بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pharmacology | FINAL 6

Insulin and Oral Hypoglycemic Drugs pt.1

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Regarding the previous lecture

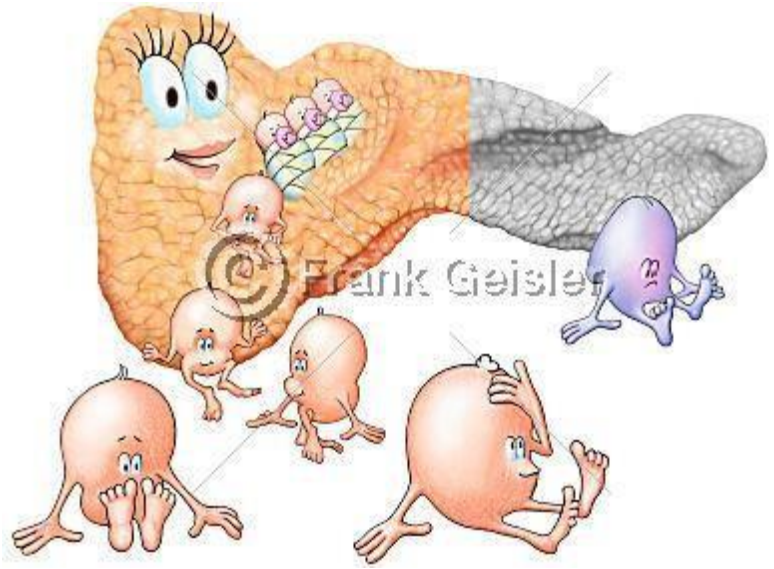
Regarding the last lecture, the effect of **cortisol** on **growth hormone** release is seen in **two phases.** The first phase, at the moment of glucocorticoid injection, increases growth hormone release.
However, after long and continuous administration, it decreases and declines growth hormone levels. And that's the reason why it causes **abnormal growth** in children when administered.

Insulin and Oral Hypoglycemic Drugs

Introduction

Pancreas produces:

1. Insulin by β cells
2. Glucagon by α cells
3. Somatostatin by δ cells



- Lack of insulin causes sever hyperglycemia >>> if not treated >>>> causes retinopathy, nephropathy, neuropathy and cardiovascular compilations.

Pancreatic Hormones and Blood Glucose

We'll concentrate on pancreatic hormones controlling blood glucose level. Because, as we know, an imbalance causes diabetes mellitus, which is a hyperglycemia case, and its **prevalence in Jordan is 33%,** which is very high. The main hormones are insulin and glucagon. **Insulin** is secreted by **beta** cells and causes a **decrease** in blood glucose level, while **glucagon** is secreted by **alpha** cells and has an **opposite** effect.

Physiology of Insulin Secretion

Now, let's talk about physiology a little bit. When you eat a meal high in sugar, glucose in your blood goes to the beta cells and enters them, and then it's phosphorylated by a kinase into **glucose-6-phosphate**, which increases the production of ATP intracellularly. This affects an **ATP-sensitive potassium efflux.** In normal cases, potassium exits the cell, and the cell becomes less positive, which means hyperpolarization, causing blockage of insulin release. In cases of increased ATP intracellularly, this **channel is inhibited,** leading to **depolarization** and positive charge accumulation inside the cell. This causes calcium voltage-gated channels to open, causing calcium influx, which causes **exocytosis** of vesicles containing insulin.

Insulin Receptor and Glucose Uptake

When insulin is released, it's an agonist, so it must bind to a receptor. In the case of insulin, it is a **tyrosine kinase-linked** receptor, found in nearly all our cells, including skeletal muscles, liver, and adipocytes. It causes the opening of **glucose transporters** in these target cells, and as a result, glucose is being used as an energy source. We revised all that because we will talk about some drugs that work on this process in treating diabetes mellitus.

Introduction

- 180 million people worldwide are affected with diabetes.

- Diabetes is NOT a single disease, it is a group of heterogenous syndromes that cause elevation in glucose blood level and insufficient insulin secretion.

- **4 clinical classifications of diabetes:**

1) Type 1: insulin dependant
2) Type 2: NON-insulin dependant
3) Gestational diabetes (during pregnancy>> affects fetus)
4) Diabetes due to other factor (genetics or medication induced).

Types of Diabetes Mellitus

Diabetes mellitus has more than two types. Diabetes **type 1**, insulin-dependent, is caused by either an **autoimmune** disease or **viral** infection, leading to nearly **no insulin** production in our cells. **Type 2**, insulin-independent, means beta cells secrete insulin, but it **doesn't bind** to its receptors, so we have insulin resistance.

Insulin Production and C-Peptide

As we know, insulin is a **peptide**, so it's **never** administered **orally**. It is first produced as proinsulin, which is then converted into active insulin and released along with **C-peptide** as a byproduct. The importance of C-peptide is that it's **more accurate** in reflecting insulin levels than insulin itself. Why? Because it has a longer half-life and it's not extracted by the liver.

