Revised & Approved

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439

MED439
KING SAUD UNIVERSITY

# Diabetic ketoacidosis

Editing File

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# Lecture Outlines :

- Diabetic Complications

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- Diabetes ketoacidosis :
  - Definition
  - Causes and mechanisms
  - Manifestations
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- Hyperosmolar hyperglycaemic state (HHS) = Hypperosmolar non-ketotic acidosis (HONK):
  - Definition
  - Causes and Mechanisms
  - Manifestations

- Hypoglycemia :
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  - Manifestations
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  - Preventing or correcting hypoglycemia

- A case of Diabetic ketoacidosis ( DKA ) : ( Presentation , Examination , Lab results & their interpretation )

- Metabolic changes in DKA :
  - Changes in CHO , Protein , and Lipid metabolism
  - Changes in water , Electrolytes , and pH

# Diabetic Emergencies

1. Diabetic Ketoacidosis ( DKA )
2. Hyperosmolar hyperglycaemic state (HHS)= Hyperosmolar non-ketotic acidosis (HONK)
3. Hypoglycemia

## Diabetic Ketoacidosis (DKA)

**It's a triad of :**

- **hyperglycemia** — high levels of sugar, or glucose, in the blood.
- **high anion gap metabolic acidosis** — is a form of metabolic acidosis characterized by a high anion gap (a medical value based on the concentrations of ions in a patient's serum). Metabolic acidosis occurs when the body produces too much acid, or when the kidneys are not removing enough acid from the body.
- **ketonemia** — the presence of an **abnormally high concentration of ketone bodies** in the blood.

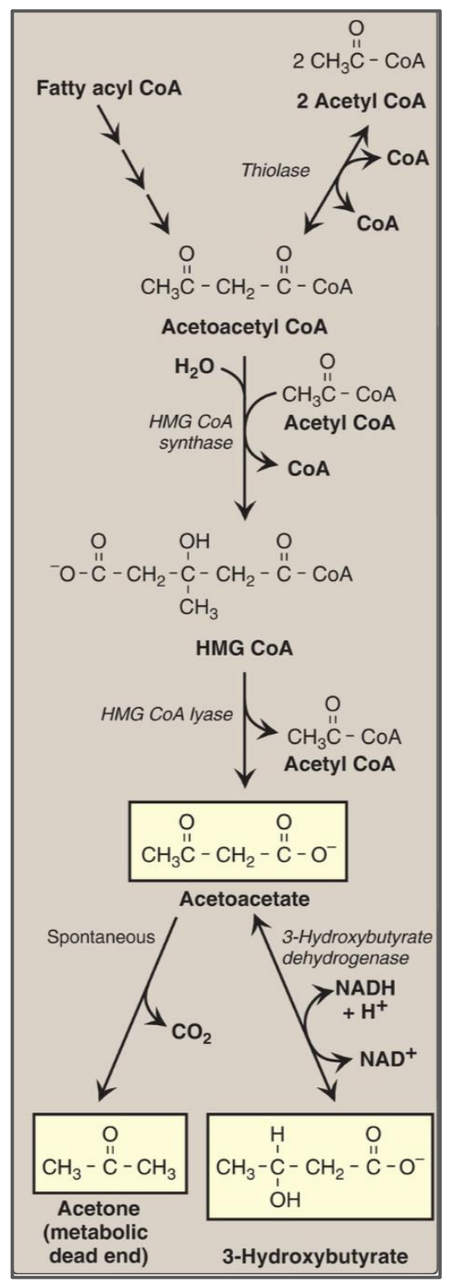
- ❖ Characteristically associated with **T1DM**
- ❖ It has become increasingly common in **T2DM**
- ❖ **DKA** may be the first presentation of **T1DM**

## Ketone Bodies

- Acetoacetate
- Acetone
- β-Hydroxybutyrate

Extra note from the reference :

