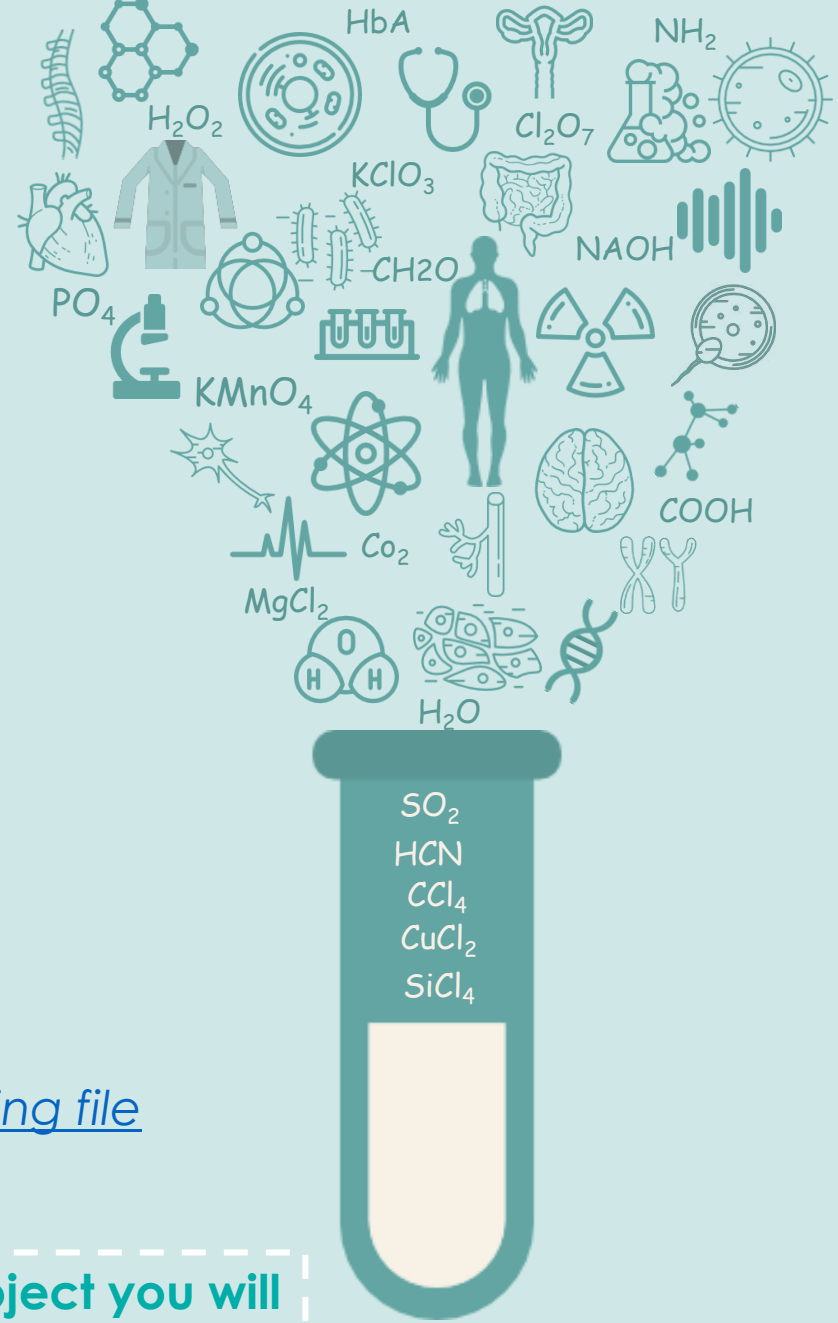


Important Doctors slides

Extra Information **Doctors notes**

Biochemistry

Diabetic Ketoacidosis

Editing file

The best project you will ever work on is YOU

OBJECTIVES

By the end of this lecture, the student should be able to know:

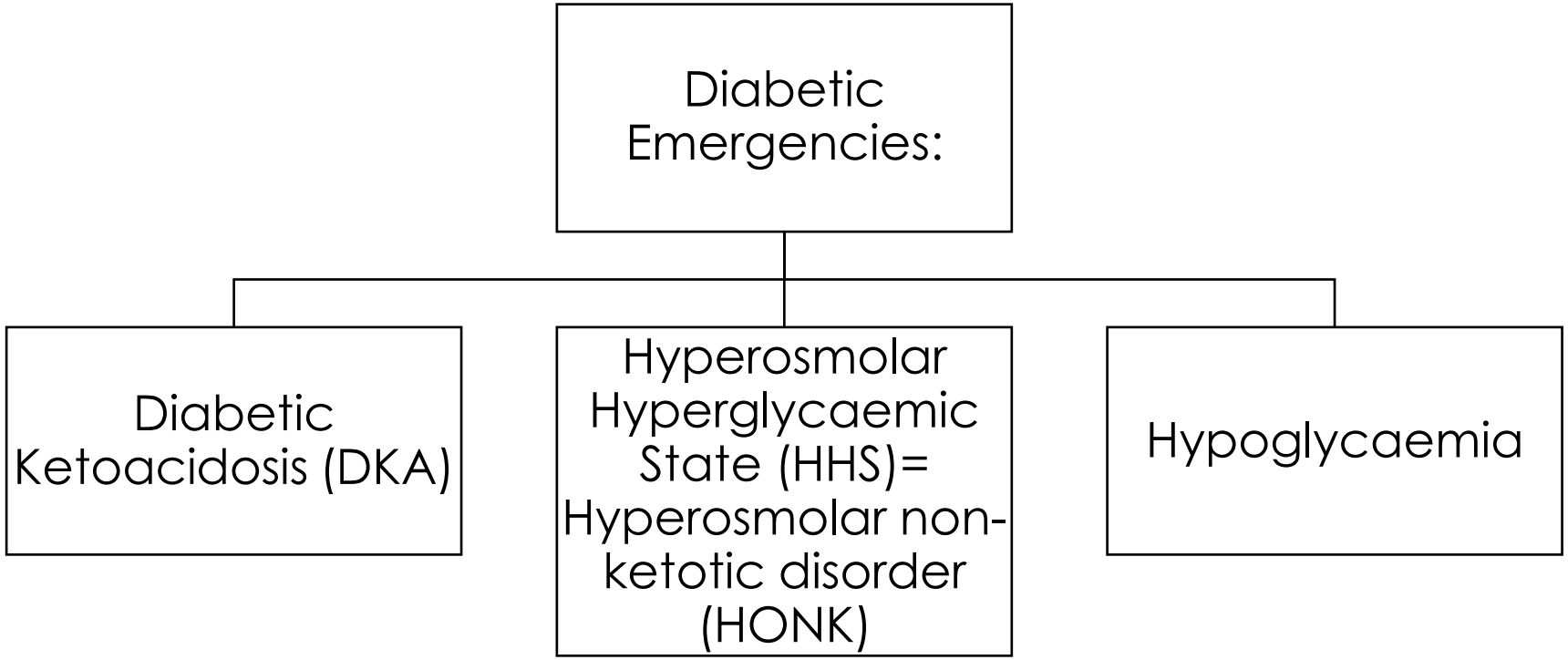
- To understand diabetic emergencies including diabetic ketoacidosis (DKA), hyperosmolar hyperglycaemic state (HHS) and hypoglycaemia
- To have knowledge about (DKA): definition, causes, mechanism, manifestations and precipitating factors
- To understand the terms of ketogenesis and ketolysis
- To have a knowledge about HHS: definition, causes, manifestations and mechanisms
- To know about hypoglycaemia, its clinical presentation, hormonal mechanisms to prevent hypoglycaemia and glycaemic threshold for various responses to hypoglycaemia

Reference: Lippin Coat

Overview:

This lecture will focus on the **acute** manifestations of diabetic patients or the symptoms that will make them go to the ER, in the previous lecture we've talked about the chronic changes

Diabetic Emergencies:



Diabetic Ketoacidosis (DKA):

You can know the characteristic of the condition from the definition itself!

