Al-Mustaqbal University
College of Pharmacy
4th stage
Pharmacology III
Lecture: 1

Drugs for Diabetes

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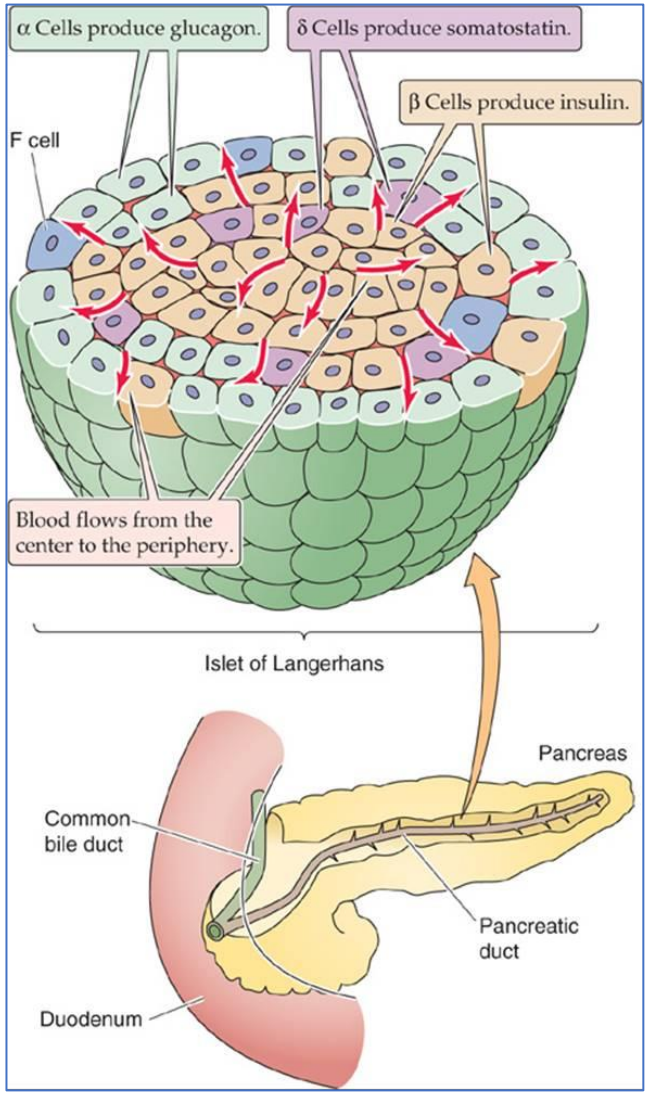
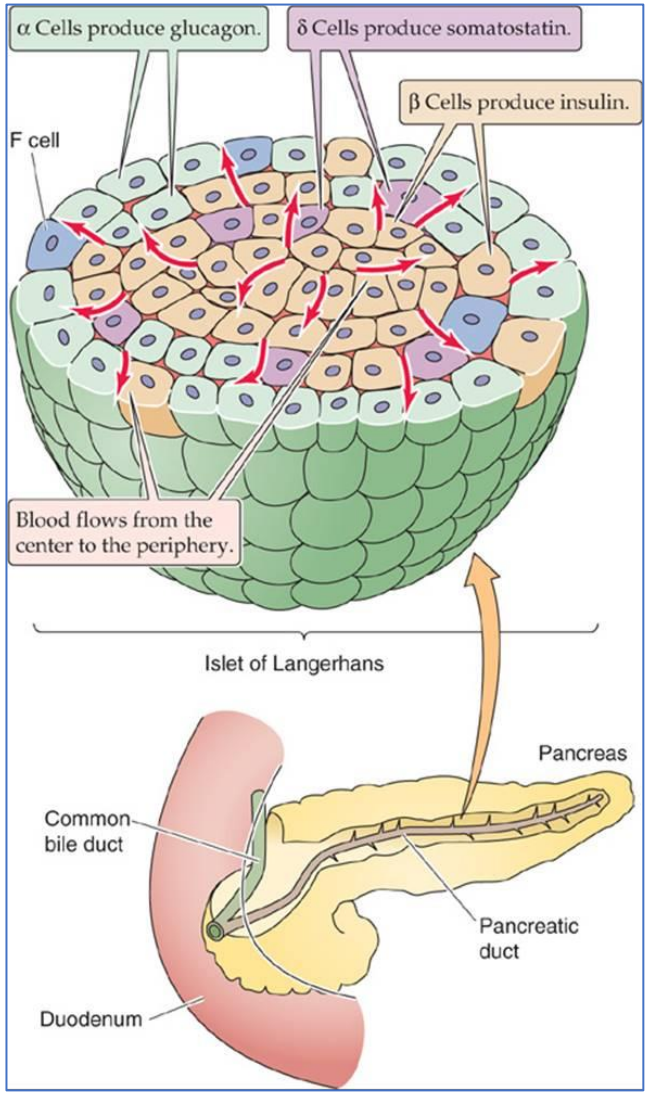
OVERVIEW

- The **pancreas** produces the peptide hormones **insulin**, **glucagon**, and **somatostatin**.
- The peptide hormones are secreted from cells in the islets of Langerhans (**β-cells** produce insulin, **α-cells** produce glucagon, and **δ-cells** produce somatostatin).
- These hormones play an important role in **regulating metabolic activities** of the body, particularly glucose homeostasis.
- A **relative** or **absolute lack** of **insulin**, as seen in **DM**, can cause serious **hyperglycemia**.
- Left untreated, **retinopathy, nephropathy, neuropathy**, and **CVS** complications may result.



OVERVIEW

- **Administration** of insulin preparations or other glucose-lowering agents can **reduce morbidity** and **mortality** associated with diabetes.
- The **incidence** of diabetes is **growing rapidly** in the United States and worldwide.
- An estimated **30.3 million** people in the **United States** and **422 million** people worldwide are afflicted with diabetes.



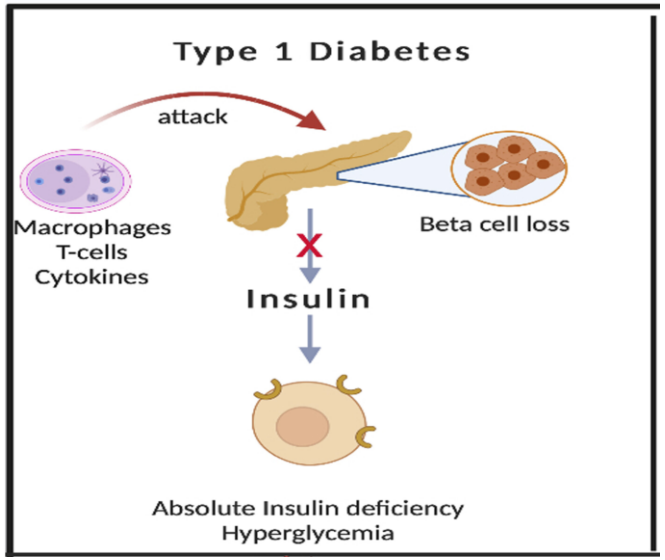
DIABETES MELLITUS

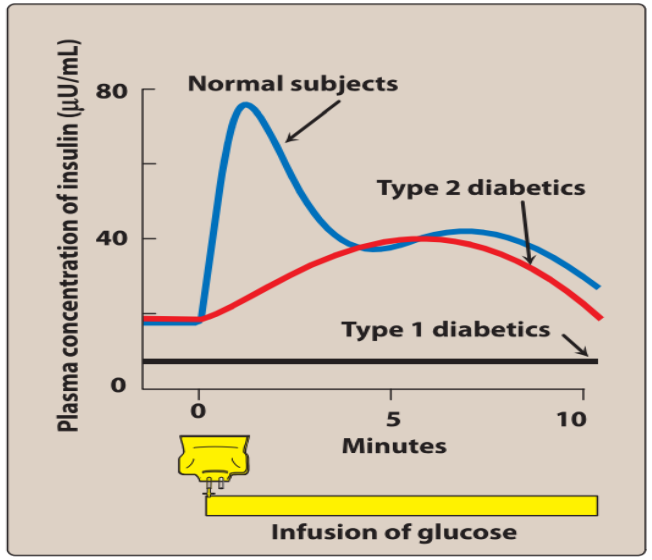
- Diabetes is **not a single disease**, rather, it is a heterogeneous group of syndromes.
- It is characterized by **elevated blood glucose** attributed to a **relative** or **absolute** deficiency of insulin.
- The American Diabetes Association (**ADA**)recognizes **four clinical classifications** of diabetes:
- **Type 1, type 2, gestational**, and **diabetes due to other causes** such as genetic defects or medications.
- **Gestational diabetes** is defined as **carbohydrate intolerance** with **onset** or **first** recognition during **pregnancy**.

