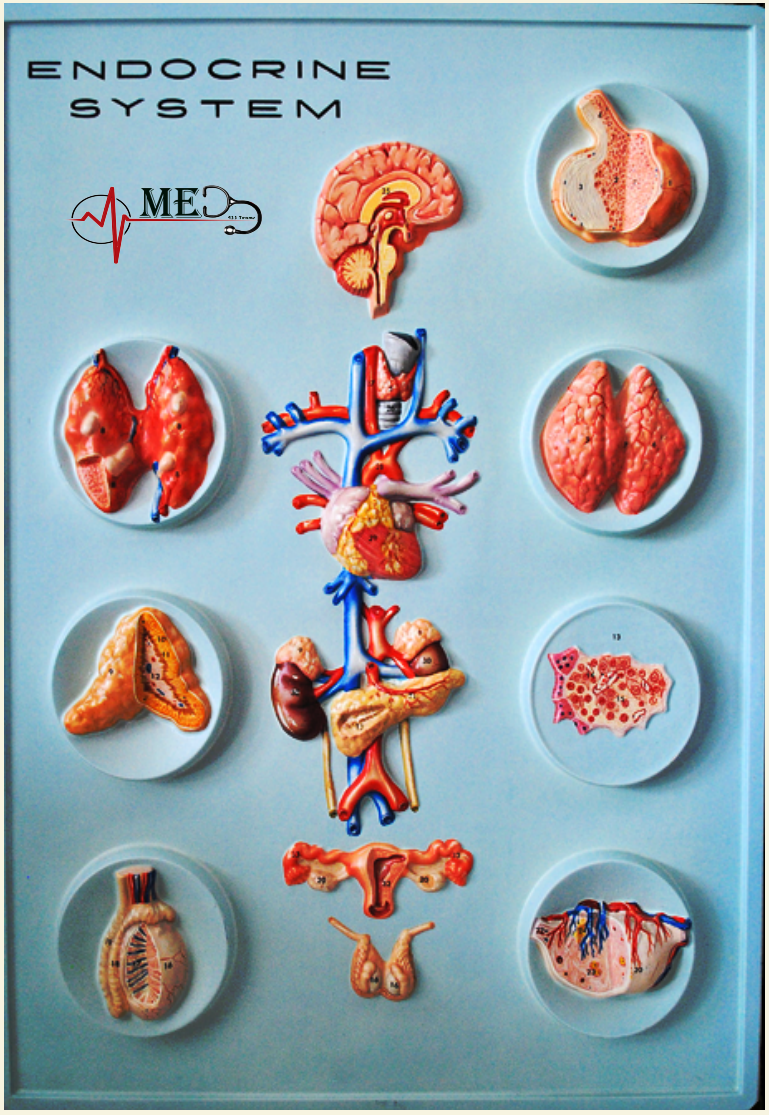
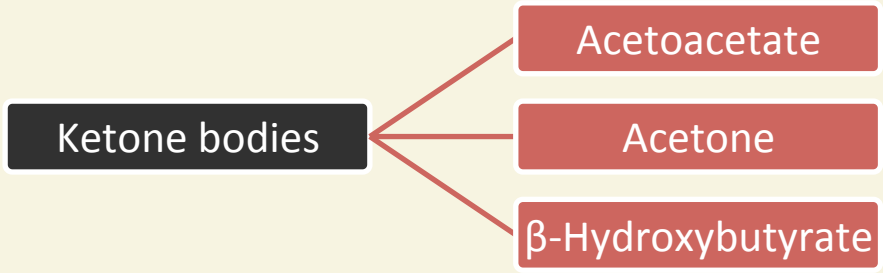


LECTURE 8 :

Diabetic ketoacidosis (DKA)

Objectives:

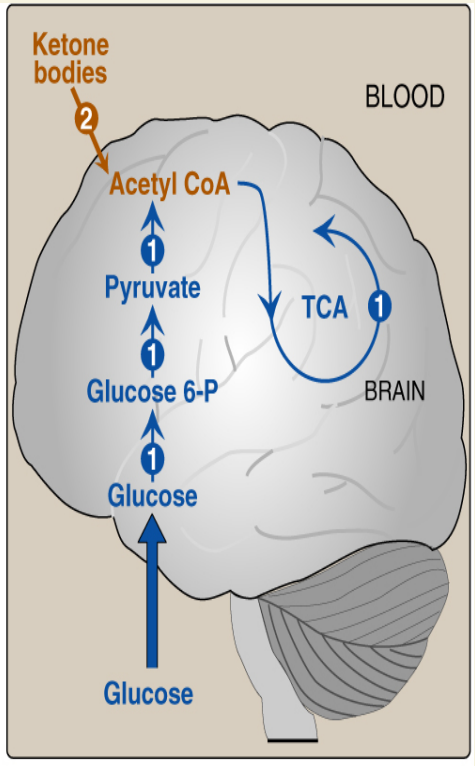
- Ketone bodies (ketogenesis & ketolysis).
- Diabetic ketoacidosis.
- Hyperosmolar hyperglycemic state.
- Hypoglycemia.



