Use of Insulin in the Treatment of Diabetes Mellitus

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(Slides are adopted and modified from Prof. Hanan Hagar)

Objectives:

By the end of this lecture, you should be able to:

- *Define diabetes and mention different types of diabetes*
- *Differentiate between difference in treating type I and type II diabetes.*
- *Explain mechanism of insulin secretion and insulin actions.*
- *Describe different types of insulin analogues*
- *Recognize the difference in pharmacokinetic profile between different types of insulin analogues.*
- *Justify uses of different insulin analogues*

Diabetes mellitus

- **Is a chronic metabolic disorder characterized by high blood glucose level caused by caused by deficiency of insulin or by increased insulin resistance.**

Diabetes mellitus

Fasting plasma glucose (no food for 8 hrs)

Normal **<100 mg/dl (5.6 mmol/l).**

Pre-diabetes 100-125 mg/dl (5.6-6.9 mmol/L).

Diabetes if Fasting >126 mg/dl (7 mmol/L)

or 2h after a meal > 200 mg/dl (11.1 mmol/L).

Types of diabetes

- **Type I diabetes (IDDM)**

  due to autoimmune or viral diseases

- **Type II diabetes (NIDDM)**

  due to genetic susceptibility and other factors (age, obesity).

Type I Diabetes
IDDM

- **10-20% occurrence.**
- **During childhood or puberty**
- **β-cells are completely destroyed.**
- **Absolute deficiency of insulin secretion**
- **Treated by insulin.**

Type II Diabetes
NIDDM

- **80-90% occurrence**
- **Over age 35**
- **Pancreatic β-cells are not producing enough insulin**
- **Obesity is an important factor.**
- **Insulin resistance in peripheral tissues.**
- **Treated by oral hypoglycemic drugs.**

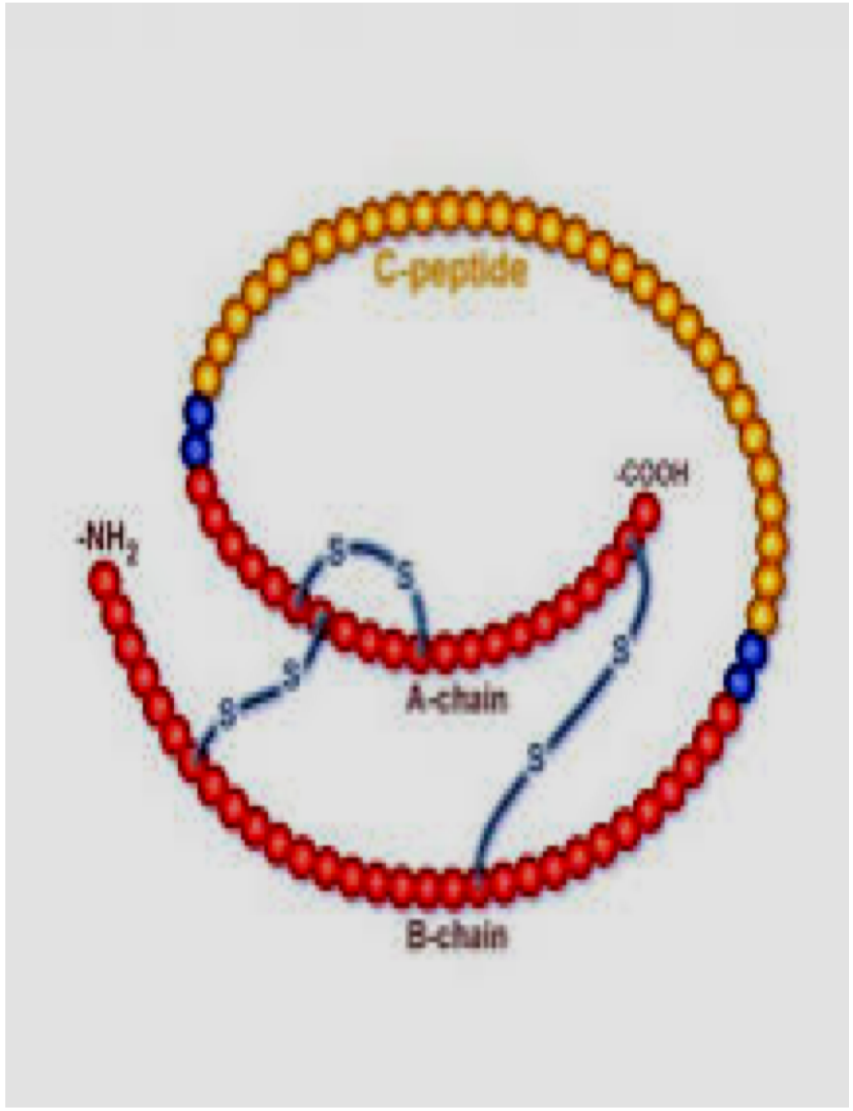
Characteristic	Type 1	Type 2
Onset (Age)	Usually during childhood or puberty	Usually over age 40
Type of onset	Abrupt	Gradual
Prevalence	10-20%	80-90 %
Genetic predisposition	Moderate	Very strong
Defects	β-cells are destroyed	β-cells produce inadequate quantity of insulin
Endogenous insulin	Absent	Present (not enough)
Insulin resistance	absent	present
Nutritional status	Usually thin	Usually obese
Ketosis	Frequent	Usually absent
Clinical symptoms	Polydipsia, polyphagia, polyuria, weight loss	Often asymptomatic
Related lipid abnormalities	Hypercholesterolemia frequent	Cholesterol & triglycerides often elevated
Treatment	Insulin injection	Oral hypoglycemic drugs

Complications of diabetes

- Cardiovascular problems
  - Micro- and macro-vascular disease
- Renal failure (nephropathy).
- Blindness (retinopathy).
- Neuropathy.
- Risk of foot amputation

