جامعة الملك سعود
King Saud University

Biochemistry437

Lactic Acidosis

Biochemistry Team 437

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Objectives:

- Define metabolic acid-base disorders including lactic acidosis
- Understand the causes and clinical effects of metabolic acidosis and alkalosis
- Recall the lactate metabolism in the body
- Differentiate between the types of lactic acidosis
- Understand the clinical significance of measuring anion gap
- Discuss the causes and diagnosis of lactic acidosis in conditions such as myocardial infarction

Overview

- Introduction to metabolic acid-base disorders
  - Metabolic acidosis and alkalosis
- Lactic acidosis
  - Definition
  - Lactate metabolism in tissue
  - Mechanisms involved in lactic acidosis
  - Types and causes of lactic acidosis
  - Diagnosis and treatment

Introduction and Some Concepts:

- Acid based disorders can be either acidosis or alkalosis
- Acidosis: increase in the acidity of body fluid, decrease in PH
- Alkalosis: increase in the alkaline condition of body fluids, increase in PH
- Acidosis/ alkalosis can be respiratory or metabolic
- Respiratory: depends on the PCO2
- Increase in PCO2 causes respiratory acidosis
- Metabolic: depends on the conc. Of bicarbonate ions [HCO3-]
- The body can compensate for metabolic acidosis by respiratory mechanisms, since both respiration and metabolism have effect on the acidity of body fluids

Metabolic Acid-base Disorders

- Changes in bicarbonate HCO_3 conc. in the extracellular fluid (ECF) cause acid-base disorders
- Occur due to: high concentration or loss of H^+ ions
- Can lead to:
    - Metabolic acidosis
    - Metabolic alkalosis

Remember :

- Respiratory acidosis/ alkalosis : depends on the PCO_2
- Metabolic acidosis/ alkalosis: depends on the conc. Of bicarbonate ions [HCO_3^-]

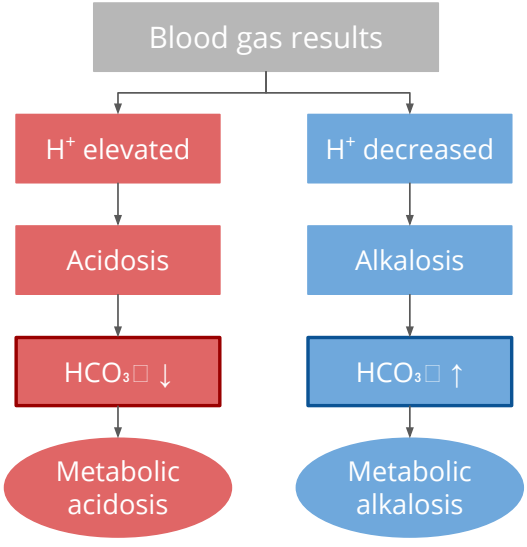
How does diagnosis take place:

- **First, you check the PH of the patient**
  - Lesser than 7.35 [decreased] = acidosis
  - More than 7.45 [increased] = alkalosis
  - Between 7.35 - 7.45 = normal

- **Then, check the PCO2 in blood**
  - If it is increased = respiratory acidosis
  - It it is decreased = respiratory alkalosis
  - If normal = suspect metabolic acidosis and check for bicarbonate conc.