- They are produced by the liver (ketogenesis) and utilized for energy production by peripheral tissues(ketolysis).

- Normally, **glucose is the primary fuel for the brain,** It can penetrate the blood brain barrier.
- The brain's GLUT is insulin-independent.
- If glucose is not available for the brain, the brain can utilize plasma ketone bodies, that can penetrate the blood brain barrier and serve as fuel molecules.

#Eating diets extremely high in fat and low in carbohydrates or starving or suffering from a severe lack of insulin (Type I diabetes mellitus) therefore, increase the synthesis and utilization of ketone bodies.



Ketone bodies synthesis=Ketogenesis

Occurs in the hepatocyte mitochondria only .

In uncontrolled DM: there is ↑ lipolysis in adipose tissue → ↑ FFA mobilization to liver

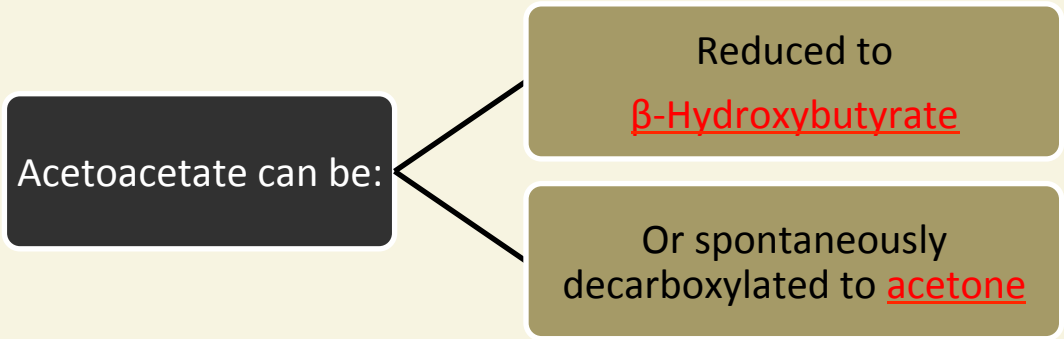
→ ↑hepatic FA oxidation →↑acetyl CoA which will be channeled into KB synthesis.

↑ Acetyl CoA production activates pyruvate carboxylase that converts pyruvic acid into OAA.

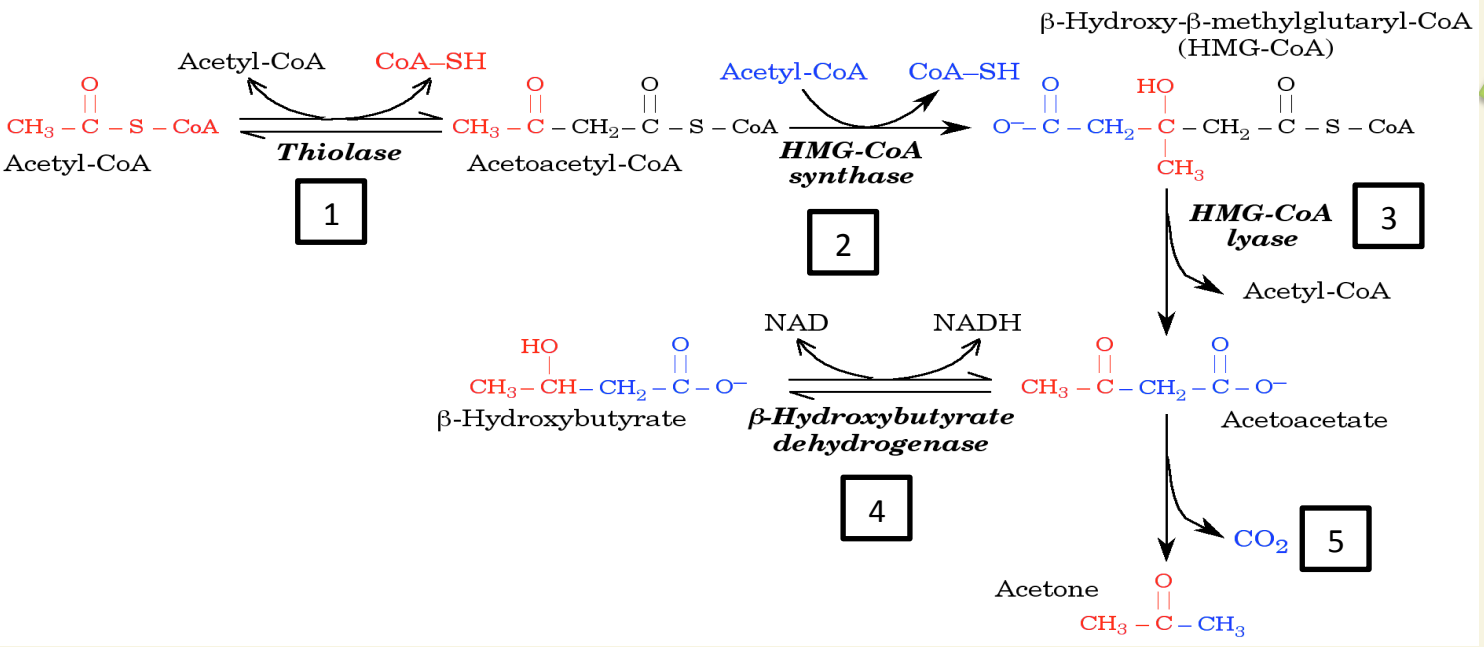
OAA is used for gluconeogenesis rather than Krebs cycle (in Krebs cycle→ Acetyl CoA + OAA)

