Hypo- hypernatremia
Pathophysiology of K, P_i, Mg, Cl and trace metals
Osmosis

Starling forces

**Table:**

<table>
<thead>
<tr>
<th>Intracellular Water (2/3)</th>
<th>Extracellular Water (1/3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 Na</td>
<td>140</td>
</tr>
<tr>
<td>150 K</td>
<td>4.5</td>
</tr>
<tr>
<td>15 Mg</td>
<td>1.2</td>
</tr>
<tr>
<td>0.01 Ca</td>
<td>2.4</td>
</tr>
<tr>
<td>2 Cl</td>
<td>100</td>
</tr>
<tr>
<td>6 HCO₃</td>
<td>25</td>
</tr>
<tr>
<td>50 Phos</td>
<td>1.2</td>
</tr>
</tbody>
</table>

**Volumes:**

- ICF = 2/3 TBW (28 L)
- ISF = 3/4 ECF (10.5 L)
- ECF = 1/3 TBW (14 L)
- IVF = 1/4 ECF (3.5 L)
- TWB = 60% weight (42 L)

**Sources:**

- Food: 700-1000 ml
- Drink: 550-1500 ml
- Metabolic: 200-300 ml

**Excretion:**

- Kidneys (urine): 500-1400 ml
- Skin*: 450-900 ml
- Lungs: 350 ml
- Feces**: 150 ml
<table>
<thead>
<tr>
<th>(1000 ml)</th>
<th>Distribution</th>
<th>Distribution of 1000 ml fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Intracellular 66%</td>
</tr>
<tr>
<td>5% dextrose in water</td>
<td>TBW</td>
<td>660</td>
</tr>
<tr>
<td>0.9% NaCl</td>
<td>EC</td>
<td>750</td>
</tr>
<tr>
<td>½ normal NaCl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water (50%)</td>
<td>TBW</td>
<td>335</td>
</tr>
<tr>
<td>0.9% NaCl (50%)</td>
<td>EC</td>
<td>375</td>
</tr>
<tr>
<td>Plasma</td>
<td>Intravascular</td>
<td></td>
</tr>
</tbody>
</table>
Salt and water balance – basic principles

- Measurement of the **total body Na content** determines the volume of ECF
  - Hyper-, hypo-, or iso (eu)volemic
- The **plasma Na concentration** reflects the **relative amounts** of Na and water present in the sample
  - Disturbance in plasma Na concentration reflects a disorder of water balance
    - Hyponatremia < 136 mmol/l or hypernatremia > 145 mmol/l
  - Relative amounts of Na and water determines plasma osmolality
    - hyper- (> 296 mOsm/kg), iso- (280-296 mOsm/kg) or hypo- (< 280 mOsm/kg) osmosis in the ECF
• **Osmolality** is a measure of the osmoles of solute per kilogram of solvent (mOsmol/kg). Osmolality is measured by osmometers (e.g. freezing point depression)
  ○ Effective osmole or **tonicity**: solute (Na [confined to the ECF by the Na/K ATPase], glucose, mannitol, K⁺ [confined to the ICF]) unable to cross from ECF compartment into the ICF compartment → ↑ oncotic pressure and capable of causing water to move across membranes from ECF to ICF.
    ■ Tonicity determines the normal state of cellular hydration and therefore cell size
  ○ Ineffective osmole: solute (urea-N, ethanol, methanol, ethylene glycol, isopropyl alcohol) that does not cause water movement across membranes so can contribute to osmolality but does NOT contribute to tonicity.
**Osmolarity**: the number of osmoles (Osm) of solute per liter (L) of solution (mosmol/L) and if the concentration of solutes is very low, osmolarity and osmolality are equivalent

- Osmolarity is **calculated** from this formula
  - \( P_{\text{osm}} = 2 [\text{Na}^+]_p + \text{urea N} + \text{glucose} [\text{mmol/l}] \) (280-296 mOsm)

**Osmolar gap** = \( P_{\text{osm}}(\text{measured}) - P_{\text{osm}}(\text{calculated}) \)

- Reference rage for osmolar gap: < 10 to 15 mOsm/kg
- Osmolar gap is in the reference rage: in poisoning with sedato-hypnotics, salicylate, paraldehyde, acetaminophen, aspirin
- Elevated osmolar gap: in the presence of osmotically active substance in the blood (urea-N, ethyl-, methyl alcohol, ethylene glycol, isopropyl alcohol etc)

**Summary**: Disorders of Na balance are manifested as hypovolemia or hypervolemia. Disorders of water balance are manifested as hypo or hypernatremia
Proximal tubule
67% Na reabsorption (various transporters)
Na-H exchange (NHE)

Osmotic diuretics
Carbonic anhydrase inhibitors

Distal tubule
5% Na reabsorption
Na-Cl cotransporter (NCC)

Thiazide diuretics
Gitelman syndrome

Thick ascending segment (TAL)
25% Na reabsorption
Na-K-2Cl cotransporter (NKCC)

Loop diuretics
Bartter syndrome

Cortical collecting tubule (CCT)
3% Na reabsorption
Epithelial Na channel (ENaC)

K sparing diuretics
Plasma osmolality (280-296 mOsm/kg)

Decrease
- Suppression of thirst
- Suppression ADH release
- Diluted urine

Increase
- Stimulation of thirst
- Stimulation of ADH release
- Concentrated urine

Impairment of free water excretion by the kidneys + Excess water intake

Impairment of concentrating ability of the kidneys + Inadequate water intake

Hyponatremia

Hypernatremia
Hyponatremia (Na < 136 mmol/l)

