Drugs used in DM type 1

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- Main text
- Male slide
- Female slide
- Important
- Dr, notes
- Extra info

EDITING FILE

Objectives

- Diabetes and different types of diabetes
- Treating type I and type II diabetes.
- Mechanism of insulin secretion and insulin actions.
- Different types of insulin analogues
- Pharmacokinetic profile of different types of insulin analogues.
- Uses of different insulin analogues

Dr. Fouda Video

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Diabetes Mellitus

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

	Normal Glucose Tolerance, mg/dL (mMol/L)	Prediabetes	Diabetes Mellitus[2]
Fasting plasma glucose mg/dL (mmol/L)	<100 (5.6)	100–125 (5.6–6.9) (impaired fasting glucose)	≥126 (7.0)
Two hours after glucose load[1] mg/dL (mmol/L)	<140 (7.8)	≥140–199 (7.8–11.0) (impaired glucose tolerance)	≥200 (11.1)
HbA_{1c} (%) (ADA criteria)	<5.7	5.7–6.4	≥6.5

Types of Diabetes

Type II diabetes (NIDDM)
Due to genetic susceptibility and other factors (age, obesity).
Absolute diabetes

Gestational diabetes (GDM)
It is any abnormality in glucose levels noted for the first time during pregnancy
Relative diabetes

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Type I diabetes (IDDM)
Due to autoimmune or viral disease

The "other " refers to multiple other specific causes of an elevated blood glucose
pancreatectomy, pancreatitis, non-pancreatic diseases, drug therapy

Female slide

Characteristic	Type 1 diabetes	Type 2 diabetes
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

Macrovascular complications: Atherosclerosis, such as myocardial infarction and stroke.

Microvascular complications: Renal failure (nephropathy), Blindness (retinopathy), Neuropathy.

Risk of foot amputation

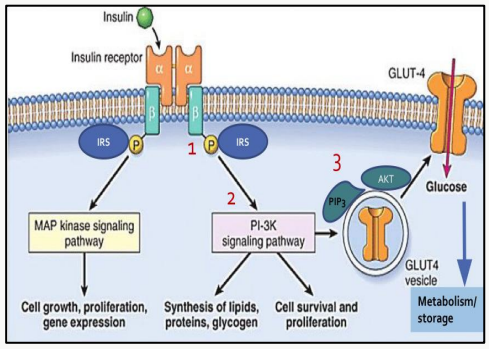
Insulin

Overview

- It is the mainstay for treatment of virtually all patients with type 1 and many with type 2 diabetes
- It is released from pancreatic beta cells at a low basal rate and much higher stimulated rate in response to increasing blood glucose levels.
- **Insulin receptors:**
  - Present on cell membranes of most tissues.
  - Liver, muscle and adipose tissue

M.O.A

- Phosphorylation of **IRS-1 and IRS-2 (insulin receptor substrate)**
- **PI3K is activated** by interaction with IRS proteins and generates **PIP3**, which regulates the localization and activity of several downstream kinases, including PKB (Akt).
- The isoform Akt2 controls the downstream steps that are important for glucose regulation in skeletal muscle, adipose tissue and liver by coordinating the translocation of GLUT to the plasma membrane

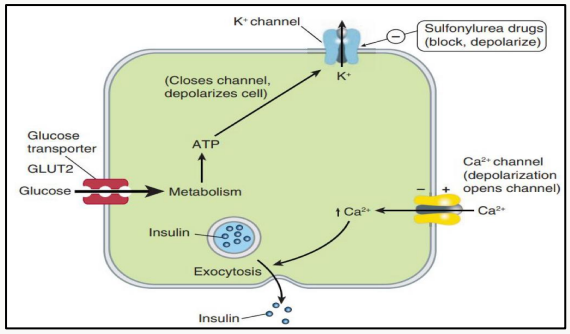


phosphoinositide 3-kinase (PI3K)

(GLUT4: in muscles and adipose tissue)

Secretion

- In the **resting cell** with normal (low) ATP levels , K diffuses down its concentration gradient through ATP-gated potassium channels, maintaining the intracellular potential at a fully polarized, negative level (minimal insulin release).
- If glucose concentration rises, ATP production increases, **K channels close** , and depolarization of the cell results.
- **Voltage-gated Ca channels open** in response to depolarization, allowing more Ca to enter the cell.
- Increased intracellular calcium results in increased insulin secretion.



