be used in patients with sulfur or sulfonylurea allergy

- Dose range: 0.5-4 mg before meals
- Maximum daily dose: Not to exceed 16 mg/day

Repaglinide	**TABLET**	**0.5 mg**	**ORAL**
Repaglinide	TABLET	1 mg	ORAL
Repaglinide	TABLET	2 mg	ORAL

- Double dose up to 4 mg with each meal until satisfactory glycemic control achieved
- Wait at least 1 week to assess response after each dose adjustment
- Skipped meals: Instruct patients to skip the scheduled repaglinide dose to reduce the risk of hypoglycemia
- If hypoglycemia occurs, reduce repaglinide dose

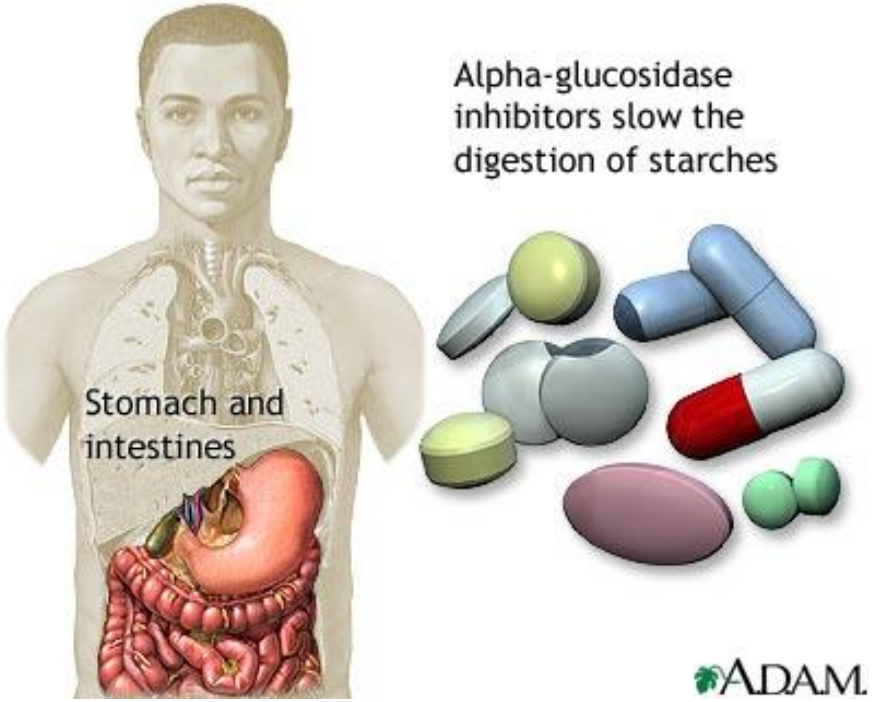
Adverse Reaction

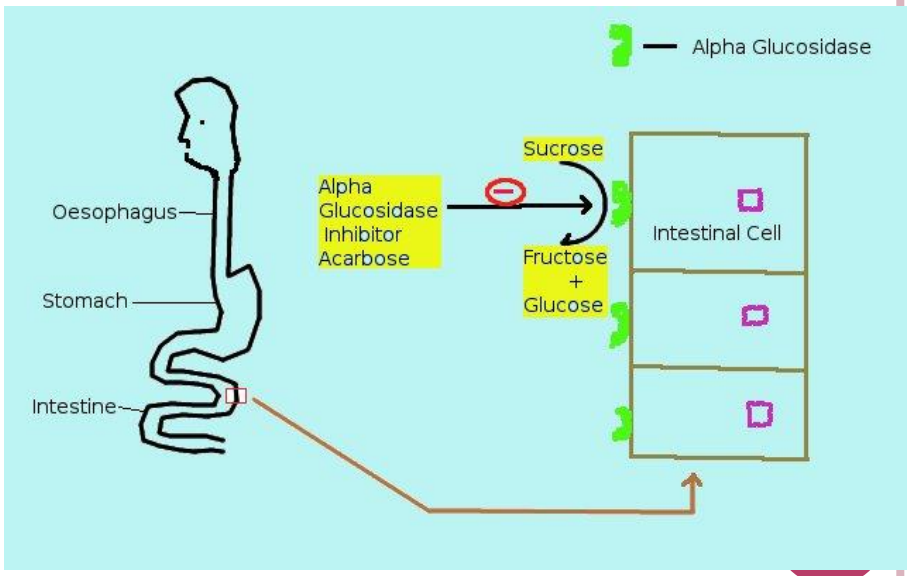


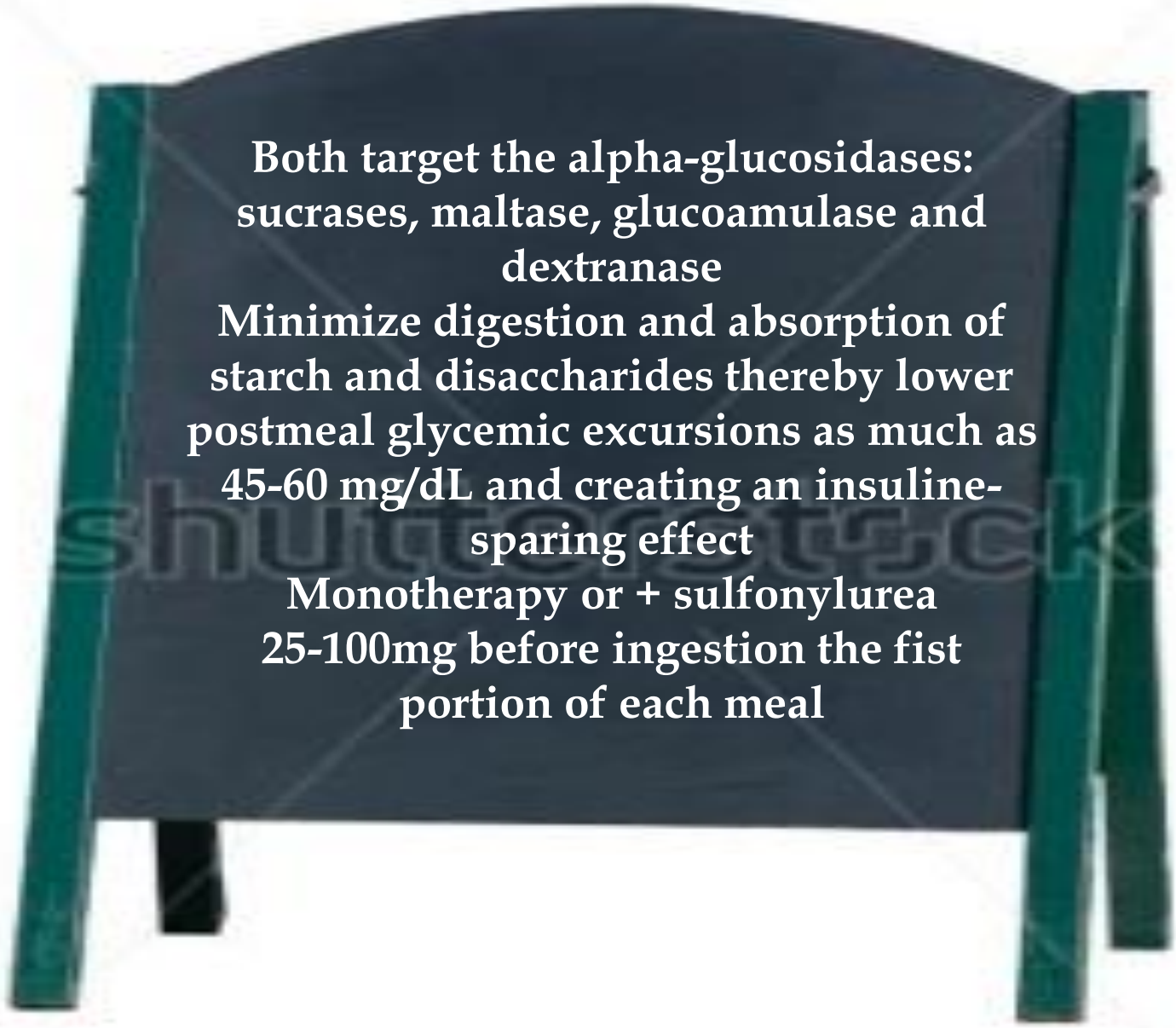
Alpha-Glucosidase Inhibitors

Acarbose

Meglitol







Both target the alpha-glucosidases: sucrases, maltase, glucoamulase and dextranase

Minimize digestion and absorption of starch and disaccharides thereby lower postmeal glycemic excursions as much as 45-60 mg/dL and creating an insuline-sparing effect

Monotherapy or + sulfonylurea

25-100mg before ingestion the fist portion of each meal

Alpha-Glucosidase Inhibitors

- Adverse effects:
  - Flatulence, diarrhea, abdominal pain(undigested carbohydrate in the colon that is fermented into short chain fatty acids, releasing gas)
  - Hypoglycemia in combination of these drugs with sulfonylurea 
  - Acarbose has been associated with reversible hepatic enzyme elevation (with caution in hepatic disease)
- Contraindicated in patients with Inflammatory bowel disease, any intestinal condition that could be worsened by gas and distention, renal impairment.