- Forms of hyponatremia
  - Hyperosmotic hyponatremia (hypertonic hyponatremia)
  - Isoosmotic hyponatremia (isotonic or pseudohyponatremia)
  - Hypoosmotic hyponatremia (hypotonic hyponatremia – results in cellular overhydration)
    - I. Hypovolemic hyponatremia
    - II. Iso / euvoletic hyponatremia
    - III. Hypervolemic hyponatremia
Hyperosmotic hyponatremia (hypertonic hyponatremia)

- Hyponatremia and high plasma osmolality (> 296 mOsm/kg)
- Hyponatremia is due to shift of water from cells in response to non-Na solute (redistributional hyponatremia)
  - Accumulation of effective osmoles (glucose, mannitol, sorbitol, mannose) in ECF → osmotic withdrawal of water from ICF (intracellular dehydration) → expansion of ECF → dilutes Na
    - Increase of glucose by 5.6 mmol/l - decrease of Na by 1.6 mmol/l
- **Solution**: treat hyperglycemia!
Isoosmotic hyponatremia (isotonic or pseudohyponatremia)

- Hyponatremia + normal plasma osmolality (280-296 mOsm/kg)
- Pseudohyponatremia is an artifact if flame emission spectrophotometry is used for Na determination and the patient has hyperlipidemia or hyperproteinemia
  - Normally 7% proteins and lipids in plasma, 93% water
  - Diseases that reduce plasma water below the usual 93%: hyperlipidemia or hyperproteinemia (macroglobulinemia, myeloma multiplex)
    - Solution: use ion-selective electrodes
- True isoosmotic hyponatremia may develop during transurethral prostate gland resection
  - Too much Na free irrigation fluid is used (glycine, sorbitol)
Hypoosmotic hyponatremia (hypotonic hyponatremia)

Hyponatremia and hypoosmolar condition (< 280 mOsm/kg) – results in cellular over hydration
All forms are characterized by relative/absolute impairment of free water clearance / excretion (limitation in urinary dilution)

Urine volume is determined by two components: osmotic and free water clearance

Physiologic requirements of normal dilution process in the kidney

1. Normal delivery of tubular fluid to the distal diluting segment of the nephron
   Normal glomerular filtration rate and proximal reabsorption of tubular fluid; if proximal reabsorption increases → causes decreased distal fluid delivery, the volume of dilute urine excreted will be limited

2. Normal function of the diluting segment
   Tubular fluid is diluted in the water-impermeable ascending limb of Henle’s loop by reabsorption of NaCl

3. Absence of vasopressin or any other substance that could render the collecting duct permeable to water
• Forms of hypoosmotic hyponatremia
  ○ I. Hypovolemic hyponatremia
  ○ II. Iso/euvolemic hyponatremia
  ○ III. Hypervolemic hyponatremia

Hyponatremia

Isotonic
Salt loss > Water loss
low EC volume

Hypotonic
Water excess
„normal” EC volume

Hypertonic
Water excess > Salt excess
high EC volume
Hypovolemic hyponatremia

- Hypovolemic hyponatremia: decrease in total body Na (TBNa⁺) > decrease in total body water (TBW)
  - Underlying compensatory mechanism: volume-contraction stimulates non-osmotic ADH secretion with continued oral or parenteral hypotonic fluid intake

- Forms of hypovolemic hyponatremia
- 1. Extra renal salt and water loss
  - Gastrointestinal (vomiting, diarrhea) and third-space losses (burns, pancreatitis, trauma)
2. Renal salt and water loss
   ○ A.) Diuretics: osmotic (with Na loss), thiazide and loop diuretics (mainly in elderly ♀)
   ○ B.) Salt-losing nephropathy
     ■ Polycystic kidney disease, analgesic nephropathy and obstructive uropathy
     ■ RTA-2: bicarbonaturia obligates renal Na and K wastage
   ○ C.) Primary adrenal cortex insufficiency (mineralocorticoid, glucocorticoid deficiency in Addison’s disease)
     ■ Salt-losing due to lack of aldosterone – ↓ ECF volume → GFR ↓ - proximal tubular Na reabsorption ↑ (glomerular-tubular feedback, minimal compensation)
     ■ Decreased ECF volume provides the non-osmotic stimulus for ADH release ↑↑
II. Iso/euvolemic hyponatremia

- Hyponatremia with ~ normal/slightly decreased TBNa⁺ (euvolemic) with slightly increased free water
  - Retention of 2-5 l of water (2/3 in cells) is not enough to produce ECF expansion and produce manifest edema

- Clinical settings
  - 1. Adrenal insufficiency with isolated glucocorticoid deficiency
    - Hyponatremia due to raised levels of ADH
      - Due to glucocorticoid deficiency CRF-ACTH axis is activated & ADH level goes parallel with CRF
      - Lack of glucocorticoid inhibition on ADH-gene expression
      - Low circulating volume stimulates ADH secretion
2. Hypothyroidism with myxoedema
   - Cardiac output and GFR are reduced; ADH secretion is increased inappropriately
3. Acute postoperative hyponatremia (frequent in postmenopausal females)
   - Infusion of excessive amounts of electrolyte-free water (hypotonic saline or 5% dextrose in water)
   - Pain, hypotension, hypoxia, anesthesia → persistent ADH stimulation
4. Syndrome of inappropriate ADH
5. Resetting of the osmostat
6. Drug-induced hyponatremia
   - ADH and analogues: vasopressin, desmopressin
   - ADH-release agonists: nicotine, vincristin
   - Potentiating the peripheral action of ADH: cyclophosphamids, NSAID
   - Psychoactive agents: fluoxetine, haloperidol, ecstasy & SSRI
7. Beer potomania

- Maximal dilution capacity of the kidney is limited to 50 mOsm
- Early distal tubule osmotic concentration (each 50 mOsm solute can capture 1 l water)
- Normal diet contains up to 1000 (550-1000) mOsm/day
  - 20l (1000/50=20) urine is lost before the patient becomes hyponatremic

Due to the small amount of osmotically active material (200 mOsm) of beer; low Na content gets to the collecting duct. The only way to keep Na by the kidneys is to produce a maximally diluted urine

- 200/50 = 4l → if the beer consumption is over 4 l/day; fluid retention and hyponatremia can be expected
8. Acute psychosis secondary to schizophrenia have a propensity to hyponatremia / primary polydipsia (compulsive water drinking)

- The mechanism may be multifactorial
  - Increased thirst perception (phenothiazine derivatives can cause dry mouth) leading to polydipsia
  - A mild defect in osmoregulation that causes ADH to be secreted at lower osmolality (resetting the osmostat)
  - Enhanced renal response to ADH
  - Antipsychotic drugs: see No. 6.

