Pathophysiology

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Lecture 5

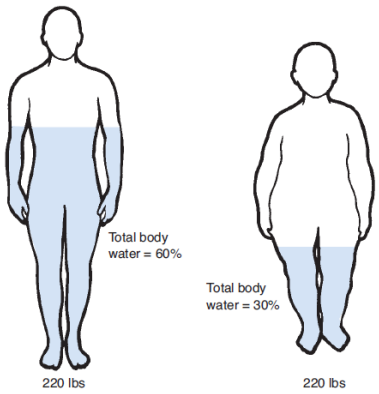
I. Disorders of Fluid, Electrolyte, and Acid-Base Balance

Learning Objectives

Upon completing this Lecture the students should be able to:
1. Comprehend the regulation of Water Balance.
2. Discuss hyponatremia, hypernatremia, hyperkalemia & hypokalemia..
3. Know the Pathophysiology of each electrolyte disturbance.
4. Know the Clinical manifestations, course, outcome of each electrolyte disturbance.

The distribution of body fluids between the ICF and ECF compartments **relies on the concentration of ECF sodium and water.** Water provides approximately 90% to 93% of the volume of body fluids and sodium salts approximately 90% to 95% of ECF solutes.
Normally, equivalent changes in sodium and water are such that the volume and osmolality of ECF are maintained within a normal range.
Because it is the concentration of sodium(in milligrams per liter) that controls ECF osmolality, **changes in sodium are usually accompanied by proportionate changes in water volume**.

I. Regulation of Water Balance



1. Total body water (TBW) accounts for approximately **60%** of body weight.
2. Individual water content **varies with the amount of adipose tissue**, which is essentially water free (i.e., fat is approximately 10% water composition compared with skeletal muscle, which is 75%).
3. **In men**, TBW approximates 60% of body weight during young adulthood and decreases to approximately 50% in old age.
4. **In young women** it is approximately 50% and in elderly women approximately 40%.
5. **Obesity** produces further decreases in TBW, sometimes reducing these levels to values as low as 30% to 40% of body weight in adults.
6. **Infants** normally have more TBW than older children or adults. TBW constitutes approximately **75% to 80%** of body weight in full-term infants and is even greater in premature infants.

7. **Infants** have relatively more water in their ECF compartment. Infants have more than half of their TBW in the ECF compartment, whereas adults have only approximately a third.

The greater ECF water content of an infant can be explained:

a. ***Higher metabolic rate***.
b. ***Larger surface area*** in relation to its body mass.
c. ***Inability to concentrate its urine*** because of immature kidney structures.

Because ECF is more readily lost from the body, infants are more **vulnerable to fluid deficit than are older children and adults.**

8. As an infant grows older, TBW decreases, and by the second year of life, the percentages and distribution of body water approach those of an adult.

Gains and Losses.

1. **Regardless of age, all healthy persons require approximately 100 ml of water per 100 calories metabolized for dissolving and eliminating metabolic wastes.** This means that a person who expends1800 calories for energy requires approximately 1800 ml of water for metabolic purposes.
2. The **metabolic rate increases with fever**, rising by approximately 12% for every 1ºC (7% for every 1ºF) increase in body temperature.
3. **Fever also increases the respiratory rate**, resulting in additional loss of water vapor through the lungs.

The main source of water gain is through:

a. Oral intake and metabolism of nutrients.
b. Tube feedings and parenterally administered fluids.
c. Metabolic processes also generate a small amount of water.

The amount of water gained from these processes varies from 150 to 300 ml/day, depending on the metabolic rate.

Water loss

a. The largest loss of water occurs through the kidneys.
b. Lesser amounts being lost through the skin, lungs, and gastrointestinal tract.

Even when oral or parenteral fluids are withheld, the kidneys continue to produce urine as a means of ridding the body of metabolic wastes. The urine output that is required to eliminate these wastes is called the ***obligatory urine output***. Water losses that occur through the skin and lungs are referred to as ***insensible water losses*** because they occur without a person's awareness. Insensible water loss through the respiratory tract averages 300 to 400 ml/day.