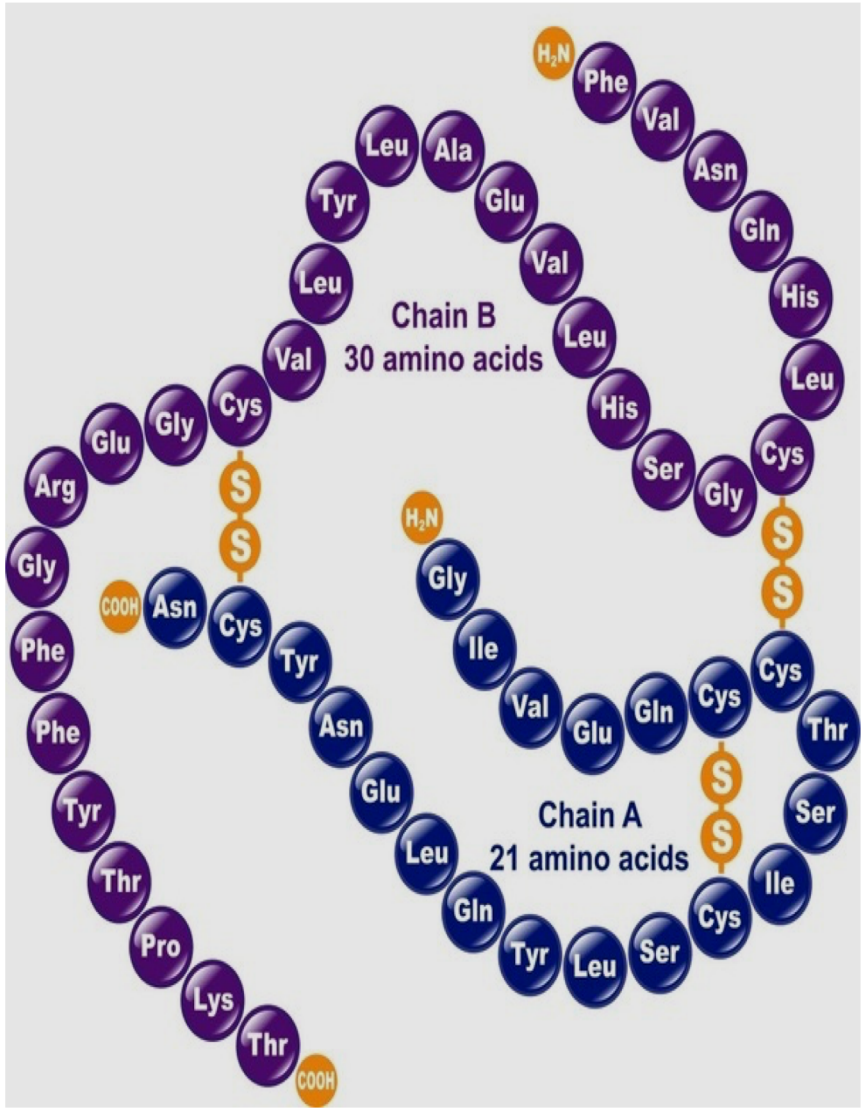
INSULIN

Proinsulin



C-peptide

Insulin

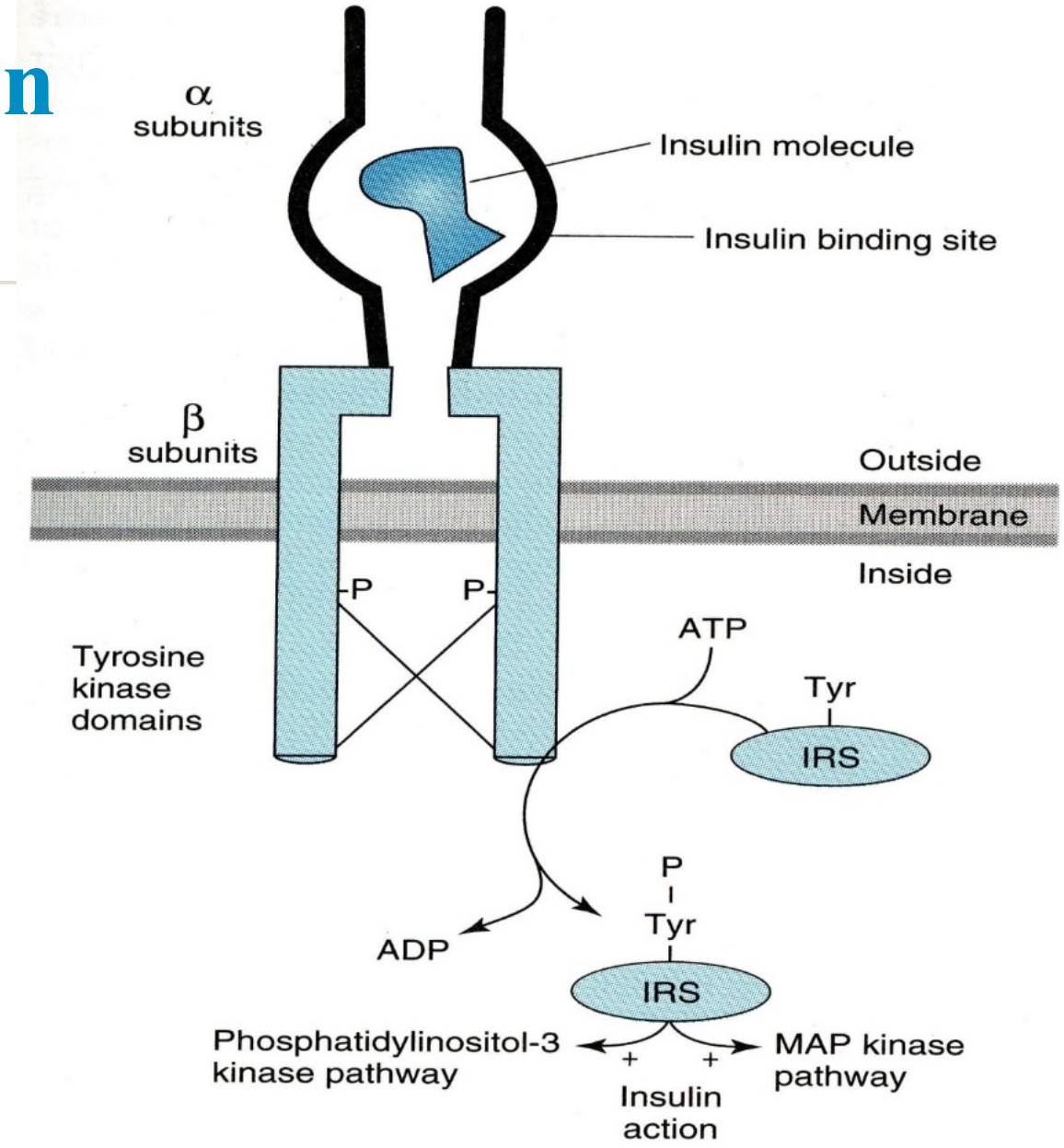


Insulin receptors

- **Present on cell membranes of most tissues.**
- **Liver, muscle and adipose tissue**

Insulin Mechanism of Action

- Phosphorylation of IRS-1 and IRS-2 (insulin receptor substrate)
- → binding and activating other kinases (e.g., PI3-K) or bind to adaptor proteins (e.g. growth factor receptor-binding protein 2) that translates insulin signal to a guanine nucleotide-releasing factor that ultimately activates the GTP binding protein Ras, and the MAPK system



Insulin Interaction with Receptor

- Results in multiple effects including:
  - **Translocation** of glucose transporters (**GLUT**) to cell membrane with resulting **increase in blood glucose uptake**
  - Glycogen synthase activity and **increased glycogen formation**
