جامعة الملك سعود
King Saud University

"اللَّهُمَّ لا سَهْلَ إلاَّ ما جَعَلْتَهُ سَهْلاً، وأنْتَ تَجْعَلُ الحَزْنَ إذَا شِئْتَ سَهْلاً "

Biochemistry437

Diabetic ketoacidosis

Biochemistry Team 437

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Endocrine block

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Lecture Outline:

- Diabetic Complications
- Ketone bodies metabolism
- DKA:
  - Definition
  - Causes and Mechanisms
  - Manifestations
  - Precipitating Factors
- Hyperosmolar hyperglycaemic state (HHS) = Hyperosmolar non-ketotic acidosis (HONK):
  - Definition
  - Causes and Mechanisms
  - Manifestations
- Hypoglycemia:
  - Causes
  - Manifestations
  - Hormonal mechanisms preventing or correcting hypoglycemia
- A case of 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

- **Triad of**: Hyperglycemia, High anion gap metabolic acidosis[1], Ketonemia

- Characteristically associated with **T1DM**[2]
- It has become increasingly common in **T2DM**[3]
- DKA[4] may be the first presentation of **T1DM**

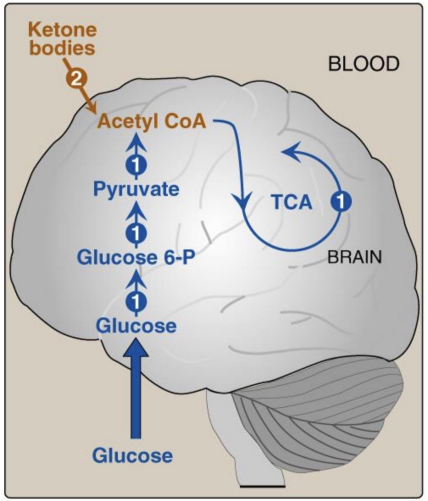
1. It means the positive ions are more than the negative.
2. Because there is absolute insulin deficiency, and insulin is an inhibitor of ketogenesis
3. As T2DM progresses,insulin levels keep going down
4. Symptoms of diabetic ketoacidosis include kussmaul breathing, NV, abdominal pain, but the patient is usually conscious

Ketone Bodies

1) Acetoacetate
2) Acetone
3) β-Hydroxybutyrate

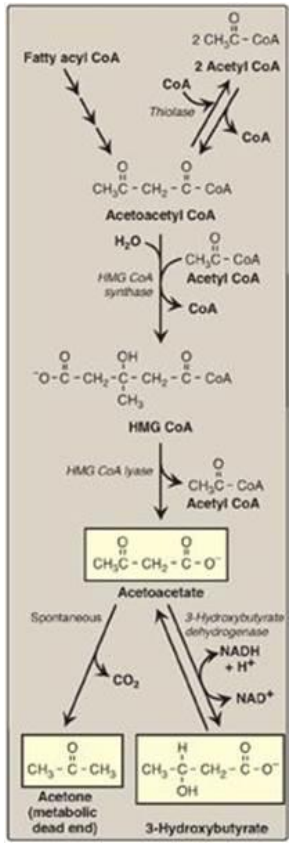
They are produced by the liver (ketogenesis) and utilized for energy production by peripheral tissues (Ketolysis)

- 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)

