Clinical biochemistry

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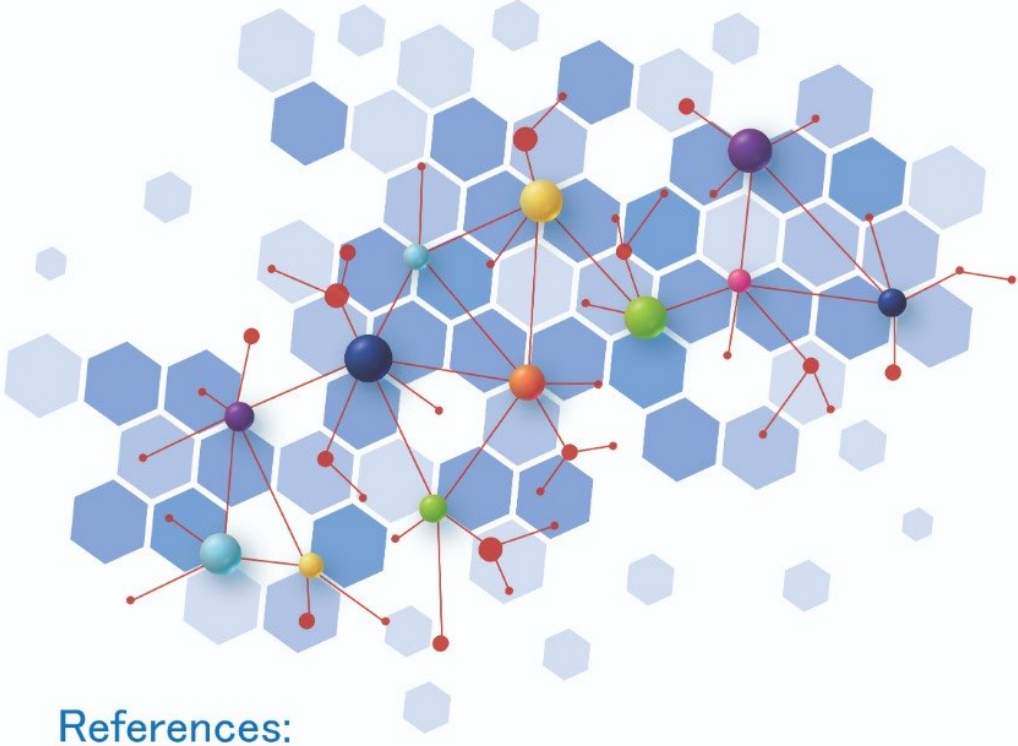


References:

- Clinical biochemistry book 13th edition.
- Doctor's slides and records.
- Past years questions.

Version: 1

Lecture #: #2: Water and Sodium balance

Water & Sodium balance:

- Internal balance and external balance are important for the balance of any substance in the body.
- **Internal balance**: distribution of the substance between different body **compartments** (intracellular and extracellular spaces)
- **External balance**: matches **input** with **output** of the substance
    - drinking water must equal urine output
    - eating and excretion of Na+
- **Na+** and **water** are always coupled → water always follows Na+
- Large amount of Na+ is excreted daily in different compartments → Water follows in large amounts too → most Na+ is reabsorbed → water reabsorbed too → no major loss of water!
    1) 25,000 mmol Na+ is filtered at the glumerulus per day → > 99% is reabsorbed.
        1) Renal failure can cause loss of Na+ → **hyponatremia**
    2) 1000 mmol Na+ enter GI tract in various secretions/day but < 0.5% is normally lost in feces.

Internal distribution of Na+ & water:

- Normally 60 % of adult mass is water
    - 2/3 are found in the ICF
    - 1/3 in the ECF;
        - 3 liters are plasma
        - the rest is interstitial fluids
- **Example**:
    - 70 kg adult has:
    - 42 L is total water
        - 28 L ICF
        - 14 L ECF
            - 3 L plasma
            - About 10 L interstitial fluid
- The total body Na+ is 4200 mmol:
    - **50% in ECF (majority of Na+ found outside cells)**
        - **Na+ is the main extracellular cation**
        - **Note: main intracellular cation is potassium**
    - 40% in bone
    - 10% in ICF

