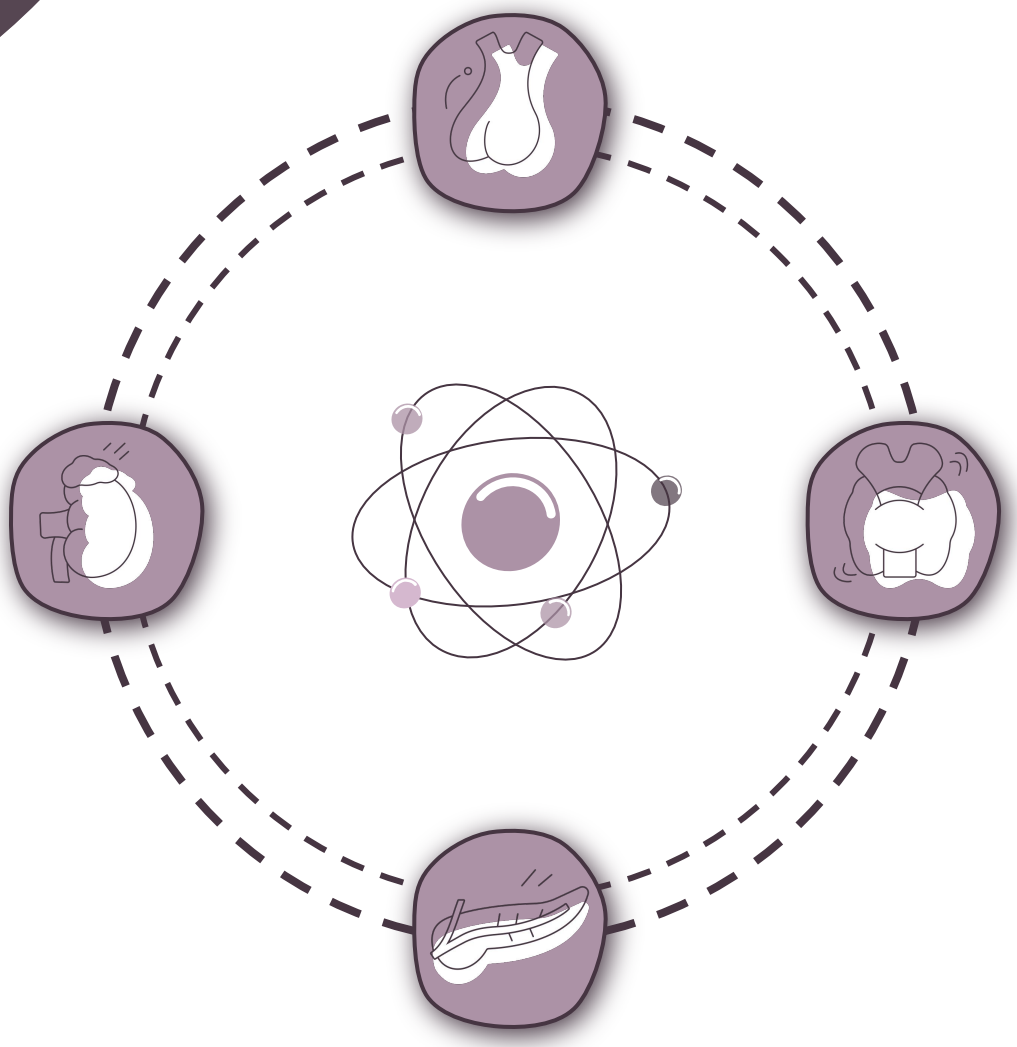
Biochemistry
Team 443



L9: Diabetic ketoacidosis

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Objectives

1. **Diabetic Complications**

2. **Ketone bodies metabolism**

3. **DKA:**
   - **Definition**
   - **Causes and Mechanisms**
   - **Manifestations Precipitating Factors**

4. **Hyperosmolar hyperglycaemic state (HHS) = Hypperosmolar non- ketotic acidosis (HONK):**
   - **Definition**
   - **Causes and Mechanisms**
   - **Manifestations**

