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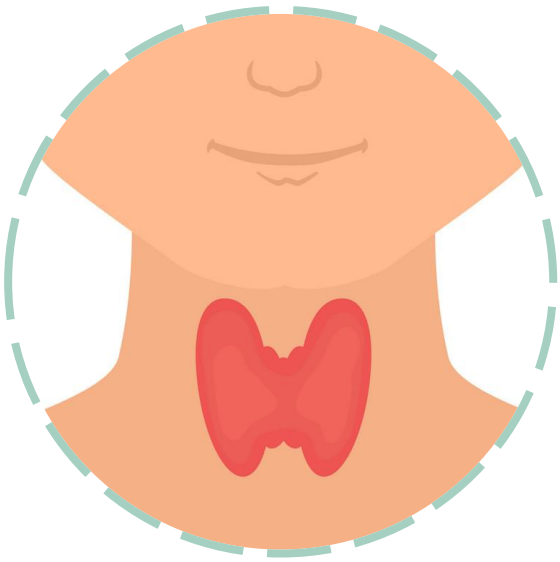
Mnemonic File



Endocrine Block

Pharmacology team 438

Uses of insulin in treatment of diabetes

Objectives:

By the end of the lecture , you should know:

- Define diabetes and mention different types of diabetes.
- Differentiate between difference in treating type I and type II diabetes.
- Understand mechanism of action, secretion, and actions of insulin.
- Describe different types of insulin analogues
- Be able to recognize the difference in pharmacokinetic profile between different types of insulin analogues.
- Know uses of different insulin analogues.

Color index:

Black : Main content
Red : Important
Blue: Males' slides only
Purple: Females' slides only
Grey: Extra info or explanation
Green : Dr. notes

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.

Fasting plasma glucose (no food for 8 hrs)

Normal	Pre-diabetes	Diabetes
<100 mg/dl (5.6 mmol/l).	**100-125 mg/dl** (5.6-6.9 mmol/L).	Fasting **>126 mg/dl** (7 mmol/L) **or** 2h after a meal **> 200mg/dl** (11.1 mmol/L).

Types of diabetes

Characteristic	Type I diabetes (IDDM) due to autoimmune or viral diseases	Type II diabetes (NIDDM) due to genetic susceptibility and other factors (age, obesity).
Onset (Age)	Usually during childhood or puberty	Usually over age 40
Type of onset	Abrupt	Gradual
Prevalence	10-20%	80-90 %
Genetic	Moderate	Very strong
Defects	β-cells are completely destroyed	β-cells produce inadequate quantity of insulin
Endogenous insulin	Absent	Present (not enough)
Insulin resistance	Absent	present
Nutritional status	Usually thin	Usually obese (Obesity is an important factor)
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 (antidiabetic drugs)**

Complications of diabetes

Blindness (retinopathy)

Neuropathy (Abnormal peripheral sensation)

BeaN's CAR

Renal failure (nephropathy)

Cardiovascular problems Micro- and macro vascular disease

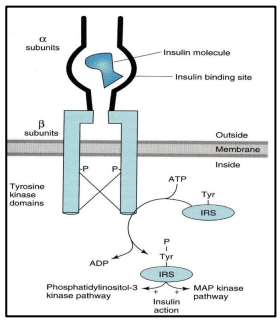
Risk of foot **A**mputation

Insulin

Insulin receptors[1]:

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

Mechanism of action of insulin[2] :



1. Phosphorylation of IRS-1 and IRS-2 (insulin receptor substrate)

2. 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 .

Effects of insulin :

Carbohydrate Metabolism

- ↑glucose uptake & utilization by peripheral tissues (Translocation of glucose transporters (GLUT) to cell membrane)
- ↑Glycogen synthesis (glycogen synthase[3])
- ↑Conversion of carbohydrate to fats.
- ↓Gluconeogenesis.
- ↓Glycogenolysis (liver).
- ↑Glycolysis (muscle).