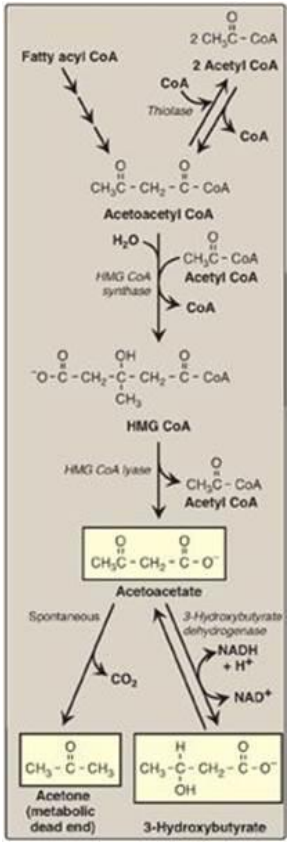
- Occurs in the hepatocyte mitochondria
- In uncontrolled DM there is ↑lipolysis in adipose tissue → ↑ [FFA] mobilization to liver → ↑hepatic FA oxidation →↑ acetyl CoA which will be channeled into KB synthesis
- HMG CoA synthase is the rate limiting enzyme[1]
- The first KB to be synthesized is acetoacetate.
- Acetoacetate can be:
  - Reduced to β-Hydroxybutyrate[2], or
  - Spontaneously decarboxylated to acetone.[3]



1. Hmg synthase her is mitochondrial, different from the one in cholesterol synthesis which is cytosolic
2. by the enzyme 3-hydroxybutyrate dehydrogenase, (Beta hydroxybutyrate = 3 hydroxybutyrate.)
3. Gives fruity breath

Ketone Bodies Synthesis (Ketogenesis)

1. Acetyl CoA is converted to acetoacetyl CoA, which is converted to HMG coA by the mitochondrial enzyme HMG CoA synthase
2. HMG CoA is acted on by the enzyme HMG CoA lyase to produce acetoacetate
3. Acetoacetate is either reduced by 3-Hydroxybutyrate dehydrogenase to β-Hydroxybutyrate or spontaneously converted to acetone



Ketone Bodies Synthesis (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)

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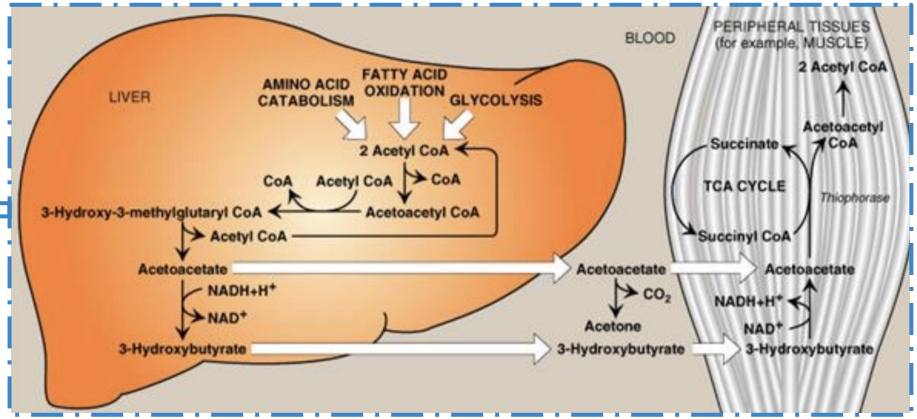
Enzymes are important!

- 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)
- 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.

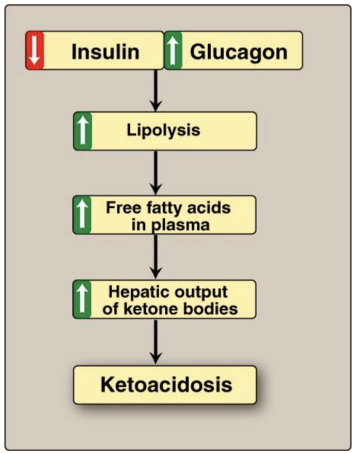
When we measure in the labs, we measure acetoacetate.
In DKA, 3 hydroxybutyric is 6 times more than acetoacetate
Then after treatment if we measure again the acetoacetate will be much higher. Why? Bc all the 3 hydroxybutyric will be degraded into acetoacetate thats why after treatment we don't measure again. We monitor the treatment by measuring PH



Mechanisms & Manifestations 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

leading to:

- Ketonemia (↑[KB] in blood)
- Ketonuria (↑[KB] in urine)

Also Glycosuria and glycosuria

Manifestations of DKA:

- Fruity odor on the breath (acetone)
- Acidosis (low pH of blood because KBs are acids)
- Dehydration (due to glucosuria)[1]

1- Glucose is hyperosmotic (pulls water with it) leading to osmotic diuresis.

