MECHANISMS OF OEDEMA (EDEMA) – AN OVERVIEW

UNIVERSITY OF PNG
SCHOOL OF MEDICINE AND HEALTH SCIENCES
DISCIPLINE OF BIOCHEMISTRY & MOLECULAR BIOLOGY
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VJ Temple

What is Oedema (Edema)?

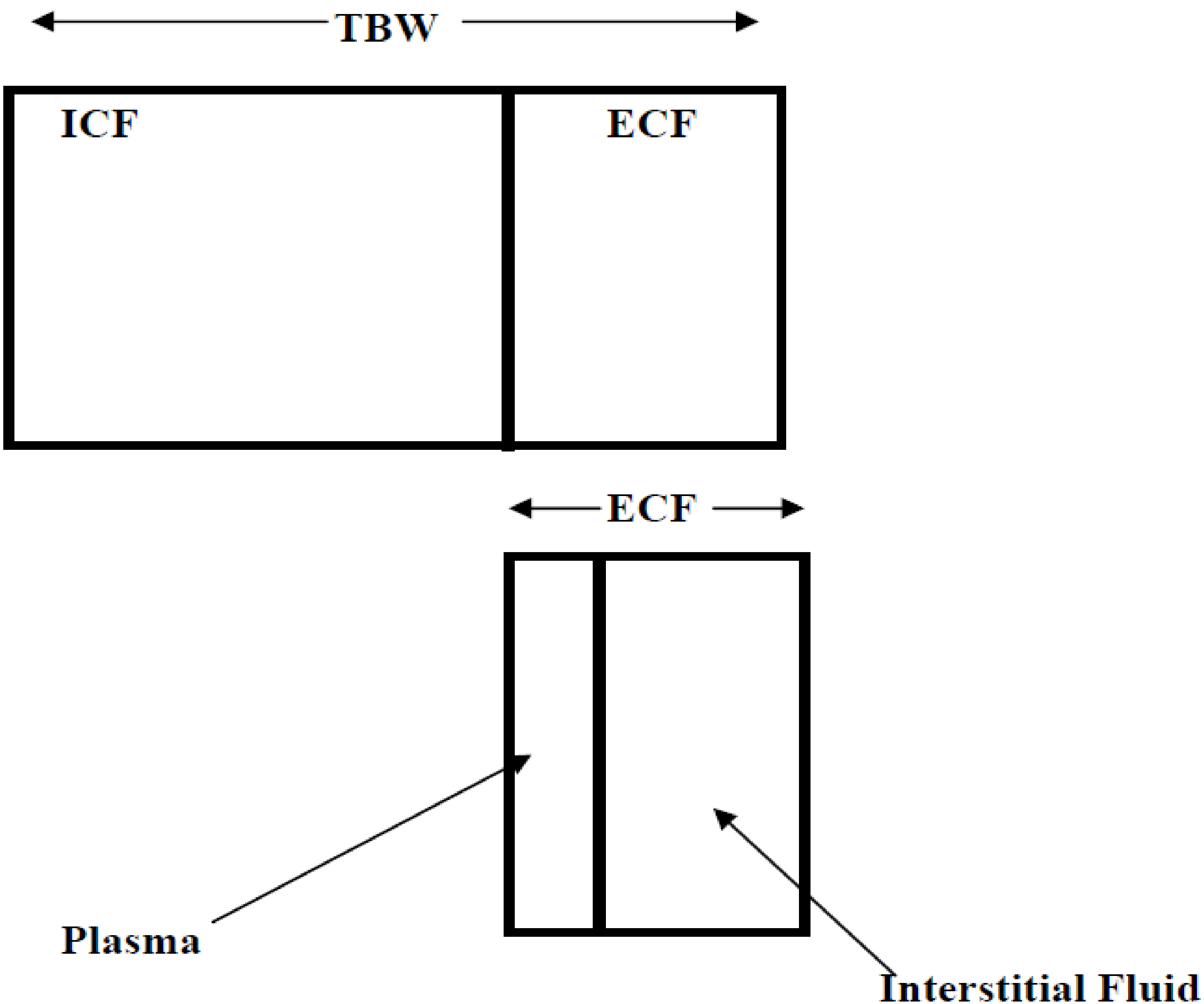
- Oedema is an accumulation of fluid in the Interstitial Compartments;
- Oedema occurs when there is more Interstitial Fluid than the Lymphatic system can return into the circulation;

How much fluid (water) is contained in the body?