- Daily intake of 10-15 l water lead to development of hyponatremia by the end of the day; can be reversed if there is no water intake during the night
III. Hypervolemic hyponatremia

- Hyponatremia with increased TBNa⁺ (hypervolemic) but TBW is increased even more, causing hyponatremia and edema (*Repetitio est...*)
  - General features of edema
    - Secondary aldosteronism: salt and water retention
    - Effective vascular volume is compromised → activates volume / pressure receptors → release of non-osmotic ADH

- Forms of hypervolemic hyponatremia
  - 1. Congestive heart failure
  - 2. Hepatic insufficiency and cirrhosis
  - 3. Nephrotic syndrome with normal renal function
  - 4. Advanced chronic renal insufficiency
    - A profound increase in fractional excretion of Na keeps the patient in normal salt balance (adaptation)
    - Edema usually develops when the Na ingested exceeds the kidney's capacity to excrete this load
Hypernatremia (Na > 145 mmol/l)

- Hypernatremia occurs when water intake is less than daily obligatory, insensible, GI and renal losses or if ADH is decreased or ineffective, but iatrogenic salt overdose can occur.
- The proportion of TBW < TBNa⁺ All forms are hyperosmolal (> 296 mOsm/kg) and hypertonic → IC dehydration.
- Forms
  - Hypovolemic / Iso/euvolemic / Hypervolemic hypernatremia

```
Hypernatremia

Water loss > Salt loss
low EC volume

Water loss
„normalis” EC volumet

Salt excess > Water excess
high EC volume
```
Hypovolemic hypernatremia

- Na\(^+\) and free water loss, with a relatively greater loss of water
- Cause: see hypovolemic hyponatremia + water absorption disorders (hypodipsia) or worsening renal function
- Clinical settings
  - 1. Extra renal Na loss + hypodipsia; Urine [Na\(^+\)] excretion <10 mmol/l, the urine is concentrated
    - GI: diarrhea, vomiting, ileus, pancreatitis
    - Skin: profuse sweating, pemphigus vulgaris
  - 2. Renal Na loss – urine [Na\(^+\)] excretion >10 mmol/l
    - Severe osmotic diuresis (DM, mannitol)
    - Other diuretics + hypodipsia
    - Obligatory polyuria in renal failure or postobstructive diuresis (urea)
Iso/euvolemic hypernatremia

- Euvolemic with normal TBNa⁺ & free water loss (mainly from IC)
- 1. Extra renal free water loss + hypodipsia
  - Insensible losses: skin and respiratory tract
    - In febrile or other hypermetabolic states. Urine osmolality is very high, reflecting an intact osmoreceptor–ADH–renal response
  - Primary hypodipsia
    - Hypothalamic defect of thirst center (due to cancer, trauma, etc.)
    - Essential hypernatremia a variant of primary hypodipsia
      - The osmotic threshold move upwards in the event of the release of vasopressin and thirst
      - The threshold remains normal for hemodynamic stimulus
2. Renal free water loss

- Damage of renal concentrating function → loss of free water ↑
  - For *physiologic requirements* of normal concentrating mechanism see before
- Diabetes insipidus (*repetitio...*)
  - Defect in vasopressin production and/or release (central diabetes insipidus)
  - Failure of the collecting duct to respond to the hormone (nephrogenic diabetes insipidus)
  - Gestational diabetes insipidus
Hypervolemic hypernatremia

- Hypernatremia with increased TBNa$^+$
- TBNa$^+$ > water intake
- This is the least common form of hypernatremia; usually iatrogenic
  - Na gain w hypertonic solutes
    - 3% NaCl, intra-amniotic instillation for therapeutic abortion
    - NaHCO$_3$ for treatment of metabolic acidosis, hyperkalemia, and cardio respiratory arrest
    - Accidentally in dialysis against a high-Na dialysate
    - Consumption of salt tablets
  - Urine [Na$^+$] > 10 mmol/l
Consequences of hypo- and hypernatremia

*myo*-inositol and taurine
Disorders of Sodium and Water Balance

Proportionate changes in sodium and water

- Loss of sodium and water
  - Isotonic fluid deficit in ECF compartment
  - Contraction of fluids in interstitial and vascular compartments of the ECF

- Gain of sodium and water
  - Isotonic fluid excess in ECF compartment
  - Expansion of fluids in the interstitial and vascular compartments of the ECF

Disproportionate changes in sodium and water

- Loss of sodium or gain of water
  - Hyponatremia
    - Water movement from extracellular to intracellular compartment

- Gain of sodium or loss of water
  - Hypernatremia
    - Water movement from intracellular to extracellular compartment
● Saltwater (isontonic salt) is confined to ECF
  ○ Pathologic conditions
    ■ Saltwater ↓ - volume depletion
    ■ Saltwater ↑ - edema formation
  ○ Not altered primarily
    ■ Plasma Na concentration
    ■ Cell volume

