DEMYSTIFYING DIABETES:
PATHOPHYSIOLOGY OF DIABETES MELLITUS

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Introduction:

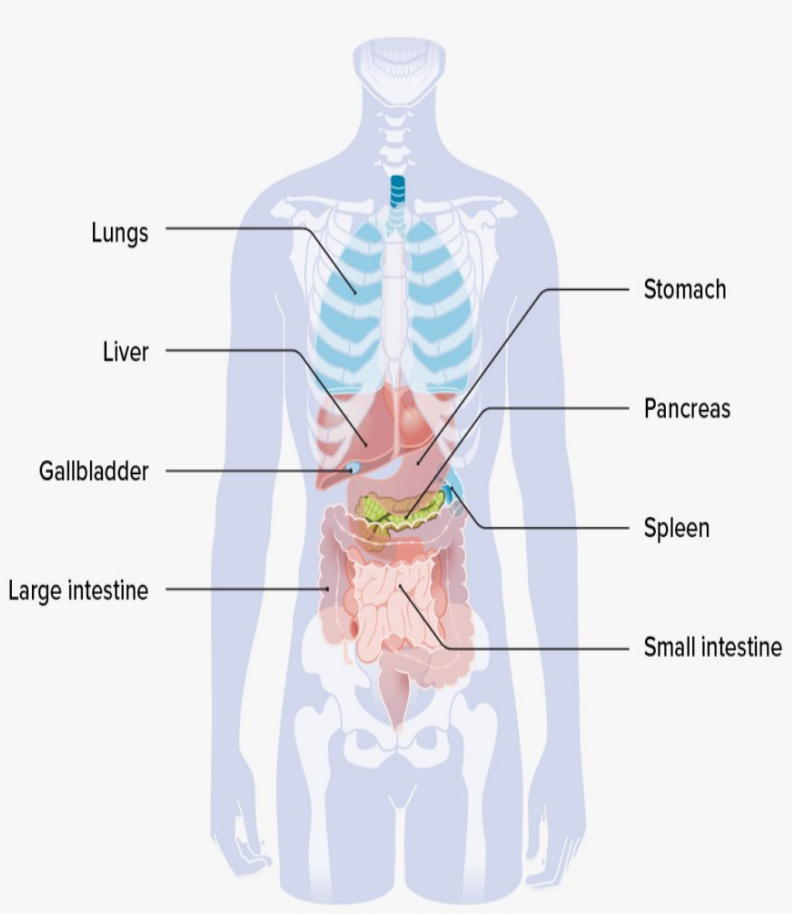
- Diabetes mellitus impacts society through significant economic, social, and health burdens, leading to increased healthcare costs, decreased productivity, and a lower quality of life.
- It contributes to high mortality rates from complications like kidney disease and cardiovascular issues, causes psychological distress and social stigma, and disproportionately affects disadvantaged communities.
- The rise in diabetes cases, particularly in lower-income countries, highlights the need for urgent public health interventions and research

Key statistics for 2024

- **Adults with diabetes:** 89.8 million (ages 20–79)
- **Type 2 diabetes:** An estimated 77 million adults
- **Prediabetes:** An estimated 25 million adults
- **Global impact:** One in four people globally with diabetes is from India
- **undiagnosed cases:** More than half of people with diabetes are unaware of their condition

Why to know about Pancreas:

- The pancreas is directly linked to diabetes mellitus because it produces insulin, a hormone that regulates blood sugar.
- In diabetes, the pancreas either doesn't make enough insulin or the body can't use the insulin it produces effectively, leading to high blood sugar levels.
- This is why the pancreas's role in producing insulin is a central reason to study it in the context of diabetes.



Pancreas:

- The pancreas (pan= all , kreas = flesh) is a gland that is partly exocrine and partly endocrine. The exocrine part secretes the digestive pancreatic juice, and the endocrine part secretes hormones,
  eg. Insulin.
- It is soft, lobulated and elongated organ
- https://www.youtube.com/watch?v=ygJWymFSY70

Pancreas:

LOCATION:

✓ The pancreas lies more or less transversely across the posterior abdominal wall, at the level of first and second lumbar vertebrae

SIZE AND SHAPE :

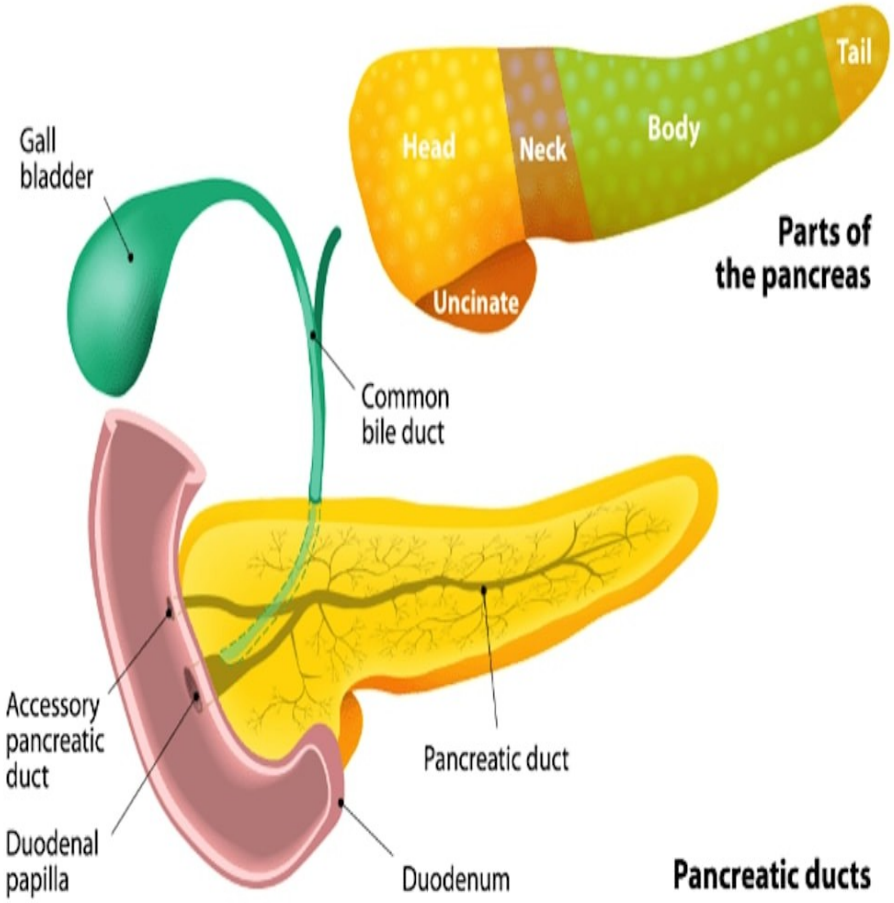
✓ It is J – shaped or retort shaped, set obliquely.

✓ The bowl of the retort represents its head , and the stem of the retort , its neck , body and tail.

✓ It is about 15-20 cm long ↙2.5-3.8 cm broad and 1.2-1.8 cm thick and weighs about 90 g

DIVISION

- The pancreas is divided(from right to left) into the head , the neck, the body and tail.
- The head is enlarged and lies within the concavity of the duodenum.
- The tail reaches the hilum of the spleen.
- The entire organ lies posterior to the stomach separated from it by the lesser sac



Physiology of Pancreas:

THE EXOCRINE PANCREAS:

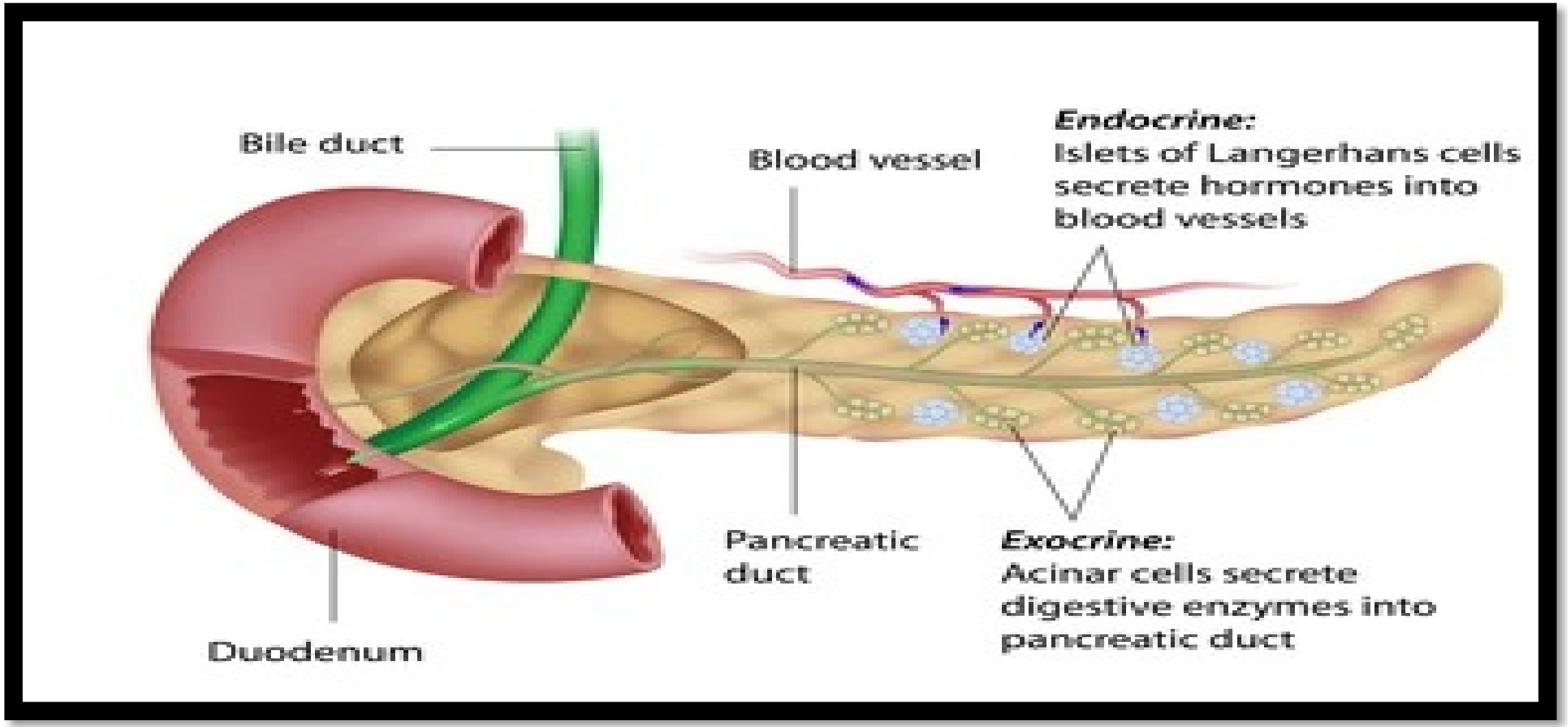
- This consists of a large number of lobules made up of small acini, the walls of which consist of secretory cells.
- Each lobule is drained by a tiny duct and these unite eventually to form the pancreatic duct, which extends the whole length of the gland and opens into the duodenum.
- The function of the exocrine pancreas is to produce pancreatic juice containing enzymes that digest carbohydrates , proteins and fats.
- As in the alimentary tract, parasympathetic stimulation increases the secretion of pancreatic juice and sympathetic stimulation depress it.

