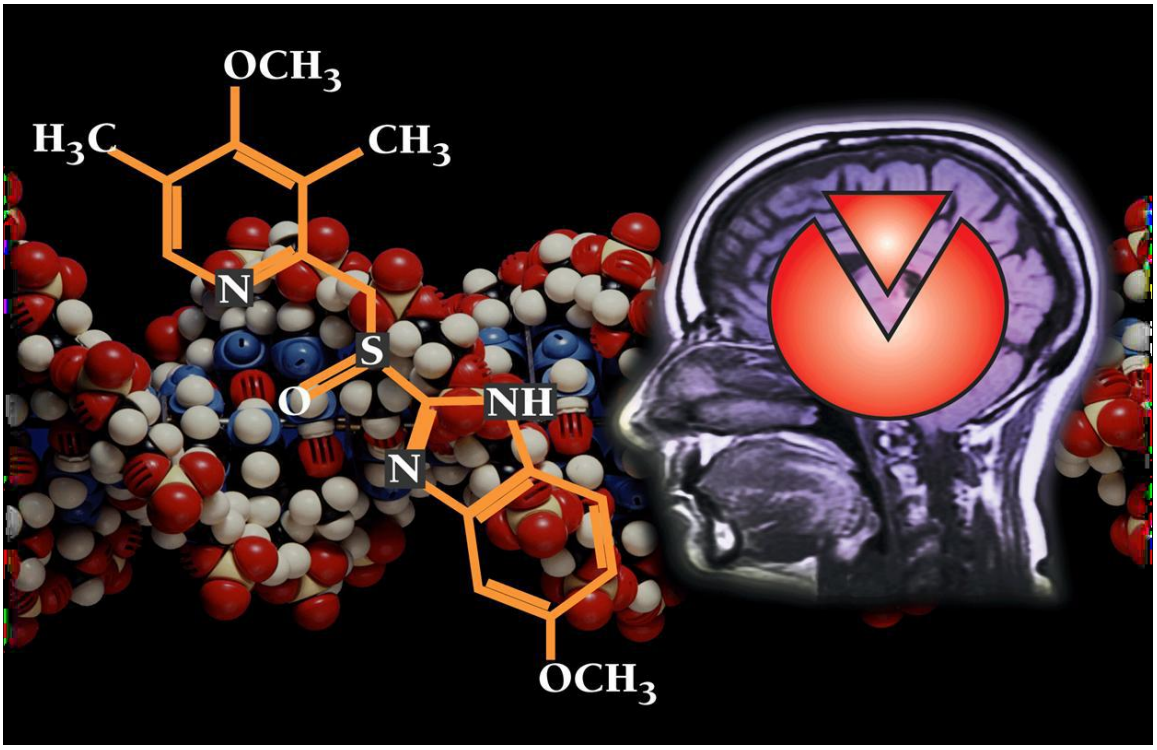
King Saud University
College Of Medicine
Pharmacology Team 430
Endocrine Block

06-*Use of Insulin in the treatment of diabetes mellitus*



Note: First page is an introduction Text in **red is important info** & textboxes with thick blue margins are additional info.

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Introduction

Definition of Diabetes mellitus: Is a chronic metabolic disorder **characterized by high blood glucose level** caused by **insulin deficiency** and sometimes accompanied **with insulin resistance.**

- Fasting plasma glucose > 7 mmol/L
- Plasma glucose > 11.1 mmol/L 2h after a meal)

Types of diabetes mellitus

➢ Type I (Treated by Insulin)

- ✓ 10-20% occurrence.
- ✓ During childhood or puberty
- ✓ β-cells are destroyed.
- ✓ No insulin secretion due to autoimmune or viral diseases
- ✓ **Treated by insulin.**

Type II Diabetes

- ✓ 80-90% occurrence
- ✓ Over age 35
- ✓ **Pancreatic β-cells are not producing enough insulin** *due to genetic susceptibility and other factors (age, obesity)*
- ✓ Obesity is an important factor.
- ✓ Insulin resistance in peripheral tissues.
- ✓ Treated by **oral hypoglycemic drugs.**

Effects of insulin

I. Carbohydrate Metabolism:

Lowers of blood glucose by:

- ↑ **Glucose uptake & utilization**
- ↑ **Glycogen synthesis**
- ↑ **Conversion of carbohydrate to fats.**
- ↓ **Gluconeogenesis.**
- ↓ **Glycogenolysis (liver).**
- ↑ **Glycolysis (muscle).**

II. Fat Metabolism:

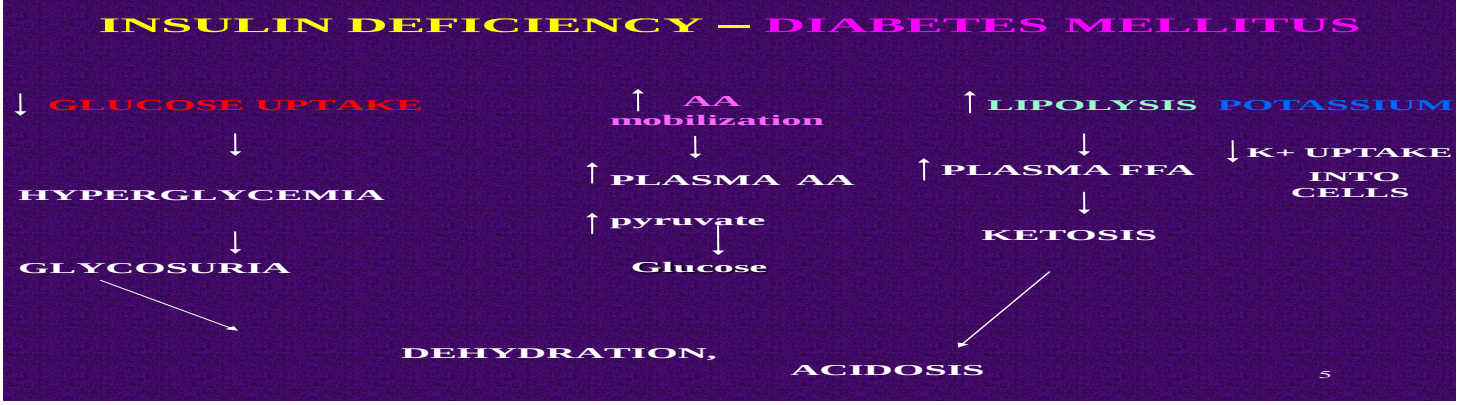
- **Liver:**
  - ↑ **Lipogenesis.**
  - ↓ **Lipolysis.**
  - **Inhibits conversion of fatty acids to keto acids.**
- **Adipose Tissue:**
  - ↑ **Triglycerides storage.**
  - ↑ **Fatty acids synthesis.**
  - ↓ **Lipolysis**

III. Protein Metabolism:

- **Liver:**
  - ↓ **protein catabolism.**
- **Muscle:**
  - ↑ **Amino acids uptake.**
  - ↑ **Protein synthesis.**
  - ↑ **Glycogen synthesis (glycogenesis).**

IV. Potassium:

- ↑ **potassium uptake into cells.**



Insulin preparations

Exogenous Insulin :

- **Prepared by recombinant DNA techniques.**
- **Modifications of amino acid sequence can change pharmacokinetics.**

Differs in ***pharmacokinetics*** mainly

- **Onset of action (rate of absorption)**
- **Duration of action.**

Variation is due to

- **Change of amino acid sequence.**
- **Size and composition of insulin crystals in preparations.**

1-is usually given subcutaneously (s.c.) by:

- ❖ Syringes (arms, abdomen, thighs)
- ❖ Portable pin injector (pre-filled).
- ❖ Continuous S.C. insulin infusion (pump).

2. Or intravenously (I.V.) in **hyperglycemic emergency.**

Types of insulin preparations: (Vary in onset and duration of action)

All forms of insulin must be injected (S.C./I.V.). Insulin cannot be taken orally, because insulin is a polypeptide and stomach acids break it down before it has a chance to work

- ➢ Ultrashort acting insulins
  - e.g. Lispro, aspart
  - Very fast onset and short duration
- ➢ Short acting insulins (Regular)
  - Fast onset and short duration
- ➢ Intermediate acting
  - e.g. NPH, lente
- ➢ Long acting
  - e.g. insulin glargine(lantus)
  - Slow onset and long duration of action.

It's universal.