Sources of Body Water Gains and Losses in the Adult			
Gains		**Losses**	
Oral intake		Urine	**1500 ml**
As water	**1000 ml**	Insensible losses	
In food	**1300 ml**	Lungs	**300 ml**
Water of oxidation	**200 ml**	Skin	**500 ml**
		Feces	**200 ml**
Total	**2500 ml**	**Total**	**2500 ml**

Sodium (Na^+)

The **normal concentration of sodium in the blood plasma is 136-145 mEq/l.** In contrast, only a small amount (10 to 14 mEq/l [10 to 14 mmol/l]) is located in the ICF compartment. **Serum osmolality** (normal range, 275 to295 mOsm/kg) ***usually changes with changes in serum sodium concentration.***

Because sodium is part of the sodium bicarbonate molecule, it is important in regulating **acid-base balance**, and as a **current-carrying ion**, it contributes to the function of the nervous system and other excitable tissue.

II. Hypernatremia

Hypernatremia is defined as a serum sodium level over 145 mEq/l.

Severe hypernatremia, with serum sodium above 152 mEq/l, can result in **seizures and death**.

It occurs in patients with inadequate access to water or impaired thirst mechanism **usually in infants or elderly adults**.

Hypernatremia is seen in about **1%** of hospitalized patients and is more common(**7%**) in intensive care unit patients.

Mortality rate as high as 40% is reported with hypernatremia, though it is uncommonly identified as the primary cause of death.

Causes of Hypernatremia

1- Pure Water deficit

a) **Inadequate intake** (e.g., Poor water access due to debility, Adipsic hypernatremia).
b) **Insensible losses** by Skin, Respiratory tract (mechanical ventilation).
c) **Renal Loss**:
   Diabetes insipidus:
   i-Primary Central or Nephrogenic DI.
   ii- Secondary Central or Nephrogenic DI.
   e.g., head trauma, neoplasm, renal disease, hypercalcemia, hypokalemia, pregnancy, **Lithium, Demeclocycline, Methoxyflurane, Foscarnet, Aminoglycosides, Amphotericin B, Cidofovir, Vaptans**).

2- Water and Sodium deficit

a) **Extrarenal Loss**: **Skin** (burns, excessive sweating) **Gastrointestinal Tract** (viral gastroenteritis, **osmotic diarrhoea** e.g. lactulose, vomiting.
b) **Renal Loss**: Loop Diuretics, Osmotic diuresis (Hyperglycemia, Mannitol, High Protein Diet, Tissue catabolism), Renal disease, Post obstructive diuresis, Resolving or polyuric Acute Tubular Necrosis.

3- Sodium Gain

(Iatrogenic, hyperaldosteronism, Cushing's syndrome, sea water intake, ingestion of salt or baking soda, hypertonic feeding).

4- Transient

After seizures or vigorous exercise.

Pathophysiology of hypernatremia

The serum sodium concentration (Na^+) can be seen as *a function of the total exchangeable sodium and potassium in the body and the total body water*.
The formula is expressed below:

$$Na^+ = \frac{\text{Na total body} + \text{K total body}}{\text{total body water}}$$

Hypernatremia can only develop as a result of either a loss of free water or a gain of sodium or a combination of both. **Hypernatremia by definition is a state of hyperosmolality**, because sodium is the dominant extracellular cation and solute.

The normal plasma osmolality lies between **275 and 290 mOsm/kg** and is primarily determined by the concentration of sodium salts.

$$\textbf{Calculated plasma osmolality} = \frac{2(\text{Na})\ \text{mEq/L} + \text{serum glucose (mg/dL)}}{18} + \frac{\text{BUN (mg/dL)}}{2.8}.$$

"BUN= blood urea nitrogen"

Regulation of the plasma osmolality and the plasma sodium concentration is mediated by changes in water intake and water excretion. This occurs via two mechanisms:

1. **Urinary concentration** (via pituitary secretion and renal effects of the antidiuretic hormone arginine vasopressin.
2. **Thirst**.