Physiology of Pancreas:

THE ENDOCRINE PANCREAS:

- Distributed throughout the gland are groups of specialized cells called the pancreatic islets (islets of langerhans).
- The islets have no ducts so the hormones diffuse directly into the blood.
- The endocrine pancreas secretes the hormones insulin and glucagon, which are principally concerned with control of blood glucose levels.
- Production of Pancreatic Hormones by Three Cell Types 🏁 Alpha cells produce glucagon. 🏁 Beta cells produce insulin. 🏁 Delta cells produce somatostatin

Physiology of Pancreas:



Hormones of the Pancreas:

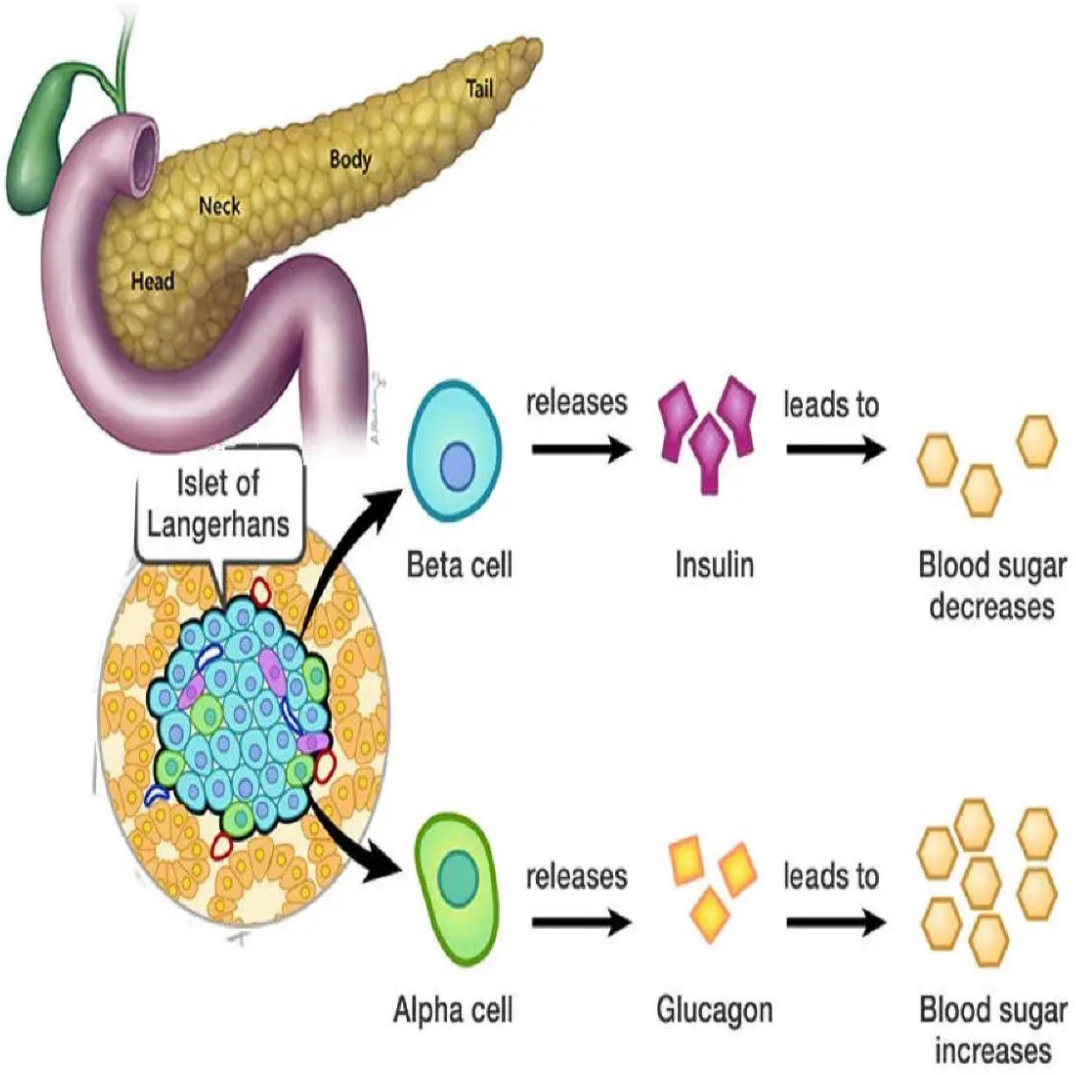
Islets of Langerhans:

Within the pancreas are clusters of cells called the Islets of Langerhans, which produce hormones that control blood sugar.

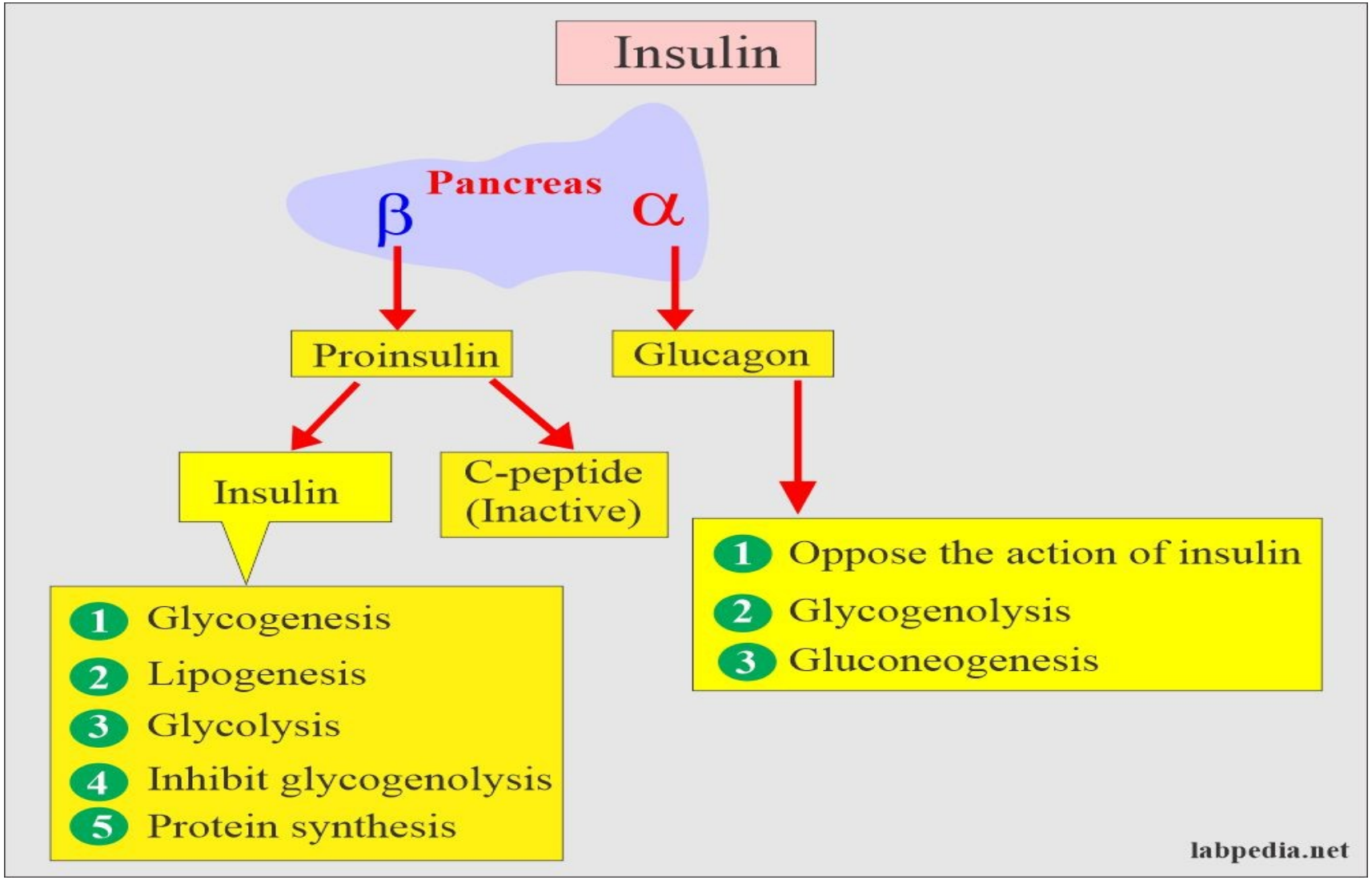
Alpha and beta cells: The islets contain two key types of cells:

Alpha cells produce glucagon, which raises blood sugar levels when they drop too low.

Beta cells produce insulin, which lowers blood sugar after a meal.

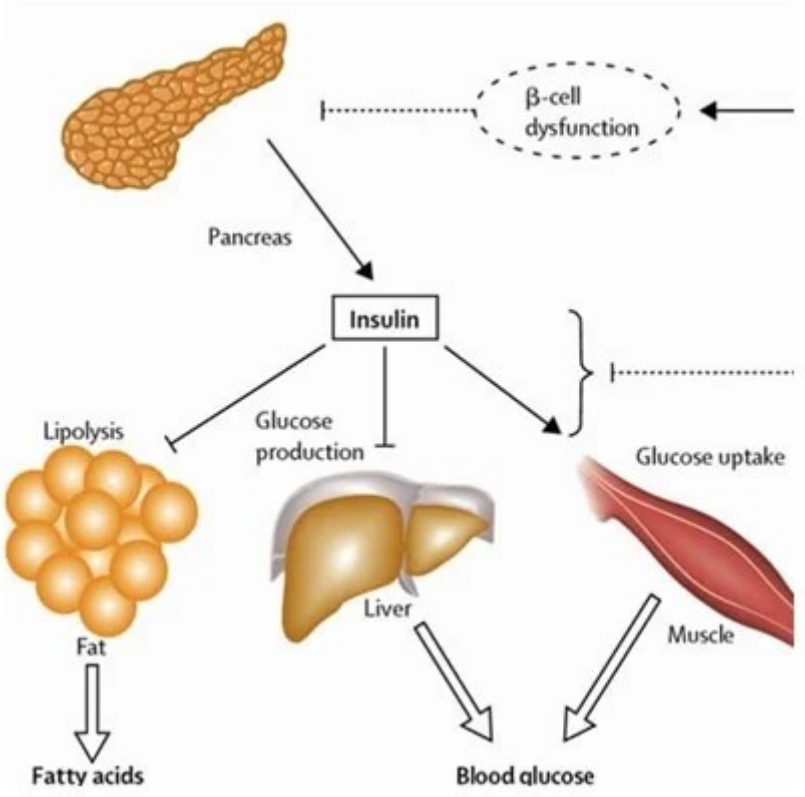


Hormones of the Pancreas:

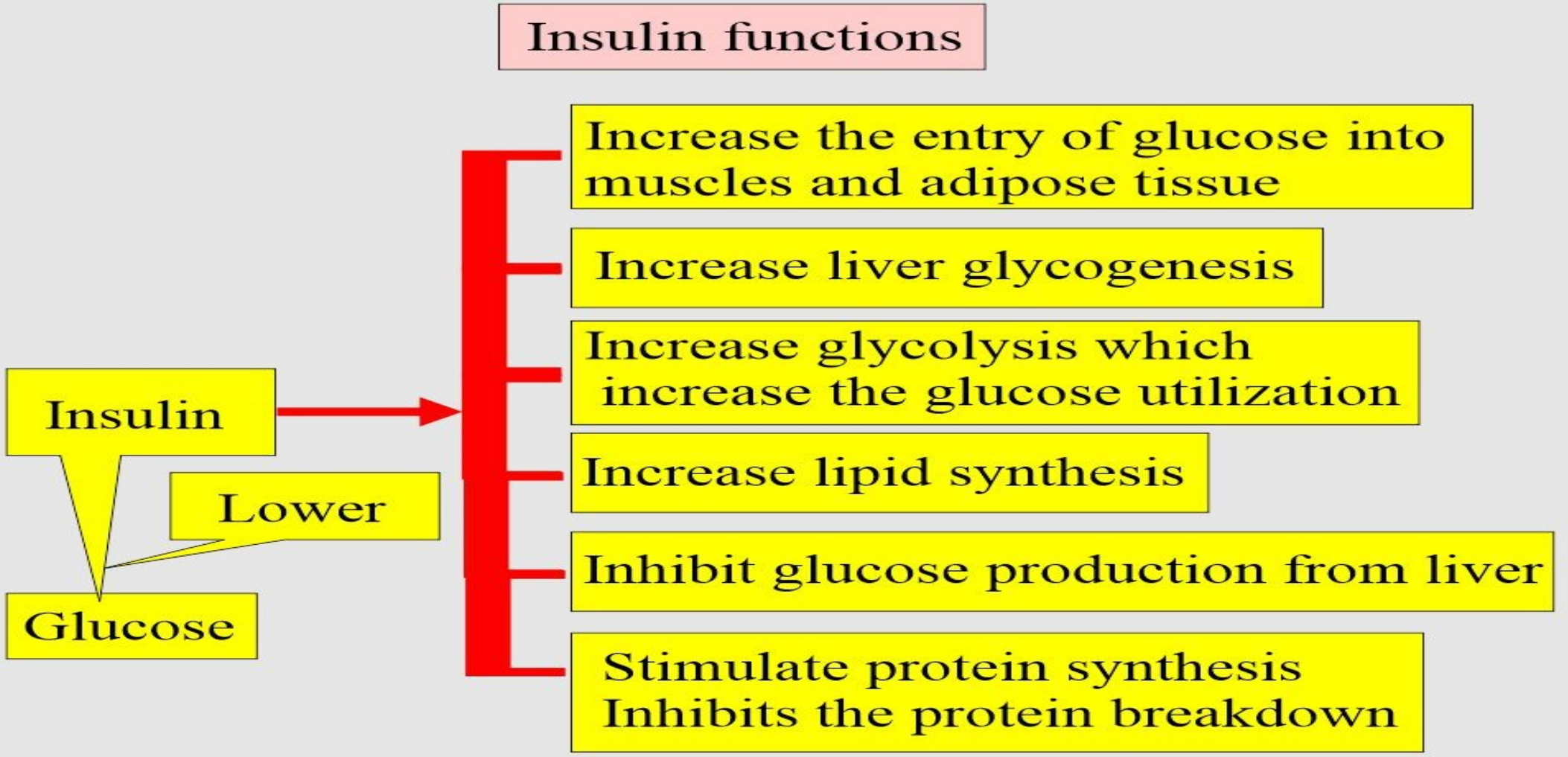


Insulin

- Insulin is a hormone central regulating carbohydrate and fat metabolism in the body
- Insulin secreted by the Islets of Langerhans of pancreas which catabolizes glucose in blood.
- Insulin causes liver cells, muscle cells and fat tissue to take up glucose from the blood and store it as glycogen in the liver and muscle.



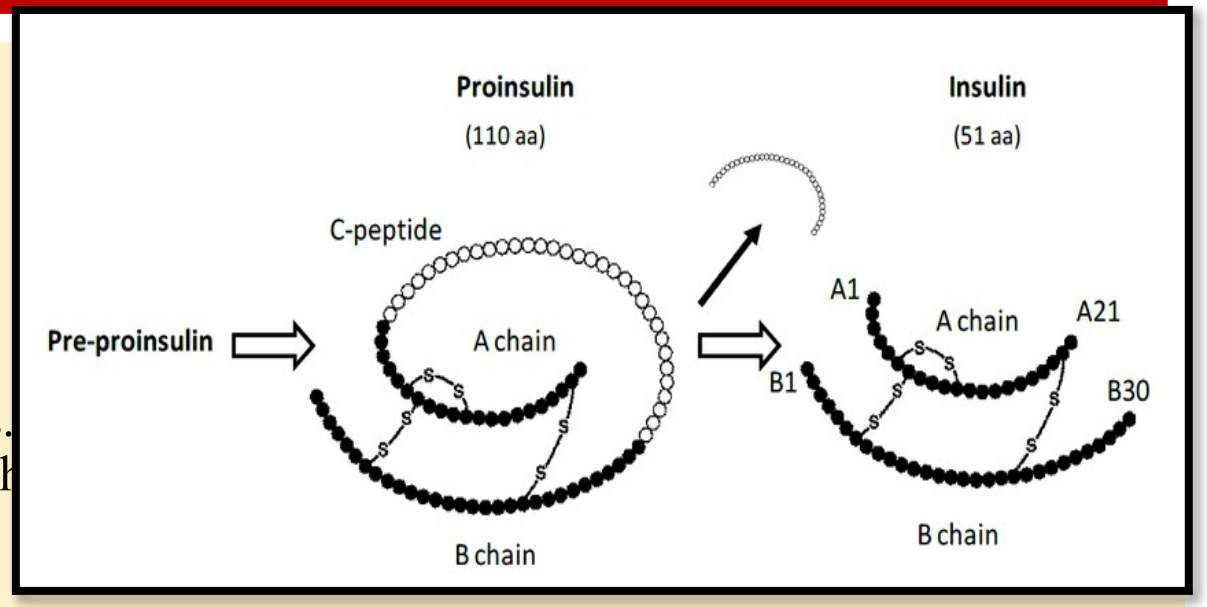
Insulin Function:



Insulin Structure and Production:

Structure

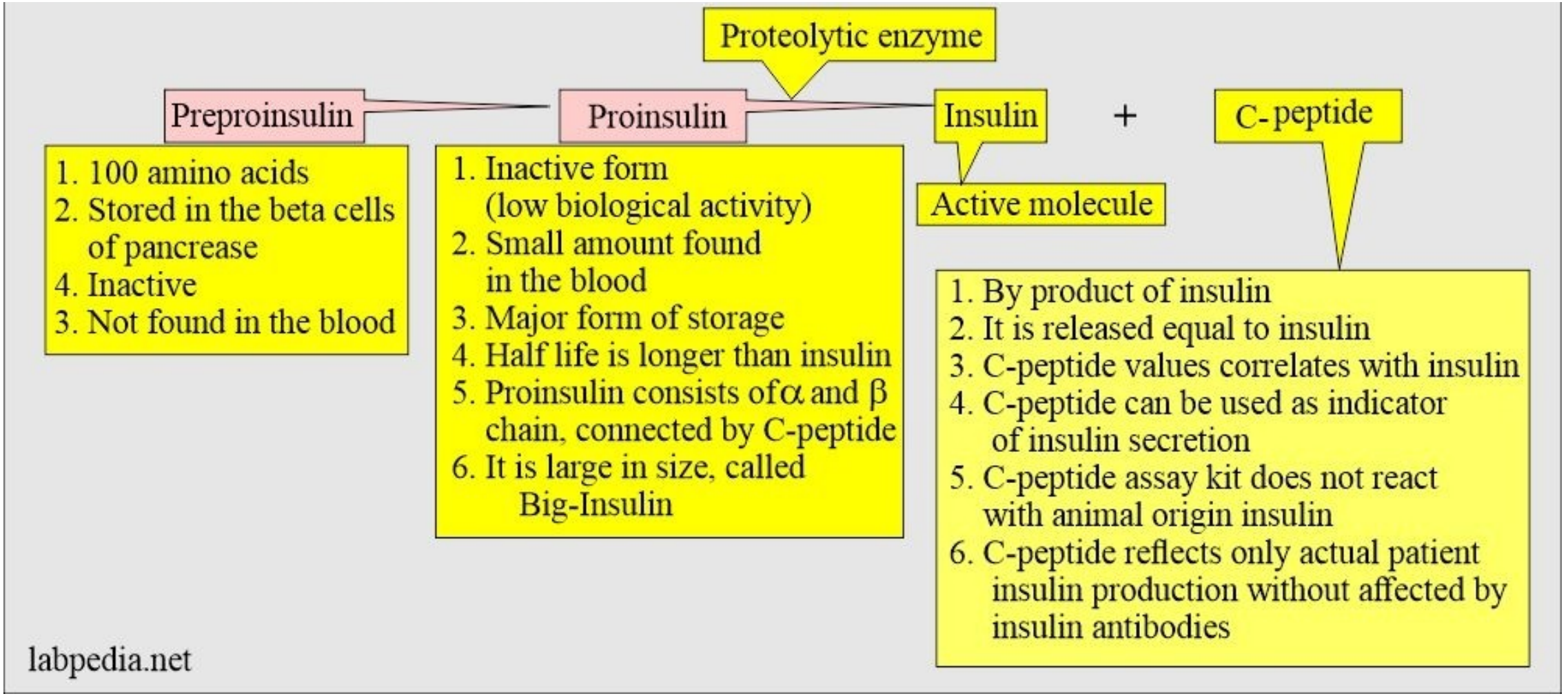
- **Chain A**: 21 amino acids
- **Chain B**: 30 amino acids
- **Total Amino Acids**: 51
- **Disulfide Bonds**: 3
  - **Interchain**: Two bonds link the A and B chains.
  - **Intrachain**: One bond is located within the A ch



Production in the human body

- Insulin is a protein hormone.
- It is produced and secreted by the beta cells within the islets of Langerhans in the pancreas.
- The gene for human insulin is located on chromosome 11.
- The initial precursor is a 110-amino-acid molecule called preproinsulin.
- This precursor is processed into a less active form called proinsulin, which is a single chain.
- Proinsulin is then cleaved, removing a C-peptide to leave the active A and B chains, which are then linked by the disulfide bonds.