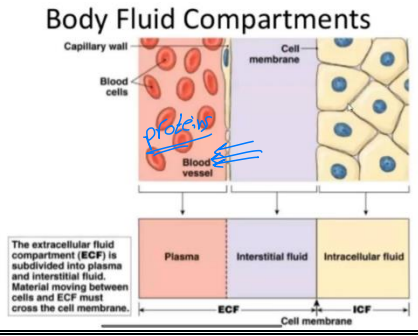
❖ 2 important factors influence the distribution of fluid between these compartments:

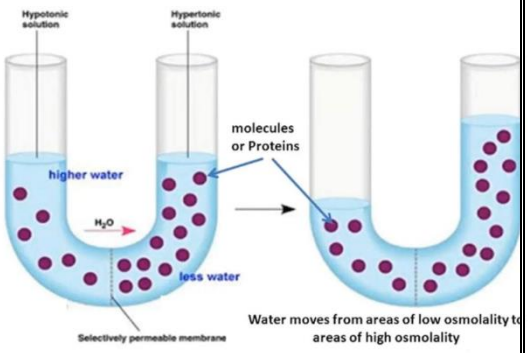
1) Osmolality:

- affects the movement of **water across the cell membrane.**
- Depends mainly on **Na+** concentration
- Water follows Na+ → water moves to high osmolality areas (high Na+ areas)

2) Colloid osmotic pressure (Oncotic pressure):

- Depends mainly on **proteins** (mainly albumin)
- Has effect on attracting **water** and **low Mwt solutes** (Na& Cl) between the **blood** and **interstitial space**.





1) Osmolality, osmolarity & tonicity:

❖ **Osmolality:**

- **<u>number</u>** of **solute particles** per unit weight of water **irrespective of the size (molecular weight/ Mwt) or nature** of the particles
- for example:
  - 1 liter of water containing 100 albumin particles and another 1 liter of water containing 100 Na+ particles → both have the same **osmolality**
- When we calculate the **osmolality**→ we mean **<u>plasma</u> osmolality**
- Plasma **osmolality** = 285-295 mmol/Kg
- **Low Mwt solutes contribute much more to the osmolality than high Mwt solutes.**
  - Large Mwt has minor contributors because they are found in **low numbers**.
- When we calculate the actual **osmolality** → we measure the most important particles in the plasma → the result is **approximated** value (not the actual value)

✓ Calculated osmolality = 2[Na+] + 2[K+] + [glucose] + [urea]

i. Na+ & K+ are doubled due to their associated anions (ex: cl^-).
   ➔ This is called **electrochemical neutrality**
ii. The value calculated is just an **<u>estimation</u>** → usually close to the true measured osmolality.

- **The calculated (Estimated) & measured (real) osmolalities may differ considerably when:**

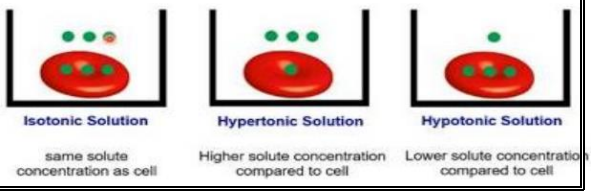
iii. gross (large) increases in **large Mwt** components of plasma;
   1. protein &lipid.
iv. **Large** amounts of **unmeasured** low Mwt solutes present in plasma
   ➔ Increased **ethanol** in plasma → indicates toxicity of unmeasured particles

❖ **Osmolarity:**

- the number of particles of solute per 1**L** of solution (**<u>mmol/L</u>**).

❖ **Tonicity**

- interchangeable with osmolality.
- only used in relation to osmotic pressure created by some solutes (**Na+**) that exert their effects across **<u>cell membranes</u>** causing **movement of water into or out of the <u>cells</u>**.
- The tonicity of ICF & ECF **<u>equilibrate</u>** with one another by movement of **<u>water</u>** across cell membrane
  a. When the fluids outside the cell has **more** osmotic pressure (more Na+) → it's called **hypertonic** solution → water flows from low tonicity (**inside** the cell) to high tonicity (**outside** the cell) → cell **shrinkage**
  b. When the fluids outside the cell has **less** osmotic pressure (less Na**+**) → it's called **hypotonic** solution → water flows from low tonicity (**outside** the cell) to high tonicity (**inside** the cell) → cell **swells** and **bursts**
  c. When solution outside the cell has the same tonicity (**isotonic** fluids) → **no net** diffusion across the membrane



- We have hypotonic /hypertonic/ isotonic normal saline (fluids given to patents in hospitals)