An increased osmolality draws water from cells into the blood, thus dehydrating specific neurons in the brain that **serve as osmoreceptors or "tonicity receptors**."
On stimulation, they signal to other parts of the brain to initiate thirst and activate vasopressin release, resulting in increased water ingestion and urinary concentration, rapidly correcting the hypernatremia state.

- Cell initially responds to extracellular hypertonicity through **passive osmosis** of water extracellularly, resulting in cell shrinkage.
- Cell actively responds to extracellular hypertonicity and cell shrinkage in order to limit water loss through transport of **organic osmolytes** across the cell membrane, as well as through intracellular production of these osmolytes.
- **A rapid correction** of extracellular hypertonicity results in passive movement of water molecules into the relatively hypertonic intracellular space, causing cellular swelling, damage, and ultimately death.

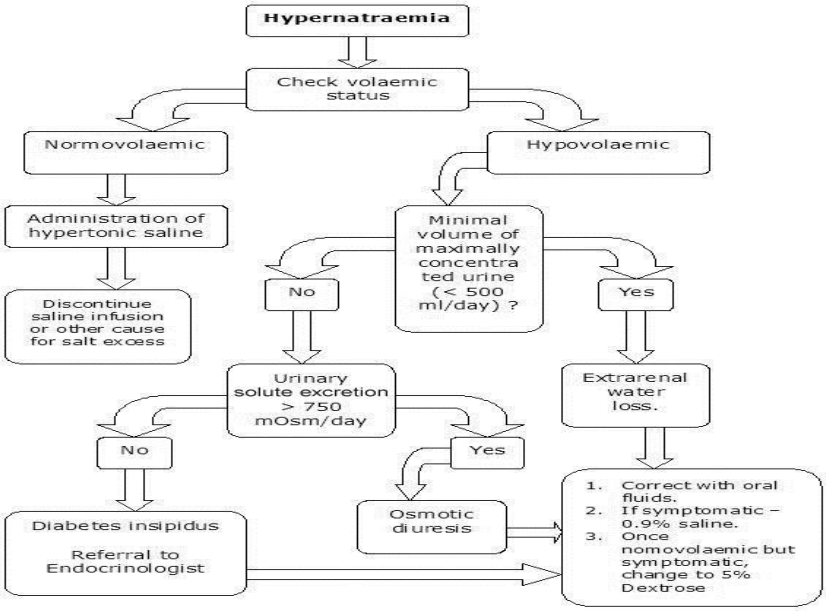
Clinical manifestations of hypernatremia

It can be

1. **Subtle.**
2. **Lethargy.**
3. **Weakness & irritability.**
4. **Neuromuscular excitability.**
5. With more severe elevations of the sodium level, **seizures and coma** may occur.

Severe symptoms are usually due to acute elevation of the plasma sodium concentration to **above 157 mEq/l** (*normal blood levels are typically about 136-145 mEq/l for adults and elderly*).

6. Values above 180 mEq/L are associated with a **high mortality rate**, particularly in adults. However such high levels of sodium **rarely occur without severe coexisting medical conditions.**



II. Hyponatremia

Hyponatremia is the **most common disorder of electrolytes** encountered in clinical practice, occurring in up to **15% to 30%** of both acutely and chronically hospitalized patients.