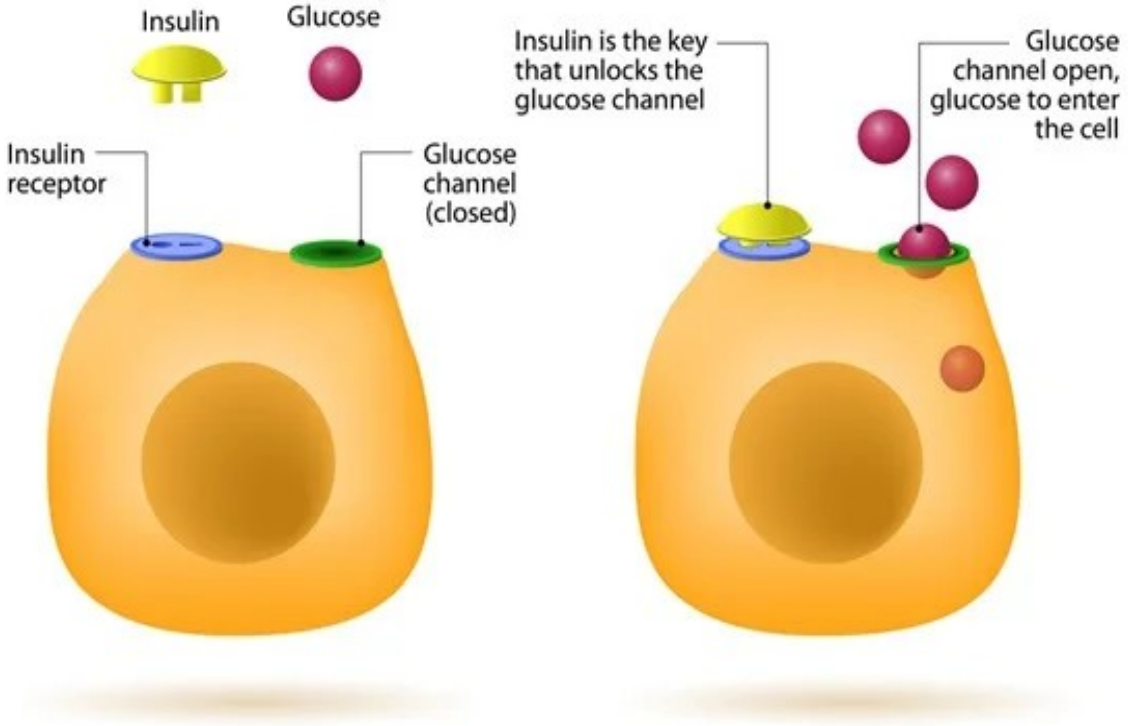
Formation of Proinsulin, Insulin and C-Peptide

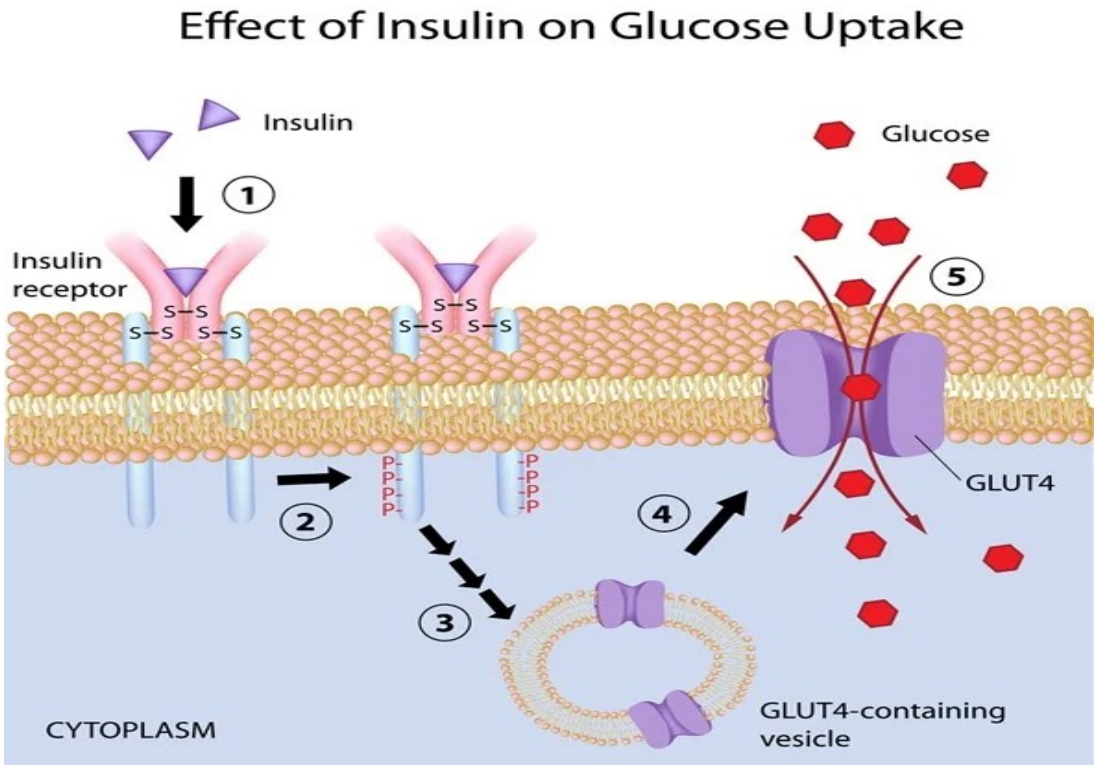


METABOLISM OF INSULIN

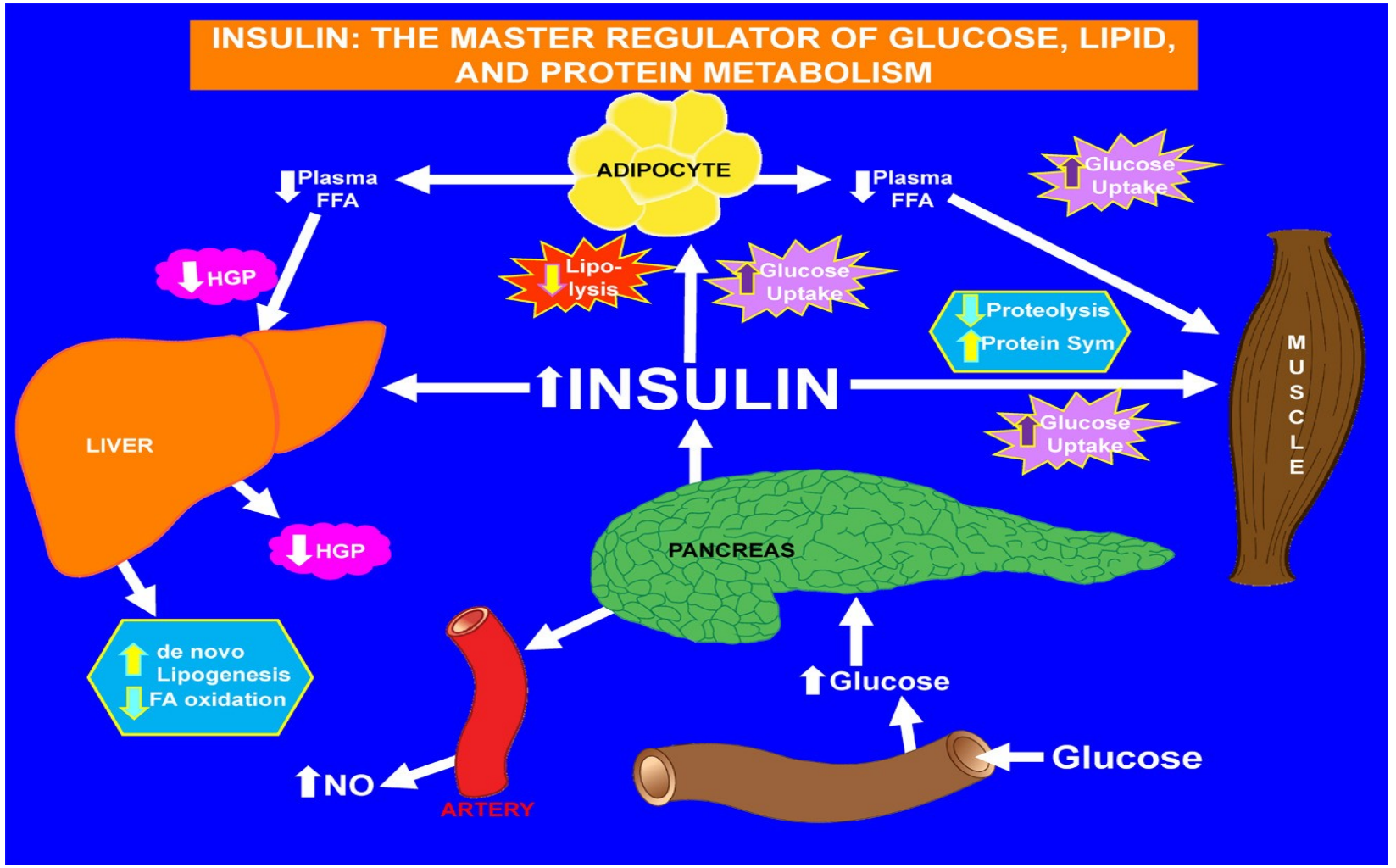
- Insulin circulates freely in plasma
- Its half life is 5- 8 min
- Metabolic clearance is 800 ml/min
- Basal insulin release to the circulation is about 0.5 – 1 unit/ hr
- Total release into peripheral circulation in a day is 30 units
- Metabolized mainly in liver and kidneys