  - **Effects on protein synthesis**
  - **Lipogenesis**
  - **Activation** of **transcription factors**

Effects of insulin

I. Carbohydrate Metabolism:

- ↑ **glucose uptake & utilization by peripheral tissues.**
- ↑ **Glycogen synthesis (glycogen synthase)**
- ↑ **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.**

Routes of administrations of exogenous insulin

- **Can not be given orally (why?)**
- **Insulin syringes (S.C., arms, abdomen, thighs).**
- **Portable pin injector (pre-filled).**
- **Continuous S.C. infusion (insulin pump).**
  - **More convenient**
  - **Eliminate multiple daily injection**
  - **Programmed to deliver basal rate of insulin.**

Routes of administrations of exogenous insulin

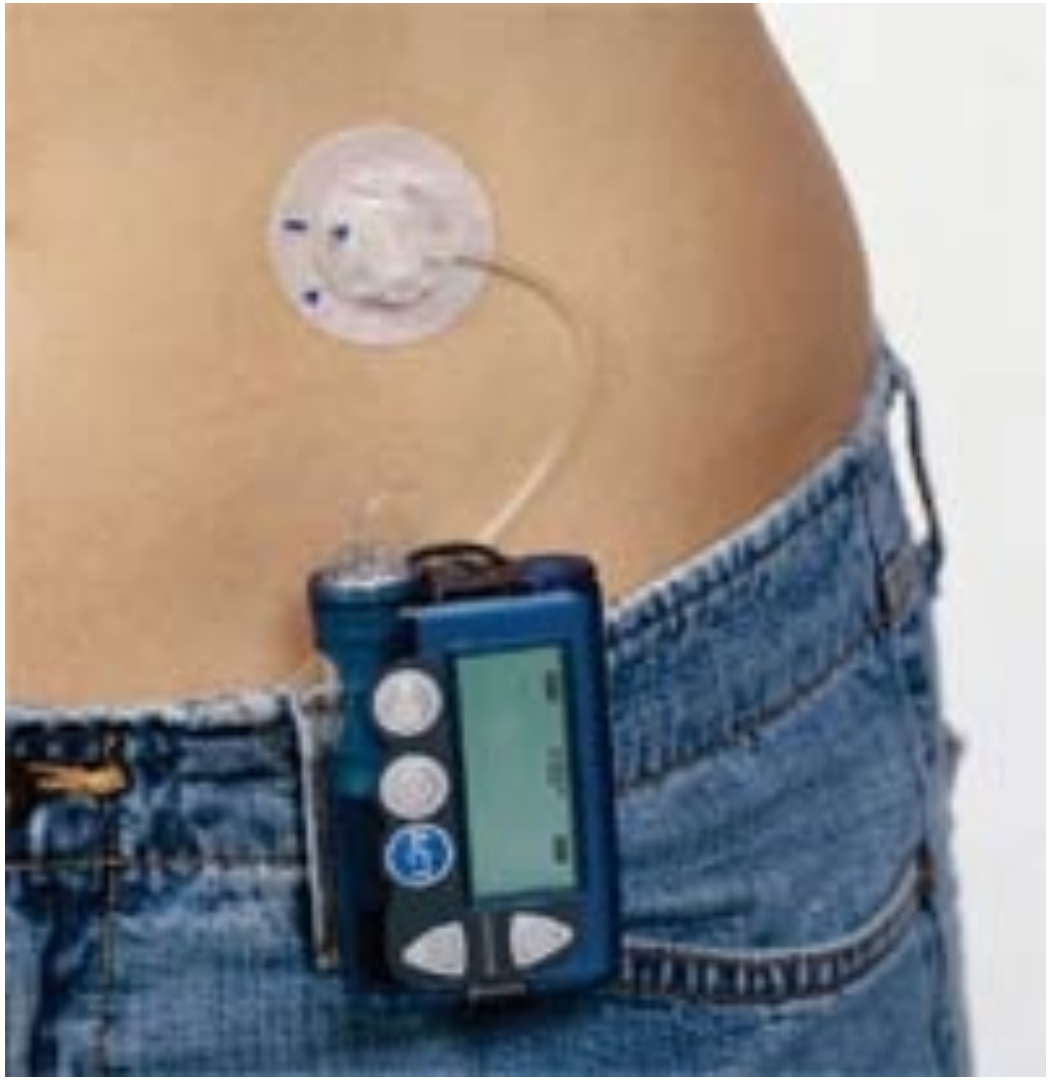
- **Intravenously (in a hyperglycemic emergency)**