Initially 25 mg PO q8hr, at meals (with first bite)

Can increase to 50 or 100 mg PO q8hr at 4- to 8-wk intervals based on 1 hour postprandial glucose or glycosylated hemoglobin levels, and on tolerance

Acarbose	**TABLET**	**100 mg**	**ORAL**
Acarbose	TABLET	50 mg	ORAL

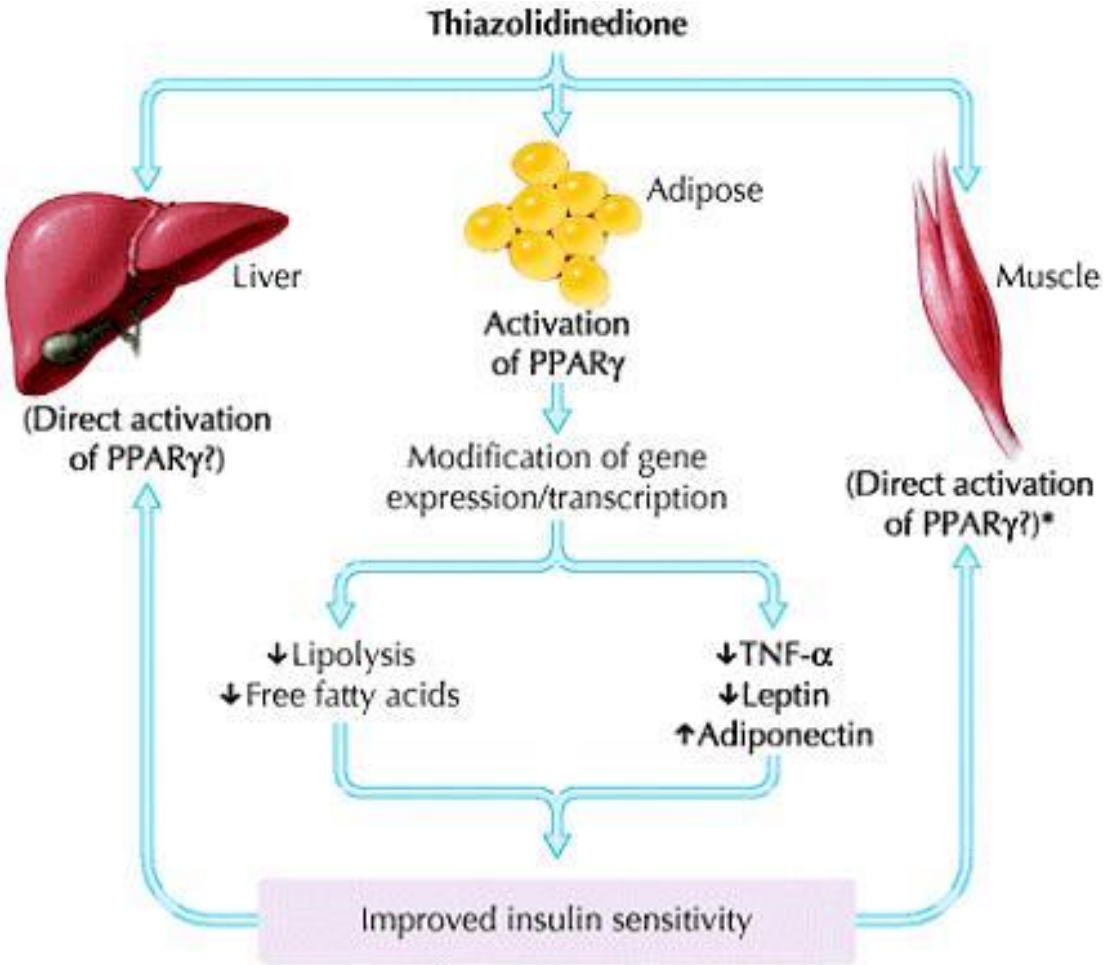
Maximum Dose

<60 kg: 50 mg q8hr

>60 kg: 100 mg q8hr

Peroxisome proliferator-activated receptor-gamma(PPAR-γ)
Decrease insulin resistance