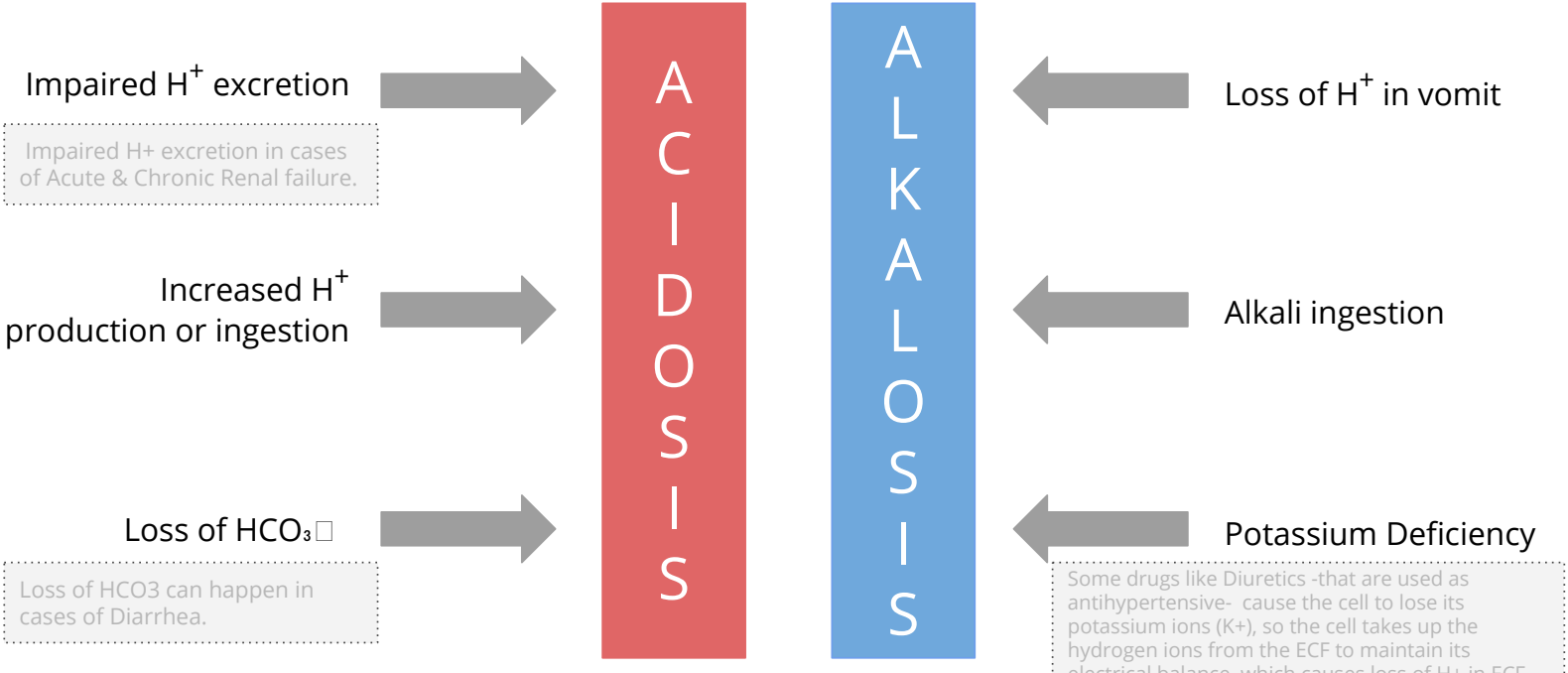
- **Lastly, check the conc. Of bicarbonate**
  - low= metabolic acidosis
  - high = metabolic alkalosis

To assess respiratory acidosis/ alkalosis : check PCO2
To assess metabolic acidosis/ alkalosis: check bicarbonate conc.



Recognizing primary metabolic acid-base disorders by inspecting the HCO_3 concentration.

Reasons for Metabolic Acidosis and Alkalosis



Metabolic Acidosis >11 mEq/L

Reduction in bicarbonate conc. of ECF

Causes are:

Increased production of H^+ ions

Impaired excretion of H^+

Ingestion of H^+ or drugs metabolized to acids

Clinical Effects of Acidosis:

Hyperventilation is the compensatory physiological response to acidosis

- Increased H^+ conc. stimulates respiratory response
- Hyperventilation: deep, rapid, and gasping respiratory pattern (kussmaul breathing)
- Arrhythmia, cardiac arrest
- Loss of consciousness, coma, death

Metabolic Acidosis

Anion Gap

It is the difference between: [cations (+ions) - anions (-ions)]

The sum of Na^+ and K^+ (cations) And The sum of Cl^- and HCO_3^- (anions)

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

Notice that bicarbonate is one of the anions, a change in its concentration affects the anion gap

Function:

- Helps in assessing acid-\base problems
- Normal anion gap: 3-11 mEq/L Milliequivalent per Liter
- High anion gap: >11 mEq/L (acidosis)
- Low anion gap: <3 mEq/L (alkalosis)

the Milliequivalent per Liter is the unit used for measuring anion gap.

High anion gaps occur in:

"Anything affecting bicarbonate conc."