C-Peptide as a Clinical Marker

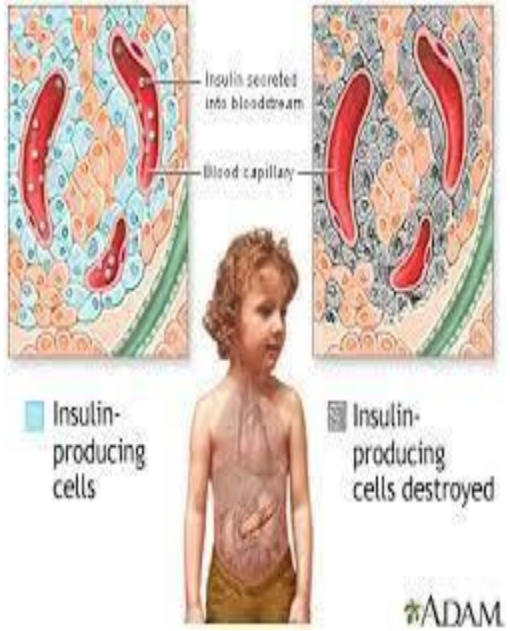
We also use it to differentiate between type 1 and type 2. Type 1 has little C-peptide, while type 2 has a lot of C-peptide in the blood. Something that is very important to note is that exogenous insulin used in treatment does not contain C-peptide. That's why it is a marker for **knowing endogenous** insulin levels.

Extra information regarding the liver extraction part:

Insulin: After pancreatic secretion, insulin enters the **portal vein** and reaches the liver first. The liver extracts a large proportion of insulin before it reaches the systemic circulation.
C-peptide: It is secreted **in equimolar amounts with insulin**, but the liver has very little first-pass extraction of C-peptide. Therefore, much more of it reaches the systemic circulation. So if we measure C-peptide in the blood, it gives us a **better reflection of the insulin being produced by the pancreas**than measuring insulin itself.

Type 1 diabetes

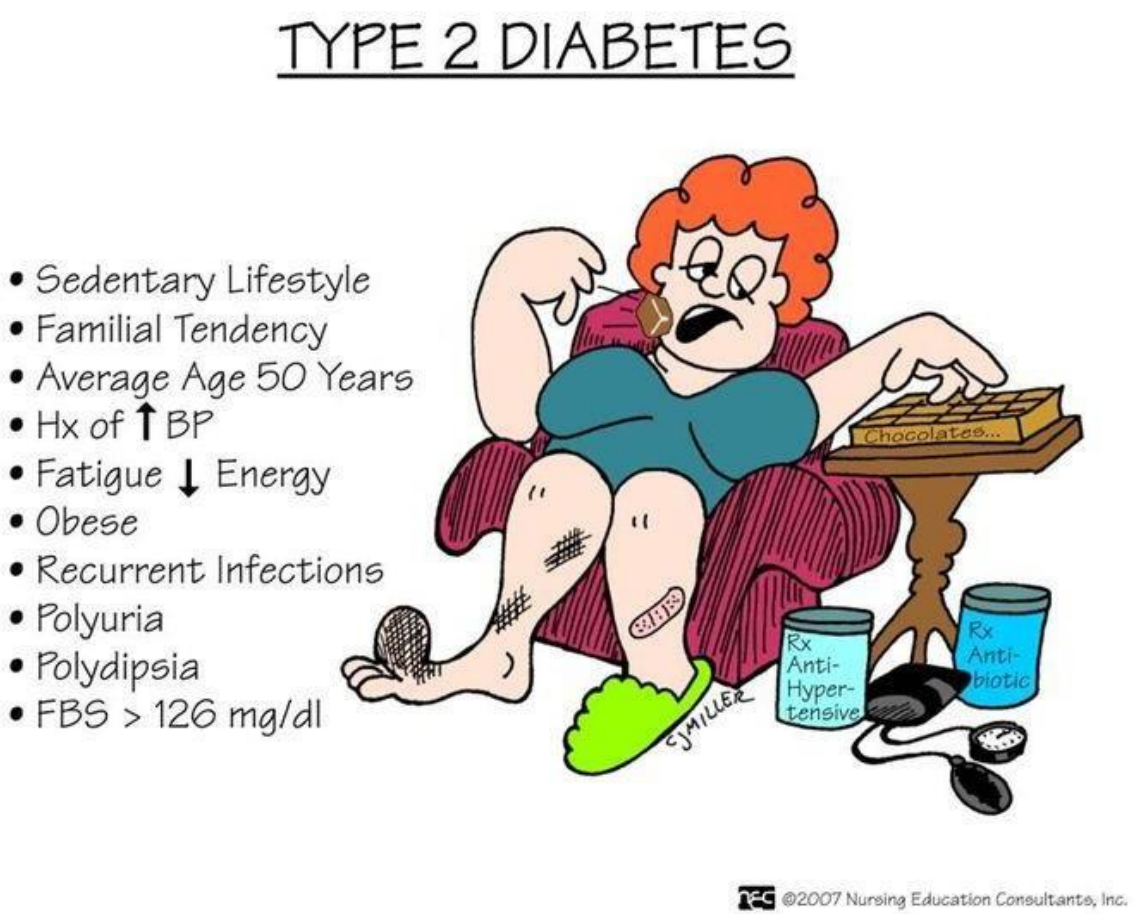
- Most common affects individuals in puberty or early adulthood.
- Absolute deficiency of insulin caused by massive β-cell necrosis.
- Autoimmune mediated process directed against β-cell and it may be due to virus invasion or chemical toxins.
- **Symptoms:** Polydipsia, polyuria and weight loss
- Life threatening Ketoacidosis.
- Requires exogenous insulin (important) to control hyperglycemia and ketoacidosis and to maintain the accepted level of glyosylated hemoglobin (HbA1c) to avoid the long term complications.
- Can neither maintain normal insulin secretion level nor respond to variations in the circulating glucose and amino acid.



