Pharmacology
Team 437

MED437
KING SAUD UNIVERSITY

Use of Insulin in Diabetes + Management of Diabetic Ketoacidosis

by the end of this lecture, students should be able to:

- 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:
Important
Note
Extra

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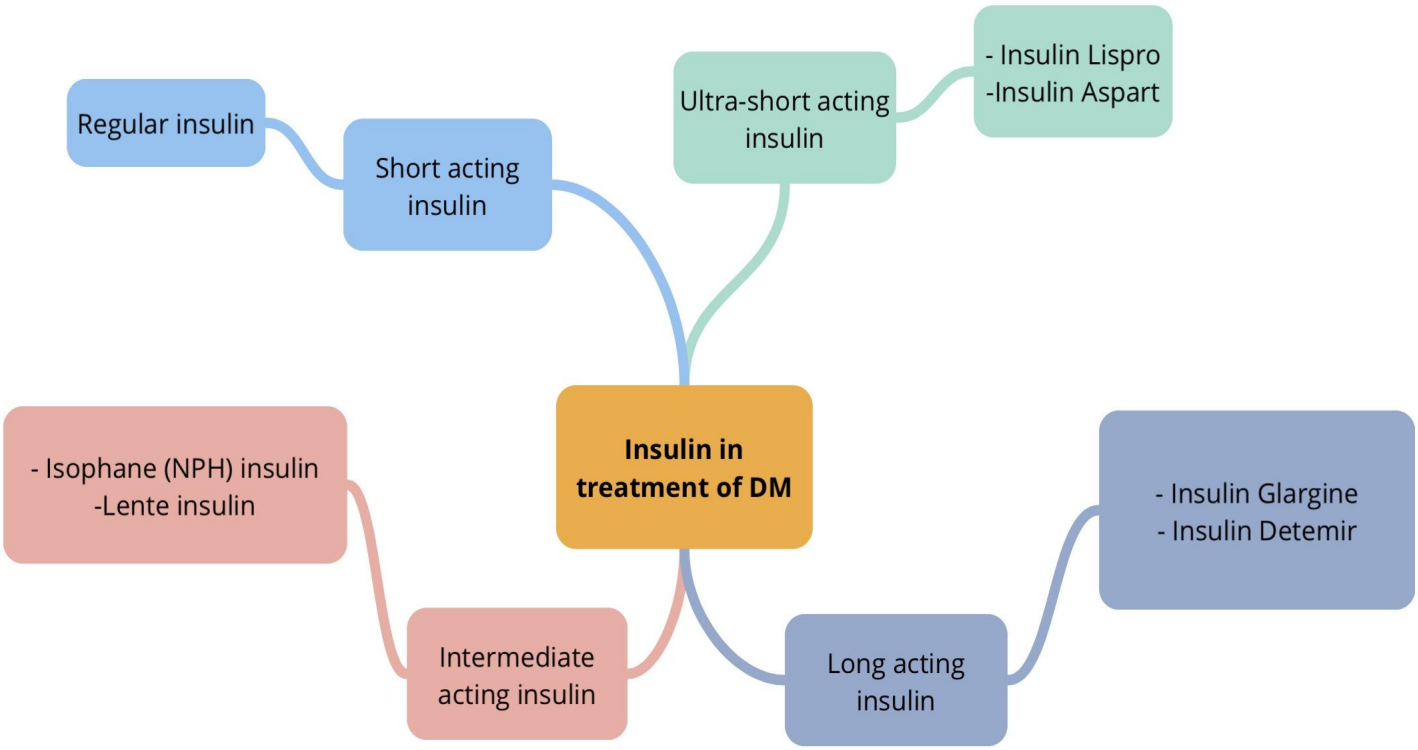
Editing File

Mind Map


Insulin in treatment of DM
Short acting insulin
Regular insulin
Ultra-short acting insulin
- Insulin Lispro
-Insulin Aspart
Intermediate acting insulin
- Isophane (NPH) insulin
-Lente insulin
Long acting insulin
- Insulin Glargine
- Insulin Detemir

