DISORDERS OF WATER & ELECTROLYTE METABOLISM

LECTURE FROM PATHOPHYSIOLOGY
DENTAL MEDICINE
2016/2017

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Water
AGE DEPENDENCE OF FLUID HOMEOSTASIS

<table>
<thead>
<tr>
<th>Age</th>
<th>Total water %</th>
<th>Daily exchange %</th>
</tr>
</thead>
<tbody>
<tr>
<td>newborn</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>3-6 mo.</td>
<td>70</td>
<td>14-16</td>
</tr>
<tr>
<td>7-12 mo.</td>
<td>60</td>
<td>12-15</td>
</tr>
<tr>
<td>adult man</td>
<td>60</td>
<td>2-4</td>
</tr>
<tr>
<td>adult woman</td>
<td>51</td>
<td>2-4</td>
</tr>
</tbody>
</table>

*ECS > ICS, danger of dehydration in old age further & impaired adaptation, danger of dehydration*

DISTRIBUTION OF WATER IN HUMAN BODY

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Volume litres</th>
<th>% of body mass</th>
<th>% of total water</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICS</td>
<td>28</td>
<td>40</td>
<td>67</td>
</tr>
<tr>
<td>ECS</td>
<td>14</td>
<td>20</td>
<td>33</td>
</tr>
<tr>
<td>ISF</td>
<td>11</td>
<td>15,7</td>
<td>26</td>
</tr>
<tr>
<td>IVF</td>
<td>3</td>
<td>4,3</td>
<td>7</td>
</tr>
<tr>
<td>SUMMA</td>
<td>42</td>
<td>60</td>
<td>100</td>
</tr>
</tbody>
</table>
**Water intake**

- beverages 1,0 - 1,5 l/d
- water in food cca 1 l/d
- water from metabolism cca 0.3 l/d
  - oxidation of 100 g proteins 35 ml water
  - 100 g sugar 60 ml water
  - 100 g fat 107 ml water

- Total intake of water cca 2.0 – 2.5 l/d

**Water output**

- Urine 1.0 – 1.5 l/d
- Perspiratio 0.3 – 0.6 l/d
  - Skin (sweating) 0.2 – 0.4 l/d
    (more – hot environment, physical activity, fever)
  - Lungs – respiration cca 0.2 l/d
- feces 0.1 – 0.2 l/d (more in diarrhea)

- Increased output
  - vomiting
  - bleeding
  - redistribution of water - edema

- Total output of water cca 2.0 – 2.5 l/d
Water homeostasis

Water balance – equilibrium between intake and output of water
Water deficiency - ↑ thirst

Water excess - ↑ urination
# Electrolytes

<table>
<thead>
<tr>
<th>Ion</th>
<th>Amount in body</th>
<th>Plasma mmol/l</th>
<th>Cells mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium, Na⁺</td>
<td>92 g 4 mol</td>
<td>141</td>
<td>10</td>
</tr>
<tr>
<td>Potassium, K⁺</td>
<td>100-140 g 2,5-3,5 mol</td>
<td>4</td>
<td>155</td>
</tr>
<tr>
<td>Calcium, Ca²⁺</td>
<td>1200 g 30 mol</td>
<td>2,5</td>
<td>&lt; 0,001 (uneven in organelles)</td>
</tr>
<tr>
<td>Magnesium, Mg²⁺</td>
<td>26,5 g 1,1 mol</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Chloride, Cl⁻</td>
<td>50 g 1,4 mol</td>
<td>103</td>
<td>8</td>
</tr>
<tr>
<td>Phosphate (as phosphorus)</td>
<td>775 g 25 mol</td>
<td>1</td>
<td>65</td>
</tr>
</tbody>
</table>
Osmolality of plasma

Osmolality - mmol/kg of solvent
Osmolarity - mmol/l of solvent

Osmolarity of plasma = 2*[Na] + [glucose] + [urea]

cca 290 ± 5 mmol/l
(kations 140 mmol/l + anions 140 mmol/l + glucose 5 mmol/l + urea 5 mmol/l)
Regulation of water and sodium homeostasis

