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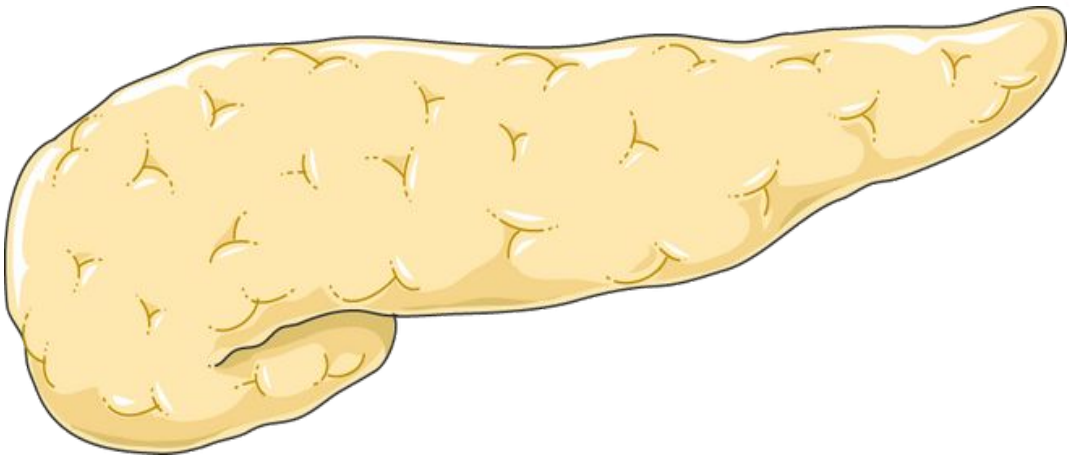


Physiology of the Pancreas and Pathophysiology of Diabetes Mellitus

ENDO Physiology

Editing File

Color Index :

- Main Text
- Important
- Girls Slides
- Boys Slides
- Notes
- Extra

Objectives

- Identify the principal hormones of the pancreas, their cells of origin, and their chemical nature.
- Understand the mechanisms that regulate pancreatic hormone release.
- List the principal target organs for insulin and glucagon action and their major physiologic effects.
- Identify the disease states caused by undersecretion, or decreased sensitivity to insulin, and describe the principal manifestations of each.

كَانَ أَكْثَرُ دُعَاءِ رَسُولِ اللَّهِ ﷺ: رَبَّنَا آتِنَا فِي الدُّنْيَا حَسَنَةً، وَفِي الْآخِرَةِ حَسَنَةً، وَقِنَا عَذَابَ النَّارِ.

سُورَةُ الأَحْزَابِ

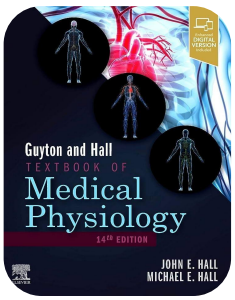
إِنَّ ٱللَّهَ وَمَلَٰٓئِكَتَهُۥ يُصَلُّونَ عَلَى ٱلنَّبِيِّۚ يَٰٓأَيُّهَا ٱلَّذِينَ ءَامَنُواْ صَلُّواْ عَلَيْهِ وَسَلِّمُواْ تَسْلِيمًا ٥٦

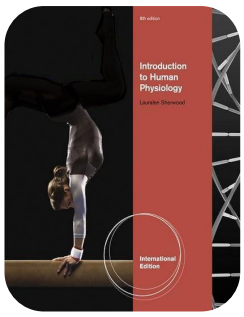
اللهم اغفر لنا ما قدَّمنا، وما أخَّرنا، وما أسررنا، وما أعلنا، وما أنت أعلم به منا، أنت المقدم، وأنت المؤخر، لا إله إلا أنت.

دعواتكم لفريق الفيزيولوجي دفعة ٤٤٣ و كل من قام على هذا العمل

Resources

Only ENDO chapters included





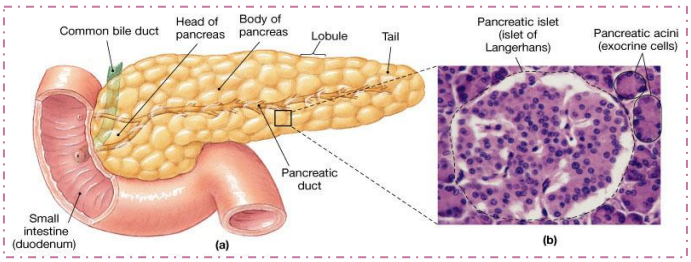
sherwood-human-physiology

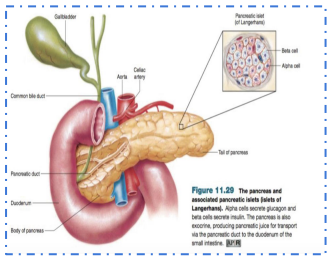
This lecture was presented by:
Dr. Manan Al Hakbany - Dr. Thamir Alkhlaiwi

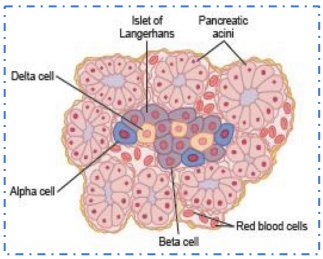
Pancreas

Functions of pancreas

- A triangular gland, which has both exocrine and endocrine cells, located behind the stomach, Strategic location.
- Acinar cells produce an enzyme-rich juice used for digestion (exocrine product) , Exocrine: secrete digestive enzymes into the duodenum, by Acinar cells.
- Pancreatic islets (islets of Langerhans) produce hormones involved in regulating fuel storage and use.
- Endocrine: The **islets of Langerhans** (German physician, 1869) which **produce:**
  - **Insulin**
  - **Glucagon**
  - Somatostatin
  - Pancreatic polypeptide





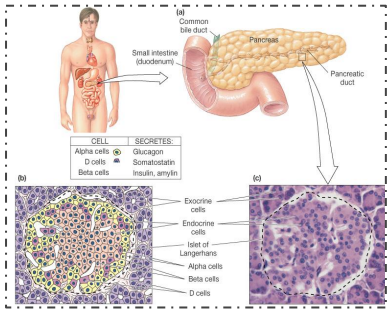


Physiological anatomy of the pancreas, Islets of langerhans

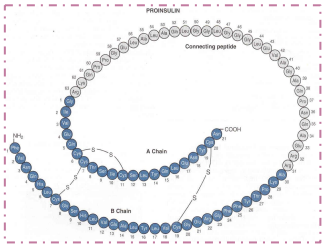
Human pancreas has I to 2 million islets of Langerhans (2%). Each islet is only about 0.3 millimeter in diameter and is organized around small capillaries.

Cells	Action	Distribution	Notes
Beta (β) Cells	produce insulin, amylin	60% - 70%	lie mainly in the middle of each islet and secrete **insulin and amylin**, a hormone that is often secreted in parallel with insulin, although its function is not well understood.
Alpha (α) Cells	produce glucagon	20% - 25%	secrete glucagon.
Delta (δ) Cells	produce somatostatin	5%-10%	secrete somatostatin.
(PP) F cells	produce pancreatic polypeptide	5%	secretes pancreatic polypeptide (regulation of ion transport in the intestine).

Insulin inhibits glucagon secretion
amylin inhibits insulin secretion
somatostatin inhibits the secretion of both insulin and glucagon.