● Electrolyte-free water is distributed between ICF and ECF space
  ○ Pathologic conditions
    ■ Water ↑ - hyponatremia
    ■ Water ↓ - hypernatremia
  ○ Primarily influences
    ■ Plasma Na concentration
    ■ Tonicity
    ■ Cell volume
    ■ ECF space - 1/3 (see volume distribution)
Physiology of potassium balance

- Potassium amount: 70 mmol/kg, 98% intracellular
- Physiologic functions in
  - Cell metabolism
    - Protein and glycogen synthesis
  - Neuromuscular transmission (resting membrane potential)
    - Major determinant is the ratio of [K]c/[K]e
    - Hypokalemia
      - Cell becomes more electronegative – hyperpolarizes membrane, less excitable
    - Hyperkalemia
      - Cell becomes less electronegative – depolarizes membrane, more excitable
Cell depolarization and hyperpolarization depend on extracellular K. An action potential is generated when the cell depolarizes from its resting potential (RP) to the threshold potential (TP). Hyperkalemia moves the RP closer to the TP and results in depolarization muscle paralysis. Hypokalemia hyperpolarizes the cell and thereby impairs depolarization. The flaccid paralysis caused by hypokalemia or hyperkalemia is clinically similar. Ca raises the TP, ameliorating the effects of hyperkalemia, while hypocalcemia has the opposite effect.
K balance regulated by
1. K uptake by the cells (transcellular distribution)
2. Urinary K excretion

Transcellular distribution
Active transport process
- Na⁺/K⁺-ATPase
- Insulin
- β₂-agonist agents
Passive transport process
- Acidosis → hyperkalemia
- Alkalosis → hypokalemia
- Cellular shrinkage

Urinary K⁺ excretion
K is extensively reabsorbed in the proximal tubule and thick ascending limb of the loop of Henle.

Urinary K excretion is determined primarily by K secretion by the principal cells in the CCT and outer medullary collecting tubule.
2. Urinary $K^+$ excretion (principal cells in the CCT) depends on

- 1. Aldosterone
  - $\uparrow$ in activity of $Na^+-K^+-ATPase$ pump in the basolateral membrane
  - Aldosterone $\uparrow K^+$ secretion: increase in number of K and Na channels in the apical membrane

- 2. Distal flow of Na and water to CCT determines amount of $K^+$ secreted by principal cells
  - Increased $Na^+$ delivery to the distal nephron will enhance distal $Na^+$ reabsorption and $K^+$ secretion - e.g. loop diuretic induced hypokalemia
  - Decreased $Na^+$ delivery to the distal nephron will diminish distal $Na^+$ reabsorption and $K^+$ secretion - predisposes to hyperkalemia (cardiac failure)

- 3. Plasma $K^+$ concentration
  - Increase in plasma K concentration
    - stimulates aldosterone synthesis and release
    - stimulates $Na^+-K^+-ATPase$ in principal cells
Low potassium

- Normal K⁺ stores with low plasma/serum K⁺ level (hypokalemia, K⁺ < 3.5 mmol/l); transcellular distribution (EC→IC shift)
- Depleted body K⁺ stores with low plasma/serum K⁺ level (K⁺ < 3.5 mmol/l)
- K⁺ depletion without hypokalemia
  - 1. Severe renal failure
    - Hyperkalemia with depleted IC K⁺ stores
  - 2. Diabetic ketoacidosis
    - Body K⁺ depletion (lack of insulin) and hyperkalemia
  - 3. Congestive heart failure
    - Systemic K⁺ depletion without hypokalemia
Normal K\(^+\) stores, hypokalemia due to transcellular distribution (EC→IC)

- 1. Insulin administration
- 2. Catecholamine release or therapy
  - Few cups of coffee decreases plasma K\(^+\) by 0.4 mmol/l
  - Ethanol withdrawal, hyperthyreosis, ß-mimetics
- 3. Redistribution: cellular compensation in alkalosis
- 4. Treatment of pernicious anemia
  - Rapid uptake of K\(^+\) by newly-formed cells; (similar mech: after fasting, rapid expansion of tumor disease)
- 5. Barium, chloroquin poisoning
  - Blocking the exit of K from cells
- 6. Hypokalemic periodic paralysis
  - Familial, autosomal disease, dihydropyridine receptor mutation
    - Hyperthyroidism (with Asian or Latino ancestors) or periodic paralysis upon sports (concealed hyperthyroidism)
    - Exaggerated insulin response to carbohydrate meals
Hypokalemia due to depleted body $K^+$ stores

- 1. Poor $K^+$ intake
  - Alcoholism, anorexia nervosa
- 2. Skin loss of $K^+$: burn
- 3. GI loss of $K^+$ (urinary $K^+$ loss < 20 mmol/day)
  - Gastric (metabolic alkalosis generated by HCl loss and maintained by EC volume depletion and consequent renal $K^+$ wasting)
  - Bile, diarrhea, laxatives, repeated enemas and uretero-sigmoidostomy
- 4. Renal $K^+$ loss (urinary $K^+$ loss > 40 mmol/day)
### Renal K⁺ loss (urinary K⁺ loss > 40 mmol/day)

