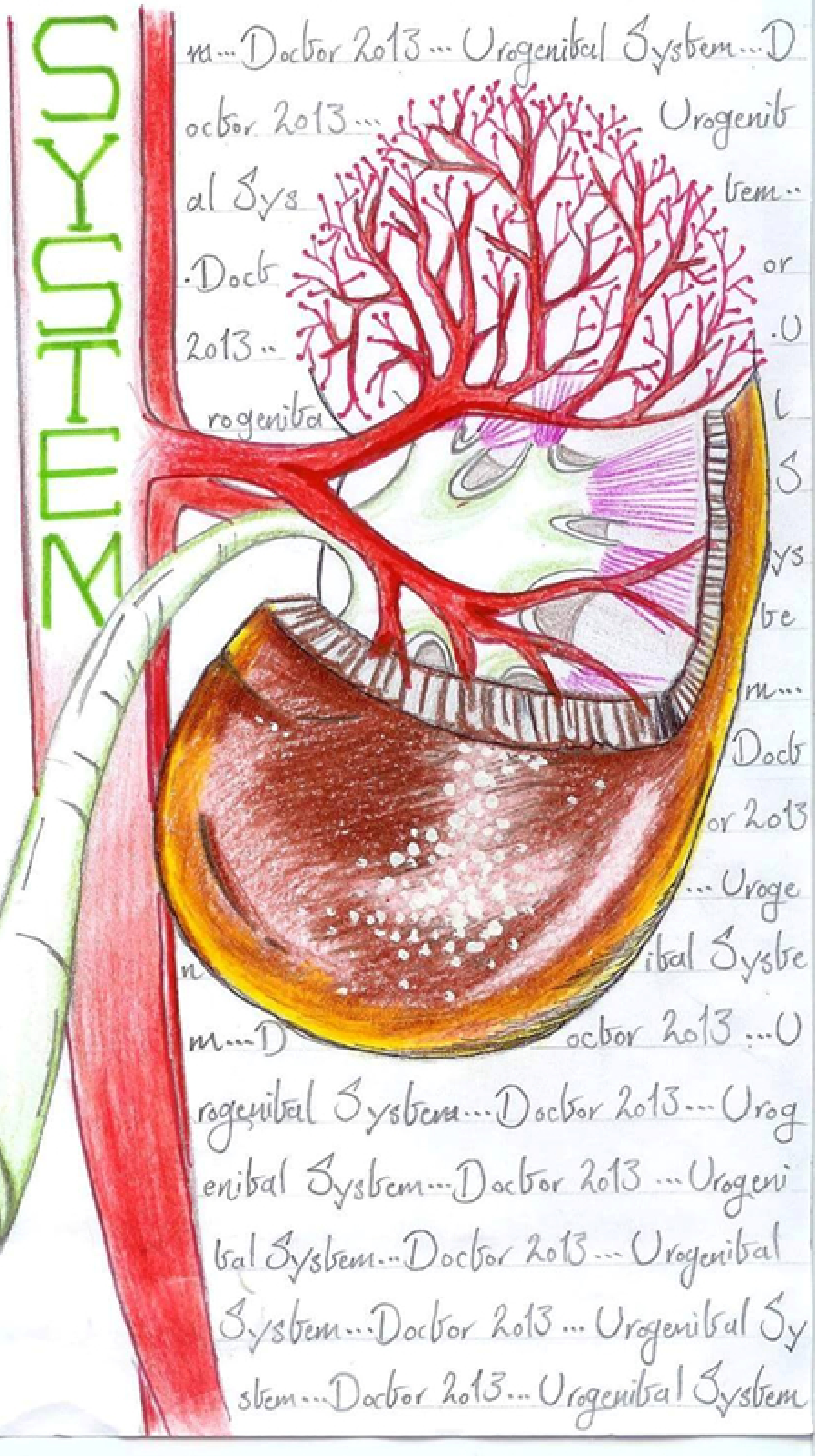
URO-GENITAL SYSTEM

- ○ Handout
- ● Sheet
- ○ Slide

- ○ Anatomy
- ● Physiology
- ○ Pathology
- ○ Biochemistry
- ○ Microbiology
- ○ Pharmacology
- ○ PBL



Done By: **Salam AlKhreasha**

Dr. Name: **Dr. Yanal**

Lec. #: **9**

Drawn By Tariq Bushnaq..