- Water/Fluid is a major body constituent;
- An average person (Wt 70 kg) contains about 42 liters of Total Body Water (TBW);
- TBW is about 60% of the total body weight;

What are the fluid compartments in the body?

- Two major fluid compartments:
  - Intra-Cellular Fluid Compartment **(ICF)**: Volume of Fluid Inside Cells;
    - **ICF constitute about 66.6% of TBW**
  - Extra-Cellular Fluid Compartment (**ECF**): Volume of Fluid Outside Cells;
    - **ECF constitute about 33.3% of TBW**
- ECF is made up of **Plasma** and **Interstitial Fluid**
- Plasma is about 25% of ECF
- Interstitial Fluid is about 75% of ECF


TBW
ICF
ECF
ECF
Plasma
Interstitial Fluid

What are some of the consequences of fluid loss?

- Selective loss of fluid from either ICF or ECF compartments gives rise to distinct signs and symptoms:
- Loss of ICF, can cause Cellular Dysfunction: resulting in Lethargy, Confusion and Coma;
- Loss of ECF (e.g., Blood loss) can lead to Circulatory Collapse, Renal shutdown and Shock;
- Loss of TBW produces similar effects as loss of ICF or ECF;
- Signs of (substantial) fluid loss is spread across ICF & ECF;

- **State of Hydration** (volume of body fluid compartments) of a patient is usually assessed on Clinical grounds, by looking for appropriate Clinical signs that indicate:
- Dehydration (loss of fluid) or
- Over-hydration (accumulation of fluid in compartments)

What is “Water Steady State” or Water Balance?

- Water (Fluid) steady state is an important concept that simply means:
  - **Amount of water (fluid) consumed each day must equal the amount of water (fluid) eliminated from the body over the same period of time;**
- If not, then body will have:
  - Net water gain: Over-hydration;

  Or

  - Net water loss: Dehydration

What are the major sources and routes of fluid intake?

- Some major sources of fluid intake:
- Water Drinking;
- Water contained in our various foodstuffs;
- Metabolic water;

What are some of the major routes in the body for fluid loss?

- Some major routes of fluid loss:
- Urinary loss, Fecal loss
- Insensible water loss – such as evaporation from the Respiratory Tract and Skin Surface (not including sweat which is sensible since it has a purpose)

- Sweat Losses –
  - At normal room temperature, sweating accounts for about 25% of heat losses;
  - In cold environments, H_2O losses in sweat decreases;
  - In warm environments, or with exercise, sweat losses increases;
- Pathological losses: vascular bleeding, vomiting, and diarrhea;

What is “Electrolyte Steady State” or Electrolyte Balance?

- Electrolytes are Na^+, K^+, Cl^- and $H_2CO_3^-$ ions;
- Amount of electrolytes consumed must be equal to amount eliminated within certain period;
- Na^+, K^+, Cl^- ions normally enter the body by ingestion;
- Clinically, Electrolytes can enter the body via parenteral route, e.g., administration of Intravenous (i.v.) Solutions;

- Possible routes for Electrolyte losses:
- Renal excretion,
- Stool losses,
- Sweating,
- Pathological routes: eg. Vomit and Diarrhea;

What is OSMOLALITY or OSMOLARITY?

- **OSMOLALITY** : Number of solute particles per unit weight of water, irrespective of the size or nature of the particles;
- Solute with low molecular weight contributes much more to the Osmolality than solute with high molecular weight;
- Osmolality determines the **osmotic pressure** exerted by a solution across a semi-permeable membrane;

- **OSMOLARITY:** Number of particles of solute per liter of solution;
- Water moves easily through semi permeable membranes that separate ECF from ICF;
- **Osmolality of ICF is always the same as Osmolality of ECF**;
- ECF and ICF compartments contain Isotonic solutions;

How is Osmolality of Serum or Plasma calculated?