Under Clinical Trials

- **Inhaled aerosols, transdermal, intranasal.**

Pen injector

Insulin pump



https://www.youtube.com/watch?v=Crkyl9bqfC0

Insulin degradation

1. **Basal level of endogenous insulin is 5-15 µU/ml.**
2. **Half life of circulating insulin is 3-5 min.**
3. **60% liver & 40% kidney (endogenous insulin)**
4. **40% liver &60% kidney (exogenous insulin)**

Sources of Exogenous Insulin

- **Beef Insulin**
  - **Differs from human insulin by 3 amino acids (antigenic).**
- **Porcine Insulin**
  - **Differs by one amino acid (antigenic).**

Human Insulin analogues

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

Types of insulin preparations

Differ in pharmacokinetic properties 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 (monomers, dimers, hexamers).**

Types of insulin preparations
Insulin Analogues

- **Ultra-short acting insulins**

  e.g. Lispro, aspart

  very fast onset of action and short duration

- **Short acting insulins**

  e.g. regular insulin e.g. Humulin R

  fast onset of action and short duration.

Types of insulin preparations

- **Intermediate acting insulins**
  - **e.g. NPH, lente**
  - **Slow onset, intermediate duration of action.**

- **Long acting insulins**
  - **e.g. glargine, detemir**
  - **Slow onset and long duration of action.**

Ultra-short acting insulins

Insulin lispro, insulin aspart

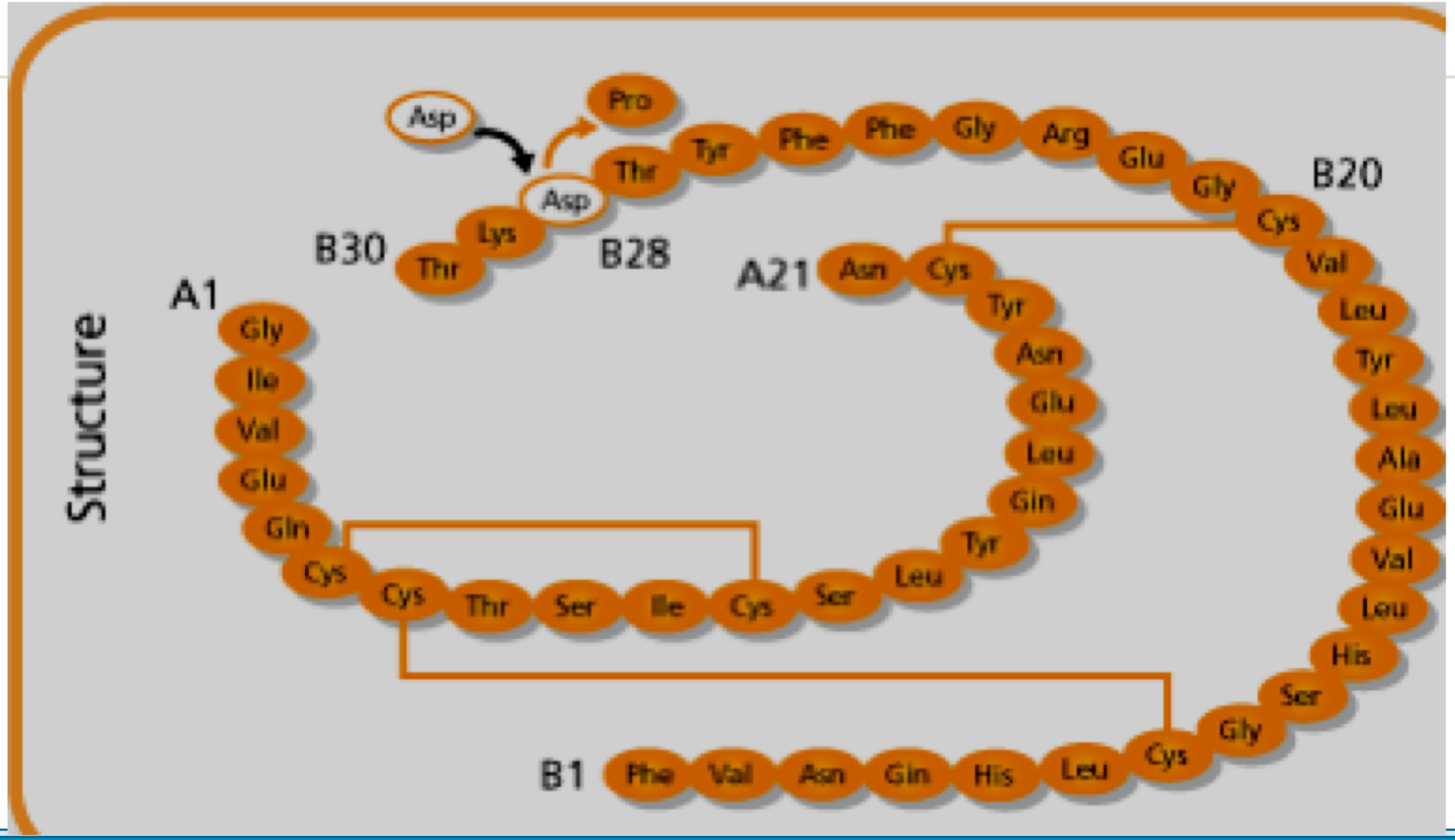
- **Clear solutions at neutral pH.**
- **Do not aggregate or form dimers or hexamers (monomeric analogue).**
- **Fast onset of action (5-15 min)**
- **S.C. (5 -15 min before meal).**
- **Short duration of action (3-5 h)**