اللهم إني أسألك فهم النبيين و حفظ المرسلين و الملائكة المقربين ، اللهم اجعل ألسنتنا عامرة و قلوبنا بخشيتك و أسرارنا بطاعتك إنك على كل شئ قدير و حسبنا الله و نعم الوكيل .

Role of the kidney in acid –base balance

The doctor said that the slides are enough for this lecture and he put a lot of examples in them, I tried to put everything in the slides mentioned by the doctor. It's your choice to study slides or sheet. "الشيت طويلة بس اغلبها أمثلة"

Let's start ::

The kidneys have big role in maintain acid-base balance, we can summarize this role into 4 points:

I. **Elimination of non-volatile acids (H_2SO_4, H_3PO_4): the kidneys eliminate 80mmol\day of these acids. "Non–volatile acids: acids can't be eliminated by lungs"**
II. **Secretion of H^+**
III. **Reabsorption of HCO_3^-**
IV. **Production of new HCO_3^- " about 80mmol\day "**

In this lecture we will talk mainly about last 2 points.

Reabsorption of HCO_3^-

- HCO3- is very precious: we can't really afford losing any in urine.
- The filtered load of the bicarbonate is equal to

  180L/day * 24mEq/L = 4320 mEq/day . "large number "
- The clearance of HCO_3^- is **negative** because the amount of bicarbonate enter the arteries less than the amount which is found in the veins.

Written by Salam alkhreasha

- The mechanism of reabsorption :

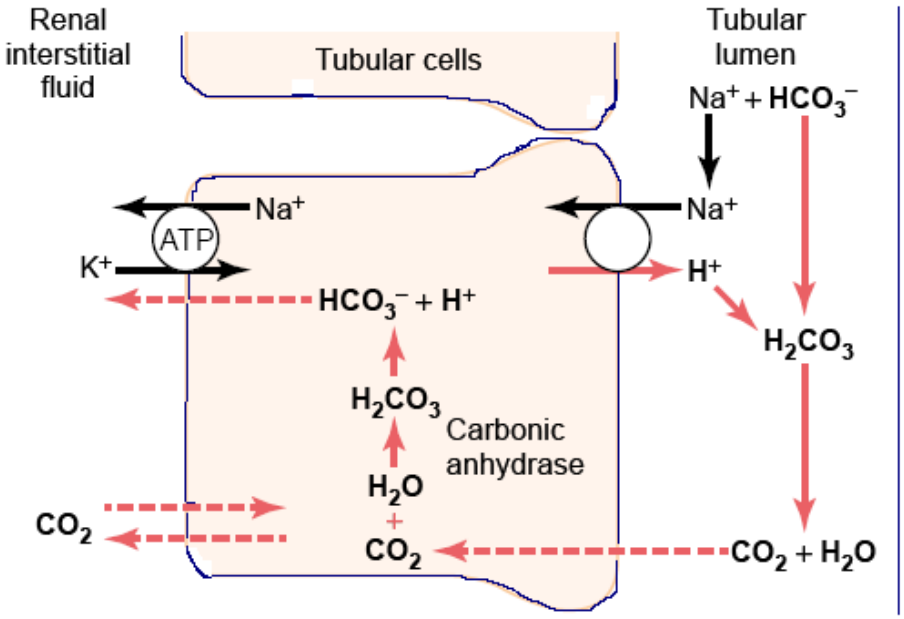


Figure "1"

- **The reabsorption mainly happen in the proximal tubules (mainly 85% of bicarbonate is reabsorbed at this level), thick segment of henle loop, and early distal tubules (15%).**
- **Bicarbonate is a charged molecule that cannot cross the membrane easily "we can't reabsorb it as it is" .**

So how we can reabsorb it, what's the mechanism??

