King Saud University

College of Medicine

2nd Year, Endocrine Block

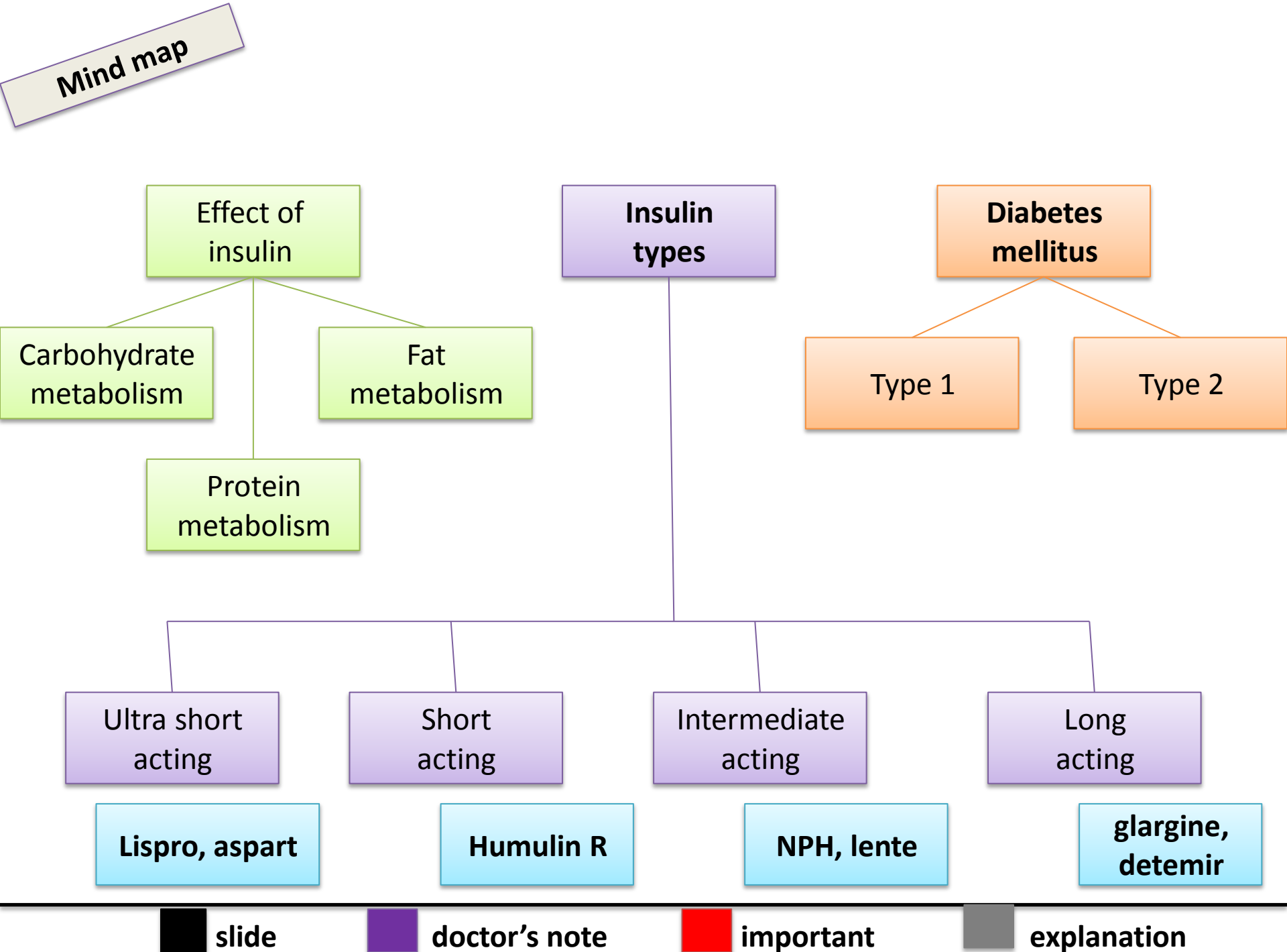
PHARMACOLOGY 433

MED 433 Teams

L6 Use of insulin in the treatment of diabetes mellitus

Objectives

- ✓ *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*


Mind map
Effect of insulin
Carbohydrate metabolism
Fat metabolism
Protein metabolism
Insulin types
Diabetes mellitus
Type 1
Type 2
Ultra short acting
Short acting
Intermediate acting
Long acting
Lispro, aspart
Humulin R
NPH, lente
glargine, detemir
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doctor's note
important
explanation

