UNIT 6

INVESTIGATION OF FLUID AND ELECTROLYTE DISORDERS

LEARNING OBJECTIVES:

At the end of this chapter students must:
1. Describe body fluid compartments and how they can be measured
2. List the clinical signs of dehydration and hyperhydration
3. Describe the causes and consequences of sodium and potassium abnormalities

I. INVESTIGATION OF FLUID COMPARTMENTS

Total body water (TBW) – represents approximately 60% of a person body weight, depending on the age and sex, and is distributed in 2 major compartments:
- intracellular fluid compartment (ICF)
- extracellular fluid compartment (ECF)

1. The intracellular fluid compartment (ICF) is the largest and represents approximately 40% of the body’s weight (two thirds of the TBW)

2. The extracellular fluid compartment (ECF) represents 20% of the body weight (one third of the TBW) and comprises:
   1. Plasma volume (PV) – represents 25% of the ECF and 5% the body’s weight.
   2. Interstitial fluid – represents 75% of the ECF and 15% of the body’s weight.

\[
\text{Essential rule: } 20 + 40 = 60
\]
ECF (20%) + ICF (40%) = TBW (60%)

3. Transcellular fluid – represents 1,5-2% of the body weight (approximately 1 litre). This compartment comprises: digestive fluids (1/2 of the transcellular fluid), bile, sweat, spinal fluid, pleural, pericardial, peritoneal, synovial and intraocular fluids. Abnormal increase of this compartment is denominated the third space, since it does not participate in normal fluid exchanges.

Example:
An adult that weighs 70 kg, has a total of 42 litres of body water, divided into the:
- intracellular fluid compartment (ICF) = 28 L
- extracellular fluid compartment (ECF) = 14 L:
  - plasma volume = 3.5 L
  - interstitial fluid = 10.5 L

In healthy individuals, the composition and volume of the two compartments remain constant, due to the preservation of the balance between fluid intake and fluid loss.

II. MEASUREMENT OF FLUID COMPARTMENTS

The dilution principle

The volume (V) of a hydric compartment in which a certain substance is injected, can be determined by knowing the initial concentration of that substance (Q) and its concentration after it has been equally distributed in the studied compartment (C). The volume of that hydric compartment can be determined using the formula: \( V = \frac{Q}{C} \).

The main substances that can be used for fluid compartment measurement are presented in Table 1.

<table>
<thead>
<tr>
<th>Compartments</th>
<th>Indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBW</td>
<td>(^3)H(_2)O, (^2)H(_2)O, antipyrine</td>
</tr>
<tr>
<td>ECF</td>
<td>(^{23})Na, thiosulphate, inuline</td>
</tr>
<tr>
<td>ICF</td>
<td>TBW-ECF</td>
</tr>
<tr>
<td>Plasma vol.</td>
<td>(^{125})I-albumine, Evans blue (T-1824)</td>
</tr>
<tr>
<td>Interstitial fluid</td>
<td>ECF-plasma volume</td>
</tr>
</tbody>
</table>

The substance may leave the studied compartment through one of the following mechanisms:


- urine excretion
- transfer into another compartment in case of different concentrations
- metabolisation of the substance
- perspiration or breathing

Regardless of the studied compartment, the substances used must meet the following conditions:
- to be measurable
- to remain long enough in the measured compartment
- to be non-toxic
- to not modify the balance of the fluids existing in the studied compartment

1. Assessment of TOTAL BODY WATER (TBW)

A certain amount of a substance, usually radioactive water (tritium), heavy water (deuterium) or antipyrine, which can distribute uniformly in all the fluids of the body, will be administered to the patient, either orally or intravenously. A few hours later, after the substance was allowed to reach the tissues, a blood sample is taken in order to measure the plasma concentration of the substance that was administered. Total body water can be then measured using the dilution principle.

2. Assessment of the EXTRACELLULAR FLUID COMPARTMENT (ECF)

The extracellular volume can be estimated using substances that diffuse into the plasma and interstitial fluid, but DO NOT pass through the cellular membrane. Such substances are: sodium thiocyanate, sodium thiosulphonate, inuline, radioactive sodium. Sodium thiocyanate is used more frequently than other substances, the estimated value of the ECF being 26% (higher than the normal value of 20%) due to partial distribution in the gastric mucosa and some other organs.

a) Plasma volume can be measured using:
   - substances that remain in the vascular system and do not enter the red cells, such as:
     o Evans blue (T-1284)
     o radioactive albumin (125I – albumin)

b) Interstitial fluid volume can not be measured directly, because no substance can diffuse exclusively into this compartment. Therefore, it will be calculated as the difference between the extracellular fluid and plasma volume.