Fat Metabolism

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

Protein Metabolism

- **Liver:**
- ↓protein catabolism.
- **Muscle:**
- ↑amino acids uptake.
- ↑protein synthesis
- ↑glycogen synthesis (glycogenesis).

potassium

- ↑potassium uptake into cells.

Pharmacokinetics of insulin :

Routes of administrations of exogenous insulin

- Can not be given orally because its a protein and it will be digested
- Insulin syringes, given s.c in arms, abdomen, thighs[4]
- Portable pin injector (pre-filled)
- Continuous S.C. infusion[5] (insulin pump)
  - More convenient
  - Eliminate multiple daily injection
  - Programmed to deliver basal rate of insulin
- Intravenously in a hyperglycemic emergency
- Inhaled aerosols, transdermal, intranasal (Under Clinical Trials)

Insulin degradation

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

1: act by tyrosine kinase cascade
2: chain A: 21 AA, chain B: 30 AA, and 3 disulfide bonds.
3: unregulated/stimulated.
4: alternate area of injection to avoid lipodystrophy
5: not given IM due to fast degradation.

Insulin Cont...

- **Source of insulin :**

Exogenous Insulin	Human Insulin analogues[1]
• **Beef Insulin :** Differs from human insulin by 3 amino acids (antigenic). • **Porcine Insulin:** Differs by one amino acid (antigenic).	• Prepared by **recombinant DNA techniques.** • **Less immunogenic.** • Modifications of amino acid sequence of human insulin can change pharmacokinetics .

Types of insulin preparations

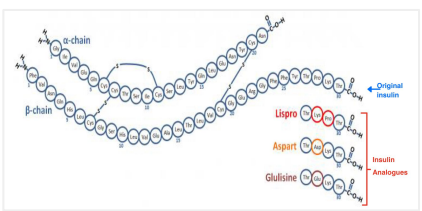
★ **Differ in pharmacokinetic properties mainly in:**
- Onset of action (Rate of absorption)
- Duration of action.

- **Variation is due to:**
  - Change of amino acid sequence[2].
  - Size and composition of insulin crystals in preparations (monomers[3], dimers, hexamers).

Prof. Hanan= For each type, you should know the onset and the duration

Ultra-short acting insulins	Short acting insulins	Intermediate acting insulins	Long acting insulins
e.g. Lispro, aspart **-very fast onset of action and short duration .**	**e.g. regular insulin , Humulin R[4]** **-fast onset of action and short duration.**	**e.g. NPH, lente** **-Slow onset, intermediate duration of action.**	**e.g. glargine, detemir** **-Slow onset and long duration of action (24hrs).**

Ultra-short acting insulins

Drug	Insulin lispro, insulin aspart
P.K	• **Clear**[5] solutions at neutral pH. • Do not aggregate or form dimers or hexamers (**monomeric analogue**). ★ **Fast onset** of action (**5-15 min**) ★ **Short duration** of action (**3-5 h**) • S.C. (5 -15 min before meal), 3 times/day[6] ★ **I.V. in emergency.** • Reach peak level 30-90 min after injection. • Mimic the prandial mealtime insulin release. 
Uses	• Preferred for external insulin pump • used to control post-prandial hyperglycemia (s.c.) and emergency diabetic ketoacidosis (i.v).

1: multiplicated by e.coli in labs, then purified.
2: changes pharmacokinetics of insulin ONLY. pharmacological action is not affected.
3: small: fast onset of action but less duration of action.
4: R= regular = short acting insulin.
5: clear = can be given IV
6: patient should skip dose if they skip meal (only take with meals) to avoid hypoglycemia.

short acting insulins

Drug	Humulin (Regular insulin)
P.K	• Soluble crystalline zinc insulin[1] • **Clear** solutions at neutral pH • Forms hexamers ★ Onset of action **30-45 min** (s.c.) ★ Duration **6-8 h** ★ **I.V. in emergency situations** • Peak 2-4 h • 2-3 times/day
Uses	• Control postprandial hyperglycemia (s.c.) & emergency diabetic ketoacidosis (i.v.) ★ **Can be used in pregnancy**[2]