Diabetic → Diabetic Patient

Keto-acidosis → Accumulation of ketone bodies (Ketonemia)

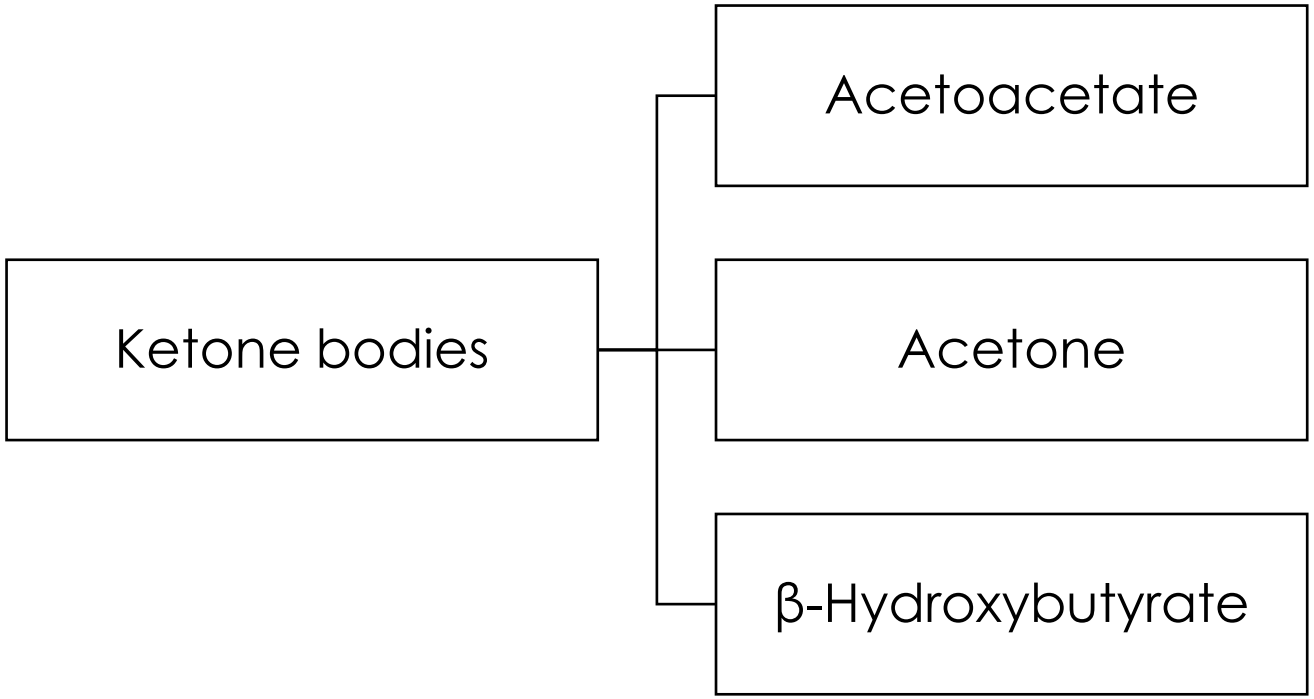
Keto-acidosis → Low pH

- **Definition:** Triad of hyperglycemia, high anion gap, metabolic acidosis, and ketonemia
- Characteristically associated with T1DM and it may be it's first presentation

  because of the absolute deficiency of insulin causes adipose tissue to degrade into free fatty acids and other contents that will go to the liver to get converted to ketone bodies.
- It has become increasingly common in T2DM

  (in advanced stages or precipitating factor such as stress from infection)

Diabetic Ketoacidosis (DKA):



They are produced by the liver (ketogenesis)

Production of ketone bodies

utilized for energy production by peripheral tissues (Ketolysis)

Break down of ketone bodies

When a person is in hyperglycemic state and the body muscles and tissue are not getting the glucose for energy because of insulin defects or absence, the body becomes in an energy craving state, so to get energy the body compensate by going to lipid stores to produce ketone bodies which can be used by the brain and muscles to produce energy.

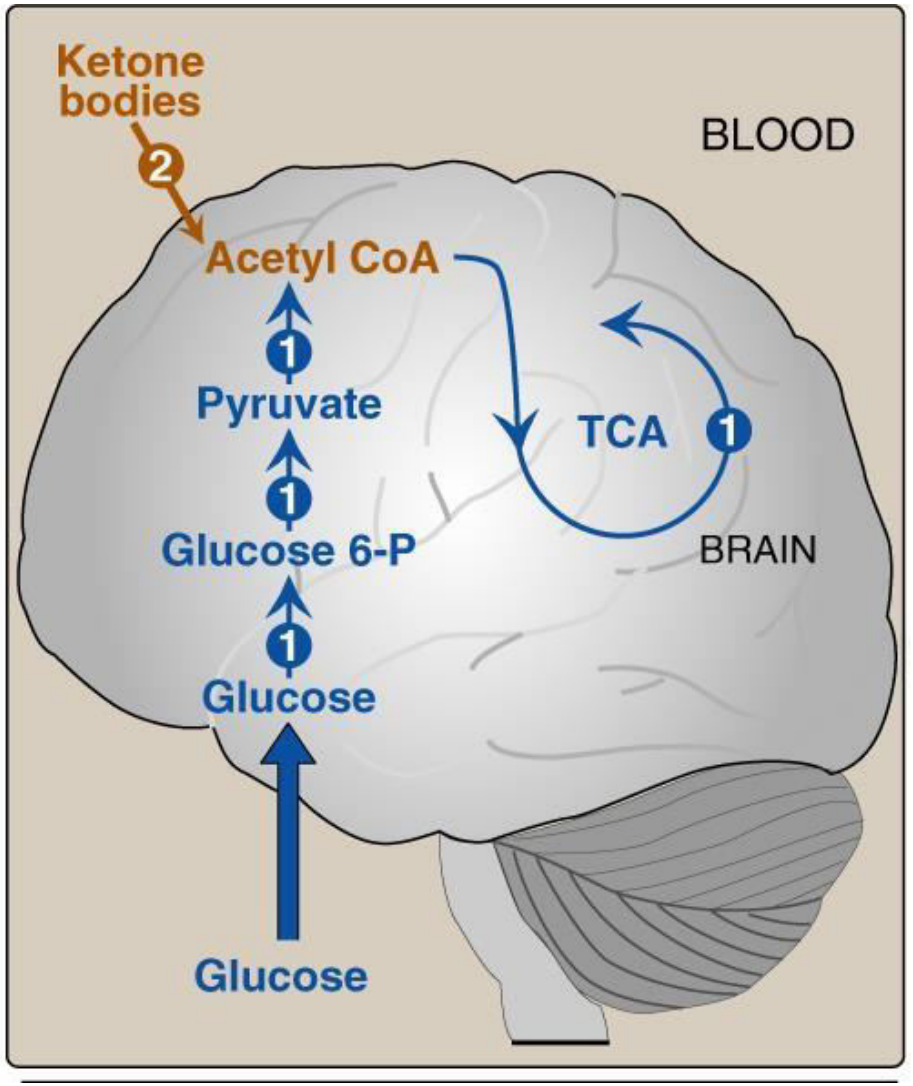
Diabetic Ketoacidosis (DKA):

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.

So ketone bodies are degraded in the brain into Acetyl CoA which enters Krebs cycle and generate energy.

Fat is a big molecule that's why it can not cross the BBB



Ketone bodies synthesis= Ketogenesis

Occurs in the hepatocyte mitochondria

- 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
- HMG CoA synthase is the rate limiting enzyme
- The first KB to be synthesized is acetoacetate.
- Acetoacetate can be:
  1. reduced to β-Hydroxybutyrate, or
  2. spontaneously decarboxylated to acetone.