#HMG CoA synthase is the rate limiting enzyme.

#The first KB to be synthesized is acetoacetate.



*FFA=Free fatty acid
*OAA=Oxaloacetate
*KB= Ketone bodies



For understanding

#Ketone bodies are synthesized in the liver(mitocondria) from acetyl-CoA.

1-First enzyme in the ketone body synthesis pathway is **thiolase** that catalyzes the condensation of two acetyl-CoA molecules to form acetoacetyl-CoA.

2-The next enzyme, **HMG-CoA synthase(**rate limiting enzyme**)** adds a third acetyl CoA molecule to form β-hydroxy-β-methylglutaryl-CoA (usually abbreviated HMGCoA).

3-The third enzyme, **HMGCoA lyase**, releases an acetyl-CoA from HMG-CoA to form acetoacetate.

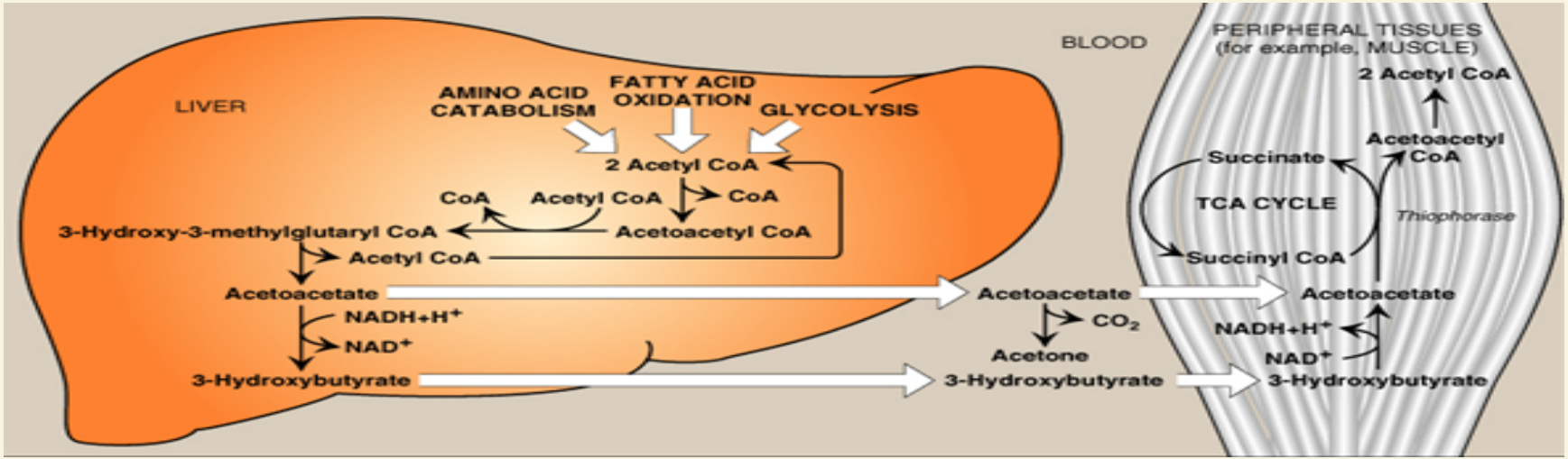
4-β-hydroxybutyrate dehydrogenase reduces acetoacetate to form β-hydroxybutyrate .