Diabetes mellitus

- **Is a chronic metabolic disorder characterized by high blood glucose level caused by deficiency of insulin or by increased insulin resistance.**
- **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 (post-prandial) > 200 mg/dl (11.1 mmol/L).**

Types of Diabetes

Type I diabetes (IDDM)

- due to autoimmune or viral diseases
- 10-20% occurrence.
- During childhood or puberty
- β-cells are completely destroyed.
- Absolute deficiency of insulin secretion
- Treated by insulin.

Type II diabetes (NIDDM)

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

But when the disease progresses we use insulin

Complications of diabetes

Renal failure (nephropathy)

neuropathy

Blindness (retinopathy)

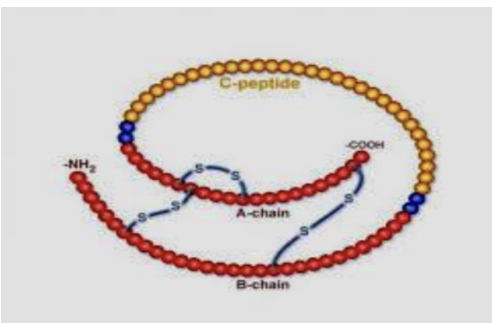
Risk of foot amputation

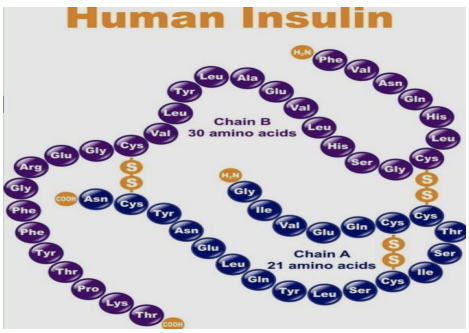
Cardiovascular problems
Micro and macro vascular diseases

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 receptors

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



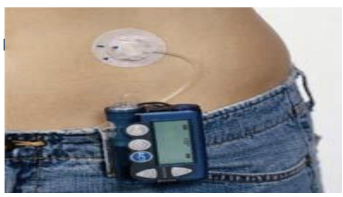


Effects of insulin

I. Carbohydrate Metabolism:	II. Fat Metabolism:
–↑ glucose uptake & utilization by peripheral tissues. –↑ Glycogen synthesis (glycogen synthase) – ↑Conversion of carbohydrate to fats. – ↓ Gluconeogenesis. – ↓ Glycogenolysis (liver). – ↑ Glycolysis (muscle). Net action → decrease blood glucose level	**Liver:** – ↑ Lipogenesis. – ↓ Lipolysis. – Inhibits conversion of fatty acids to ketoacids. This is why when people don't have enough insulin they generate more ketoacids **Adipose Tissue:** – ↑ Triglycerides storage. – ↑ Fatty acids synthesis – ↓ Lipolysis
III. Protein Metabolism:	**IV. potassium**
Liver: – ↓ protein catabolism. **Muscle:** – ↑ amino acids uptake. – ↑ protein synthesis. – ↑ glycogen synthesis (glycogenesis).	–↑ potassium uptake into cells Overdose of insulin → **hypo**kalemia.

Routes of administrations of exogenous insulin	Sources of Exogenous Insulin
• **Can not be given orally** (why ?) it will be destructed • 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. Dose is by IU/day (other drugs doses are by mg) • Intravenously (in a hyperglycemic emergency) • Under Clinical Trials Inhaled aerosols, transdermal, intranasal. • Rotate injection → to avoid lipodystrophy	• Beef Insulin Differs from human insulin by 3 amino acids (antigenic). • Porcine Insulin Differs by one amino acid (antigenic). • To avoid antigenicity, we use **human** insulin analogues Disadvantage of insulin pump: If a person increases his activity he/she will develop hypoglycemia and vice versa → so activity has to be constant to avoid side effects **and we monitor the patient by checking blood glucose level**