Precipitating Factors for DKA

- Infection (30-40%)[1]
- Inadequate insulin treatment or noncompliance[2] (20%)
- Severe illness e.g.,Myocardial infarction
- Trauma
- Drugs: e.g., steroids

1. Because stress increases metabolic rate so increase FA
2. Patients forgets to take insulin

Hyperosmolar hyperglycemic state (HHS)= Hyperosmolar non-ketotic acidosis (HONK)

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- 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%)

HONK: symptoms happen in days
DKA : Is acute because symptoms happen in 24h
Usually, the serum glucose in a patient with HONK is much greater than in a person with DKA, because DKA has early manifestation that will cause the person to seek the emergency before the glucose levels get that high.

Hypoglycemia

- Common complication of treatment with insulin or oral Hypoglycemics
- More common in patients with T1DM[1]
- 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

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:

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

1. Because they depend only on insulin so if they took higher dose the body can't control it.

Hypoglycemia

Clinical presentation

Symptoms of sympathetic overactivity

(Plasma [glucose] **<3.6** mmol/L, abrupt fall):

- Anxiety
- Tremors
- Sweating
- Palpitation

Symptoms of neuroglycopenia

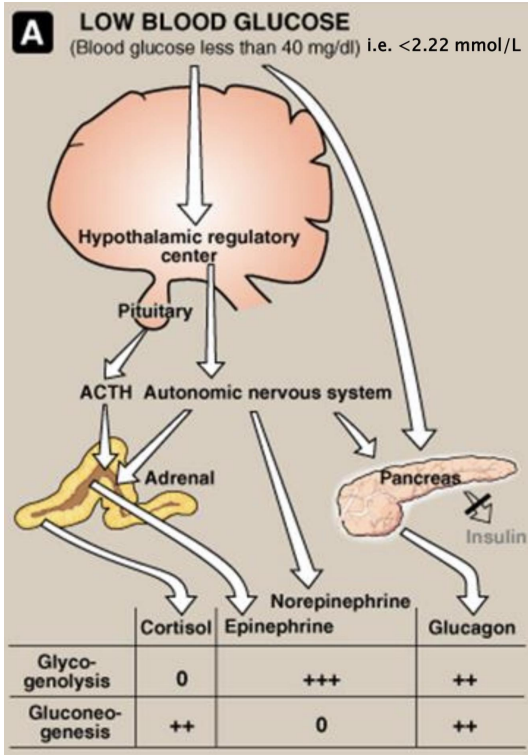
(Plasma [glucose] **<2.6** mmol/L, gradual fall):

↳ **Headache, confusion**

(at plasma [glucose] **<1.5** mmol/L)