<table>
<thead>
<tr>
<th>Hypertension + renal K⁺ loss</th>
<th>Normotension + renal K⁺ loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Aldosterone excess</td>
<td>1. <strong>Diuretics</strong> (osmotic, thiazide and loop diuretics)</td>
</tr>
<tr>
<td>Primary hyperaldosteronism (low renin)</td>
<td>2. Poorly resorbable anions: bicarbonate, penicillin, ketone bodies</td>
</tr>
<tr>
<td>Secondary hyperaldosteronism: renin mediated, malignant hypertension</td>
<td>3. Electrolyte disorders (Ca↑, Mg ↓)</td>
</tr>
<tr>
<td>2. Other mineralocorticoid excess (low renin and aldosterone level)</td>
<td>4. Mineralocorticoid excess</td>
</tr>
<tr>
<td>Endogenous: 11, 17-ßOH-ase deficiency, Liddle’s syndrome (ENaC gain of function mutation)</td>
<td><strong>Edema-forming states</strong></td>
</tr>
<tr>
<td>Exogenous: mineralocorticoid excess, licorice ingestion</td>
<td>EC volume depletion → secondary aldosteronisms → increased Na⁺ uptake in the kidney (lumen electronegativity ↑) → K⁺ and H⁺ excretion ↑</td>
</tr>
<tr>
<td>3. Glucocorticoid excess (low renin, variable aldosterone)</td>
<td>5. Acid-base balance disorders</td>
</tr>
<tr>
<td>Endogenous: Cushing’s syndrome</td>
<td>Metabolic (RTA-1 and 2) acidosis</td>
</tr>
<tr>
<td>Exogenous glucocorticoid excess</td>
<td>Metabolic alkalosis</td>
</tr>
</tbody>
</table>
Signs of hypokalemia

- Neuromuscular effects
  - Fatigue, skeletal and respiratory muscle weakness, constipation, ileus
- ECG effects ($K^+ < 2.5$ mmol/l)
  - Prolongation of PR interval
  - $P$ wave and QRS complex: amplitude and width $\uparrow$
  - ST segment depression
  - Flattening or inversion of T wave
  - Prominent U wave (often misdiagnosed as T wave)
  - Long QU time (if Ca & Mg $\downarrow$)
  - Atrial and ventricular arrhythmias may develop. The latest can develop into fatal *torsades*, VT and VF (mainly if Mg $\downarrow$)
Hypokalemia causes **ST depression, flattening of the T waves, and prominent U waves**. This progresses to fusion of the T and U waves into a single wave and the ST segment becomes negative and descending. The **QU** interval lengthens, especially if hypocalcemia or hypomagnesemia is present.
ST segment depression and low amplitude of the T wave are seen in leads I, II, aVF, and V₄–V₆.
Prominent U waves are best seen in leads II, III, aVF, and V₃–V₆.
Serum K⁺ level is 2.4 mmol/l.
Hyperkalemia (K > 5.1 mmol/l)

1. Normal total body K
   ○ Pseudohyperkalemia: *In vitro* phenomenon in hemolysis, thrombocytosis, leukocytosis
     ■ se K⁺ elevated, plasma K⁺ normal
   ○ Transcellular distribution of K⁺ (shift from IC to EC)
     ■ Exercise: physiologic reaction – vasodilation
     ■ Lack of insulin (hyperglycemia in DM)
     ■ Cell destruction
     ■ Acidosis: cellular buffering (0.1 unit pH ↓ ≈ 0.6 mmol/l K⁺ ↑)
2. Elevated total body $K^+$
   ○ Increased $K^+$ load
     ■ Dietary (salt substitutes: KCl)
     ■ Iatrogenic (not more than 20 mmol/hr $K^+$ iv)
   ○ Decreased renal $K^+$ excretion
     ■ Reduced glomerular filtration rate
       □ Acute and chronic renal failure (GFR is 5-20 ml/min)
       □ Decreased distal flow, $\downarrow K^+$ excretion
     ■ Reduced tubular secretion – hypoaldosteronism
       □ RTA-4, Addison’s disease ($\downarrow$aldosterone activity), ACE inhibitors ($\downarrow$AT-II), heparin ($\downarrow$aldosterone production), inhibition of $Na^+$ transport in CCT
     ■ Renal transplants, urinary tract obstruction
Signs of hyperkalemia

- Neuromuscular
  - Paresthesia, muscle weakness, flaccid paralysis

- ECG changes
  - P wave
    - Flat and wide P wave → absent P wave
  - QRS complex
    - QRS wide → sine wave-like (QRS + T wave) → asystole
  - ST segment and T wave
    - ST elevation or depression
    - Peaked, tall T waves (II., III., V₂-V₄) or T wave > R wave (more than one lead)

- Death (K⁺ > 8.0 mmol/l): VF, asystole
Mild hyperkalemia

- **5.5-6.5 mmol/l**: fusion of QRS with T (sine wave appearance), idioventricular rhythm, and finally ventricular tachycardia and fibrillation, and asystole

Severe hyperkalemia

- **6.5-7.5 mmol/l**: loss of P wave
- **7.0-8.0 mmol/l**: widened QRS with tall T wave
- **8.0-10.0 mmol/l**: fusion of QRS with T (sine wave appearance), idioventricular rhythm, and finally ventricular tachycardia and fibrillation, and asystole
Hyperkalemia
Phosphates

- Relatively concentrated in ICF
- Roles
  - Cell signaling (cAMP, cGMP)
  - Activate / deactivate enzymes as cofactors (coenzyme A, FAD, NAD, and NADP⁺)
  - Buffer pH of body fluids
- Components of
  - Bones, nucleic acids (DNA, RNA), nucleoside triphosphates (ATP, GTP, etc), phospholipids, various other phosphorylated molecules

- Exist as mixture of three forms
  - $\text{PO}_4^{3-}$ or $\text{P}_i$ (phosphate ion)
  - $\text{HPO}_4^{2-}$ (monohydrogen phosphate ion)
  - $\text{H}_2\text{PO}_4^-$ (dihydrogen phosphate ion)

<table>
<thead>
<tr>
<th>Renal phosphaturia</th>
<th>Renal phosphate retention</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-phosphate diet</td>
<td>Low phosphate diet</td>
</tr>
<tr>
<td>PTH, phosphatoninos, glucagon, glucocorticoids</td>
<td>Thyroxin, insulin</td>
</tr>
<tr>
<td>Volume expansion, diuretics</td>
<td>Volume depletion</td>
</tr>
<tr>
<td>Chronic acidosis</td>
<td></td>
</tr>
</tbody>
</table>
Dietary or endogenous $P_i$ load → expression of FGF-23 (from bone) and PTH (from parathyroid gland) and together stimulate renal NaPi-2a (phosphaturia)

FGF-23 expression is controlled by two negative feedback loops:

1. FGF-23 inhibits activation and induces catabolism of vitamin D, whereas active vitamin D, upregulates FGF-23. 1,25-dihydroxyvitamin D also augments phosphate uptake from the GI tract by upregulation of NaPi-2b.