Pin injector



Insulin pump

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)

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 (Insulin Analogues)			
1-Ultra-short acting insulins	2-short acting insulin	3-Intermediate acting insulins	4-Long acting insulins
e.g.Lispro , aspart	e.g. regular insulin, humulin R	e.g. NPH, lente	e.g glargine, detemir
very fast onset of action and short duration	fast onset of action and short duration	Slow onset, intermediate duration of action	Slow onset and long duration of action so they can cover the full day

If insulin preparation has:

Long duration → risk of **hypoglycemia**

Short duration → **frequent administration** (3 times per day; one with each meal)

Differ in pharmacokinetic properties:

- Rate of absorption (Onset of action).
- Duration of action.

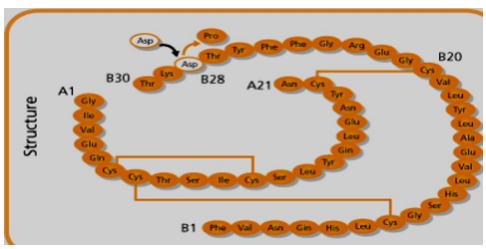
These variations are due to:

- Change of amino acid sequence.
- Size and composition of insulin crystals in preparations (monomers, dimers, hexamers).

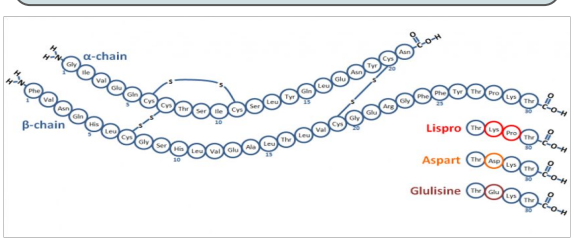
Insulin Analogues

Drug	Ultra-short acting insulins(Lispro,aspart)
Physical characteristics	**Clear** solutions at neutral pH. Clear → can be used IV
Chemistry	Do not aggregate or form dimers or hexamers **(monomeric analogue).** Monomer → low molecular weight → faster absorption → faster onset NB/ physiological insulin is a hexamer
Route and time of admin	• **S.C. (5 -15 min before meal) routine use** • **I.V. in emergency.**
Onset	**Fast onset** of action (5-15 min)
Peak level	Reach peak level 30-90 min after injection.
Duration	**Short duration** of action (3-5 h) average: 4 hours
Usual admin	• 3 times/day. • **Mimic the prandial mealtime** insulin release (take with every meal. If a patient skips a meal, he/she should skip the dose)
Indications	• Preferred for external insulin pump because they're monomers + clear (Lispro does not form hexamers) • **used to control postprandial hyperglycemia** (s.c.) and emergency diabetic ketoacidosis (i.v.).

Insulin aspart



Ultra-short acting insulins



Insulin Analogues

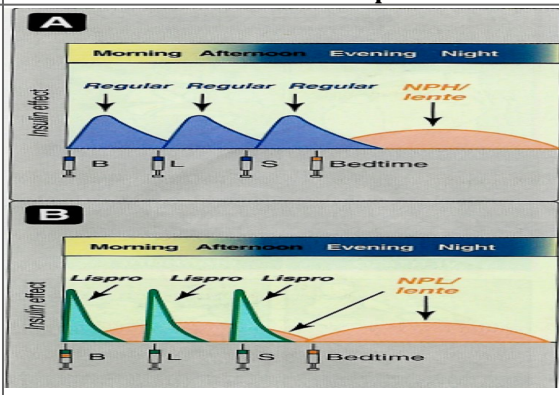
Drug	Short acting insulin (regular insulin)
Physical characteristics	• **Soluble** crystalline zinc insulin • **Clear** solutions at neutral pH.
Chemistry	Forms hexamers. This is why i cant use it with the pump
Route and time of admin	I.V. in emergency situations.
Onset	Onset of action 30-45 min (s.c.). onset : 30 min
Peak level	Peak 2-4 h.
Duration	Duration 6-8 h. Duration 8 hours
Usual admin	2-3 times/day.
Indications	• **Control postprandial hyperglycemia** (s.c.) **& emergency diabetic ketoacidosis** (i.v.). • **Can be used in pregnancy**: why? 1- no teratogenic effect 2- similar to physiological insulin (hexamer)