3. Assessment of the INTRACELLULAR FLUID COMPARTMENT (ICF)

ICF can not be measured directly using the dilution technique, due to the fact that no substance can remain exclusively into this compartment (after intravenous administration). Therefore, the ICF volume is obtained from the difference between TBW and ECF.

III. DISTURBANCES OF BODY FLUID COMPARTMENTS

General concepts
- Volume. Volume disturbances are hypovolemia or dehydration, and hypervolemia or hyperhydration, respectively, both being associated with abnormalities of extracellular fluid volume.
- Tonicity of a solution is linked to its effect upon the volume of a cell, for instance the erythrocyte:
  - isotonic solutions do not modify the cell volume
  - hypotonic solutions determine a swelling of the cell
  - hypertonic solutions can cause cellular dehydration

1. Hypovolemia

   - Definition: represents a decrease in extracellular fluid volume caused by both water and sodium deficit (unlike dehydration that refers only to a water deficit).

   - Causes:
     The most frequent causes of extracellular fluid loss include: vomiting, diarrhea, severe burns, high doses of diuretics and chronic kidney disease.

   - Clinical signs: diminished skin turgor, dry skin and mucosae, tachycardia, orthostatic hypotension.

2. Hypervolemia

   - Definition: represents an increase in extracellular fluid volume due, in most cases, to high sodium concentration (unlike hyperhydration which refers only to an increase of the volume of water).
Causes: The most frequent causes which are responsible of hypervolemia include: cardiac failure, nephrotic syndrome, cirrhosis of the liver.

Clinical signs: edema, increase in weight and othopnea.

In both types of fluid compartment disturbances, the diagnosis is firstly a clinical one, the major signs and symptoms being detailed in Table 2.

Table 2. The main signs/symptoms in fluid volume disturbances.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Dehydration</th>
<th>Hyperhydration</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>vomiting, diarrhea, reduced liquid intake</td>
<td>excess in sodium intake, renal impairment, cardiac failure, excess of corticosteroids, excess of i.v. fluid administration</td>
</tr>
<tr>
<td>Pulse</td>
<td>weak, rapid</td>
<td>strong</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>↓</td>
<td>N/↑</td>
</tr>
<tr>
<td>Skin</td>
<td>reduced skin turgor</td>
<td>edema</td>
</tr>
<tr>
<td>Eye balls</td>
<td>hypotonic eye balls</td>
<td>N</td>
</tr>
<tr>
<td>Mucosae</td>
<td>dry</td>
<td>N</td>
</tr>
<tr>
<td>Thirst</td>
<td>↑</td>
<td>-</td>
</tr>
<tr>
<td>Weight</td>
<td>acute weight loss</td>
<td>acute weight increase</td>
</tr>
<tr>
<td>Urine output</td>
<td>olyguria, concentrated urine</td>
<td>variable</td>
</tr>
<tr>
<td>Consciousness</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Venous circulation</td>
<td>↓</td>
<td>venous distention, pulmonary edema</td>
</tr>
<tr>
<td>Capillary nail refill time</td>
<td>↑</td>
<td>N</td>
</tr>
<tr>
<td>Ht, urea</td>
<td>hemoconcentration</td>
<td>hemodilution</td>
</tr>
</tbody>
</table>

Body weight
Body weight must be measured daily, in the same conditions as the day before. A decrease/increase in weight of 2% is considered mild, between 5% and 8%, moderate and above 8%, severe.

Skin turgor
Water allows the skin and tissues to maintain a certain elasticity, which is referred to as the skin turgor. It can be evaluated by making a skin crease using the first and index fingers. The skin should normally get back to its original state after releasing the crease. A loss of water between 3-5% (especially in children) determines a loss of skin elasticity, as it remains deformed for a few seconds. This clinical sign loses its clinical value in older patients, where the skin loses elasticity due to ageing.