2. PTH stimulates FGF-23 secretion, whereas in physiological conditions FGF-23 inhibits PTH
Hypophosphatemia ($P_i < 0.81$ mmol/l)

- 1. Transcellular distribution (EC → IC)
  - Respiratory alkalosis (cellular compensation)
  - Recovery from malnutrition, alcoholism
  - Recovery from diabetic ketoacidosis – insulin administration
  - Hormonal and other agents (insulin, glucagon, epinephrine, cortisol, glucose, fructose, lactate)
    - Stimulate glycolysis, leading to the formation of phosphorylated glucose compounds and a intracellular shift of phosphorus
  - Hungry bone syndrome
    - Massive deposition of phosphorus and Ca in the bone results in hypocalcemia and hypophosphatemia
2. Decreased intestinal phosphate absorption
   ○ Fasting: anorexia nervosa, alcoholism (lack of intake, increased $P_i$ + Mg loss)
   ○ Severe dietary phosphorus restriction
   ○ Antacid abuse: binds phosphate $\rightarrow$ osteomalacia
   ○ Vitamin D deficiency or resistance
     ■ Low intestinal Ca, $P_i$ absorption
     ■ Rickets (children), osteomalacia (adults)
       □ Lack of 1-OH in kidney or resistance to active vitamin D
   ○ Chronic diarrhea
   ○ Steatorrhea
3. Increased urinary excretion
   ○ Hyperparathyroidism
     ■ Primary hyperparathyroidism
     ■ Secondary hyperparathyroidism with normal kidney function
   ○ X-linked hypophosphatemic rickets
     ■ FGF-23 is stimulated due to gene mutation
   ○ Renal tubular defects
     ■ RTA-2 (Fanconi syndrome), carbonic anhydrase inhibition
     ■ Dent syndrome: Cl channel mutation
     ■ Kidney transplantation
   ○ Volume expansion
   ○ Oncogenic osteomalacia
     ■ Circulating factor produced by mesenchymal tumors impairs renal P_i metabolism
Clinical consequences of hypophosphatemia

- Intracellular ATP ↓
- I. Hematological disturbances
  - 1. Hemolytic anemia (ATP ↓: phosphate deficiency stimulates hexokinase, pyruvate kinase activity. The stimulation of glycolysis and utilization of ATP in the first portion of Embden-Meyerhof pathway; results in ATP and 2,3-DPG depletion)
  - 2. Reduction in 2,3-DPG (decrease in oxygen carrying capacity)
  - 3. Leukocyte migration decreased
    - Impaired phagocytosis and granulocyte chemotaxis
  - 4. Platelet dysfunction
II. Neuromuscular and skeletal abnormalities
   ○ CNS dysfunctions: irritability, confusion, coma
   ○ Peripheral neurons: paresthesia, nerve conduction velocity increased
   ○ Muscle weakness
      ■ Proximal myopathy, dysphagia, ileus, respiratory muscles (respiratory failure), rhabdomyolysis (alcoholic patients)
   ○ Bone: osteomalacia
III. Cardiovascular changes
   ○ Impaired myocardial function, cardiomyopathy, hypotension
IV. Renal dysfunction
   ○ GFR ↓
   ○ Tubular transport abnormalities (loss of Ca, Mg, bicarbonate and glucose)
      ■ Hypercalciuria – no stone formation (lack of phosphate for crystal growth)
Hyperphosphatemia ($P_i > 1.45$ mmol/l)

- 1. Transcellular distribution (IC → EC)
  - Tissue destruction (extended inflammation, tumor-lysis syndrome, leukemia, rhabdomyolysis, bowel infarction, malignant hyperthermia, hemolysis, fulminant hepatitis)
  - Release $P_i$ from endogenous stores (lactic acidosis, diabetic ketoacidosis)

- 2. Increased exogenous load
  - *Per os*, intravenous infusion, acute poisoning
  - Cow’s-milk feeding to premature babies
  - Vitamin D intoxication (PTH suppression + hypercalcemia-induced kidney failure)
  - Phosphate-containing enemas ($Pi$ is absorbed paracellularly)
3. Reduced urinary phosphate excretion
   ○ Childhood: Higher P$_i$ values are related to decreased P$_i$ excretion in the kidney (physiologic!)
   ○ Renal failure – the most common cause of hyperphosphatemia (repetitio..)
   ○ Primary reduced renal P$_i$ excretion – without kidney failure
     ■ Pseudohypopathyreosis: due to PTH resistance
     ■ Tumoral calcinosis: Young black males, ectopic calcification around major joints
       □ Increased tubular Ca and P$_i$ reabsorption
       □ GALNT3 [UDP-GalNAc transferase 3] and FGF-23 loss of function mutations are present
   ○ Secondary reduced renal P$_i$ excretion – without kidney failure
     ■ Hypoparathyroidism, acromegaly
   ○ Bisphosphonate therapy (prevent the loss of bone mass)
     ■ Cellular redistribution, decreased P$_i$ renal excretion
4. Increased bone reabsorption
   ○ Osteoporosis, chronic kidney disease – mineral and bone disorder

