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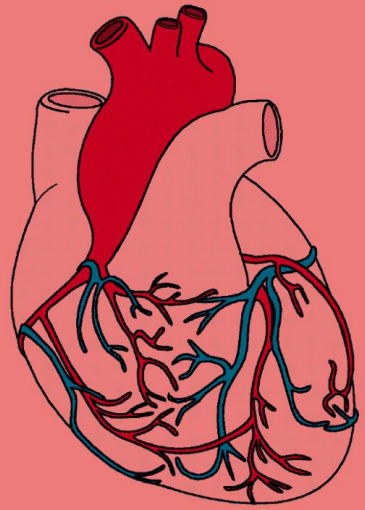
Lactic acidosis



Color index :

Main text

IMPORTANT

Extra Info

Drs Notes

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Cardiovascular Block - Biochemistry Team

MED439

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

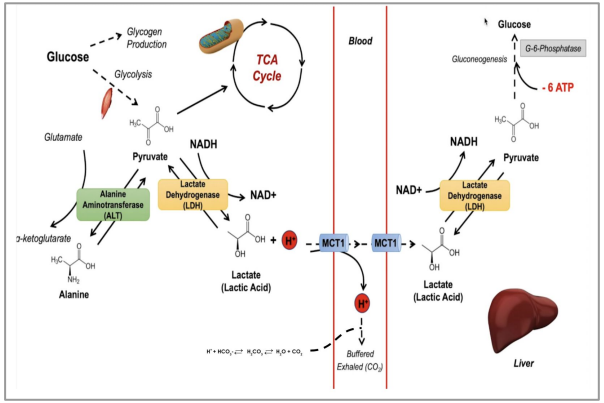
Introduction (important explanations)

Hyperlactemia is when lactate levels in blood exceeds 2mmol/L
When the lactate levels exceeds 5mmol/L, it's called **lactic acidosis**

Occurs when the existence of lactic acid in blood exceeds the excretion of lactic acid, makes sense right?

Glucose can be directed into different pathways. Such as glycogen production or glycolysis. In glycolysis, the end product is **pyruvate**

If you recall in MSK block pyruvate can then be directed into krebs (TCA)cycle , it can be converted to **alanine** by ALT or it can be converted to **lactate** by **lactate dehydrogenase**



To sum it up, the body can deal with lactate in two ways:
1) Buffered and exhaled as CO_2
2) Cori Cycle

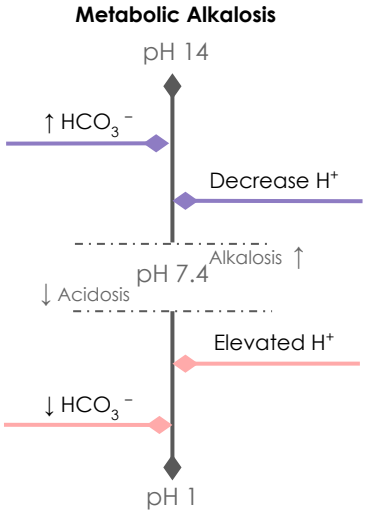
Or can be taken up to the liver to convert it back to pyruvate by the same enzyme **lactate dehydrogenase** where gluconeogenesis takes place (Cori cycle)

Lactic acid will essentially be dumped to the blood as a **buffering system** and get exhaled as CO_2

As we know In anaerobic conditions, the lactic acid pathway is the most likely to occur due to lack of oxygen

Metabolic acid-base disorders

Changes in bicarbonate conc. (HCO_3^-) in the extracellular fluid (ECF)" plasma " cause acid-base disorders.