Sunken anterior fontanelle in infants
A depressed anterior fontanelle represents a sign of dehydration and it is caused, most frequently, by fluid loss or by a decrease in the pressure of cerebrospinal fluid (CSF). The anterior fontanelle is a diamond-shaped membrane located at the intersection of the sagittal, coronal and frontal cranium sutures that usually closes between 9 months and 2 years. In normal conditions, if palpated, the anterior fontanelle should be firm, flat, and delineated from the near cranium bones. A bulging, tensioned fontanelle, with visible pulsation is a sign of high intracranial pressure or fluid retention.

Capillary nail refill test
Pressure that is applied on the nail for 5 seconds will determine a discoloration of the nail, which indicates that the blood was forced to leave the tissue. The necessary time for the blood to come back into the tissue in order for it to regain its pink colour should be under 2 seconds. Increased pallor of the nail, over 2 seconds can indicate: dehydration, shock, hypothermia.

IV. INVESTIGATION OF PLASMA ELECTROLYTES

Definition: electrolytes are negative and positive ions, which can be found in the body’s fluids:
- sodium is the main extracellular cation
- potassium is the main intracellular anion
- proteins and phosphate represent intracellular anions
- chloride and bicarbonate are the main extracellular anions

The normal values for plasma electrolytes are detailed in Table 3.

Table 3. Plasma electrolytes.

<table>
<thead>
<tr>
<th>Cations</th>
<th>Plasma (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (Na⁺)</td>
<td>135-145</td>
</tr>
<tr>
<td>Potassium (K⁺)</td>
<td>3,5-5</td>
</tr>
<tr>
<td>Calcium (Ca²⁺)</td>
<td>1,25-2,75</td>
</tr>
<tr>
<td>Magnesium (Mg²⁺)</td>
<td>0,8-1,2</td>
</tr>
<tr>
<td>Chloride (Cl⁻)</td>
<td>98-106</td>
</tr>
<tr>
<td>Bicarbonate (HCO₃⁻)</td>
<td>22-26</td>
</tr>
<tr>
<td>Phosphate (HPO₄²⁻)</td>
<td>1,3-2,1</td>
</tr>
<tr>
<td>Sulphate (SO₄²⁻)</td>
<td>0,1-0,65</td>
</tr>
</tbody>
</table>
Osmolality/Osmolarity

The number of particles dissolved in a volume unit, can be referred to as osmolality or osmolarity. Osmolality refers to the number of osmols per kilogram of water (therefore, the total volume will be 1 litre of water to which a small volume of substance can be added).

Osmolarity refers to the number of osmols per litre of solution (therefore, the water volume is less than 1 litre). Due to the low concentration of dissolved substances in the body fluids, the difference between osmolality and osmolarity can be neglected. Plasma osmolality can be estimated using the following formula:

$$\text{Serum osmolarity (mOsm/L) = 2 x plasma Na}^+ \text{ (mmol/L)}$$

This simple formula can be used only in cases in which plasma glucose and urea are in normal range. If one or both are pathologically increased, their concentrations should be considered for the calculation plasma osmolality. Therefore, the formula for osmolarity becomes:

$$\text{Total plasma osmolarity (mOsm/L) = 2 x [Na}^+ + K^+] + \text{[urea/60 + [glucose]/18}}$$

(Sodium and potassium are measured in mmol/L, while urea and glucose in mg/dL).

1. DISORDERS OF SODIUM METABOLISM

1. Hypernatremia

- **Definition:** increase of plasma levels of sodium > 145 mmol/L

- **Causes:** water deficit (usually it is proof of an absolute deficit in total body water) or increased sodium intake/retention.

Table 4. The main causes for hypernatremia.

<table>
<thead>
<tr>
<th>Extrarenal causes:</th>
<th>Renal causes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory: tachypnea</td>
<td>Gastrointestinal: vomiting, diarrhea (water deficit &gt; sodium)</td>
</tr>
<tr>
<td>Skin: increased sweating in cases with fever, burns</td>
<td></td>
</tr>
<tr>
<td>Digestive system: appetite loss, nausea, vomiting, cramps, diarrhea</td>
<td></td>
</tr>
</tbody>
</table>

2. Hypertonic solution administration (hypertonic saline, sodium bicarbonate, total parenteral nutrition)

3. Increased mineralocorticoid production
   - Primary hyperaldosteronism
   - Cushing syndrome

4. Other causes:
   - lack of access to water (bedridden patients)

- **Clinical signs:** thirst (main symptom), neurological signs due to disturbances of intracellular volume (neuromuscular signs, confusion, seizures, coma).

- **Diagnosis:** Plasma sodium, osmolarity, Ht, urea (Table 5).