Type 2 diabetes

- Most diabetes are type 2
- Is influenced by genetic factors, aging, obesity and peripheral insulin resistance.
- Milder metabolic alterations than type 1.
- **No** ketoacidosis.
- The pancreas retains some β-cell function, but variable insulin secretion is insufficient to maintain glucose homeostasis.
- The β-cell mass may become gradually reduced in Type 2 diabetes.
- Lack of sensitivity of target organs to insulin >>> The major cause of type 2 diabetes.
- **Treatment:** to prevent the long time compilation.
- As the disease progress, β-cell function declines and insulin therapy is often required to achieve the satisfactory serum glucose levels.

Type 2 diabetes

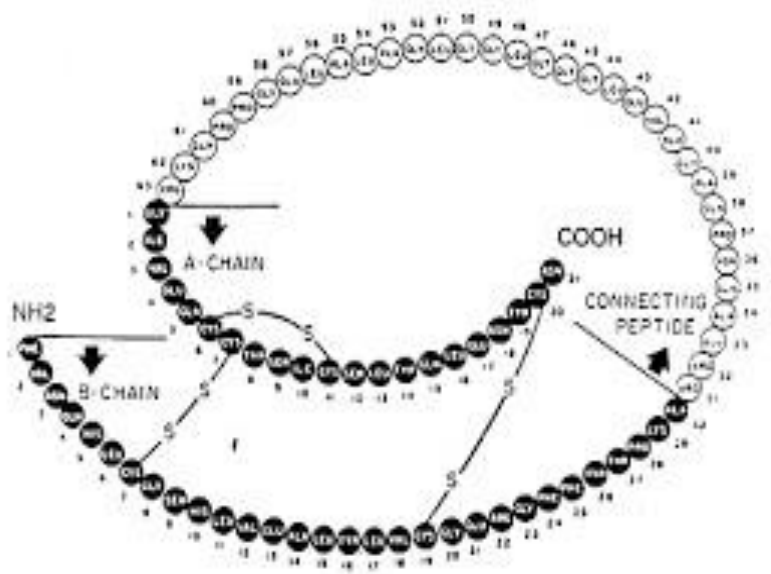


Insulin and Its Analogs

Insulin

- Is a polypeptide hormone >>> it is degraded in the GIT if taken orally >>>> administered by subcutaneous injection.
- It is synthesized as a precursor (pro-insulin) that undergoes proteolytic cleavage to form insulin and C peptide, both of which are secreted by the β cells of the pancreas.
- Measurement of circulating C peptide provides a better index of insulin levels!!!! (WHY?!)
- **Insulin secretion is regulated by:**

1) Blood glucose (The most important)
2) Certain amino acids
3) Gastro intestinal hormones
4) Autonomic mediators



Insulin and Its Analogs

- Glucose is taken into the pancreas >>> Glucose is posphoralated by glucokinase >> ATP production >>>> inhibits K+ influx >> depolarization >> Increased intracellular Ca++ secretion >>> Insulin secretion.

EFFECTS OF INSULIN

CARBOHYDRATES

- ↑ GLUCOSE UPTAKE
- ↑ GLYCOGEN SYNTHESIS(↑ STORAGE)
- ↓ GLUCONEOGENEIS(LIVER)
- ↑ GLYCOLYSIS (MUSCLE)
- ↑ CONVERSION OF CARBOHYDRATE TO FAT (LIPOGENESIS)

FAT

- ↓ LIPOLYSIS

PROTEIN

- ↑ AMINO ACID UPTAKE (PROTEIN SYTHESIS)

Metabolic Effects of Insulin

Insulin is an **anabolic** hormone. It increases protein synthesis and increases **lipogenesis** (which is crucial regarding the conversion of sugar eaten into fat stored). And that's why patients with diabetes mellitus taking insulin treatment always complain of weight gain. It also decreases lipolysis, INCREASES glycolysis, increases glycogenesis, and decreases gluconeogenesis, until reaching the main purpose, which is decreasing blood glucose level.

Insulin and Its Analogs

- Insulin preparations vary primarily in their times of onset and durations of activity. (WHY?!) due to differences in the amino acid sequences of the polypeptides and the type of formulation.

- For example, three such insulins (lispro, aspart, and glulisine) have a faster onset and shorter duration of action than regular insulin (Ultra short Ultra rapid), because they do not aggregate or form complexes. On the other hand, glargine and detemir are long-acting insulins and show prolonged, flat levels of the hormone following injection.

Insulin and Its Analogs

Adverse reactions to insulin

- Hypoglycemia is the most serious and common adverse reaction to an overdose of insulin.
- Weight gain
- Lipodystrophy (less common with human insulin)
- Allergic reactions, and local injection site reactions.

Classification of Diabetes Mellitus

Nowadays, it's not completely accurate to say type (juvenile) and type 2 for adults. It's more appropriate to say insulin-dependent and insulin-independent because many children nowadays develop **type 2** due to **obesity**. There is a strong correlation between obesity and diabetes mellitus type 2. **Why?** Because **visceral fat** is a place for **macrophages** to settle. When they reside there, they start producing and secreting cytokines (pro-inflammatory mediators), which **inhibit** insulin binding to its receptor, thus contributing more to the development of type 2 diabetes.