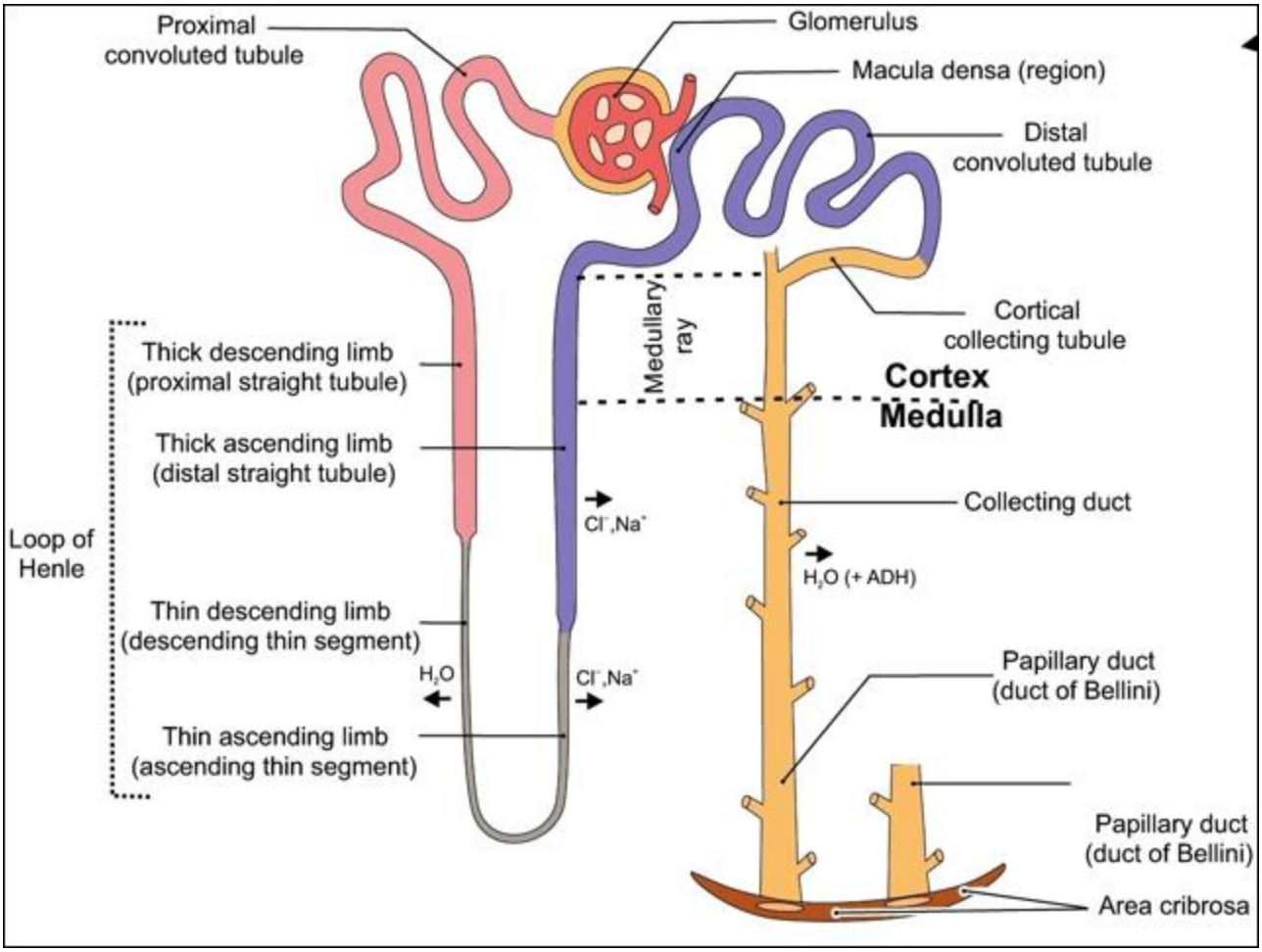
Pathophysiology of hyponatremia

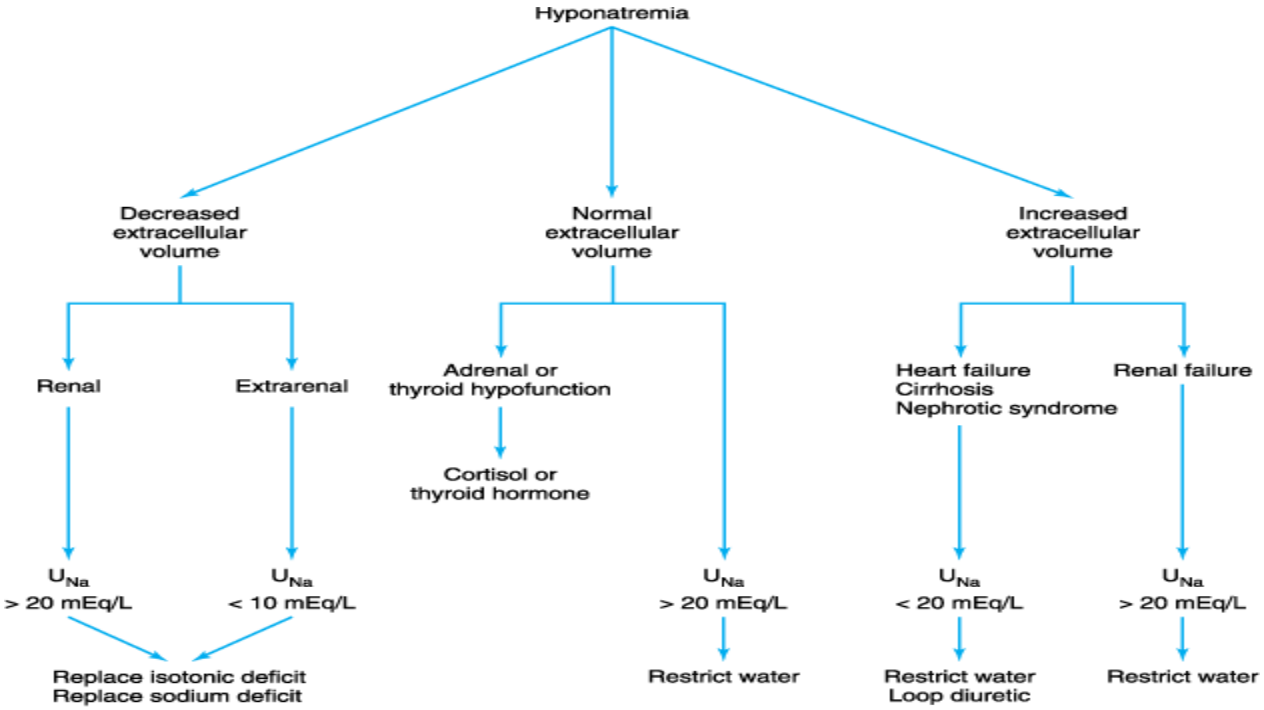
1) "**Renal water excretion depends on the diluting ability of the nephron**".
   "Dilution of urine" occurs with reabsorption of solutes by the
   A. **Na-K-2Cl transporter in the thick ascending limb of loop of Henle**.
   B. **NaCl transporter in the distal convoluted tubule.**
   C. A**bsence of ADH action at the collecting tubule**.

Dysfunction in these steps limits the ability to dilute urine and the maximum amount of urine that can be excreted.

For example, *if urine cannot be diluted below **350mOsm/ kgH2O**, the maximum amount of water that can be excreted is 700/350=2 liters (as opposed to 700/50=14 liters of urine that can be excreted with maximum dilution to 50mOsm/ kgH2O).*

2) Another cause is: **water intake in excess** of this renal (and extrarenal) water loss causes hyponatremia.





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Causes

1- **Isotonic Hyponatremia:**
   a) Hyperproteinemia.
   b) Hyperlipidemia.

2- **Hypertonic hyponatremia:**
   a) Hyperglycemia.
   b) Mannitol infusion.

3- **Hypervolemic hypotonic hyponatremia:**
   a) Congestive heart failure.
   b) Nephrotic syndrome.
   c) Cirrhosis.

4- **Euvolemic hypotonic hyponatremia:**
   a) Glucocorticoid insufficiency.
   b) Hypothyroidism.
   c) Syndrome of inappropriate antidiuretic hormone secretion (SIADH).
   d) Drugs causing euvolemic hyponatremia resembling SIADH:
      i. Carbamazepine.
      ii. Opioids.
      iii. Barbiturates.
      iv. Vincristine.
      v. Cyclophosphamide.
      vi. Chlorpropamide.
      vii. Phenytoin.
      viii. Co-trimoxazole.

5- **Hypovolemic hypotonic hyponatremia:**
   a) Severe diarrhea and vomiting.
   b) Diuretics (particularly thiazide diuretics, less commonly with loop diuretics).