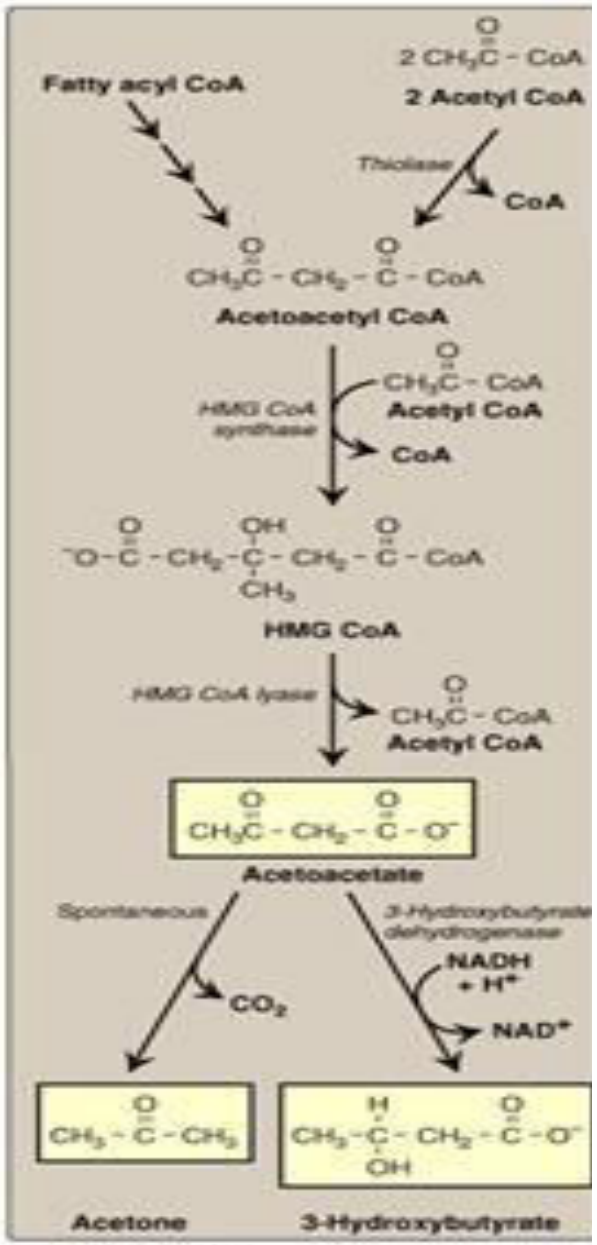


Figure 16.22
Synthesis of ketone bodies. HMG = hydroxymethylglutaryl CoA.

General definition of the terminology

- In the mitochondria we have the Krebs cycle and Beta-oxidation which is the fatty acids oxidation.
- **Why do we call it Beta oxidation?**
- When you are breaking down your fatty acids, the way that you break them is breaking 2 carbon units, and that is why when you breaking fatty acids you produce a lot of Acetyl CoA (2 carbons unit).

- **Why this Acetyl CoA is channeled to Ketone bodies? Why t doesn't go to the Krebs cycle?**
- To enter Krebs cycle, Acetyl CoA has to bind to Oxaloacetate. How Oxaloacetate is being made? Actually by the conversion of pyruvate by the help of the enzyme pyruvate carboxylase is converted into Oxaloacetate.
- But what happens when you have too much of Acetyl CoA it activates pyruvate carboxylase, so we will have a lot of Oxaloacetate. But then what happens to Oxaloacetate? Instead of going to krebs cycle it will go to gluconeogenesis in the liver. That's why these ketone bodies when they go into the peripheral tissue they break down into Acetyl CoA, Acetyl CoA in the peripheral tissues can bind to oxaloacetate because there is no gluconeogenesis is happening in the peripheral tissue, so it can enter the krebs cycle.

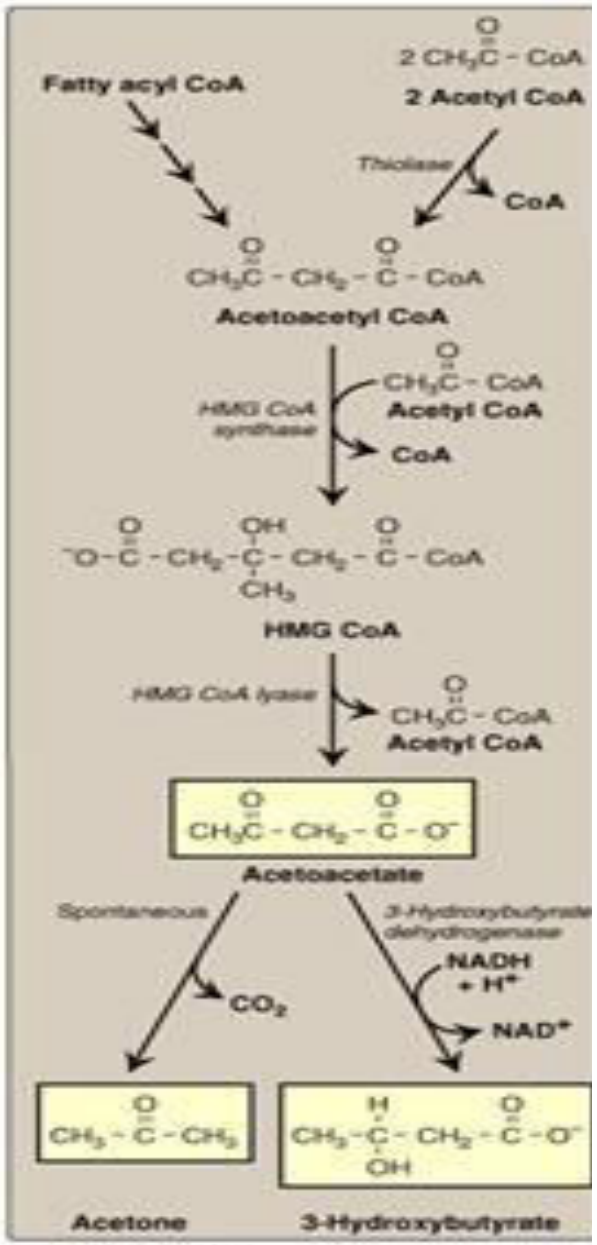


Figure 16.22
Synthesis of ketone bodies. HMG = hydroxymethylglutaryl CoA.

Explanation of the figure

VERY IMPORTANT!
Don't worry about the other enzymes

- In hepatocytes mitochondria there is Fatty acyle CoA which break down into a lot of acetyl CoA, and these 2 molecules of Acetyl CoA join to make acetoacetyl CoA. Now acetoacetyl CoA by the action of the enzyme HMG CoA synthase (which requires one more Acetyl CoA) So basically 3 Acetyl CoA يعني اسيتواسيتيت ونص are required for the synthesis of HMG CoA.
- Actually HMG CoA synthase is also involved in cholesterol synthesis, but this is different because the enzyme here is in the mitochondria, while the HMG CoA synthase which is involved in cholesterol synthesis is in the cytosol of the cell, and not the mitochondria.
- REMEMER THAT, IT IS AN IMPORTANT THING!
- So after HMG CoA is synthesized then the HMG CoA lyase removes an Acetyl CoA and produces the first ketone body, which is Acetoacetate.
- After this, acetoacetate has 2 things. First, it can spontaneously become decarboxylated to acetone, there is no energy or enzyme required for this process. Or, it can be reduced to Beta-Hydroxybutyrate with the help of the enzyme Beta-hydroxybutyrate dehydrogenase.
- So now you have made 3 ketone bodies
- Out of these Acetone is very volitile, the patient will quickly exhale it out producing fruity breath smell, so it is one of the first signs of ketoacidic patient.
- Beta-hydroxybutyrate or 3-hydroxybutyrate are the same thing.

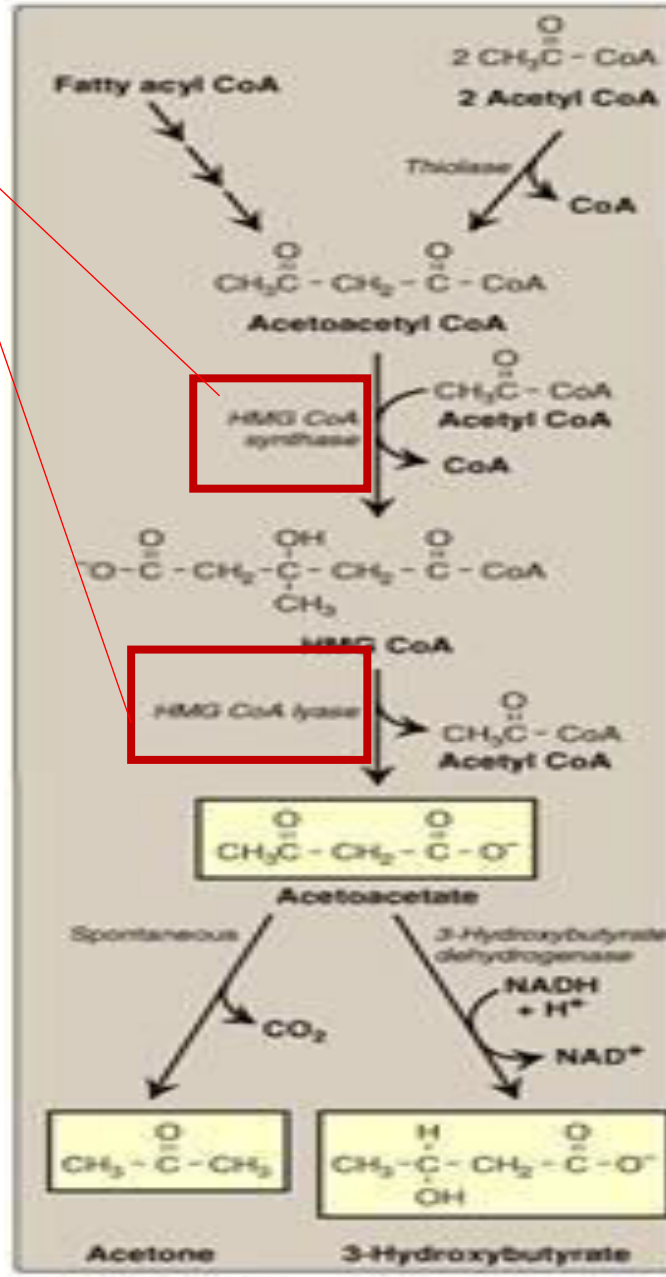


Figure 16.22
Synthesis of ketone bodies. HMG = hydroxymethylglutaryl CoA.