- Renal disease Impaired excretion
- Diabetic ketoacidosis*
- Lactic acidosis
- Chronic diarrhea
- Poisoning

*Diabetic ketoacidosis: When the body cannot use glucose, it will break down the fatty acids in the body producing ketones (ketoacidosis)

Metabolic Alkalosis <3 mEq/L

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Increase in bicarbonate conc. of ECF

Causes are:

Loss of H^+ ions in gastric fluid due to vomiting

Ingestion of sodium bicarbonate

Potassium deficiency as a result of diuretic therapy

Clinical Effects of Alkalosis:

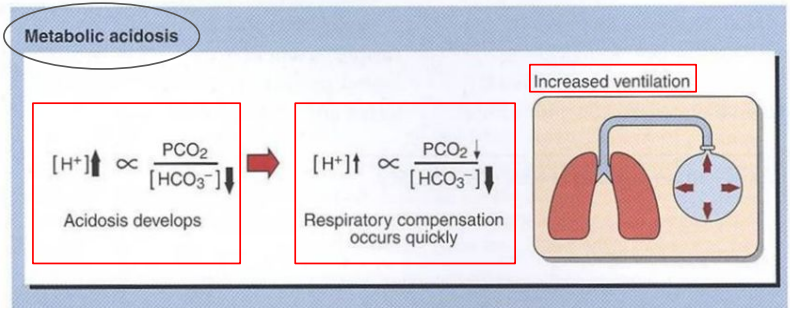
Hypoventilation (depressed breathing)

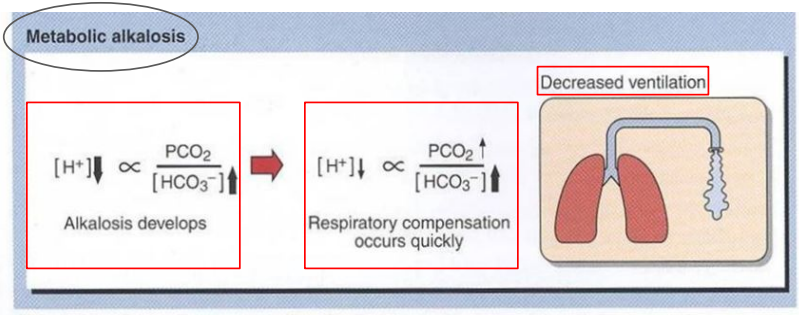
- Increases PCO_2 to compensate alkalosis
- Respiratory arrest (Stop and Cessation of breathing due to failure of lung to function).
- Confusion, coma, death

Table for next slide

	Acidosis	Alkalosis
H+	↑↑	↓↓
PCO2	↓	↑
HCO3	↓↓	↑↑
Ventilation	↓	↑

Concentration of [H+] is directly proportional to PCO2 and inversely proportional to [HCO3-]





- If there was an increase in H+ conc. And a decrease in bicarbonate conc., the person develops metabolic **acidosis**
- To compensate, the body has to either decrease PCO2 " البسط" or increase HCO3 "المقام"
- To decrease PCO2, the person will **hyperventilate**
- We can't control HCO3 so no compensation regarding this molecule

- If there was a decrease in H+ conc. And an increase in bicarbonate conc., the person develops metabolic **alkalosis**
- To compensate, the body has to either increase PCO2 or decrease HCO3
- To increase PCO2, the person will **hypoventilate**
- We can't control HCO3 so no compensation regarding this molecule

Lactic Acidosis

Elevated conc. of plasma lactate is called lactic acidosis.

Occurs either due to:

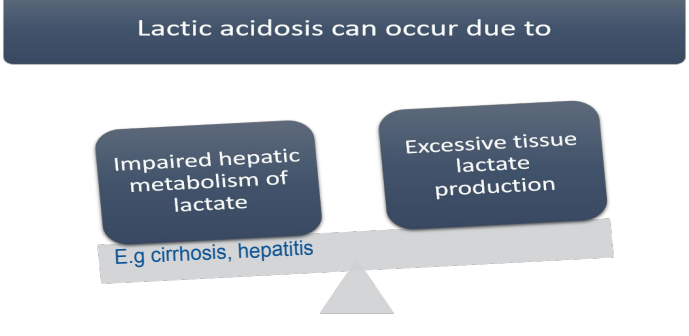
- Failure of circulatory system (hypoxia)
- Disorders of carbohydrate metabolism "the enzyme that converts pyruvate to acetyl CoA is not working, so all pyruvate will be converted to lactic acid, causing hyperlactemia"