6- **Environmental causes**
   a) Low dietary solute intake such as that seen in beer drinkers and malnourished patients.
   b) Pediatric: prematurity (euvolemic) or oral rehydration with tap water (hypovolemic, eg, in gastroenteritis).

7- **Rare causes**
   - Laboratory or phlebotomy sampling error.

Risk factors

a) Extremes of age.
b) Debilitating disease.
c) Malnutrition.
d) Alcoholism.
e) CNS disorders (infectious, vascular, metabolic, traumatic).

Hyponatremia signs and symptoms may include:
Most patients present with "neurological manifestations" ranging from **mild Headache & Nausea, vomiting to sever like disorientation, Confusion, Seizures to Unconsciousness and it might even reach Coma.**
Other clinical features which are associated like: **Loss of energy, Fatigue Restlessness and irritability Muscle weakness & spasms or cramps.**

III. Hyperkalemia

Hyperkalemia refers to an **increase in the serum level above 5.0 mEq/l.**
It is a common, silent, and potentially lethal clinical condition.
Hyperkalemia develops when the regulation between potassium intake and excretion or the distribution between intra- and extracellular potassium is **disturbed**. The vast majority of total body potassium is present in the intracellular fluid. The ubiquitous Na^+- K^+ ATPase transports potassium from the extracellular space into the intracellular space, against its electrochemical gradient. Estimates of total body potassium suggest that approximately 98% of total body potassium is present in the intracellular space, with primarily in muscle & **2% in the extracellular fluid**. Total body potassium stores amount to approximately 50 mEq/kg (3500 mEq in a 70-kg person).

Pathophysiology of hyperkalemia

A- Intake of K^+
Potassium is obtained through the diet. Common potassium-rich foods include meat, beans, tomatoes, potatoes, and fruits such as bananas. Gastrointestinal (GI) absorption is complete, resulting in daily excess intake of about 1 mEq/kg (60-100 mEq).

B- Execration of K^+
90% of potassium excretion occurs in the urine, with less than 10% excreted through sweat or stool. Within the kidneys, potassium excretion occurs mostly in the **principal cells of the cortical collecting duct** (CCD). **Urinary potassium excretion depends on adequate luminal sodium delivery to the distal convoluted tubule** (DCT) and the (CCD), as well as the effect of **aldosterone and other adrenal corticosteroids with mineralocorticoid activity**.
A family of signaling molecules, the **WNK (with no lysine [k])** kinases, plays a critical role in the **regulation of sodium and potassium transport in the distal nephron**.
The WNK kinases are suspected of playing a role in the pathogenesis of several forms of hypertension.
The basic pathophysiology of hyperkalemia states involves **either:**
a- **Extracellular potassium shifts**.
b- **Decreased renal excretion**.
The Common etiologies leading to measurement of hyperkalemia include:
i-**Pseudohyperkalemia**.
ii- Decreased renal excretion.
iii- Abnormal potassium distribution.

C- Increased dietary potassium intake or other exogenous sources **rarely** cause more than **transient hyperkalemic** states unless underlying pathology is present.
D- Similarly, during increased potassium release from endogenous sources, such as high cell turnover or tissue damage, hyperkalemic states are **transient**, *unless concomitant renal pathology is present.*

Etiology of Hyperkalemia

1- **Pseudohyperkalemia**
   a. Prolonged tourniquet time.
   b. Test tube hemolysis.
   c. Sample taken from a limb infused with IV fluids containing potassium.
2- **Transcellular shift** (intracellular to extracellular compartment).
   a. Acidosis (including diabetic ketoacidosis).
   b. Drugs (digoxin poisoning, succinylcholine, arginine, b-blocker).
3- **Renal causes**
   a. Acute or chronic renal failure.
   b. Mineralocorticoid deficiency (hypoaldosteronism states).
   c. Drugs that interfere with potassium excretion (amiloride, spironolactone).
   d. Drugs that interfere with the renin-angiotensin system (angiotensin converting enzyme inhibitors, angiotensin II receptor blocker, nonsteroidal anti-inflammatory agents, **heparin**).
4- **Increase circulating potassium** - Exogenous or Endogenous.
   a. Exogenous (potassium supplementation).
   b. Endogenous (tumor lysis syndrome, rhabdomyolysis, trauma, burns).