Insulin



Insulin

Female slides

- Hormone of nutrient abundance.
- A protein hormone consisting of two amino acid chains linked by disulfide bonds.
- Synthesized as part of proinsulin (86 AA) and then excised by enzymes, releasing functional insulin (51 AA) and C peptide (29 AA).
- Has a plasma half-life of 6 minutes.

Insulin synthesis

Female slides

- 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.

The process of insulin synthesis

DNA

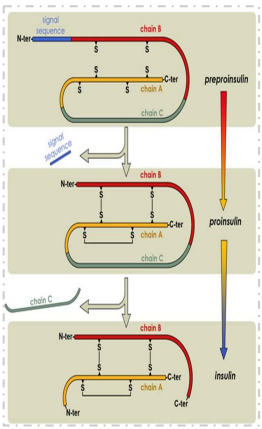
Synthesized from DNA (chromosome 11) in β cells as a preproinsulin

mRNA

Glucose rapidly increase the translation of the insulin mRNA and slowly increases transcription of the insulin gene.

Preproinsulin Cleaved in ER to form proinsulin Composed of:

- Signal peptide/sequence segment/initial segment
- A chain
- B chain
  - Peptide C (connects between A and B chains)



Can we use C peptide as a biomarker?

Proinsulin (86AA)

Proinsulin folds and forms S-S bonds
In proinsulin: A and B chains are connected by a C peptide (29 AA)
formed by:1- After removal of the initial (signal) segment →it's called proinsulin
2-Disulfide bonds between A chain and B chain will be formed
3-Folding of the polypeptide in the rER then it'll packed into Golgi apparatus

Insulin

Proinsulin is cleaved in the Golgi apparatus of pancreatic beta cells to form; connecting peptide: C peptide, and insulin (51 AA) .
Insulin synthesis is stimulated by glucose or feeding and decreased by fasting
Threshold of glucose-stimulated insulin secretion is 100 mg/dl.
In the golgi apparatus C peptide is cleaved from the proinsulin to Insulin become insulin

Packaged

C peptide and insulin and a little zinc are packed into vesicles, some of the C peptides in the vesicles are not cleaved yet. Equal amounts of C peptide and insulin are packaged into vesicles
This is important in the diagnosis of D.M. Measuring the C peptide will give us the natural insulin level when using exogenous insulin.

Released

Finally, release of insulin into the cytoplasm when needed (exocytosis).

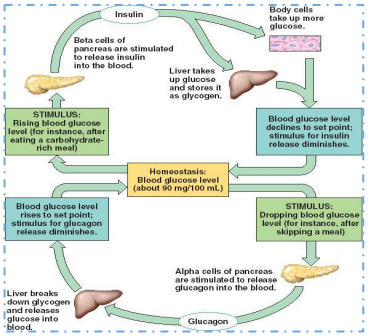
Insulin

Insulin

- Secreted by β cells in response to elevated blood glucose.
- Functions: Increases transport of glucose to skeletal muscle, liver and adipose tissue (lowers blood glucose levels).
- The ONLY metabolically active hormone capable of lowering blood glucose levels.
- Every other metabolically active hormone causes hyperglycemia except Insulin.
- Degraded within the liver, kidneys, muscles, and less in most of other tissues.
- 80% metabolized in the liver.
- Half-life of about 5-6 minutes.
- Degraded by hepatic glutathione insulin dehydrogenase (insulinase).
- Enzyme disrupts S-S bonds.

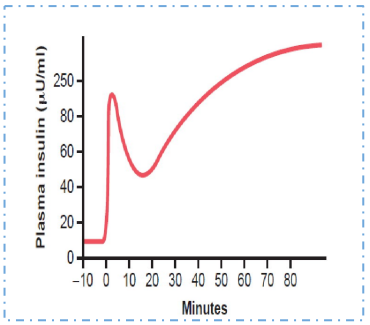
Control of blood glucose

- The normal concentration of insulin measured by radioimmunoassay in the peripheral venous plasma of fasting normal humans is 0–70 μU/mL (0–502 pmol/L).
- The amount of insulin secreted in the basal state is about 1 U/h, with a fivefold to 10-fold increase following ingestion of food. Therefore, the average amount secreted per day in a normal human is about 40 U (287 nmol).



Control of Insulin secretion

1. Insulin in plasma increases almost 10-fold within 3 to 5 minutes after acute elevation of the blood glucose. This results from immediate dumping of preformed insulin from beta cells. Insulin concentration decreases about halfway back toward normal in another 5 to 10 minutes.
2. About 15 minutes, insulin rises a second time and reaches a new plateau in 2 to 3 hours, this time usually at a rate of secretion greater than that in the initial phase due to both the additional release of preformed insulin and from activation of the enzyme system that synthesizes and releases new insulin from the cells.



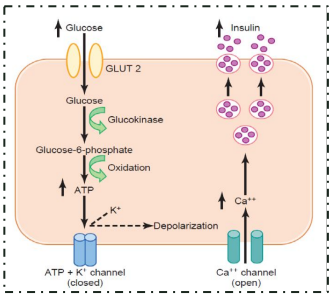
Insulin dependent & independent tissues

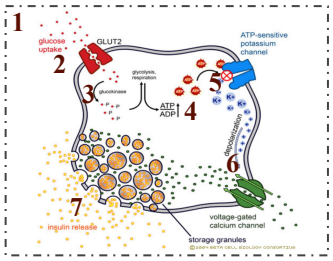
Insulin Dependent	Insulin Independent
• All muscles (except during heavy exercise) • Adipose tissues. • Leukocytes. • Pituitary. • Memory cells. • Lenses of the eyes.	• Brain (Except parts of the Hypothalamus) • Kidney tubules. • Intestinal mucosa. • RBCs.

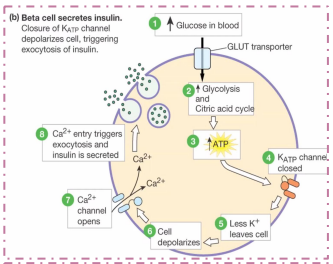
Glucose enters cells by:

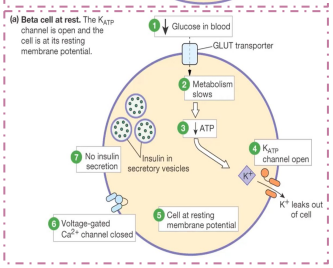
1. facilitated diffusion through Glucose transporters.
2. secondary active transport with Na (in the intestine and kidney).

Mechanism of glucose stimulation of insulin Secretion









1	Increase in blood glucose level after eating. why is that the first step? Because Glucose is the primary stimulator of insulin secretion.
2	Glucose enter beta cells by GLUT2
3	Glucose changed to glucose-6- phosphate by **glucokinase**. Glucose-6-phosphate oxidizes to form ATP.
4	increased ATP inhibit K channels. This will cause depolarization due to the high concentration of K+ inside the cell.
5	Voltage-gated Ca++ channels open.
6	Ca++ enter the cell and stimulate fusion of insulin-containing vesicles and secretion of insulin into ECF by exocytosis.

What is the most important step in releasing insulin?

The conversion of glucose to glucose 6 phosphate by Glucokinase. This is the rate limiting step which accelerate or decelerate the release of insulin.
- If there is a mutation in the glucokinase enzyme they will have MODY diabetes (Maturity Onset Diabetes of the Young), they will have the insulin (because the synthesis is normal) but it can't be released.

Regulation and secretion

Male slides

Regulation and secretion

Direct stimulation :

- Increased glucose
- Increased amino acid or fatty acid directly stimulate β cells (These compounds generate ATP when metabolized, and this closes ATP-sensitive K + channels in the B cells).