How Does Insulin Work

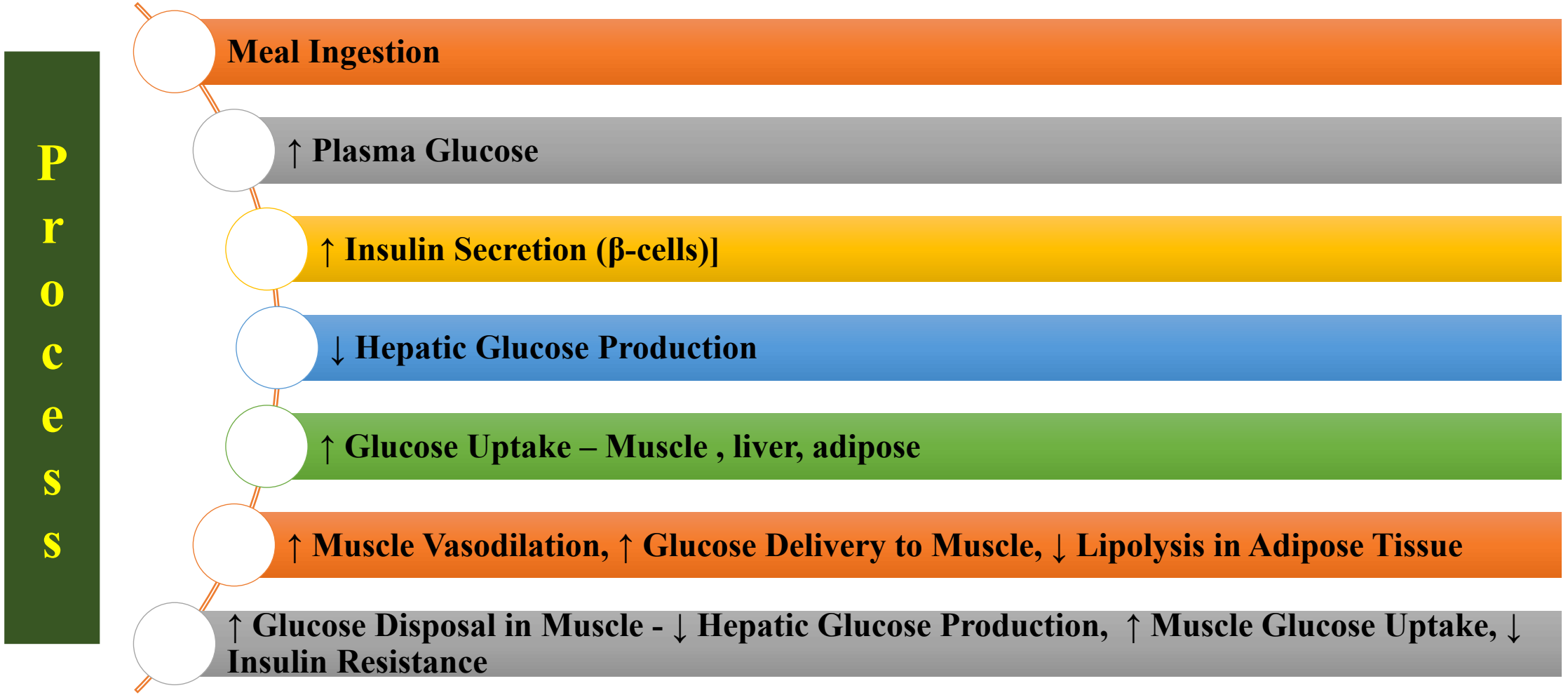




Insulin : The Master Regulator



Insulin: Master regulator of Glucose, Protein, Lipid Metabolism



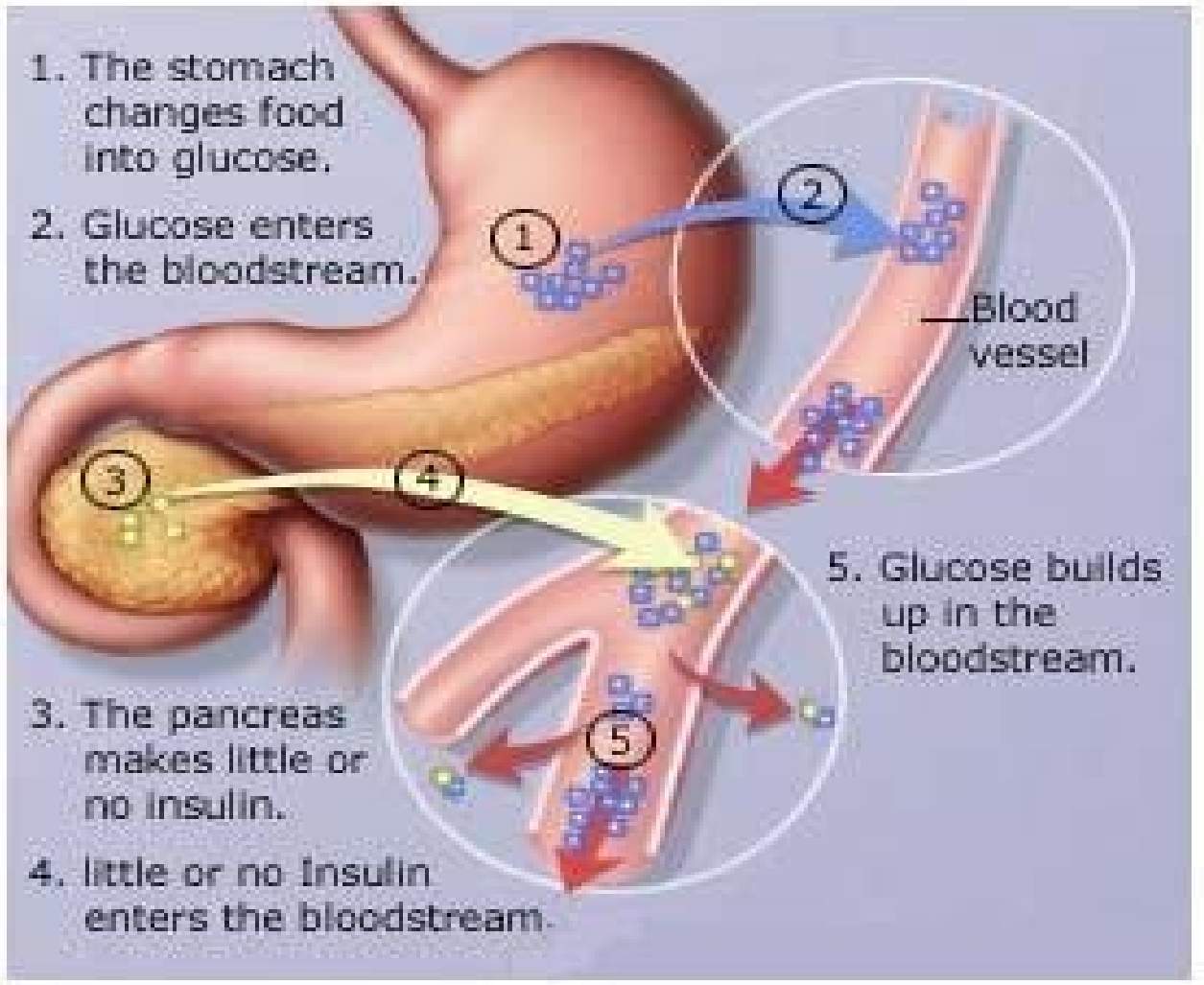
Process Of Insulin Release :

Insulin: The blood sugar key
Think of insulin as a key that unlocks cells to let glucose enter and be used for energy.

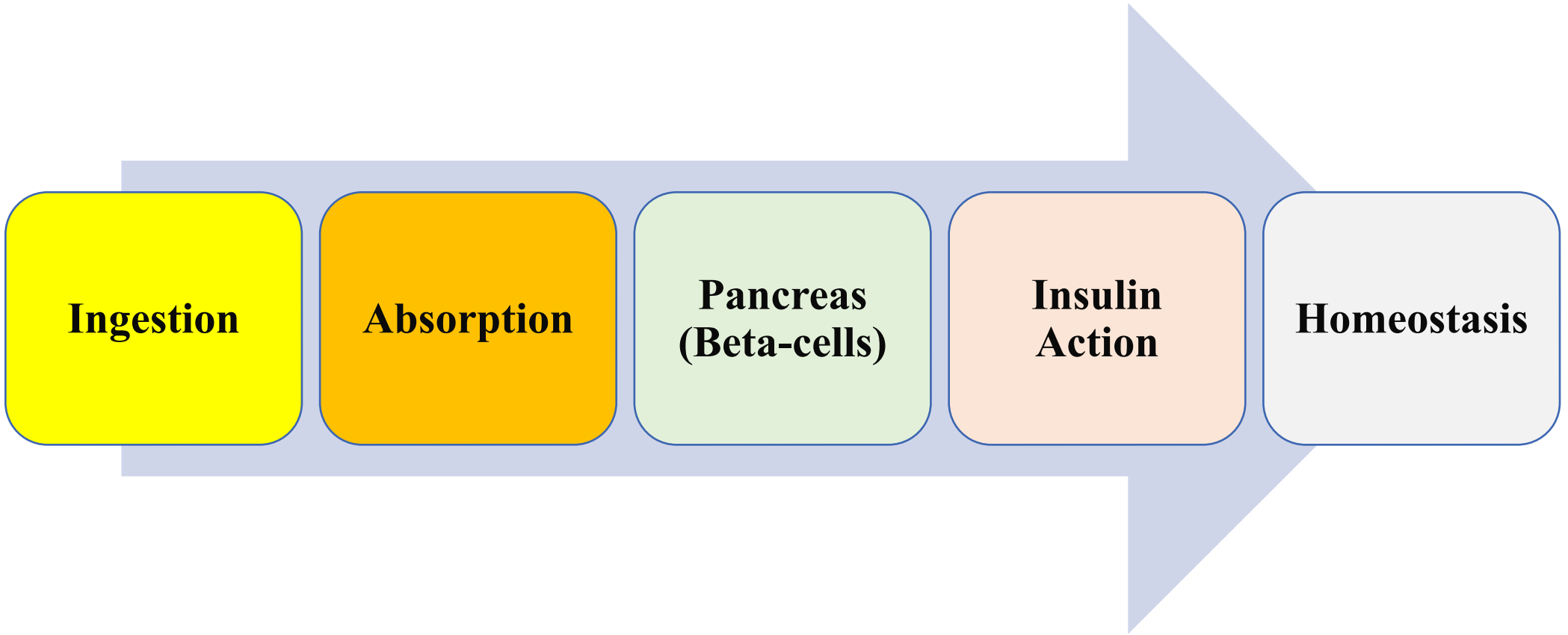
- **How it works:** When we eat, blood sugar rises, prompting the pancreas to release insulin.

- **Effects on the body:**
  - It helps move glucose from the bloodstream into muscle, fat, and liver cells.
  - It tells the liver to store excess glucose as glycogen for later use.

- **The balancing act:** Insulin and glucagon work together to maintain a stable blood glucose level, a state called glucose homeostasis.



The Normal Homeostatic Loop



What will result without insulin

- In the absence of insulin, the body is not able to utilize glucose as energy in the cells.
- As a result, the glucose remains in the bloodstream and can lead to hyperglycemia.
- Chronic hyperglycemia is characteristic of diabetes mellitus and, if untreated, is associated with severe complications, such as damage to the nervous system, eyes, kidneys, and extremities.