Clinical manifestations

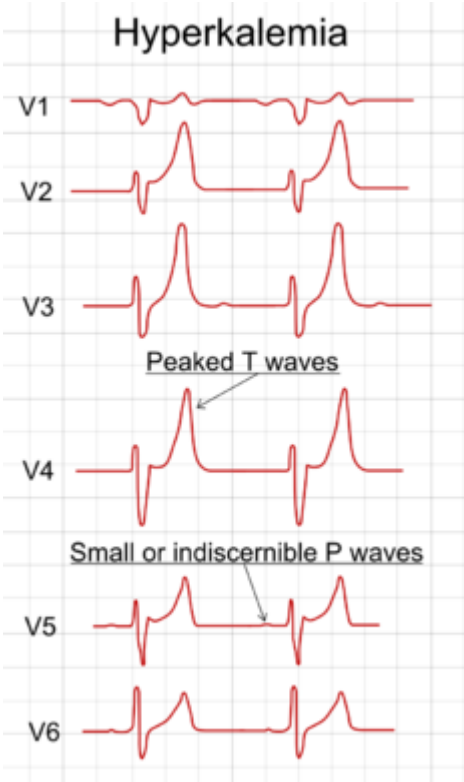
Hyperkalemia is classified as –
• **Mild** K^+(5.5 - 6.0)
• **Moderate** K^+ (6.1 - 6.9) or
• **Severe** K^+(7.0)

ECG changes & symptoms (muscle weakness or flaccid paralysis palpitations, paresthesias) occurring at ANY level or serum potassium ≥5.5mmol/l.

Clinical manifestations of mild to moderate hyperkalemia are usually **non-specific** and may include generalized weakness, fatigue, nausea, vomiting, intestinal colic, and diarrhea. Severe hyperkalemia may lead to life-threatening conditions such as **cardiac arrhythmias and muscle paralysis**.

(Note) *When the potassium level increases in the extracellular space, the potassium concentration gradient across the cellular wall decreases; and this decreases the resting membrane potential. The change in resting membrane potential caused by hyperkalemia is the principle pathophysiologic mechanism behind most of its symptoms.*

Hyperkalemia can cause a progression of ECG changes such as:
1- **Increased T wave** amplitude (peaked T-waves).
2- **Prolongation of the PR** interval.
3- **Prolongation QRS duration**.
4- **Loss of P waves**.
5- **AV conduction delay**.
6- Culminating in the **merging of the QRS complex with the T wave** producing a sine wave pattern.
7- **Asystole**.



Clinically, patients can present with

- Palpitations.
- Syncope.
- Sudden cardiac death.
- Furthermore, hyperkalemia causes **sustained spontaneous depolarization of skeletal muscles** that leads to **inactivation of sodium channels** of the muscle membrane. These changes can produce the symptoms of **muscle weakness** and in extreme cases, **paralysis.**

IV. Hypokalemia

Hypokalemia is generally defined as a serum potassium level of **less than 3.5** mEq/L (3.5 mmol/l).
Severe hypokalemia is a level of less than 2.5 mEq/l. Hypokalemia is a potentially life-threatening imbalance that may be iatrogenically induced (***Medical error***).

Pathophysiology

Most symptoms are caused by changes in the **cellular resting potential** and **membrane excitability**, which are related to the ratio of intracellular to extracellular potassium.

- Hypokalemia causes a hyperpolarization of the resting membrane potential, resulting in impaired muscle contraction.
- Many patients with mild hypokalemia have **no symptoms**.
- In progressing hypokalemia, nonspecific symptoms such as **generalized weakness and fatigue** can occur.
- Patients with a **chronic loss** of potassium may have few symptoms because intracellular potassium moves extracellularly, thus restoring the intracellular to extracellular potassium ratio.