	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 ** they have a higher risk of hypoglycemia and hyperinsulinemia
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 hyperinsulinemia.
    - Decreased risk of postprandial hypoglycemia

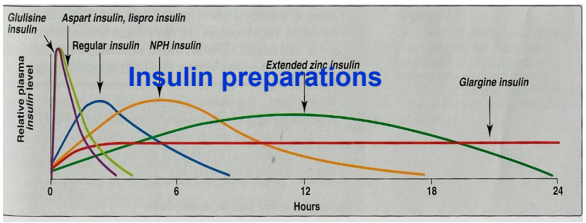
Intermediate acting insulin

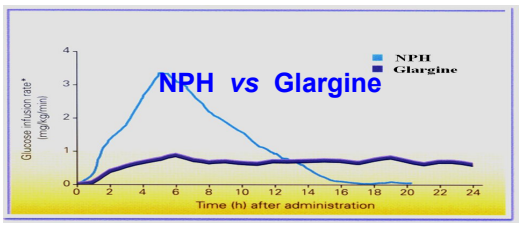
Drug	Isophane (NPH) insulin	Lente insulin (Humulin L, Novolin L
	NPH, is a Neutral Protamine Hagedorn(complex) insulin in phosphate buffer. recall : protamine was the antidote of heparin NPH insulin is combination of **protamine & crystalline zinc insulin** (1:6 molecules). proteolysis release insulin	**Mixture of:** – 30% **semilente insulin** (amorphous precipitate of zinc insulin in acetate buffer) – 70% **ultralente insulin** (poorly soluble crystal of zinc insulin) - **should not be mixed with insulin in the same syringe.**(boys)
Physical characteristics	**Turbid suspension at neutral pH**	
Route and time of admin	**Given subcutaneously only not i.v** **Can not be used in ketoacidosis or emergency**	
Onset	Onset of action 1-2 h. Average: 1 hour	Delayed onset of action (1-3 h)
Peak level	Peak serum level 5-7 h.	Peak serum level 4-8 h.
Duration	Duration of action 13-18 h average: 16 hours	Duration of action 13-20 h.
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. 1st → lispro/ aspart 2nd→ NPH • Why do i do these combinations ? NPH takes 1-2 hrs to work, so we give another drug that works temporarily until NPH works	**Prandial and basal insulin replacement**  Lente and NPH insulins are equivalent in activity.

Long acting insulins
Insulin glargine (lantus), Insulin detemir (Levemir)

Drug	Insulin glargine (lantus)
Physical characteristics	• **Clear** solution BUT forms **precipitate** (hexamer) at injection site.
Route and time of admin	• **Given s.c.,** not intravenously • Should not be **mixed** with other **insulins** in the **same syringe.** It is sensitive to PH and may precipitate in the syringe
Onset	• Slow onset of action 2 h. • absorbed less rapidly than NPH & Lente insulin.
Peak level	• Maximum effect after 4-5 h
Duration	• Prolonged duration of action (24 h). Covers the whole day
Usual admin	• **Once daily** • produce broad plasma concentration plateau **(low continuous insulin level).** • **Glargine** must be used in regimens with rapid or short acting insulins.
Advantages	Advantages over intermediate-acting insulins: 1. Constant circulating insulin over 24 hr with no peak (peakless profile). 2. Produce flat prolonged hypoglycemic effect. 3. Safer than NPH & Lente insulins (reduced risk of nocturnal hypoglycemia). 4. Clear solution(not require resuspension before use) Mimics basal insulin release
Uses	Used in type 1 and type 2 diabetes.