Summary for the previous slide

Fatty acyle CoA

Break down

2 Acetyl CoA

join

Acetoacetyl CoA
+ Acetyl CoA

HMG CoA Synthase

HMG CoA

HMG CoA Lyase removes

Acetyl CoA

Acetoacetate

Beta hydroxyl butarate dehydrogenase

Decarboxylated to acetone
(no enzyme needed)

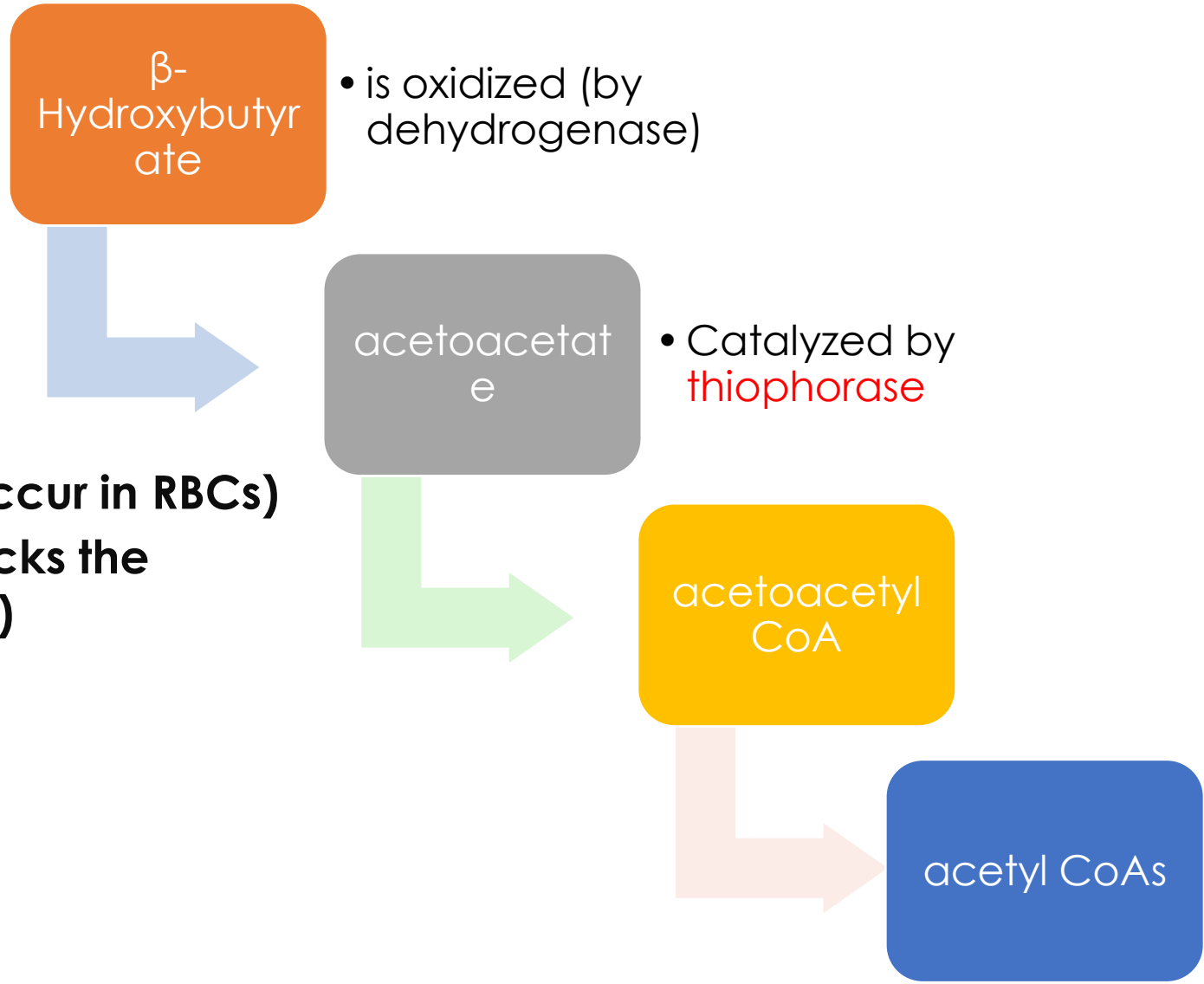
reduces to Beta hydroxybutarate

Ketogenesis

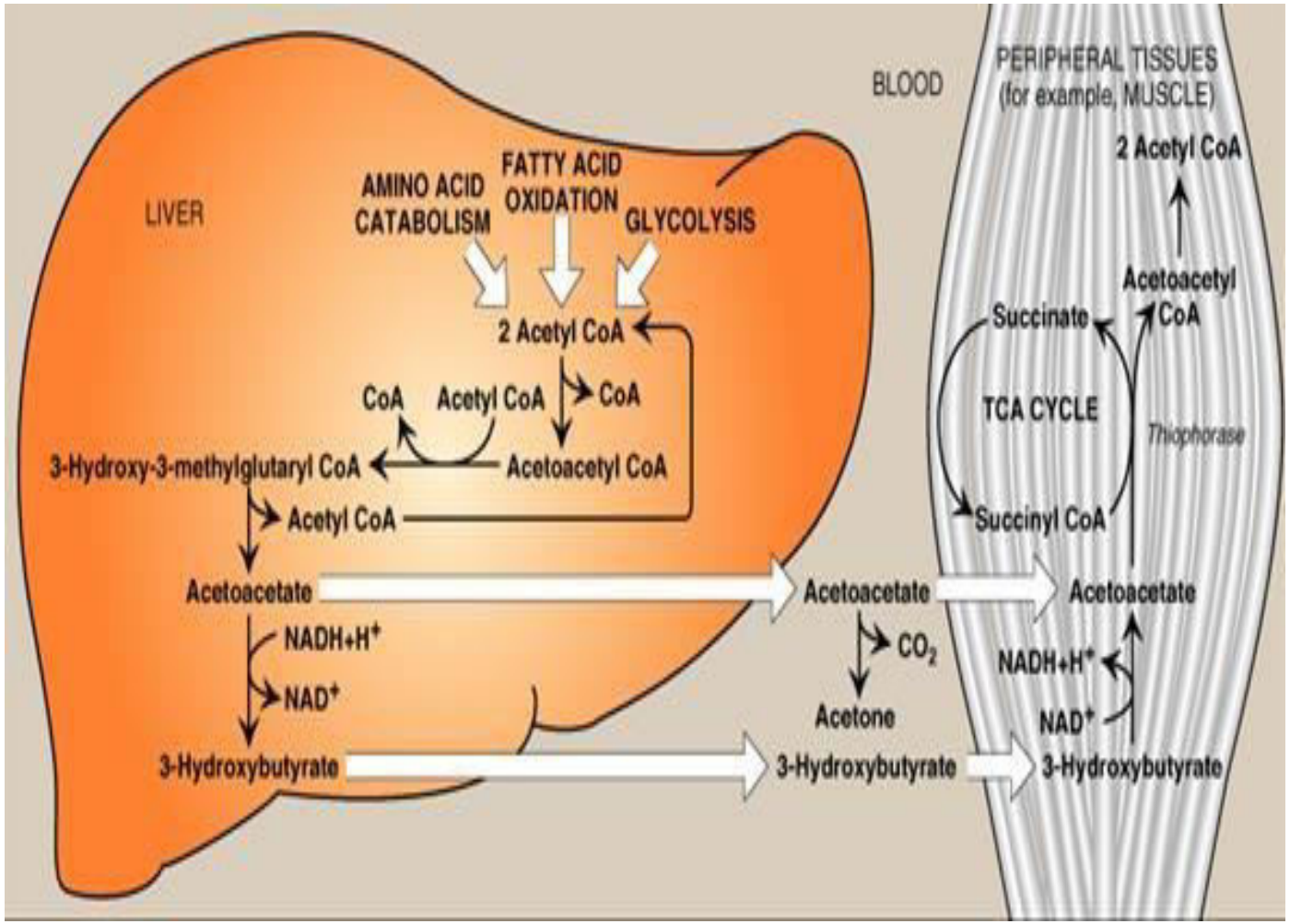
- ↑hepatic FA oxidation □ ↑ acetyl CoA which will be channeled into KB synthesis
- Acetyl CoA + oxaloacetate (OAA) > Krebs cycle
- ↑ Acetyl CoA production activates pyruvate carboxylase
- Pyruvate carboxylase converts pyruvic acid into OAA
- OAA is used for gluconeogenesis (rather than Krebs cycle)
- Acetyl CoA is channeled into KB synthesis