	Type 1	Type 2
Age at onset	Usually during childhood or puberty	Commonly over age 35
Nutritional status at time of onset	Commonly undernourished	Obesity usually present
Prevalence among diagnosed diabetics	5%–10%	90%–95%
Genetic predisposition	Moderate	Very strong
Defect or deficiency	β Cells are destroyed, eliminating the production of insulin	Inability of β cells to produce appropriate quantities of insulin; insulin resistance; other defects

Type 1 diabetes

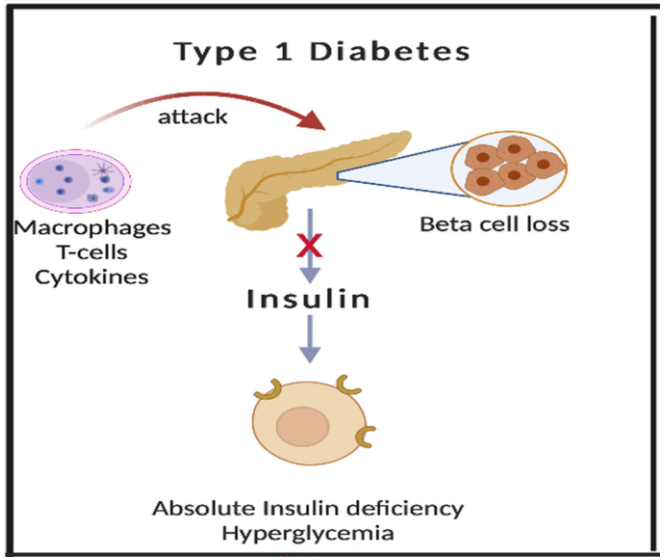
- Type 1 diabetes most **commonly** afflicts **children, adolescents, or young adults**, **but** some latent forms occur **later in life**.
- The disease is **characterized** by an **absolute deficiency** of insulin due to the **destruction** of β cells.
- **Without** functional β cells, the pancreas **fails** to respond to glucose.
- A person with type 1 diabetes shows **classic symptoms** of insulin deficiency (**polydipsia, polyphagia, polyuria, and weight loss**).

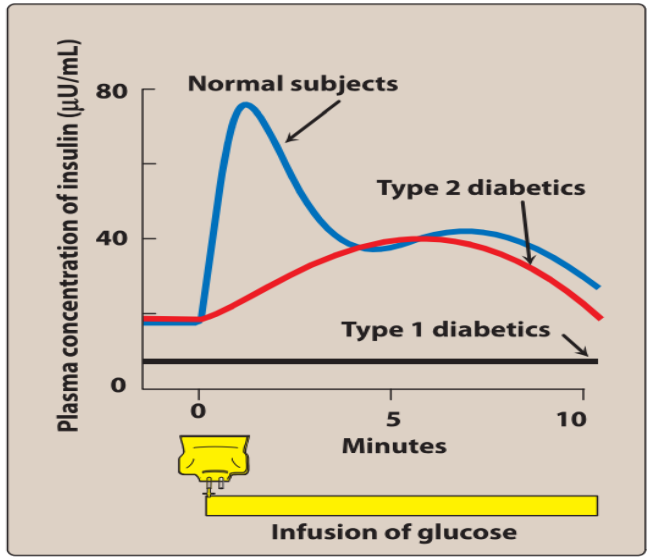




Type 1 diabetes Cause

- Loss of beta-cell function in type 1 diabetes results from **autoimmune-mediated processes** that may be **triggered** by **viruses** or other environmental **toxins**.
- In persons **without diabetes**, constant beta-cell secretion **maintains low basal levels** of circulating insulin, which **suppresses** lipolysis, proteolysis, and glycogenolysis.
- A **burst** of insulin secretion occurs within **2 minutes** after ingesting a meal, in response to **transient increases** in circulating **glucose and amino acids**.
- This **lasts for up to 15 minutes**, followed by the **postprandial** secretion of insulin.
- However, without functional beta-cells, those with **type 1** diabetes can **neither maintain basal secretion** of insulin **nor respond** to variations in circulating **glucose**.

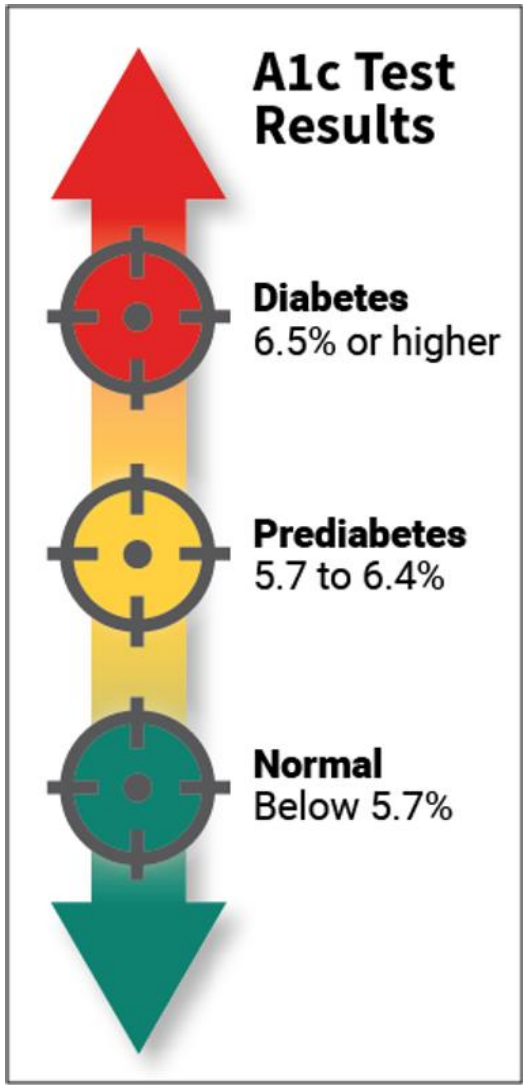




Type 1 diabetes Treatment

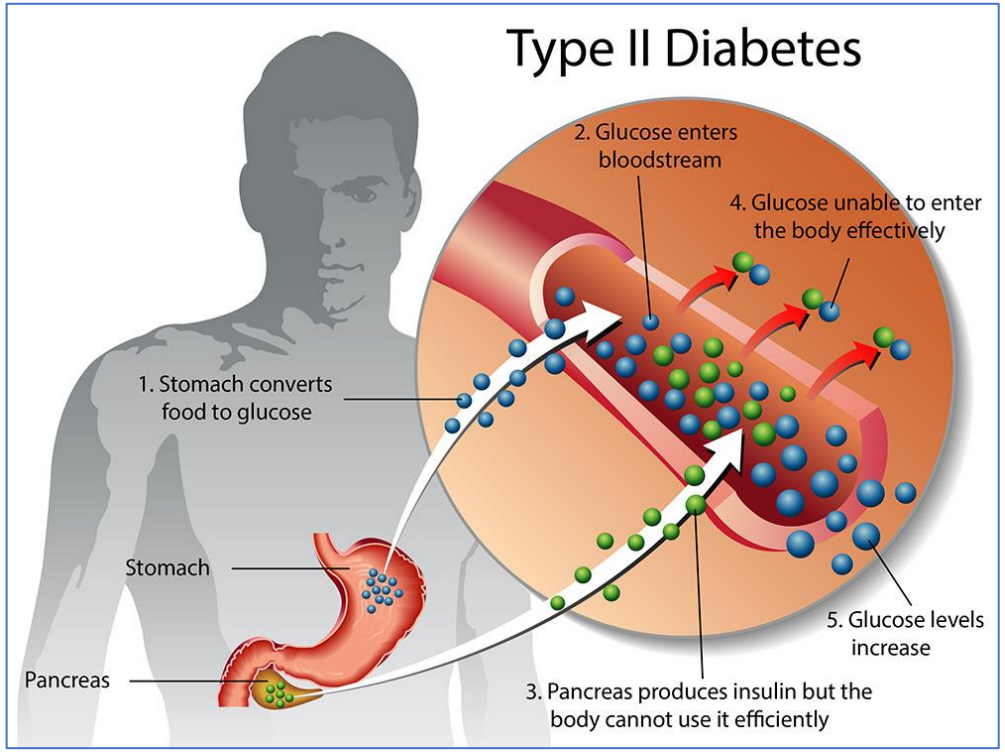
- A person with type 1 diabetes must rely on **exogenous insulin** to **control hyperglycemia**, **avoid ketoacidosis**, and **maintain** acceptable levels of glycosylated hemoglobin (**HbA1c**).
- The goal of insulin therapy in type 1 diabetes is to maintain blood glucose as close to normal as possible and to avoid wide fluctuations in glucose.
- The use of **home** blood glucose **monitors** facilitates frequent **self-monitoring** and treatment with insulin.