5-Decarboxylation of acetoacetate to form acetone excreted via the lungs.

Ketone bodies utilization=Ketolysis

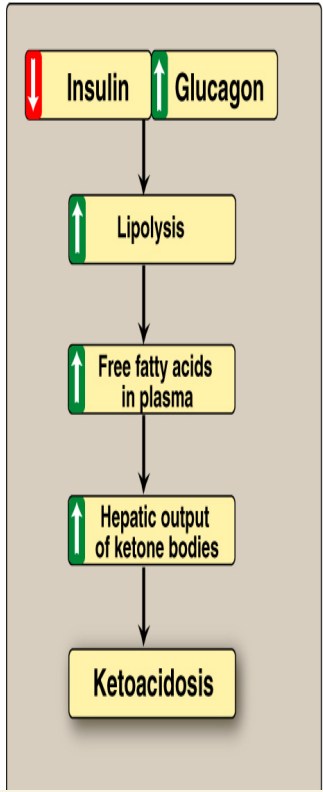
#Takes place in extrahepatic tissues. (in the mitochondria so, cannot occur in RBCs).
#Does not occur in the liver (as the **liver lacks the thiophorase enzyme** required for ketolysis).

β-Hydroxybutyrate	Oxidized by dehydrogenase	Acetoacetate
Acetoacetate	Catalyzed by thiophorase	Acetoacetyl CoA
Acetoacetyl CoA	Converted to	Acetyl CoAs



Diabetic ketoacidosis (DKA)

#Triad of hyperglycemia , high anion gap metabolic acidosis and ketonemia.
#Characteristically associated with T1DM (due to absence of insulin).
#It has become increasingly common with T2DM.
#DKA may be the first presentation of T1DM.z



Mechanisms of DKA

#In uncontrolled DM there is ↑lipolysis in adipose tissue → ↑ FFA

→ ↑ mobilization of FFA to liver → ↑hepatic FA oxidation

→ **↑ hepatic acetyl CoA** which will be utilized in KB synthesis (ketogenesis)
→ **ketoacidosis**.

#In uncontrolled DM the rate of ketogenesis is **>** the rate of ketolysis

→ ketonemia (↑KB in blood)→ ketonuria (↑KB in urine).

#Anion gap is the difference in the measured cations (positively charged ions) and the measured Anions (negatively charged ions) in plasma.
#In DKA due to absence of insulin that is responsible for potassium entering the cell, potassium will accumulate in the blood (hyperkalemia) , so if we measure the anion gap it will be high.

Manifestations of DKA

#**Fruity odor on the breath**(Acetone).
#**Acidosis**(low PH of blood because KBs are acids).
#**Dehydratio**n(Due to glucosuria →↑ Osmotic diuresis → Polyuria).

Precipitating factors for DKA

#**Infection (30-40%).**
#Inadequate insulin treatment or non compliance (20%).
#Severe illness e.g. myocardial infarction.
#Trauma.
#Drugs e.g. steroid.

Hyperosmolar hyperglycemic state(HHS)

=

Hyperosmolar non ketotic acidosis(HONK)

- **Little or no accumulation of ketone bodies.**
- Serum glucose is often > 50 mmol/L.
- **Plasma osmolality may reach 380 mosmol/kg** (Normal= 275-295).
- Neurological abnormalities are frequently present.

- Insulin levels are insufficient to allow appropriate glucose utilization but are adequate to prevent lipolysis and subsequent ketogenesis.

- **Usually occurs in elderly patients with T2DM.**
- Has a substantially **higher mortality** than DKA (up to 15%)

Hypoglycemia

- ❑ **Common complication of treatment with insulin or oral hypoglycemic drugs**
- ❑ **More common in patients with T1DM.**
- ❑ Characterized by :

1-CNS symptoms(confusion , aberrant behavior or coma).
2-Low blood glucose.
3-Symptoms resolved within minutes following the administration of glucose.

Hypoglycemia is a medical emergency, why?