The blood will enter the kidney by renal artery >>segmental arteries >>interlobar arteries >>arcuate arteries >> interlobular arteries >>afferent arterioles >>glomerular capillaries. In the capillaries, bicarbonate is freely filtered into the tubular lumen. In the lumen, the bicarbonate (HCO3-) will react with H+ to form carbonic acid (H2CO3). The carbonic acid will dissociate into CO_2 + H_2O. CO_2 moves freely cross the membranes; so it will move from the lumen to the tubular cells. In the tubular cell, CO2 will react with H_2O under the effect of carbonic anhydrase to form again carbonic acid. Carbonic acid will dissociate again and form H+ and HCO_3^-. So, source of H+ is from tubular cells that will, later, undergo active exchange with Na+.

FINALLY bicarbonate will cross the basolateral membrane toward the interstitial fluid to be reabsorbed. (Please look to the figure "1" to make sure you understand the mechanism)

** Note: in this process there is no net secretion of H+ ,ONE single H+ can reabsorb all the filtered bicarbonate**; 4320 molecules of bicarbonate can be reabsorbed by only one proton (H^+).**

(H+ recycle again and again).

Net secretion of H+

- After complete HCO3- reabsorption: any further H^+ secretion is net secretion resulting in:

- HCO3- gain

- Shift of TF pH below 7.4

Production of new HCO_3^-

Every day the kidneys produce 80mMol of bicarbonate, why ????

Because bicarbonate is a very important anion in the body that is needed for eliminating the non-volatile acids (or fixed acid) from the blood and excreting them into the urine.

Bicarbonate is produced by 2 ways:

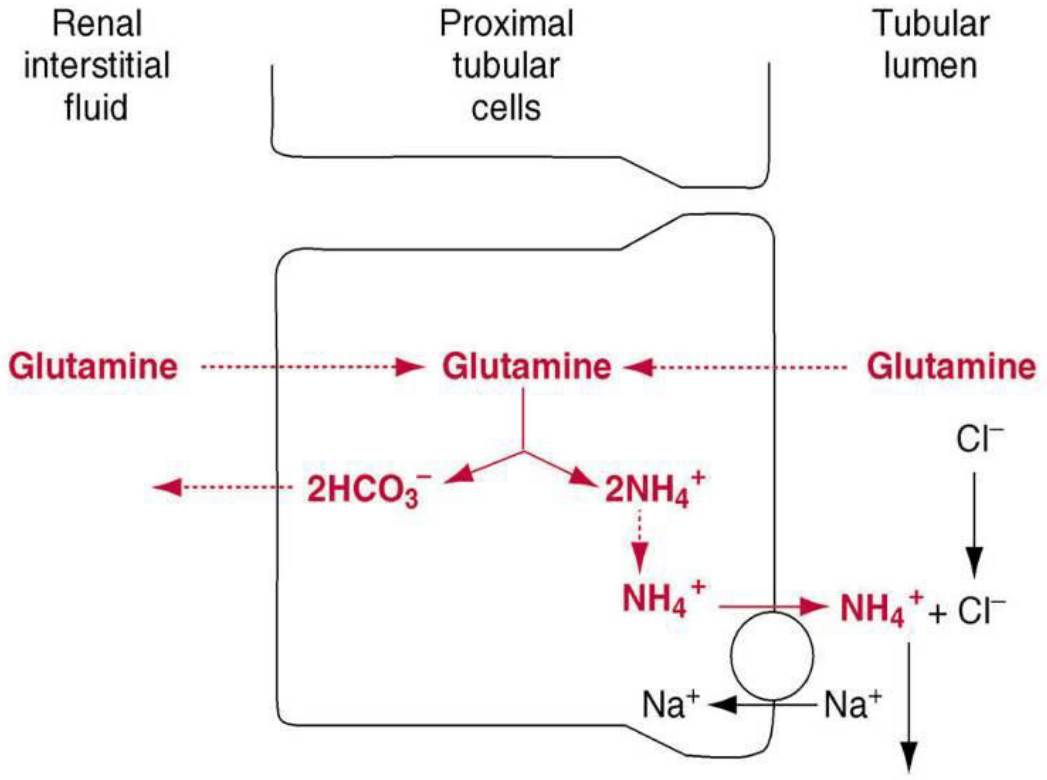
1) TF buffers "titratable acid":
   The presence of TF buffers allows us to secrete H+ (net secretion) and make new HCO_3^-: Main TF buffers are phosphate $HPO_4^=$ which binds to H^+ to form $H_2PO_4^-$. (This process is more clarified in page 6)