Hormonal regulation :

- Gastrointestinal hormones stimulate β cells.

Neural regulation :

- Parasympathetic NS stimulates β cells. Branches of the right vagus nerve innervate the pancreatic islets and when stimulated, it causes increased insulin secretion.
- Sympathetic NS inhibits β cells.

Drugs :

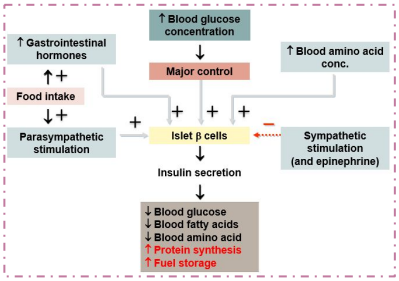
- Sulfonylurea derivatives - close ATP-sensitive K+ channels → insulin ↑↑

Other Stimuli :

- K+ depletion (hyperaldosteronism, diuretics) → insulin↓↓

Regulation of Insulin Secretion (Very Important): Female slides

If the blood glucose concentration is high, Major control (CNS) will increase Beta-cell activity so insulin will be secreted as a negative feedback process. How does that happen? The body will detect high blood sugar and will send a report to the major control or the CNS. In this case, the CNS will influence the pancreas. Which will make it release insulin causing its different actions. Insulin will act also as a growth hormone by increasing hormone synthesis and storing fuel by storing glycogen in the liver. PNS is a "Rest and digest" system and the SNS is a "Fight or flight" system. PNS will increase insulin secretion because PNS is activated after meals. SNS will decrease insulin.



Stimulators

- ↑ Serum glucose The most important one (Master regulator).
- ↑ Serum amino acids(I)
- ↑ Serum free fatty acids (I)
- ↑ Serum ketone bodies
- Parasympathetic nervous system (2)
- (Feeding)

Hormones:

- Epinephrine (β-Receptor)
- Gastric Inhibitory peptide (GIP).(4)
- Glucagon.
- Gastrin.
- Cholecystokinin (CCK).
- Secretin.
- Vasoactive intestinal peptide (VIP).

Inhibitors

- ↓ Serum glucose
- ↓ Serum amino acids
- ↓ Serum free fatty acids
- ↓ Serum ketone bodies
- Sympathetic nervous system (3)

Hormones:

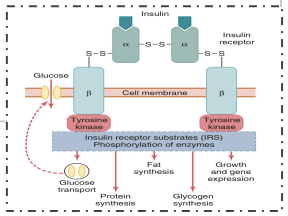
- Epinephrine (α-Receptor)
- Somatostatin

(Insulin Receptors) Activation of target cell receptors by insulin

- It is the activated receptor that causes the subsequent effects The insulin receptor is a transmembrane receptor
- Belongs to the large class of tyrosine kinase receptors.
- Found in liver ,adipose tissue,skeletal muscle.

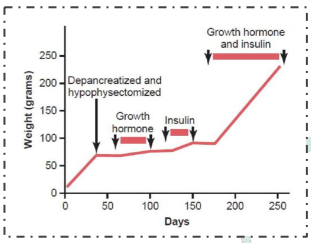
The insulin receptor is a combination of four subunits held together by disulfide linkages:
two alpha subunits α (extracellular) that lie entirely outside the cell membrane and two beta subunits β (intracellular) that penetrate through the membrane, protruding into the cell cytoplasm.
The insulin binds with the alpha subunits on the outside of the cell, but because of the linkages with the beta subunits, the portions of the beta subunits protruding into the cell become autophosphorylated.

- Insulin-receptor complex is internalized and enter lysosomes, where it is broken down or recycled.
- The half-life of the insulin receptor is about 7 h.



Effect of growth hormone, insulin, and growth hormone plus insulin on growth

The two hormones function **synergistically** to promote growth, with each performing a specific function separate from that of the other.
Perhaps a small part of the necessity for both hormones results from the fact that each hormone promotes cellular uptake of a different selection of amino acids, all of which are required if growth is to be achieved.



(I) Any fuel (nutrients) because they will cause glycolysis, an increase in ATP and close the ATP sensitive K channel... (same as glucose) (have greatest effect with glucose on insulin stimulation)
(2) In the rest situations when you are eating, increase in insulin release will cause glucose uptake by the cells and storage of glucose also it will be used for energy.
(3) we need high glucose in the blood. Why it will cause inhibition? Sympathetic stimulation on Beta 2 will increase the insulin secretion while in alpha 2 it will decrease the insulin secretion and because the beta cells have more alpha 2 receptors the net result is inhibition of insulin secretion.
(4) Which one will increase the blood insulin level more ? the oral glucose or I.V glucose? The oral glucose because of the GIT hormones (Incretin) .When you eat, the GIT hormones will stimulate the pancreas to release insulin.

- so, there are two stimuli of insulin release the glucose itself and the GIT hormones.
- GIT hormones reduce motility and increase the sense of satiety.
- Some drugs prevent the degradation of incretin, they are used in D.M type 2 to increase insulin secretion.

Glucose Metabolism Terms

Female slides

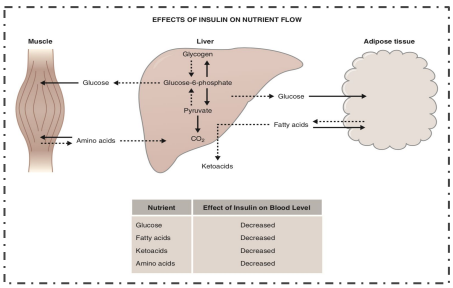
Gluconeogenesis	Synthesis of glucose from noncarbohydrate precursors, Lactic acid, glycerol, amino acids, liver cells synthesis glucose when carbohydrates are depleted.
Glycogenesis	Formation of glycogen, glucose stored in liver and skeletal muscle as glycogen, important energy reserve.
Glycogenolysis	breakdown of glycogen (polysaccharide) into glucose molecules (monosaccharide).
Glycolysis	the breakdown of glucose into pyruvate by cells for the production of ATP.

Glucose Transporters (facilitated diffusion):

Transporters	Present in
GLUT-1	Placenta, Blood brain barrier, RBCs, Kidneys and Colon.
GLUT-2	β cells of Pancreas, Liver, Epithelial cells of small intestines and Kidneys. Mnemonic: GLUT 2 LIKes Beta cells. Present in: L:liver , I: intestine, K:kidney , beta cell
GLUT-3	Brain, Placenta and Kidneys.
GLUT-4 Insulin sensitive	Skeletal Muscles, Cardiac muscles and Adipose tissue.
GLUT-5	Jejunum and sperm.

Main effects of insulin stimulation

1. Within seconds after insulin binds with its membrane receptors, membranes of 80% of the body's cells increase uptake of glucose. This is especially true of muscle cells and adipose cells, but not true of most neurons. The increased glucose transport is to result from translocation of intracellular vesicles to the cell membranes, which carry glucose transport proteins, which bind with the cell membrane and facilitate glucose uptake into the cells.
2. Cell membrane becomes more permeable to many of the amino acids, potassium ions, and phosphate ions. (Increases their uptake by cells)
3. Slower effects occur during the next 10 to 15 minutes.
4. Much slower effects continue to occur for hours and even several days. They result from changed rates of translation of messenger RNAs to form new proteins and still slower effects from changed rates of transcription of DNA in the cell nucleus.