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

some people have metabolic acidosis but the pH is normal why ? because the body control it completely and this called **full compensate**

↑ **H+** production or ingestion (or drugs metabolized to acids)
e.g lactate production, ketoacidosis

Loss of HCO_3^-
e.g. **Chronic diarrhea** and **renal tubular acidosis**

- Metabolic acidosis : occurs when the body produces too much acid
- Metabolic alkalosis : occurs when the blood becomes overly alkaline

Impaired **H+** excretion
e.g. renal failure

Metabolic Alkalosis

Metabolic Acidosis

Ingestion of sodium bicarbonate(Alkali)
The more salt you eat ($NaHCO_3$) → leads to ↑ HCO_3^- → alkalosis

Loss of **H^+**
e.g. in gastric acid due to **vomiting**

the strongest acid in our body is HCl which is in the stomach so if there's **severe vomiting** the body will lose a lot of H+

Potassium **K^+** deficiency as a result of diuretic therapy

when the body loss K+ (intracellular cation +) the cell become more -ve ,so H+ will move from extracurricular fluid to the cell (inside the cell) to reach equilibrium

↓ H+ Extracellular

↓

alkalosis

★ important slide

A helpful video

Anion gap : physiologically there is no gap, it's only a mathematical tool.

The sum of all cations and anions should be **zero** in normal cases but since it's extremely difficult to measure some of the ions we measure **one major cation or two** and **two major anions** and the difference is called the **anion gap**, because it represents the anions that couldn't be **measured**.

- Anion gap helps in assessing acid-base problems .
- It is the difference between the sum of Cations (+) and Anions (-).

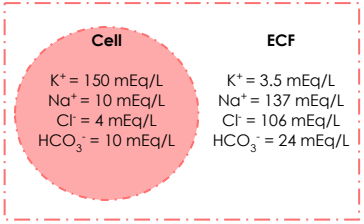
alkalosis	$(Na^+ + K^+) - (Cl^- + HCO_3^-)$	acidosis It can be both (high anion gap/ normal anion gap)
Low anion gap ↓ 3 mEq/L	Normal anion gap 3 -11 mEq/L	High anion gap ↑ 11 mEq/L
due to ↑ HCO_3^- "Associated with alkalosis"	Might be normal in our bodies **or** there's ↓ HCO_3^- but Cl^- will increase to compensate " direct effect on bicarbonate " and that will cause acidosis . metabolic acidosis may happen with **normal anion gap** in people who have **diarrhea** and **Renal tubular acidosis**(1) (more details in the next slide)	due to ↓ HCO_3^- because of the production of lactate that will decrease the conc. of HCO_3^- "Associated with acidosis "

High anion gap occurs in

- Renal disease — Impaired excretion.
- Diabetic ketoacidosis(2)
- Lactic acidosis
- Poisoning — e.g huge amount of aspirin because during its metabolism it makes a lot of lactate and causes lactic acidosis

(1) because diarrhea and Renal tubular acidosis will decrease HCO_3^- so the Cl^- will increase to compensate as result the ratio will be normal (3-11 mEq/L).
(2) Diabetic ketoacidosis: When the body cannot use glucose, it will break down the fatty acids in the body producing ketones (ketoacidosis) , ketones bodies are acids have the same effect of lactate that decrease the conc of HCO_3^- how ? ketone bodies like (3-beta-hydroxybutyrate) It will be degraded into H+ ions as a result the anion gap will be high (more details in the next slide)

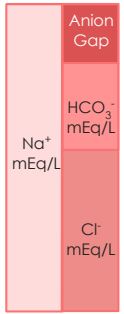
★ important explanation



The numbers just to show you, no need to memorize them

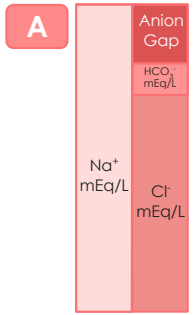
- -The figure on the left can show you the normal distribution of ions inside and outside the cell. When they want to measure the levels of ions, they can only measure the ECF ions. Because it's hard to go inside the cell.
  - Normal **Na^+** level is : **137 mEq/L**
  - Normal **K+** level is : **3.5 mEq/L**
  - Normal level for blood **Cl^-** is : **106 mEq/L**
  - Normal **HCO_3^-** level is: 24 **mEq/L**
- -If we sum the cations (+) and anions (-) : **(137 + 3.5) - (24 + 106) = 10.5 mEq/L or 137- (24 + 106)= 7 mEq/L** which is normal anion gap "as you can see on the right" and it represents the other anions that couldn't be measured.