- [Note: **HbA1c** is a **marker** of overall glucose control and is used to monitor diabetes in clinical practice. The **rate of formation** of HbA1c is **proportional** to the **average** blood glucose conc. over the previous **3 months**. A higher average glucose results in a higher HbA1c·]



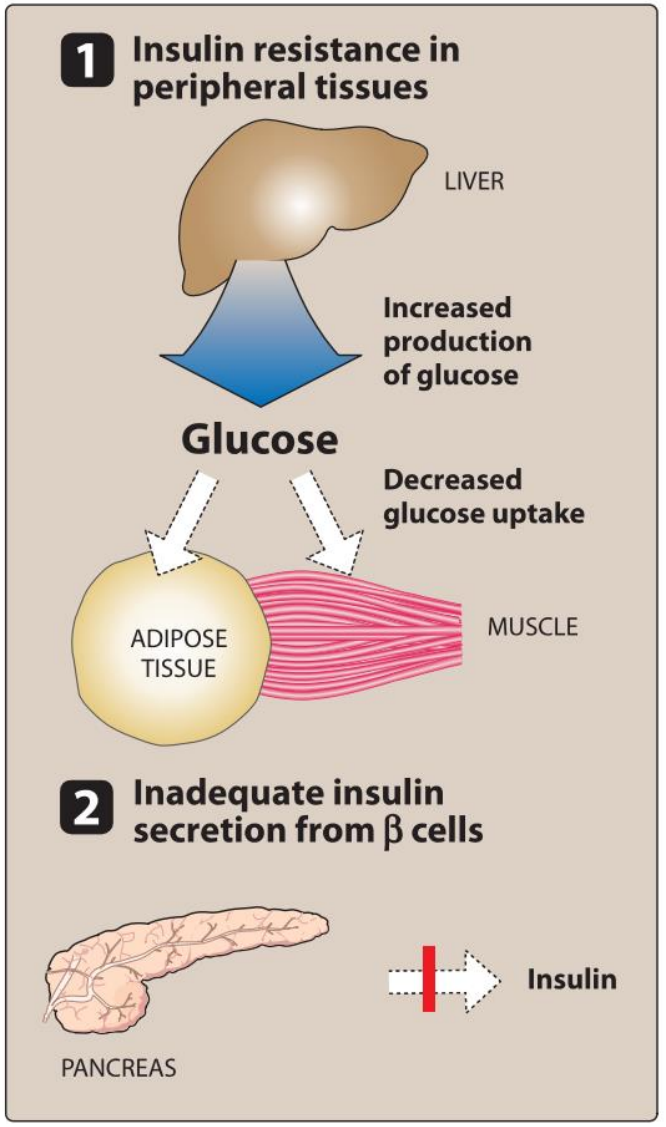
Type 2 diabetes

- Type 2 diabetes accounts for greater than **90%** of cases.
- Type 2 diabetes is **influenced** by genetic factors, aging, obesity, and peripheral insulin resistance, **rather** than **autoimmune** processes.
- The **metabolic alterations** are generally **milder than** those observed in **type 1** diabetes (for example, patients with type 2 diabetes typically are **not ketotic**), but the **long-term** clinical consequences are **similar**.



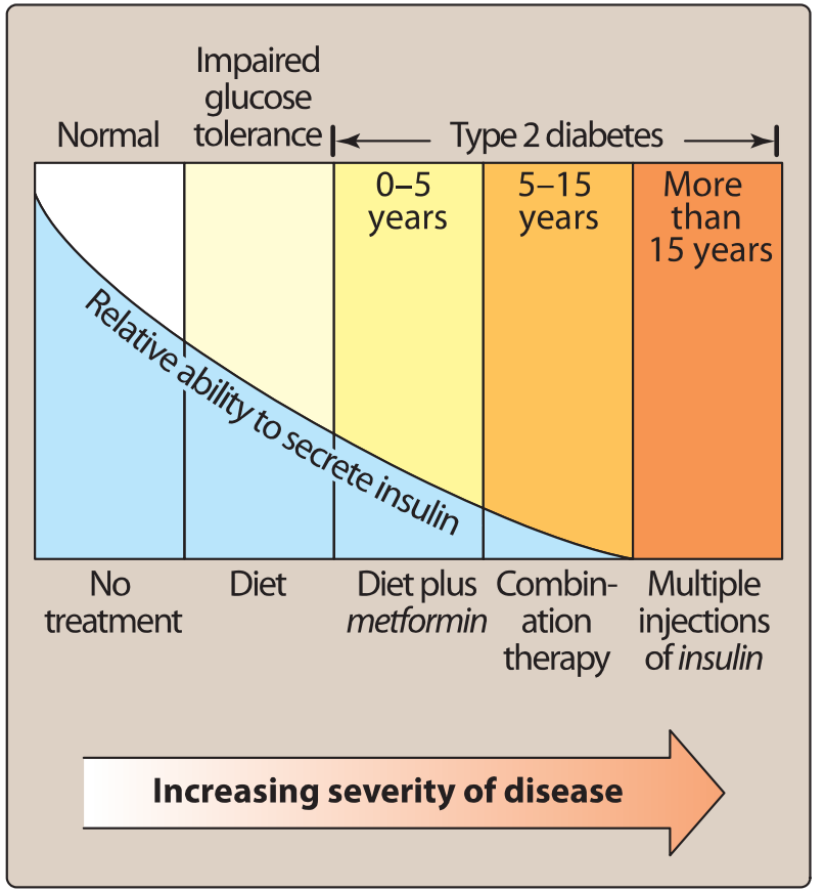
Type 2 diabetes Cause

- **Type 2 diabetes** is characterized by a **lack of sensitivity** of target organs to insulin.
- In type 2 diabetes, the pancreas retains some beta-cell function, **but** insulin secretion is insufficient to maintain glucose homeostasis in the face of **increasing peripheral insulin resistance**.
- The **beta-cell mass may gradually decline** over time in type 2 diabetes.
- In **contrast** to patients with **type 1** diabetes, those with **type 2** diabetes are often **obese**.
- **Obesity** contributes to **insulin resistance**, which is considered the major underlying defect of type 2 diabetes.



Type 2 diabetes Treatment

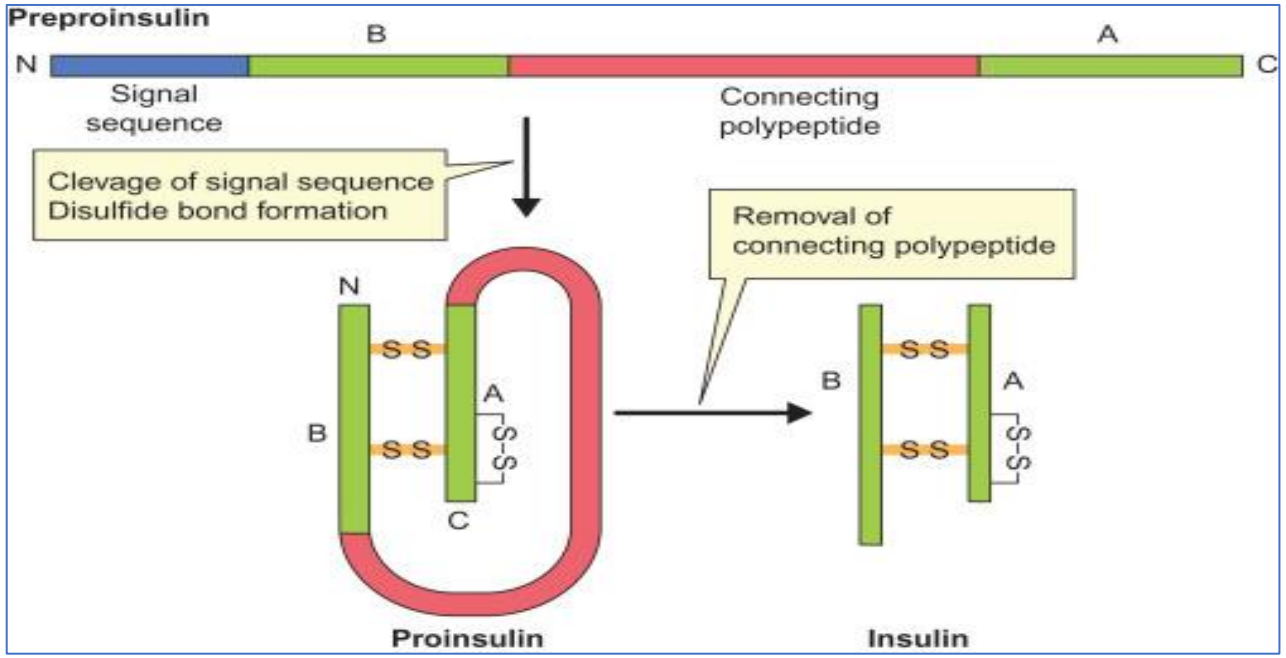
- The **goal** in treating type 2 diabetes is to **maintain blood glucose** within normal limits and to **prevent** the development of long-term **complications**.
- Weight reduction, exercise, and dietary modification **decrease insulin resistance** and **correct hyperglycemia** in some patients with type 2 diabetes.
- However, **most** patients require **pharmacologic intervention** with oral glucose-lowering agents.
- As the disease **progresses**, beta-cell function **declines**, and **insulin** therapy is often **needed** to achieve satisfactory glucose levels.