Insulin in Advanced Type 2 Diabetes

Now, in advanced stages of diabetes mellitus type 2, especially when glycosylated hemoglobin, which is hemoglobin A1c, is very high, it's recommended to prescribe insulin. Because chronic increases in blood glucose levels cause **complications** such as neuropathy, nephropathy, retinopathy, and cardiovascular system complications, leading to patients' mortality. So, preventing complications is our gold standard approach.

Development of Recombinant Human Insulin

In the **past**, they used to **kill an animal**, like a cow or a pig, in order to extract insulin for treatment. So, insulin in the past was from an **animal source**. And that's a disadvantage because our bodies could recognize it as a **foreign antigen** and start secreting antibodies. It was also very expensive as a process; killing an animal and then extracting its insulin is very expensive. So, it was limited to wealthy people.

When biotechnology was developed and they knew the cellular mechanisms of protein synthesis, they developed something called **recombinant human insulin** by combining the wanted human insulin gene with the plasmid and then inserting it into the bacteria. The bacteria starts synthesizing this human insulin, and we can simply culture the bacteria in large amounts. Here, there is **no rejection** produced because it's a human gene.

Routes of Administration of Insulin

The routes of administration of exogenous insulin are three routes: **intramuscular**, **intravenous**, or **subcutaneous**, which are parenteral routes. Now, we **prefer subcutaneous** over IM since muscles have a higher blood supply than skin, which means a higher rate of absorption and release into the blood. So, we fear a major risk factor, which is **hypoglycemic shock,** since insulin reaches the blood through the IM route faster. We prefer subcutaneous because it has a slower rate of absorption.

Why Isn't Insulin Administered Intranasally?

Why isn't the drug administered intranasally? Because the nasal cavity has a very **thick mucous** membrane. So, to make a peptide drug have a systemic effect intranasally is very challenging. Some drugs, such as cocaine in powder form, may be taken intranasally, and the presence of small abrasive particles mixed with the powder can cause tiny breaks or damage in the nasal mucosal barrier, facilitating absorption. However, this is obviously not a safe or appropriate method for administering medications.

Management of Hypoglycemic Shock

Remember, hypoglycemic shock is managed by immediate sugar intake: intravenous if the person was unconscious, and orally if he was conscious. Don't give people anything orally when they are unconscious, so that no aspiration occurs. So we give IV dextrose (very similar to glucose with faster pharmacokinetics parameters

Emergency Management of an Unconscious Patient

Dextrose is the same as **D-glucose** (has faster pharmacokinetic parameters) . We mainly fear hypoglycemic shock. When an unconscious patient comes to the emergency department, keep three important possibilities in your mind:

1.Hypoglycemic shock
2.Alcohol overdose
3.Opioid overdose.

Confirmed by Doctor:
N-acetylcysteine (NAC) is NOT part of the standard Coma Cocktail and is NOT an antidote for Alcohol overdose.
NAC is specifically the antidote for Paracetamol (Acetaminophen) Toxicity to prevent hepatotoxicity by restoring glutathione reserves in the liver.

- We can give the patient a **cocktail** containing **three things**:

1. Sugar
2. Thiamine to prevent Wernicke's Encephalopathy in patients with chronic alcohol abuse/malnutrition
3.substance against opioids

Adverse Effects of Insulin Therapy

If you decide to administer insulin **parenterally** for a long period of time, the patient may complain of :

1. Lipodystrophy

- Normally, the skin and the subcutaneous layer are smooth, but in lipodystrophy, the injection site may become irregular, with elevated and depressed areas.

- **Lipodystrophy** means an abnormal accumulation or distribution of lipid at the injection site.

- **This happens because :**

1. Insulin is an anabolic hormone
2. Atrophy can occur due to an immune reaction.

The main cause is repetitive administration of insulin at the same site.
The solution is simply to change and rotate the injection site to reduce this problem.