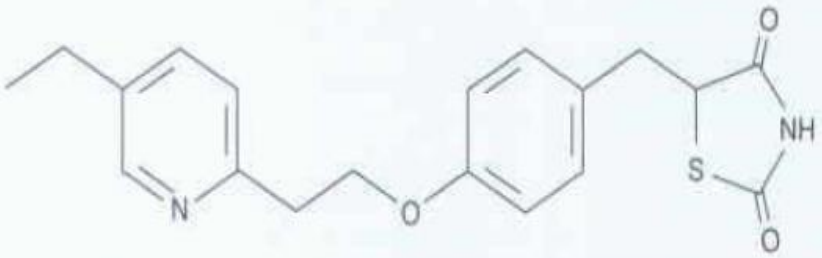
THIAZOLIDINEDIONES



Major site of Tzd action is adipose tissue: promotes glucose uptake and utilization and modulated synthesis of lipid hormones or cytokines and other proteins involved in energy regulation

Has PPAR-α & PPAR–γ activity
Absorbed within 2hrs, food delay absorption
CYP2C8 & 3A4 to active metabolite
TG-lowering effect is more significant than that observed with rosiglitazone (PPAR-α)
reduces mortality and macrovascular events (MI and stroke)
Monotherapy or + metformin, sulfonyurea and insuline for type 2

Pioglitazone (Actos) 15–45 mg once daily



Rosiglitazone (Avandia) 2–8 mg once daily

Rapidly absorbed and highly protein bound
CYP2D8 and to a lesser extent CYP2C9
Monotherapy or + biguanides or sulfonylurea for type 2 diabetes

THIAZOLIDINEDIONES

Euglycemic

- Type 2 Diabetes
- Prevention of diabetes in high risk patients

THIAZOLIDINEDIONES

- Hypoglycemia (in combination therapy with sulfonylurea and insulin)
- Fluid retention which presents as a mild anemia and peripheral edema esp. in combination therapy with insulin or insulin secretagogues
- Increase risk of heart disease
- Weigh gain (1-3kg)
- Slow onset and offset of activity
- Increased bone fractures in women due to decrease osteoblast formation
- Drop in TG levels and a slight rise in HDL and LDL values
- Not be used during pregnancy or in the presence of significant liver disease or with a concurrent diagnosis of heart failure
- Weigh gain, CHF, increased bone fracture risk in women, possible worsening of cardiovascular risk : limit their future use

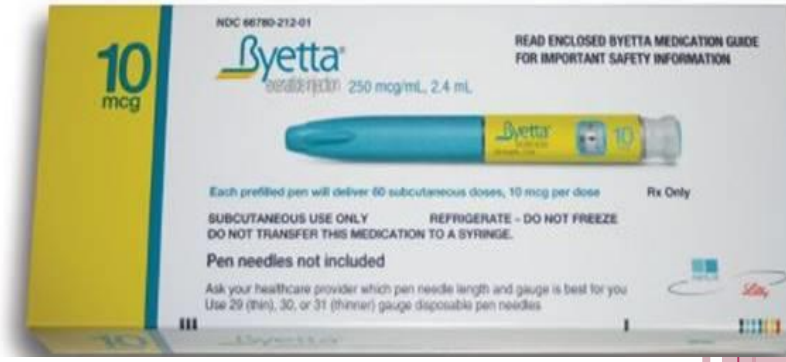
Indicated as monotherapy or with insulin or insulin secretagogues
15-30 mg PO with meal qDay initial; may increase dose by 15 mg with careful monitoring to 45 mg qDay maximum
Monitor ALT at start of treatment, qMonth for 12 months, q3Months thereafter

Pioglitazone	TABLET	15 mg	ORAL	
Pioglitazone	TABLET	30 mg	ORAL	
Pioglitazone	TABLET	45 mg	ORAL	
Pioglitazone+Glimepiride	TABLET		ORAL	Pioglitazone HCl 30 mg+Glimepiride 2 mg
Pioglitazone+Glimepiride	TABLET		ORAL	Pioglitazone HCl 30 mg+Glimepiride 4 mg

Dosage Modification
Coadministration with insulin secretagogue (eg, sulfonylurea): Decrease insulin secretagogue dose
Coadministration with insulin: Decrease insulin dose by 10-25%
Coadministration with strong CYP2C8 inhibitors (eg, gemfibrozil): Limit maximum pioglitazone dose to 15 mg qDay