بس هون في مشكله , والمشكلة أأأأأنه :

Do we have 80 mMole of phosphate to be excreted in the urine? If yes, then we can gain 80 mMole/D of HCO_3^- by buffers only → → The problem is solved!!!Unfortunately, we excrete only 20-30 mMole of phosphate. So, we cannot get rid of this through urine.

We still need additional 50-60 mMole of new HCO_3^- through other source→ By ammonium production

2) ammonium production :



As we said before, the major production of bicarbonate is through ammonium production. How does this happen?

Glutamine from blood enters the proximal cells where it is converted to glutamate by the enzyme glutaminase (an enzyme that is activated by low PTH). Glutamine will form $2NH_4^+ + 2HCO_3^-$ ....

$$NH_4^+ + CL^- \longrightarrow NH_4CL$$

NH4Cl is Excreted by the urine

*If we have 25mMol of glutamine it will give 50mMol of bicarbonate .

* **This method it's not limited as the previous one because the kidney can produce up to 500mMol ammonium per day. But it takes 5 days to give us full response.**

Q: How can we measure the HCO_3^- gain\day ??

HCO3- added /day = NH4Cl excretion + titratable acids - HCO3-

1) We take urine sample, [Normally the PH of the urine is 5.5], then we add OH^- to the urine until we get urine with PH= 7.4.

 # if we add 30mMol of OH^- which means that we titrated 30mMol of titratable acid.

2) Then we take serum sample and measure the NH4CL concentration in it. (around 50 mMol)

Then we sum these two result to get the HCO_3^- gain\day .

TO SUM UP ::

1)Total H^+ secretion = 4400 mmol/day

= HCO_3^- reabsorption (4320 mmol/d)

+ titratable acid ($NaHPO_4^-$) (30 mmol/d)

+ NH_4^+ excretion (50 mmol/d)

2)Net H^+ excretion = 79 mmol/day

= titratable acid (30 mmol/d)

+ NH_4^+ excretion (50 mmol/d)

- HCO_3^- excretion (1 mmol/d)

** we subtract here because in each time we have bicarbonate in the urine , we have hydrogen ion added to the blood so the net H+ excretion will decrease .

Clinical note :

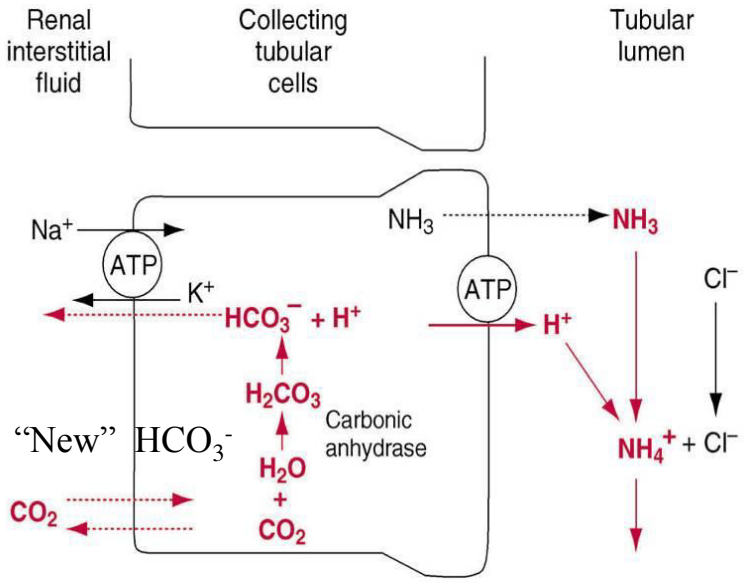
We have 1000mMol buffers in our bodies in the form of protein, bicarbonate, and phosphate. The kidney can produce 500 mMol of ammonium, so whatever food we eat or exercise we do, we shouldn't develop acidosis. If someone develops acidosis, then it will be due to 2 reasons:

1) The patient didn't give his kidney time to get rid of these acids.