5. **Hypoglycemia:**
   - **Causes**
   - **Manifestations**
   - **Hormonal mechanisms preventing or correcting hypoglycemia**

6. **A case of DKA:**
   (Presentation, Examination, Lab results & their interpretation)

7. **Metabolic changes in DKA:**
   -Changes in CHO, protein and lipid metabolism
   -Changes in water, electrolytes, and pH

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Diabetic Emergencies

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

Triad of Diabetic Ketoacidosis (DKA)

- **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)

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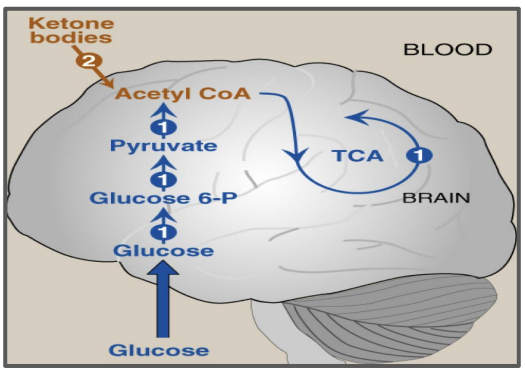
Brain's fuel

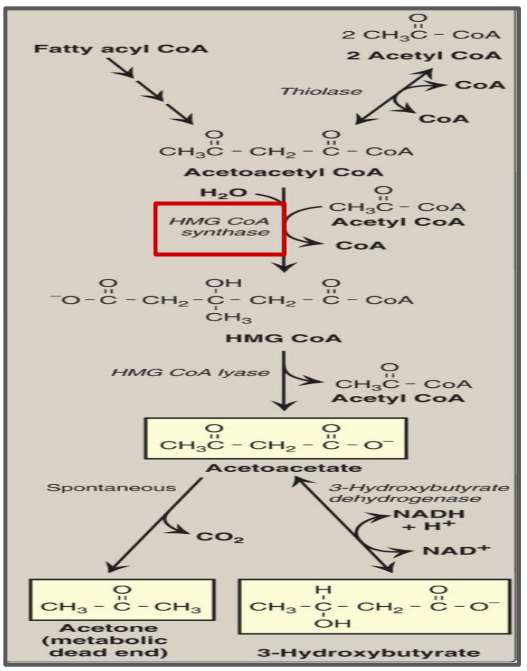
❖ Normally, glucose is the primary fuel for the brain. It can penetrate the blood brain barrier.
❖ The brain's GLUT is **insulin-independent.**
❖ If glucose is not available for the brain, the brain can utilize plasma ketone bodies, that can penetrate the blood brain barrier, and serve as fuel molecules.



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.**

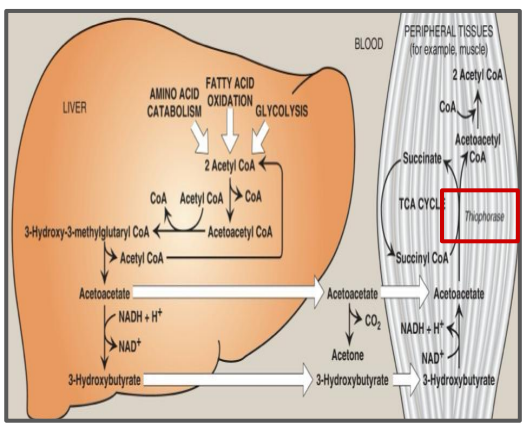


Extra note from the reference :

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.



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Precipitating factors for DKA