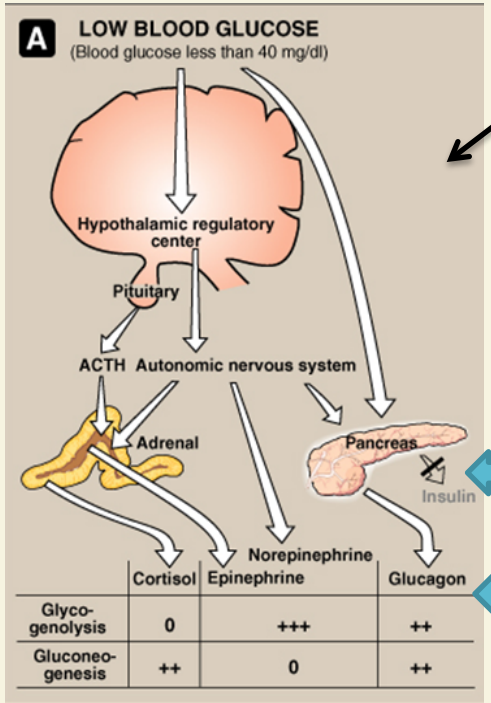
- ✓ **The brain has absolute requirement for a continuous supply of glucose.**
- ✓ Transient hypoglycemia → cerebral dysfunction.
- ✓ Severe, prolonged hypoglycemia → Brain death.

Hypoglycemia occurs due to impaired protective responses to hypoglycemia :

1- Insulin is supplied exogenously and its release cannot be turned off.
2-Glucagun & adrenaline response to hypoglycemia becomes impaired later in the course of DM.

Clinical presentation of Hypoglycemia

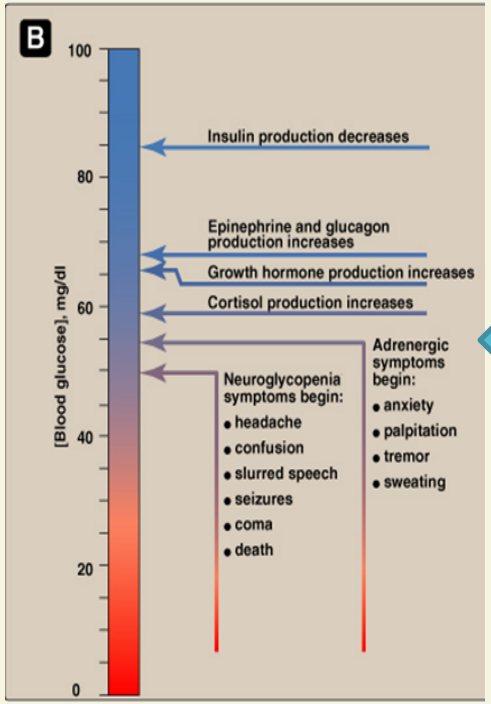
1-Symptoms of sympathetic over activity (Plasma glucose<3,6mmol/L, abrupt fall) :
Anxiety, tremors, sweating & palpitation.
2-Symptoms of neuroglycopenia (Plasma glucose<2.6mmol/L, Gradual fall) :
Headache , confusion , drowziness & ultimately loss of consciousness or seizures(at plasma glucose<1,5mmol/L).



Hormonal mechanism to prevent or correct hypoglycemia

↓ Production of insulin

↑Production of:
1.Epinephrine & glucagon
2. GH
3. Cortisol



Glycemic thresholds for the various responses to hypoglycemia

Metabolic changes in DM & DKA

Diabetes Mellitus

CHO metabolism

↓ Glucose uptake by certain tissues (adipose tissue & muscle)

↑ Glycogenolysis

↑ Gluconeogenesis

Lipid metabolism

↑ lipolysis

↑ fatty acid oxidation

↑ production of Ketone bodies

Protein metabolism

↓ protein synthesis

↑ protein degradation

Diabetic ketoacidosis

K^+, Water & pH

↓ entry of K^+ into the cells

Water loss secondary to glycosuria

Acidosis due to ↑ production of ketone bodies

Case study

A 14-year-old girl was admitted to a children's hospital in coma. Her mother stated that the girl had been in good health until approximately 2 weeks previously, when she developed a sore throat and moderate fever.
She subsequently lost her appetite and generally did not feel well.
Several days before admission she began to complain of undue thirst and also started to get up several times during the night to urinate. However, on the day of admission the girl had started to vomit, had become drowsy and difficult to arouse, and accordingly had been brought to the emergency department.