Ultra-short acting insulins

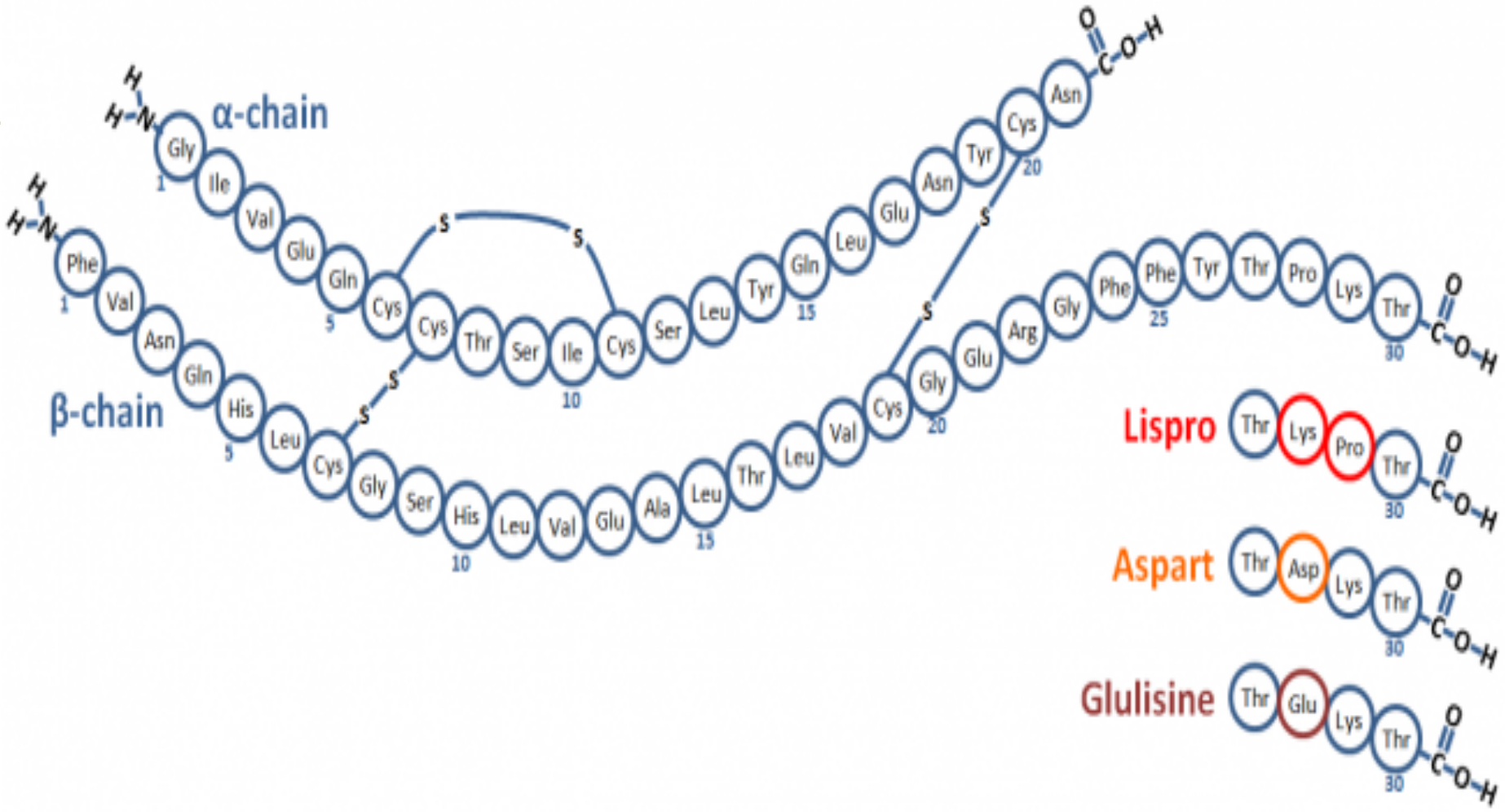
Insulin Lispro, insulin aspart

- **Reach peak level 30-90 min after injection.**
- **3 times/day.**
- **Mimic the prandial mealtime insulin release.**
- **I.V. in emergency.**

Insulin aspart



Ultra-short acting insulins



Ultra-short acting insulins

insulin lispro, insulin aspart

- **Preferred for external insulin pump**
- **Used to control post-prandial hyperglycemia (s.c.) and emergency diabetic ketoacidosis (i.v).**

Short acting insulins (Regular insulin)

- **Soluble crystalline zinc insulin**
- **Clear solutions at neutral pH.**
- **Forms hexamers.**
- **Onset of action 30-45 min (s.c.).**
- **I.V. in emergency situations.**
- **Peak 2-4 h.**
- **Duration 6-8 h.**

Short acting insulins (regular insulin)

- **2-3 times/day.**
- **Control postprandial hyperglycemia (s.c.) & emergency diabetic ketoacidosis (i.v.).**
- **Can be used in pregnancy**

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

Advantages of Ultra-short vs Short Insulin

- **Rapid onset of action (patients will not wait long before they eat).**
- **Its duration of action is no longer than 3-4 hrs regardless of the dose:**
  - **Decreased risk of hyper insulinemia.**
  - **Decreased risk of postprandial hypoglycemia**