INTRODUCTION

Diabetes mellitus

Definition

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

Diagnosis of diabetes mellitus

Fasting plasma glucose > 7 mmol/L (126 mg/dl) is diagnostic of diabetes

Plasma glucose > 11.1 mmol/L (200 mg/dl), 2h after a meal confirms a diagnosis of diabetes

Complications

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

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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

Insulin

INTRODUCTION+IMP

Insulin receptors	Carbohydrate Metabolism	Fat Metabolism	Protein Metabolism	potassium	Sources of Exogenous Insulin
present on cell membranes of most tissues. Liver, muscle and adipose tissue	glucose uptake & utilization Glycogen synthesis (glycogen synthase) Conversion of carbohydrate to fats ↓ Gluconeogenesis ↓ Glycogenolysis (liver) ↑ Glycolysis (muscle)	Liver ↑ Lipogenesis ↓Lipolysis Inhibits conversion of fatty acids to keto acids Adipose Tissue ↑Triglycerides storage ↑Fatty acids synthesis ↓Lipolysis	Liver: ↓ protein catabolism Muscle: ↑ amino acids uptake. ↑ protein synthesis. ↑ glycogen synthesis (glycogenesis).	↑ potassium uptake into cells	Beef Insulin Differs by 3 AA from human insulin (antigenic). Porcine Insulin Differs by one AA (antigenic)

Human Insulin	Routes of administrations of exogenous insulin	Insulin degradation
Prepared by recombinant DNA techniques. Less immunogenic. Modifications of amino acid sequence of human insulin can change pharmacokinetics That means we can control the onset of action and duration of action	Can not be given orally. To avoid amino acid destruction. 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 Normally, in between meals there is basal rate of insulin Secretion Intravenously (in a hyperglycemic emergency) Under Clinical Trials Inhaled aerosols, transdermal, intranasal.	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)

Insulin pump

Pin injector

insulin preparations

Differs in pharmacokinetic properties mainly

- Rate of absorption
- Onset of action and duration of action.

Variation is due to:

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

Types of insulin preparations Insulin Analogues

1- Ultra-short acting insulins

e.g. **Lispro, aspart**
very fast onset of action and short duration

2- Short acting insulins

e.g. **regular insulin**
fast onset of action and Short duration.

3- Intermediate acting insulin:

e.g. **NPH, lente**
Slow onset, intermediate duration of action.

4- Long acting insulin:

e.g. **glargine, detemir**
Slow onset and long duration of action.

Insulin Preparation

	1-Ultra-Short acting insulins e.g. Lispro, aspart, glulisine	2-Short-acting (regular) insulins e.g. Humulin R, Novolin R
Physical Characteristics	**Clear solution** at neutral pH Mimic the prandial mealtime insulin release	**Clear solution** at neutral pH Soluble crystalline zinc insulin
Chemistry	**Monomeric analogue**	**Hexameric analogue**, soluble crystalline(more than 1 molecule) zinc insulin (Hexameric+crystalline zinc insulin) = The same structure of endogenous insulin So we can use it in pregnancy
Rout & time of adminstration	S.C.&I.V. 5-15 min (no more than 15 min) before meal , you can eat after taking it	S.C.&I.V 30 – 45 min before meal
Onset of action	5 – 15 min (S.C) (very fast onset of action)	30 – 45 min (S.C) fast action
Peak level **=Maximum Effect**	30 – 90 min	2 – 4 hr
Duration	3 –5hr (very short duration)	6 – 8 hr short duration
Usual admistiration	2 – 3 times / day or more If the patient skip the meal, He must also skip the insulin	2 – 3 times/day or more
Indication	✓postprandial hyperglycemia (S.C) (Postprandial =after eating) ✓ emergency diabetic ketoacidosis (I.V) ✓**Preferred for external insulin pump (Lispro does not form hexamers)**	✓postprandial hyperglycemia (S.C) (Postprandial =after eating) ✓ emergency diabetic ketoacidosis (I.V) ✓ **Can be used in pregnancy**

Insulin Preparation

Advantages of Insulin Lispro vs Regular Insulin:

- ✓ **Rapid onset of action** (patients will not wait long before they eat).(due to rapid absorption)
- ✓ **Its duration of action is no longer than 3-4 hrs regardless of the dose.**
- ✓ **Decreased risk of postprandial hypoglycemia**. (due to sjort duration of action)
- ✓ **Decreased risk of hyperinsulinemia** (due to sjort duration of action)

NORMALLY, Insulin is released in response to food, then glucagon come and antagonize it to make BALANCE.
But in with these drugs (exogenous insulin), patient develop postprandial hypoglycemia because there is nothing antagonize them.