- Lactate is the ionised form of lactic acid
- It is produced by **anaerobic glycolysis**, in case of **oxygen deficiency**
- O2 deficiency can result from either a physiological cause like severe exercise or pathological cause like **hypoxia**
- Hypoxia can be caused by a lot of reasons including MI , CO poisoning, HB abnormality
- Lactic acid is cleared in the **liver** by cori cycle
- Lactic acidosis happens when there is an increase in lactic acid conc. (hyperlactemia) Or impaired lactic acid clearance
- Lactate is from unmeasured anions (measured anions are $HCO3^-$ and Cl^-)

→ therefore, it has High anion gap (Explained more at the end of the lecture)

Severe exercise will not cause lactic acidosis, why?
If the liver is healthy then it will be able to clear lactic acid, and if the person continues exercising he will start aerobic glycolysis before the lactic acid conc. Is high enough to cause acidosis

Mechanism Involved in Lactic Acidosis

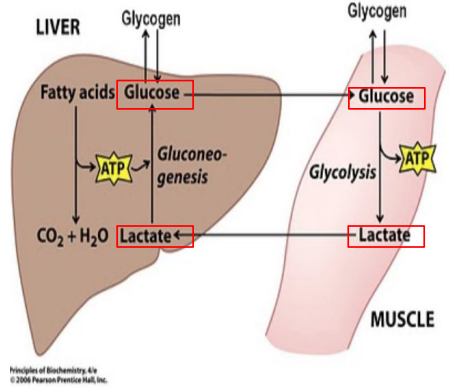


Lactate Metabolism in Tissue

- The body tissues produce ~ 1500 mmoles of lactate each day.
- The lactate enters bloodstream and metabolized mainly by the liver (Cori cycle).
- All tissues can produce lactate under anaerobic conditions.
- Pyruvate is converted to lactate by lactate dehydrogenase enzyme.
  - Pyruvate + NADH + H+ —(lactate dehydrogenase)→ Lactate + NAD+

- The skeletal muscles produce high amounts of lactate during vigorous exercise.
- Lactate is metabolized in liver (60%) and kidney (30%) to glucose.
- Some lactate is metabolized to CO2 and water (Krebs cycle).

- RBCs produce high amount of lactate because it doesn't have mitochondria.



The Cori cycle

Remember:
- NADH is a reducing agent (give e^-)
- NAD is an oxidizing agent (accept e^-)

Types and Causes of Lactic Acidosis

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Type A

- Due to **hypoxia** (due to inadequate supply of oxygen to tissues) (most common)
- Hypoxia causes impaired oxidative phosphorylation and decreased ATP synthesis.
- To survive, the cells switch to anaerobic glycolysis for ATP synthesis
- This produces lactate as a final product
- The amount of oxygen required to recover from oxygen deficiency is called oxygen debt.

Seen in:

- Myocardial infarction
- Pulmonary embolism
- Uncontrolled hemorrhage
- Tissue hypoperfusion (shock, cardiac arrest, acute heart failure, etc.)
- Anaerobic muscular exercise "if other complications are present"

Type B

- Due to disorders in **carbohydrate metabolism**
  - Congenital lactic acidosis is due to deficiency of pyruvate dehydrogenase enzyme
- Chronic hepatic disease accompanied by shock or bleeding
- Liver failure
- Drug intoxication

" e.g. is salicylate -Aspirin- intoxication, death is due to buildup of lactic acid"

Diagnosis and Treatment

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Diagnosis

Diagnosis done by measuring blood lactate levels :

(normal range of lactate in the blood = 1 mmols/L)

Hyperlactemia: 2 – 5 mmols/L

Severe lactic acidosis: > 5 mmols/L

Treatment

- Correcting the underlying conditions
- Restoring adequate tissue oxygen*
- Avoiding sodium bicarbonate**

*because hypoxia is the most common cause of acidosis and it is very urgent.
**because the enzyme PFK - the one responsible for converting pyruvate to lactic acid- is inhibited by low bicarbonate conc. , so if we suddenly increase bicarbonate conc. It will reactivate this enzyme and cause rapid conversion of pyruvate to lactic acid making the acidosis even worse.

This slide is an extra, but it's **important** for you to know why!