Insulin

P.K

- **Routes of administration of exogenous insulin:**
- Cannot be given orally why? Peptide→ digested by gastric pH & enzymes
- The standard mode of insulin therapy is S.C injection with:
  -Conventional disposable needles and syringes (S.C., arms, abdomen, thighs)
  -Portable pen injector (pre-filled)
- Continuous S.C. infusion (insulin pump): **More convenient-Eliminate multiple daily injection-Programmed to deliver 24h basal rate of insulin- Manual adjustments in the rate of delivery can be made to accommodate changes in insulin requirements (eg, before meals or exercise)**
- Intravenously IV -in a hyperglycemic emergency-
- Under Clinical Trials: Inhaled aerosols, transdermal, intranasal

Sources

- **Exogenous:**
- 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 .

Effects of insulin

Liver

- Increases the storage of glucose as glycogen in the liver by:
- Translocating the glucose transporters (GLUT2) to cell membrane
- Inducing glucokinase and glycogen synthase, inhibiting phosphorylase
- ↓ Glycogenolysis
- Increases Lipogenesis + Decreases Lipolysis.
- Inhibits conversion of fatty acids to ketoacids.
- Inhibits conversion of amino acids to glucose
- Increases triglyceride synthesis and VLDL formation

Adipose tissue

- Increases Triglycerides storage by
- Increasing glucose transport into cells via GLUT4 transporters
- Reducing intracellular lipolysis.
- Activating plasma lipoprotein lipase
- Increases Fatty acids synthesis.

Muscle

- Glucose transport into muscle cells is facilitated by insertion of GLUT4 transporters into cell plasma membranes
- Increased protein synthesis
- Increases amino acid transport
- Increases ribosomal protein synthesis
- Increased glycogen synthesis (glycogenesis)
- Increases glucose transport
- Induces glycogen synthase and inhibits phosphorylase
- Insulin also increases K uptake by cells.

Insulin Preparations

Types of insulin preparations:

- Differ in pharmacokinetic properties mainly
  1. Onset of action (Rate of absorption)
  2. Duration of action.
- Variation is due to:
  1. Change of amino acid sequence.
  2. Size and composition of insulin crystals in preparations (monomers, dimers, hexamers

1. Ultra-Short Acting Insulins

Drug	Lispro Insulin	Aspart Insulin
P.K	• Clear solutions at neutral pH • Do not aggregate or form dimers or hexamers -monomeric analogue- • Very Fast onset of action (5-15 min) | Short duration of action (3-5 h) • S.C. (5 -15 min before meal) | I.V in emergency. • Reach peak level 30-90 min after injection | 3 times/day • Mimic the prandial mealtime insulin release. "better than short for postprandial use" Both the fast onset & the short DOA make the (ultra-short acting) better than the short-acting.	
Uses	• Preferred for external insulin pump • Used to control postprandial hyperglycemia (S.C.) • Emergency diabetic ketoacidosis (I.V)	

2. Short Acting Insulins

Drug	Humulin (Regular insulin)
P.K	• Soluble crystalline zinc insulin. • Clear solutions at neutral pH • Forms hexamers • Onset of action 30-45 min (s.c.) • it requires administration 1 h or more before a meal • Fast onset of action and short 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** (best choice even in T2DM)

Comparison Between Ultra-short & Short Acting Insulin

Characteristic	Ultra-Short acting insulins Lispro, Aspart, Glulisine	Short-acting (regular) insulins Humulin R, Novolin R
Physical characteristics	Clear solution at neutral pH	
Chemistry	**Monomeric** analogue	Hexameric analogue
Route & time of administration	S.C. 5 min (≤15 min) before meal I.V. in **emergency** (e.g. DKA)	S.C. 30–45 min before meal I.V. in **emergency** (e.g. DKA)
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	
Uses	**Postprandial hyperglycemia & emergency diabetic ketoacidosis (DKA)**	
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** Most diabetic patients are on ultra short or long acting insulin or both rarely on short acting	

Insulin Preparations

3. Intermediate Acting Insulins

Drug	Isophane (NPH) insulin	Lente insulin
Overview	• **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.**	- Mixture of: 1- 30% semilente insulin,**amorphous** -more soluble- precipitate of zinc insulin in acetate buffer 2- 70% ultralente insulin (poorly soluble crystal of zinc insulin) • **Turbid** suspension at neutral pH :**Not intravenously(I.V)** • Given S.C.
P.K	• Turbid suspension at neutral pH,hence given S.C. only, **not I.V** because it's not a clear solution • Can't be used in ketoacidosis or emergency due to the **slow onset (Onset of action 1-2 h)** • Duration of action 13-18 h • Peak serum level 5-7 h • NPH insulin is often combined with regular and rapid-acting insulins.	• **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.**