Ketone bodies utilization "Ketolysis"

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



Ketone bodies utilization "Ketolysis"



In the muscle, Beta-hydroxybutyrate is converted to acetoacetate by a dehydrogenase, which will convert it to Acetoacetyl CoA by the enzyme thiophorase. And that is going to be broken down into Acetyl CoA which will enter TCA cycle.

In the liver, Acetyl CoA is produced by Amino acids catabolism, fatty acid oxidation and glycolysis, which will be converted to Acetoacetyl CoA and then 3-Hydroxybutyrate and then Acetoacetate which both go to the peripheral tissues.

When you test the blood, you have both 3-Hydroxybutyrate and acetoacetate.

Lab investigation results

At this point, I want to make something clear to you, it is not there in the slides.
When we do lab investigation for a patient with diabetic ketoacidosis which is present with (ketonemia, hyperventilation as a compensatory mechanism, fruity odor of breath, vomiting), usually the amount of B-hydroxylasebutyrate and acetoacetate cannot be measured in any lab because not all labs have the investigations for both, they only can measure acetoacetate which will be high in patients with diabetic ketoacidosis. But if you want to compare 3-hydroxybutyrate and acetoacetate the ratio is like 1:6 so it's much more 3-hydroxybutyrate in the blood than acetoacetate, and 3-hydroxybutyrate measuring test is usually expansive so you measure acetoacetate which is fine.
You should not do a serial measurement of ketone bodies after you start the treatment. Because after the treatment ketone bodies start degrading and you'll have high acetoacetate number as a result of ketone bodies degradation so the results will be higher, So it will lead to false positive result.

Mechanisms of DKA

In uncontrolled DM there is:

↑lipolysis in adipose tissue

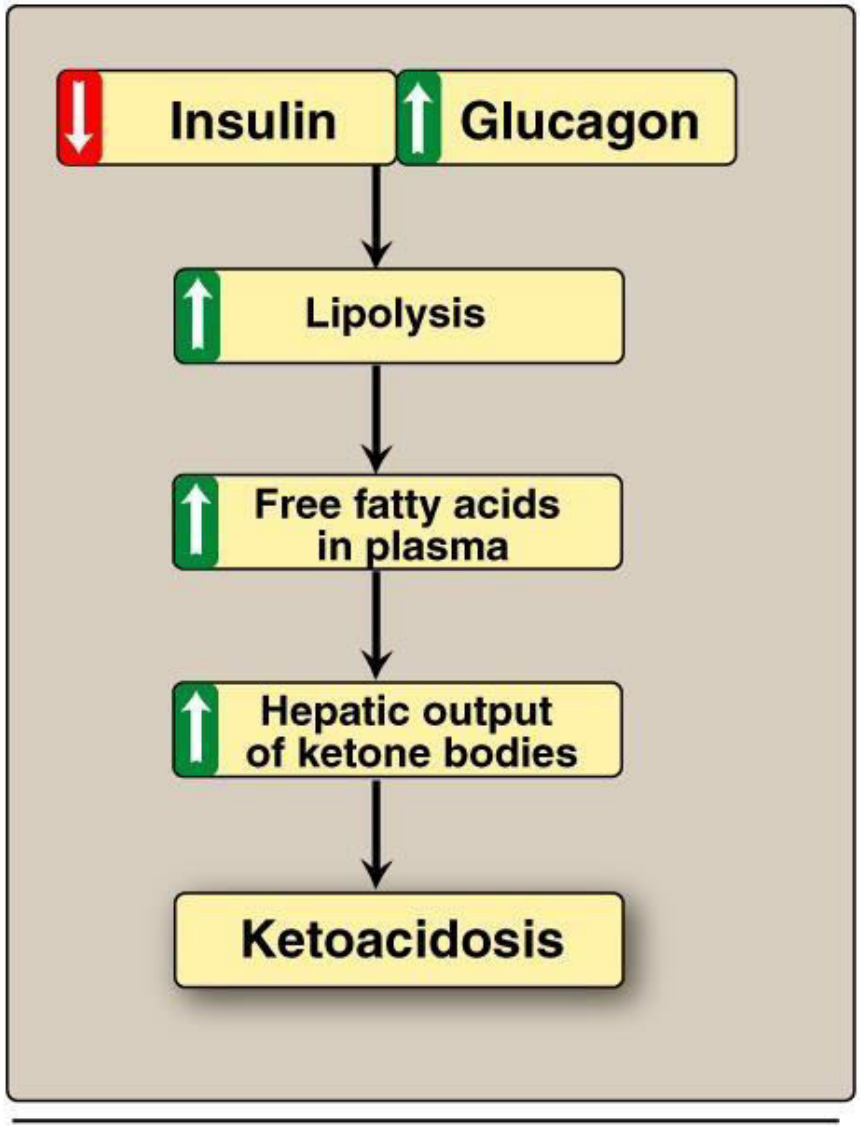
↑ [FFA]

↑ mobilization of FFA to liver

↑hepatic FA Oxidation

↑ hepatic acetyl CoA which will be utilized in KB synthesis (ketogenesis)

ketoacidosis



Mechanisms &Manifestations of DKA

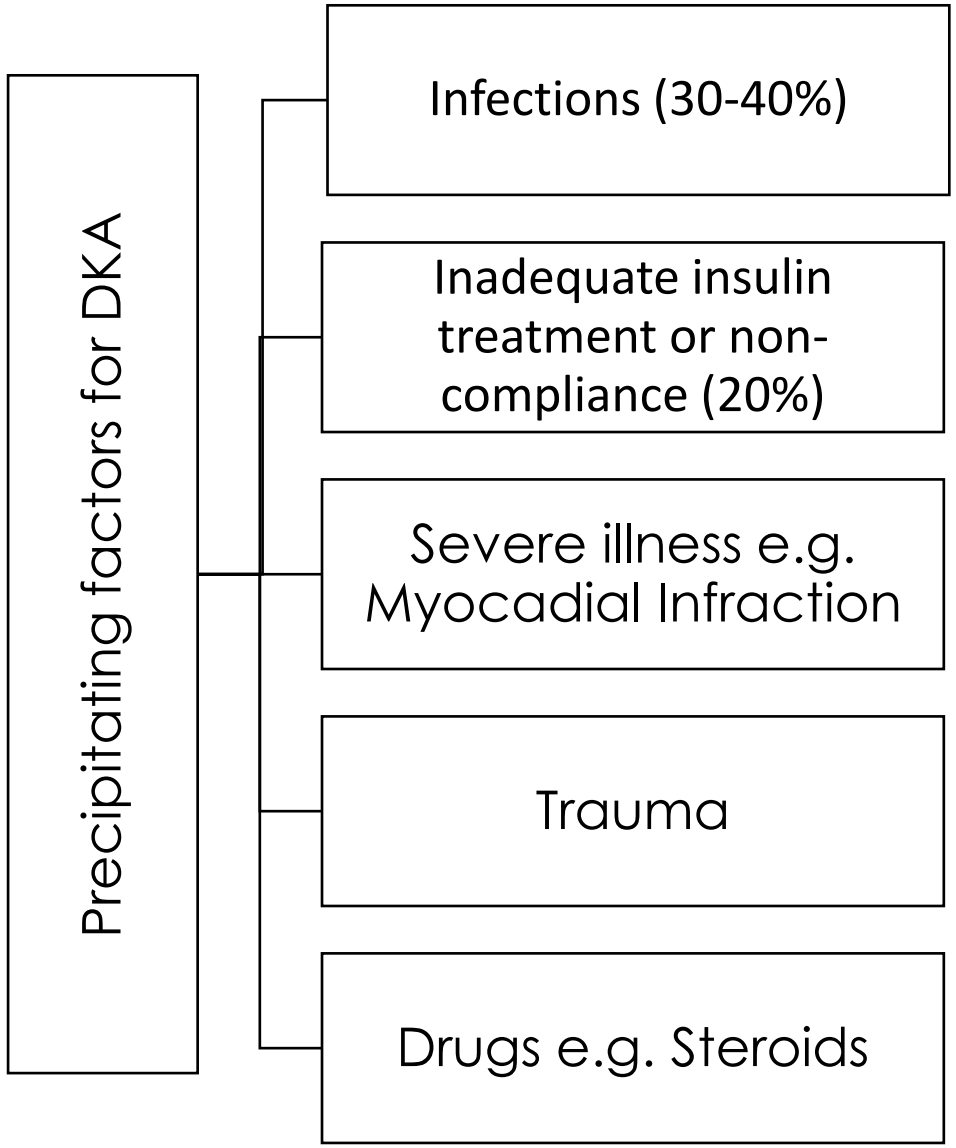
In uncontrolled DM the rate of ketogenesis is > the rate of ketolysis
ketonemia (↑[KB] in blood)
ketonuria (↑[KB] in urine).