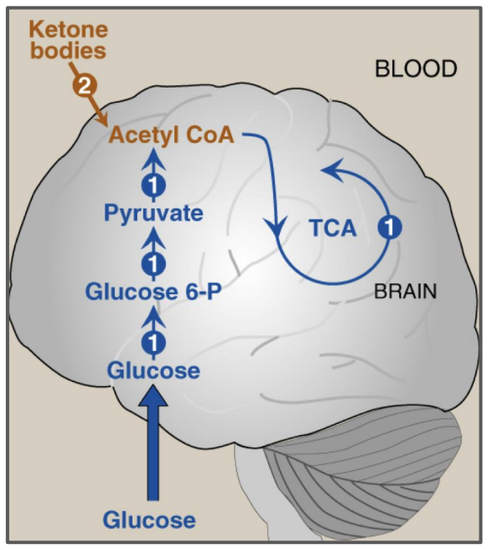
**Ketone body synthesis:** HMG CoA is cleaved by HMG CoA lyase to produce acetoacetate and acetyl CoA, as shown in the Figure. Acetoacetate can be reduced to form 3-hydroxybutyrate with NADH as the electron donor. [Note: Because ketone bodies are not linked to CoA, they can cross the inner mitochondrial membrane.] Acetoacetate can also spontaneously decarboxylate in the blood to form acetone, a volatile, biologically non metabolized compound that can be detected in the breath. The equilibrium between acetoacetate and 3-hydroxybutyrate is determined by the NAD+/NADH ratio. Because this ratio is low during fatty acid oxidation, 3-hydroxybutyrate synthesis is favored.




- ❖ They are **produced** by the liver (**ketogenesis**) , and **utilized** for energy production by peripheral tissues (**Ketolysis**)

# Brain‘s fuel

- 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.




# 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:

➔ reduced to β-Hydroxybutyrate,

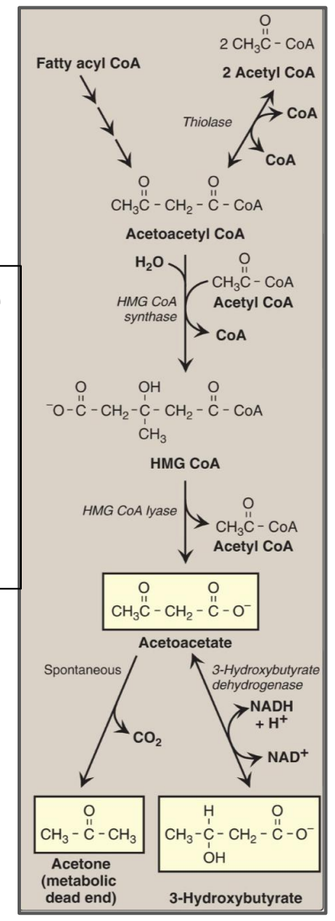
OR

➔ spontaneously decarboxylated to acetone.

- 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.

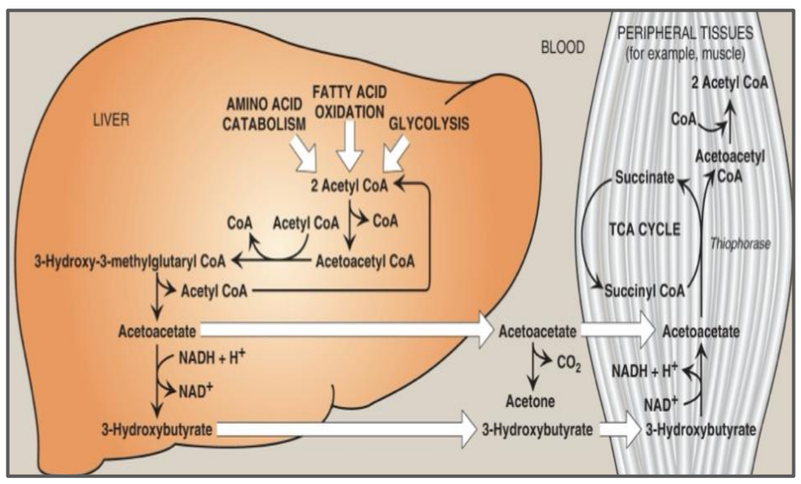
Extra note from the reference :

Acetoacetate can also spontaneously **decarboxylate** in the blood to form **acetone**, a volatile, biologically non-metabolized compound that can be detected in the **breath**. The **equilibrium** between **acetoacetate** and **3-hydroxybutyrate** is determined by the **NAD+/NADH ratio**. Because this ratio is low during fatty acid oxidation, 3-hydroxybutyrate synthesis is favored.