2. Weight Gain
The patient may also develop weight gain because insulin is an anabolic hormone

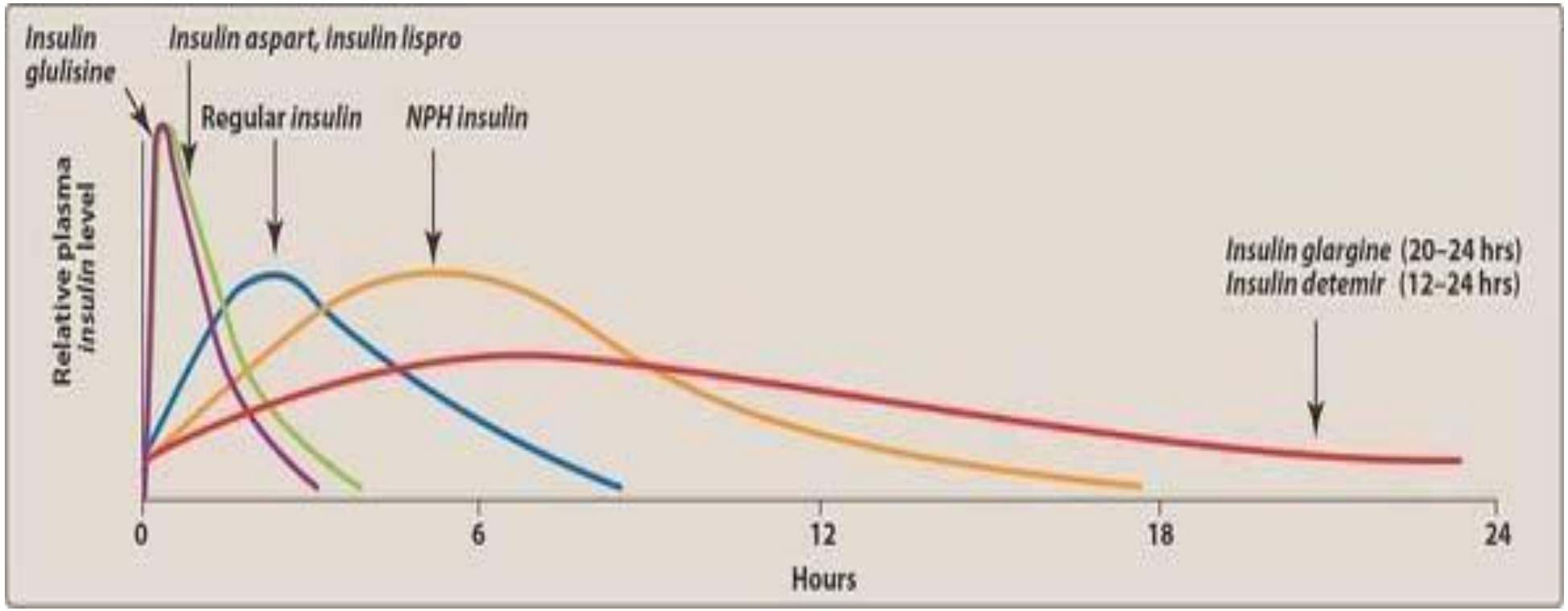
3. Hypoglycemic shock

4. Hypokalemia – **Minor effect**
As a minor effect , insulin can also affect potassium , causing hypokalemia.
Hypokalemia may affect **the heart** and can be associated with **Tachycardia**

SO, when a patient is receiving insulin, we mainly worry about **three important adverse effects**:

1.hypoglycemic shock
2. weight gain
3. lipodystrophy

Types of Insulins



Classification of Insulin Preparations

We classified the insulin types based on the **onset of action** and the **duration of action**, and this classification is important clinically.

We have four types :

1. Ultra-rapid acting insulin
2. Short-acting insulin – Regular insulin
3. Intermediate-acting insulin – NPH
4. Long -acting insulin

Types of Insulins

1) Rapid-acting and short-acting insulin preparations

- Four insulin preparations fall into this category:

1. Regular insulin (soluble >> can be given intravenously in emergencies)
2. Insulin lispro
3. Insulin aspart
4. Insulin glulisine

more rapid absorption after SC injection than is seen with regular insulin; as a consequence, insulin lispro acts more rapidly.

- Rapidly lowers blood glucose.
- Pregnancy category B.
- They are administered to mimic the prandial (mealtime) release of insulin, and they are usually not used alone but, rather, along with a longer-acting insulin to assure proper glucose control.
- Usually administrated immediately before or following the meal.

1. Ultra-Rapid Acting Insulin

Just remember **SONIC**, which includes three:
- Lispro
- Aspart
- Glulisine

Clinically, they have the fastest onset of action when you inject them.
- **Onset of action**: about 5–10 minutes
- **Duration of action**: ultra-short, about 2–3 hours

Why Are They So Rapid?
For ultra-rapid, modifications were made to human insulin by changing some of its amino acids. When these amino acids were changed through **biotechnology**, the **rate of absorption became faster than that of regular insulin.**

2-Regular Insulin — Short-Acting

Regular insulin is human insulin that we can synthesize. It is classified as short-acting insulin.

Its effect is fast, but compared to ultra-rapid insulin, it is slower.
Its duration of action is short, but compared to the first group, it is longer.

- **Onset of action**: about 30–60 minutes
- **Duration of action**: almost 7–8 hours

Understanding the Peak of Insulin

- You have to notice the meaning of the peak on your axis.
- Peak = **the time at which insulin reaches its maximum effect.**
- Therefore: ↑ Insulin effect → ↑ Hypoglycemic effect

The risk of hypoglycemic shock is highest at the peak.

So, you have to know that: **The higher the peak → the higher the risk of the hypoglycemic effect**.

Types of Insulins

2) Intermediate-acting insulin

- Neutral protamine Hagedorn (NPH) insulin = insulin isophane.
- Is a suspension >>>> should only be given subcutaneously (never intravenously)
- Neutral pH with a positively charged polypeptide, protamine >>> forming a less-soluble complex >>>> delayed absorption of the insulin >>>> Its duration of action is intermediate.

Types of Insulins

2) Intermediate-acting insulin

- Is useful in treating all forms of diabetes except diabetic ketoacidosis or emergency hyperglycemia (WHY?!)
- Is usually given along with rapid- or short-acting insulin for mealtime control.
- A similar compound called neutral protamine lispro (NPL) insulin, has been prepared that is used only in combination with insulin lispro.
- Various premixed combinations of human insulins, such as 70-percent NPH insulin plus 30-percent regular insulin, 50 percent of each of these, or 75 percent NPL insulin plus 25 percent insulin lispro.