Manifestations of DKA:

- Fruity odor on the breath (acetone)
- Acidosis (low pH of blood because KBs are acids)
- Dehydration (due to glucosuria)

Usually the rate of production of ketone bodies is equal to the degradation. But in excess amount of ketone bodies the tissues are not able to use all the ketone bodies and its amount will be elevated in the blood (ketonemia), and then excreted in urine (ketonurea) which leads to ketoacidosis

Precipitating factors for DKA



Also too much insulin deficiency, so either it is the first episode of ketoacidosis so the patient has not been diagnosed or the patient misses his dos of insulin so (non-complince) by the patient. Or if there is sever illness causes physical stress but not the stress you get from exams.

Hyperosmolar Hyperglycaemic State (HHS)= Hyperosmolar Non-Ketotic Acidosis

- 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%)

Important Comparison between DKA and HHS:

These two conditions (DKA & HHS) has overlaps, because they both have uncontrolled diabetes leading to hyperglycemia and glucoseurea leading to dehydration.

In HHS, hyperglycemia level is much higher than DKA.

Complications and symptoms from DKA will lead the patient to ER.

Usually the dehydration from HSS leads the patient to have altered mental status.

So in HSS 3 basic symptoms (dehydration, hyperglycemia and altered mental status).

In DKA usually the patient will be in alert mental status but will present with (bad berating, vomiting…)

Hypoglycaemia

Usually patients with DM may have hypoglycemia because of the drugs, and it is most common in type 1 DM

- Common complication of treatment with insulin or oral hypoglycemia
- More common in patients with T1DM
- Manifestations: Characterized by:
  1. CNS Symptoms (confusion, aberrant behavior, or coma): *see details later*
  2. Low blood [Glucose]
  3. Symptoms resolved within minutes following the administration of glucose

Why hypoglycaemia is a medial condition ?

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

Hypoglycaemia

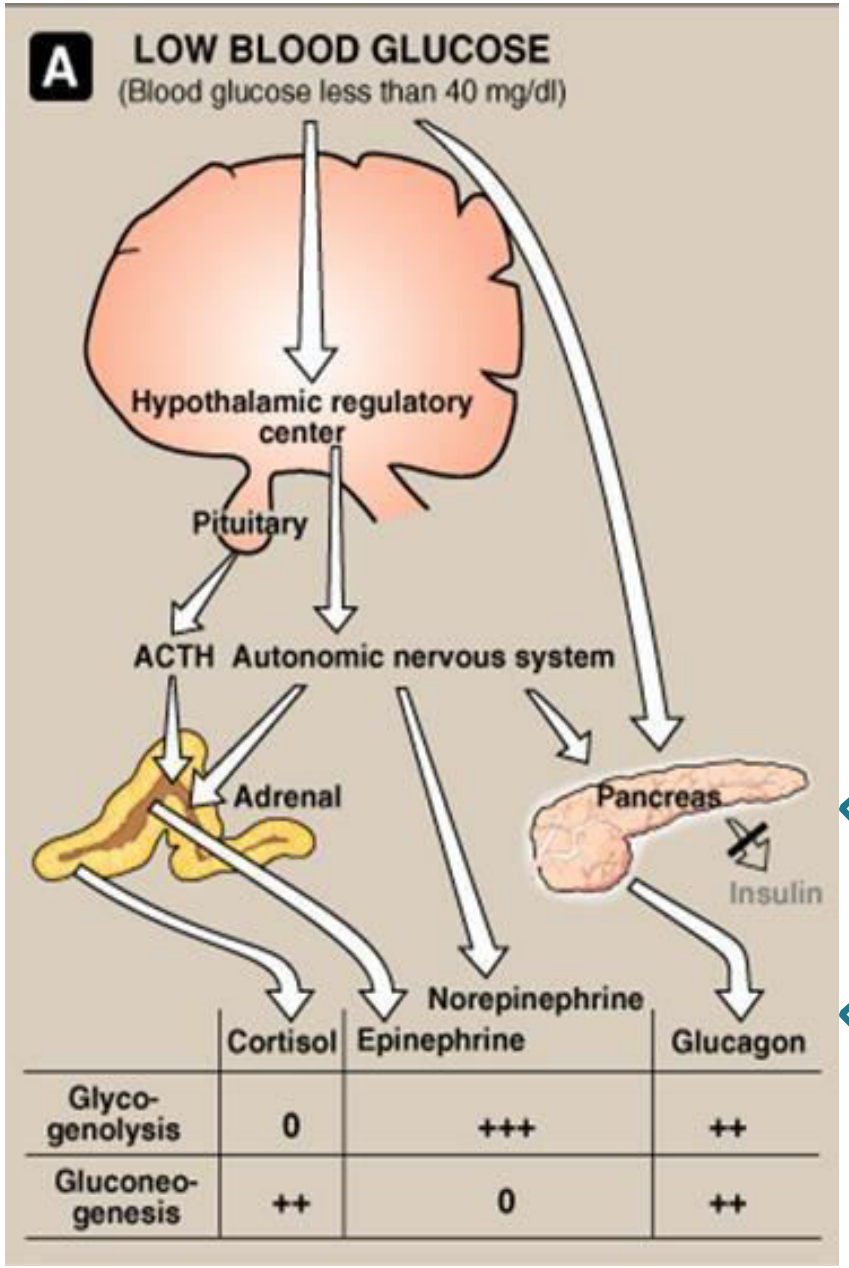
- Hypoglycemia occurs due to impaired protective responses to hypoglycemia:
  - Insulin is supplied exogenously and its release cannot be turned off

    After administration of insulin into the blood there is no possibility to stop it or remove it.
  - Glucagon & adrenaline response to hypoglycemia becomes impaired later in the course of DM

- Clinical presentation: Depends on the level of glucose.