# ketone bodies utilization ( ketolysis )

- Takes place in extrahepatic tissues(not in the hepatocytes like ketogenesis)
- 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)**
- β-Hydroxybutyrate is oxidized to acetoacetate (by a dehydrogenase)
- Acetoacetate is converted to acetoacetyl CoA (catalyzed by **thiophorase**)
- Acetoacetyl CoA is converted to acetyl CoAs.

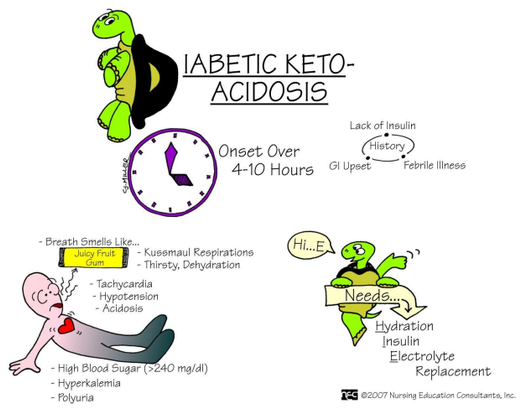


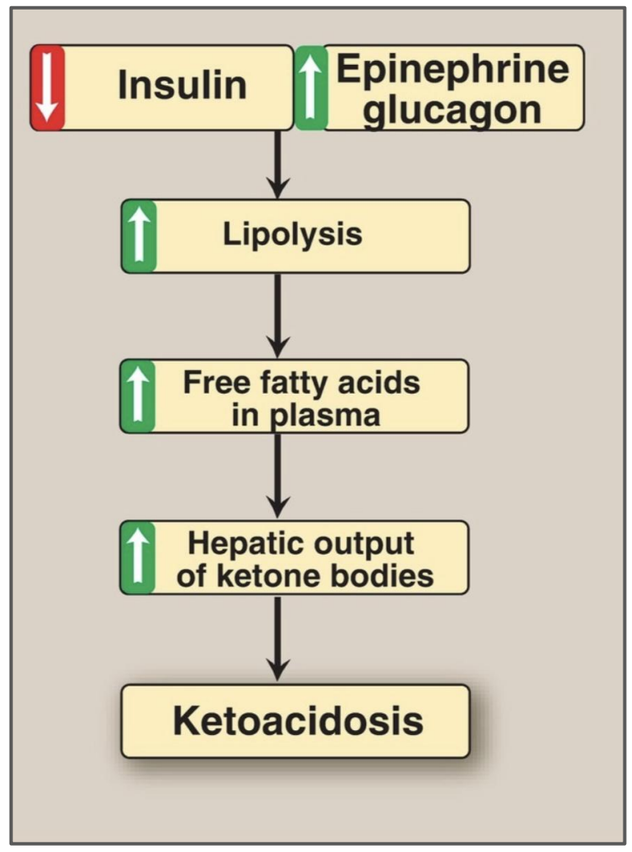
# DKA Mechanisms & Manifestations

- 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 **more than** 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)




# Precipitating factors for DKA

- **Infection ( 30-40%)**
- Inadequate insulin treatment or non-compliance (20%)
- Severe illness e.g. Myocardial infarction
- Trauma
- Drugs: e.g., steroids

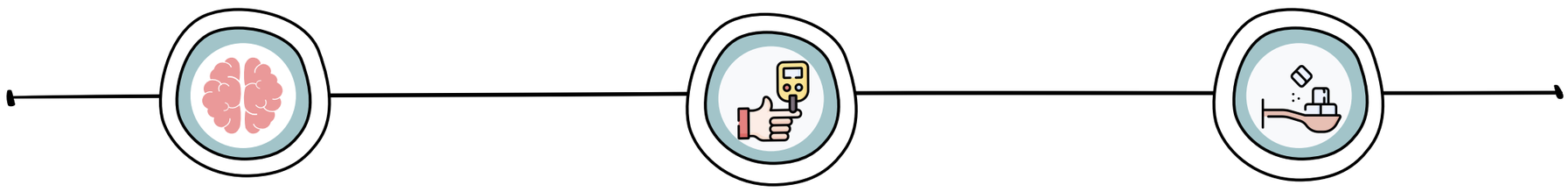
# Hyperosmolar Hyperglycemic state (HHS)= Hyperosmolar non Ketotic acidosis ( HONK )