- Peak → maximum effect
- Peakless → it is an **advantage** because it mimics basal insulin release and **NO RISK OF HYPOGLYCEMIA**
- ** which insulin preparation mimics basal insulin release? **Long acting insulins**





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 temperature** before use.

Complications of Insulin Therapy:

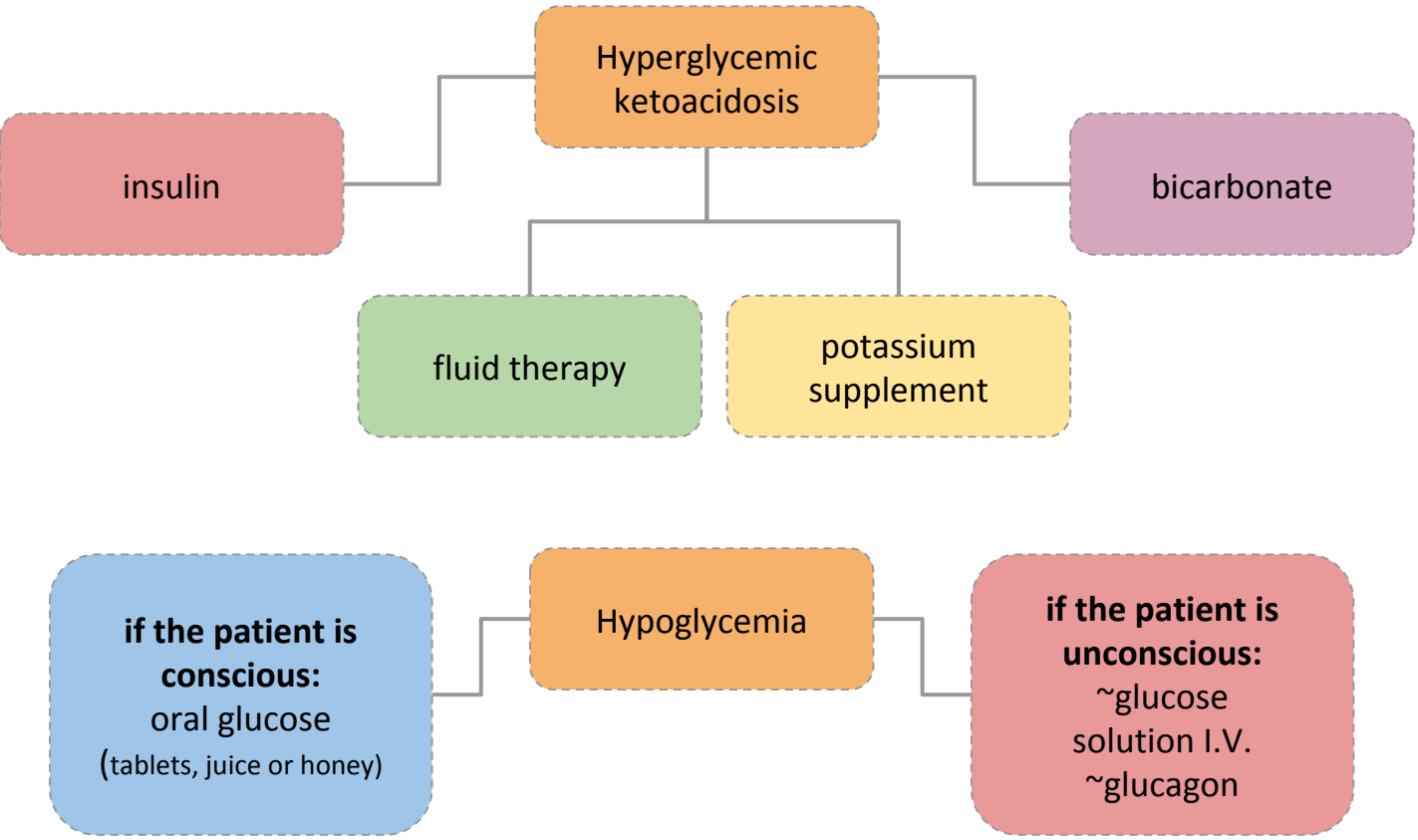
- **Hypoglycemia**
- **Hypersensitivity reactions.**
- **Lipodystrophy (a buildup of fatty tissue) at the injection sites.**
- **Weight gain (due to anabolic effects of insulin)**
- **Insulin resistance**
- **Hypokalemia**

