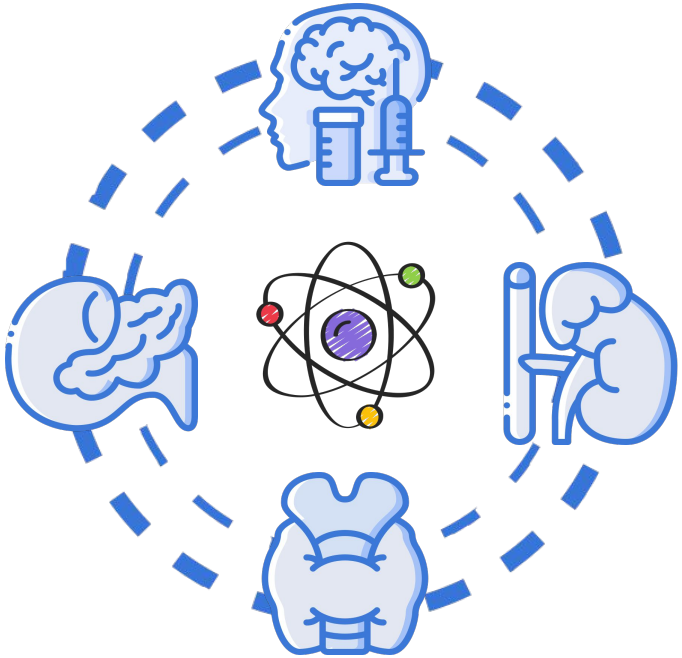
Diabetic Ketoacidosis



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- Main Topic
- Main content
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- Extra info

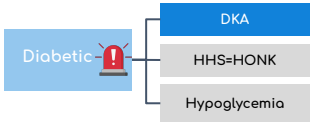
Editing File

Lecture's Outlines:

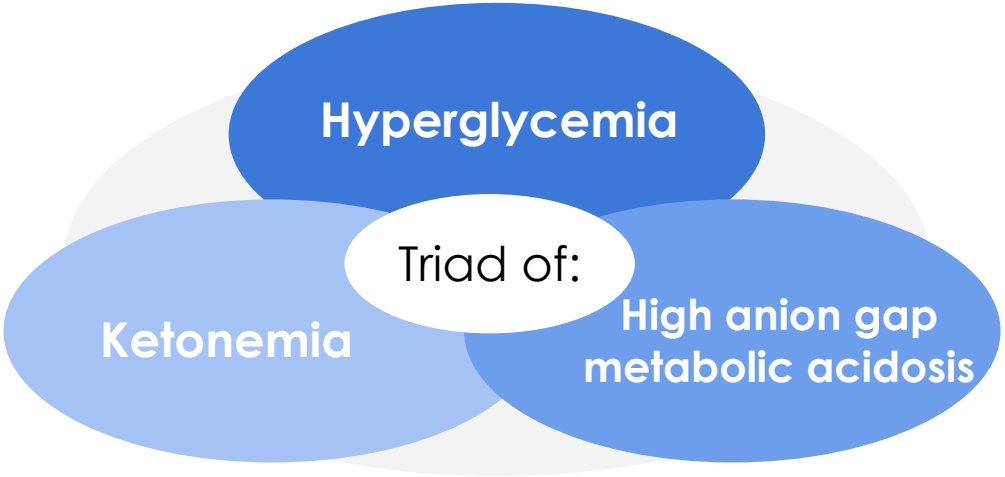
- **Diabetic Complications**
- **Ketone bodies metabolism**
- **DKA:**
  Definition
  Causes and Mechanisms
  Manifestations
  Precipitating Factors
- **Hyperosmolar hyperglycaemic state (HHS) = Hypperosmolar non- - ketotic acidosis (HONK):**
  Definition
  Causes and Mech
  anisms
  Manifestations
- **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

3 Diabetic Emergencies

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



Diabetic Ketoacidosis (DKA)

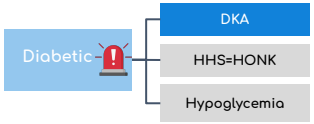


- Characteristically associated with T1 DM
- It has become increasingly common in T2 DM
- DKA may be the first presentation of T1 DM

Ketone Bodies

1. Acetoacetate
2. Acetone
3. β-Hydroxybutyrate

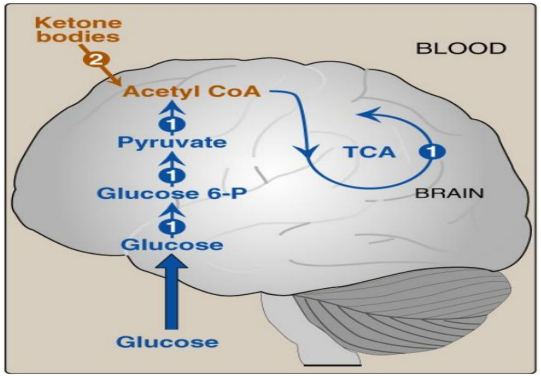
They are produced by the liver (ketogenesis) and utilized for energy production by peripheral tissues (Ketolysis)



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**.