2) The production of the acids in the patient body is very high .

Last thing we will talk about in the production of bicarbonate is the role of ammonia and buffers in producing bicarbonate:

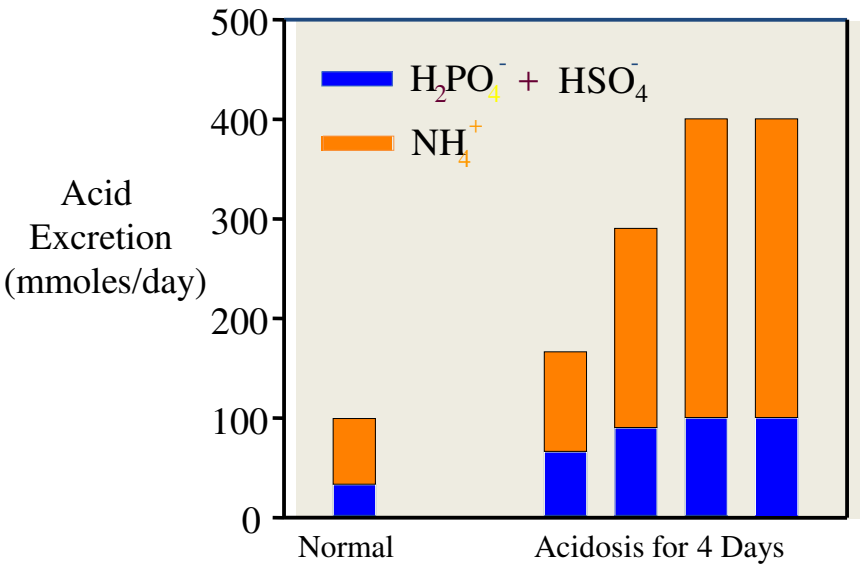
Buffering of hydrogen ion secretion by ammonia (NH_3) in the collecting tubules.



Ammonia will go from the cells to lumen and react with H+ "secreted" to form ammonium (a charged molecule that will be trapped in the tubular fluid) and produce a new bicarbonate. This happens in the presence of a buffer or else this process will not occur.

Written by Salam alkhreasha

Phosphate and Ammonium Buffering In Chronic Acidosis



As we see in normal person, the concentration of phosphate is 1.25 .

In patients with acidosis, the phosphate will increase slightly, but the ammonium will increase a lot.

The kidney tries to correct acidosis by producing more ammonium.

Acid –base disorders

First of all let's refresh our minds by this equation:

PH= PK + Log[kidney]\[lung]

=PK +Log[HCO_3^-]\[CO_2]

=PK +Log 24\1.2

=PK + Log 20 ⟶

= PK +1.3

If this ration become 10 the result will be 1 and the patient will be diagnosed with acidosis

If this ration become 30 the result will be 1.5 and the patient will be diagnosed with alkalosis

SO:

Acidosis

A condition in which the blood has too much acid CO_2" (or too little base HCO_3"), resulting in a decrease in blood pH (< 7.35)

Alkalosis

A condition in which the blood has too much base "HCO_3" (or too little acid"CO_2"), resulting in an increase in blood pH (> 7.45)

Classification of Acid-Base Disorders

Acidosis:

1)Metabolic acidosis "keto-acidosis" :
The PH and bicarbonate is low "same direction". The body will compensate for this change through the respiratory system. The excess CO_2 will be decreased by hyperventilating to get rid of the excess CO2 in the body.
This is called **Metabolic acidosis and respiratory compensation.**
*It is very important to note that if there is dysfunction in the respiratory system, then it will not be able to compensate for this acid-base disturbance.
(NOTE: compensation could be partial or no compensation at all)

Causes of Metabolic acidosis:
a) increase production of acids in the body "in Diabetes Mellitus"
b) ingestion of too much acid "ingesting too much aspirin"
c) lose bicarbonate by diarrhea or deep vomiting
d) renal tubular acidosis

**How can we know the exact cause of metabolic acidosis ???

We can use the anion gap which is a great diagnostic tool for metabolic acidosis.