5. Pseudohyperphosphatemia
   ○ Hemolysis in vitro
   ○ Hypertriglyceridemia
   ○ Multiple myeloma
     ■ Myeloma proteins bind phosphate and interfere with the colorimetric measurement of serum phosphate
Clinical manifestations of hyperphosphatemia

● Short-term consequences
  ○ Hypocalcemia and tetany especially in tumor lysis syndrome and rhabdomyolysis
    ■ Hyperphosphatemia inhibits renal 1α-hydroxylase → less 1,25(OH)₂ D₃ is produced → intestinal Ca reabsorption ↓ and PTH resistance in bones

● Long-term consequences
  ○ Ectopic (extra skeletal) calcification or heterotopic (soft tissue) mineralization
  ○ Secondary hyperparathyreosis and development of chronic kidney disease – mineral and bone disorder
Magnesium balance

- Magnesium is the fourth most common and is the second most abundant intracellular cation in the body
- Magnesium
  - Activates coenzymes needed for carbohydrate and protein metabolism
  - Plays an essential role in neurotransmission, cardiac function, and neuromuscular activity
  - Essential for PTH activity
- Control mechanisms of magnesium are poorly understood
  - There is a renal transport maximum for magnesium
Hypomagnesemia (Mg < 0.66 mmol/l)

● 1. Hypomagnesemia due to gastrointestinal losses
   ○ Prolonged nasogastric suction, severe malnutrition
   ○ Malabsorption syndromes, primary intestinal hypomagnesemia (Mg channel mutation)
   ○ Acute and chronic diarrhea, steatorrhea
   ○ Extensive bowel resection, intestinal fistulae
   ○ Acute pancreatitis (Mg, Ca soap)
2. Renal losses
   ○ Volume expanded states
   ○ Congential kidney diseases
     ■ Primary renal tubular magnesium wasting: Welt’s syndrome
     ■ Gitelman’s syndrome
     ■ RTA
   ○ Hypercalcemia, hypercalciuria, hypokalemia and Pi depletion
     ■ Inhibit tubular Mg reabsorption
   ○ Increased fluid transport in the kidney
     ■ Diuretics (osmotic [DM, urea, mannitol], thiazide and loop)
     ■ Renal transplantation, diuretic phase of acute renal failure, postobstructive nephropathy
3. Hypomagnesemia due to complex mechanisms
   ○ Chronic alcoholism: decreased GI intake, increased GI and kidney loss
Clinical manifestations of hypomagnesemia

- Neuromuscular
  - Erb, Trousseau and Chvostek signs
  - Seizures
  - Vertigo and ataxia
  - Muscular weakness
  - Depression, psychosis

- Metabolic
  - Carbohydrate intolerance
  - Hyperinsulinemia
  - Atherosclerosis

- Cardiovascular
  - Prolongation of PR interval, widening of QRS complex, inversion of T wave, U waves
  - Severe ventricular arrhythmia: torsades de pointes
  - Sensitivity to cardiac glycosides ↑
  - See hypokalemia!

- Bone
  - Osteoporosis and osteomalacia
Hypermagnesemia (Mg > 1.07 mmol/l)

- Hypermagnesemia is a rare condition
- 1. Renal insufficiency: acute and chronic renal failure
- 2. Mg intake exceeds renal excretion
  - Endogenous: diabetic ketoacidosis, tumor lysis, rhabdomyolysis
  - Exogenous: usually iatrogenic
    - After intravenous magnesium administration
    - Magnesium-containing laxatives, cathartics (stronger than laxatives) or antacids
    - Drowning into the Dead Sea (~400 mg/dl)
- 3. Increased renal Mg absorption
  - Familial hypocalciuric hypercalcemia (Ca-sensing receptor mutation), hypothyroidism, hyperparathyroidism, lack of mineralocorticoids
Clinical manifestations of hypermagnesemia

- **Cardiovascular signs**
  - Hypotension
  - Bradycardia, cardiac standstill (↓ ACh effect on end-plates)
  - ECG abnormalities: AV block and prolonged PR, QRS, QT interval

- **Neuromuscular signs**
  - Respiratory depression
  - Hyporeflexia, areflexia, paralysis of voluntary muscles

- **CNS signs**
  - Malaise
  - Depressed mental status
  - Fixed, dilated pupil
Pathophysiology of chloride homeostasis

- Most abundant anion in ECF (98-107 mmol/l)
  - Major contribution to development of osmolarity
- Major physiological roles
  - Formation of HCl
  - Chloride shift
    - CO₂ loading/unloading
  - Regulation of body pH
- Chloride homeostasis
  - Cl⁻ strongly attracted to some cations (Na⁺, K⁺, Ca²⁺)
  - Homeostasis achieved as an effect of Na⁺ homeostasis
    - Cl⁻ passively follows Na⁺
• Effects: alteration in acid-base balance
  ○ Metabolic acidosis
    ■ Elevated anion gap acidosis – normochloremic metabolic acidosis
    ■ Normal anion gap acidosis – hyperchloremic metabolic acidosis
  ○ Metabolic alkalosis
    ■ Chloride-responsive (hypochloremic) metabolic alkalosis due to EC chloride and volume depletion
    ■ Chloride-unresponsive metabolic alkalosis due to volume expansion in aldosteronism and hypokalemia
Trace elements/metals

- Carbohydrate, cholesterol, fatty acids metabolism: Zn, Mn, Cr
- Membrane structure integrity
  - Superoxide dismutase: Cu, Zn, Mn
  - Catalase: Fe
  - Glutathione peroxidase: Se

Iron (see reference values)

- Iron requirements, iron metabolism, and iron-deficiency anemia
- Deficiency: anemia
- Toxicity: hemochromatosis
A short summary of iron metabolism