Can be used in type I & type II diabetes mellitus

Should not be used in type II, because of its long duration of action which **can lead to severe hypoglycemia.**

So, it's only used in type I diabetes mellitus

1-Ultra-short acting insulins: (e.g. Insulin lispro, Insulin aspart)

- **Clear solutions** at neutral pH.
- Monomeric analogue.
- Fast onset of action (0-15 min)
- S.C. (5 min no more than 15 min before meal).
- Peak 30-90 min after injection
- **I.V. in emergency.**
- Short duration of action (3-5 h)
- 2-3 times/day
- **Mimic the prandial mealtime insulin release**

Postprandial: after a meal.

So, it must be taken before a meal to avoid/control hyperglycemia that occurs after a meal.

Note: incidence of hypoglycemia is low, because of the short duration of action

Uses:

Control **postprandial hyperglycemia (S.C.) & emergency diabetic ketoacidosis (I.V.)**

2-Short acting insulins: (regular insulin)

- Clear solutions at neutral pH.
- **Hexameric analogue.(**Forms hexamers)
- Onset of action 30-45 min (S.C.)
- Peak 2-4 h.
- Duration 6-8 h.
- Soluble crystalline zinc insulin (stability –shelf half life)
- **Clear solutions** at neutral pH.

Note: incidence of hypoglycemia is higher in **regular insulin** compared with **lispro & aspart**

Note: Regular tend to **complex with zinc i**n the blood, **forming hexamers**. Insulin in the form of a **hexamer** will not bind to **its receptors,** so the **hexamer has** to slowly equilibrate back into its **monomers** to be biologically Active. **Hexameric insulin delivered subcutaneously** is not readily available for the body when insulin is needed in larger doses, such as after a meal. Intravenously dosed insulin, however, is distributed rapidly to the cell receptors, and therefore, avoids this problem.

Uses:

- ✓ Control postprandial hyperglycemia (S.C.)
- ✓ **emergency ketoacidosis (I.V.)**
- ✓ can be used in Pregnancy.

Advantages of Insulin Lispro vs Regular Insulin :

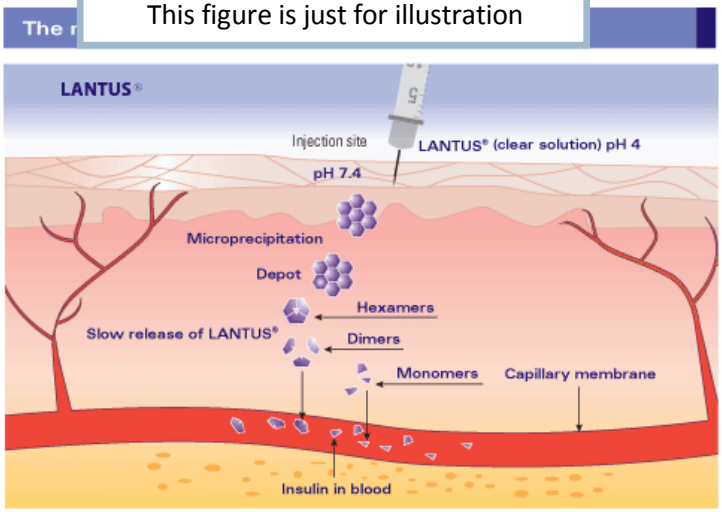
- ✓ Rapid onset of action (due to rapid absorption)
- ✓ Reduced risk of postprandial hypoglycemia (due to short duration of action)

3-Intermediate acting insulins: (Isophane (NPH), Lente insulin)

A)Isophane (NPH (Neutral protamine Hegedron)

- ✓ **NPH, is a Neutral Protamine Hagedorn insulin in phosphate buffer.**
- ✓ **NPH insulin is combination of protamine & crystalline zinc insulin (1: 6 molecules). proteolysis release insulin.**
- ✓ Turbid suspension at neutral pH
- ✓ **Given S.C. only**
- ✓ Onset of action 1-2 h.
- ✓ Peak serum level 5-7 h.
- ✓ Duration of action 13-18 h.
- ✓ NPH is not used in emergencies (diabetic ketoacidosis).