Anion gap:

The difference between [Na^+] (cation) and the sum of [$HC0_3^-$] and [Cl^-] (anion) .

Anion Gap as a Diagnostic Tool

In body fluids: total cations = total anions

$Na^+ = Cl^- + HCO_3^- +$ unmeasured anions

unmeasured anions = $Na^+ - Cl^- - HCO_3^-$ = anion gap

$= 142 - 108 - 24 \quad = 10$ mEq/L

Normal anion gap = 8 - 16 mEq / L

**Patients with keto-acidosis will lose all bicarbonates in their body, so we expect the anion gap to increase.

**Patients with diarrhea, Na+ and HCO3- will decrease, so the anion gap is normal.

*The doctor only read these slides:

Use of "Anion Gap" as a Diagnostic Tool for Metabolic Acidosis

Increased Anion Gap (normal Cl^-)

- diabetes mellitus (ketoacidosis)
- lactic acidosis
- aspirin (acetysalicylic acid) poisoning
- methanol poisoning
- starvation

Normal Anion Gap (increased Cl^-, hyperchloremia)

- diarrhea
- renal tubular acidosis
- Addison' disease
- carbonic anhydrase inhibitors

The most common causes of increased Anion Gap in Metabolic Acidosis

- Salicylates raise the gap to 20.
- Renal failure raises gap to 25.
- Diabetic ketoacidosis raises the gap to 35-40.
- Lactic acidosis raises the gap to > 50.
- Largest gaps are caused by ketoacidosis and lactic acidosis.

M Suliman: 2009

Examples:

We will look at some examples now. We should be able to diagnose the type of acid-base disturbance in each case, but for us to do that, we need to know the normal set of values:

pH = 7.35-7.45 // PCO2= 40 mmHg // $[HCO3^-]_{plasma}$ = 24 mM/L

Laboratory values for an uncontrolled diabetic patient include the following:

Arterial pH = 7.25 >>>> low

Plasma HCO_3^- = 12 >>>> low

Plasma PCO_2 = 28 >>> low

Plasma Cl^- = 102

Plasma Na^+ = 142

What type of acid-base disorder does this patient have?

Metabolic Acidosis with Respiratory Compensation

What is his anion gap ?

Anion gap = 142 - 102 -12 = 28 >>> high

Answer :::

A. diarrhea

B. diabetes mellitus

C. Renal tubular acidosis

D. primary aldosteronism

2) Respiratory acidosis: the PH is low, but the CO2 is high "opposite direction", normally if we give the kidney enough time it will compensate by increase of the bicarbonate.

Happens mainly to patients with problems in respiratory system like:

- CNS Damage to the respiratory Center. Trauma and tumors.
- pneumonia
- emphysema

Problem in Gas exchange:

↓ Ability of the lung to eliminate CO_2, lack of lung tissue, airway obstruction ↓surface area.

- Respiratory muscles: phrenic paralysis, diaphragmatic fatigue

- other lung disorders

Because they can't wash CO2 out so it will accumulate in their bodies and cause acidosis.

Alkalosis:

1)Metabolic alkalosis:
the PH and bicarbonate is high "same direction", if CO2 increase so there is compensation, if not then there is no compensation.

Causes of Metabolic alkalosis:

1. Diuretics with the exception of Carbonic Anhydrase inhibitors: ↑ flow → ↑ Na+ reabsorption → ↑ H+ secretion.

**Note : C.A inhibitors in proximal tubules "like acetazolamide" >>> causes metabolic acidosis

2. ↑ aldosterone.

3. Vomiting of gastric content only (Pyloric stenosis): Loss of gastric acid

4. Administration of $NaHCO_3$

2) Respiratory alkalosis: the PH is high but the CO2 is low "opposite direction", normally if we give the kidney enough time it will compensate by decreasing the bicarbonate plasma levels through excretion via urine.