DR.'s Summary

Insulin analogues are used to treat **type I** diabetes.

1. **Fast** acting insulins (lispro, aspart), given s.c. or i.v., produce fast action, used to mimic postprandial insulin.
2. **Short** acting insulin (Regular insulin), given s.c. or i.v. produce rapid action, used to mimic postprandial insulin.
3. **Intermediate** acting insulin (lente, Isophane) produce slower action, than regular insulin, given s.c. **not i.v.**
4. **Long** acting insulins (glargine, detemir) produce constant circulating insulin over 24 hr with no peak (**peakless profile**), s.c. not i.v.

Mind Map

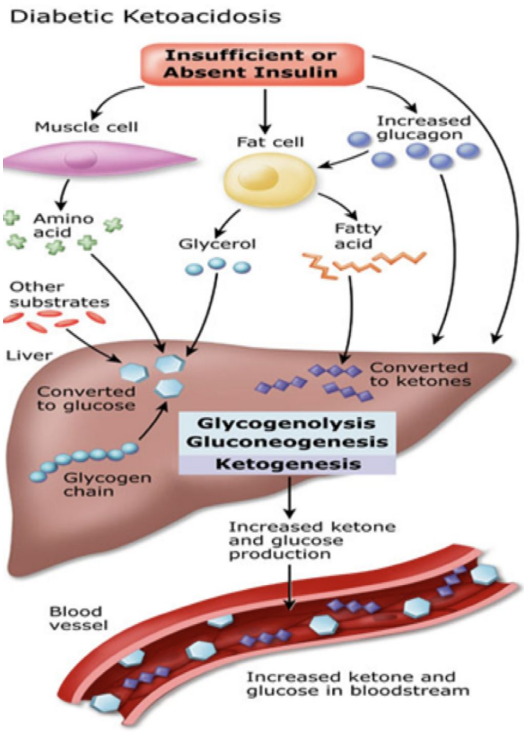

Hyperglycemic ketoacidosis
insulin
bicarbonate
fluid therapy
potassium supplement
Hypoglycemia
if the patient is conscious:
oral glucose
(tablets, juice or honey)
if the patient is unconscious:
~glucose solution I.V.
~glucagon

Diabetic ketoacidosis

- **Is a serious acute emergency situation that requires admission to hospital with a risk of death.**
- **It develops as a result of insulin deficiency**
- **It is a characteristic feature of type I diabetes but may occur with type II especially during Stress.**

metabolic changes

- **Carbohydrates**
- ↑ Glycogenolysis
- ↑ Gluconeogenesis
- **Protein**
- ↑ proteolysis thus providing amino acid as precursors for gluconeogenesis.
- **Fats**:
- ↑ Lipolysis & ketogenesis
- Fat breakdown to free fatty acids then to acetyl-CoA that is converted to ketone bodies
- Acetoacetic acid, β-hydroxybutyric acid and acetone (↑ ketogenesis).
- Hypoglycemia is more serious than hyper.
- **BOTH** hyper and hypo can lead to coma



Insulin deficiency lead to

- **↑ glycogenolysis, ↑ gluconeogenesis, ↑ protein catabolism, ↑ Lipolysis**
  - **↑ Hyperglycemia + glycosuria**
    - **Osmotic diuresis → Dehydration**
- **↑ Lipolysis**
  - **↑ Free fatty acids**
    - **↑ Ketone bodies (ACAC, β-OHB, Acetone)**
      - **Ketonemia + ketonuria**
        - **Acidosis**

Diabetic ketoacidosis

- Hyperglycemia-induced glucosuria, osmotic diuresis & severe fluid loss.
- Fluid loss induces dehydration & electrolyte imbalance.
- Metabolic acidosis induces hyperventilation.