Clear solution = we can use it in case of emergency by I.V injection

3-Intermediate acting insulins

Chemistry	**Isophane (NPH)** is a Neutral Protamine Hagoderon (complex of insulin) insulin in phosphate buffer	**Lente insulin (Humulin L, Novolin L)**
Physical Characteristics	**Turbid suspension** at neutral pH (cant be given I.V). Both are equivalent in activity	
Rout	**S.C. only NOT I.V**	
Onset of action	1-2 h (slow onset of action)	1-3 h (Delayed onset of action)
Peak level	5-7 h	4-8 h
Duration	13-18 h (relatively long duration of action bcuz it's a bigger molecule)	13-20 h (relatively long duration of action)
Composition	Combination of protamine and crystalline zinc insulin	30% semilente (means partial size half half) insulin + 70% ultralente (very big+long acting insulin)
Indication	**Not used in emergency or diabetic ketoacidosis**	
Mixture	Can be mixed with ultrashort or short duration: NPL= NPH/ Lispro NPA = NPH/ Aspart 50\50 70\30 75\25 (NPH/regular)	

With short acting insulin there is risk of hypergylcemia druing night bcuz of it's short duration, so we prescribe drugs with longer duration such as NPH (sometimes given 2/day)
* We treat depending on blood glucose level

slide | doctor's note | important | explanation

Insulin Preparation

4-Long acting insulins detemir (Levemir) & Insulin glargine (lantus)	
Should not be mixed with other insulin (All the above could be mixed except long acting)	
Physical Characteristics	**Clear solution but precipitate at injection site**
Rout	**Given s.c not I.V.**
Onset of action	2 h slow onset of action Absorption less rapidly than NPH & Lente insulin
Peak level	4-5 h produce broad plasma concentration plateau (low continuous insulin level).
Duration	Prolonged (24h)
Usual administiration	Once daily
	Produce broad plasma concentration plateau (low continuous (like panceras) level over 24 h low) **(reduce risk of hyperinsulinemia)**

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Insulin Preparation

Aspart produces peak with (short onse+duration)

NPH ponounce peak and shorter in action than Lente

Lente (extended zinc insulin)

Grigline (constant level with long duration)

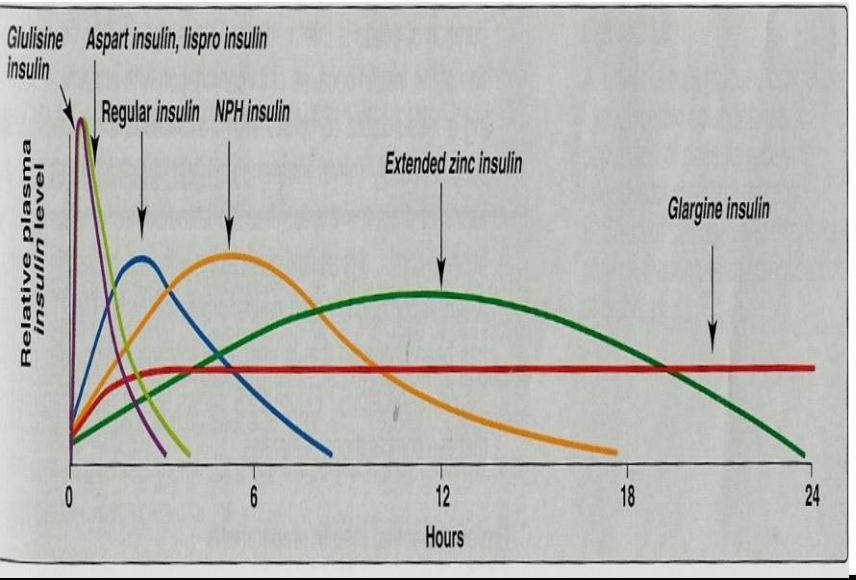
Advantages of Insulin glargine over intermediate-acting insulins:

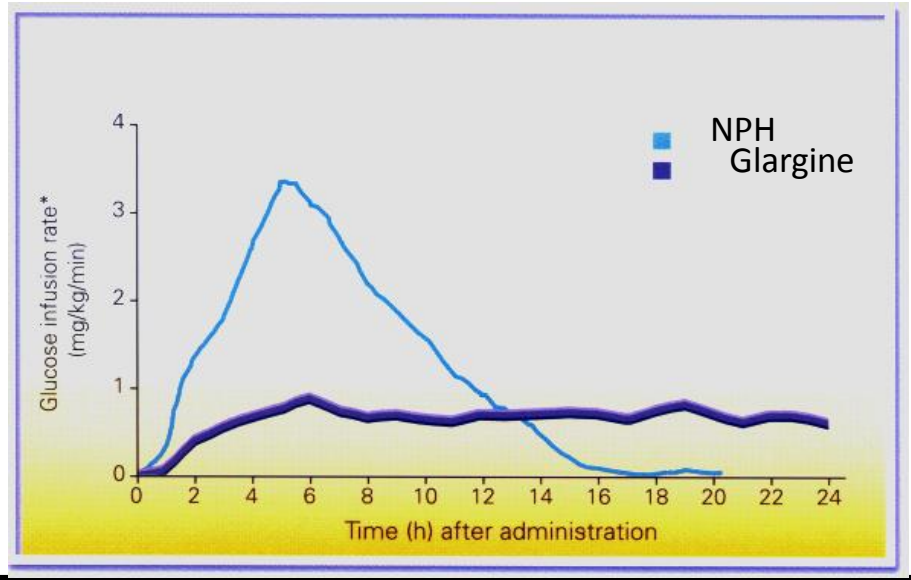
❖Constant circulating insulin over 24 hr with no pronounced peak.(not absorbed rapidly)

❖Produce flat prolonged hypoglycemic effect.

❖ More safe than NPH & Lente insulins **(reduced risk of hypoglycemia).**

❖ NPH >> there is pronounced peak (maximum concentration)then decline in concentration





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Complications of Insulin Therapy

- ✓ **Hypoglycemia**

Caused by:
– Overdose of insulin
– Excessive (unusual) physical exercise
– A meal is missed

- ✓ **Hypersensitivity reactions.**
- ✓ **Lipodystrophy =hypertrophy at injection site** (don't inject at the same area many times)
- ✓ **Weight gain** (due to anabolic effects of insulin)
- ✓ **Insulin resistance**
- ✓ **Hypokalemia**

Summary

1- Ultra-short acting insulins (lispro,aspart)	2- Short acting insulins= regular insulin (Humulin R) Like human	3-Intermediate acting insulin (NPH, lente)	4- Long acting (glargine,detemir)	Complications of Insulin Therapy
Given: IV or S.C	Given: IV or S.C	Given: S.C only	Given: S.C only	**Hypoglycemia**
Monomeric analogue **Fast onset of action (0-15 min)**	**Hexameric analogue.** **Onset of action 30-45 min**	**Onset of action 1-2 h.** **Insulin mixtures** --- **(lente) onset of action (1-3 h)**	**Slow onset of action 2 h. Prolonged duration of action (24 h).** **Once daily**	**Overdose of insulin** **Excessive physical exercise** **A meal is missed**
Use: **postprandial hyperglycemia &** **emergency diabetic ketoacidosis** **Can be used in pregnancy (Regular insulin only)**		**Not used in emergencies**	**Should not be mixed with other insulin**	**How it is treated?** **1. Conscious patient:** **Oral glucose tablets, juice or honey.** **2. Unconscious patient** **glucose solution I.V. infusion, OR Glucagon**

Quiz yourself

Q1: which of the following carry fewer risks to develop nocturnal hypoglycemia?
A) Insulin glargine
B) Lente insulin
C) Lispro

Q2: Which of the following statements is correct regarding insulin detemir?
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.

Q3: Sara had diabetes type1, her friends made party for her . The party start with surprise torte . Which form of insulin is the best choice to used in this case?
A) Humilin R
B) Lente insulin
C) aspart

Q4: Ultra-short and short acting we don't use them alone we should give long or intermediate acting insulin before sleep. True or False
A) True
B) False

Q5: Which insulin form of the following used in case of pregnancy ?
A) Humilin R
B) Aspart
C) Lente

Q6: which one of the following can mixed with regular insulin or lispro ?
A) Insulin detemir
B) Insulin glargine
C) NPH

Q7: Which insulin form of the following used for management of hyperglycemic emergencies ?
A) Insulin glargine
B) Lente insulin
C) Lispro

Q8: What is the standard route for administration of insulin ?
A) Oral
B) subcutaneous injection
C) I.V

Q9: what is the main complication of insulin therapy?
A) Diabetic ketoacidosis
B) Hypoglycemia
C) Both

Q10: When we don't eat the meal , we have to skip the insulin dose. True or False?
A) True
B) False

Answers: 1-A 2-B 3-C 4-A 5-A 6-C 7-C 8-B 9-B 10-A

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We hope that we made this lecture easier for you
Good Luck !