Causes of Respiratory alkalosis:
- hysterical hyperventilation >> wash out a lot of CO2
- high altitude

In these 2 conditions, the lungs will wash out a lot of CO2, so the kidneys will respond by washing out the bicarbonate anions in the urine >> in order to get PH compatible with life .

Written by Salam alkhreasha

Take home messages:

Acidosis is more common than alkalosis.

Metabolic disturbances is more common than respiratory disturbances.

Metabolic acidosis is the most common disturbance.

The most common cause of metabolic acidosis is diarrhea " which is characterized by loss of bicarbonate" .

TO SUM UP:

Classification of Acid-Base Disturbances

	Plasma			
Disturbance	pH	HCO_3^-	pCO_2	Compensation
metabolic acidosis	↓	↓	↓	↑ ventilation ↑ renal HCO_3 production
respiratory acidosis	↓	↑	↑	↑ renal HCO_3 production
metabolic alkalosis	↑	↑	↑	↓ ventilation ↑ renal HCO_3 excretion
respiratory alkalosis	↑	↓	↓	↑ renal HCO_3 excretion

Written by Salam alkhreasha

Renal Compensations for Acid-Base Disorders

- Acidosis:
  - increased H^+ secretion
  - increased HCO_3^- reabsorption
  - production of new HCO_3^-
- Alkalosis:
  - decreased H^+ secretion
  - decreased HCO_3^- reabsorption
  - loss of HCO_3^- in urine

NOW:

What's the mechanism of renal compensation in respiratory or metabolic acidosis and respiratory or metabolic alkalosis ??

Renal Responses to Respiratory Acidosis

$H_2O + CO_2 \longleftrightarrow H_2CO_3 \longleftrightarrow H^+ + HCO_3^-$

Respiratory acidosis : ↓ pH ↑ PCO_2 ↑ HCO_3^-

↑ PCO_2 → ↑ H^+ secretion → complete HCO_3^- reabs. + excess tubular H^+

↓ pH → Buffers (NH_4^+, $NaHPO_4^-$) → ↑ H^+ Buffers$^-$ + new HCO_3^-

↑ pH ⊖

Renal Responses to Metabolic Acidosis

Metabolic acidosis : ↓ pH ↓ pCO_2 ↓ HCO_3^-

↓ HCO_3^- → ↓ HCO_3^- filtration → complete HCO_3^- reabs. + excess tubular H^+

↓ pH → Buffers (NH_4^+, $NaHPO_4$-) → ↑ H^+ Buffers + ↑ new HCO_3^-

⊖ (pH)

Renal Responses to Respiratory Alkalosis

Respiratory alkalosis : ↑ pH ↓ pCO_2 ↓ HCO_3^-

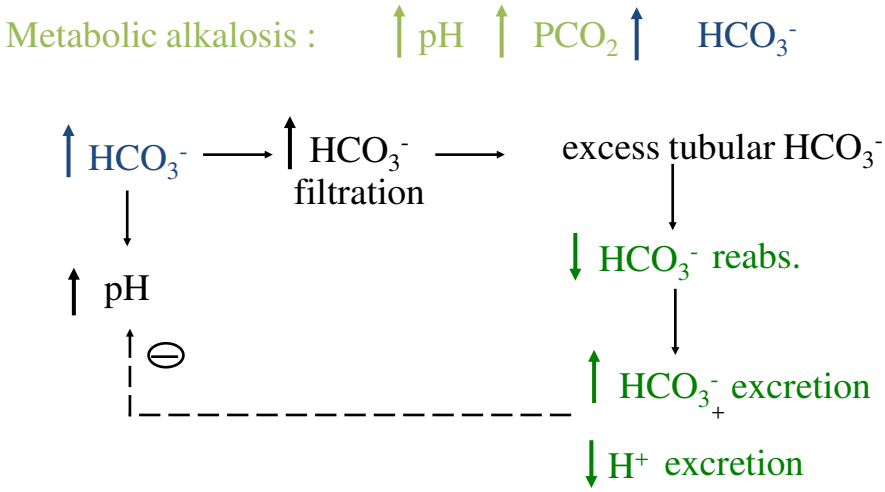
↓ PCO_2 → ↓ H^+ secretion → ↓ HCO_3^- reabs. + excess tubular HCO_3^-

↑ pH → ↑ HCO_3^- excretion + ↓ H^+ excretion

⊖ (pH)

Written by Salam alkhreasha

Renal Responses to Metabolic Alkalosis



Mixed disorder:

"metabolic + respiratory disturbances " both together.