Insulin Synthesis

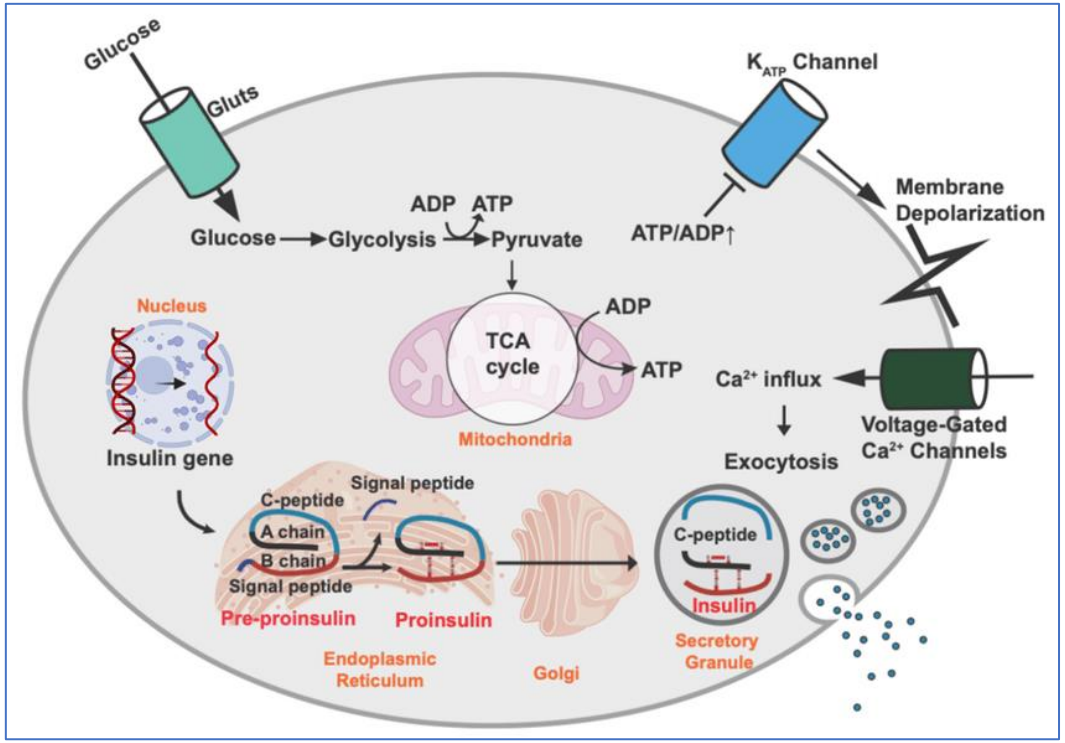
- **Insulin** is a **polypeptide** hormone consisting of **two peptide chains** that are connected by **disulfide** bonds.
- It is synthesized as a precursor (**proinsulin**) that undergoes **proteolytic cleavage** to form **insulin** and **C-peptide**, both of which are **secreted by the beta cells** of the pancreas.
- [**Note**: Because insulin undergoes significant hepatic and renal extraction, plasma insulin levels may not accurately reflect insulin production. Thus, measurement of C-peptide provides a better index of insulin levels.]
- **Insulin secretion is regulated** by:

1. blood **glucose** levels
2. certain **amino acids**
3. other **hormones**
4. **autonomic** mediators