| Features | Manifestation | Mortality |
|---|---|---|
| ❖ Little or no accumulation of ketone bodies<br>❖ Serum [glucose] is often >50 mmol/L<br>❖ Plasma osmolality may reach 380 mosmol/Kg (normal 275-295) | ❖ Neurological abnormalities are frequently present<br>❖ 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<br>❖ Has a substantially higher mortality than DKA (up to 15%) |

# Hypoglycemia

Common complication of treatment with insulin or oral hypoglycaemics
More common in patients with **T1DM (Because of the insulin intake)**

**Manifestations: Characterized by:**



**CNS** Symptoms (confusion, aberrant behavior, or coma)

**Low blood** [Glucose]

Symptoms resolved within minutes following the administration of glucose

## Why hypoglycemia is a medical emergency ?

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:**

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

# Clinical presentation

**Symptoms of sympathetic overactivity**
(plasma glucose <3.6 mmol/L) abrupt fall

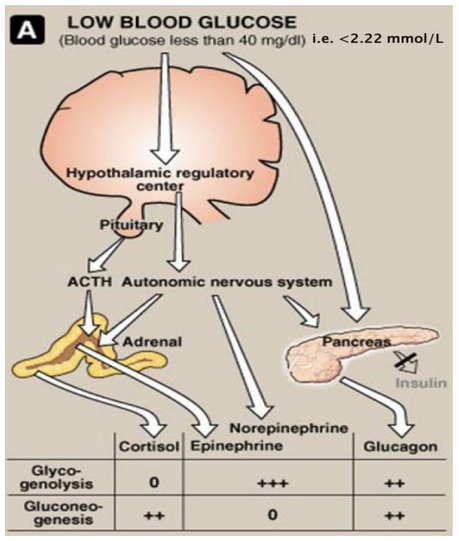
- anxiety
- **tremors**
- sweating
- **palpitation**

**Symptoms of neuroglycopenia**
(plasma glucose <2.6 mmol/L) gradual fall

- headache
- confusion
- **drowsiness**
- ultimately **loss of consciousness** or seizures (at plasma [glucose] <1.5 mmol/L)

# Hypoglycemia

Hormonal mechanisms to prevent or correct hypoglycemia:

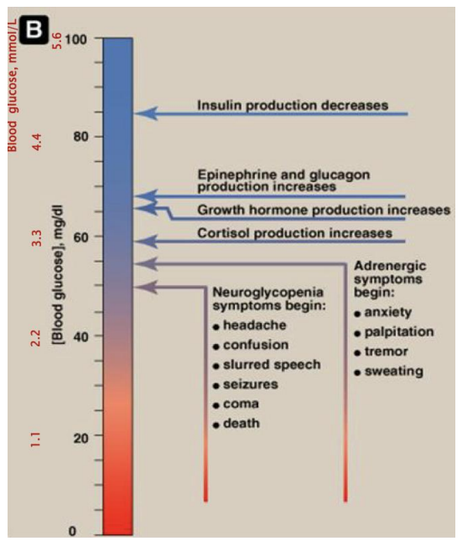



⬇ Production of insulin

⬆ Production of:

- Epinephrine & glucagon
- Growth hormone
- Cortisol

Net result: increase glucose level




**B:** Glycemic thresholds for the various responses to hypoglycemia

#MED438

What you have to know from here :

- The sequence of which hormones are released in case of hypoglycemia
- The adrenergic and neuroglycopenic symptoms and at what level they start