Euglycemia versus hyperglycemia

Normal Glucose Homeostasis (Euglycemia)

Process	Hormone Involved	Effect on Blood Glucose
Glucose uptake (muscle, fat)	**Insulin**	🔽 Decreases
Hepatic glucose production (HGP)	**Insulin**	🔽 Suppressed
Gluconeogenesis, glycogenolysis	**Glucagon, Cortisol**	🔼 Increases

➡️ **Balanced action** of insulin vs. counter-regulatory hormones (glucagon, cortisol) maintains **euglycemia**

Disrupted State: Insulin Resistance + Glucose Intolerance

Defect	Result
↓ Insulin sensitivity	Glucose uptake by tissues is impaired
↑ Hepatic glucose production	Liver continues producing glucose
↓ Glucose clearance from blood	Persistent hyperglycemia

➡️ Leads to **disturbed glucose homeostasis → hyperglycemia**

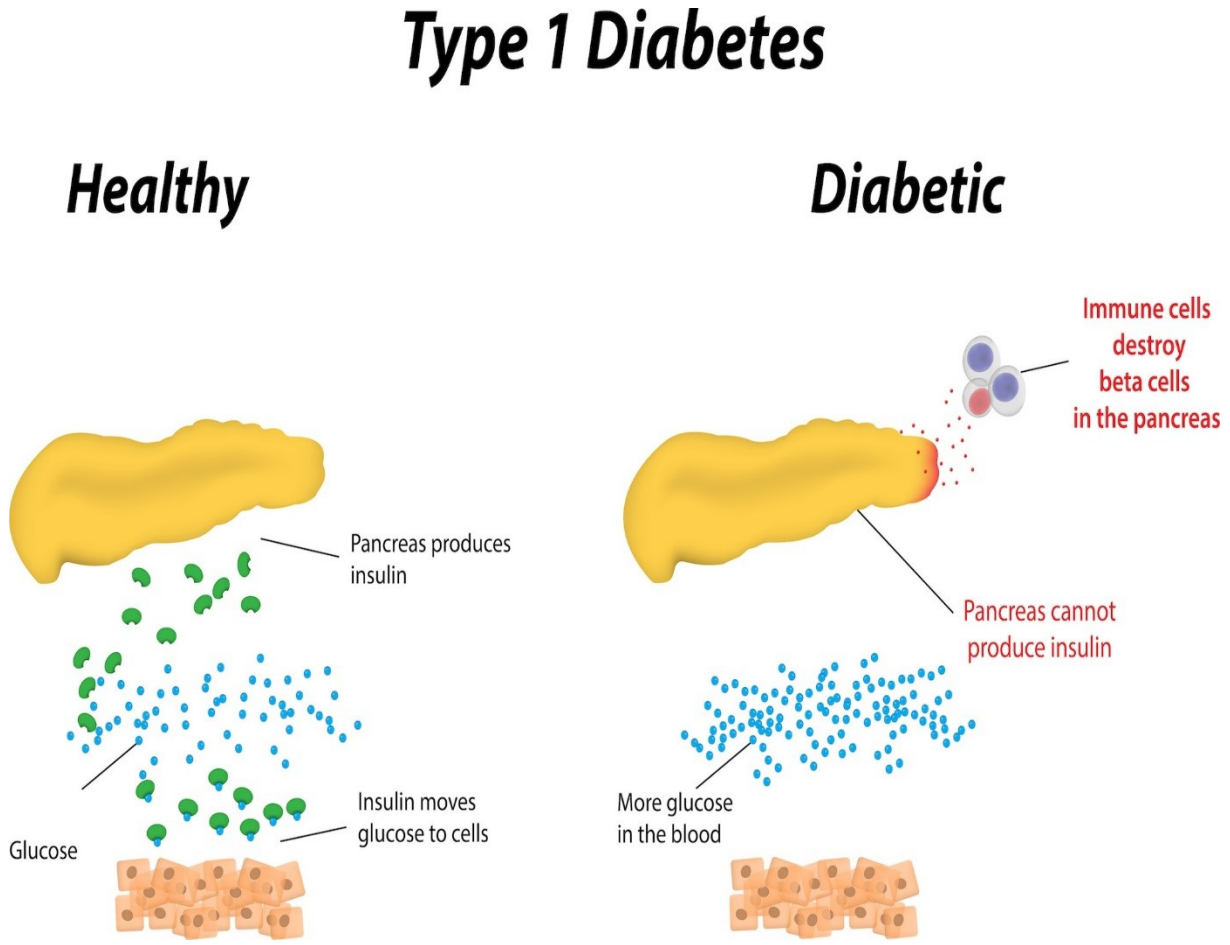
➡️ Often a precursor to **Type 2 Diabetes Mellitus**

Insulin and diabetes

- Insulin is produced by the pancreas' beta cells. Insulin acts on receptors of the liver, skeletal muscle, and adipose tissue to use/store blood glucose from food.
- Type 1 Diabetes – immune system stops the production of insulin by damaging and destroying the pancreas' beta cells resulting in uncontrolled blood sugars within the individual
- Type 2 Diabetes – an individual's body becomes resistant to insulin and the pancreas' ability to produce insulin decreases resulting in worsening blood glucose levels

Type 1 Diabetes mellitus

- Result from the pancreas's failure to produce enough insulin.
- This form was previously referred as insulin dependent diabetes mellitus (IDDM) or Juvenile diabetes.
- The cause is unknown.



Type 1 diabetes: Pathophysiology

This is an autoimmune process that destroys the insulin-producing beta-cells.

Step 1: Genetic Predisposition & Environmental Triggers

•**Genetic Susceptibility:** An individual inherits specific genes (e.g., HLA alleles) that make them susceptible to autoimmune diseases.

•**Environmental Trigger:** Exposure to a virus (e.g., Coxsackievirus) or other environmental factors triggers an autoimmune response.

Step 2: Autoimmune Attack

•The immune system (T-cells, macrophages) mistakenly identifies pancreatic beta-cells as foreign.

•Immune cells infiltrate the pancreas, causing inflammation and insulitis.

•The beta-cells are progressively destroyed.

Type 1 diabetes: Pathophysiology

Step 3: Absolute Insulin Deficiency

•With the beta-cells destroyed, the pancreas can no longer produce insulin.

•The body's cells cannot take up glucose, regardless of the blood sugar level.

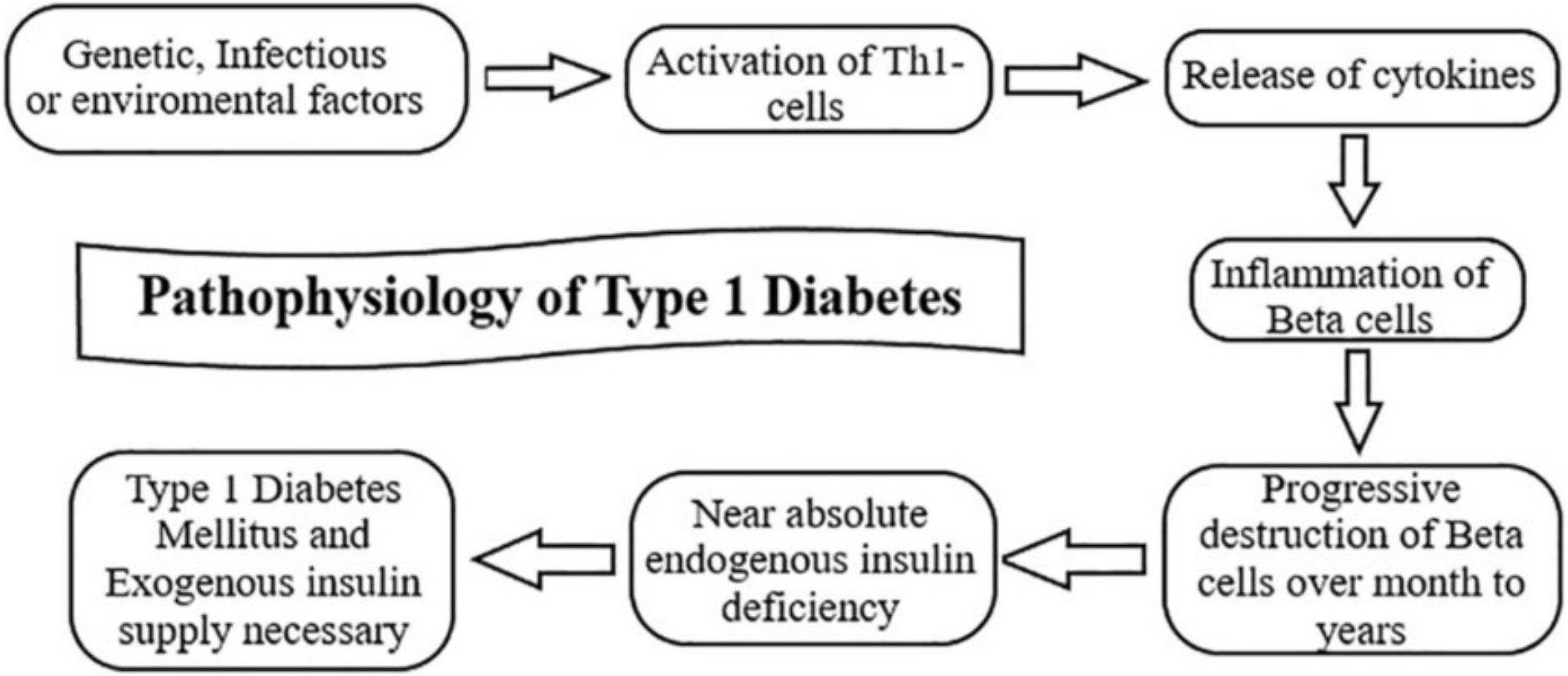
Step 4: Hyperglycemia & Metabolic Consequences

•**Hyperglycemia:** Without insulin, glucose builds up in the bloodstream.

•**Lipolysis & Ketogenesis:** Since cells can't use glucose, the body switches to breaking down fat for energy. This produces acidic byproducts called ketones.

•**Diabetic Ketoacidosis (DKA):** An uncontrolled buildup of ketones leads to a life-threatening state of metabolic acidosis.

Type 1 diabetes: Pathophysiology



Type 2 Diabetes mellitus

- Begins with insulin resistance , a condition in which cells fail to respond to insulin properly.

- This form was referred as non insulin dependent diabetes mellitus (NIDDM) or adult onset diabetes.
- The primary cause is excessive body weight and not enough exercise.

Type 2 diabetes: Pathophysiology

This condition is driven by a combination of insulin resistance and beta-cell dysfunction, largely influenced by lifestyle factors.

Step 1: Genetic Predisposition & Lifestyle Factors

- **Genetic Susceptibility:** Inherited genes can influence susceptibility to insulin resistance and beta-cell failure.
- **Risk Factors:** Factors like obesity, a sedentary lifestyle, and high-calorie diets lead to chronic metabolic stress.

Step 2: Insulin Resistance (IR)

- Chronic exposure to high glucose and fatty acids causes muscle, fat, and liver cells to become less responsive to insulin.
- **IR in Liver:** The liver fails to suppress glucose production, even when blood glucose is high.
- **IR in Muscle/Fat:** Muscle and fat cells are unable to absorb glucose efficiently.

Type 2 diabetes: Pathophysiology

Step 3: Compensatory Hyperinsulinemia

- The pancreas initially compensates by producing and releasing more insulin to overcome the cellular resistance.