This figure is just for illustration



Insulin mixtures

- 75/25 - 70/30 - 50/50 (NPH/regular).
- (NPL= NPH / lispro) (NPA= NPH / aspart)
-

Note: Using these mixtures gives the advantage of having a **rapid onset** of action (**Aspart ,lispro, regular insulin**), **a long duration** of action **(NPH), and a less number of injections**

B)Lente insulin

- Mixture of 30% semilente insulin + 70% ultralente insulin
- **Turbid suspension** at neutral pH
- Given S.C.
- onset of action (1-3 h)
- Peak serum level 4-8 h.
- Duration of action 13-20 h.
- Lente and NPH insulins are equivalent in activity.
- Lente is Not used in emergencies (diabetic ketoacidosis).

Note: Lenate can't be mixed with regular insulin, aspart, or lispro in one vial

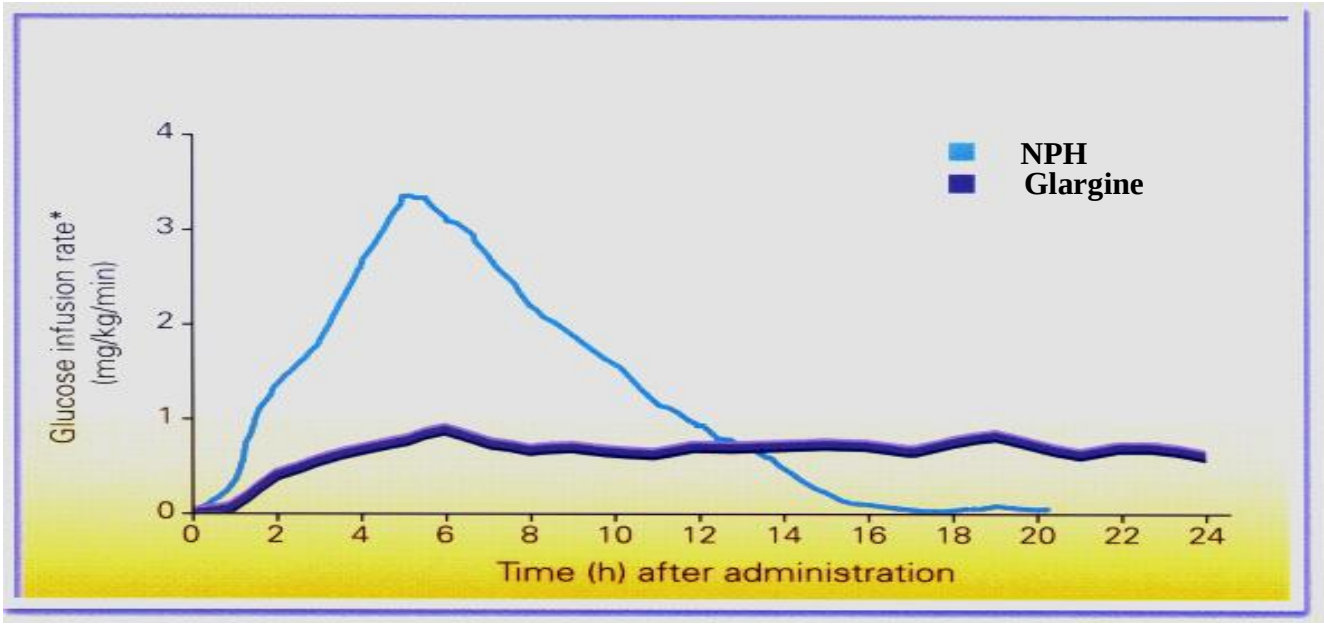
4-Long acting insulins: (Insulin glargine (lantus)

- Clear solution **BUT forms precipitate *(depot)* at injection site.**
- Slow onset of action 2 h.
- Given S.C.
- Maximum effect after 4-5 h
- Produce broad plasma concentration plateau (low continuous insulin level).
- Prolonged duration of action (24 h).
- Once daily
- Should not be mixed with other insulin in one vial

Note: After injection into the subcutaneous tissue, the acidic solution is neutralized by the body to a neutral pH. **Because glargine is not soluble at a neutral pH,** it precipitates out into a form that's not soluble in subcutaneous fat, and there forms a relatively insoluble depot. From that pool, or depot, of precipitated glargine in the tissues, small amounts slowly move back into solution over time and then go to the bloodstream.