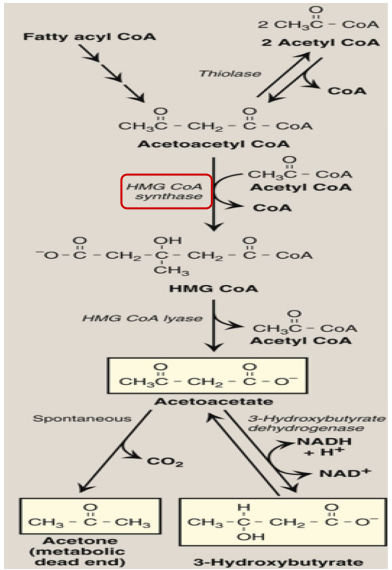
If glucose is not available for the brain, the brain can utilize plasma ketone bodies, that can penetrate the blood brain barrier, and serve as fuel molecules.



Ketone Bodies Synthesis (Ketogenesis)

Occurs in hepatocyte mitochondria

1. In uncontrolled DM there is ↑ lipolysis in adipose tissue
2. ↑ [FFA] mobilization to liver
3. ↑ Hepatic FA oxidation
4. ↑ Acetyl CoA which will be channeled into KB synthesis
5. HMG[1] CoA synthase is the rate limiting enzyme.
6. The first KB to be synthesized is acetoacetate
7. Acetoacetate can be:
   - Reduced to β-Hydroxybutyrate
   - or Spontaneously decarboxylated to acetone



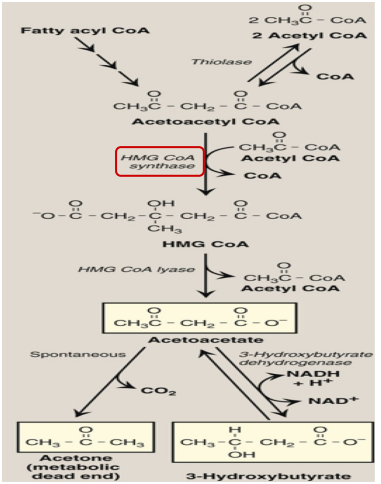
Synthesis of Ketone bodies

1- HMG = hydroxymethylglutaryl CoA

Diabetic
- DKA
- HHS=HONK
- Hypoglycemia

Ketogenesis

1. ↑hepatic FA oxidation →↑ acetyl CoA which will be channeled into KB synthesis
2. Acetyl CoA + oxaloacetate (OAA) → Krebs cycle
3. ↑ Acetyl CoA production activates pyruvate carboxylase
4. Pyruvate carboxylase converts pyruvic acid into OAA
5. OAA is used for gluconeogenesis (rather than Krebs cycle)
6. Acetyl CoA is channeled into KB synthesis

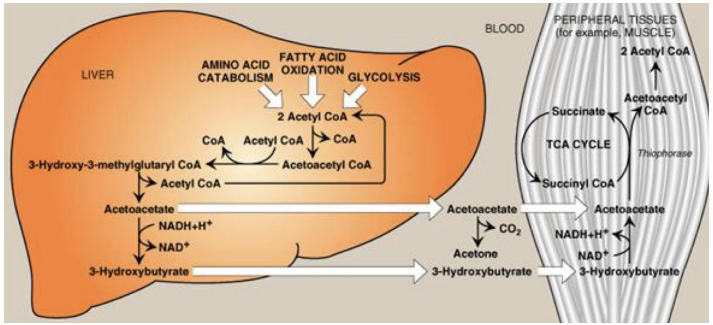


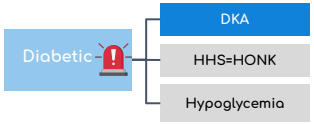
Synthesis of Ketone bodies

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)

1. β-Hydroxybutyrate is oxidized to acetoacetate (by a dehydrogenase)
2. Acetoacetate is converted to acetoacetyl CoA (catalyzed by thiophorase)
3. Acetoacetyl CoA is converted to acetyl CoAs





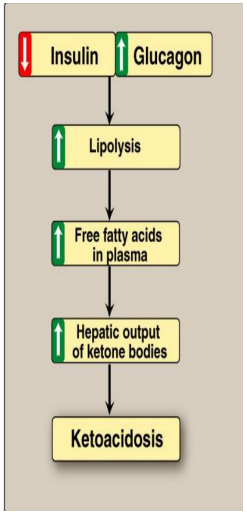
Mechanisms & Manifestations of DKA

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 more than the rate of ketolysis leading to:

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

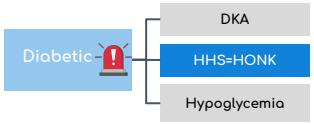


Manifestations of DKA:

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

Precipitating Factors for DKA

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



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

Features

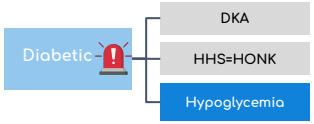
- Little or no accumulation of ketone bodies
- Serum [glucose] is often >50 mmol/L
- Plasma osmolality may reach 380 mosmol/Kg (normal 275-295)

Manifestation

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

Mortality

- 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 hypoglycemics

More common in patients with T1DM[1]

Manifestations are characterized by:

CNS Symptoms (confusion, aberrant behavior, or coma)

Low blood [Glucose]

Symptoms resolved within minutes following the administration of glucose

1- because T1DM is insulin-dependent

Hypoglycemia

Why hypoglycemia is a medical emergency ?

The brain has absolute requirement for a continuous supply of glucose

cerebral dysfunction → **Transient** → **Severe prolonged** → brain death

Hypoglycemia occurs due to impaired protective responses to hypoglycemia:

Insulin is supplied exogenously and its release cannot be turned off

impaired Protective responses

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
- drowziness[1]
- ultimately loss of consciousness or seizures[1]

1. at plasma glucose <1.5 mmol/L

Hypoglycemia

Hormonal mechanisms to prevent or correct hypoglycemia:

Don't skip this picture

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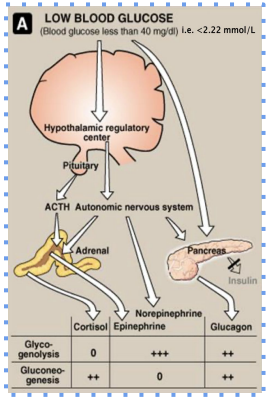
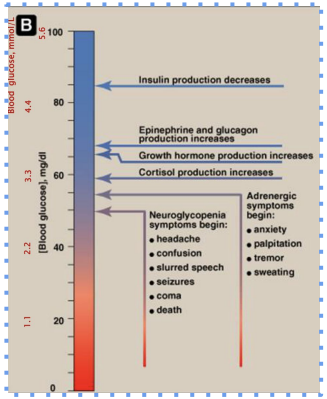


- Production of insulin
- Production of:
  - Epinephrine & glucagon
  - Growth hormone
  - Cortisol

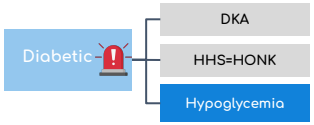


What you have to know from here:

- 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



Hypoglycemia

Case study

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.

Urine results:

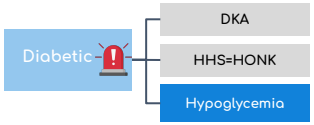
	Result	Normal Range
Glucose	++++	-
Ketoacids	++++	-

Blood results:

The interpretation of the results in the next slide

	Result	Normal Range
Glucose	50	(3.9-5.6 mmol/L)
Ketoacids	++++	(trace)
Bicarbonate	6	(3.5-4.5 mmol/L)
Arterial blood pH	7.07	(7.35-7.45 mmol/L)
Na+	136	(136-146 mmol/L)
Cl-	100	(102-109 mmol/L)
PCO 2	2.7	(4.3-6.0 kPa)
* Anion gap	35.5	(7-16 mmol/L)
K+	5.5	(3.5-5.0 mmol/L)
Urea nitrogen	15	(2.5-7.1 mmol/L)
Creatinine	200	(44-80 mol/L)
Albumin	50	(41-53 g/L)
Osmolality	325	(275-295 mOsm/kg serum water)
Hematocrit	0.500	0.354-0.444