- Concentrations of osmotically active solutes are used:
- Very simple formula for calculating Osmolality :

Serum Osmolality = 2 x [Serum Sodium ions] = 2[Na^+]

  - (Note: Unit for Osmolality is either, **mmol/kg,** or **mOsmol/Kg** or **mOsmol/L**; Unit for Plasma or Serum Sodium ion is always in **mmol/L**)

- Simple formula can be used ONLY if the Serum or Plasma Concentrations of **Urea** and **Glucose** are within the reference ranges;
- If either or both are abnormally high, the concentration of either or both (in mmol/L) must be included in the calculation of the Osmolality;
- **NB**: In human, Normal Osmolality of Serum or Plasma (and other body fluids except urine) is in the range **285 to 295 mmol/kg** (**285 to 295 mOsmol/L**)

Example for calculating Osmolality

Normal Conditions (i.e., Plasma or Serum concentrations of Urea and Glucose are within normal range)

- ECF Osmolality can be roughly estimated as: → $$P_{osm} = 2 \cdot [Na]_p = 270 - 290 \text{ mOsm}$$

{Where P_{osm} is plasma Osmolality;. Since intracellular Osmolarity is the same as extra-cellular Osmolality under normal conditions, this also provides an estimate of intracellular Osmolality}

Example for calculation of Osmolality

Clinical Laboratory Measurement:

- Plasma Osmolarity measured in Clinical laboratory also includes contributions from Glucose and Urea;
- Normally the contribution from Glucose and Urea is small
- Under certain Pathological conditions, the concentrations of these substances can be very high;
- Plasma Osmolality measured in clinical laboratory:

$$\mathbf{P = 2[Na^+] + 2[K^+] + [Glucose] + [Urea]}$$

(**P** = Plasma or Serum Osmolality)

How is effective Osmole different from ineffective Osmole?

- **Ineffective Osmole:**
  - Urea crosses the semi-permeable cell membranes just as easily as water, therefore it does not contribute to redistribution of water between ECF and ICF;
- **Effective Osmoles:**
  - Glucose, Na^+ and Anions associated with Na^+ do not cross the semi-permeable cell membrane;
  - They have concentration gradients across the cell membrane and are osmotically active;
  - They determine the distribution of water between ECF and ICF;

How is Effective Osmole calculated?

Two ways for calculating Effective Osmole:

- Effective Osmole:

$$\mathbf{P\ (effective) = 2[Na^{+}] + [Glucose]}$$

- Effective Osmole:

$$\mathbf{P\ (effective) = P\ (measured) - [Urea]}$$

- (**P** = plasma or serum Osmolality)

What is Osmolal Gap and how is it calculated?

OSMOLAL GAP (OG):

- Difference between **Measured Osmolality (MO)** and **Calculated Osmolality (CO)**

Osmolal Gap (OG) = MO – CO

- Large positive OG helps to identify presence in serum of osmotically active substances, such as, Ethanol, Methanol, Iso-propanol, Ethylene Glycol and Acetone
- Proper interpretation of OG also requires knowledge of **Anion Gap (AG)**, and blood pH

$$\textbf{Anion Gap} = [Na^+] - \{[HCO_3^-] + [Cl^-]\}$$

What does "Hyponatraemia" mean?

- **Hyponatraemia** is a significant fall in Serum Na^+ ion concentration below the reference range;
    - (what reference range is used for Serum Na^+ ion in PMGH?)

- **"Hypo-Osmolality"** is synonymous with **Hyponatraemia** because Sodium is the only ion present in the ECF in sufficient amount such that a decrease in concentration would significantly affect the Osmolality;

List two possibilities of Hyponatraemia?

- Hyponatraemia due to Fluid **Retention:**
  - More fluid than normal is retained in the body compartments and dilutes the constituents in ECF causing Hyponatraemia;
- Hyponatraemia due to **Loss of Sodium:**
  - When loss of Sodium ions exceeds loss of fluid, Hyponatraemia may result
  - Example: if body fluids (from vomiting or from fistulae) that contain Sodium are replaced simply by water;

What are some of the causes of Hyponatraemia with fluid retention?