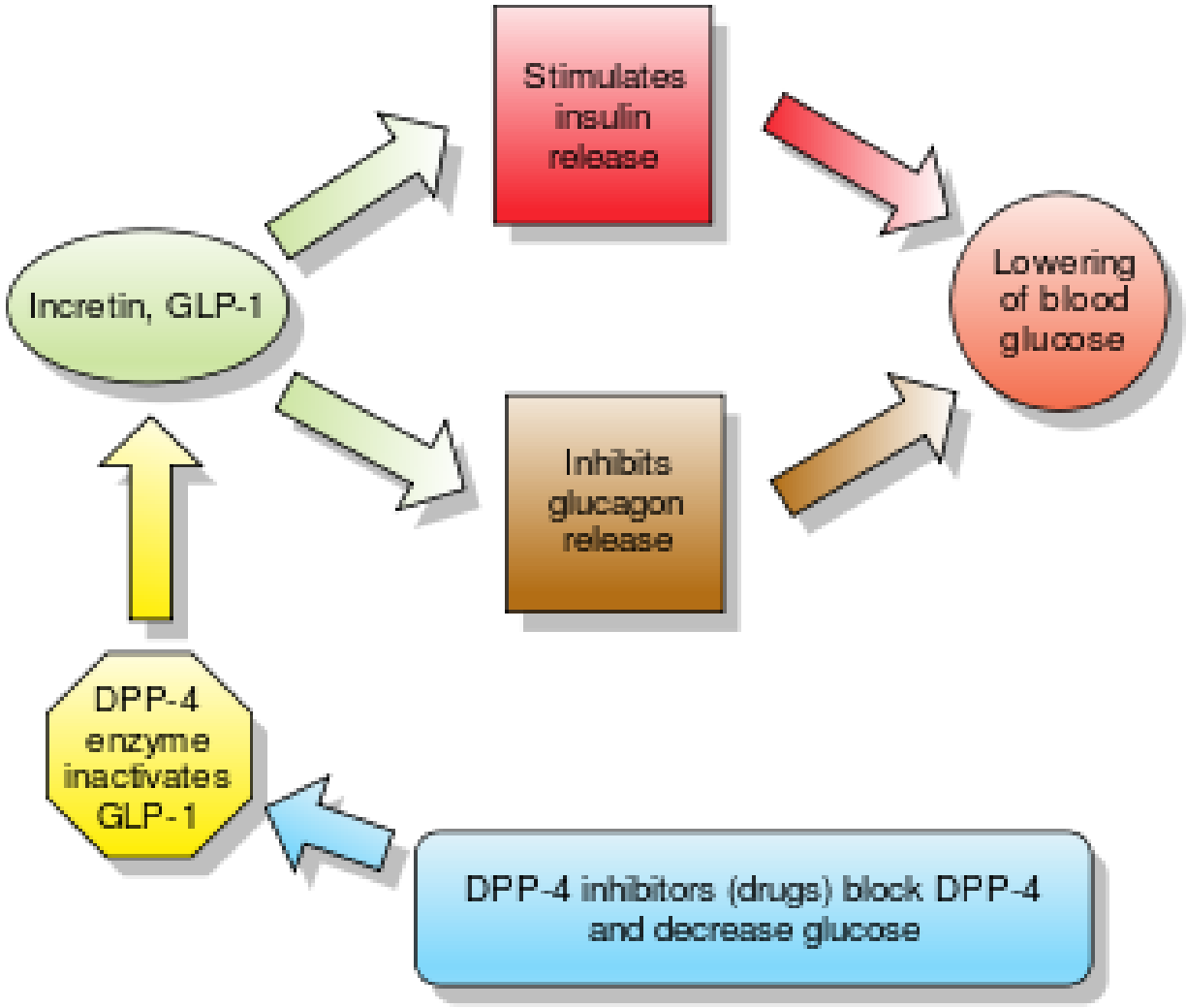
EXENATIDE

- Synthetic analog of glucagon-like-polypeptide 1(GLP-1)
- First incretin therapy
- Injection, adjunctive therapy for type 2 diabetes treated with metformin or metfromin+ sulfonylureas who still have suboptimal glycemic control
- Potentiation of glucose-mediated insulin secretion(increase beta cell mass), suppression of postprandial glucagon release, slowed gastric emptying, central loss of appetite
- Absorbed equally from arm, abdomen or thigh injection site,60 mins before meals SC.
- + sulfonylurea: sulfonylurea doses may need to be decreased to prevent hypoglycemia
- Nausea, vomiting, diarrhea, weigh loss
- Necrotizing and hemorrhagic pancreatitis



Immediate-release: 5mcg Sc q12hr within 60 min prior to meal initially; after one month, may increase to 10 mcg q12hr
Dose adjustment in renal impairment
ER: 2 mg SC per week