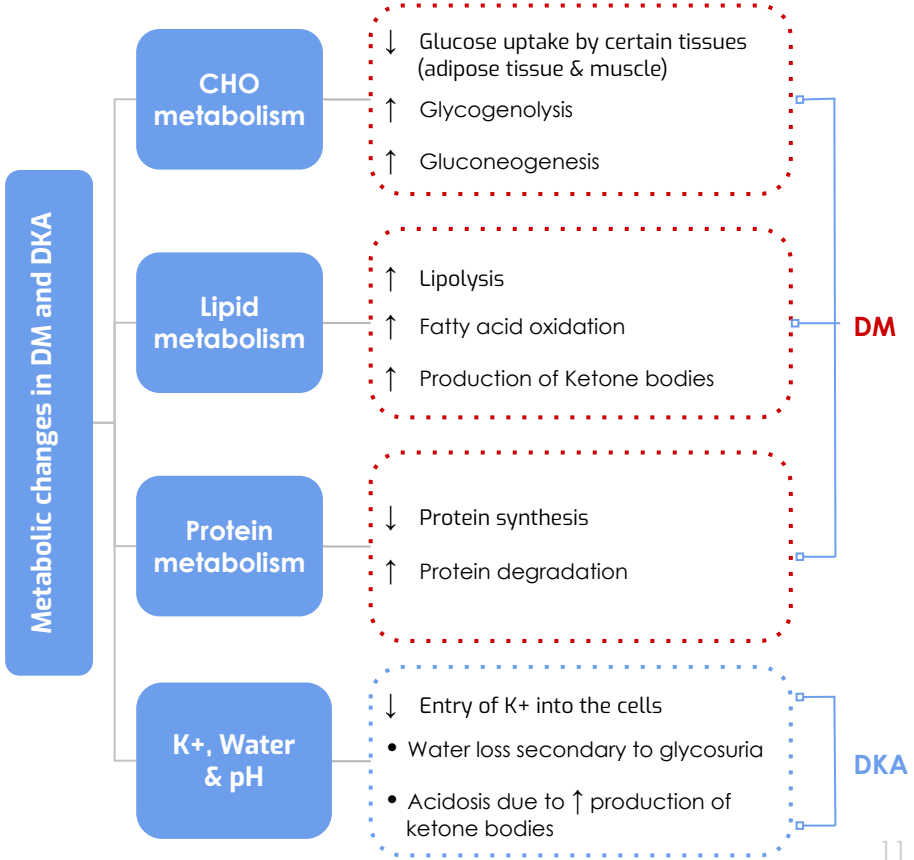
* Anion gap $(A^-) = (Na^+ + K^+) - (HCO_3^- + Cl^-)$



Hypoglycemia

Interpretation of the Laboratory findings

Result	Interpretation
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



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.**

Summary

Diabetic Emergencies

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.

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.

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

Quiz

MCQs :

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

a) Dehydration **b)** Palpitations **c)** Alkalosis **d)** Hypo-osmolar

Q2: Where does the ketogenesis occur ?

a) Extrahepatic tissue **b)** Hepatocyte mitochondria **c)** Cytoplasm **d)** Golgi

Q3: Which one of the following ketone bodies is first to be synthesized in ketogenesis ?

a) Acetyl CoA **b)** Acetone **c)** B-Hydroxybutyrate **d)** Acetoacetate

Q4: Which symptom do you expect to see in diabetic patient when plasma glucose <3.6 mmol/L ?

a) confusion **b)** seizures **c)** sweating **d)** diarrhea

Q5: Which of the following components causes ketonemia in DKA?

a) acetoacetate **b)** glucose **c)** sodium bicarbonate

Q6: Which one of the following is the cause of production of ketone bodies in patient with DKA?

a) ↓ lipolysis in adipose tissue **b)** ↑ hepatic glucose output
c) ↑ hepatic uptake of FFAs **d)** ↑ protein degradation in muscle

SAQs :

Q1: What are the triad of DKA?

Q2: What are the Manifestations of DKA?

Q3: Why hypoglycemia is a medical emergency?

Q4: What is the neuroglycopenia symptoms and at which PG level occurs?

★ **MCQs Answer key:**

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

★ **SAQs Answer key:**

1) Ketonemia , Hyperglycemia,High anion gap metabolic acidosis
2) Fruity odor on the breath (acetone) , acidosis , dehydration
3) The brain has absolute requirement for a continuous supply of glucose otherwise he will loss his function or die
4) Headache, Confusion, drowsiness and loss of consciousness or seizure. Lower than 2.6 mol/L.

Team members

Girls Team:

- Ajeed Al-Rashoud
- Alwateen Albalawi
- Amira AlDakhilallah
- Deema Almaziad
- Ghaliah Alnufaei
- Haifa Alwaily
- Leena Alnassar
- Lama Aldakhil
- Lamiss Alzahrani
- Nouf Alhumaidhi
- Noura Alturki
- Sarah Alkhalife
- Shahd Alsalamah
- Taif Alotaibi

Boys Team:

- Alkassem Binobaid
- Fahad Alsultan
- Fares Aldokhayel
- **Khayyal Alderaan**
- Mashal Abaalkhail
- **Naif Alsolais**
- Omar Alyabis
- Omar Saeed
- Rayyan Almousa
- Yazen Bajeaifer

Team Leaders

Lina Alosaimi

Mohannad Alqarni

★ **We must all suffer one of two things: the pain of discipline or the pain of regret and disappointment**

438 BIOCHEMISTRY TEAM

We hear you