On examination:

- **She was dehydrated**
- **Her skin was cold**
- **She was breathing in a deep sighing manner (Kussmaul respiration) WATCH BELOW**
- **Her breath had a fruity odor**
- **Her blood pressure was 90/60 mmHg (N: 120/80)**
- **Her pulse rate 115/min.**
- **She could not be aroused**

A provisional diagnosis of T1DM with complicating ketoacidosis and coma (DKA) was made by the intern on duty

Blood test results:

Plasma analytes	Patient's results	Normal levels
Glucose (mmol/L)	50	4.2-6.1
Ketoacids	++++	(trace)
Bicarbonate (mmol/L)	6	22-30
Arterial blood pH	7.07	7.35-7.45
Na^+ (mmol/L)	136	136-146
Cl^- (mmol/L)	100	102-109

Watch : Kussmaul respiration
https://www.youtube.com/watch?v=TG0vpKae3Js

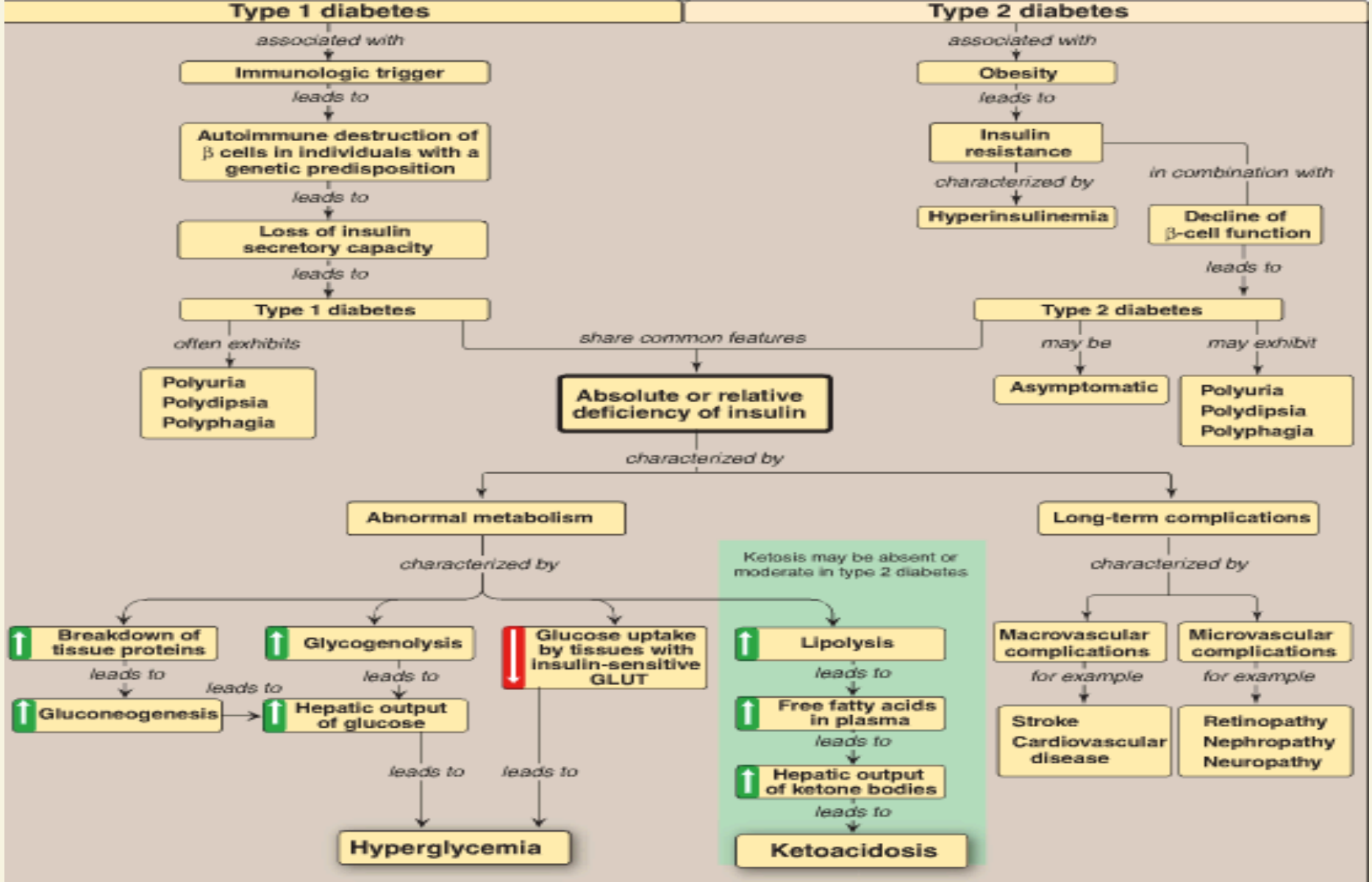
CONT'D : Blood test results

Plasma analytes	Patient's results	Normal levels
PCO_2 (kPa)	2.7	4.3-6.0
*Anion gap (mmol/L)	35.5	7-16
K^+ (mmol/L)	5.5	3.5-5.0
Urea nitrogen (mmol/L)	15	2.5-7.1
Creatinine (μmol/L)	200	44-80
Albumin (g/L)	50	41-53
Osmolality (mOsm/kg serum water)	325	275-295
Hematocrit	0.500	0.354-0.444