3.Intermediate-Acting Insulin — NPH

NPH = Neutral Protamine Hagedorn insulin

- Its common name is **isophane insulin**.
- The letter **P** explains why it has a longer duration of action, because it refers to protamine.

Why Does Protamine Prolong Its Action?

In this insulin:

Protamine is added to insulin → insulin–protamine complex becomes **more stable** → slower release from the subcutaneous tissue into the blood → slower rate of absorption → **delayed onset + longer duration of action**

- It is injected subcutaneously.

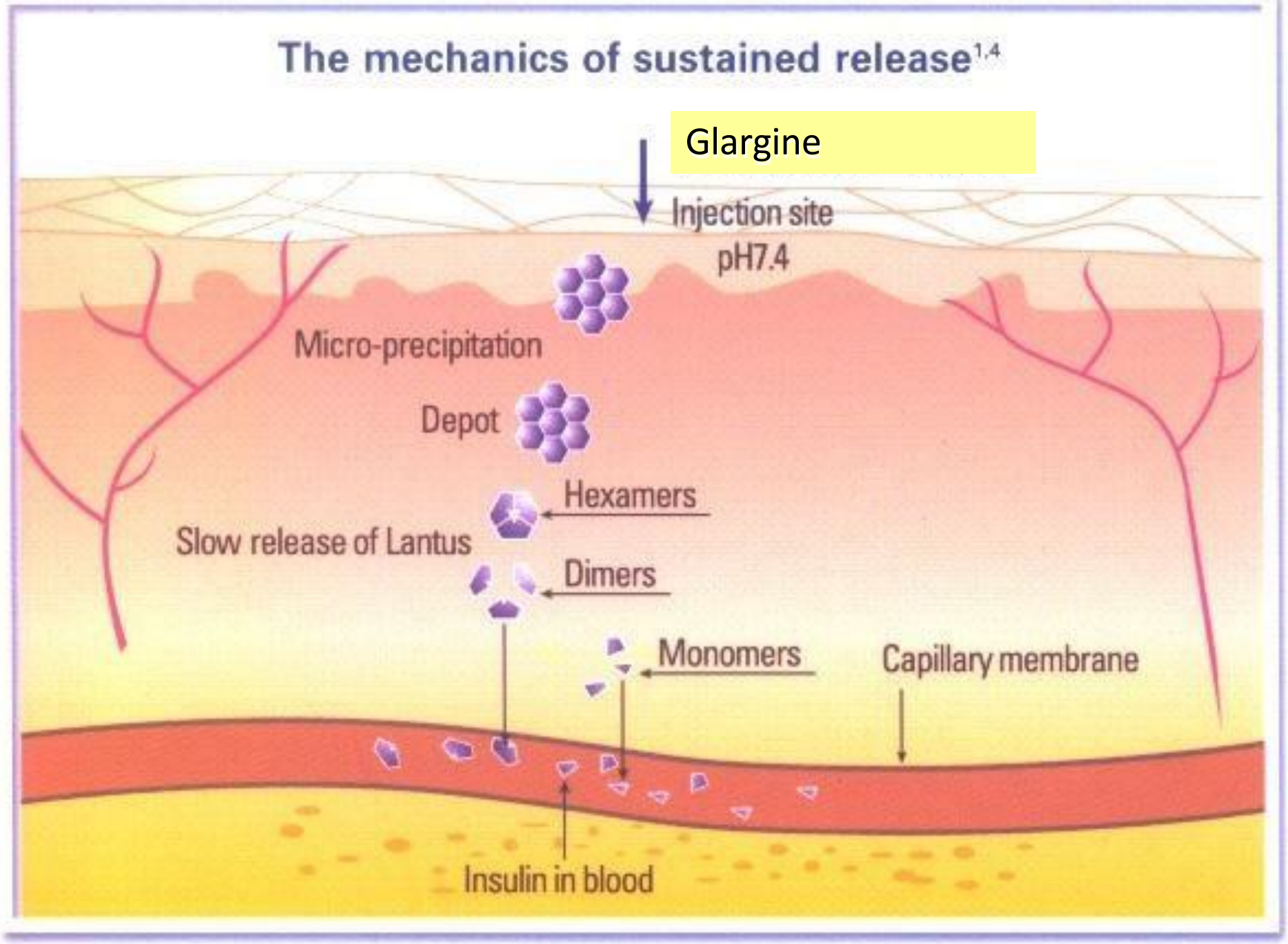
– **Duration of action**: about 12 hours

Types of Insulins

4) Long-acting insulin preparations

Insulin glargine

- The isoelectric point of insulin glargine is lower than that of human insulin, leading to precipitation at the injection site, thereby extending its action.
- It is slower in onset than NPH insulin
- Prolonged hypoglycemic
- It has no peak. (flat)
- It must be given subcutaneously.