Table 5. Manifestations of hypo- and hypernatremia.

<table>
<thead>
<tr>
<th>Lab tests results:</th>
<th>Hyponatremia</th>
<th>Hypernatremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma sodium</td>
<td>&lt;135 mmol/L</td>
<td>&gt;145 mmol/L</td>
</tr>
<tr>
<td>Plasma osmolarity</td>
<td>Reduced</td>
<td>Increased</td>
</tr>
<tr>
<td>Hemodilution:</td>
<td>↓ Ht</td>
<td>↑ Ht</td>
</tr>
<tr>
<td>↓ urea</td>
<td>↑ urea</td>
<td></td>
</tr>
</tbody>
</table>

**CLINICAL signs**

- **Water enters the cells**
  - Muscles: cramps and muscle weakness, decreased tendonous reflexes.
  - Nervous system: headaches, disorientation, seizures and coma (brain swelling due to water intoxication)

- **Water exits the cells**
  - Nervous system: headaches, disorientation, anxiety, decreased nervous reflexes, seizures and coma.

- **Compensatory mechanisms:** thirst increased ADH production with olyguria
2. Hyponatremia

- **Definition:** decreased plasma levels of sodium < 135 mmol/L
- **Causes:** water excess (dilution hyponatremia) or a decrease of sodium intake/ increased sodium loss. The major causes of hyponatremia are detailed in Table 6.

### Table 6. The main causes of hyponatremia.

1. **Dilution hyponatremia:**
   - a. Water and sodium retention from:
     - decompensated liver cirrhosis
     - congestive heart failure
     - acute renal lesions (oliguria phase)
     - renal failure
   - b. Pathological ADH production and release:
     - opium drugs
     - postoperative, pain, emotional stress
     - inadequate ADH secretion syndrome – paraneoplastic syndromes (pulmonary tumors)

2. **Decreased sodium intake:**
   - low sodium diet (associated with increased loss in patients treated with diuretics).

3. **Excessive sodium loss:**
   a. Extrarenal causes:
     - gastrointestinal: vomiting, diarrhea (sodium loss > water loss)
     - third space formation: acute pancreatitis, peritonitis, intestinal occlusion
   b. Renal causes:
     - mineralocorticoid deficit (hypoALDO)
     - glucocorticoid deficit (Addison’s disease)
     - diuretics
     - osmotic diuresis (glucose, urea, manitol)
     - sodium loss nephropathies

- **Diagnosis:** Plasma sodium, osmolarity, Ht, urea (Table 5).

  a) **Calculation of plasma osmolarity:**
     - normal – false hyponatremia
     - increased – check for hyperglycemia
     - decreased – check for dehydration
  
  b) **In case of hypovolemia,** check for urinary sodium output:
     - Urinary Na⁺ < 20 mEq/L – gastrointestinal losses, diuretic administration

- **Urinary Na⁺ > 20 mEq/L –** renal losses, diuretic administration

c) **In case of hypovolemia** check the urinary sodium output:

- Urinary Na⁺ < 20 mEq/L – hepatic disorders, cardiac failure
- Urinary Na⁺ > 20 mEq/L – renal disorders

2. DISORDERS OF POTASSIUM METABOLISM

Potassium is the most abundant intracellular cation and a major determining factor for intracellular osmolarity.

1. **Hypokalemia**

- **Definition:** decrease in plasma levels of potassium < 3.5 mmol/L.

- **Clinical features:** muscle weakness, polyuria; increased cardiac activity can appear in cases with severe hypokalemia (Table 7). The diagnosis must be established by measuring plasma levels of potassium.

- **Causes:** potassium deficit or abnormal potassium migration into the cells. The most frequent causes are renal or gastrointestinal losses:
  - **Increased renal losses:**
    - mineralocorticoid excess
    - diuresis: diuretics, osmotic diuresis
    - metabolic alkalosis
    - iatrogenic
    - renal tubular acidosis
  - **Gastrointestinal losses:**
    - vomiting
    - diarrhea
  - **Shift between the intra- and extracellular compartments:**
    - acute alkalosis
    - insulin therapy
    - glucose administration

2. **Hyperkalemia**

- **Definition:** increase in plasma levels of potassium > 5.5 mEq/L

- **Clinical features:** neuromuscular, muscle weakness, cardiac toxicity, which in severe cases can lead to ventricular fibrillation or asystoly.
**Causes:** the main cause is renal failure, but it can also be present in metabolic acidosis or poorly controlled diabetes mellitus.