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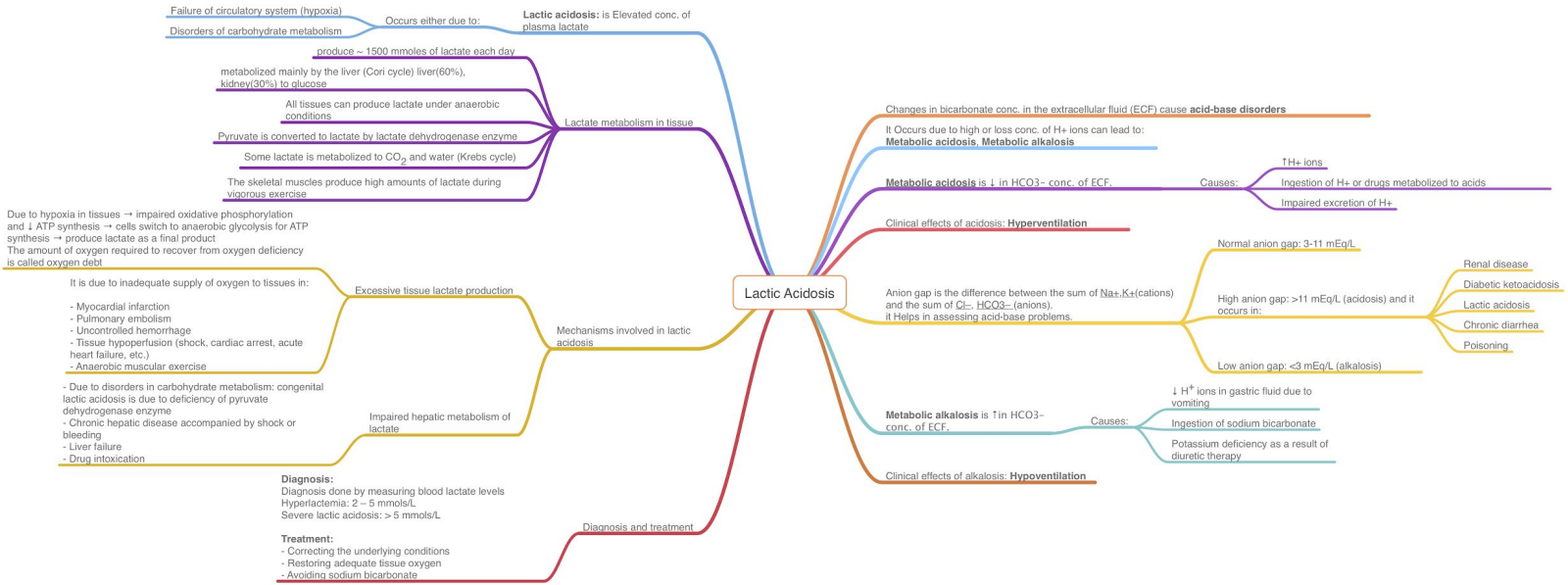
Why does Lactic Acidosis cause high anion gap in Metabolic Acidosis ?

Let's say someone has Acidosis , now we know that in acidosis HCO^-_3 will decrease , but normally our body compensates the loss of HCO3 by increasing Cl (Chlor) absorption to maintain the anion gap , therefore the person will have acidosis but with NORMAL ANION GAP !

Now in case of Lactic Acidosis , there is NO change in HCO3 , therefore the body will not increase Cl absorption to maintain the acidity.

This is why we say Lactate is an **Unmeasured Anion** .. There will be increase in Cations (+) with no compensation (No change) in anions (-) , this will cause a HIGH ANION GAP.