Advantages of Insulin glargine over intermediate-acting insulins:

- ✓ Constant circulating insulin over 24 hr with no pronounced peak.
- ✓ More safe than NPH & Lente insulins (Reduced risk of hypoglycemia).



Notice the plateau effect of Glargine, which is beneficial to reduce the incidence of hypoglycemia

Complications of Insulin Therapy:

- Hypoglycemia, can be happened in case of:
  - Overdose of insulin
  - Excessive (unusual) physical exercise
  - A meal is missed

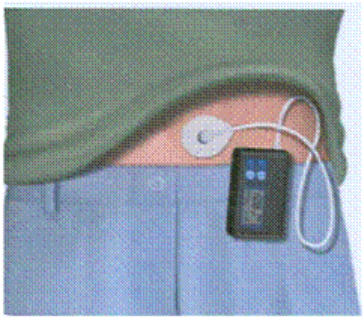
we can reduce the dose in case of one of the above to control blood glucose level ,

- Weight gain
- Hypersensitivity reactions (rare)
- Lipohypertrophy at injection site

To avoid lipohypertrophy patients are advised to *rotate* their injections among several areas.

- Insulin resistance (rare)
- Hypokalaemia

Other methods to take insulin:



Insulin Pump: a portable battery-powered instrument that delivers a measured amount of insulin through the abdominal wall. It can be programmed to deliver varied doses of insulin according to the body's needs at the time.

Pen injector: Has the advantages:

- More convenient and easier to transport than traditional vial and syringe
- Repeatedly more accurate dosages
- Easier to use for those with visual or fine motor skills impairments
- Less injection pain

Summary

	Short-acting (regular) insulins e.g. Humulin R, Novolin R	Ultra-Short acting insulins e.g. Lispro, aspart, glulisine
Uses	postprandial hyperglycemia & emergency diabetic ketoacidosis	postprandial hyperglycemia & emergency diabetic ketoacidosis
Physical characteristics	Clear solution at neutral pH	Clear solution at neutral pH
chemistry	Hexameric analogue	Monomeric analogue
Route & time of administration	S.C. 30 – 45 min before meal I.V. in emergency (e.g. diabetic ketoacidosis)	S.C. 5 min (no more than 15 min) before meal I.V. in emergency (e.g. diabetic ketoacidosis)
Onset of action	30 – 45 min (S.C)	0 – 15 min (S.C)
Peak level	2 – 4 hr	30 – 90 min
Duration	6 – 8 hr	3 – 5 hr
Usual administration	2 – 3 times/day or more	2 – 3 times / day or more

- Ultrashort acting insulins & Short acting insulins (regular) are universal, NPH, lente, and glargine are only used in type I diabetes mellitus.
- lispro and aspart are faster than regular insulin.
- Regular insulin has high incidence of hypoglycemia compared with lispro and aspart.
- Both ultrashort acting insulin & Regular insulin can be used in case of pregnancy, because they don't have a teratogenic effect.
- None of the NPH, lente, and glargine can be used in emergencies (diabetic ketoacidosis).

- NPH, lente, and glargine are available in S.C. form only
- NPH can be mixed with regular insulin or lispro
- Glargine has a prolonged duration of action (24h.), so it's given once daily. And should not be mixed with other insulin.
- Advantages of Insulin glargine over intermediate-acting insulins:
    - Constant circulating insulin over 24 hr with no pronounced peak.
    - More safe than NPH & Lente insulins (Reduced risk of hypoglycemia).

- Hypoglycemia is the most common complication of insulin therapy.

Review questions

1-Which of the following statements is correct regarding insulin glargine?

A. It is primarily used to control postprandial hyperglycemia.
B. It is a "peakless" insulin.
C. The prolonged duration of activity is due to slow dissociation from albumin.
D. It should not be used in a regimen with insulin lispro or glulisine.
E. It may be administered intravenously in emergency cases.

2- Most common complication insulin therapy?

A. lipodystrophies
B. hypotension
C. gallstones
D. hypoglycemia
E. retinopathy

3- Which of the following should be administered to achieve rapid control in a patient suffering from severe ketoacidosis ?

A. Crystaline zinc insulin
B. Glyburide
C. Glargine
D. NPH
E. Tolbutamide

Answer key: 1-B,2-D,3-A