Comparison between Ultrashort and short acting insulins

Characteristic	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	
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
Uses	postprandial hyperglycemia & emergency diabetic ketoacidosis	

Advantages of Ultra-short vs Short Insulin :

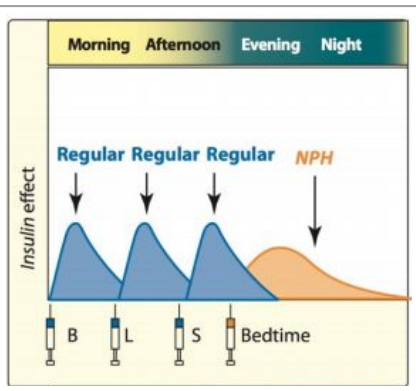
- Rapid onset of action (patients will not wait long before they eat).
- Its duration of action is no longer than 3-4 hrs regardless of the dose:
  - Decreased risk of hyperinsulinemia .
  - Decreased risk of postprandial hypoglycemia
    - Thus, they are preferable in elderly

1 just like endogenous insulin that is also found linked to zinc, making short acting insulin the most similar to endogenous in both crystallization form and duration of action/onset.
2: preferred form to be used in pregnancy as S.C injection.

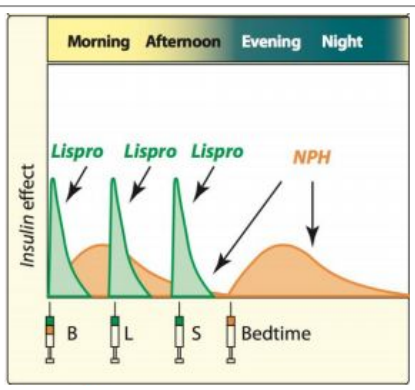
Intermediate acting insulins

Drug	1- Isophane (NPH) insulin
Characteristics	• NPH, is a Neutral Protamine[1] Hagedorn insulin in phosphate buffer. • NPH insulin is combination of protamine & crystalline zinc insulin (1:6 molecules) proteolysis release insulin.
P.K	• **Turbid suspension** at neutral pH • Given S.C. only, **not I.V**[2] • Can not be used in ketoacidosis or emergency ★ Onset of action **1-2 h** ★ Duration of action **13-18 h** • Peak serum level 5-7 h
Insulin Mixtures	1. NPH/regular insulin a. 75/25 , 70/30 , 50/50 . 2. (NP**L**= NPH / **L**ispro) (NP**A**= NPH / **A**spart) , NPL & NPA have the same duration as NPH, have two peaks[3].

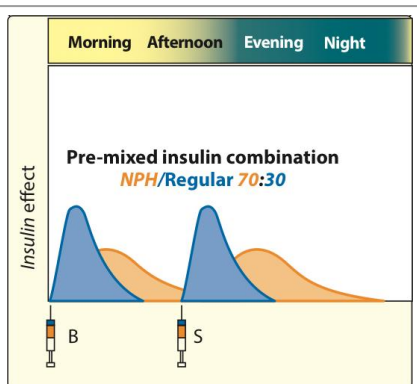
Prandial and basal insulin replacement (special thanks to 436 team)



(intermediate & short acting insulin)
Before meals : diabetic patients takes short acting insulin which is regular insulin used to cover the daily need of the insulin after meals.
Before sleeping : no need for strong and fast action because glucose levels before sleeping not high like after meals so, to avoid hypoglycemia and coma the patients takes instead of short acting insulin the insulin intermediate.



(intermediate & Ultra short acting insulin)
Same idea but the short acting insulin is replaced with the ultra-short acting insulin which has a rapid effect As long as the body needs the insulin as a basal level between meals , the patients take double dose of the insulin intermediate to control the glucose level for the whole day not only before meals or sleeping time.



(Insulin mixture(combination) = intermediate + short acting insulin)[4]
Is a helpful drug to reduce the use of injections for the diabetic patients and provide a basal level of insulin during the day and once the patient eat a meal short acting insulin is ready.