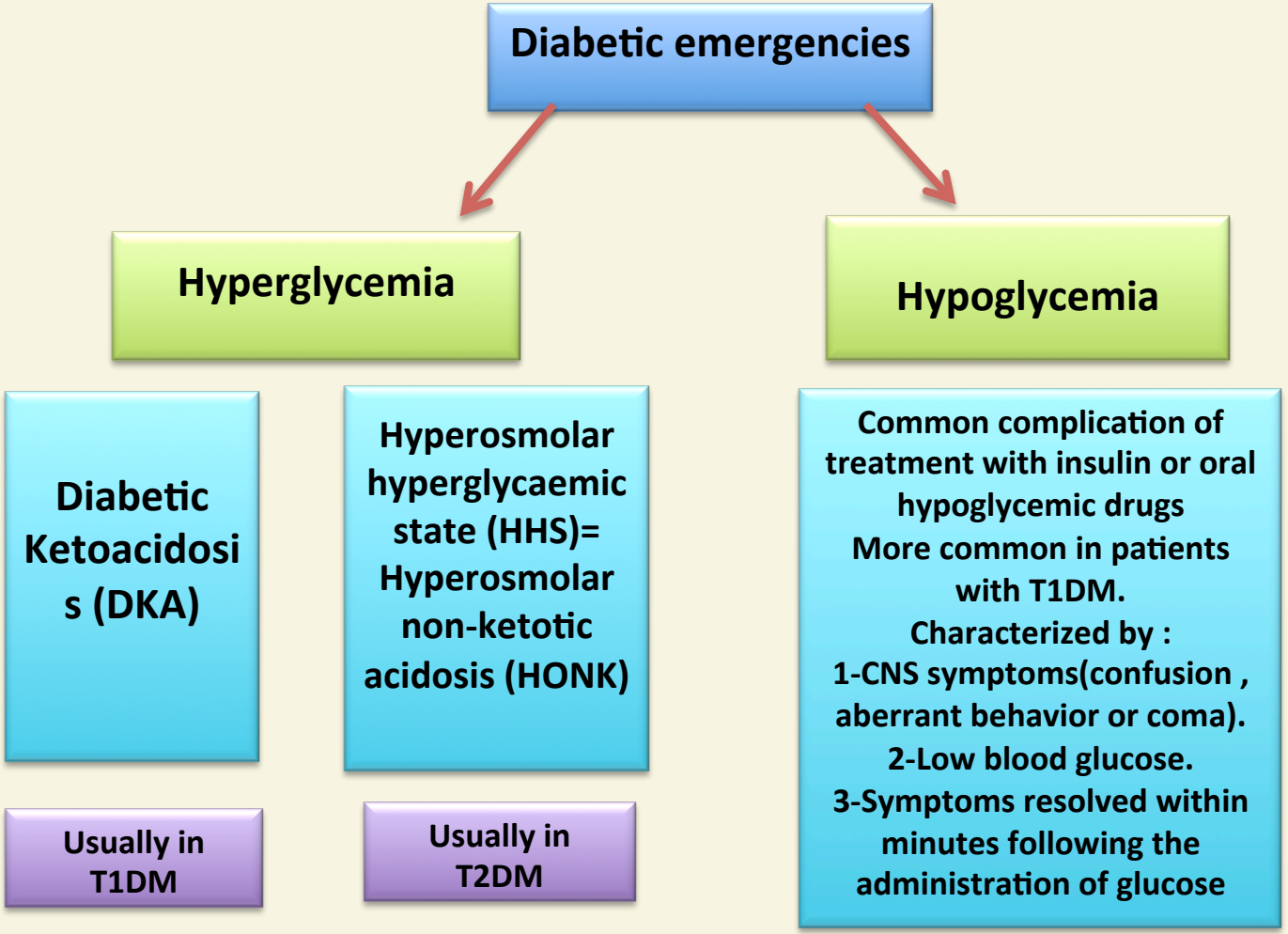
Urine analysis	Patient's results	Normal level
Glucose	++++	-
Ketoacids	++++	-