Note that we can calculate it without K+ because potassium doesn't have a significant effect



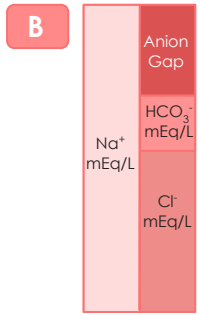
A: HCO_3^- is affected without the presence of other substances :

- excessive loss of HCO_3^- will lead to acidosis. BUT as mentioned before, Cl^- will make up for it thus there is no change in anion gap (**normal anion gap acidosis**) (another name is **hyperchloremic acidosis** which means an increase in the Cl- levels in the plasma but it can maintain a normal anion gap)
- In another word, if there's a decrease in HCO_3^- (without any effect of other substances such as lactic acid, I.e the HCO_3^- get excreted from the body in this form) due to diarrhea and Renal tubular acidosis, as a result the Cl^- will increase to compensate " it's direct effect on bicarbonate" and that will keep the serum electroneutral in **normal anion gap .**
- So Keep in mind that Cl^- can make up for HCO_3^- as long as there is a decrease only in the HCO_3 (without the effect of other substances) .



B: HCO_3^- is affected due to the presence of lactic acid :

- excessive acids (lactate or ketones bodies both of them carry negative charge that affect on the conc. of HCO_3^-) , an increase in anion gap will occur as well as acidosis (**high anion gap acidosis**)
- to make it clear we have to know that lactic acid will lose its hydrogen ion to become lactate and now it carries a negative charge (anion) because it lost its hydrogen ion . H+ ion is free now and it will react with HCO_3^- to form carbonic acid , If you remember "$H + HCO_3^- = H_2CO_3 = H_2O + CO_2$ " (CO_2 exhaled) . Keep in mind that we have a new anion (lactate) and it's unmeasured anion (Cl- and HCO_3- are measured anions). The same concept applied in the ketones bodies because ketones bodies like (3-beta-hydroxybutyrate) will be degraded & it will release H+ ions that react with HCO_3^- as mentioned before , this will result in Diabetic ketoacidosis .
- so high anion gap represents that there're new unmeasured / undetectable "call it whatever you want" anions, that's why lactic acidosis is related to high anion gap.



★ important slide

Clinical effects of alkalosis and acidosis

acidosis

01 Hyperventilation to compensate the acidosis ,deep, rapid, and gasping respiratory pattern

02 Increased H+ conc. stimulates respiratory response so a lot of CO_2 gets washed out and we call it kussmaul respiration[1]

03 Arrhythmia , cardiac arrest

04 Loss of consciousness, coma, death

alkalosis

01 Hypoventilation To increase PCO_2 by keeping CO_2 and decreasing pH to compensate alkalosis

02 Respiratory arrest (Stop and Cessation of breathing due to failure of lung to function).

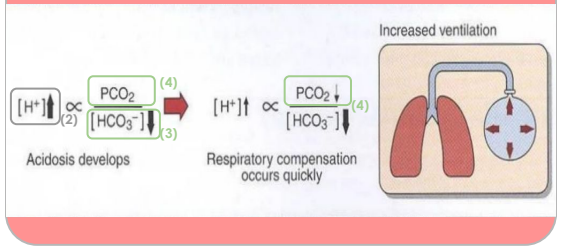
03 Confusion

04 Coma and death

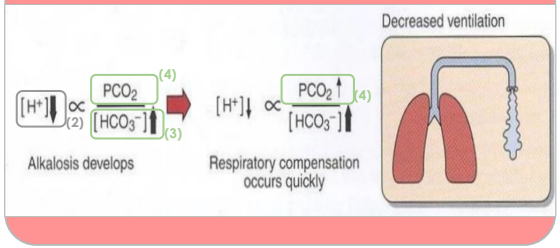
respiratory system is the First and Faster system work to compensate any change in pH or H+ renal system become after it