Exenatide	**INJECTION, POWDER, EXTENDED RELEASE**	**2 mg**	**PARENTERAL**
Exenatide	INJECTION,	250 mcg/ml	PARENTERAL


Stimulates insulin release
Incretin, GLP-1
Lowering of blood glucose
Inhibits glucagon release
DPP-4 enzyme inactivates GLP-1
DPP-4 inhibitors (drugs) block DPP-4 and decrease glucose

LIRAGLUTIDE

Obesity

- Victoza, Saxenda
- analogue of human glucagonlike peptide-1 (GLP-1Administer SC in abdomen, thigh, or upper arm; rotate injection site
- Administer SC qDay at any time, independent of meals.Must not be administered IV or IM
- 0.6 mg SC qDay for 1 week initially, THEN increase to 1.2 mg qDay
- If glycemic control not achieved, can increase to 1.8 mg qDay
- Unused pens: Refrigerate at 2-8°C; Used injectable pens: Store at room temperature (15-30°C) or refrigerate (2-8°C)
- Victoza: Nausea (26%), Diarrhea (17%), Vomiting (11%)
- Saxenda: Nausea (39.3%), Hypoglycemia in T2DM (23%), Diarrhea (20.9%),Constipation (19.4%), Vomiting (15.7%),
- Headache (13.6%)

Liraglutide	**INJECTION, SOLUTION**	**6 mg/ml**	**PARENTERAL**

SITAGLIPTIN

- Inhibitor of dipeptidyl peptidase-4, the enzyme that degrades incretin and other GLP-1-like molecules
- Increase circulating levels of GLP-1

Decrease postprandial glucose excursions by increasing glucose-mediated insulin secretion and decreasing glucagon levels

- Adverse effects: nasopharyngitis, upper respiratory infection, headaches
- Monotherapy or + metformin or Tzds

Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus 100 mg PO qDay

Dosage Modifications in Renal impairment

Hepatic impairment: Mild to moderate impairment: Dose adjustment not necessary

Sitagliptin	**TABLET**	**25 mg**	**ORAL**	
Sitagliptin	TABLET	50 mg	ORAL	
Sitagliptin	TABLET	100 mg	ORAL	
Sitagliptin+Metformin	TABLET		ORAL	Sitagliptin (as Phosphate) 50 mg+ Metformin Hydrochloride 500 mg
Sitagliptin+Metformin	TABLET		ORAL	Sitagliptin (as Phosphate) 50 mg+ Metformin Hydrochloride 1000 mg
Sitagliptin+Metformin	TABLET. EXTENDED RELEASE		ORAL	Sitagliptin (as Phosphate) 50 mg+ Metformin Hydrochloride 500 mg
Sitagliptin+Metformin	TABLET. EXTENDED RELEASE		ORAL	Sitagliptin (as Phosphate) 50 mg+ Metformin Hydrochloride 1000 mg
Sitagliptin+Metformin	TABLET. EXTENDED RELEASE		ORAL	Sitagliptin (as Phosphate) 100 mg+ Metformin Hydrochloride 1000 mg

LINAGLIPTIN

- Dipeptidyl peptidase 4 (DPP-4) inhibitor; increases and prolongs incretin hormone activity which is inactivated by DPP-4 enzyme
- 5 mg PO qDay
- Hepatic or renal impairment: No dosage adjustment required
- Nasopharyngitis (4.3%), Cough (2.4%; with metformin and sulfonylurea) ,Hypertriglyceridemia (2.4%; with sulfonylurea), Weight gain (2.3%; with pioglitazone), Hypoglycemia (7.6% overall incidence)

Linagliptin	TABLET	5 mg	ORAL	
Linagliptin+Metformin	TABLET		ORAL	Metformin HCL 500 mg + Linagliptin2.5 mg
Linagliptin+Metformin	TABLET		ORAL	Metformin HCL 1000 mg + Linagliptin2.5 mg
Linagliptin+Metformin	TABLET, EXTENDED RELEASE		ORAL	Metformin HCL 1000 mg + Linagliptin 5 mg
Linagliptin+Metformin	TABLET, EXTENDED RELEASE		ORAL	Metformin HCL 1000 mg + Linagliptin 2.5 mg

EMPAGLIFLOZIN

- Selective sodium-glucose transporter-2 (SGLT2) inhibitor
- SGLT2 is expressed in the proximal renal tubules and is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen; SGLT2 inhibitors reduce glucose reabsorption and lower the renal threshold for glucose, thereby increasing urinary glucose excretion

EMPAGLIFLOZIN

- Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes
- Also indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and cardiovascular disease
- 10 mg PO qDay, May increase to 25 mg/day if needed and tolerated

Canagliflozin, also known as Invokana, is a **sodium-glucose cotransporter 2 (SGLT2) inhibitor** used in the management of type 2 diabetes mellitus along with lifestyle changes including diet and exercise.