Physiological roles of insulin

- Enhances transport of glucose into cells.
- Activates glycogen synthase.
- Activates glucokinase (storage of glucose).
- Enhances conversion of sugar to glycerol.
- Stimulates lipid synthesis.
- Stimulates transport of amino acids (by specific transporters) and protein synthesis.
- Stimulates K+ uptake by cell (increases the activity of Na-K ATPase in cell membranes). Increase K+ influx

Action of Insulin	Effect on Blood Level
Increases glucose uptake into cells	Decreases blood [glucose]
Increases glycogen formation	
Decreases glycogenolysis	
Decreases gluconeogenesis	
Increases protein synthesis (anabolic)	Decreases blood [amino acid]
Increases fat deposition	Decreases blood [fatty acid]
Decreases lipolysis	Decreases blood [ketoacid]
Increases K^+ uptake into cells	Decreases blood [K^+]

Role of hormones in switching between carbohydrate and lipid metabolism:

Growth hormone, cortisol, epinephrine, and glucagon:

Growth hormone and cortisol are secreted in response to hypoglycemia, and both inhibit cellular utilization of glucose while promoting fat utilization. The effects of these hormones develop slowly, usually requiring many hours to days.

Epinephrine is important in increasing plasma glucose concentration and fatty acid concentration during stress when the sympathetic system is excited.

The reasons are:

1. Potent effect of causing glycogenolysis in the liver, thus releasing large quantities of glucose into the blood within minutes.
2. A direct lipolytic effect on the adipose cells because it activates adipose tissue hormone-sensitive lipase. The enhancement of fatty acids is far greater than the enhancement of blood glucose. Epinephrine enhances the utilization of fat in stressful states as exercise, circulatory shock, and anxiety.

Lack of effect of insulin on glucose uptake and usage by the brain:

1. The brain is different from most other tissues of the body in that insulin has little effect on uptake or use of glucose. Instead, most of the brain cells are permeable to glucose and can use glucose without the intermediation of insulin.
2. The brain cells are different from most other cells of the body in that they normally use only glucose for energy and can use other energy substrates, such as fats, only with difficulty.
3. When the blood glucose level falls into the range of 20 to 50 mg/100 ml, symptoms of hypoglycemic shock develop, characterized by progressive nervous irritability that leads to fainting, seizures, loss of fine motor skills,and even coma.

Insulin deficiency increases use of fat for energy:

- The enzyme hormone-sensitive lipase in the fat cells becomes strongly activated
- Releasing large quantities of fatty acids and glycerol into the circulating blood
- In the mitochondria, oxidation of fatty acids occurs, releasing acetyl-CoA
- Acetyl-CoA is then condensed to form acetoacetic acid (released into the circulation)
- Acetoacetic acid is also converted into β-hydroxybutyric acid and acetone
- These two substances, along with the acetoacetic acid, are called ketone bodies. The hydrogen ions from these acids are buffered, but the buffering capacity is soon exceeded if production is increased.

Insulin effects on:

Skeletal muscle

During much of the day (between meals), muscle tissue depends not on glucose but on fatty acids for its energy. The normal resting muscle membrane is only slightly permeable to glucose, except when the muscle fiber is stimulated by insulin. The amount of insulin that is secreted is too small to promote significant amounts of glucose entry into the muscle cells.
Under two conditions, the muscles use large amounts of glucose:
I. During moderate or heavy exercise. This usage of glucose does not require large amounts of insulin because muscle contraction increases translocation of glucose transporter 4 (GLUT 4) to the cell membrane.
2. During few hours immediately after a meal. At this time, the blood glucose concentration is high, and the pancreas is secreting large quantities of insulin.

Liver

I. Inactivates liver phosphorylase, the principal enzyme that causes liver glycogen to split into glucose.
2. Insulin causes enhanced uptake of glucose from the blood by the liver cells by increasing the activity of the enzyme glucokinase. Once phosphorylated, the glucose is temporarily trapped inside the liver cells because phosphorylated glucose cannot diffuse back through the cell membrane.
3. Insulin activates glycogen synthase.
4. Inactivates lipase inside the hepatocytes.

When the blood glucose level begins to fall to a low level between meals, several events cause the liver to release glucose back into the circulating blood :
I. Pancreas decreases its insulin secretion.
2. The lack of insulin activates the enzyme phosphorylase, which causes the splitting of glycogen into glucose and phosphate.
3. The enzyme glucose phosphatase, which had been inhibited by insulin, now becomes activated.

Fat Metabolism

Glucose transport into adipocytes ↑
Enzyme activity (Lipoprotein Lipase) in capillary walls of adipose tissues ↑
FFA entry into adipocytes ↑
Lipolysis ↓
Hence it builds up fat reserves.
Inhibition of lipase in fat cells.
Synthesis of glycerol from glucose.

-Insulin increases utilization of glucose by most of the body's tissues, which automatically decreases the utilization of fat, thus functioning as a fat sparer.
- Insulin promotes fatty acid synthesis, especially when more carbohydrates are ingested than can be used for immediate energy, thus providing the substrate for fat synthesis. Almost all this synthesis occurs in the liver cells.

- 50% of an ingested glucose load is normally burned to CO2 and H2O; 5-I0% is converted to glycogen; and 30–40% is converted to fat in the fat depots.
-In diabetes, less than 5% of ingested glucose is converted to fat, despite a decrease in the amount burned to CO2 and H2O, and no change in the amount converted to glycogen.

Protein Metabolism

(Anabolic Effect)

I. Stimulates transport of many amino acids into cells sharing with growth hormone.

2. Insulin increases the rate of transcription of selected DNA, thus forming increased quantities of RNA and more protein synthesis especially promoting enzymes for storage of carbohydrates, fats, and proteins.

3. Inhibits catabolism of proteins, especially in muscle cells. This results from the ability of insulin to diminish the normal degradation of proteins by cellular lysosomes.

4. In the liver, insulin depresses the rate of gluconeogenesis by decreasing activity of the enzymes that promote gluconeogenesis.

Insulin Effect

Rapid (seconds) | **Intermediate (minutes)** | **Delayed (hours)**

1. ↑ Transport of glucose, amino acids, K+ into insulin sensitive cells
2. ↑ Protein synthesis
   ↑ Of glycolytic enzymes and glycogen synthase.
   ↓ Protein degradation
   ↓ Phosphorylase and gluconeogenic enzymes
3. ↑ mRNAs for lipogenic and other enzymes

Action of insulin

Action of insulin	
On muscles	**On glucose:** • ↑ Glycolysis , glycogenesis • ↓ Glycogenolysis • ↑ Glucose entry / uptake by increasing GLUT-4 availability • ↑K^+ uptake • ↑ Ketone uptake • ↑ Glycogen synthesis • ↓ Release of gluconeogenic amino acids A.A that help in glucose synthesis
	On proteins: • ↑ Amino acid uptake (particularly branched chain A.A) • ↑ Protein synthesis in ribosomes • ↓ Protein catabolism • ↓ Proteolysis
on Adipose Tissue	• Glucose entry (uptake) by ↑ Glut-4 availability + K+ uptake • ↑ α-glycerol phosphate synthesis • ↑ triglyceride deposition • ↑ lipoprotein lipase • ↓ hormone-sensitive lipase • ↑ Esterification of fat • ↓ Lipolysis
On liver	• ↑ Glucose uptake (if blood glucose level is high) • ↑ Glycolysis , glycogenesis (glycogen synthesis) • ↓ Ketogenesis • ↓ Glycogenolysis , gluconeogenesis • ↑ protein synthesis , lipid synthesis • ↓ Urea cycle activity • ↑ Fatty acid synthesis and very-low-density lipoprotein formation.
General	• ↑ cell growth

Glucagon

Definition

- Hormone secreted by Alpha cells of the islets of Langerhans, in the lower gastrointestinal tract, and in the brain.
- A 29-amino-acid polypeptide hormone that is a potent hyperglycemic agent.
- Secreted When blood glucose concentration falls (skipping meals, fasting), Glucagon has several functions that are opposed to those of insulin.
- Like insulin, glucagon is a large polypeptide.