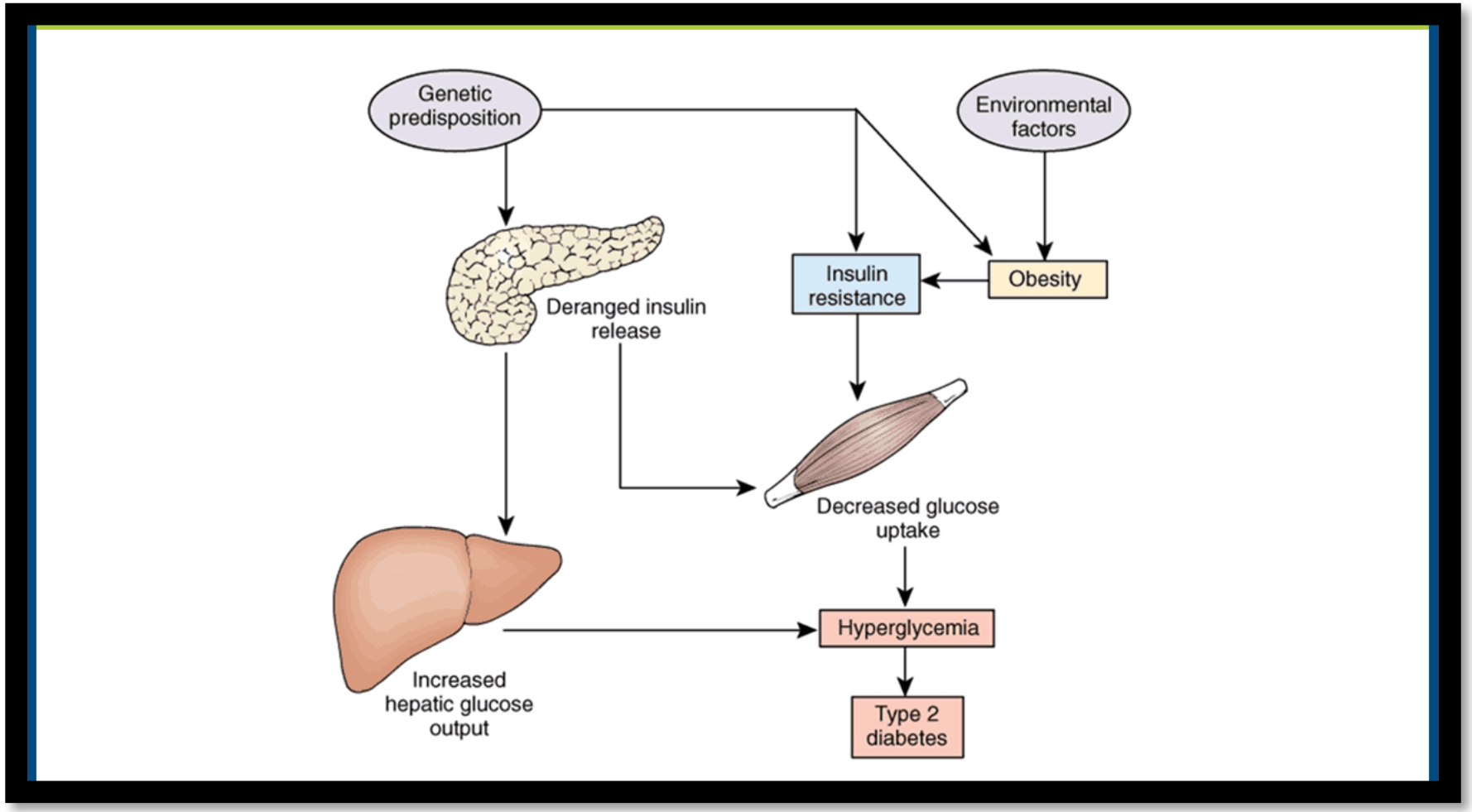
Step 4: Beta-cell Dysfunction and Failure

- Over time, the beta-cells become exhausted from overproduction of insulin.
- **Glucotoxicity and Lipotoxicity:** Chronic high levels of glucose and fats damage the beta-cells.
- **Decreased Beta-cell Mass:** Beta-cell numbers gradually decline through apoptosis (cell death).
- **Relative Insulin Deficiency:** Insulin production falls, exacerbating the hyperglycemia.

Step 5: Hyperglycemia & Long-term Complications

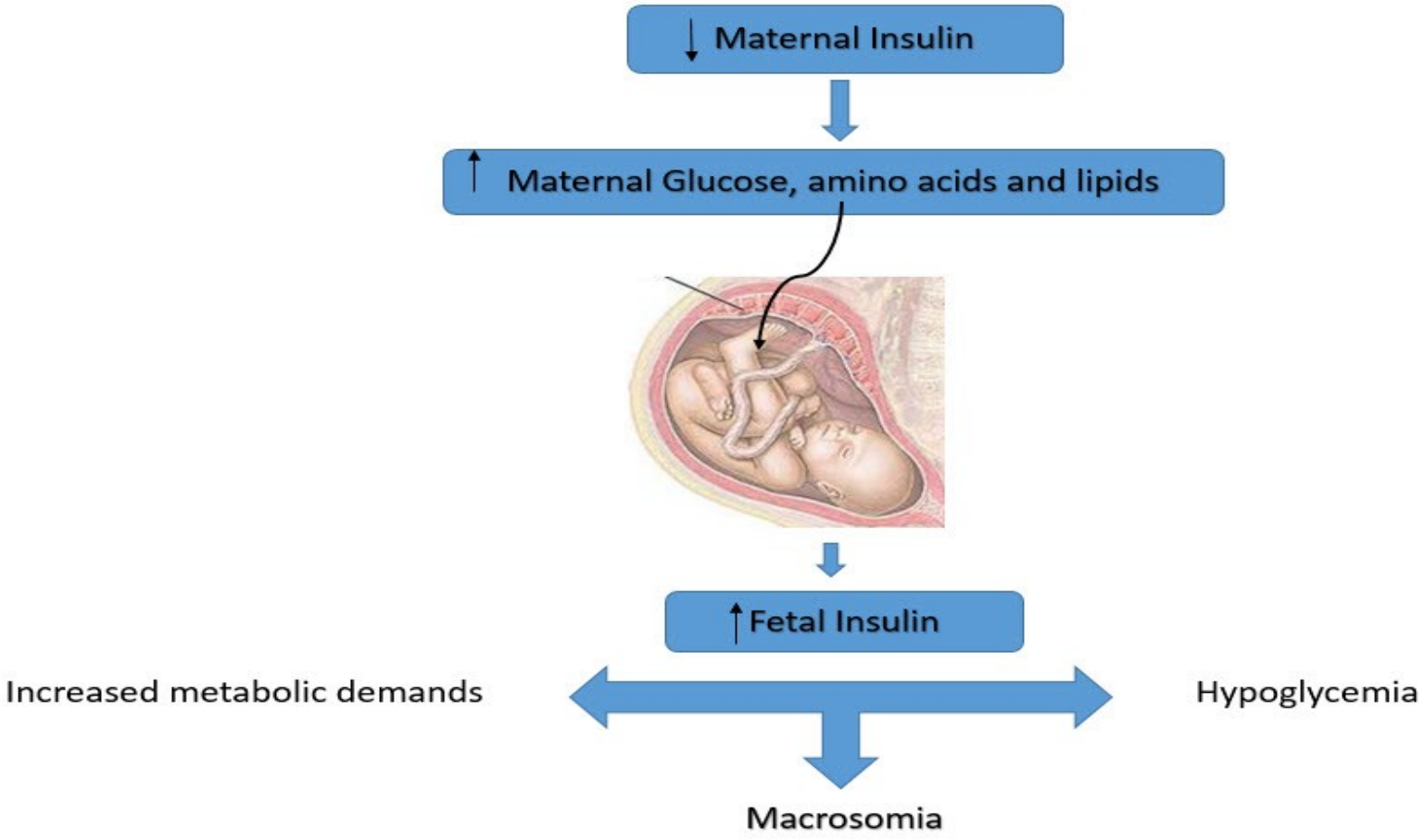
- **Hyperglycemia:** The dual defects of insulin resistance and insufficient insulin secretion cause high blood sugar.
- **Microvascular Damage:** High blood sugar damages small blood vessels, leading to retinopathy (eyes), nephropathy (kidneys), and neuropathy (nerves).
- **Macrovascular Damage:** Damage to large blood vessels increases the risk of cardiovascular events like heart attacks and strokes.