EMPAGLIFLOZIN

Empagliflozin	TABLET	10 mg	ORAL	
Empagliflozin	TABLET	25 mg	ORAL	
Empagliflozin+Linagliptin	TABLET		ORAL	Empagliflozin 10 mg+Linagliptin 5mg
Empagliflozin+Linagliptin	TABLET		ORAL	Empagliflozin 25 mg+Linagliptin 5mg
Empagliflozin+Metformin	TABLET		ORAL	Empagliflozin 5 mg+Metformin HCl 500 mg
Empagliflozin+Metformin	TABLET		ORAL	Empagliflozin 12.5 mg+Metformin HCl 500 mg
Empagliflozin+Metformin	TABLET		ORAL	Empagliflozin 5 mg+Metformin HCl 1000 mg
Empagliflozin+Metformin	TABLET		ORAL	Empagliflozin 12.5 mg+Metformin HCl 1000 mg
Empagliflozin+Metformin	TABLET, EXTENDED RELEASE		ORAL	Empagliflozin 10 mg+Metformin HCl 1000 mg
Empagliflozin+Metformin	TABLET, EXTENDED RELEASE		ORAL	Empagliflozin 25 mg+Metformin HCl 1000 mg
Empagliflozin+Metformin	TABLET, EXTENDED RELEASE	Empagliflozin 5 mg+Metformin HCl 1000 mg	ORAL	Empagliflozin 5 mg+Metformin HCl 1000 mg
Empagliflozin+Metformin	TABLET, EXTENDED RELEASE	Empagliflozin 12.5 mg+Metformin HCl 1000 mg	ORAL	Empagliflozin 12.5 mg+Metformin HCl 1000 mg
Empagliflozin+ Linagliptin+ Metformin	TABLET, EXTENDED RELEASE		ORAL	Empagliflozin 5mg+ Linagliptin 2.5 mg+ Metformin 1000 mg
Empagliflozin+ Linagliptin+ Metformin	TABLET, EXTENDED RELEASE		ORAL	Empagliflozin 10 mg+ Linagliptin 5 mg+ Metformin 1000 mg
Empagliflozin+ Linagliptin+ Metformin	TABLET, EXTENDED RELEASE		ORAL	Empagliflozin 12.5 mg+ Linagliptin 2.5 mg+ Metformin 1000mg
Empagliflozin+ Linagliptin+ Metformin	TABLET, EXTENDED RELEASE		ORAL	Empagliflozin 25 mg+ Linagliptin 5 mg+ Metformin 1000mg

PRAMLINTIDE

- Synthetic analog of amylin
- Injectable antihyperglycemic agent that modulates postprandial glucose levels and approved for preprandial use in type 1 and 2 diabetes
- With insulin for better postprandial glucose control
- Suppress glucagon release
- Delays gastric emptying
- CNS –mediated anorectic effects
- SC ,immediately before meals
- Hypoglycemia, GI symptoms(nausea, vomiting, anorexia)

COMBINATION THERAPY—ORAL ANTIDIABETIC AGENTS & INJECTABLE MEDICATION

Combination Therapy in Type 2 Diabetes Mellitus

Progressive decrease in beta-cell mass, reduction in physical activity, decline in lean body mass or increase in ectopic fast deposition

First line: a biguanides

Second line therapy: a biguanides + a second agent (Insuline secretagogue,Tzd, incretin-based therapy, amylin analog or a glucosidase inhibitors) or insulin is added

Third line therapy: biguanide, multiple other oral medication or a noninsulin injectable and a biguanide and intesified insulin therapy

Fourth line : intensified insulin management with or without a biguanide or Tzd

Combination therapy in Type 1 Diabetes Mellitus

- Not approved: insulin secretagogues, Tzds, biguanides, alpha-glucosidase inhibitors, incretin-based agents
- Approved: pramlintide for concurrent mealtime administration in individuals with type 1 diabetes who have poor glucose control after eating
- Pramlintide leads to significant reduction in early postorandial glucose excursion
- Insulin dose reduced to prevent hypoglycemia

SUMMARY Drugs Used for Diabetes[1]