- Symptoms of sympathetic overactivity (plasma [glucose] <3.6 mmol/L, abrupt fall): anxiety, tremors, sweating & palpitation
- Symptoms of neuroglycopenia (plasma [glucose] <2.6 mmol/L, gradual fall): headache, confusion, drowziness and ultimately loss of consciousness or seizures (at plasma [glucose] <1.5 mmol/L)

Hormonal mechanisms to prevent or correct hypoglycemia



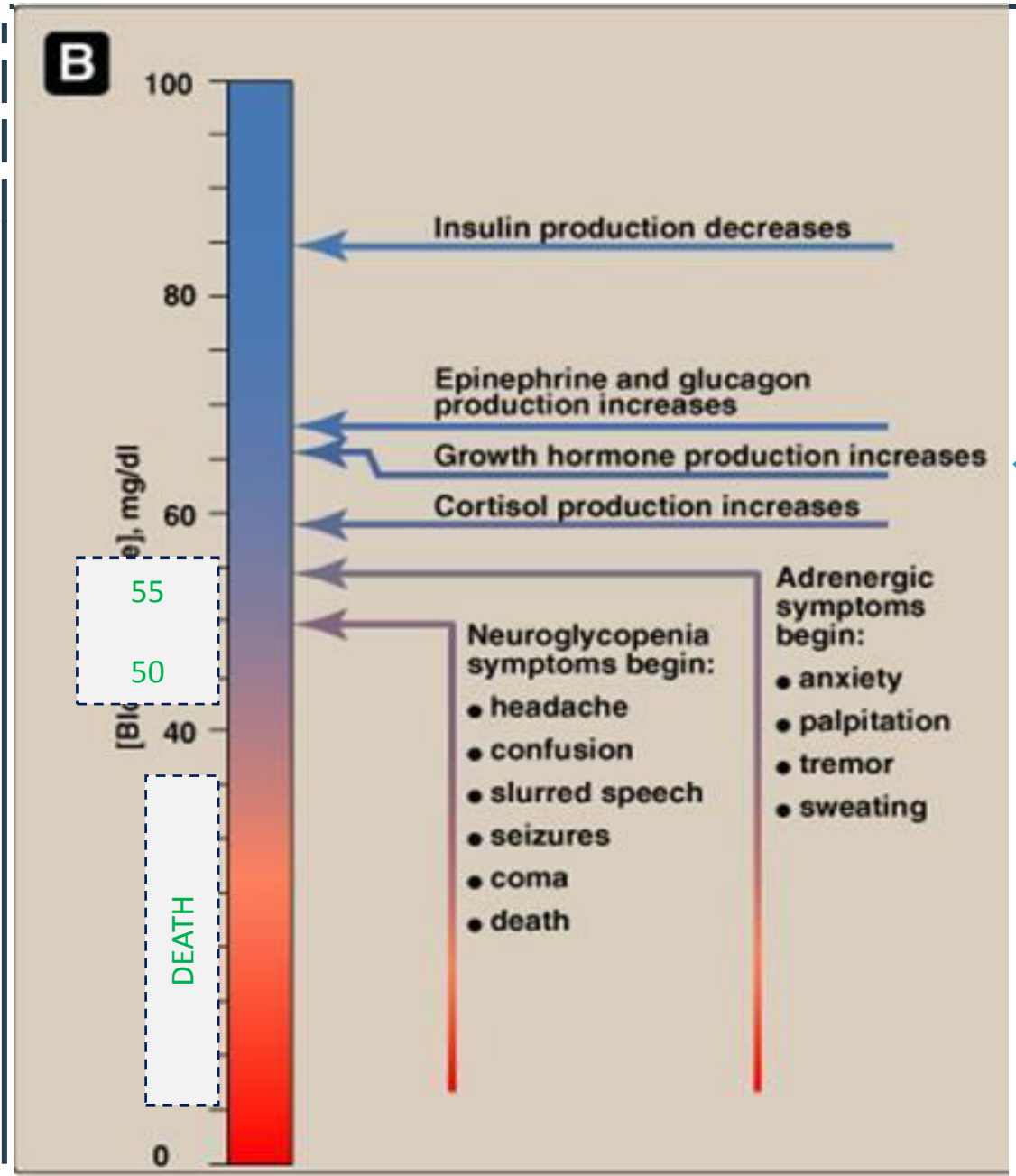
Glucagon, adrenaline and cortisol are mechanisms that raise blood sugar but later they may become weak and the patient undergo hypo glycaemia which is life threatening condition.

Hypoglycemia is a stress condition, so the hypothalamus activates the pituitary to secret ACTH which will act on the adrenals and the pancreas to release glucagon, cortisol, epinephrine & norepinephrine.

⇐ ↓ Production of insulin

⇐ ↑production of:
- Epinephrine & glucagon
- Growth hormone
- Cortisol

Hypoglycaemia



Each level of hypoglycemia has its own presentation and responses

Glycemic thresholds for the various responses to hypoglycemia:

A case of DKA

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.

Incidence of infection

A case of DKA

- On examination:
- She was dehydrated which caused Her skin to be cold
- She was breathing in a deep sighing manner to compensate her acidic state
  - (Kussmaul respiration)
- Her breath had a fruity odor because of acetone
- Her blood pressure was 90/60 mmHg (120/80) because of hypovolemia and dehydration
- Her pulse rate 115/min. to compensate the hypovolemia and acidosis
- She could not be aroused
  - A provisional diagnosis of T1DM with complicating ketoacidosis and coma (DKA) was made by the intern on duty

Laboratory findings: blood results

The admitting diagnosis was confirmed by the laboratory findings shown below:

Plasma analytes	Patient's results	Normal levels
Glucose (mmol/L)	50	3.9-5.6
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

Laboratory findings: blood 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 (□mol/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

*Anion gap (A^-)= (Na^+ + K^+)– (HCO_3^- + Cl^-)

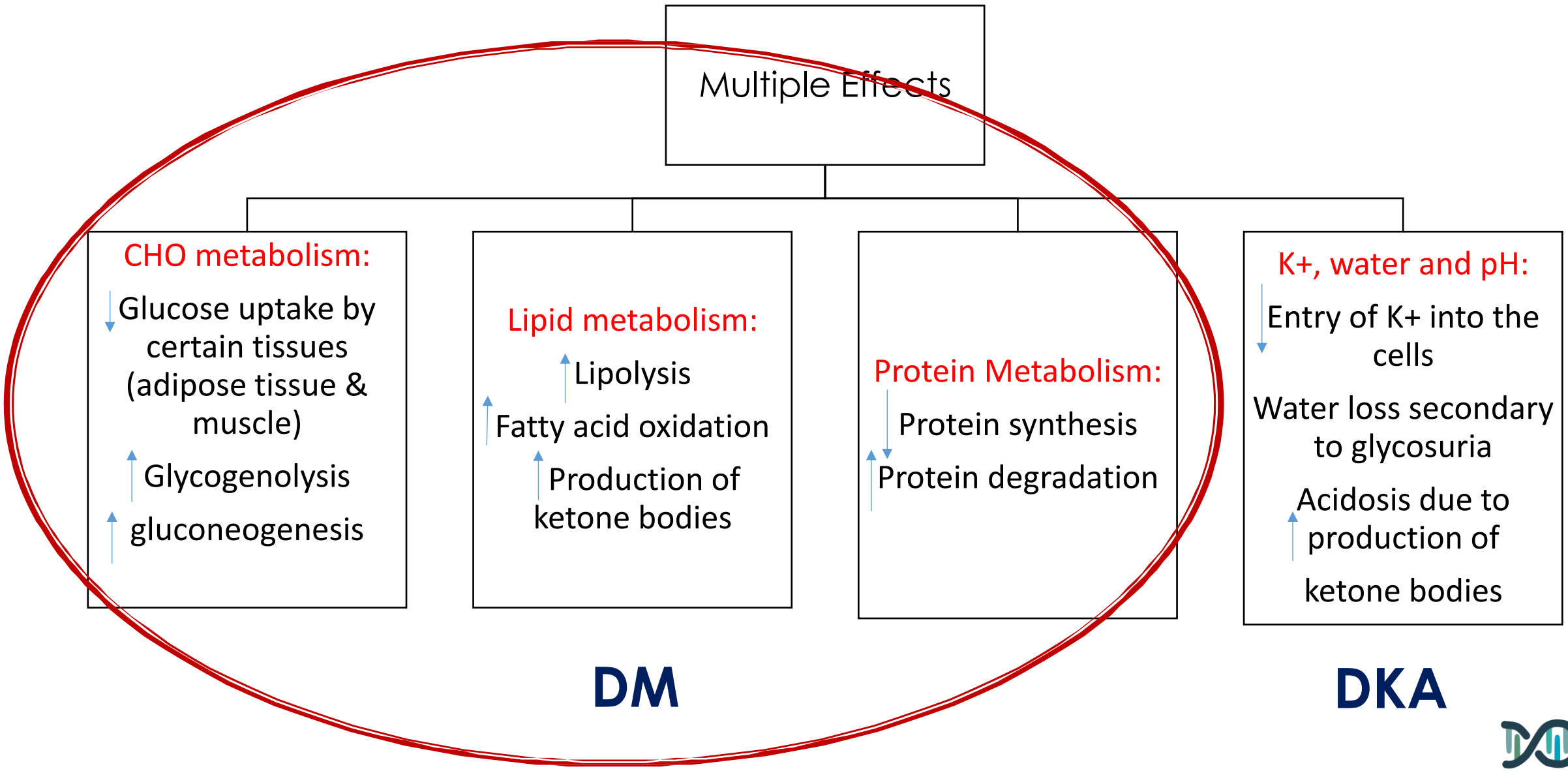
Laboratory findings: urine results

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

Interpretation of laboratory findings

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

Interpretation of laboratory findings



Take Home Messages

- Acute complications of DM include: DKA, HHS, and hypoglycemia
- DKA is a triad of hyperglycemia, ketonemia and high anion gap metabolic acidosis, and can be precipitated by several stressful factors.
- Ketone bodies (KB) are synthesized in the liver (HMG CoA synthase is
- the rate limiting enzyme) and utilized by peripheral organs and not
- the liver (liver lacks thiophorase enzyme)
- KB can serve as energy source (this is important for the brain in case
- of hypoglycemia)