Characters of Diabetic ketoacidosis

- Hyperglycemia
- Glucosuria
- Osmotic diuresis
- Polyuria
- Thirst

- Polydipsia (increased drinking).
- Dehydration
- Electrolyte imbalance
- Ketogenesis (ketonemia, ketonuria)
- Metabolic acidosis

Clinical symptoms for diabetic ketoacidosis

- Classic features of hyperglycemia (thirst, polyuria)
- Nausea, vomiting, abdominal pain
- Tachycardia
- Kussmaul–Kien respiration (rapid & deep).
- Ketotic breath (fruity, with acetone smell)
- Mental status changes (confusion, coma)

Diagnostic Criteria in diabetic ketoacidosis

- Blood glucose level > 250 mg/dl
- Arterial pH < 7.35
- Serum bicarbonate level < 15 mmol/L
- Ketonemia
- Ketonuria

Lines of treatment of diabetic ketoacidosis

Adequate correction of :

Treatment is symptomatic

Dehydration (Fluid therapy)	Hyperglycemia (Insulin)	Electrolyte deficits (Potassium therapy)	Ketoacidosis (Bicarbonate therapy)

Treatment of diabetic ketoacidosis

❖ Fluid therapy (Rehydration)

- Restore blood volume and perfusion of tissues. First step
- Infusion of isotonic saline (0.9% sodium chloride) at a rate of 15–20 ml/kg/hour or lactated Ringer solution..

❖ Insulin therapy (Short acting insulin)

We can use ultra short insulin but regular insulin is preferable

- Regular insulin, should be administered by means of continuous intravenous infusion in small doses through an infusion pump (0.1 U/kg/h). Low rate of infusion
- Subcutaneous absorption of insulin is reduced in DKA because of dehydration; therefore, using intravenous routes is preferable.
- Insulin stops lipolysis and promotes degradation of ketone bodies.

❖ Potassium therapy

- potassium replacement must be initiated.
- potassium is added to infusion fluid to correct the serum potassium concentration.

Sometimes its used and sometimes not, depending on the concentration in blood.

❖ Bicarbonate therapy

** not corrected unless PH is **less than** 7

- Correct for metabolic acidosis
- bicarbonate therapy should be used only if the arterial pH < 7.0 after 1 hour of hydration, (sodium bicarbonate should be administered every 2 hours until the pH is at least 7.0).

Why do we use IV insulin therapy?

- Rapid onset
- Better distribution (the patient is dehydrated, so if we inject him/her subcutaneously the drug won't distribute)

Only in girls slides

Hypoglycemia

Info.	• Blood sugar of less than 70 mg/dl is considered hypoglycemia. • Is a life threatening disorder that occurs when blood glucose level becomes < 50 mg/dl. • One of the common side effects of insulin in treating type I diabetes. • Can it happen to patients with type 2? Depending on the type of oral hypoglycemic (drugs that increase insulin release) -next lecture-
Causes	• Overdose of insulin or oral hypoglycemic drugs (sulfonylureas - meglitinides). • Excessive physical exercise • Missed or delayed meal. • Hypoglycemia can be an early manifestation of other serious disorders (sepsis, congenital heart disease, brain hemorrhage). • ****RULE : IF YOU MISS A MEAL, MISS THE DOSE.**
Characters	**Autonomic features** • ↑ sympathetic: tachycardia, palpitation, sweating, anxiety, tremor. • ↑ parasympathetic: nausea, vomiting. **Neurological defects:** • Headache, visual disturbance, slurred speech, dizziness. • Tremors, mental confusion, convulsions. • Coma due to ↓ blood glucose to the brain.
Precautions	**Hypoglycemia can be prevented by:** • Monitoring of blood glucose level (blood sugar level should be checked routinely). • Patients should carry glucose tablets or hard candy to eat if blood sugar gets too low. • Diabetic patient should wear a medical ID bracelet or carry a card. • Patient should not skip meals or eat partial meals. • Patient should eat extra carbohydrates if he will be active than usual • Be careful with b-blockers as they can mask the manifestations of hypoglycemia