- Decreased water excretion:
  - Examples: Nephrotic Syndrome, Renal Failure;
- Increased Water Intake:
  - Examples: Inappropriate IV Saline, Compulsive water drinking

TAKE NOTE:

- In general if fluid loss is not apparent from the Clinical history of a patient then the reason for the Hyponatraemia is usually WATER RETENTION;
- Hyponatraemia due to water overload without a decrease in total body Sodium is the commonest Biochemical disturbance encountered in clinical practice;
- Further consideration of Hyponatraemia of this type, depends on whether the patient has **Oedema**:
- Two possible conditions are:
  - **Oedematous Hyponatraemia**
  - **Non-Oedematous Hyponatraemia**

OEDEMATOUS HYPONATRAEMIA

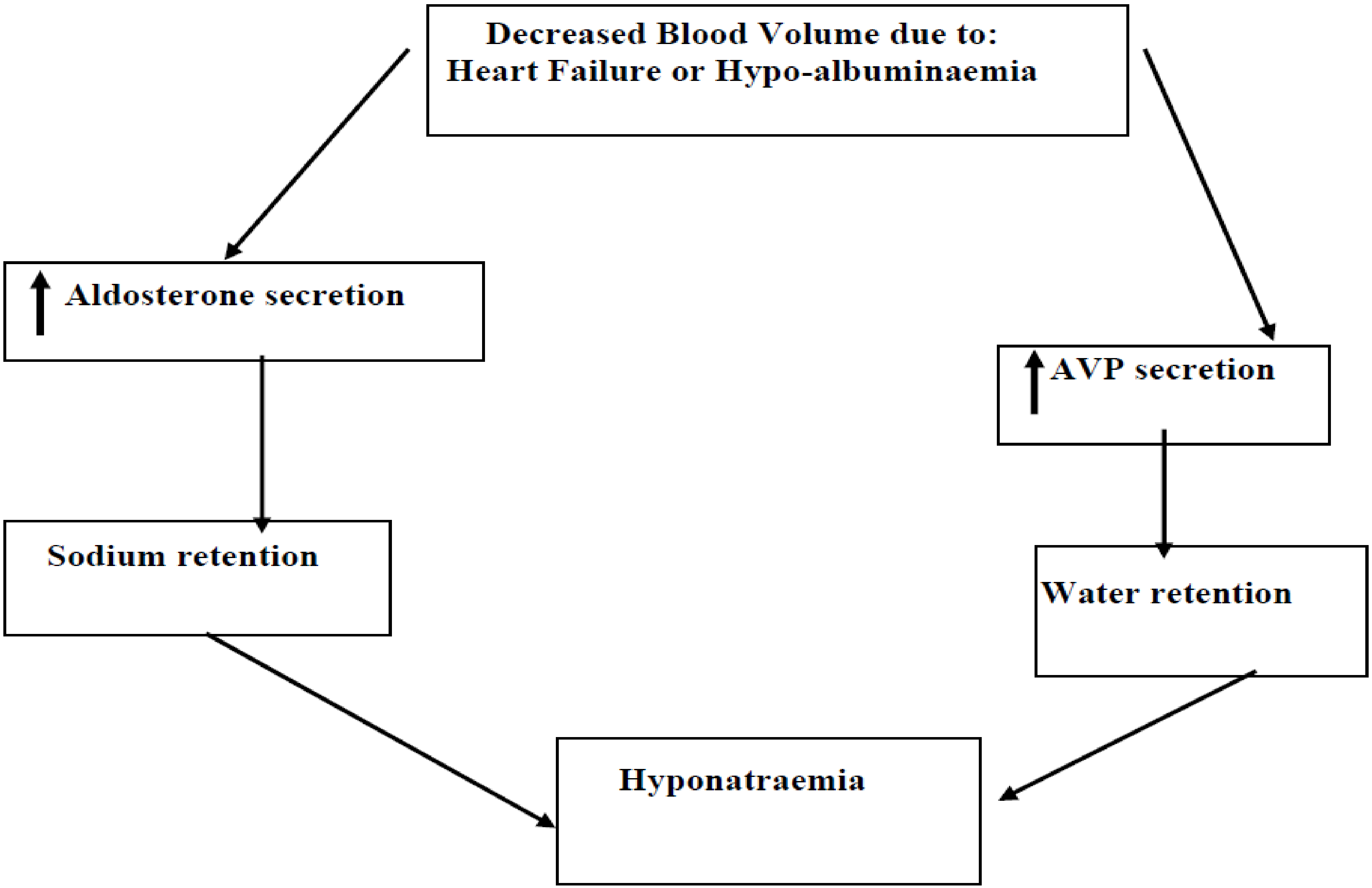
- Patients who have generalized Oedema have an increase in both Total Body Sodium and Water:
- Causes of Oedema include:
- **Heart Failure:**
  - Effective blood volume may be reduced because pumping action of the heart is unable to maintain a satisfactory circulation of Blood and ECF;
- **Hypo-albuminaemia**,
  - Effective blood volume may be reduced because Hypo-albuminaemia lowers Plasma Oncotic Pressure, which disrupts normal exchange of solutes and fluid in capillary bed resulting in unsatisfactory circulation of Blood and ECF;
  - Albumin makes the biggest contribution to the plasma Oncotic pressure;
  - Oedema may occur if blood albumin concentration falls very low;