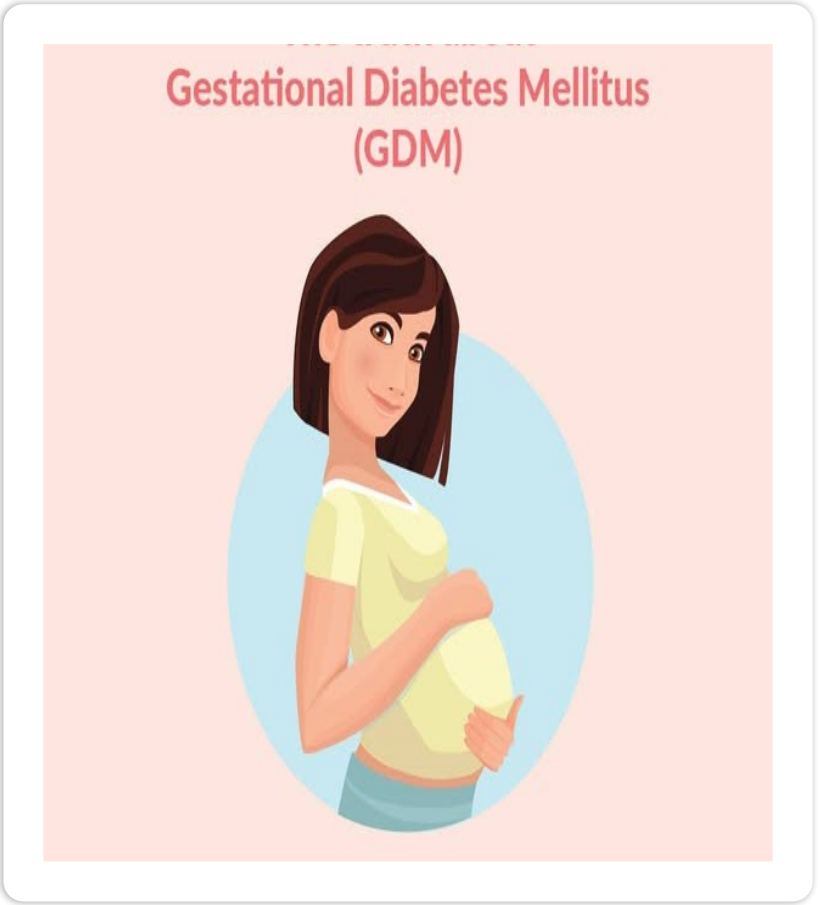
Type 2 diabetes: Pathophysiology



Gestational Diabetes mellitus

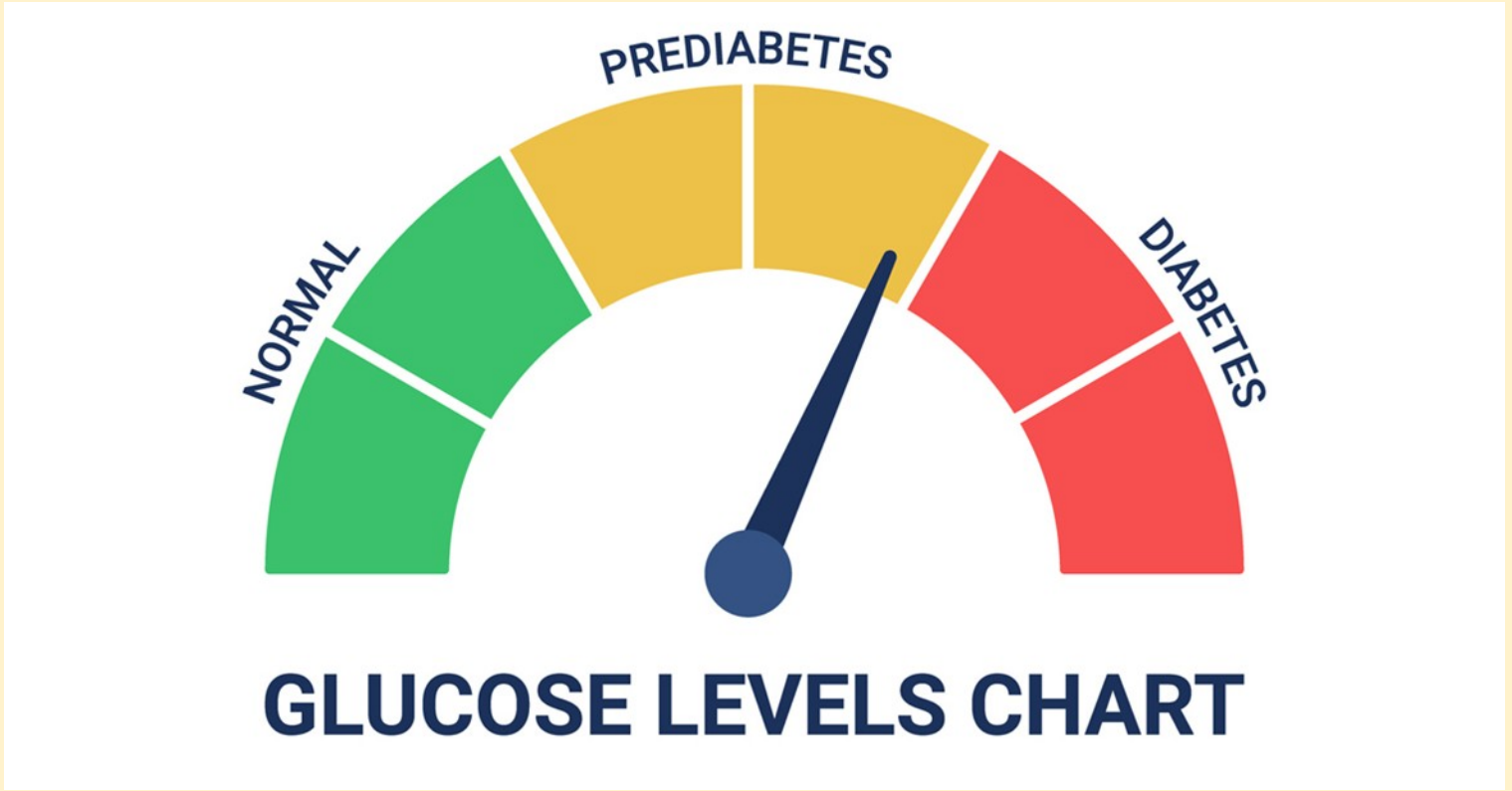
- Is the third main form and occurs in pregnant women with out a previous history of diabetes.





Prediabetes:

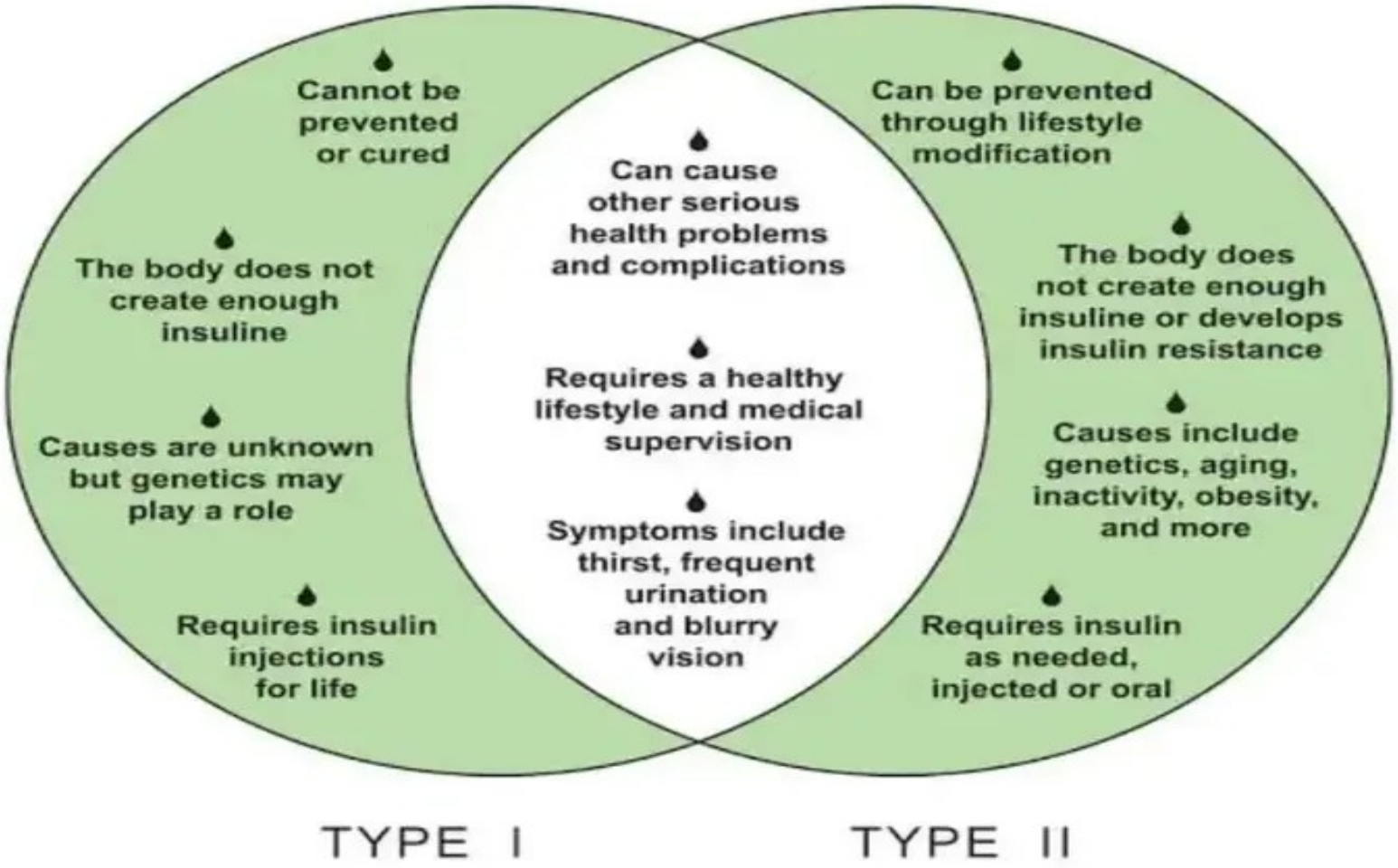
- Prediabetes is a condition where blood sugar level is elevated, but not high enough to be diagnosed with type 2 diabetes.



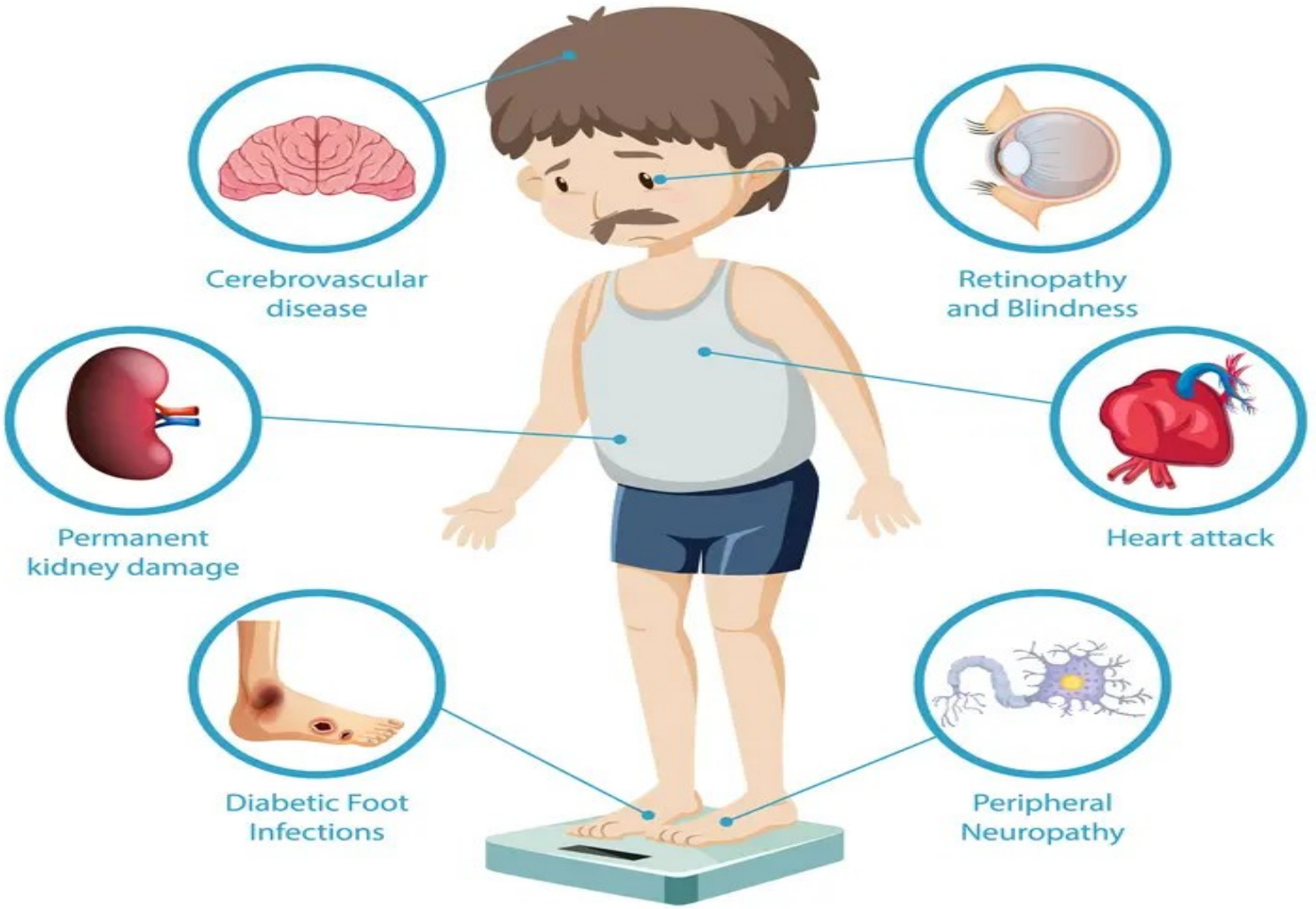
Blood Glucose Chart

Person's Category	Fating State		Postprandial
	Glucose Minimum Value (mg/dl)	Glucose Maximum Value (mg/dl)	2-3 Hours after Eating (mg/dl)
Hypoglycemia	-	< 59	< 60
Early hypoglycemia	60	79	60 - 70
Normal	80	100	< 140
Early diabetes	101	126	140-200
Diabetic	> 126	-	> 200

differences between diabetes 1 and 2



Diabetes complications



Thank you all

Live a long life