In case of acidosis If there's ↑ in H+ in the blood the body will compensate by moving K+ from inside the cell to the ECF as a result there will be hyperkalemia and this will lead to neuromuscular irritations or arrhythmia, arrhythmia leads to cardiac arrest → Loss of consciousness → coma or death

Metabolic Acidosis



Metabolic Alkalosis



More explanation about the two pictures

(1) Kussmaul respiration is a deep breathing often associated with severe metabolic acidosis that reduces carbon dioxide in the blood due to increased rate or depth of respiration.
(2)firstly we have to check conc. of H+ to know if it's acidosis or alkalosis (you should know that the concentration of H+ is directly proportional to PCO_2 and inversely proportional to HCO_3^-)
(3) if you see any change in HCO_3^- Conc. You will suspect that it's **metabolic** alkalosis-acidosis. More details in the link
(4) if you see any change in conc. of PCO_2 you will suspect **respiratory** alkalosis-acidosis , if you see normal levels of PCO_2 you will suspect **metabolic** alkalosis-acidosis so you will check the conc. of HCO_3 or H+ to know if it's acidosis or alkalosis

Lactic acidosis

Lactic acidosis happens when there is an increase in lactic acid conc. (hyperlactemia) or impaired lactic acid clearance .
Lactate is unmeasured anion (measured anions are HCO_3^- and Cl^-) → therefore, it has High anion gap.

Lactic acidosis : is elevated conc. of plasma lactate is called lactic acidosis , occurs either due to :

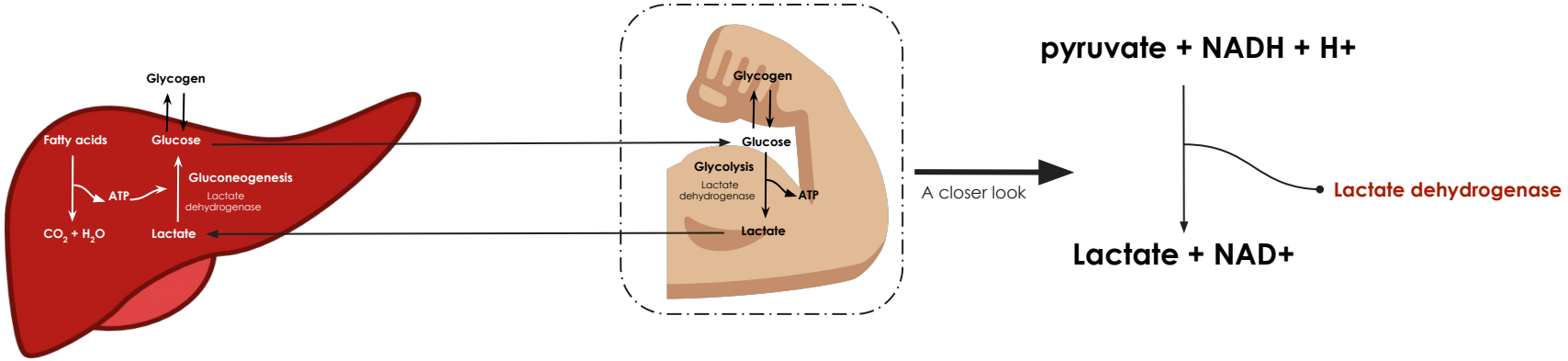
1. Failure of circulatory system (hypoxia) type A

2. Disorders of carbohydrate metabolism type B
   The enzyme that converts pyruvate to acetyl coA is not working so the pyruvate will be converted to lactic acid , causing hyperlactemia

Lactate metabolism in tissue

- The body tissues produce ~ 1500 mmoles of lactate each day .
- All tissues can produce lactate under anaerobic conditions , mainly in the skeletal muscles that produce high amounts of lactate during vigorous exercise .
- Lactate is metabolized in liver (60%) and kidney(30%) to glucose .
  So if there's **hepatic failure** it will cause lactic acidosis since 60% of lactate is metabolized in liver(huge percentage)
- The lactate enters blood stream and metabolized mainly by the liver (Cori cycle) .
- Some lactate is metabolized to CO_2 and water (Krebs Cycle) .
- Lactic acidosis can occur due to:
  - Excessive tissue lactate **production** • Impaired **hepatic** metabolism of lactate

Cori cycle



If you recall in MSK block , we learnt that In anaerobic glycolysis, the glucose is converted to lactate[1] .