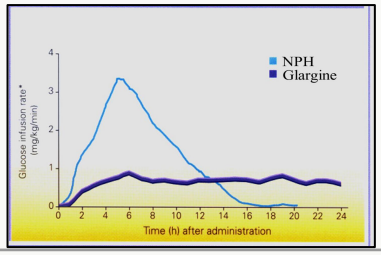
Insulin Preparations

4. Long-Acting Insulins

Drug	Insulin glargine (Lantus)	Insulin detemir
Overview	• Clear solution but forms precipitate (hexamer) at injection site • Slow onset of action 2 hr • Absorbed less rapidly than NPH & Lente insulin • Given S.C. only, Not intravenously so not for emergency • 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, which is more convenient for the patient • Produce broad plasma concentration **plateau (low continuous insulin level)** • **Provides a peakless basal insulin level lasting more than 20 h,** • **Helps control basal glucose levels without producing hypoglycemia.** • Glargine must be used in regimens with rapid or short acting insulins to produce peaks at meal times	

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.**



Female slide

Prandial and basal insulin replacement

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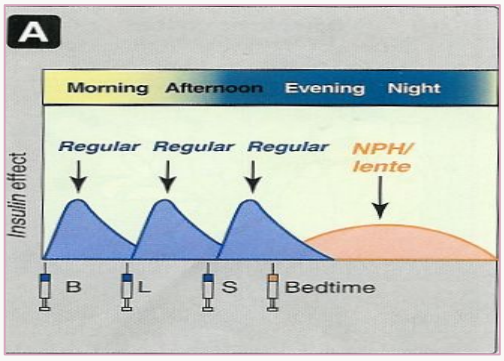
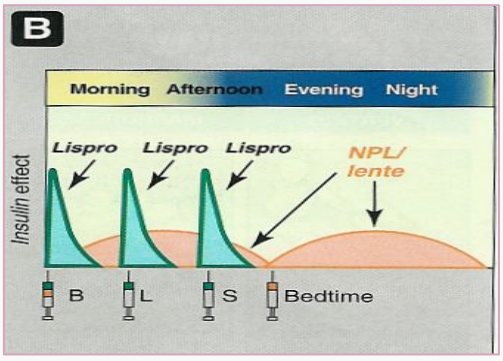


- Regular Insulin (short acting) is given once before every meal, if the patient's glucose levels are not well controlled, (hyperglycemia during their sleep for example) intermediate acting insulins like NPH could be added at bedtime for better control



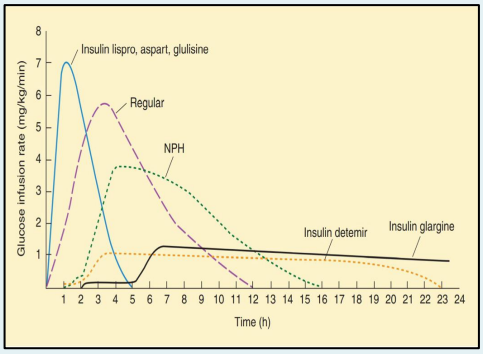
- Ultra- short acting insulins like Lispro are also taken 3 times/day (before every meal)
- Intermediate acting insulins could be taken twice for better control -depending on the patient's condition-
- Long acting insulins are generally more preferred especially when combined with shorter acting insulins

Insulin Preparations

Inhaled insulin (Afrezza)

- is formulated for inhalation using a manufacturer-specific device (Leahy, 2015).
- This formulation should be used in combination with a long-acting insulin
- It has a more rapid onset and shorter duration than injected insulin analogues.
- It is not widely used.
- Adverse events include: Cough and throat irritation. It should not be used in individuals who smoke

Extent and duration of action of various types of insulin as indicated by the glucose infusion rates (mg/kg/min) required to maintain a constant glucose concentration. The durations of action shown are typical of an average dose of 0.2–0.3 U/kg.
The durations of regular and NPH insulin increase considerably when dosage is increase



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Complications of insulin

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

MCQ

Q1- Which one of these insulin drugs is a clear solution at neutral PH and has monomeric analoge?

A-Regular insulin	B-Aspart	C-Isophane	D-Lantus

Q2- Which one of the following insulin preparations has the shortest duration of action?

A-Detemir	B- NPH	C- Glargine	D- Lispro

Q3- Which of the following drugs reduced risk of nocturnal (night) hypoglycemia?

A- NPH	B- Regular insulin	C- Glargine	D- Glulisine

Q4- Which of the following drugs is used as inhaled insulin?

A-Novolin	B-Afrezza	C-Humulin	D-Lispro

Q5- Longest acting insulin is

A- Insulin glargine (lantus)	B- Insulin lispro	C- Lente insulin	D- Isophane insulin (NPH)

1:B ,2: D ,3:C ,4: B ,5:A

SAQ

1. **What are the differences between ultra-short and short acting insulins?**

   Answer: Slide 7

2. **Give 2 advantages of long acting insulin over intermediate-acting insulins.**

   Answer: Slide 8

3. **What is the mechanism of action of insulin?**

   Answer: Slide 4

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