Hypokalemia can result in a variety of cardiac arrhythmias, ranging from **bradycardia to ventricular fibrillation**; however, they are **very rare**. In patients with cardiovascular ischemia or heart failure, even small decreases in serum potassium can result in arrhythmias. **Polyuria and polydipsia** may also occur.

Causes of Hypokalemia

Common causes

1- Medications:

a) Thiazide and loop diuretics, aminoglycosides, amphotericin B, β2-agonists, and adrenal steroids.
b) Chronic laxative abuse.

2- Gastrointestinal:

a) **Vomiting**, which may be self-induced in patients with some eating disorders, causes loss of hydrochloric acid, metabolic alkalosis, a low urinary chloride level, and increased renal potassium excretion.
b) **Gastric outlet obstruction**, which may be caused by peptic ulcers in adults or by pyloric stenosis in infants and children, produces a similar metabolic pattern to that of vomiting.
c) **Severe diarrhea** can cause hypokalemia and metabolic acidosis.
d) **Poor dietary intake**.
e) **Hypothermia**.

3- Renal:

a) Renal tubular acidosis.
b) Magnesium deficiency associated with alcoholism can cause refractory hypokalemia.
c) Use of cisplatin, gentamicin, or levodopa also can cause refractory hypokalemia.
d) Primary hyperaldosteronism caused by a single adrenal adenoma (**Conn syndrome**) and bilateral adrenal hyperplasia.
e) Renal tubular acidosis, which may be distal (severe hypokalemia) or proximal (milder hypokalemia).
f) Salt-losing nephropathies.

Serious causes

a) **Diabetic ketoacidosis** causes potassium depletion, but hypokalemia can be masked until insulin and fluids are administered, which leads to a rapid influx of potassium into cells.
b) **Vitamin B12 therapy for megaloblastic** anemia produces new erythrocytes, resulting in an intracellular influx of potassium, which may produce severe and potentially lethal hypokalemia.

Risk factor

1- More common in **hospitalized patients** (approximately 15%) than in outpatients (approximately 3%).

2- Age Can occur at any age but is **uncommon** in children.

Elderly patients are at risk because of poor dietary intake and/or use of diuretics.

Clinical manifestations

Mild Hypokalemia: 3.0-3.5 mEq/L

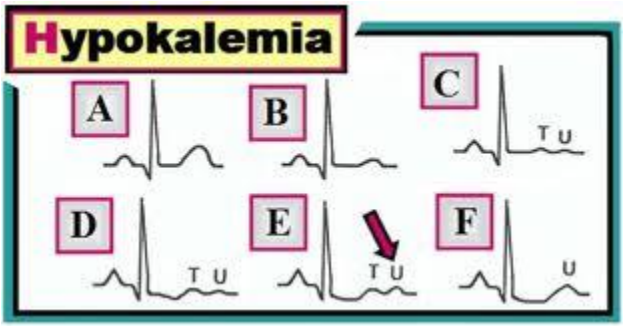
Moderate Hypokalemia: 2.5-3.5 mEq/L

Severe Hypokalemia: <2.5 mEq/L

- **Mild** hypokalemia is most often **asymptomatic**.

- As plasma levels drop below 3.0mEq/dL nonspecific symptoms like
  i-Weakness.
  ii- Malaise.
  iii- Constipation appear.
- At levels less than2.5mEq/dL,
  i- **Hypotension.**
  ii- Rhabdomyolysis secondary to decreased glycogen synthesis may occur.
- Below2.0mEq/dl
  i-Interstitial nephritis.
  ii- An ascending paralysis may appear.
  Hypokalemia & cardiac arrhythmias increase, especially in the presence of ischemia, hypertension or digitalis therapy.

Effects Of Hypokalemia On The ECG

Changes appear when K+ falls below about 2.7 mmol/l.

A. Increased **amplitude and width** of the **P wave.**
B. **Prolongation of the PR** interval.
C. **T wave flattening** or inversion.
D. **ST depression**.
E. **Prominent U waves** (best seen in the precordial leads).
F. Apparent **long QT** interval due to fusion of the T and U waves (= long QU interval).