Males' doctor : The number in the graph is for Your info only

## 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)
- 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

### Diagnosis:

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

### Laboratory findings: Urine results

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

### Laboratory findings: Blood results

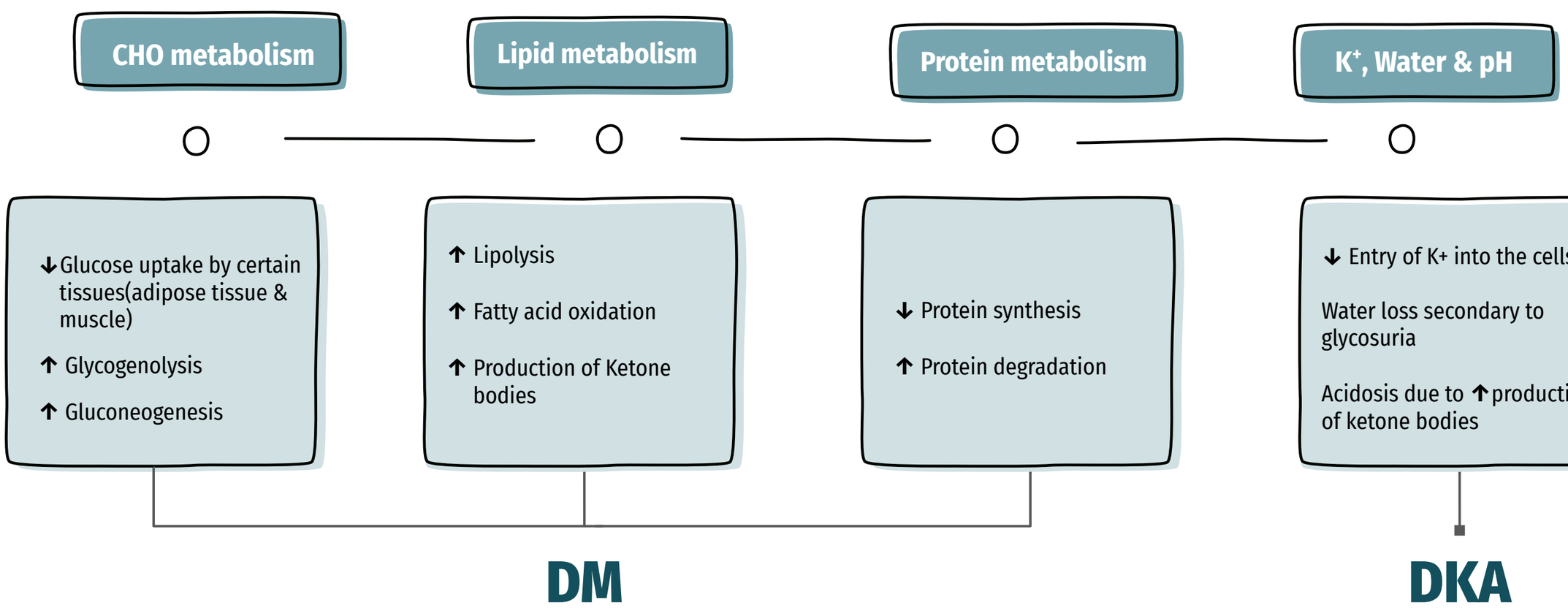
| Plasma analytes | Patient's results | Normal levels |
|---|---|---|
| Glucose (mmol/L) | 50 | 3.9-5.6 |
| Ketoacids | ++++ | (trace) |
| Bicarbonate (mmol/L) | 6 | 22-30 |
| Arterial blood pH | 7.07 | 7.35-7.45 |
| Na+ (mmol/L) | 136 | 136-146 |
| Cl- (mmol/L) | 100 | 102-109 |
| PCO2 (kPa) | 2.7 | 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 (micro 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+ )– (HCO3- + Cl-)

# Interpretation Laboratory findings

| Results | interpretation (Very imp !) |
|---|---|
| Hyperglycemia | Confirm the diagnosis of DKA |
| Glucosuria | |
| Ketonemia | |
| Ketonuria | |
| ↓pH | Severe metabolic acidosis due to ↑ production of ketone bodies |
| ↓bicarbonate and PCO2 | 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)<br>2. Dehydration<br>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 |

# Metabolic Changes in DM and DKA(very imp)



# 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)
- 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.

# Summary

# Diabetic Emergencies

## 1 Diabetic ketoacidosis

- Triad of **hyperglycemia**, **high anion gap metabolic acidosis**, and **ketonemia**
- Characteristically associated with T1DM