Glucagon Synthesis

It acts via Gs to activate adenylyl cyclase and increase intracellular cAMP.
This leads to activation of protein kinase A to activate phosphorylase and therefore to increased breakdown of glycogen and an increase in plasma glucose.

DNA in α cells (chromosome 2)

↓

mRNA (processed differently in different tissues)

↓

Preproglucagon

↓

proglucagon

↓

Glucagon (Half life 5-10 min, degraded by the liver)

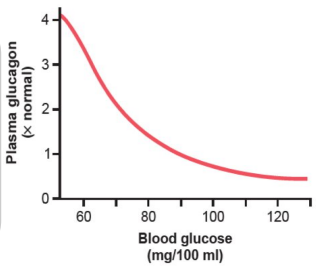
Glucagon regulation

STIMULI

- Low blood glucose (Hypoglycaemia)
- Sympathetic
- ↑ Amino acid (arginine, alanine)
- Stress
- Exercise

Inhibitors

- High blood glucose (hyperglycemia)
- Parasympathetic
- Somatostatin
- Insulin

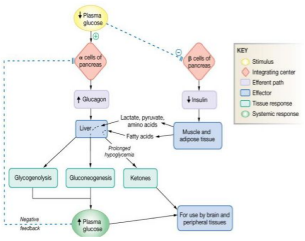


Blood glucose concentration is the most potent factor that controls glucagon secretion, which is exactly the opposite direction from the effect of glucose on insulin secretion.

High concentrations of amino acids, such as those that occur in the blood after a meal containing protein (especially the amino acids alanine and arginine), stimulate the secretion of glucagon. This is the same effect that amino acids have in stimulating insulin secretion.

During exercise, blood concentration of glucagon increases 4-5-fold. A beneficial effect of the glucagon is that it prevents a decrease in blood glucose.

Glucagon



Glucagon

Action on Cells

Its **major** target is **liver** :

- Glycogenolysis.
- Gluconeogenesis.
- Lipid oxidation (fully to CO2 or partially to produce keto acids "ketone bodies").
- Release of glucose to the blood from liver cells.

Glucagon deficiency

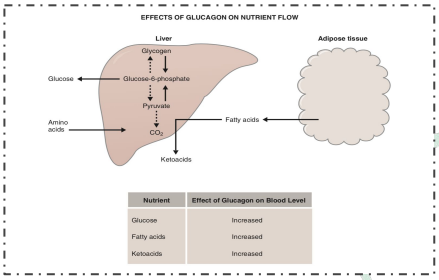
Glucagon deficiency can cause : hypoglycemia, and glucagon excess makes diabetes worse.

Other actions for glucagon

Other actions for glucagon	
Carbohydrates	• Increases blood glucose level by stimulating: I. glycogenolysis by liver 2. gluconeogenesis (conversion of amino acids to glucose)
Protein	• **In muscle:** Breakdown of protein. • **In liver:** Decrease protein synthesis.
Lipid	• Stimulates lipolysis in liver & adipose tissue. • Increases FFA in blood. • Increases blood keto acid.
Adipose cell	• activates adipose cell lipase, making increase in quantities of fatty acids available to the energy systems of the body.
Triglyceride	• Glucagon inhibits the storage of triglycerides in the liver, which prevents the liver from removing fatty acids from the blood.

Glucagon in high concentrations

1. enhances the strength of the heart
2. increases blood flow in some tissues,especially the kidneys
3. enhances bile secretion
4. inhibits gastric acid secretion. These effects of glucagon are probably of much less importance in the normal function of the body compared with its effects on glucose.



Solid arrows indicate that the step is stimulated; dashed arrows indicate that the step is inhibited.

Extra: تعرفون ليش؟
Normally your body reabsorbs glucose as it passes through your kidneys, but when diabetes raises your blood sugar, your kidneys may not be able to bring it all back in. This causes the body to make more urine. Because you're urinating so much, you can get thirsty. When you drink more, you'll also urinate more.

Somatostatin

All Male slides
Except for the red found in Both

Somatostatin

- Delta cells secrete somatostatin, a 14–amino acid polypeptide that has an extremely short half-life of only 3 minutes in blood.
- Somatostatin inhibits glucagon and insulin secretion
- Excess pancreatic production of somatostatin (somatostatinomas) develop hyperglycemia and other manifestations of diabetes that disappear when the tumor is removed.

Factors stimulate somatostatin include:

- increased blood glucose
- increased amino acids
- increased fatty acids
- increased concentrations of several gastrointestinal hormones released from the upper gastrointestinal tract in response to food intake.
- Excess pancreatic production of somatostatin (somatostatinomas) develop hyperglycemia and other manifestations of diabetes that disappear when the tumor is removed

Somatostatin has multiple inhibitory effects:

- Somatostatin acts locally within the islets of Langerhans themselves to depress secretion of both insulin and glucagon (paracrine effect).
- (2) Somatostatin decreases motility of the stomach, duodenum, and gallbladder.
- (3) Somatostatin decreases both secretion and absorption in the gastrointestinal tract.

Importance of glucose regulation

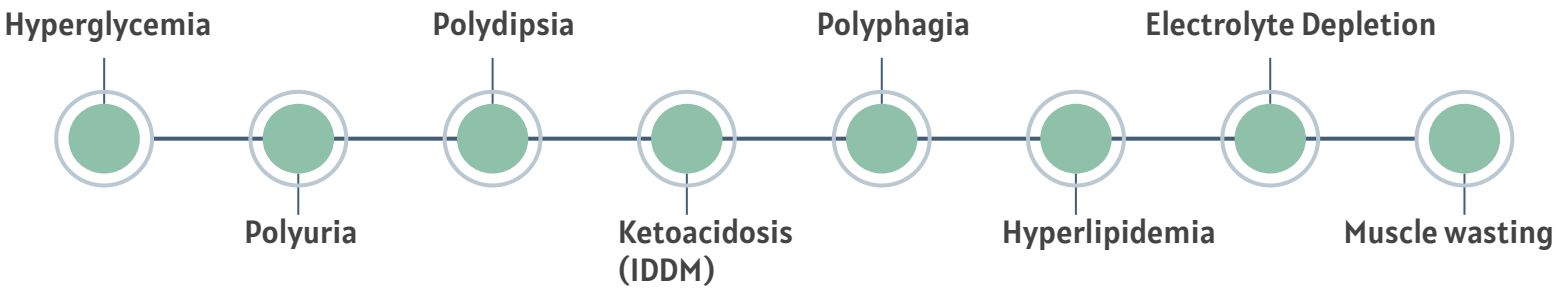
1	Glucose exerts osmotic pressure in extracellular fluid, and a rise in glucose concentration to excessive values can cause considerable cellular dehydration.
2	An excessively high level of blood glucose concentration causes loss of glucose in the urine.
3	Loss of glucose in the urine also causes osmotic diuresis by the kidneys, which can deplete the body of its fluids and electrolytes.
4	Long-term increases in blood glucose may cause damage to many tissues, especially to blood vessels (endothelial dysfunction). Vascular injury associated with uncontrolled diabetes mellitus leads to increased risk for heart attack, stroke, end-stage renal disease, and blindness.
5	If glucose falls into 50-70mg /100ml, central nervous system becomes excitable (trembles, sweat).
6	When blood glucose level falls to 20-50 mg/100 ml, loss of fine motor skills, clonic seizures and loss of consciousness (hypoglycemic shock).