01 Infection (30-40%)

02 Inadequate insulin treatment Or non-compliance(20%)

03 Severe illness e.g. Myocardial infarction

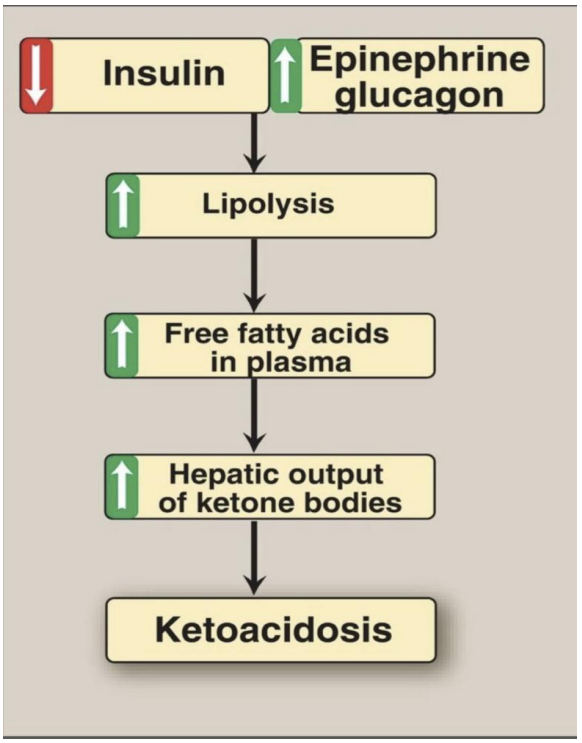
04 Trauma

05 Drugs E.g.steroids

DKA Mechanisms & Manifestations

DKA Mechanisms:

- 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).

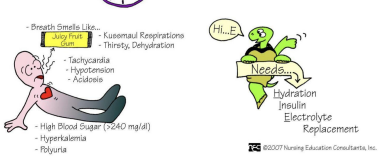


Manifestations of DKA:

1-**Fruity odor** on the breath (acetone)

2-**Acidosis** (low pH of blood because KBs are acids)

3-**Dehydration** (due to glucosuria)



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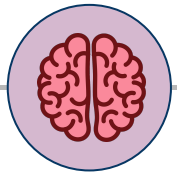
Hyperosmolar Hyperglycemic state (HHS)= Hyperosmolar non Ketotic acidosis (HONK)

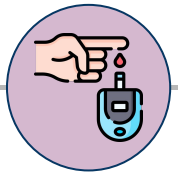
Features	Manifestation	Mortality
• Little or no accumulation of ketone bodies • Serum [glucose] is often >50 mmol/L • Plasma osmolality may reach 380 mosmol/Kg (normal 275-295)	• Neurological abnormalities are frequently present • Insulin levels are insufficient to allow appropriate glucose utilization 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

- Definition :Common complication of treatment with insulin or oral hypoglycemics
  More common in patients with **T1DM** (Because of the insulin intake)
- Manifestations: Characterized by:



CNS Symptoms as 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)

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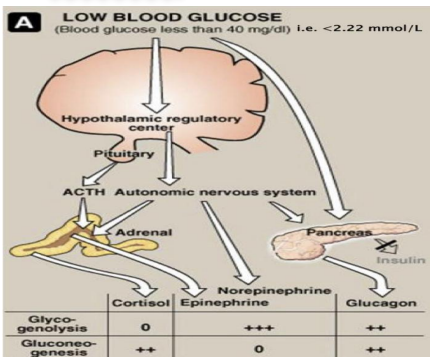
Hypoglycemia

Hormonal mechanisms to prevent or correct Hypoglycemia



(A)

Reduce Production Of insulin

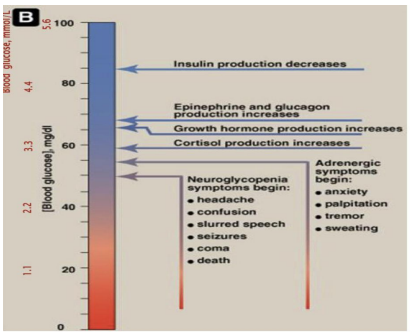
Increase Production of :

-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

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	++++	-

Anion gap (A-)= (Na+ + K+)– (HCO3- + Cl-)