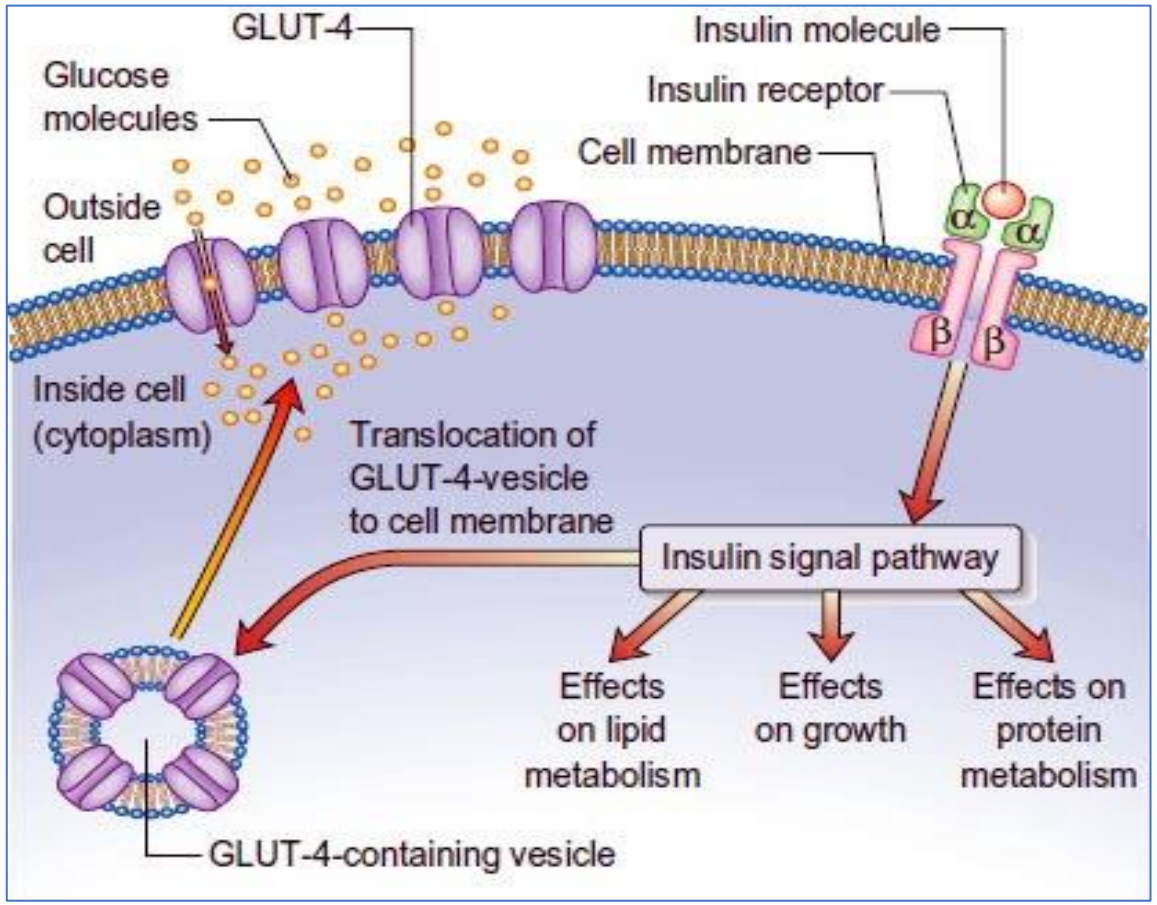
Insulin Release

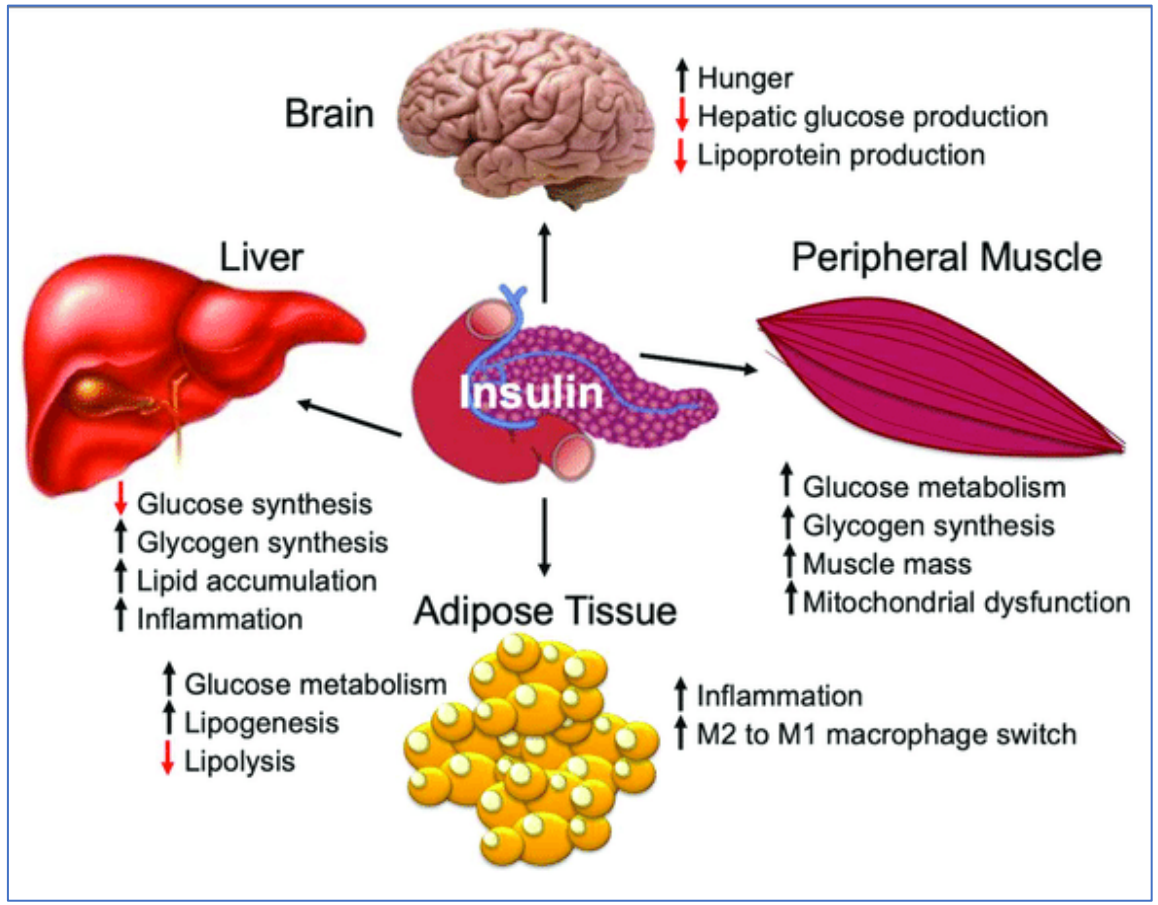
- **Secretion** is most often **triggered by increased blood glucose**, which is taken up by the **glucose transporter** into the **beta cells** of the pancreas.
- There, it is **phosphorylated** by glucokinase, which acts as a glucose sensor.
- The **products** of glucose metabolism enter the mitochondrial respiratory chain and generate **ATP**.
- The **rise in ATP levels** causes a **blockade of K^+ channels**, leading to membrane **depolarization** and an **influx of Ca^{2+}**.
- The increase in intracellular Ca^{2+} causes **pulsatile insulin exocytosis**.



Insulin Mechanism of Action

- **Exogenous** insulin is administered to **replace absent insulin** secretion in **type 1 diabetes** or to **supplement insufficient** insulin secretion in **type 2 diabetes**.



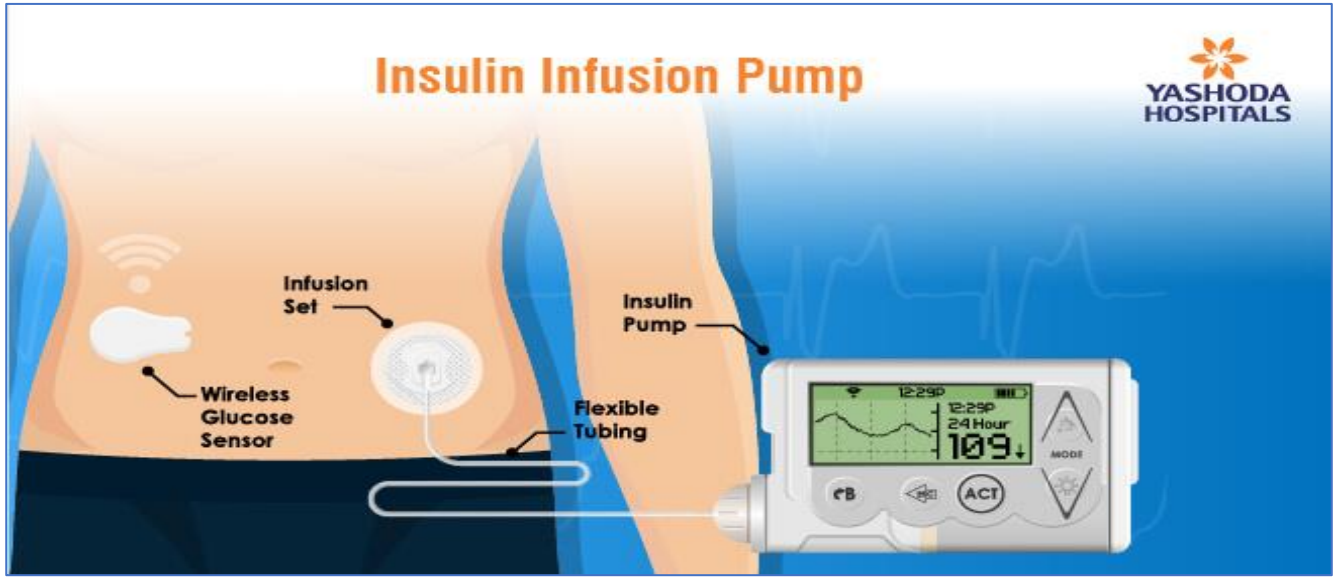


Insulin Pharmacokinetics

- Human insulin is produced by **recombinant DNA technology** using strains of ***Escherichia coli*** or **yeast** that are genetically altered to contain the gene for human insulin.
- **Modification** of the **amino acid sequence** of human insulin produces insulins with different **pharmacokinetic properties**.
- Insulin preparations **vary** primarily in their **onset and duration** of activity.
- **Dose, injection site, blood supply, temperature,** and **physical activity** can also **affect** the **onset** and **duration** of various insulin preparations.
- Because insulin is a **polypeptide**, it is degraded in the GIT if taken **orally**, therefore, it is generally administered by **SC injection**, although an **inhaled** insulin formulation is also available.
- Note: In a hyperglycemic **emergency**, **regular insulin** is administered **intravenously** (IV).

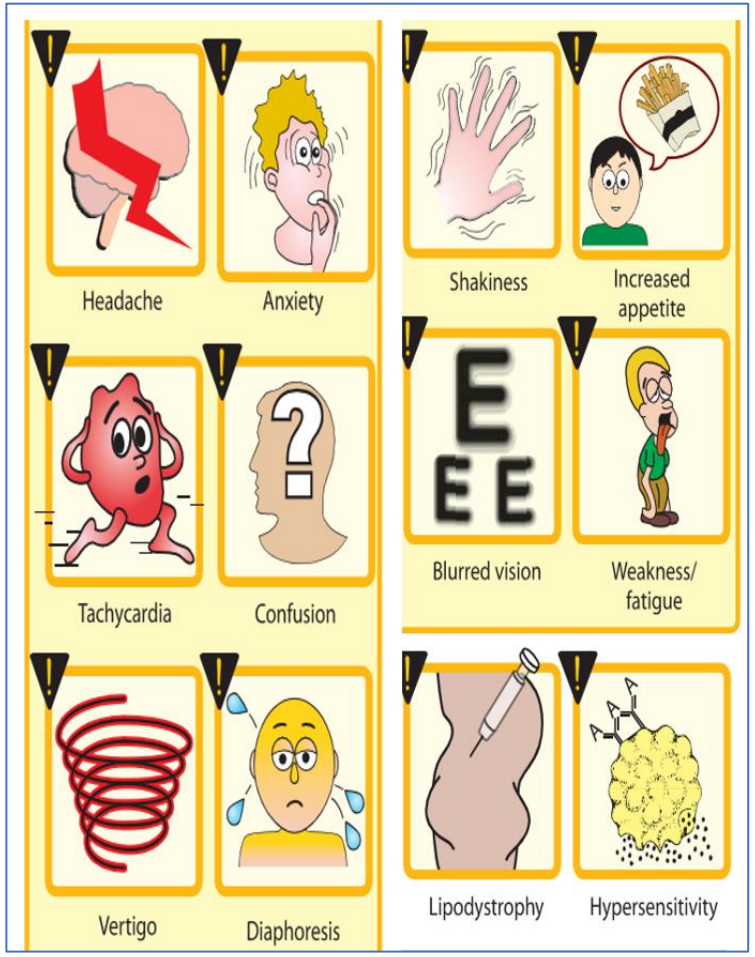
Insulin Pharmacokinetics

- **Continuous** SC insulin infusion (also called the **insulin pump**) is another method of insulin delivery.
- This method of administration may be **more convenient** for some patients, **eliminating multiple** daily injections of insulin.
- The pump is **programmed** to deliver a **basal rate** of insulin.
- In addition, it allows the patient to **deliver a bolus of insulin** to cover mealtime carbohydrate intake and compensate for high blood glucose.