Intermediate acting insulins

Isophane (NPH) insulin

Lente insulin

Isophane (NPH) Insulin

- **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.**

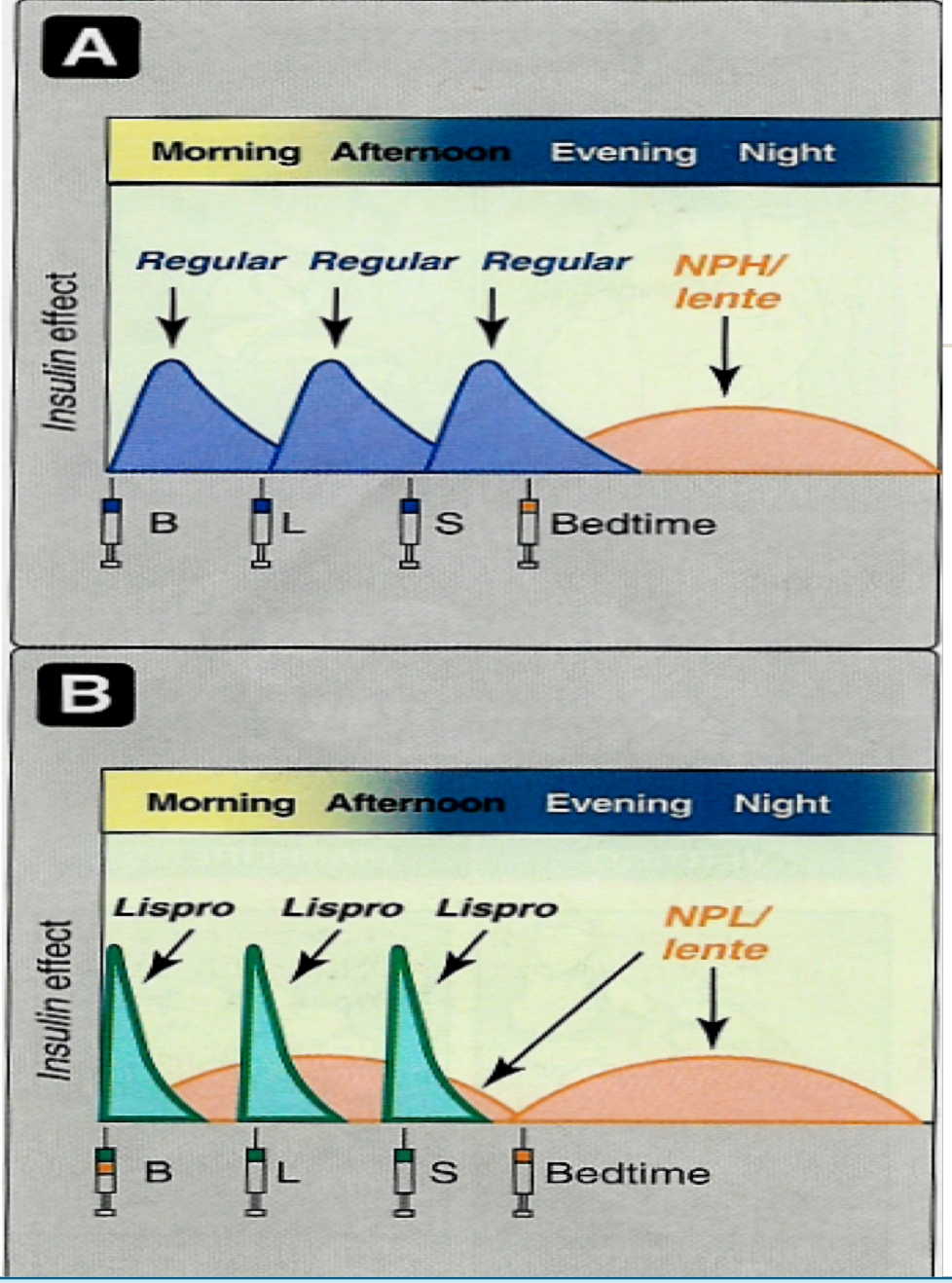
Isophane (NPH) Insulin

- **Turbid suspension at neutral pH.**
- **Given S.C. only not i.v.**
- **Can not be used in ketoacidosis or emergency**
- **Onset of action 1-2 h.**
- **Peak serum level 5-7 h.**
- **Duration of action 13-18 h.**

Isophane (NPH) Insulin

Insulin mixtures

- **NPH/regular insulin**
  - **75/25 , 70/30 , 50/50**
- **(NPL= NPH / lispro) (NPA= NPH / aspart)**
- **NPL & NPA have the same duration as NPH**
- **Have two peaks.**



Prandial and basal insulin replacement

Lente insulin

- **Mixture of:**
  - **30% semilente insulin (amorphous precipitate of zinc insulin in acetate buffer)**
  - **70% ultralente insulin (poorly soluble crystal of zinc insulin)**
- **Turbid suspension at neutral pH**
- **Given S.C., not intravenously**

Lente insulin
(Humulin L, Novolin L)

- **Delayed 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 diabetic ketoacidosis or emergency.**

Long acting insulins

Insulin glargine (lantus), Insulin detemir (Levemir)

Insulin glargine (Lantus)

- Clear solution BUT forms precipitate (hexamer) at injection site.
- Slow onset of action 2 h.
- Absorbed less rapidly than NPH & Lente insulin.
- Given s.c., not intravenously
- Should not be mixed with other insulins in the same syringe.

Insulin glargine (Lantus)