**Ketone bodies:**
1-Acetoacetate
2- Acetone
3- β-Hydroxybutyrate

- They are **produced** by the liver (**<u>ketogenesis</u>**) , and **utilized** for energy production by peripheral tissues (**<u>Ketolysis</u>**)

**Manifestations of DKA:**

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

| Ketogenesis | Ketolysis |
|---|---|
| Occurs in the **hepatocyte mitochondria**<br>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 | Takes place in **extrahepatic tissues (mitochondria)**<br>- β-Hydroxybutyrate is oxidized to acetoacetate (by **a dehydrogenase**)<br>- Acetoacetate is converted to acetoacetyl CoA (catalyzed by **thiophorase**)<br>- Acetoacetyl CoA is converted to acetyl CoAs. |

## 2 Hypoglycemia

More common in patients with **T1DM** (Because of the insulin intake)

**Manifestations of hypoglycemia :**
1- **CNS** symptoms (confusion,
2- **LOW blood glucose**

Hormonal mechanisms to correct hypoglycemia:

**↓ Production of insulin**
↑ Production of:
- Epinephrine& glucagon
- Growth hormone
- Cortisol

Net result: increase glucose level

## 3 Hyperosmolar Hyperglycemic state (HHS)

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

**Manifestations of HHS:**

- Neurological abnormalities are frequently present
- Insulin levels are insufficient to allow appropriate glucose utilization, **but** are adequate to prevent lipolysis and subsequent ketogenesis

# MCQs

| | | | |
|---|---|---|---|
| **1- A patient was brought to the ER unconscious. He has a fruity odor coming from his mouth. His ABG shows normal pO2 and low pCO2. What is the diagnosis?** | | | |
| A- DKA with metabolic compensation | B- DKA with respiratory compensation | C- DKA | D- Diabetes insipidus |
| **2- Which one of the following is a manifestation of DKA?** | | | |
| A- Cushing Syndrome | B- Edema | C- Polyuria | D- Dehydration |
| **3- Which of the following is considered a characteristic finding of uncontrolled type 1 diabetes?** | | | |
| A- DKA | B- Decreased Lipolysis | C- Increased blood volume | D- Hypertension |
| **4- Which one of the following is a metabolic change in DM ?** | | | |
| A-↑ Glycogenolysis | B- ↓Lipolysis | C- ↑Protein synthesis | D-↓ Entry of K+ into the cells |
| **5- Which of the following is a clinical presentation of Hypoglycemia due to sympathetic overactivity?** | | | |
| A- headache | B-palpitation | C-ultimately loss of consciousness or seizures | D-confusion |
| **6-Which of the following is a metabolic change in DKA?** | | | |
| A-↓ Entry of K+ into the cells | B- Water loss secondary to glycosuria | C-Acidosis due to ↑production of ketone bodiea | D-All of the above |

Answers key

1- B 2- D 3- A 4- A 5- B 6- D

# SAQs

## 1- Enumerate the 3 Emergent diabeteic conditions :

Answer
Diabetic Ketoacidosis ( DKA )
Hyperosmolar hyperglycaemic state (HHS)= Hypperosmolar non-ketotic acidosis (HONK)
Hypoglycemia

## 2- Why hypoglycemia is a medical emergency ?

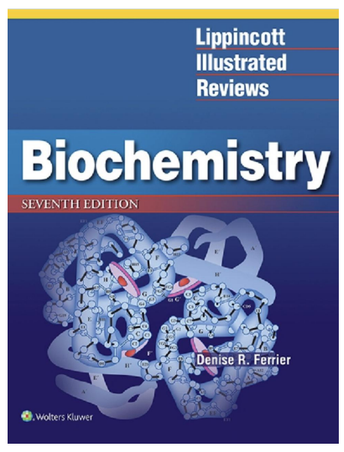
The brain has absolute requirement for a continuous supply of glucose
- Transient hypoglycemia → cerebral dysfunction
- Severe, prolonged hypoglycemia → brain death

## 3- What are the hormonal mechanisms that prevent or correct hypoglycemia

↓Production of insulin
↑Production of: - Epinephrine & glucagon - Growth hormone - Cortisol

# Resources

Click on the book to download the resource



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