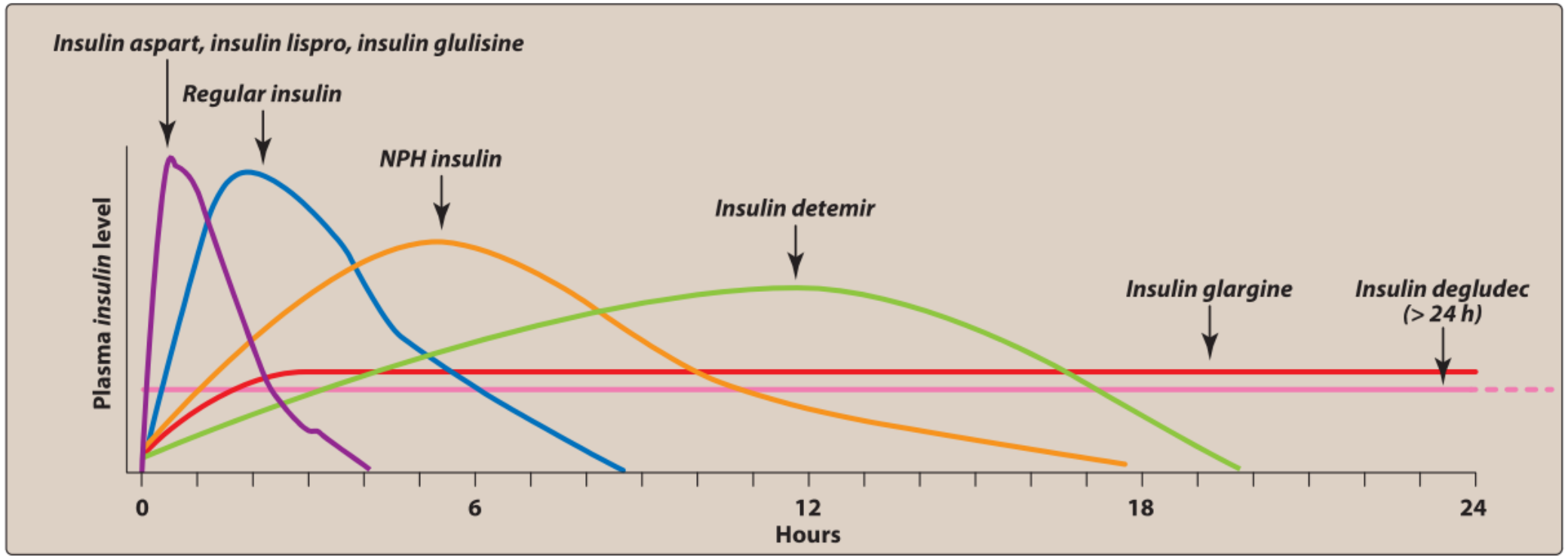
Insulin Adverse Effects

- **Hypoglycemia** is the most serious and common adverse reaction to insulin.
- Other adverse effects include **weight gain, local injection site reactions, and lipodystrophy**.
- **Lipodystrophy** can be **minimized** by rotation of injection sites.
- Diabetics with **renal insufficiency** may require a **decrease in insulin dose**.
- Due to the **potential** for **bronchospasm** with **inhaled insulin**, patients with asthma, COPD, and smokers should **not use this formulation**.



Insulin Preparations and Treatment

- Insulin preparations are classified as **rapid-, short-, intermediate-, or long-acting**.
- They **differ** in the **onset of action, timing of peak level, and duration of action** for the various types of insulin.
- It is important that **clinicians exercise** caution when adjusting insulin treatment, paying strict attention to the **dose and type** of insulin.



1. Rapid-acting and short-acting insulin preparations

- **Five** preparations fall into this category: **regular insulin, insulin lispro, insulin aspart, insulin glulisine, and inhaled insulin**.
- **Regular** insulin is a **short-acting**, **soluble**, **crystalline zinc** insulin.
- **Insulin lispro, aspart, and glulisine** are classified as **rapid-acting** insulins.
- **Modification** of the amino acid sequence of **regular insulin** produces analogs that are **rapid-acting insulins**.
- This modification results in more **rapid absorption, a quicker onset, and a shorter duration** of action after SC injection.

1. Rapid-acting and short-acting insulin preparations

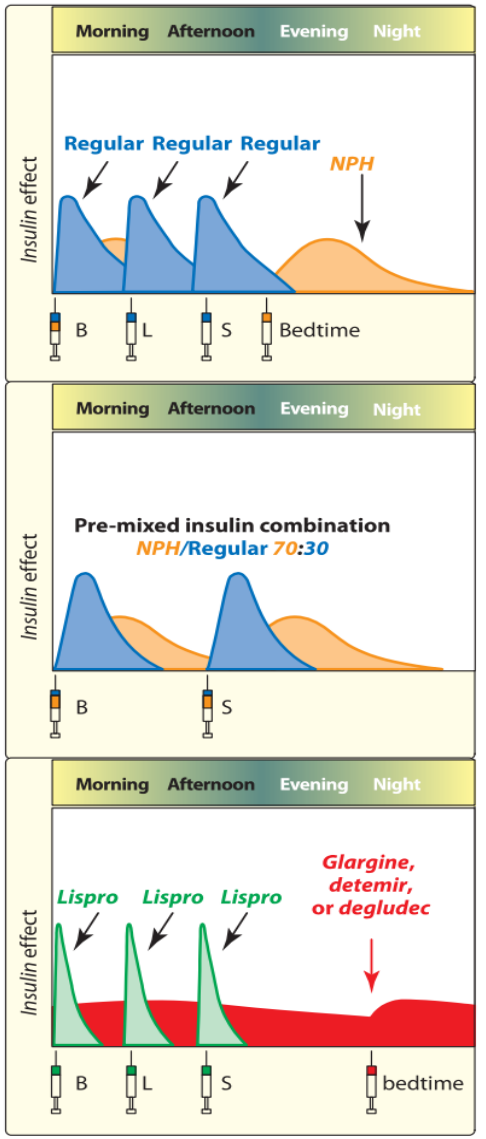
- **Peak levels** of insulin **lispro** are seen at **30 to 90 minutes**, as compared with **50 to 120 minutes** for **regular** insulin.
- Insulin **aspart** and insulin **glulisine** have pharmacokinetic and pharmacodynamic properties similar to those of insulin **lispro**.
- **Inhaled** insulin is also considered **rapid-acting**.
- This dry powder formulation is inhaled and absorbed through **pulmonary** tissue, with **peak levels** achieved within **45 to 60 minutes**.

1. Rapid-acting and short-acting insulin preparations

- **Rapid- or short-acting insulins** are administered to **mimic the prandial** (mealtime) release of **insulins** and to **control postprandial glucose**.
- They may also be used in cases where **swift correction** of elevated glucose is needed.
- Rapid- and short-acting insulins are usually **used in conjunction** with a **longer-acting** basal insulin that provides control of **fasting glucose**.
- **Regular** insulin should be injected SC **30 minutes before a meal**, whereas **rapid-acting** insulins are administered in the **15 minutes preceding** a meal or within **15 to 20 minutes after** starting a meal.
- **Rapid-acting** insulin suspensions are commonly used in external **insulin pumps**, and they are suitable for **IV** administration, although **regular** insulin is most **commonly** used when the **IV** route is needed.

2. Intermediate-acting insulin

- Neutral protamine Hagedorn (**NPH**) insulin is an intermediate-acting insulin **formed by the addition of zinc and protamine to regular insulin**, it is also called **insulin isophane**.
- The combination with **protamine** forms a **complex** that is **less soluble**, resulting in **delayed absorption** and a **longer** duration of action.
- NPH insulin is used for **basal (fasting) control** in **type 1 or 2** diabetes and is usually given along with **rapid- or short-acting** insulin for mealtime control.
- NPH insulin should be given **only subcutaneously (never IV),** and it should **not be used** when **rapid glucose lowering** is needed (for example, diabetic ketoacidosis).