2) Colloid (oncotic) osmotic pressure:

- the osmotic pressure exerted by **plasma proteins** across the **cell membrane** is negligible compared with the osmotic pressure exerted by NaCl (small solutes) because proteins are large and present at **lower** molar concentrations.
- However; the osmotic pressure across **capillaries** are mainly determined by the **proteins**!!
  - NaCl cross readily across capillary pores → no effect
  - **Colloid (oncotic) osmotic pressure** usually refers to the pressure across **capillaries walls (between blood and interstitial fluids)**
  - Water moves from **low oncotic pressure (interstitium) to high oncotic pressure (blood)**
- The hydrostatic pressure (pressure of the blood on the vessel wall) opposes the colloid osmotic pressure
  a. it moves water from area of high to area of low hydrostatic pressure (from blood to the interstitium)

❖ Clinical scenario:

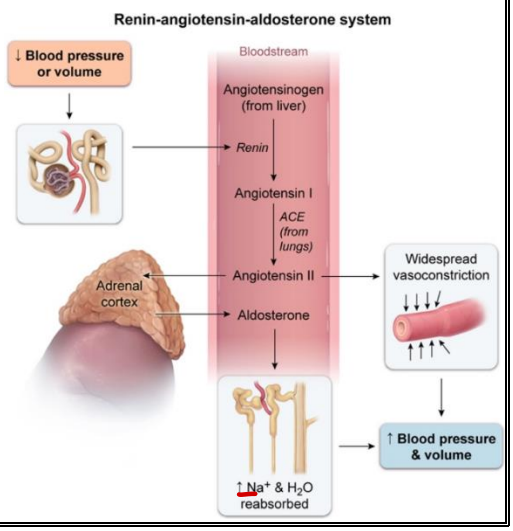
➢ During liver failure (**cirrhosis**) → the liver doesn't synthesize enough **albumin** → low proteins in the blood → **low oncotic pressure** → the hydrostatic pressure predominates→ fluids accumulate outside blood vessels (interstitium) → **pitting edema** develops.

Regulation of external water balance: (Input & output)

- Water **intake** is controlled by the sensation of **thirst**.
- Water **output** is controlled by the action of **vasopressin/antidiuretic hormone (ADH) on kidneys**
- **Steps of water regulation:**

➔ Decrease water intake or increase water loss→ increase in plasma osmolality (tonicity) resulting in:

A. **Water shift from ICF to ECF** due to increased tonicity in ECF (plasma)
B. Stimulation of **hypothalamic osmoreceptors**:
   - ➢ stimulation of **thirst** → increase water intake
   - ➢ Increase vasopressin secretion (**ADH**) → increase **free** water reabsorption from the **collecting ducts**
C. **Baroreceptors** detect low blood pressure because blood volume decreased→ decrease baroreceptor firing (less volume)→ increase sympathetic nervous system stimulation → vasopressin (**ADH**) is secreted and the Renin-angiotensin aldosterone system (**RAAS** system) is activated
   - **Angiotensin II** of the RAAS system causes vascular **vasoconstriction** and secretion of **aldosterone** hormone
   - **Aldosterone** causes **Na+ reabsorption** in distal tubules and collecting ducts → **water** follows (from urine bac to blood) → blood pressure back to normal



Difference between Vasopressin (ADH) & Aldosterone on body compartments:

- **ADH** causes **free water** retention (water without Na+) in kidneys leading to relatively **ineffective expansion** of intravascular compartment because water diffuses freely throughout **all** compartments.
    - **Water retained here will expand all compartments (not only ECF)**
- **Aldosterone** causes **Na+ & water** retention (isotonic solution) and is **effective in expanding** the intravascular compartment because it is **isotonic** to blood (does not diffuse to intracellular compartment).
    - Na+ retention with its iso-osmotically associated water, contributes solely **(only) to ECF volume.**

❖ **So:**

➔ Losses or gains of **pure** water are distributed across **all** fluid compartments (ICF & ECF)

➔ Losses or gains of **isotonic** fluid (water & Na+) are from or to the **ECF** compartment **only**.