↳ **Drowsiness and ultimately loss of consciousness or seizures**

Hormonal mechanisms to prevent or correct hypoglycemia



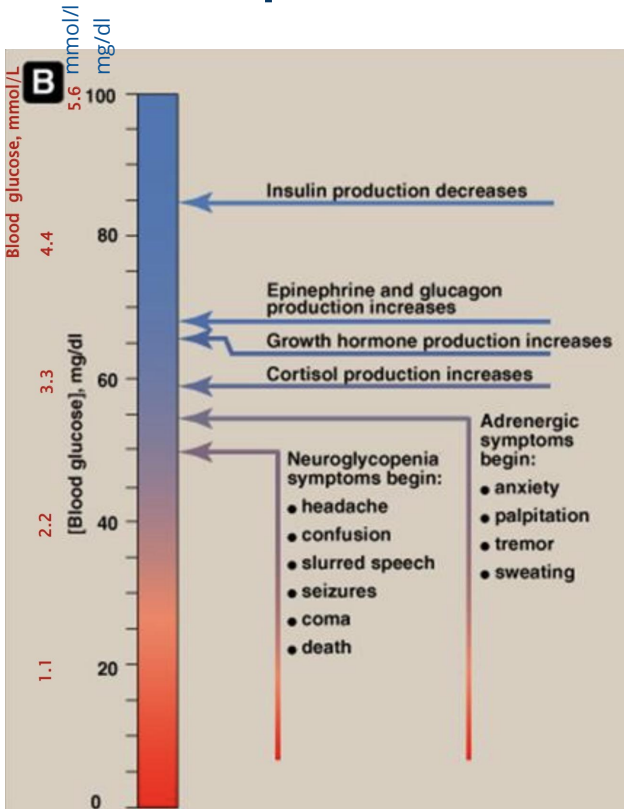
Don't skip the picture

↓ Production of insulin

↑ Production of:

- Epinephrine & glucagon
- Growth hormone
- Cortisol

Glycemic thresholds for the various responses to hypoglycemia



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

tip

mg/dl ←× 18— —÷ 18→ mmol/l

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 "polydipsia" and also started to get up several times during the night to urinate "polyuria". 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.

*The age and the presence of an immune trigger are hinting to **type 1** diabetes mellitus.

On examination:

She was dehydrated "polyuria" | Her skin was cold "dehydration" | She was breathing in a deep sighing manner (Kussmaul respiration) "respiratory compensation" | Her breath had a fruity odor "presence of acetone" | Her blood pressure was 90/60 mmHg (N: 120/80) "hypovolemia" | Her pulse rate 115/min. "compensation" | She could not be aroused

Diagnosis:

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

A Case of DKA

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 "but it usually low"	136-146
Cl^- (mmol/L)	100 "lost in the urine"	102-109