Diabetes

Definition

Diabetes is probably the most important metabolic disorder.
Types of Diabetes:
I- Type I diabetes, called insulin- dependent diabetes mellitus, is caused by lack of insulin secretion.
2. Type 2 diabetes, called non–insulin- dependent diabetes mellitus, is initially caused by decreased sensitivity of target tissues to the metabolic effect of insulin. This reduced sensitivity to insulin is often called insulin resistance.
3. Gestational Diabetes (during pregnancy)
4. Diabetes insipidus (ADH).

Symptoms of Diabetes:



Pathophysiology	Respond
Reduced glucose entry into cells. Increased glucose release from liver. Extracellular glucose excess, intracellular glucose deficiency. Impaired glucose tolerance. Decreased Amino Acid entry into cells. Lipolysis↑.	Hyperglycemia Hyperosmosis → osmotic shrinking of the cells Glycosuria → Polyuria → Polydipsia Dehydration Fat mobilization → Abnormal Deposition → Micro and Macro- vascular disease (Atherosclerosis) → Ineffective blood supply

Organs/tissue involved	Organ/tissue responses to insulin deficiency	Resulting condition of:		Signs and symptoms
		Blood	Urine	
	Decreased glucose uptake and utilization	Hyperglycemia	Glycosuria	**Polyuria** - dehydration - soft eyeballs
	Glycogenolysis		Osmotic diuresis	**Polydipsia** Fatigue Weight loss
	Protein catabolism and gluconeogenesis			**Polyphagia**
	Lipolysis and ketogenesis	Lipidemia and ketoacidosis	Ketonuria	Acetone breath Hyperpnea
			Loss of Na^+, K^+; electrolyte and acid-base imbalances	Nausea/vomiting/ abdominal pain Cardiac irregularities Central nervous system depression; coma

= Muscle = Adipose tissue = Liver

Types of Diabetes:

Diabetes Mellitus Type I insulin dependent (Autoimmune attack) (10%)	
Epidemiology	- Mainly affects children - Juvenile onset
Cause	Immune-mediated selective destruction of β cells, leading to: Hyposecretion of insulin.
Pathogenesis	β cells are destroyed while α cells are preserved: - No insulin&↑ glucagon > High production of glucose and ketones by liver. - ↑ Glucose & ketones > Osmotic diuresis - ↑ Keto acids > Diabetic ketoacidosis (common complication in uncontrolled diabetes) - Defect in insulin might lead to Hyperkalemia - Injury to the beta cells of the pancreas or diseases that impair insulin production can lead to type I diabetes. Viral infections or autoimmune disorders may be involved. Various anti-B cell antibodies are present in plasma, but the current thinking is that type I diabetes is primarily a T lymphocyte-mediated disease. - Heredity also plays a major role in determining the susceptibility of the beta cells to destruction by these insults. In some instances, persons may have a hereditary tendency for beta cell degeneration even without viral infections or autoimmune disorders.
Management and Treatment	Insulin dependent, so the treatment is: Insulin Injection
Diabetes Mellitus Type II (90%-95%)	
Epidemiology	- More common in some ethnic groups. - Late onset, genetic and family related risk factors. - In most cases, onset of type 2 diabetes occurs after age 30 years, often between the ages of 50 and 60 years, and the disease develops gradually. Therefore, this syndrome is often referred to as adult- onset diabetes. - In recent years, there has been an increase in the number of younger individuals, some younger than 20 years old, with type 2 diabetes. This trend appears to be related mainly to the increasing prevalence of obesity, the most important risk factor for type 2 diabetes in children and adults.
Cause	- Unhealthy foods and inactive lifestyles with sedentary behaviour - Resistance of body cells to insulin keeps blood glucose too high - الأسباب: قلة الحركة + fast food + ونظام الأكل, ربع المجتمع (كل أربعة أشخاص شخص مصاب) في السعودية فيهم سكر.
Management and Treatment	- Lifestyle modification with physical activity and/or healthy diet - Diet and oral hypoglycemic agents > يحفز إفراز الإنسولين
Complications	- Atherosclerosis. - Renal failure. - Blindness.
Gestational Diabetes (during pregnancy)	
Epidemiology	Occurs in 2-5% of pregnancies.
Cause	Associated with decreased insulin levels and/or insulin resistance.
Pathogenesis	Resembles Type 2 Diabetes.
Management and Treatment	Usually transient: symptoms improve following delivery.
Complications	If untreated → macrosomia (high birth weight). (The child might encounter hypoglycemia at birth)

Long Term Complications of Uncontrolled Diabetes (microvascular disease):

Note!

Intestinal absorption of glucose is unaffected, as is its reabsorption from the urine by the cells of the proximal tubules of the kidneys, Glucose uptake by most of the brain and the red blood cells is also normal.
Fifty percent of an ingested glucose load is normally burned to CO2 and H2O; 5-10% is converted to glycogen; and 30–40% is converted to fat in the fat depots. In diabetes, less than 5% of ingested glucose is converted to fat, despite a decrease in the amount burned to CO2 and H2O, and no change in the amount converted to glycogen.

1. Diabetic retinopathy → Vision loss
2. Diabetic nephropathy→ Kidney damage →chronic renal failure
3. Diabetic neuropathy →
   - Damage to the nerve
   - Most common cause of amputation in western world
   - problems in proprioception
4. Atherosclerosis
5. Hyperlipidimia (increase cholesterol). once diabetic patient is admitted we give anti-cholesterol drugs even if they don't have it yet
6. CVS complication and circulatory problems (gangrene) due to micro and macrovascular disease. Microvessels formation might lead to death.

Glucose Tolerance Test:

Female slides

Glucose Tests :
- fasting blood glucose (FPG)
- oral glucose tolerance test (OGTT)

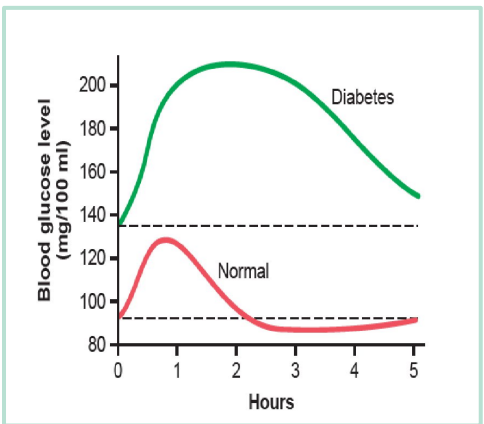
Both tests require that the patient fast for at least 8 hours (ideally 12 hr) prior to the test.

- The oral glucose tolerance test (OGTT) (the most sensitive test to pancreas B-cell insulin secretary reserve):
  - FPG test then the patient drinks a special glucose solution with (75g glucose) → blood is then taken 2 hours after drinking
  - Following the oral administration of a standard dose of glucose → the plasma glucose concentration normally rises but returns to the fasting level within 2 hours
  - If insulin activity is reduced → the plasma glucose concentration takes longer than 2 hours to return to normal & often rises above 200 mg/dL
  - Measurement of urine glucose allows determination of the renal threshold for glucose (180-200 mg/dL)

Diagnosis of diabetes:

- Urinary Glucose. - Insulin and C-peptide levels. -Glucose Tolerance Test (GTT).
- Acetone Breath. -HbAIc

This table is imp	FPG	2hr PPG
Normal values	<100 mg/dL <5.6 mmol/L	<140 mg/dL <7.8 mmol/L
Impaired glucose tolerance (IGT) Prediabetic	100-125 mg/dL 5.6-6.9 mmol/L	140-199 mg/dL 7.8-11.1 mmol/L
Diabetes	≥126 mg/dL ≥6.9 mmol/L	≥200 mg/dL ≥11.1 mmol/L



Treatment of diabetes:

Treatment of diabetes:

Type 1 diabetes mellitus:

administration of insulin Different type of insulin:

- Bovine, Porcine, Human insulin produced by bacteria by recombinant DNA technology.
- Three categories: rapid, intermediate, and long-acting (24–36 h).