1: protamine is clinically used as heparin antidote
2: cannot be used in emergency (slow onset of action)
3: first peak due to ultra short acting part of the preparation, second peak due to NPH.
4: basal insulin level is maintained at all times

Intermediate acting insulins Cont..

Drug	2- Lente insulin (Humulin L, Novolin L)

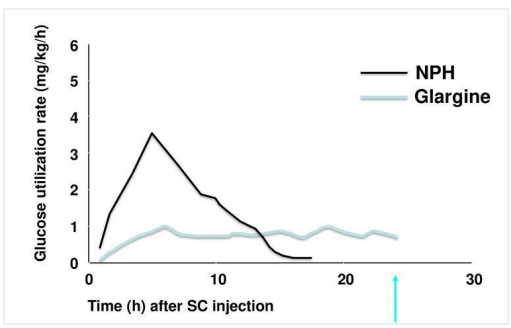
Characteristics	• **Mixture of :**
	  ○ 30% semilente insulin **(amorphous precipitate of zinc insulin in acetate buffer)**
	  ○ 70% ultralente insulin **(poorly soluble crystal of zinc insulin)**
	• **Turbid suspension** at neutral pH.
	• Given S.C. , **not intravenously**

P.K	• 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)

Drug	Insulin glargine (lantus)
Characteristics	• Clear solution **BUT forms precipitate**[1] (hexamer) at injection site. ★ Slow onset of action **2 hr** • Absorbed less rapidly than NPH & Lente insulin • Given S.C. only, **not intravenously** • Should not be mixed with other insulins in the same syringe.
P.K	• Maximum effect after 4-5 h ★ Prolonged duration of action (**24 h**) • Once daily. • Produce broad plasma concentration plateau **(low continuous insulin level)**[2] • Glargine must be used in regimens with rapid or short acting insulins[3].
Advantages over intermediate-acting insulins	• Constant circulating insulin over **24 hr** , with no peak **(peak-less profile).** ★ **Produce flat prolonged hypoglycemic effect.** • reduced risk of nocturnal hypoglycemia → Safer than NPH & Lente insulins.