The mechanics of sustained release[1,4]
Glargine
Injection site
pH7.4
Micro-precipitation
Depot
Hexamers
Slow release of Lantus
Dimers
Monomers
Capillary membrane
Insulin in blood

Types of Insulins

4) Long-acting insulin preparations

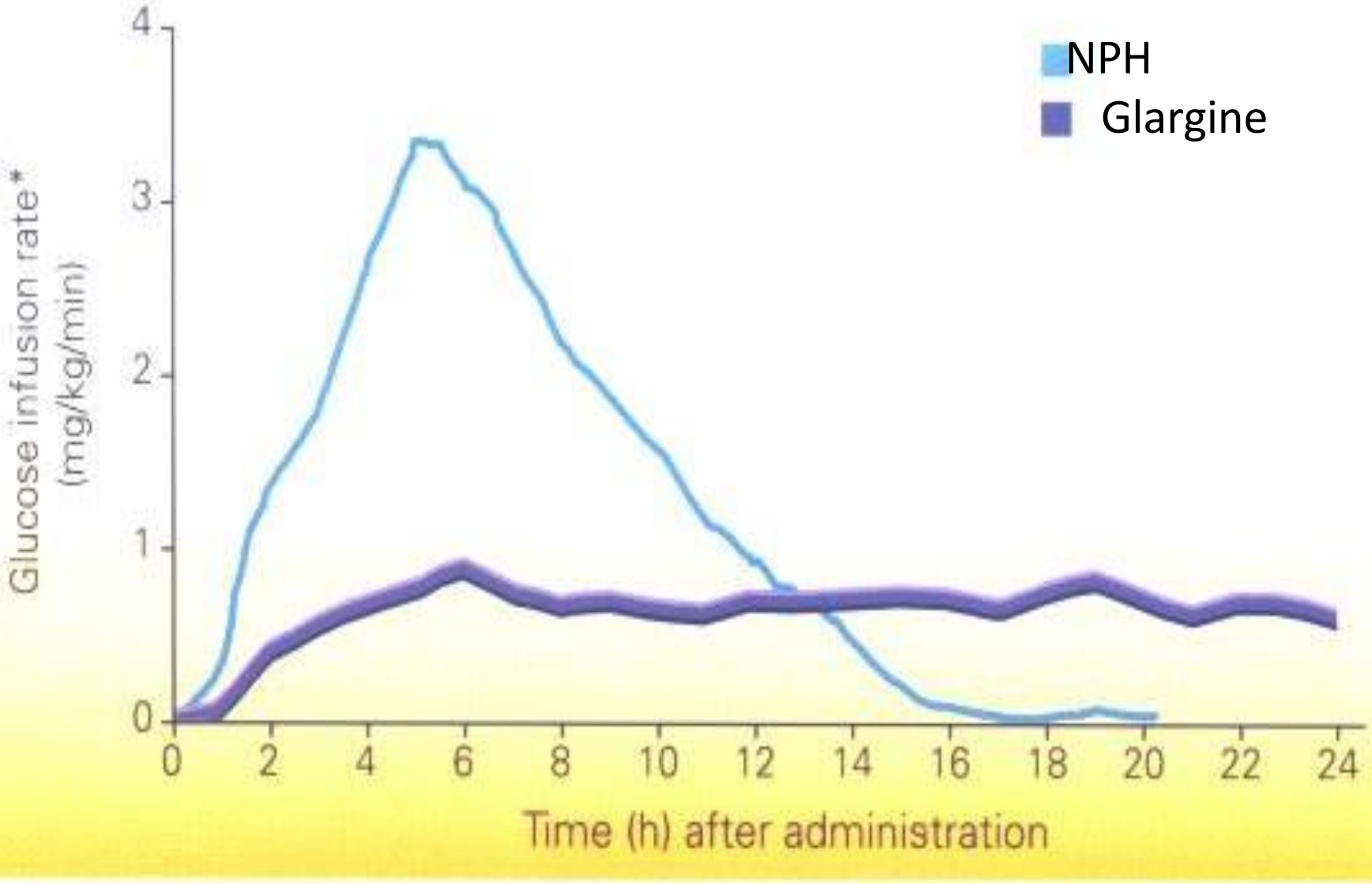
Insulin detemir

- Insulin detemir has a fatty-acid side chain >>>> enhances association to albumin.
- Slow dissociation from albumin results in long-acting properties similar to those of insulin glargine.

4.Long-Acting Insulin

- Long-acting insulin, like **glargine**, has a delayed onset of action, which is slower in comparison with other types of insulin, but it has a longer duration of action.
- **Why Is Detemir Longer-Acting?**
- **Detemir** is insulin modified by adding a fatty acid. When it reaches the blood: Fatty acid modification → binds to albumin → gradual dissociation from albumin → prolonged duration of action
- **As we studied**, when a drug is bound to albumin, there is a **dissociation rate** through which it changes from the bound form → free form.
- The slower this dissociation rate is, the longer the duration of action of the drug.

Profile of Insulin Glargine vs NPH



Water Solubility and Appearance of Insulin Preparations

Regular insulin :

- is the only one that is water-soluble.
- When you hold the ampule, it looks **clear like water**.

However, the other types of insulin, when you hold the ampule, look **turbid**, meaning cloudy, because their **water solubility decreased when these modifications were made.** Therefore, they were prepared in the form of a suspension.

So:

- **Regular insulin** → water-soluble → clear like water
- **Other types of insulin** → suspension form → turbid/cloudy

The other types of insulin are in suspension form, **except** regular insulin, which is water-soluble and looks clear like water

Clinical Use and Administration of Insulin

Route of Administration

- Clinically, we said that insulin is administered parenterally, but the only one that can be given IV is regular insulin because it is water-soluble.