- In response to reduced effective blood volume, **Aldosterone** is secreted and causes Sodium retention to allow the ECF volume to expand;

- Reduction in effective blood volume is one of the Non-Osmotic Stimuli for the secretion of AVP (Arginine Vasopressin) and consequently water is retained;

- **Hyponatraemia results from the Retention of relatively more water than Sodium in the ECF;**

Sequence of events leading to the development of Hyponatraemia in Patient with Oedema is schematically presented below:



What are some of the causes of Hypo-albuminaemia?

- **Decreased biosynthesis** of albumin due to:
  - Liver disease causing inadequate biosynthesis of Albumin;
  - Loss of albumin exceeds biosynthetic capacity of liver as occurs in Nephrotic syndrome;
  - Malnutrition or Mal-absorption;
- **Abnormal distribution or dilution:**
  - Hypo-albuminaemia can be induced by over-hydration or if there is increased capillary permeability as occurs in Septicaemia
- **Abnormal excretion or degradation:**
  - Nephrotic Syndrome, Protein-losing Enteropathies, Burns, Haemorrhage and Catabolic states

NON-OEDEMATOUS HYPONATRAEMIA

- Patients with Non-Oedematous Hyponatraemia have normal total body sodium and exhibit the features of **Syndrome of Inappropriate Antidiuresis (SIAD)**
- Patients are Hyponatraemic, Normotensive, have normal Glomerular Filtration Rate (GFR) and normal serum Urea and Creatinine concentration;
- Urine Flow Rate is usually less than 1.5 liter/day;

- SIAD is usually encountered in conditions:
  - Infections, e.g. Pneumonia,
  - Malignancy, e.g. Carcinoma of Bowel or Lung,
  - Trauma, e.g. Abdominal Surgery,
  - Drug-induced, e.g. Thiazide Diuretics,Chlorpropamide
    - Patients suffering from any of the above may haveNon-Osmotic AVP stimulation and, if they are exposed to excessive water loads, in the form of oral drinks or intravenous glucose solutions, they will become Hyponatraemic

HYPONATRAEMIA DUE TO SODIUM LOSS

- Occurs during Pathological Sodium Loss
- May be from GIT or in Urine
- Vomiting (severe and protracted as occurs in Pyloric Stenosis)
- Diarrhoea;
- Fistula

Table below shows electrolyte composition of GIT

Fluid	Na^+ (mmol/L)	K^+ (mmol/L)	Cl^- (mmol/L)
Gastric juice	70	10	110
Small intestine fluid	120	10	100
Diarrhoea	50	30	50
Rectal mucus	100	40	100
Bile, Pleural and Peritoneal Fluids	140	5	100

Urinary loss may be due to

- Aldosterone deficiency due to failure of the Adrenal Glands (Addison's disease);
- Drugs that antagonize Aldosterone action;
- Initially in all of the above
  - Sodium loss is accompanied by Water loss and Serum Sodium ion concentration remains normal;
  - As Sodium loss proceeds, the reduction in ECF and blood volume stimulates AVP secretion;
  - Non-osmotic control of AVP secretion overrides osmotic control mechanism;
  - Increased AVP secretion causes water retention and thus the patient becomes Hyponatraemic;
  - Patient becomes Hyponatraemic because a deficit of Isotonic Sodium-containing fluid is replaced only by water, either Orally or Intravenously;