1-Lactate synthesized in the muscles by glycolysis . pyruvate (from glucose) is converted to lactate by **lactate dehydrogenase enzyme** then the lactate will be released to the blood (its target is the liver)

2-gluconeogenesis takes place to convert lactate to glucose
3-Glucose is formed and sent back to the muscles to be used for energy again.

4-Lactate produced from white muscle fibers is sent back to liver to establish cori cycle again

(1) In anaerobic metabolism there's no oxygen to accept the electrons from NADH and reoxidizing it to NAD+. so, NADH will accumulate in the cell. the reduction of pyruvate into lactate is mediated by the conversion of NADH ⟶ NAD+ and thus it prevent accumulation of NADH which is a serious problem .

Mechanisms involved in lactic acidosis

type A

Most common

Due to :

inadequate supply of oxygen (**hypoxia**) to tissues in:

- Myocardial infarction.
- Pulmonary embolism.
- Uncontrolled hemorrhage.
- Tissue **hypo**perfusion (shock, cardiac arrest, acute heart failure, etc.)
- Anaerobic muscular exercise[1].

As a result :

- Hypoxia causes : impaired oxidative phosphorylation and decreased ATP synthesis.
- To survive : the cells switch to anaerobic glycolysis for ATP synthesis and This produces lactate as a final product.

Adaptive response

- **oxygen debt** : The amount of oxygen required to recover from oxygen deficiency.

type B[2]

Due to :

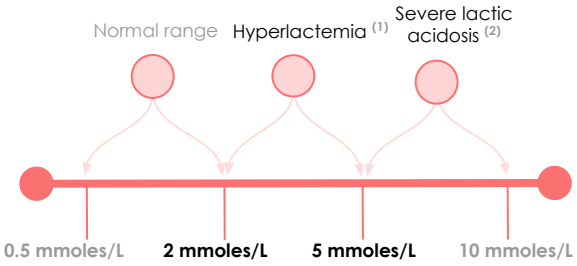
disorders in carbohydrate metabolism: in other word type B is anything that not related to oxygen

- **congenital deficiency** of pyruvate dehydrogenase enzyme.[3]
- Chronic hepatic disease accompanied by shock or bleeding (disturbing cori cycle).
- Liver failure (disturbing cori cycle).
- Drug intoxication is the physical state in which impairment is caused after exposing to some substances e.g methanol and ethanol (alcohol) consumption in big amounts.

(1) 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. rises enough to cause acidosis.
(2) Type B has a lot of causes so it has a lot of subtypes (type B1 , type B2 ..etc).
(3) There are two enzymes work on pyruvate either **pyruvate dehydrogenase** producing AcetylCoA or **lactate dehydrogenase** producing lactate. So, if the pyruvate dehydrogenase enzyme is not present all the pyruvates will be converted into lactate by the other enzyme. (there will be accumulation of lactate)

Diagnosis

- Diagnosis done by measuring blood lactate levels .



Correlation
In case of cardiogenic shock, due to oxygen deprivation of tissues, the body will switch to anaerobic metabolism thus producing more lactic acid and now we know that it gives protons (H+ ions) . Eventually the patient might develop metabolic acidosis and this itself, can have a negative effect on the heart.