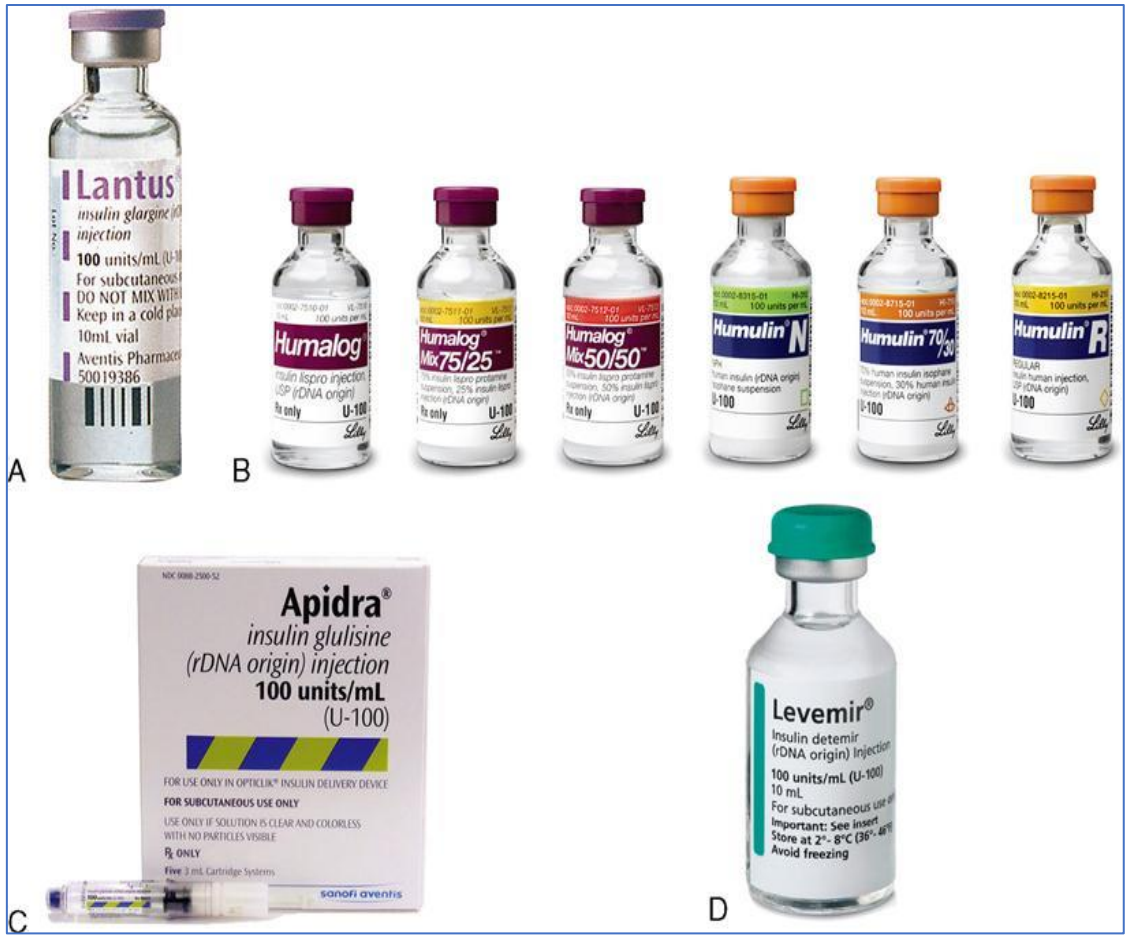


3. Long-acting insulin preparations

- The **isoelectric point** of **insulin glargine** is **lower** than that of human **insulin**, leading to formation of a **precipitate** at the injection site that releases insulin over an extended period.
- It has a **slower onset** than **NPH insulin** and a **flat, prolonged** hypoglycemic effect with **no peak**.
- **Insulin detemir** has a fatty acid side chain that **enhances** association to albumin, leading to **slow dissociation** from albumin results in **long-acting** properties similar to those of insulin glargine.
- **Insulin degludec** remains in solution at physiologic pH, with a **slow release** over an extended period with the **longest half-life** of the long-acting insulins.
- **As with NPH** insulin, insulin glargine, insulin detemir, and insulin degludec are used for **basal control** and should **only** be administered **subcutaneously**.
- Long acting insulins should **not be mixed in the same syringe** with other insulins, because doing so may **alter the pharmacodynamic profile**.

Insulin combinations

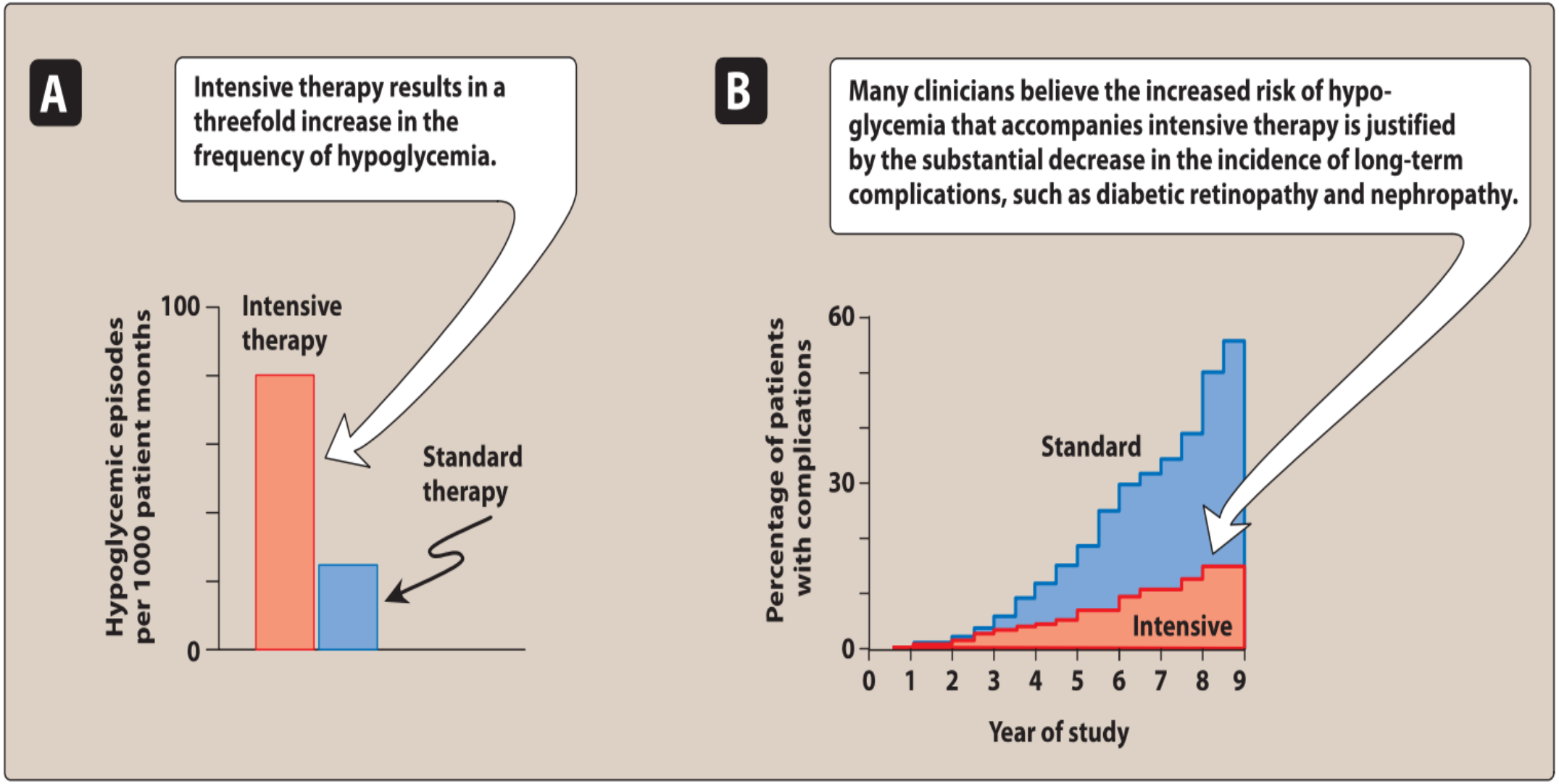
- Various premixed combinations of human insulins, such as **70% NPH insulin plus 30% regular insulin** or **50% of each** of these, are also available.
- **Use of premixed** combinations **decreases** the number of daily injections but **makes it more difficult** to adjust individual components of the insulin regimen.



Standard treatment versus intensive treatment

- **Standard** insulin therapy involves **twice daily injections**. In contrast**, intensive** treatment utilizes **three or more injections** daily with **frequent monitoring** of blood glucose levels.
- The **ADA recommends** a target mean blood glucose level of **154 mg/dl or less (HbA1c ≤7%)** for most patients, and **intensive treatment is more likely to achieve this goal**.
- The **frequency** of hypoglycemic episodes, coma, and seizures is **higher with intensive** insulin regimens.
- However, patients on **intensive** therapy show a **significant reduction in microvascular complications** of diabetes such as retinopathy, nephropathy, and neuropathy compared to patients receiving **standard** care.
- Intensive therapy should **not be recommended** for patients with long-standing diabetes, significant microvascular complications, advanced age, and those with hypoglycemic unawareness.