- The other types should not be given IV because they are suspensions, and these particles may **aggregate** in small vessels, **block** the blood supply, and kill the patient.

«If you make this mistake, you will go to Juwaideh prison!»

Regular Insulin in Emergency Hyperglycemic Crisis

In emergency cases, such as a patient presenting with a hyperglycemic crisis, for example, a patient with a fasting blood glucose of 600 mg/dL, the blood glucose is very high, and you need to lower it rapidly because this is an emergency case.

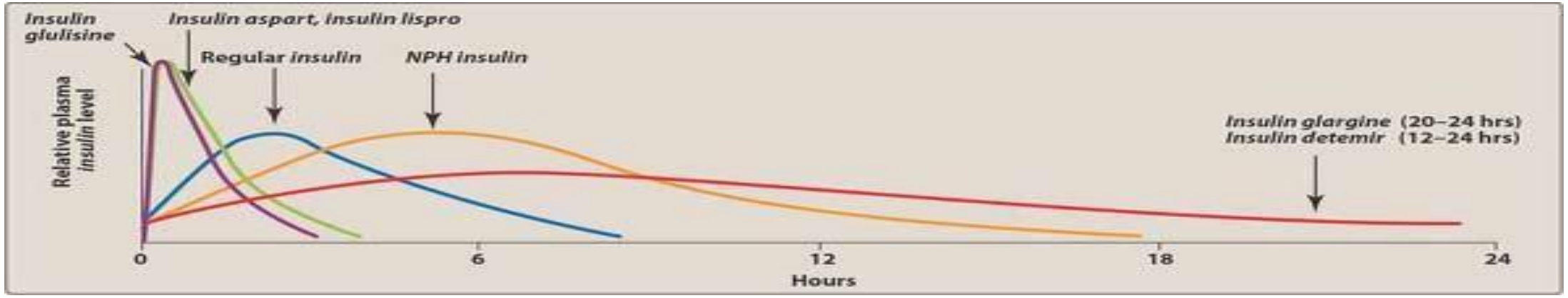
- **You need a rapid-acting effect**

You have two options:

1.The three ultra-rapid insulins:

- Lispro
- Aspart
- Glulisine

2. Regular insulin IV



However, pay attention to the differences BETWEEN the Ultra-rapid insulin and regular insulin shown in the figure:
These differences apply when the drugs are administered **subcutaneously.**

Why Is IV Regular Insulin Preferred?
With regular insulin, we can benefit from the fact that it is water-soluble and administer it IV.

- With IV administration:

No absorption step → drug goes directly into the blood → rapid distribution → rapid decrease in blood glucose
When regular insulin is administered IV, clinically its response is **faster** than that of ultra-rapid insulins administered subcutaneously.
According to the book, when a patient presents with an **emergency hyperglycemic crisis**, the preferred option is: **Regular insulin by IV administration**.

Timing of Insulin Administration

Ultra-Rapid Insulin

When a patient asks: “When should I inject my ultra-rapid insulin?”

-You tell them to take it immediately before the meal because its effect starts within about 5–10 minutes.

-If the patient injects it and does not eat, they may develop hypoglycemic shock.

Regular Insulin

-Regular insulin can be taken about 30 minutes before the meal.

Intermediate-Acting Insulin

-Intermediate-acting insulin is taken as an injection twice daily. It does not have to be taken immediately before a meal because its effect is delayed.

Long-Acting Insulin

-Long-acting insulin is taken once daily. It also does not have to be taken immediately before a meal because its effect is delayed. However, the patient should not take insulin and then fast, because this can increase the risk of hypoglycemic shock.

Insulin and Risk of Hypoglycemic Shock

Important Exam Question
Which type of insulin has the **lowest risk** of hypoglycemic shock?
-Answer: Long-acting insulin.
- Long-acting insulin is described as **peakless**, meaning that it does not have a pronounced peak.
-Remember the relationship between the peak and hypoglycemic shock: Higher / more pronounced peak → greater risk of hypoglycemia

Therefore: Long-acting insulin → no pronounced peak → lower risk of hypoglycemic shock
Since diabetes mellitus is a chronic disease and patients may use insulin for a long time, long-acting insulin is preferred because:
- It can be given once daily
- It has a lower risk of hypoglycemia

Mixtard Insulin

There is also an insulin preparation called Mixtard.
It is a mixture of:
- 30% Regular insulin
- 70% Intermediate-acting isophane (NPH) insulin

Why Are They Combined?
Intermediate-acting insulin:
- Has a longer duration of action.
- Covers about 12 hours.
- Has a delayed onset of action.
Regular insulin:
- Has a faster onset of action.
- Has a shorter duration of action.
Therefore: Regular insulin + Intermediate-acting insulin → relatively rapid onset + long duration of action

Route and Appearance
- Route of administration: Subcutaneous.
- One component is cloudy and the other is clear.
- Therefore, the final mixture appears cloudy.

Additional Resources:

رسالة من الفريق العلمي:

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	Slide 19 Slide 13 Slide 37	Coma cocktail contains: 1.. 2. N-acetylcysteine as antidote for alcohol Insulin effect box: decrease glycolysis Regular insulin	Coma cocktail contains: 1.. 2. Thiamine N-acetylcysteine is an antidote for paracetamol Insulin effect box: INCREASES glycolysis Regular insulin IV
V1 → V2			