Comparison between the onset and the duration of actions

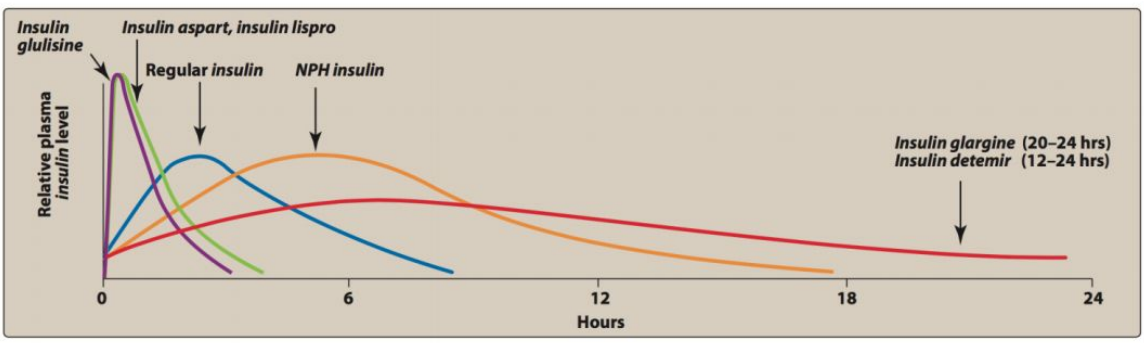


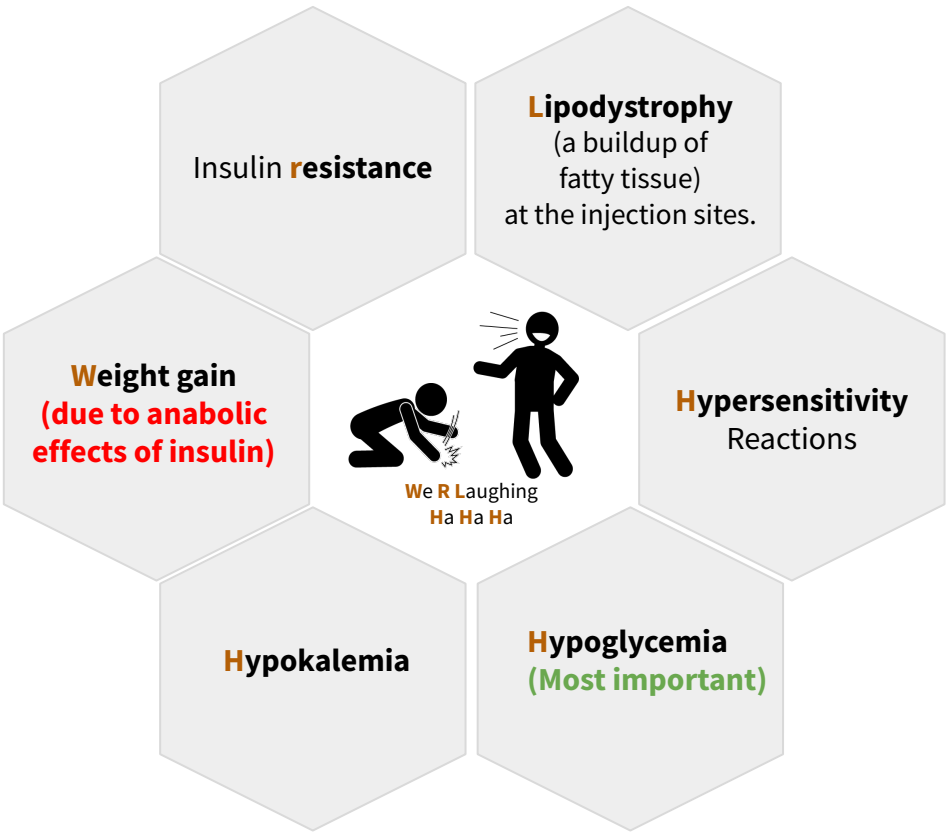
Figure 24.7
Onset and duration of action of human *insulin* and insulin analogs. NPH = neutral protamine Hagedorn.

1: precipitation is induced by the body's pH, is why it should not be given IV.
2: ADVANTAGE.
3: to produce peaks at meal times

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



Summary from dr slides

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)	• given s.c. not i.v. • slower action, than regular insulin
Long acting insulins (glargine, detemir)	• Given s.c. not i.v. • Produce constant circulating insulin over 24 hr with no peak (peakless profile)

Quiz

MCQ

Q1 : Which one of the following is an advantage for lispro over humulin ?

A- Fast onset of action. **B-Longer duration.** **C- Form dimers and hexamers .**

Q2: Which one of the following is an insulin in combination with protamine & crystalline zinc ?

A- Insulin lispro. **B-Lente insulin.** **C- Isophane.**

Q3: What is the treatment for Type I Diabetes ?

A- Insulin injection. **B- I.V dextrose.** **C- Oral hypoglycemics.**

Q4: Which one of the following is a complication of insulin therapy?

A- Hyperglycemia. **B- hypokalemia.** **C- Weight loss.**

Q5: Which one of the following sources provide the least immunogenic insulin ?

A- Beef Insulin **B- Porcine Insulin** **C- Human Insulin analogues**

SAQ

1- 30 years old diabetic patient presented at emergency unit because of emergency diabetic ketoacidosis .

Q1 : Mention the fastest insulin analogue that will control his condition.

Q2 : Mention 2 complications that can result from the treatment you mentioned in (**Q1**) .

Q3: What is the variation between different insulin preparation? (Mention 2)

Answers:

MCQ

Q1	A
Q2	C
Q3	A
Q4	B
Q5	C

SAQ

Q1	Insulin lispro or Insulin Aspart
Q2	1. Hypoglycemia . 2. Hypokalemia
Q3	• Change of amino acid sequence. • Size and composition of insulin crystals in preparations (monomers, dimers, hexamers).

pharmacology
Team 438

Thank you for all your love and support.

Good luck future doctors!

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