Standard treatment versus intensive treatment

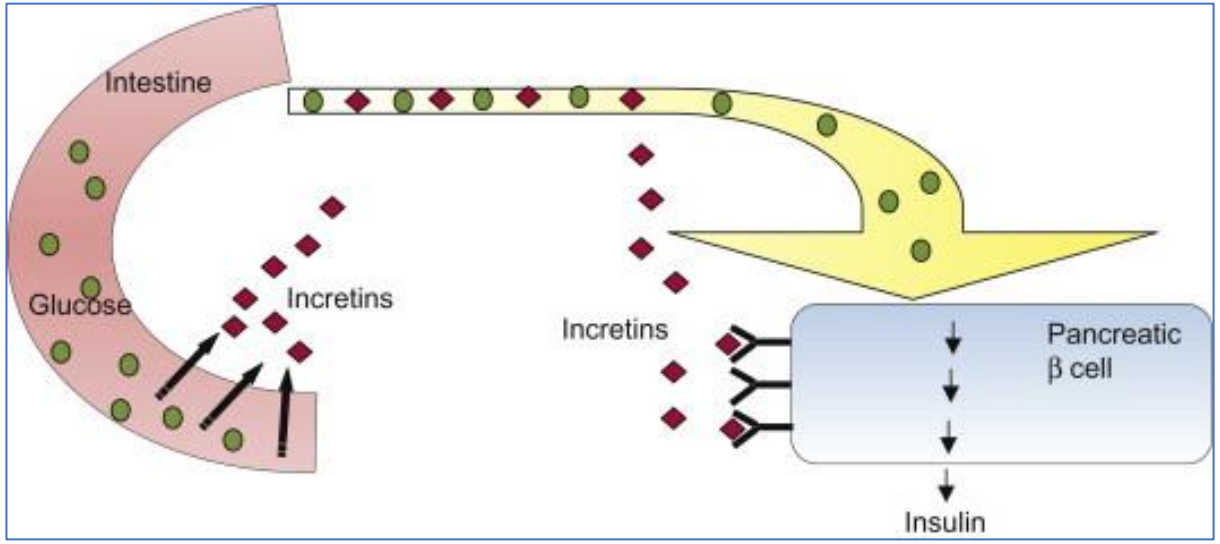


SYNTHETIC AMYLIN ANALOG

- **Amylin** is a hormone that is **co-secreted** with **insulin** from **beta-cells** following food intake.
- It **delays** gastric emptying, **decreases** postprandial glucagon secretion, and **improves** satiety.
- **Pramlintide** is a synthetic **amylin analog** that is indicated as an **adjunct** to mealtime insulin therapy in patients with type **1** and type **2** diabetes.
- Pramlintide is administered by **SC** injection **immediately before** meals.
- When pramlintide is initiated, the **dose** of mealtime **insulin** should be **decreased by 50%** to avoid a risk of **severe hypoglycemia**.
- Other adverse effects include nausea, anorexia, and vomiting.
- Pramlintide may **not be mixed** in the same syringe with insulin, and it should **be avoided** in patients with **diabetic gastroparesis** (delayed stomach emptying), **cresol hypersensitivity**, or **hypoglycemic unawareness**.

GLUCAGON-LIKE PEPTIDE RECEPTOR AGONISTS

- **Oral intake of glucose** results in a **higher** secretion of **insulin** than occurs when an **equal load of glucose** is given **IV**.
- This effect is referred to as the **"incretin effect'** and is markedly **reduced** in type **2 diabetes**.
- The incretin effect occurs because the **gut releases incretin** hormones, notably glucagon-like peptide-1 (**GLP-1**) and glucose-dependent insulinotropic polypeptide (**GIP**), in response to a **meal**.
- **Incretin** hormones are responsible for **60% to 70%** of postprandial **insulin secretion**.



GLUCAGON-LIKE PEPTIDE (GLP-1) RECEPTOR AGONISTS

- Albiglutide, dulaglutide,exenatide, liraglutide, lixisenatide, & semaglutide are **injectable GLP-1 receptor agonists** used for the treatment of **type 2 diabetes**.
- **Liraglutide** is also **approved** to reduce the risk of CVS events and CVS mortality in patients with type 2 diabetes and CVS disease.
- **Two premixed** preparations of long-acting insulins and GLP-1 receptor agonists are available: **insulin glargine plus lixisenatide** and **insulin degludec plus liraglutide**.
- **Use** of these combinations may **decrease** daily insulin requirements and the number of daily injections.

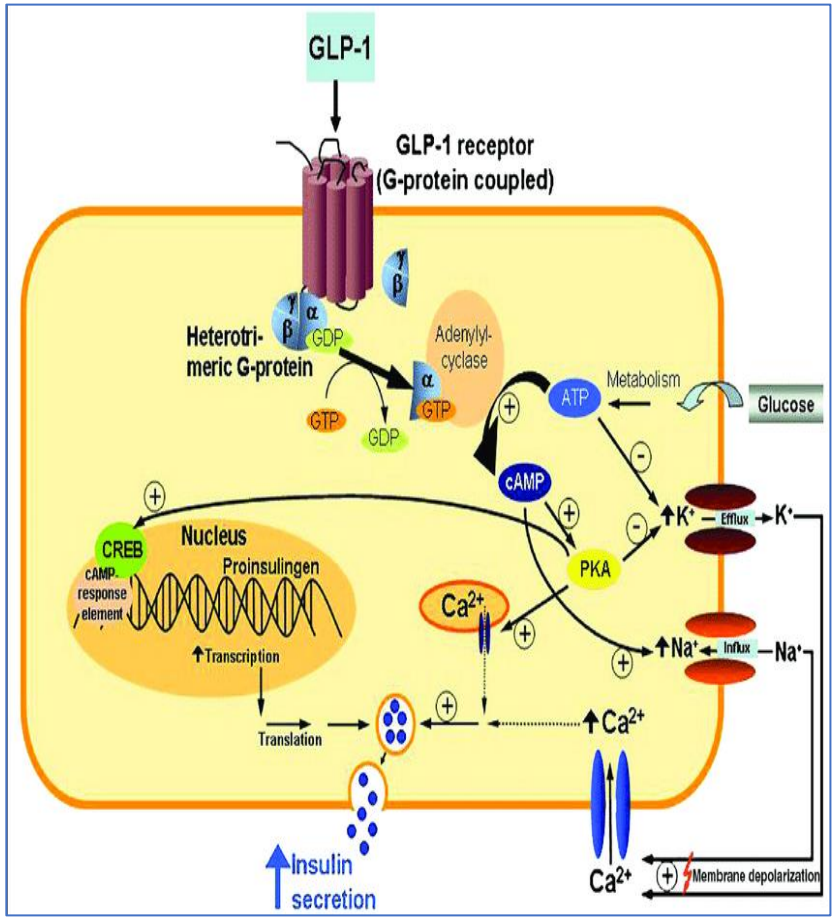
GLUCAGON-LIKE PEPTIDE RECEPTOR AGONISTS

Mechanism of action:

- These agents are **analogs of GLP-1** that exert their activity by

1. improving glucose-dependent **insulin secretion**
2. slowing **gastric emptying** time
3. reducing **food intake** by enhancing **satiety** (a feeling of fullness)
4. decreasing **postprandial glucagon** secretion
5. promoting **B-cell proliferation**

- **Consequently**, postprandial hyperglycemia is reduced, HbA1c levels decline, and weight loss may occur.



GLUCAGON-LIKE PEPTIDE RECEPTOR AGONISTS

Pharmacokinetics:

- GLP-1 receptor agonists are **administered SC,** since they are **polypeptides**.
- **Albiglutide, dulaglutide, liraglutide,** and **semaglutide** are considered **long-acting** GLP-1 receptor agonists.
- **Albiglutide, dulaglutide, and semaglutide** are dosed **once weekly**, while **liraglutide** is available as a **once-daily** injection.
- **Lixisenatide** is a **short-acting** GLP-1 receptor agonist that is dosed **once daily**.
- **Exenatide** is available as both a **short-acting** (dosed twice daily) and **extended-release** preparation (dosed once weekly).
- **Exenatide** should be **avoided** in patients with severe **renal impairment**.

GLUCAGON-LIKE PEPTIDE RECEPTOR AGONISTS

Adverse effects:

- The main adverse effects of the incretin mimetics consist of **nausea, vomiting, diarrhea, and constipation**.
- GLP-1 receptor agonists have been associated with **pancreatitis** and should be **avoided** in patients with chronic pancreatitis.
- **Longer-acting** agents have been associated with **thyroid C-cell tumors in rodents**.
- It is **unknown** if GLP-1 receptor agonists cause these tumors or thyroid carcinoma **in humans**,
- Although they are **contraindicated** in patients with a history of **medullary thyroid carcinoma** or **multiple endocrine neoplasia type 2**.

THANK YOU FOR YOUR ATTENTION