Question to you: will this be considered a high or normal anion gap acidosis? 🤔

Treatment

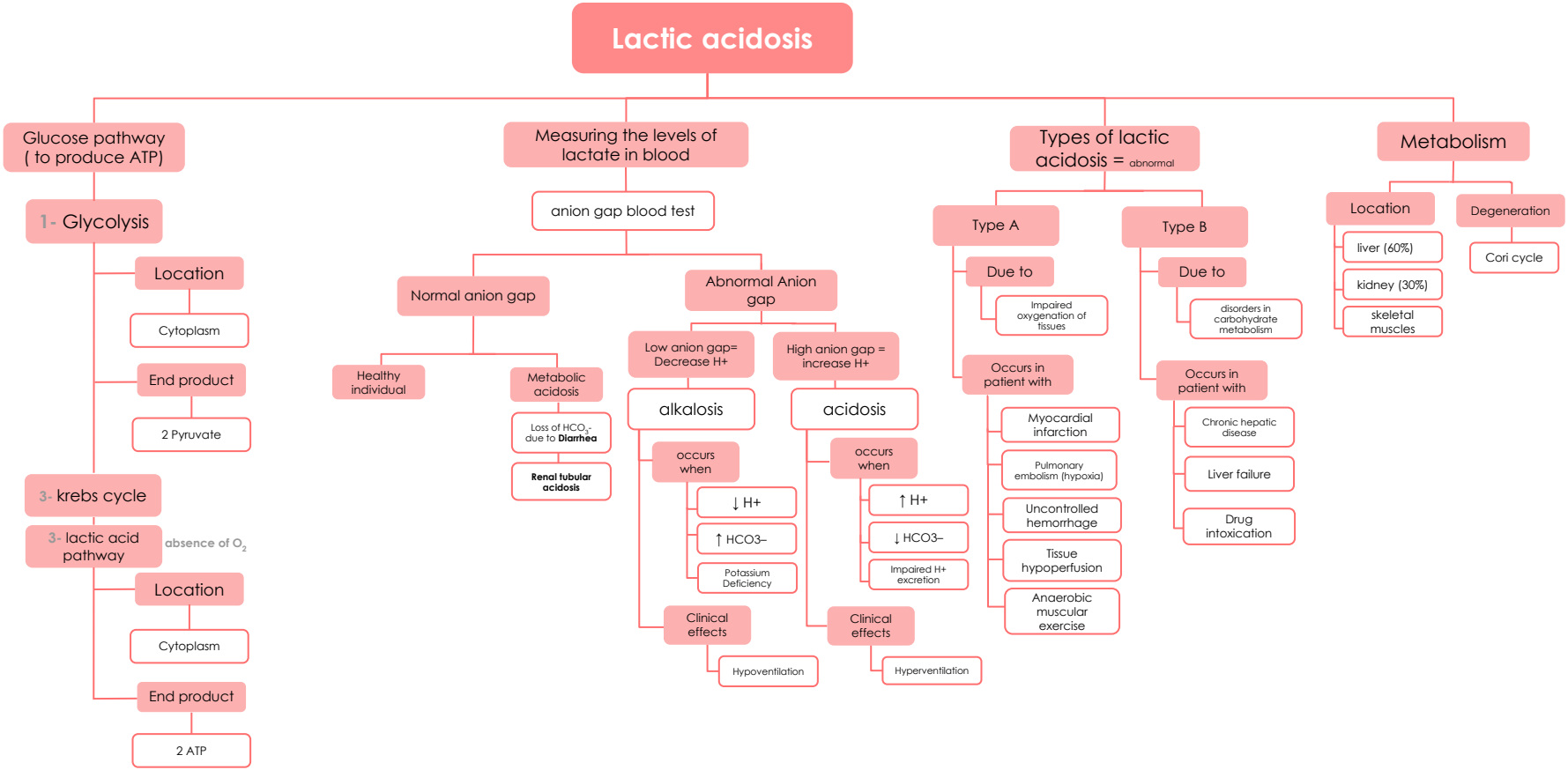
- Correcting the underlying conditions
- Restoring adequate tissue oxygen[3] type A
- Avoiding sodium bicarbonate[4]