Laboratory Findings: Urine Results

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

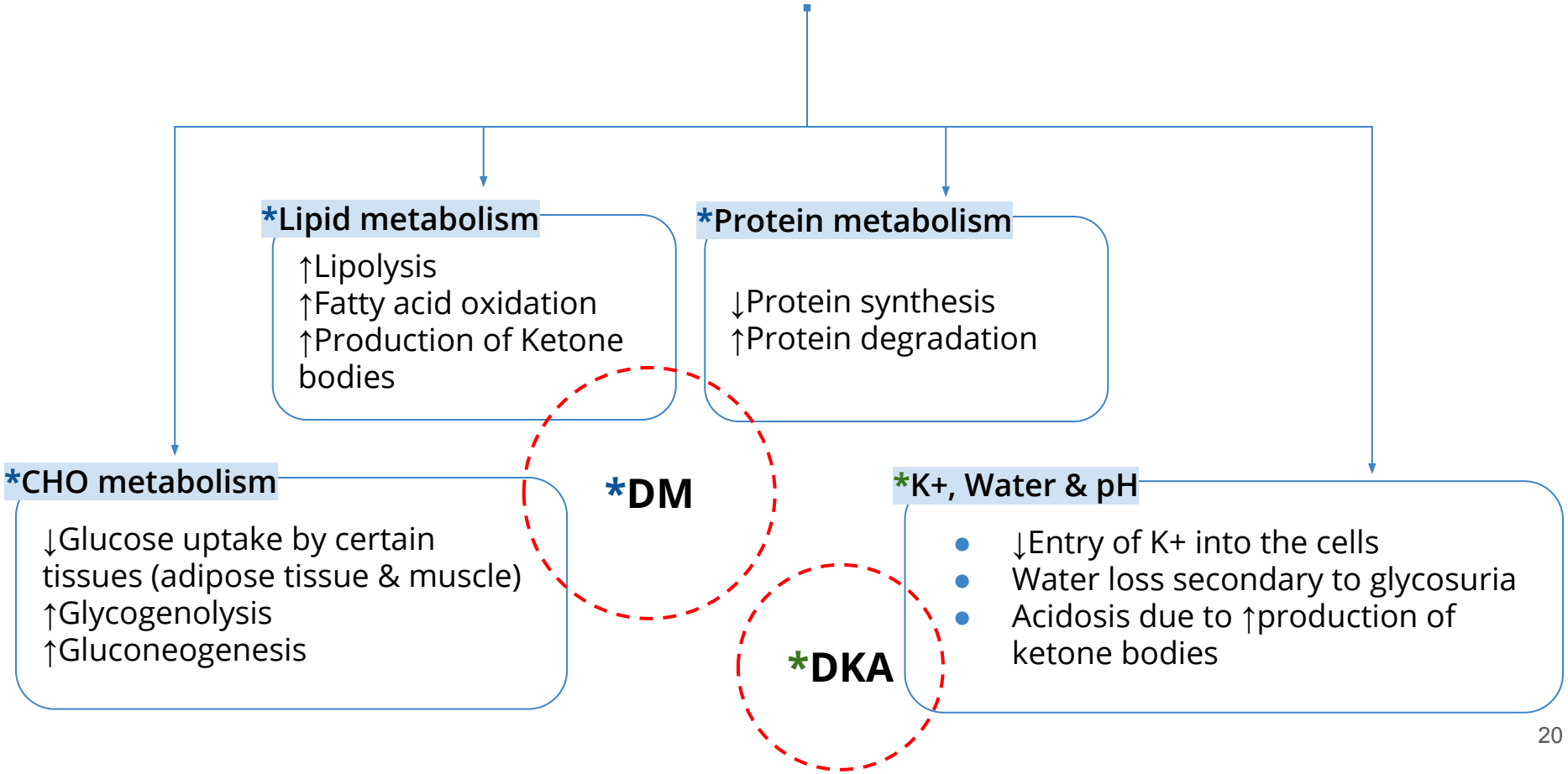
Plasma analytes	Patient's results	Normal levels
PCO_2 (kPa)	2.7 "respiratory compensation"	4.3-6.0
*Anion gap (mmol/L)	35.5	7-16
K^+ (mmol/L)	5.5	3.5-5.0
Urea nitrogen (mmol/L)	15 "dehydration"	2.5-7.1
Creatinine (mmol/L)	200	44-80
Albumin (g/L)	50	41-53
Osmolality (mOsm/kg serum water)	325	275-295
Hematocrit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

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

Interpretation of Laboratory Findings

Results		Interpretation
Hyperglycemia	**Glucosuria**	Confirm the diagnosis of DKA
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

Metabolic Changes in DM and DKA



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

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Diabetic Emergencies			
1. Diabetic Ketoacidosis (DKA)	◦ Associated with T1DM ◦ Ketone bodies : 1. Acetoacetate 2. Acetone 3. β-Hydroxybutyrate	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. ◦ Liver lacks the thiophorase enzyme required for ketolysis.
2. Hypoglycemia	◦ Common complication of treatment with insulin or oral hypoglycemics. ◦ More common in patients with T1DM. ◦ 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 and ultimately loss of consciousness or seizures (at plasma [glucose] < 1.5 mmol/L) ◦ Hormonal mechanisms to prevent or correct hypoglycemia: ↓ Production of insulin ↑ production of: 1-Epinephrine, 2-glucagon, 3-Growth hormone, 4-Cortisol.		
3. Hyperosmolar hyperglycaemic state (HHS)=(HONK)	◦ Usually occurs in elderly patients with T2DM ◦ Serum [glucose] is often >50 mmol/L ◦ Plasma osmolality may reach 380 mosmol/Kg ◦ Insulin levels are adequate to prevent lipolysis and subsequent ketogenesis		

MCQs:

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 rate limiting enzyme in ketogenesis?

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

Q4 : Which one of the following is the end product of ketoylysis in peripheral tissues?

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

4- C
3- B
2- A
1- D

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Girls team

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Boys team

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