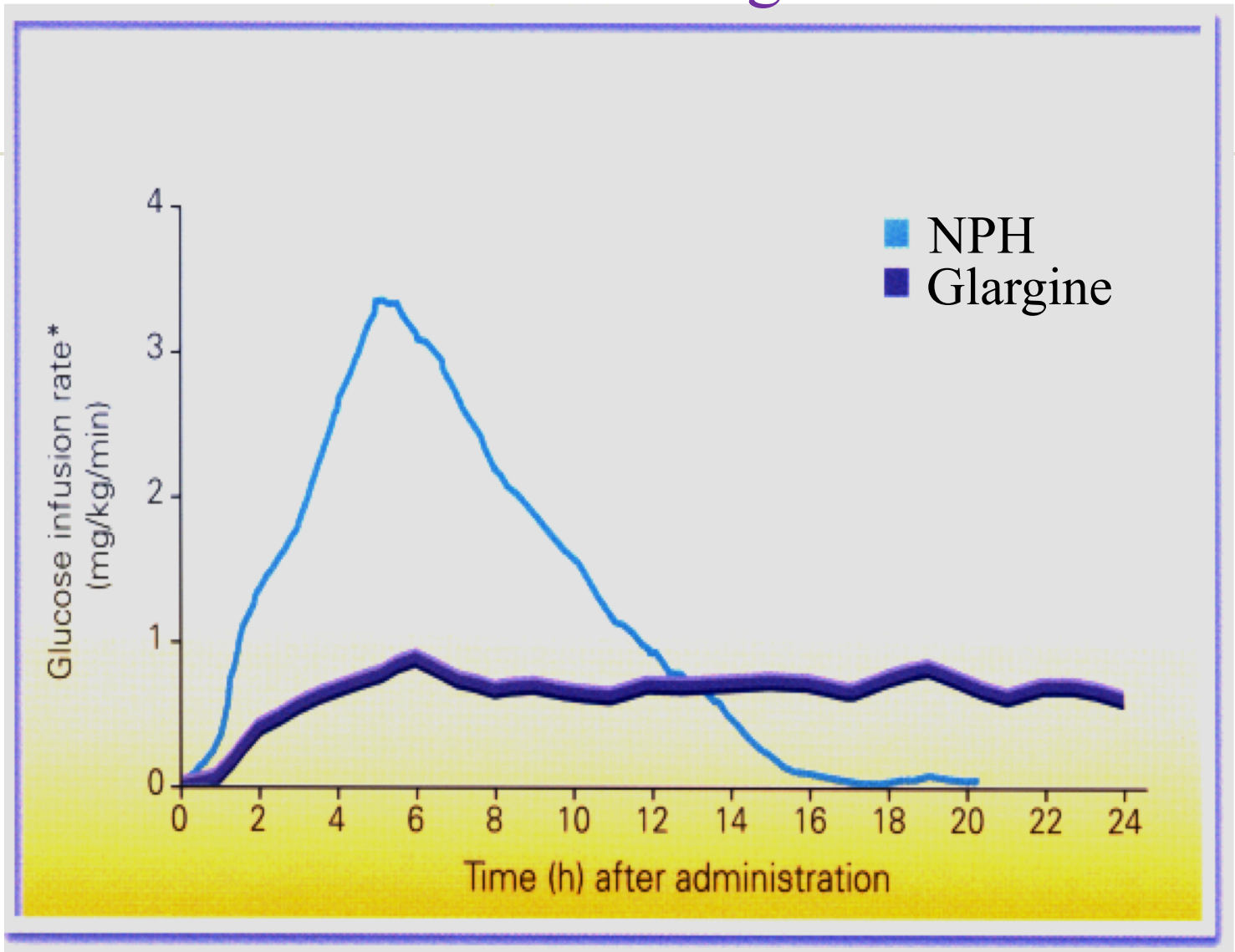
- **Maximum effect after 4-5 h**
- **Prolonged duration of action (24 h).**
- **Once daily**
- **Produce broad plasma concentration plateau (low continuous insulin level).**
- **Glargine must be used in regimens with rapid or short acting insulins.**

Advantages over intermediate-acting insulins:

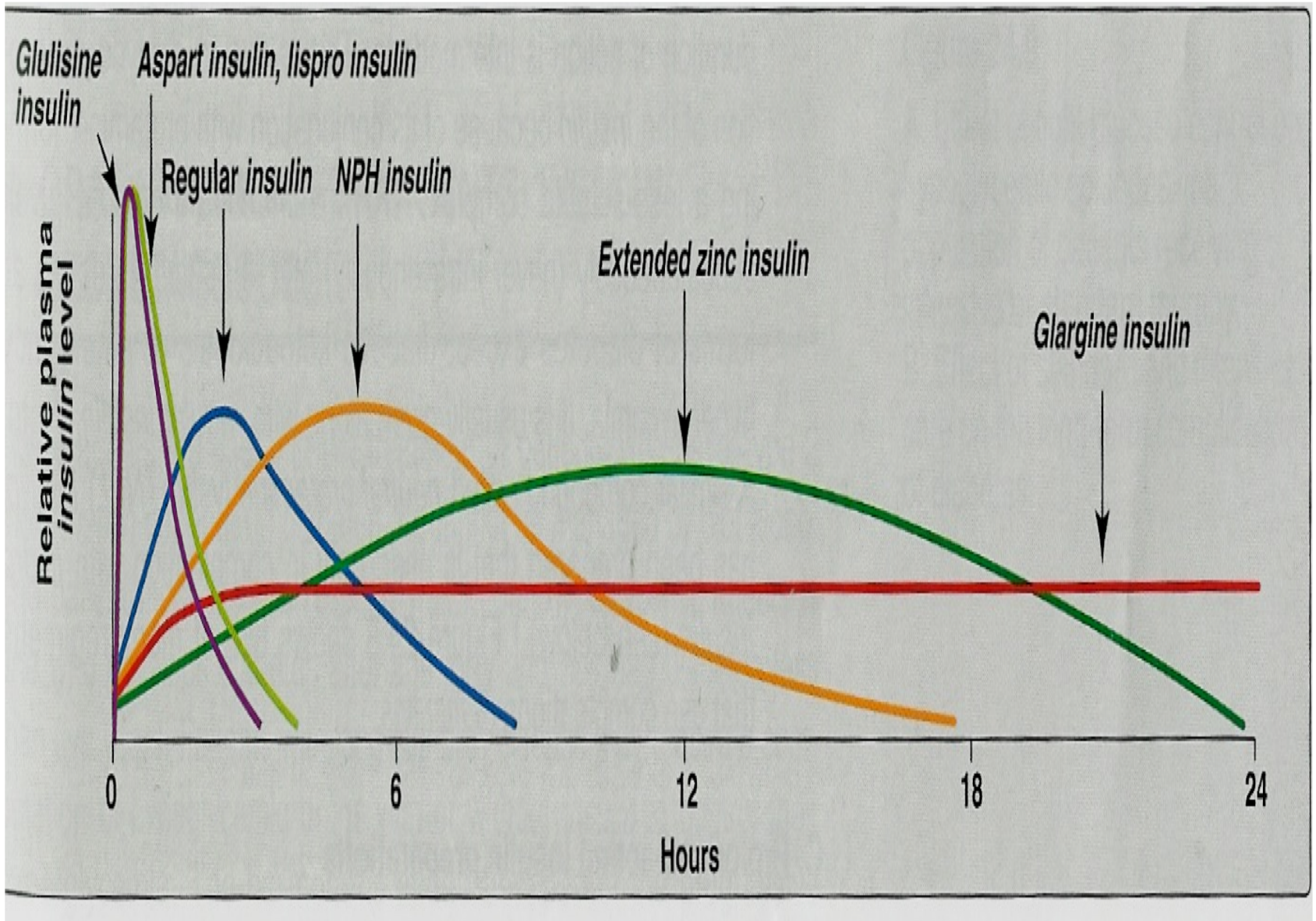
- **Constant circulating insulin over 24 hr with no peak (peakless profile).**
- **Produce flat prolonged hypoglycemic effect.**
- **Safer than NPH & Lente insulins**

(reduced risk of nocturnal (night) hypoglycemia).