DMT  divalent metal transporter
FPN  ferroportin transporter
HOX  heme oxidase
HAMP Hepcidin antimicrobial peptide
HFE  (HighFe) Human hemochromatosis protein
HJV  Haemojuvelin protein
TfR  Transferrin receptor
Disorders with hepatic iron overload

<table>
<thead>
<tr>
<th>Congenital</th>
<th>Acquired</th>
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<tbody>
<tr>
<td>Hereditary hemochromatosis (juvenile)</td>
<td>Chronic liver diseases</td>
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<tr>
<td>HJV associated</td>
<td>Hepatitis B and C viruses</td>
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<tr>
<td>HAMP associated</td>
<td>Alcohol, insulin resistance</td>
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<td>TfR2/HFE associated</td>
<td>End-stage liver disease*</td>
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<tr>
<td>HFE/HJV-HAMP associated</td>
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<tr>
<td>Hereditary hemochromatosis (adult)</td>
<td>Transfusion-dependent iron overload</td>
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<tr>
<td>HFE</td>
<td>(thalassemia, sideroblastic anemia)</td>
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<tr>
<td>TfR2 associated</td>
<td>Increased enteral (e.g., Bantu**), parenteral</td>
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<tr>
<td>FPN associated</td>
<td>iron overload</td>
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<tr>
<td>Ferroportin disease</td>
<td>Anemia of chronic inflammation</td>
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<td>Atransferrinemia</td>
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<td>Aceruloplasminemia</td>
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<td>DMT-deficiency</td>
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*Direct inhibition of hepcidin transcription

**Ferroportin polymorphism (African, African/American population
Serum iron

- Gonadal dysfunction
- Glucose intolerance
- Diabetes mellitus (bronze)

Cardiomyopathy
- Arrhythmia
- Heart failure

*brain and retinal involvement

Fibrosis
- Cirrhosis
- Hepatocellular carcinoma
- Arthritis, endocrine and heart symptoms

Gene
- HAMP, HJV, lack of ceruloplasmin* and transferrin
- Transferrin receptor-2 (TfR2)
- HFE, FPN

*brain and retinal involvement
Hemochromatosis

- Primary or hereditary hemochromatosis
  - Inherited disorder resulting from inborn errors of iron metabolism causing hepcidin deficiency that leads to progressive loading of mesenchymal cells: liver, pancreas, heart, joints, skin and endocrine organs

- Secondary iron overload or secondary hemochromatosis
  - Iron overload
    - Repeated transfusions [ineffective erythropoiesis (thalassemia, sideroblastic anemia)]
    - Increased dietary iron uptake (Bantus)
  - Chronic liver diseases: alcoholic, HCV
Calcium fluoride (CaF$_2$), fluorite (fluorspar)

- **Deficiency**
  - Dental caries
  - Osteoporosis

- **Toxicity: fluorosis**
  - Chalky-white, irregularly distributed patches on the enamel
  - Fluorosis weakens the enamel
  - Bone
    - Osteosclerosis
    - Exostoses of the spine
    - *Genu valgum* (knock-knees)
Zinc deficiency

- Decreased uptake/absorption
  - *Acrodermatitis enteropathica*, malabsorption, parenteral feeding, astronaut’s diet

- Acute/chronic tissue damage
  - Bacterial infections, postoperative states
  - Burns, cutaneous ulcers, MI
  - Collagenosis, rheumatoid arthritis

- Kidney disease
  - Renal insufficiency, nephrotic syndrome

- Hematological disease
  - Sickle cell anemia, hemolytic anemia

- Endocrine
  - Pregnancy

- Liver damage
  - Alcoholic hepatitis

- Iatrogenic
  - EDTA, d-penicillamine, antimetabolites, cortisol, contraceptives
• Signs of zinc deficiency
  ○ Retarded growth
  ○ Anemia
  ○ Hypogonadism, oligospermia
  ○ Mental changes, apathy
  ○ Hepato-splenomegaly
  ○ Impaired sense of smell and taste
  ○ Anorexia
  ○ Mouth ulcers
  ○ Night blindness
Disorders of copper metabolism

- Menkes disease or Menkes kinky hair syndrome (deadly X-linked disease)
  - Defect of ATP7A gene → impaired intestinal Cu absorption
  - CNS degeneration in boys, twisted hair (SH groups ↑) and growth defect
- Wilson’s disease (autosomal recessive disease, fatal if not treated)
  - Defect in ATP7B gene
  - In the liver ATP7B is responsible for transporting Cu to ceruloplasmin and/or bile
Wilson’s disease

Cu accumulation in the brain, liver, kidney, cornea

Liver necrosis (Cu generates free radicals) → cirrhosis
Degeneration of basal ganglia (hepatolenticular degeneration)
   Signs: intention tremor (tremor occurs at the end of a purposeful movement), athetosis (slow, sinuous, writhing movements, typically of the hands and feet), dysarthria (motor speech disorder), dysbasia (difficulty in walking), Kayser-Fleischer ring (Descemet membrane is golden brown, brownish green, bronze)
## Selenium & chromium

### Selenium
- **Deficiency**
  - In China low-selenium areas (in soil) of
    - Keshan disease: myocardium necrosis, enlarged heart
  - Total parenteral nutrition
  - Severe GI disorders: poor absorption
- **Selenium deficiency may worsen the effects of iodine deficiency**
  - Kashin–Beck disease

### Chromium
- **Deficiency**
  - Glucose intolerance
  - Peripheral neuropathy
- **Toxicity**
  - Trivalent chromium $\text{CrCl}_3$
    - Skin irritation – administered parenterally
  - Hexavalent chromium $\text{CrO}_3$
    - Skin, lungs, and GI tract irritation
    - Perforation of the nasal septum
    - Lung carcinoma