If we have a patient with metabolic acidosis with respiratory compensation, For every ↓ 1 mEq HCO3- → 1.2 mm Hg PCO2 ↓ too. If the PCO2 decreases more than 1.2 mmHg, then the patient will develop respiratory alkalosis. This case is mixed disorder. If the PCO2 decreases less than 1.2 mmHg this means that there is no compensation.

if PCO2 ↓ more than expected→ superimposed R. alkalosis too.

if PCO2 ↓ less than expected→ superimposed R. acidosis too.

if PCO2 ↑ more than expected→ superimposed R. acidosis too.

if PCO2 ↑ less than expected→ superimposed R. alkalosis too.

if HCO3 ↑ more than expected→ superimposed M. alkalosis too.

if HCO3 ↑ less than expected→ superimposed M. acidosis too.

if HCO3 ↓ more than expected→ superimposed M. acidosis too.

if HCO3 ↓ less than expected→ superimposed M. alkalosis too.

Written by Salam alkhreasha

Important question:

In metabolic alkalosis: For every 1 mEq↑ in HCO3-→ 0.7 mmHg ↑ in PCO2

The question is why the compensation here is 0.7 rather than 1.2 ??

The answer is: acidosis induce hyperventilation while alkalosis induce hypoventilation. With hypoventilation, a low PO2 in the body will induce hyperventilation counteracting the hypoventilation effects initially present.

Note: In respiratory acidosis and alkalosis, the kidney takes a long time to compensate, so in:

Acute respiratory acidosis>> For every 10 mmHg ↑ in PCO2 → 1 mEq ↑ in HCO3- .

Chronic respiratory acidosis >> For every 10 mmHg ↑ in PCO2 →3.5 mEq↑ in HCO3-.

Acute respiratory alkalosis >> For every 10 mmHg ↓ PCO2 → 2 mEq ↓ HCO3-

Chronic respiratory alkalosis >> For every 10 mmHg ↓ PCO2 → 5 mEq ↓ HCO3-

Questions ::

1) The following data were taken from a patient:

urine volume = 1.0 liter/day
urine HCO_3^- concentration = 2 mmol/liter
urine NH_4^+ concentration = 15 mmol/liter
urine titratable acid = 10 mmol/liter

- What is the daily net acid excretion in this patient ?
- What is the daily net rate of HCO_3^- addition to the
- extracellular fluids ?

Answer: The following data were taken from a patient:

urine volume = 1.0 liter/day

urine HCO_3^- concentration = 2 mmol/liter

urine NH_4^+ concentration = 15 mmol/liter

urine titratable acid = 10 mmol/liter

net acid excretion = Titr. Acid + NH_4^+ excret - HCO_3^-

= (10 x 1) + (15 x 1) - (1 x 2)

= 23 mmol/day

net rate of HCO_3^- addition to body =23mmol\day

---

2)A plasma sample revealed the following values

in a patient:

pH = 7.12 >> low

PCO_2 = 50 >> high "normal 40"

HCO_3^- = 18 >> low "normal 24"

diagnose this patient's acid-base status:

acidotic or alkalotic ? acidotic

respiratory, metabolic, or both ? both

Mixed acidosis: metabolic and respiratory acidosis

Thank you

Dedicated to : Tasneem abuyameen , esraa odah , ghiada khreasat ,ghiada alnajdawi, , "2013 دكتورات" , and special thank to "HAMDI " .

وكل عام وانتو بخير أخر محاضرة للدكتور ينال .