Interpretation of findings in the previous lab tests

Results	Interpretation
Hyperglycemia	Confirm the diagnosis of DKA
Glucosuria	
Ketonemia	
Ketonuria	
↓ pH	Severe metabolic acidosis due to ↑ production of ketone bodies
↓ bicarbonate and PCO_2	Metabolic acidosis with partial respiratory compensation (the hyperventilation)
↑ anion gap	Due to ↑ ketone bodies in the blood
↑ urea & creatinine	1. Renal impairment (dehydration → ↓ blood volume → ↓ renal perfusion) 2. Dehydration 3. Degradation of protein (for urea)
↑K^+	↓ Uptake of potassium by cells in the absence of insulin
↑ Plasma osmolality	Due to hyperglycemia and fluid loss


Type 1 diabetes
Type 2 diabetes
associated with
Immunologic trigger
leads to
Autoimmune destruction of β cells in individuals with a genetic predisposition
leads to
Loss of insulin secretory capacity
leads to
Type 1 diabetes
often exhibits
Polyuria
Polydipsia
Polyphagia
associated with
Obesity
leads to
Insulin resistance
characterized by
Hyperinsulinemia
in combination with
Decline of β-cell function
leads to
Type 2 diabetes
may be
Asymptomatic
may exhibit
Polyuria
Polydipsia
Polyphagia
share common features
Absolute or relative deficiency of insulin
characterized by
Abnormal metabolism
characterized by
Breakdown of tissue proteins
leads to
Gluconeogenesis
leads to
Glycogenolysis
leads to
Hepatic output of glucose
Glucose uptake by tissues with insulin-sensitive GLUT
leads to
leads to
Hyperglycemia
Ketosis may be absent or moderate in type 2 diabetes
Lipolysis
leads to
Free fatty acids in plasma
leads to
Hepatic output of ketone bodies
leads to
Ketoacidosis
Long-term complications
characterized by
Macrovascular complications
for example
Stroke
Cardiovascular disease
Microvascular complications
for example
Retinopathy
Nephropathy
Neuropathy

Summary


Diabetic emergencies
Hyperglycemia
Hypoglycemia
Diabetic Ketoacidosis (DKA)
Hyperosmolar hyperglycaemic state (HHS)= Hyperosmolar non-ketotic acidosis (HONK)
Common complication of treatment with insulin or oral hypoglycemic drugs
More common in patients with T1DM.
Characterized by :
1-CNS symptoms(confusion , aberrant behavior or coma).
2-Low blood glucose.
3-Symptoms resolved within minutes following the administration of glucose
Usually in T1DM
Usually in T2DM

TEST YOURSELF!

Q1 **Which of the followings are part of triad of DKA:**

A. High anion gap metabolic acidosis
B. ketonemia
C. Hypo-glycemia
D. Both A and B

Q2 **Ketogenesis occurs in ....., while Ketolysis occurs in .....**

A. Liver - Peripheral tissues
B. Peripheral tissues - Liver
C. Liver - Liver
D. Peripheral tissues- Peripheral tissues

Q3 **The first KB to be synthesized is:**

A. Acetoacetate
B. β-Hydroxybutyrate
C. Acetone

Q4 **Which coma will lead to brain death?**

A. DKA
B. Hypoglycemia
C. Hyperosmolar hyperglycaemic state

Q5 **Which one of the followings is true about Hyperosmolar hyperglycaemic state:**

A. Usually occurs in T1DM
B. NO accumulation of ketone bodies
C. High accumulation of ketone bodies

Q6 **A clinical presentation of hypo-glycemia:**

A. Polyurea
B. Dehydartion
C. Symptoms of neuroglycopenia

Q7 **When hepatic fatty acid is elevated, Acetyl CoA will be channeled into:**

A. Krebs cycle
B. Ketone Bodies Utilization
C. Ketone bodies synthesis

Q8 **Infection is a Precipitating factors for :**

A. DKA
B. Hypoglycemia
C. Hyperosmolar hyperglycaemic state

ANSWERS: 1-D 2-A 3-A 4-B 5-B 6-C 7-C 8-A

THANK YOU ...

DONE BY :
SARA ALDOKHYAYEL
MARAM ALAGIL
KHOLOUD ALDOSARI
AHMAD ALQAHTANI
OMAR ALDHASEE

REVISED BY:
MOHAMMED ALNAFISAH
MAHA ALRAJHI