(1) Hyperlactemia can be transient or persistent .
(2) Severe lactic acidosis is life threatening and can lead to coma and death.
(3) because hypoxia is the most common cause of acidosis and it is very urgent.
(4) if you recall in foundation block , we learned that Citrate (acid) inhibits Phosphofructokinase-1 (PFK-1) "an important enzyme in glycolysis " if the glycolysis inhibited , the pyruvate and lactate production will be decreased , While treating the patient if you give him sodium bicarbonate($NaHCO_3$) glycolysis will be active and lactic acid production will be increased and may cause lactic acidosis but if the patient has metabolic acidosis because of diabetes or any other causes than lactic acid then you can treat him by sodium bicarbonate

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


Lactic acidosis
Glucose pathway (to produce ATP)
1- Glycolysis
Location
Cytoplasm
End product
2 Pyruvate
3- krebs cycle
3- lactic acid pathway
absence of O2
Location
Cytoplasm
End product
2 ATP
Measuring the levels of lactate in blood
anion gap blood test
Normal anion gap
Healthy individual
Metabolic acidosis
Loss of HCO3- due to Diarrhea
Renal tubular acidosis
Abnormal Anion gap
Low anion gap= Decrease H+
alkalosis
occurs when
↓ H+
↑ HCO3–
Potassium Deficiency
Clinical effects
Hypoventilation
High anion gap = increase H+
acidosis
occurs when
↑ H+
↓ HCO3–
Impaired H+ excretion
Clinical effects
Hyperventilation
Types of lactic acidosis = abnormal
Type A
Due to
Impaired oxygenation of tissues
Occurs in patient with
Myocardial infarction
Pulmonary embolism (hypoxia)
Uncontrolled hemorrhage
Tissue hypoperfusion
Anaerobic muscular exercise
Type B
Due to
disorders in carbohydrate metabolism
Occurs in patient with
Chronic hepatic disease
Liver failure
Drug intoxication
Metabolism
Location
liver (60%)
kidney (30%)
skeletal muscles
Degeneration
Cori cycle

Quiz

Q1 : Which one of the following causes metabolic acidosis ?			
A) Hypoventilation	B) Vomiting	C) Chronic diarrhea	D) High H^+ excretion

Q2 : Potassium K^+ deficiency may lead to ?			
A) Acidosis	B) Increase H^+ in ECF	C) Alkalosis	D) High anion gap

Q3 : person has a metabolic acidosis with normal anion gap we call it :			
A) lactic acidosis	B) hyperchloremic acidosis	C) metabolic alkalosis	D) Diabetic ketoacidosis

Q4 : the amount of oxygen required to recover from oxygen deficiency ?			
A) type B lactic acidosis	B) Cori cycle	C) anion gap	D) oxygen debt

Q5 : The lactate enters blood stream and metabolize mainly by the liver ?			
A) anion gap	B) krebs cycle	C) Cori cycle	D) Lactic acidosis

Q6 : Which typpe of lactic acidosis result from hypoxia ?			
A) type A	B) type B	C) type B1	D)type B2

SAQs :

Q1: List two causes of metabolic alkalosis

Q2: Elevated conc. of plasma lactate (lactic acidosis) Occurs either due to?

Q3: List three conditions cause type A lactic acidosis

Q4: when does metabolic acidosis coexist with normal anion gap?

★ **MCQs Answer key:**

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

★ **SAQs Answer key:**

1) 1-Loss of H+ due to vomiting
   2-Ingestion of sodium bicarbonate (Alkali)
2) 1-failure of circulation system (hypoxia)
   2-Disorders of carbohydrate metabolism
3) 1-Myocardial infarction
   2-Pulmonary embolism
   3-Uncontrolled hemorrhage
4) When the effect is directly on bicarbonate

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Abdullah Alanzan
Abdullah Almazro
Ahmad Alkhayatt
Abdullaziz Alrabiah

If the plan doesn't work , Change the plan but never the **goal**

☆ Special thanks to **Mishal Althunayan** for his efforts

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