Laboratory findings: Blood results

Plasma analytes	Patient 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

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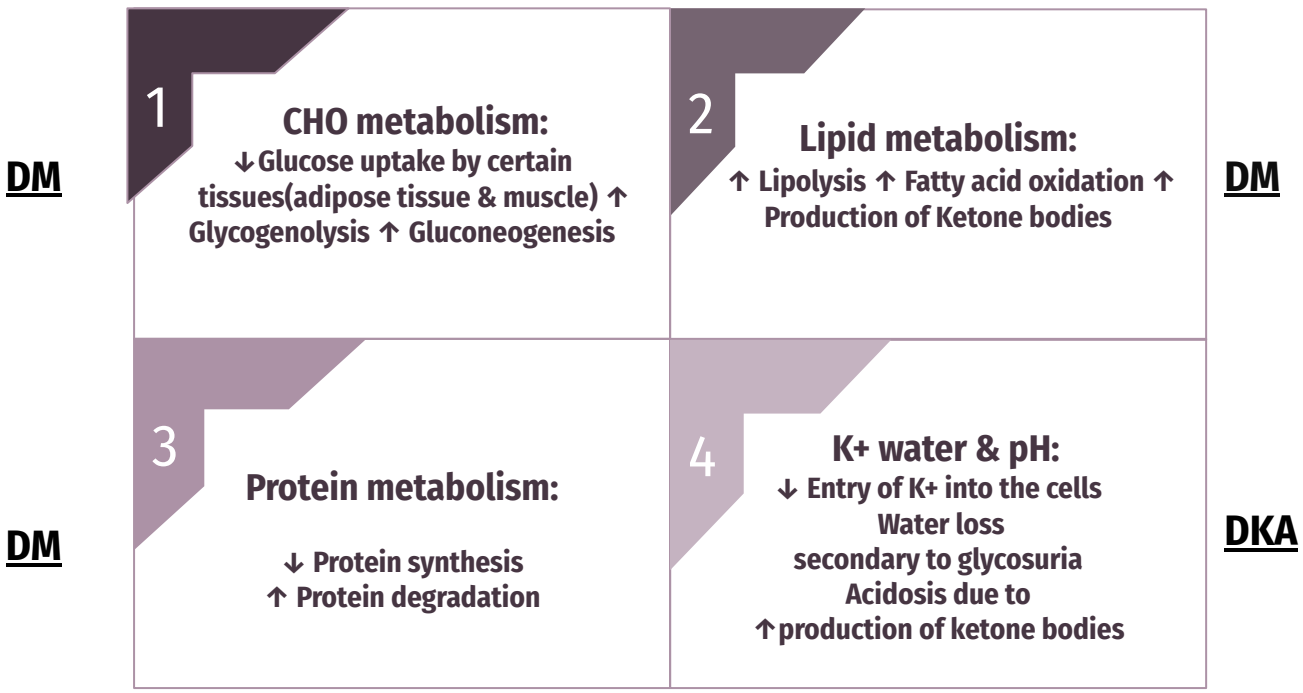
Interpretation Laboratory findings

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) 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

Metabolic Changes in DM and DKA

Important



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 (ketogenesis) , and utilized for energy production by peripheral tissues (Ketolysis).

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 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) - 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.

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:
-Decrease in Production of insulin
Increase 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

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TAKE HOME MASSAGE

- 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 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

Test Yourself!

MCQs

Answers: Q1: A | Q2: D | Q3: D | Q4: A

Q1: what is the first ketone to be produced during ketogenesis?
A. acetoacetate
B. acetone
C. Thyroid
D. B-hydroxybutyrate

Q2: which one of the following is symptoms of ketoacidosis?
A. anuria
B. edema
C. weight gain
D. electrolytes imbalance

Q3: Which one of the following associated with DM 1?
A. onset after 30 year
B. morbid obesity
C. normal or increased insulin
D. DKA

Q4: Acetoacetate can be reduce to?
A. B-hydroxybutyrate
B. acetone
C. n-acetylglutamate
D. phosphate

SAQs

Q1: 1- list the biological effect of insulin:
1. Stimulating glucose uptake
2. Promoting glycogen synthesis
3. Inhibiting gluconeogenesis

Q2: Enumerate the 3 Emergent diabetic conditions:
Diabetic Ketoacidosis (DKA)
Hyperosmolar hyperglycaemic state (HHS)= Hyperosmolar non-ketotic acidosis (HONK)
Hypoglycemia

Q3: What are the hormonal mechanisms that prevent or correct hypoglycemia?
↓Production of insulin
↑Production of: - Epinephrine & glucagon - Growth hormone - Cortisol

Meet The Team!

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