- **Excessive intake:**
  - potassium supplements
  - blood transfusions

- **Decreased renal output:**
  - decreased glomerular filter rate: renal failure
  - decreased tubular secretion: hypoaldosteronism and potassium-sparing diuretics

- **Shift from the intracellular compartment to the extracellular compartment**
  - acidosis
  - cellular lesions: hemolysis, trauma, burns, tumor necrosis, digoxin overdose, lack of insulin

### Table 7. Clinical features of hypo-and hyperkalemia.

<table>
<thead>
<tr>
<th>Lab test results</th>
<th>Hypokalemia</th>
<th>Hyperkalemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum potassium balance</td>
<td>&lt; 3.5 mmol/L Metabolic alkalosis</td>
<td>&gt; 5 mmol/L Metabolic acidosis</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>appetite loss, nausea, vomiting, abdominal distension, ileus, muscle weakness, fatigue, muscle cramps, paresthesia, paralysis</td>
<td>nausea, vomiting, intestinal cramps, diarrhea weakness, dizziness, paresthesia, paralysis</td>
</tr>
<tr>
<td>Neuromuscular</td>
<td>confusion, depression</td>
<td></td>
</tr>
<tr>
<td>Central nervous system</td>
<td>orthostatic hypotension, risk for digoxin intoxication, ECG changes, cardiac arrhythmias</td>
<td>ECG changes, cardiac arrest in severe hyperkalemia</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CHECKPOINT**

1. A 56 years old patient presents with nicturia, fatigue and muscle hypotonia. The laboratory tests show the following: BP=160/100 mmHg, Na=150 mmol/L, K=2.8 mmol/L, urea=26 mg/dL, creatinine=0.8 mg/dL, serum glucose=100 mg/dL. Which is the most likely diagnosis?
   - A. Diabetes mellitus
   - B. Acute renal failure
   - C. Primary hyperaldosteronism
   - D. Hypoaldosteronism
   - E. Addison’s disease

2. A patient presents the following electrolyte values: Na* = 105 mmol/L și K* = 6.0 mmol/L. Which is the most likely cause for these changes?
   - A. Insuline deficit
   - B. ADH deficit
   - C. Parathyroid hormone excess
   - D. Renine excess
   - E. Aldosterone deficit

3. A 58 years old female patient was diagnosed with pulmonary cancer manifests over a week polyuria with polydipsia, nausea, vomiting and headaches. Plasma levels of sodium: 108mEq/L. Which of the following can represent a cause for the patient’s hyponatremia?:
   - A. Inadequate ADH secretion syndrome
   - B. Thiazide and loop diuretic administration
   - C. Hypoaldosteronism
   - D. Hyperaldosteronism
   - E. Increased adrenal activity
4. Which of the following parameters are used to calculate plasma osmolarity?

A. Urea  
B. Creatinine  
C. Plasma glucose levels  
D. Fibrinogen  
E. Serum proteins

5. A female diagnosed with type I diabetes presents after insulin administration increased sweating, weakness and muscle hypotonia. Which of the following can be the cause for the patient's clinical manifestations?

A. Isotonic dehydration  
B. Hypokalemia due to insulin administration  
C. Hyperkalemia due to insulin administration  
D. Isotonic hyperhydration  
E. Metabolic acidosis

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**CLINICAL CASES**

1. A 64 years old female patient is admitted with severe dyspnea. Her history shows hypertension and presents with edemaæ. The following lab results were obtained shortly after hospital admission:

- \(\text{Na}^+ = 123 \text{ mmol/L}\)
- \(\text{K}^+ = 5.9 \text{ mmol/L}\)
- \(\text{Cl}^- = 106 \text{ mmol/L}\)
- Urea = 68 mg/dL
- Creatinine = 2.9 mg/dL

**Which is the most likely diagnosis?**  
**Which other investigations could be recommended?**

---

2. A 47 years old female patient, diagnosed with a brain tumor is admitted into hospital with severe headache, thirst, weakness and polyuria. The lab tests show the following values:

- \(\text{Na}^+ = 150 \text{ mmol/L}\)
- \(\text{K}^+ = 4.2 \text{ mmol/L}\)
- Diureza = 3.600 ml/24h

**Which is the most likely diagnosis?**  
**Which other investigations could be recommended?**