In Type 2 diabetes:

diet and exercise. If this strategy fails:

- Sulfonylurea: increase insulin release by closing K+-ATP channels in the pancreatic β- cell membrane.
- Biguanides: such as metformin, reduce hepatic glucose output (inhibition of gluconeogenesis and glycogenolysis) and increase insulin-stimulated glucose uptake in skeletal muscle and adipocytes.
- Alpha-glucosidase delay the intestinal absorption of carbohydrates through inhibition of the brush-border enzymes that hydrolyze polysaccharides to glucose.

In many persons, however, exogenous insulin must be used.

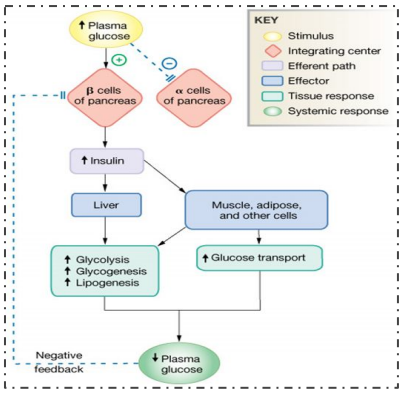
In Hypoglycemic coma:

- intravenous administration of glucose, administration of glucagon or epinephrine can cause glycogenolysis in the liver and increase blood glucose level rapidly. If treatment is not administered immediately, permanent damage to the neuronal cells often occurs.
- Transplantation and stem cells

Summary of Insulin:

Table 22-3: Insulin

Cell of origin	Beta cells of pancreas
Chemical nature	51-amino acid peptide
Biosynthesis	Typical peptide
Transport in the circulation	Dissolved in plasma
Half-life	5 minutes
Factors affecting release	Plasma [glucose] > 100 mg/dL; ↑ blood amino acids; GI hormones (feedforward reflex) and parasympathetic amplify. Sympathetic inhibits.
Target cells or tissues	Liver, muscle, and adipose tissue primarily; brain, kidney, and intestine not insulin-dependent
Target receptor	Membrane receptor with tyrosine kinase activity; pathway with insulin-receptor substrates
Whole body or tissue action	↓ Plasma [glucose] by ↑ transport into cells or ↑ metabolic use of glucose
Action at cellular level	↑ Glycogen synthesis; ↑ aerobic metabolism of glucose; ↑ protein and triglyceride synthesis



Glucose Transporters:

(secondary active transport and facilitated diffusion):

Glucose transport system

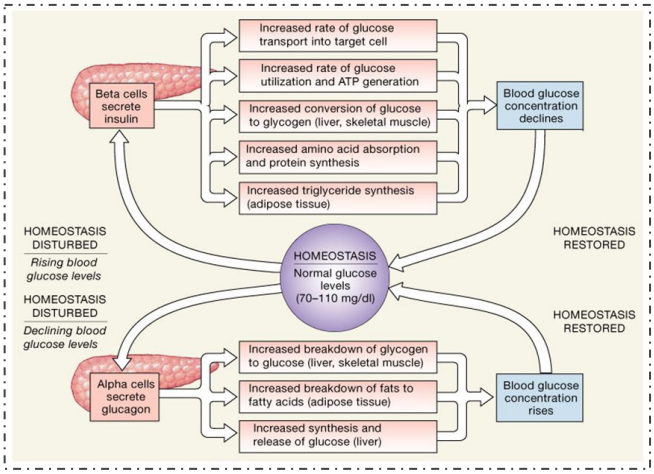
	Function	K_m (mM)*	Major Sites of Expression
Secondary active transport (Na⁺-glucose cotransport)			
SGLT 1	Absorption of glucose	0.1–1.0	Small intestine, renal tubules
SGLT 2	Absorption of glucose	1.6	Renal tubules
Facilitated diffusion			
GLUT 1	Basal glucose uptake	1–2	Placenta, blood-brain barrier, brain, red cells, kidneys, colon, many other organs
GLUT 2	B-cell glucose sensor; transport out of intestinal and renal epithelial cells	12–20	B cells of islets, liver, epithelial cells of small intestine, kidneys
GLUT 3	Basal glucose uptake	<1	Brain, placenta, kidneys, many other organs
GLUT 4	Insulin-stimulated glucose uptake	5	Skeletal and cardiac muscle, adipose tissue, other tissues
GLUT 5	Fructose transport	1–2	Jejunum, sperm
GLUT 6	Unknown	—	Brain, spleen and leukocytes
GLUT 7	Glucose 6-phosphate transporter in endoplasmic reticulum	—	Liver

*The K_m is the glucose concentration at which transport is half-maximal.

Summary of Glucagon:

Table 22-5: Glucagon

Cell of origin	Alpha cells of pancreas
Chemical nature	29-amino acid peptide
Biosynthesis	Typical peptide
Transport in the circulation	Dissolved in plasma
Half-life	4–6 minutes
Factors affecting release	Stimulated by plasma [glucose] < 200 mg/dL, with maximum secretion below 50 mg/dL; ↑ blood amino acids.
Target cells or tissues	Liver primarily
Target receptor/second messenger	G protein-coupled receptor linked to cAMP
Whole body or tissue action	↑ Plasma [glucose] by glycogenolysis and gluconeogenesis; ↑ lipolysis leads to ketogenesis in liver
Action at molecular level	Alters existing enzymes and stimulates synthesis of new enzymes
Feedback regulation	↑ Plasma [glucose] shuts off glucagon secretion
Other information	Member of secretin family along with VIP, GIP, and GLP-1

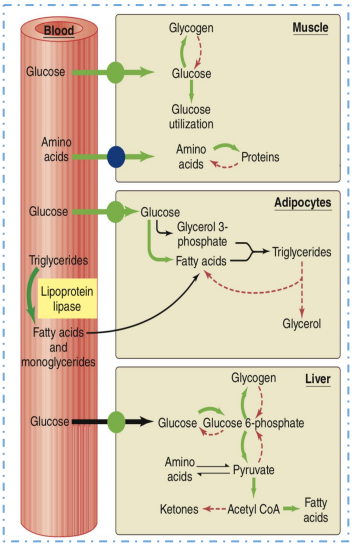


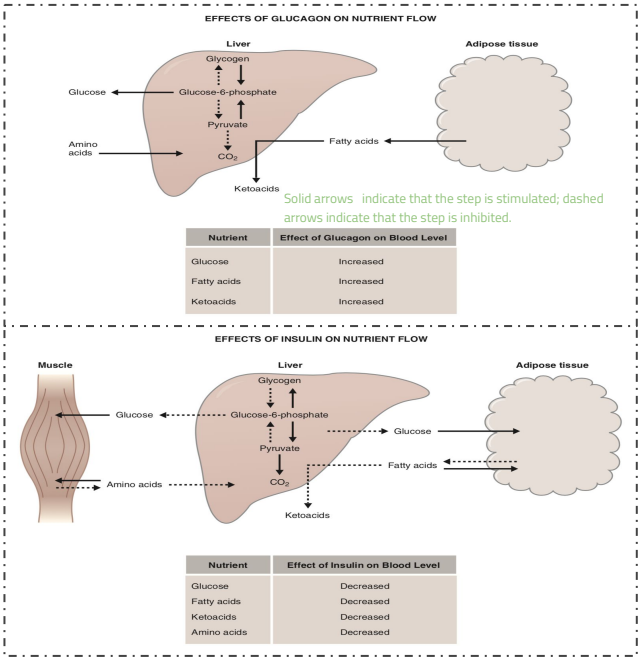
Summary of diabetes mellitus effect:

Organs/tissue involved	Organ/tissue responses to insulin deficiency	Resulting condition of: Blood	Resulting condition of: Urine	Signs and symptoms
	Decreased glucose uptake and utilization	Hyperglycemia	Glycosuria	**Polyuria** - dehydration - soft eyeballs
	Glycogenolysis		Osmotic diuresis	**Polydipsia** Fatigue Weight loss
	Protein catabolism and gluconeogenesis			**Polyphagia**
	Lipolysis and ketogenesis	Lipidemia and ketoacidosis	Ketonuria Loss of Na^+, K^+; electrolyte and acid-base imbalances	Acetone breath Hyperpnea Nausea/vomiting/ abdominal pain Cardiac irregularities Central nervous system depression; coma

= Muscle = Adipose tissue = Liver

EXTRA Insulin:



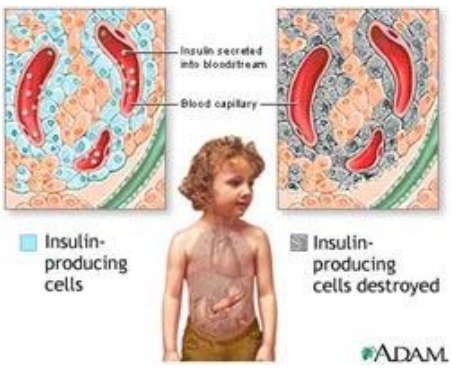


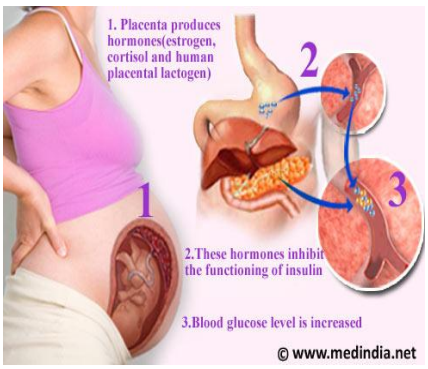
Extra: تعرفون ليش؟
Normally your body reabsorbs glucose as it passes through your kidneys, but when diabetes raises your blood sugar, your kidneys may not be able to bring it all back in. This causes the body to make more urine. Because you're urinating so much, you can get thirsty. When you drink more, you'll also urinate more.

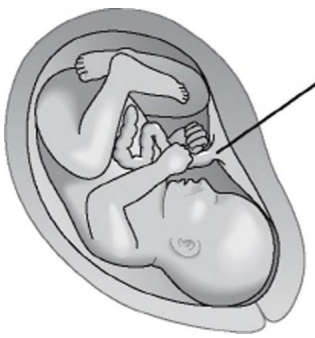
My blood sugar: *gets slightly high*
All the pee in my body:

The immune system after killing the beta cells in the pancreas that produce insulin

Pics from slides of diabetes mellitus effect:

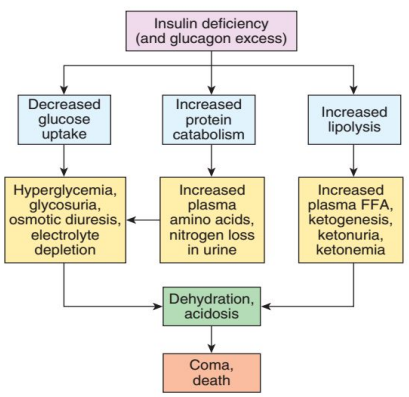






1. **Mother's blood brings extra glucose to fetus.**
2. **Fetus makes more insulin to handle the extra gluscose.**
3. **Extra glucose gets stored as fat and fetus becomes larger than normal.**

- Obesity/overweight (especially excess visceral adiposity)
- Excess glucocorticoids (Cushing's syndrome or steroid therapy)
- Excess growth hormone (acromegaly)
- Pregnancy, gestational diabetes
- Polycystic ovary disease
- Lipodystrophy (acquired or genetic; associated with lipid accumulation in liver)
- Autoantibodies to the insulin receptor
- Mutations of insulin receptor
- Mutations of the peroxisome proliferators' activator receptor γ (PPARγ)
- Mutations that cause genetic obesity (e.g., melanocortin receptor mutations)
- Hemochromatosis (a hereditary disease that causes tissue iron accumulation)



Feature	Type 1	Type 2
Age at onset	Usually <20 yr	Usually >30 yr
Body mass	Low (wasted) to normal	Visceral obesity
Plasma insulin	Low or absent	Normal to high initially
Plasma glucagon	High, can be suppressed	High, resistant to suppression
Plasma glucose	Increased	Increased
Insulin sensitivity	Normal	Reduced
Therapy	Insulin	Weight loss, thiazolidinediones, metformin, sulfonylureas, insulin

MCQs:

Q1: The islets of Langerhans which produce:

A. androgens	B.estrogens	C. Both A&B	D. Insulin .

Q2: amylin inhibits secretion of

A.Pregnenolone	B.vit D	C.insulin.	D.somatotropin

Q3: somatostatin inhibits the secretion of

A. insulin.	B. glucagon	C. Glucose	D. Both A & B

Q4: What is true regarding the activation of hormone-sensitive lipase in adipocytes ?

A. Causes increased hydrolysis of cholesterol esters	B. Is mediated by a cyclic AMP-dependent protein kinase	C. Is prevented by cortisol	D. Is stimulated by insulin

Q6: Insulin deficiency leads to which of the following?

A. Increased cellular uptake of glucose	B. Decreased intracellular a-glycerophosphate in liver and fat cells	C. Enhanced glucose uptake and use except by brain tissue	D. Decreased fatty acid release from Adipose tissue

1- D ,2-C ,3- C ,4-B (not sure) ,, 6- B or D (not sure)

SAQ :

1. List 4 types of cells in the islets of langerhans with their secretion?
2. List the type of insulin receptors with their location?
3. Which organ is the main target of glucagon hormone & list 3 effects?
4. What is the difference between type I diabetes & type 2 diabetes?
5. What the tests use to measure glucose?

Q1: -Beta cells: Insulin. -Alpha cells: Glucagon. -Delta cells: Somatostatin. -F cells: Pancreatic polypeptide.
Q2: -GLUTI: erythrocytes and brain. -GLUT2: liver, pancreas, small intestines, kidney. -GLUT3: brain. -GLUT4: adipose tissue and muscles (insulin dependent).
Q3: Liver - Glycogenolysis & Gluconeogenesis & Ketogenesis.
Q4: TypeI: affects children, caused by inadequate insulin secretion (deficiency due to destruction of beta cells), treated by insulin injection. Type2: affects adults, caused by defect in insulin action (resistance), treated by diet and oral hypoglycemic drugs.
Q5: I-FPG 2-OGTT

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Rawan Al Qahtani

Faisal Al Showier

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Yousof Badoghaish

Zeyad Al Otaibi

Aban Basfar

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