➔ Loss of pure fluid → ECF becomes hyper-osmolar → water moves from ICF to ECF (compensation)

➔ Loss of isotonic fluid→ ECF remains iso-osmolar→ NO water movement from ICF to ECF (**NO** compensation)

➔ Loss of isotonic fluid is more dangerous than loss of pure water
    - Thus, it is more urgent to replace losses of isotonic fluids than losses of pure water

➔ Also; **circulatory overload** is more likely with excessive administration of **isotonic** Na+ containing solutions than with isotonic dextrose
    - dextrose is metabolized leaving **free water** behind

➔ Also; giving patents **hypertonic saline** leads to ECF expansion → **edema** develops

Regulation of Na+ external balance:

- Na+ input = Na+ output
- controlled by **renal** mechanism which control the ECF volume.
- **70%** of Na+ is reabsorbed normally in the **proximal tubules**
- **fine adjustments** of Na+ output occurs in **collecting ducts** by **aldosterone**.
- Na+ output also depends on the GFR→ when ↓GFR → less Na+ is excreted & vice versa.

❖ **Atrial natriuretic peptide (ANP):**

A. produced in the **atrium** of the heart in case of **HTN** or **heart failure** (increased blood volume inside the atria)
B. **antagonizes aldosterone** and **promoting Na+ excretion** by the kidneys through **increasing GFR** (**natriuresis**)

note: aldosterone is the main regulatory mechanism of Na+ excretion.

- **Depletion of water:**
  1) Decreased intake:
     - Infants, elderly, coma, nausea, or dysphagia.
  2) Increased loss:
     - **Lungs**: patents on mechanical ventilation due to inadequate humidification (high vapor loss)
     - **Skin**: fever, hot climate
     - **GI tract**: diarrhea
     - **Renal**:
       - **<u>diabetes insipidus</u>**:
         - loss of **ADH** or the kidneys don't respond to **ADH** → **<u>polyuria</u>**
       - **lithium** therapy: antagonizes ADH
       - **<u>diabetic ketoacidosis</u>**: osmotic diuresis by increased glucose inside renal tubules.

- **Excess of water:**
  1) Increased intake:
     - **psychogenic polydipsia**:
       - psychiatric disorder where patents drink excessive amounts of water
     - **hypotonic** infusions after operations (**dextrose solution**).
  2) Renal retention:
     - **<u>SIADH</u>** (syndrome of inappropriate ADH):
       - ↑vasopressin (ADH) secretion → ↑ water reabsorption.

- **Depletion of Na+ mass:**
  1) Decreased oral intake:
     - rare because Na+ is present in most food.
  2) Abnormal loss via:
     - **Skin**: through increased **sweating**, burns, dermatitis.
       - Extra note: **Sweating** alone causes hypernatremia but when accompanied by excess free water intake → hyponatremia occurs
     - **GI tract**: through vomiting, diarrhea, blood loss.
     - **Renal tract (most common):**
       - **diuretic** therapy:
         - **loops and thiazides diuretics** causes diuresis trough preventing **Na+** reabsorption → Na+ loss in urine
       - **renal tubular disease:**
         - tubules can't reabsorb Na+
       - **mineralocorticoid (aldosterone) deficiency (<u>Addison's disease</u>)**:
         - aldosterone usually causes reabsorption of Na+ and excretion of K+ & H+
         - ↓aldosterone secretion → **↓ Na+** reabsorption
         - ↓aldosterone → also causes ↑K+ &↑H+ (**hyperkalemia** & **metabolic acidosis**)

- **Excess of Na+ mass:**

1) Increased intake:
    1. sea water (drowning)
    2. salt tablets
    3. post-operatively (after surgery):
        A. infusion of **hypertonic NaCl** solution.

2) Renal retention:

1. Acute & chronic renal failure:

- During renal failure → decreased GFR→ increased activity of RAAS system
- The RAAS system results in increased the amount (mass) of Na+ (due to increased reabsorption)
- However; when GFR decreases → less water gets filtered → huge amounts of water returns → **hyponatremia** with **increased mass of Na+**

2. <u>Primary</u> hyperaldosteronism:

- **Increase** in the production of **aldosterone** from **adrenal** gland due to **<u>adenoma</u>** of the adrenal gland (tumor) → increased aldosterone →increased Na+ reabsorption.