Treatment of Hypoglycemia

Conscious patient:	Unconscious patient:
Sugar containing beverage or food (30 g orally).	– Glucagon (1 mg S.C. or I.M.) – 20-50 ml of 50% glucose solution I.V. infusion (risk of possible phlebitis).

DR.'s Summary

Hyperglycemic ketoacidosis	Hypoglycemia
treated by insulin, fluid therapy, potassium supplement and bicarbonate.	treated by oral glucose tablets, juice or honey (if the patient is conscious) and by 20-50 ml of 50% glucose solution I.V. infusion or glucagon (1 mg, S.C. or I.M.) (if the patient is unconscious).

	Hypoglycemic coma (Excess insulin)	Hyperglycemic coma Diabetic ketoacidosis (Too little insulin)
Onset	Rapid	Slow - Over several days
Acidosis & dehydration	No	Ketoacidosis
B.P.	Normal	Subnormal or in shock
Respiration	Normal or shallow	air hunger
Skin	Pale and sweating	Hot & dry
CNS	Tremors, mental confusion, sometimes convulsions	General depression
Blood glucose	Lower than 70 mg/100cc	Elevated above 200 mg/100cc
Ketones	Normal	Elevated

MCQs

1- which of the following insulin preparations can be used intravenously in diabetic ketoacidosis?

A- Isophane
B- Lente
C- Lispro
D- Glargine

2- a doctor prescribed insulin to a diabetic patient and warned him to never mix it with other insulins in the same syringe when administering it at home. Which insulin did the doctor prescribe?

A- Lente
B- Humulin R
C- Isophane (NPH)
D- Glargine

3- which of the following is true about Insulin glargine?

A- it is a monomeric analogue.
B- can be given intravenously in diabetic ketoacidosis.
C- turbid suspension.
D- forms precipitate at injection site.

4- having a peakless profile is a characteristic of which one of the following insulins?

A- Glargine
B- Lispro
C- Isophane (NPH)
D- Novolin L

5- what is the first step in the management of diabetic ketoacidosis?

A- Insulin therapy
B- potassium therapy
C- Fluid therapy
D- Bicarbonate

6- which of the following is used to control postprandial hyperglycemia in type I diabetes?

A- Humulin R
B- Isophane (NPH)
C- Detemir
D- Lente

7- a patient came to the ER with palpitations , sweating , slurred speech and mental confusion. His blood sugar was 60 mg\dl. What is the treatment of choice if the patient is still conscious?

A- 1 mg of Glucagon subcutaneously.
B- 40 ml of 50% glucose solution intravenously.
C- 1 mg of Glucagon intramuscular.
D- 30 g of sugar containing beverage orally.

SAQ

A 10 year old diabetic child came to the ER with tachycardia, hyperventilation and fruity smelling breath. His parents told the doctors that he has been passing urine more than usual and that he's constantly thirsty. Investigations showed the following:
blood glucose level 260 mg\dL
Arterial pH is 7.0
Serum bicarbonate level 10 mmol/L
Blood pressure 97/60 mmHg

What is the name of the condition?
Diabetic ketoacidosis

What is the appropriate management for this condition?
1- fluid therapy (Rehydration) with isotonic saline.
2- Insulin therapy Intravenously.
3- potassium therapy.
4- bicarbonate therapy if the arterial pH is <7.0 after 1 hour of hydration.

Answers :
7-D
6-A
5-C
4-A
3-D
2-D
1-C

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References:

✓ Doctors' slides and notes

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