Summary


Lactic Acidosis
Lactic acidosis: is Elevated conc. of plasma lactate
Occurs either due to:
Failure of circulatory system (hypoxia)
Disorders of carbohydrate metabolism
Lactate metabolism in tissue
produce ~ 1500 mmoles of lactate each day
metabolized mainly by the liver (Cori cycle) liver(60%), kidney(30%) to glucose
All tissues can produce lactate under anaerobic conditions
Pyruvate is converted to lactate by lactate dehydrogenase enzyme
Some lactate is metabolized to CO2 and water (Krebs cycle)
The skeletal muscles produce high amounts of lactate during vigorous exercise
Mechanisms involved in lactic acidosis
Excessive tissue lactate production
Due to hypoxia in tissues → impaired oxidative phosphorylation and ↓ ATP synthesis → cells switch to anaerobic glycolysis for ATP synthesis → produce lactate as a final product
The amount of oxygen required to recover from oxygen deficiency is called oxygen debt
It is due to inadequate supply of oxygen to tissues in:
- Myocardial infarction
- Pulmonary embolism
- Uncontrolled hemorrhage
- Tissue hypoperfusion (shock, cardiac arrest, acute heart failure, etc.)
- Anaerobic muscular exercise
Impaired hepatic metabolism of lactate
- Due to disorders in carbohydrate metabolism: congenital lactic acidosis is due to deficiency of pyruvate dehydrogenase enzyme
- Chronic hepatic disease accompanied by shock or bleeding
- Liver failure
- Drug intoxication
Diagnosis and treatment
Diagnosis:
Diagnosis done by measuring blood lactate levels
Hyperlactemia: 2 – 5 mmols/L
Severe lactic acidosis: > 5 mmols/L
Treatment:
- Correcting the underlying conditions
- Restoring adequate tissue oxygen
- Avoiding sodium bicarbonate
Changes in bicarbonate conc. in the extracellular fluid (ECF) cause acid-base disorders
It Occurs due to high or loss conc. of H+ ions can lead to:
Metabolic acidosis, Metabolic alkalosis
Metabolic acidosis is ↓ in HCO3− conc. of ECF.
Causes:
↑H+ ions
Ingestion of H+ or drugs metabolized to acids
Impaired excretion of H+
Clinical effects of acidosis: Hyperventilation
Anion gap is the difference between the sum of Na+,K+(cations) and the sum of Cl−, HCO3− (anions).
it Helps in assessing acid-base problems.
Normal anion gap: 3-11 mEq/L
High anion gap: >11 mEq/L (acidosis) and it occurs in:
Renal disease
Diabetic ketoacidosis
Lactic acidosis
Chronic diarrhea
Poisoning
Low anion gap: <3 mEq/L (alkalosis)
Metabolic alkalosis is ↑in HCO3− conc. of ECF.
Causes:
↓ H+ ions in gastric fluid due to vomiting
Ingestion of sodium bicarbonate
Potassium deficiency as a result of diuretic therapy
Clinical effects of alkalosis: Hypoventilation

Take Home Messages

- Lactic acidosis can be caused by hypoxia, excessive production and impaired clearance of lactic acid.
- It carries clinical significance in the diagnosis of myocardial infarction, pulmonary embolism and other metabolic conditions.

MCQs:

1- Which one of the following will cause metabolic alkalosis?

A- potassium deficiency **B-** loss of bicarbonate **C-** alkali ingestion **D-** both (1,3)

2- A man came to you with chronic diarrhea which one of the following will you expect to see?

A- High anion gap **B-** low anion gap **C-** normal anion gap **D-** hypoventilation

3- Lactic acidosis due to hypoxia in the tissue is enlisted under which type of lactic acidosis?

A- type A **B-** type B **C-** both (1,2) **D-** type C

4- Congenital lactic acidosis is due to the deficiency of…?

A- pyruvate dehydrogenase enzyme **B-** Lactate dehydrogenase **C-** potassium **D-** sodium

5--Which one of the following blood lactate levels will be considered as severe lactic acidosis?

A- 2 – 5 mmol/L **B-** 11 mol/L **C-** 5 mmol/L **D-** 3 mmol/L

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

SAQ

1- What is the mechanism that causes lactic acidosis in case of hypoxia**?**

2- Why RBCs produce high amount of lactate**?**

Answers :

(1) Hypoxia causes impaired oxidative phosphorylation and decreased ATP synthesis to survive, the cells switch to anaerobic glycolysis for ATP synthesis This produces lactate as a final product.

(2) Because it doesn't have mitochondria.

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Team leaders

- رهام الحلبي
- معاذ الحمود

Boys team

- محمد الصويغ
- فيصل الطحان
- طارق العميم
- أنس القحطاني
- صالح الوكيل
- عبد الملك الشرهان
- سعيد القحطاني
- محمد الاصقه
- نواف اللويمي
- عدنان المقبل
- عبدالرحمن التركي

Girls team

- رهف الشنيبر
- شهد الجبرين
- لينا الرحمة
- منيرة المسعد
- ليلى الصّباغ
- العنود المنصور
- أرجوانة العقيل
- ريناد الغريبي
- رزان الزهراني
- ليان المانع
- مشاعل القحطاني
- ريما الديحان

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