NPH *vs* Glargine



Insulin preparations



Insulin Dosing Considerations

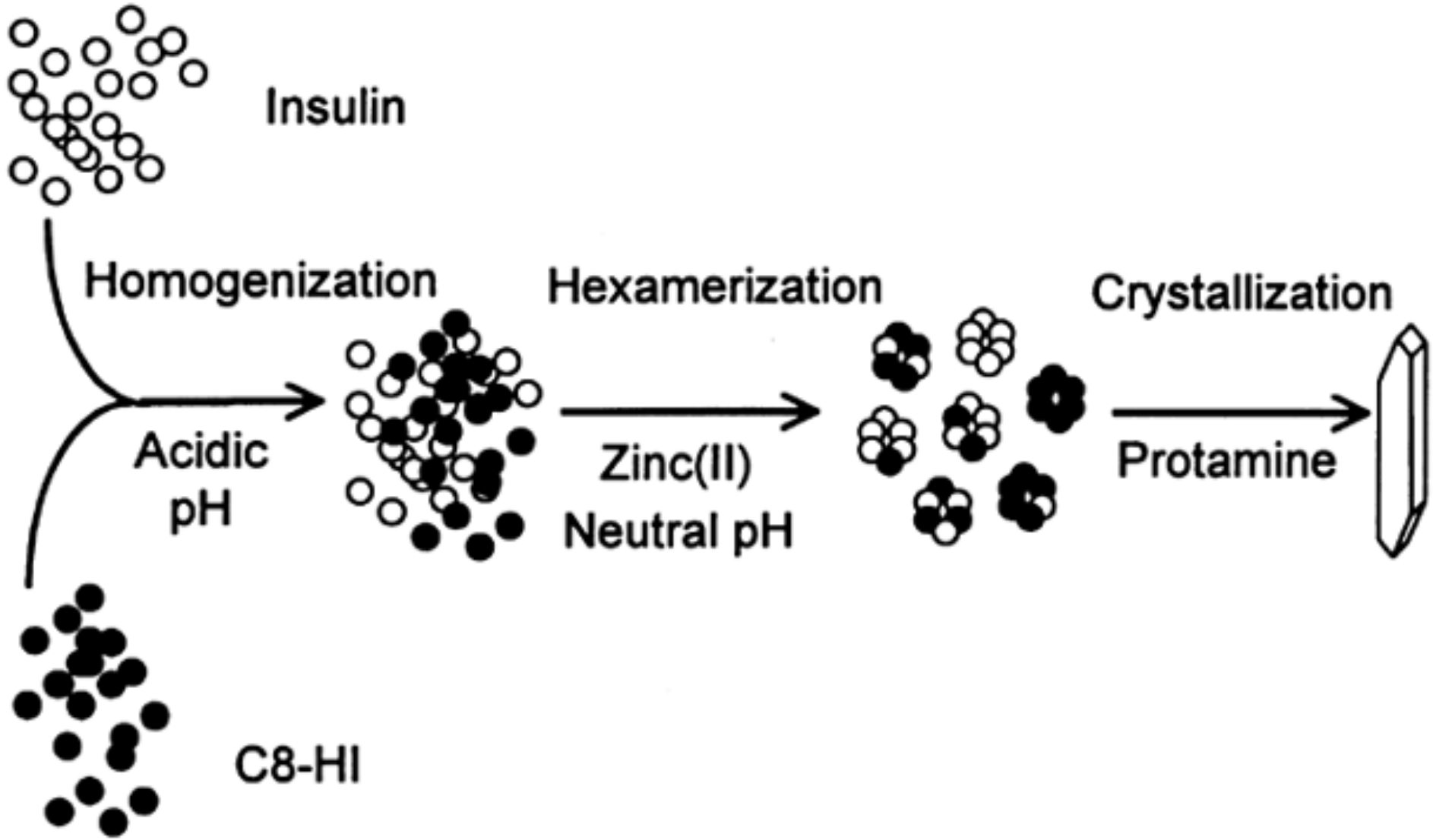
- Blood glucose monitoring is required in all patients receiving insulin
- Rotate injection sites within the same region.
- Insulin should be stored in refrigerator and warm up to room temp before use.

Complications of Insulin Therapy:

- Hypoglycemia
- Hypersensitivity reactions.
- Lipodystrophy (a buildup of fatty tissue) at the injection sites.
- Weight gain (due to anabolic effects of insulin)
- Insulin resistance
- Hypokalemia

Summary

- **Insulin analogues are used to treat type I diabetes.**
- ***Fast acting insulins*** **(lispro, aspart), given s.c. or i.v., produce fast action, used to mimic postprandial insulin.**
- ***Short acting insulin*** **(Regular insulin),** ***given s.c. or i.v.*** **produce rapid action, used to mimic postprandial insulin.**
- ***Intermediate acting insulin*** **(lente, Isophane) produce slower action, than regular insulin, given s.c. not i.v.**
- ***Long acting insulins*** **(glargine, detemir) produce constant circulating insulin over 24 hr with no peak (peakless profile), s.c. not i.v.**


Insulin
Homogenization
Acidic
pH
Hexamerization
Zinc(II)
Neutral pH
Crystallization
Protamine
C8-HI