3. **Secondary hyperaldosteronism**:

- **Increase** in **aldosterone not** due to **adenoma;** caused mainly by 3 conditions:
    1. **Nephrotic syndrome**:
        - Nephrotic syndrome involves **destruction** to the glomerular barrier→ **loss** of proteins (**albumin**) in urine → **decrease** in **oncotic pressure** → shift of **water** from **IVF** to **ISF** → decrease blood volume→ decreased blood supply to kidney → activation of **RAAS**→ Increase **aldosterone**→ **Na+** & **water** retention.
    2. **Severe liver disease (cirrhosis):** ↓protein synthesis→ ↓oncotic pressure→ same as above!
    3. **Congestive heart failure: heart can't pump blood to kidneys → ↓** blood supply to kidney and activation of **RAAS**.

→ Note: all 3 causes above involve formation of **<u>edema</u>**

4. **Cushing syndrome**:

- A disease that involve increased amounts of a hormone called **cortisol** (glucocorticoids)
- When cortisol is in excess→ it will start activating the **aldosterone receptors** (miniralocorticoid activity) → **Na+ retention**.

Summary to important notes

water problems

Depletion of water
- ↓intake → infants, elderly, coma
- ↑loss :-
  - → lungs ≈ mechanical ventilation
  - → skin ≈ sweating
  - → GIT ≈ Diarrhea
  - → Renal system
    - → Diabetes insipidus ⇒ ↓ADH
    - → Lithium → ⊖ADH
    - → DKA → osmotic diuresis

Excess of water
- ↑intake :
  - → psychogenic polydipsia
  - → dextrose solutions
- Renal retention :
  - → SIADH → ↑ADH

Na^+ problems

Depletion of Na^+
- ↓intake ≈ rare
- ↑loss :
  - → skin → sweating → Note: loss water > Na^+ → ↓water, ↓Na^+ → Hyponatremia
  - → GIT → Diarrhea, vomiting, bleeding
  - → Renal system :
    - → Diuretics therapy → ↓Na^+ reabsorption
    - → RTA → renal tubules defect
    - → Addisons disease → ↓Aldosterone → ↑Na^+, ↑H^+, acidosis

Excess of Na^+
- ↑intake : drowning, salt tablets, hypertonic solutions infusion
- Renal retention :
  - → ARF/CRF : ↓Na^+ & water filtration → ↓Na^+ & water excretion → ↑Na^+ & water in blood
    - ↑RAAS → ↑Na^+
    - water returns > Na^+ ⇒ Hyponatremia with ↑Na^+ mass
  - → 1° hyperaldosteronism : due to adrenal gland tumor
  - → 2° hyperaldosteronism :
    - → Nephrotic syndrome → ↓colloid pressure
    - → cirrhosis
    - → CHF → ↓hydrostatic pressure
    - → edema & ↓renal perfusion → ↑RAAS → ↑Aldosterone
  - → Cushing's syndrome :- ↑cortisol → ↑Aldosterone receptors

Hypervolemia

↓RAAS & ADH

↑ANP/BNP
- works opposite to RAAS
- ↑Na^+ & water excretion
- Vasodilation

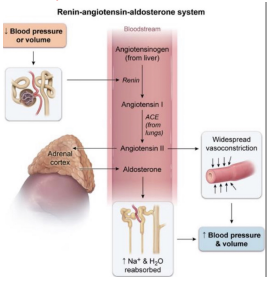
Hypovolemia

Hypothalamus
↑Thirst

↑ADH
- ↑Free water reabsorption
- less effective in IVS expansion

water shift
- from ICS → ECS

Baroreceptors & ↓renal BF



Internal distribution of water

60% → 2/3 ICF
60% → 1/3 ECF → 1/4 (Cells) → plasma
60% → 1/3 ECF → 3/4 → interstitial fluids

osmolality ≈ mmol/Kg

- depends on number of solutes rather than size/weight.
- Control water movements across cell membrane
- main contributor is Na^+
- ↑Na^+ → ↑osmolality → water follows across cell membrane
- Calculated/approximated = 2[Na^+] + 2[K^+] + [glucose] + [urea]
- when calculated osm. < Actual osm.
  1) ↑↑ proteins & lipids
  2) ↑un-measured solutes (ethanol/methanol/lactic acid...)

osmolarity ≈ mmol/Liter

Tonicity :

make sure you know the 3 scenarios :
⇒ Cellular shrinkage/swelling or no change

Colloid/oncotic osmotic pressure :

Across capillaries
- depends on Albumin
- water moves from low oncotic pressure to high oncotic pressure
- significant & important
- Decreased in :
  1) cirrhosis
  2) Nephrotic/Nephritic syndrome

Across cell membrane
- depends on Albumin
- Not important