Take Home Messages

- In DKA there is excessive ketogenesis (more than ketolysis) details of the mechanisms and consequences are required)
- HHS is a serious condition, usually occurs in elderly with T2DM, and has high mortality rate.
- Hypoglycemia is a medical emergency that might be caused by DM treatment (intensive) and impaired protective mechanisms against hypoglycemia. Its clinical manifestations are due to sympathetic overactivity and neuroglycopenia.
- Case presentation, examination of DKA can provide provisional diagnosis, and should be confirmed by comprehensive blood and urine lab investigation including measuring blood glucose, KB, pH, pCO_2, electrolytes, osmolality, protein, and kidney function test; anion gap calculation; hematocrit; and urine glucose and KB.

Diabetic emergencies

1. Diabetic Ketoacidosis (DKA)

Introduction

- ✓ Triad of hyperglycemia, high anion gap metabolic acidosis, and ketonemia.
- ✓ Characteristically associated with T1DM.
- ✓ DKA may be the first presentation of T1DM.
- ✓ It has become increasingly common in T2DM (in severe stress).

Ketone bodies

Types

Acetoacetate	Acid	They are producedby the liver (ketogenesis) and utilized for energy production by peripheral tissues (Ketolysis).
β-Hydroxybutyrate		
Acetone	Not Acid	

Brain & Ketone bodies

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

Ketogenesis

Occurs in:
Hepatocyte mitochondria.
Steps:
In uncontrolled DM there is ↑lipolysisin adipose tissue → ↑ (FFA) mobilization to liver → ↑hepatic FA oxidation → ↑ acetyl CoA

Ketolysis

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

1. β-Hydroxybutyrateis oxidized to acetoacetate (by a dehydrogenase).
2. Acetoacetateis converted to acetoacetylCoA (catalyzed by thiophorase).
3. AcetoacetylCoA is converted to acetylCoAs.

Summary

Cont.	
Mechanism of DkA	✓ In uncontrolled DM thereis: ↑lipolysis in adipose tissue ↑ [FFA] → ↑ mobilization of FFA to liver → ↑hepaticFAoxidation → ↑ hepaticacetylCoA which will be utilized in KB synthesis (ketogenesis) → ↑ ketoacidosis. ✓ In uncontrolled DM: The rate of ketogenesisis > the rate of ketolysis. 1. ketonemia(↑[KB] in blood). 2. ketonuria(↑[KB] in urine).
Manifestations of DKA	1. Fruity odor on breath 2. Acidosis 3. Dehydration
Precipitating factors for DKA	1. Infection(30-40%) 2. Inadequate insulin treatment or noncompliance (20%) 3. Severe illness (e.g. Myocardial infarction) 4. Trauma 5. Drugs (e.g. steroids)

2. Hyperosmolar hyperglycaemic state (HHS)

Overview

- ✓ Also called: Hyperosmolar Non-ketoticacidosis (HONK).
- ✓ In HHS (i.e. HONK), insulin levels are insufficient to allow appropriate glucose utilization but are adequate to prevent lipolysis and subsequent ketogenesis.
- ✓ Occurs in: in elderly with T2DM.
- ✓ Mortality: substantially higher mortality than DKA (up to 15%).

Clinical features

Serum glucose	Serum glucose is often > 50 mmol/L
Ketone bodies	Little or NO accumulation of ketone bodies
Plasma osmolality	High Plasma osmolality that could reach 380 mosmol/Kg (Normal range 275-295)
Neurological abnormalities	

3. Hypoglycemia

Occurs due to?

Impaired protective responses to hypoglycemia:

1. Insulinis supplied exogenously or oral hypoglycemic and their release can't be turned off.
2. Glucagon& adrenaline response to hypoglycemia becomes impaired later in the course of DM.

More common in patients with T1DM.

Whit's a medical emergency?

Because the brain has absolute requirement for a continuous supply of glucose.

- Transient hypoglycemia cerebral dysfunction.
- Severe prolonged hypoglycemia brain death.

Treatment

Administration of glucose (Symptoms will resolve within minutes)

Clinical manifestations

1. CNS Symptoms(confusion, aberrant behavior, or coma).
2. Low blood glucose concentration.

Summary

METABOLIC CHANGES IN DM AND DKA			
DM		**DKA**	
CHO metabolism	↓ Glucose uptake by certain tissues (adipose tissue & muscle)	**DKA K+, Water & pH**	1. Pantry of K+ into the cells. 2. Water loss secondary to glycosuria. 3. Acidosis due to ↑ production of ketone bodies.
	↑ Glycogenolysis		
	↑ Gluconeogenesis		
Lipid metabolism	↑ Lipolysis		
	↑ Fatty acid oxidation		
	↑ Production of ketone bodies		
Protein metabolism	↓ protein synthesis		
	↑ protein degradation		

QUIZ

Q1 : Which one of the following is found in a patient with Diabetic ketoacidosis?

A. Alkalosis
B. Hypo-osmolar
C. Palpitations
D. Coma

Q2 : Which one of the following is an enzyme required for ketolysis ?

A. Thiophorase
B. HMG CoA synthase
C. 3-Hydroxybutyrate Dehydrogenase
D. Thiolase

Q3 : Which one of the following is the end product of keylysis in peripheral tissues?

A. Acetoacetate
B. 3-hydroxybutyrate
C. Acetyl CoA
D. Actoacetyl CoA

Q4 : Which one of the following is the rate limiting enzyme in ketogenesis?

A. Thiophorase
B. HMG CoA synthase
C. 3-Hydroxybutyrate Dehydrogenase
D. Thiolase

Q5 : Acetoacetate is decarboxylated into which of the following?

A. Acetone
B. β-Hydroxybutyrate
C. Acetyl CoA
D. Oxaloacetate

Q6 : Which one of the following is used for Ketone body synthesis?

A. Oxaloacetate
B. Pyruvic acid
C. Acetyl CoA
D. Acetoacetyl CoA

QUIZ

Q7 : 13 year old boy, came to E.R. in a state of unconsciousness.
Upon inspection you find the following:
Increased heart rate, Excessive sweating.
After administration of glucagon, he woke up but in a state of confusion. After a few minutes you check on him again and the boy was laughing with his father
As his mother was quite horrified, she asked you a few questions.

A) What was wrong?

- Your son will be ok but he was having a Hypoglycemic crisis.

B) What is the mechanism that the body uses to prevent this?

1. Decrease insulin production
2. Increase production of:
    A. Epinephrine
    B. Glucagon
    C. Growth hormone
    D. Cortisol

C) Why is this a medical emergency?

- Because a hypoglycemic state may lead to brain death if untreated

D) How did you know he was hypoglycemic?

1. Because he was unconscious.
2. Because of the sweating
3. Because he responded to glucose and woke up.

Suggestions and recommendations

1) D 2) A 3) C 4) B 5) A 6) C

Biochemistry Team 436

THANK YOU

FOR CHECKING OUR WORK

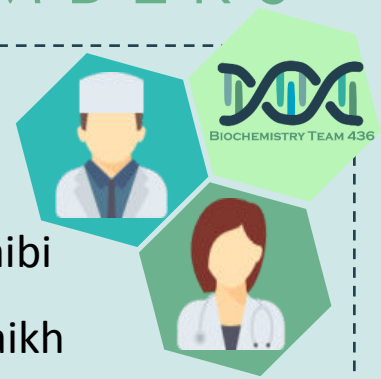
PLEASE CONTACT US IF YOU HAVE ANY ISSUE

TEAM LEADERS

Mohammad Almutlaq

Rania Alessa

TEAM MEMBERS



Amaal Alshaibi

Hanin Bashaikh

Laila Mathkour

Abdulrahman Alrashed

Abdulaziz Alhusaini

Abdullatif Alabdullatif

Talal Alhuqail