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
INSULINS				
• Rapid-acting: Lispro, aspart, glulisine • Short-acting: Regular • Intermediate-acting: NPH • Long-acting: Detemir, glargine	Activate insulin receptor	Reduce circulating glucose • promote glucose transport and oxidation, glycogen, lipid, protein synthesis, and regulation of gene expression	Type 1 and type 2 diabetes	Parenteral (subcutaneous or intravenous) • duration varies (see text) • *Toxicity:* Hypoglycemia, weight gain, lipodystrophy (rare)
SULFONYLUREAS				
• Glipizide • Glyburide • Glimepiride	Insulin secretagogue: Close K^+ channels in beta cells • increase insulin release	In patients with functioning beta cells, reduce circulating glucose • increase glycogen, fat, and protein formation • gene regulation	Type 2 diabetes	Orally active • duration 10–24 h • *Toxicity:* Hypoglycemia, weight gain
• *Tolazamide, tolbutamide, chlorpropamide: Older sulfonylureas, lower potency, greater toxicity; rarely used*				
GLITINIDES				
• Repaglinide	Insulin secretagogue: Similar to sulfonylureas with some overlap in binding sites	In patients with functioning beta cells, reduces circulating glucose • increases glycogen, fat, and protein formation • gene regulation	Type 2 diabetes	Oral • very fast onset of action • duration 5–8 h • *Toxicity:* Hypoglycemia
• Nateglinide	Insulin secretagogue: Similar to sulfonylureas with some overlap in binding sites	In patients with functioning beta cells, reduces circulating glucose • increases glycogen, fat, and protein formation • gene regulation	Type 2 diabetes	Oral • very fast onset and short duration (< 4 h) • *Toxicity:* Hypoglycemia
BIGUANIDES				
• Metformin	Obscure: Reduced hepatic and renal gluconeogenesis	Decreased endogenous glucose production	Type 2 diabetes	Oral • maximal plasma concentration in 2–3 h • *Toxicity:* Gastrointestinal symptoms, lactic acidosis (rare) • cannot use if impaired renal/hepatic function • congestive heart failure (CHF), hypoxic/acidotic states, alcoholism
ALPHA-GLUCOSIDASE INHIBITORS				
• Acarbose, miglitol	Inhibit intestinal α-glucosidases	Reduce conversion of starch and disaccharides to monosaccharides • reduce postprandial hyperglycemia	Type 2 diabetes	Oral • rapid onset • *Toxicity:* Gastrointestinal symptoms • cannot use if impaired renal/hepatic function, intestinal disorders
THIAZOLIDINEDIONES				
• Rosiglitazone	Regulates gene expression by binding to PPAR-γ	Reduces insulin resistance	Type 2 diabetes	Oral • long-acting (> 24 h) • *Toxicity:* Fluid retention, edema, anemia, weight gain, macular edema, bone fractures in women • cannot use if CHF, hepatic disease • may worsen heart disease
• Pioglitazone	Regulates gene expression by binding to PPAR-γ and PPAR-α	Reduces insulin resistance	Type 2 diabetes	Oral • long-acting (> 24 h) • *Toxicity:* Fluid retention, edema, anemia, weight gain, macular edema, bone fractures in women • cannot use if CHF, hepatic disease

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
INCRETIN-BASED DRUGS				
• Exenatide	Analog of GLP-1: Binds to GLP-1 receptors	Reduces post-meal glucose excursions: increases glucose-mediated insulin release, lowers glucagon levels, slows gastric emptying, decreases appetite	Type 2 diabetes	Parenteral (subcutaneous) • half-life ~2.4 h • *Toxicity:* Nausea, headache, vomiting, anorexia, mild weight loss, pancreatitis
• Sitagliptin	DPP-4 inhibitor: Blocks degradation of GLP-1, raises circulating GLP-1 levels	Reduces post-meal glucose excursions: Increases glucose mediated insulin release, lowers glucagon levels, slows gastric emptying, decreases appetite	Type 2 diabetes	Oral • half-life ~12 h • 24-h duration of action • *Toxicity:* Rhinitis, upper respiratory infections, rare allergic reactions
AMYLIN ANALOG				
• Pramlintide	Analog of amylin: Binds to amylin receptors	Reduces post-meal glucose excursions: Lowers glucagons levels, slows gastric emptying, decreases appetite	Type 1 and type 2 diabetes	Parenteral (subcutaneous) • rapid onset • half-life ~ 48 min • *Toxicity:* Nausea, anorexia, hypoglycemia, headache


THANKS FOR YOUR
ATTENTION