Antidiuretic hormone

↓ plasma volume
↑ osmolality  drinking of water
dry mouth  ↓
Hypothalamic osmoreceptors  ↓
↑ antidiuretic hormone (arginine-vasopressin)
↑ water reabsorption (aquaporins) and ↓ urination
Aquaporins

- Water channels
- Conduct water through cell membrane

- 2003 – Nobel price for chemistry
Renin-angiotensin-aldosteron system

- Angiotenzin II
  - Vasonconstriction – ↑ blood pressure
  - Antiinflamatory effect

- Aldosteron
  - Reabsorption of sodium
  - Secretion of potassium

Natriuretic peptides

peptides which induce natriuresis

Types:
- Atrial natriuretic peptide (ANP) – produced in atria
- Brain natriuretic peptide (BNP) - ventricles in humans, brains in pigs
- C-type natriuretic peptide (CNP)
- Dendroaspis natriuretic peptide
- Urodilatin - kidneys
Disorders of water and sodium homeostasis

DISTURBANCES OF THE SYSTEM

• No pure forms – loss of water, salt...
• Immediate reaction of compensatory systems
• ECS is in contact both with external environment and with ICS
• ICS is in contact only with ECS
• Plasmatic concentrations are not amounts and does not inform on dynamics of compounds
Loss of isotonic fluid

Reduction of ECS, thirst
no change of ICS
normal plasma sodium

Loss of hypotonic fluid

Reduction of ECS.
Hypernatremia compensated through water shift from ICS
Shrinkage of cells
Salt loss

Hyponatremia compensated through water shift from ECS into ICS, Reduction of ECS, swelling (oedema) of cells

POSSIBLE CAUSES AND MECHANISMS

✓ Extreme deviations of external environment
  Dehydratation from insufficient water intake
✓ Disturbances caused by damaged function of effector systems (kidneys, GIT, etc.)
  Diarrhoea, vomitus, kidney diseases
✓ Disturbances caused by erroneous regulation (CNS, ADH, aldosterone)
  Diabetes insipidus, Conn sy., SIADH
  Heart failure & RAA activation
WATER DEFICIENCY – REDUCTION OF ECS

Causes
- Insufficient fluid intake
- Inability to drink (loss of consciousness)
- Losses through GIT (diarrhoe, vomitus)
- Losses through kidneys
  - (diuretics, osmotic diuresis, kidney diseases, m. Addison)
- Losses through skin (increased sweating, burns)
- Displacement into third place (ileus, ascites)
- Blood loss (?)

Symptoms: hypotension, tachycardia, dry skin, thirst, oliguria & decreased sodium excretion, increase of hematocrit

Water deficiency signs in oral cavity

- Xerostomia
  - Decreased amount of saliva
  - Dry skin and mucous
  - Salivary gland swelled and painful
  - Inflammatory changes – cheilosis, glossitis
  - ↑ risk of caries
  - ↑ risk of infection - candidiasis

- Dysphagia – problem with swallowing
- Dysfonia – loss of voice
- Dysgeusia – loss of taste
WATER RETENTION – ECS EXPANSION

Causes
- Increased fluid intake
  - Increased intake & disturbed regulation – SIADH
  - kidney failure
  - nephrotic sy.
  - heart failure
  - liver cirrhosis

Symptoms: Oedema.

Hypernatraemia
>150 / 160 mmol/l

- Increased sodium intake
  - per os
  - parenteral

- Decreased elimination of sodium
  - Heart decompensation
  - Liver cirrhosis
  - Nefrotic syndrome
  - Renal insufficiency
  - Endocrine diseases – hyperaldosteronism (Conn syndrome)
**Hypernatraemia**

Low osmolality of urine – diabetes insipidus
Osmolality of urine & plasma – osmotic diuresis
*(diabetes mellitus)*
Osmolality of urine > plasma – dehydration
*diarrhoea, vomitus sweating*
Conn syndrome (hyperaldosteronism)
→ hypernatremia, hypokalemia

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**Hyponatraemia**

*<130 / 120 mmol/l*

- Extrarenal loss
  - GIT
  - Skin
  - Bleeding, burns
  - Sekvestration of Na+

- Renal loss
  - diuretics
  - nephritis with loss of salts
  - Addison disease
Hyponatraemia

Plasma osmolality high → hyperglycemia ?!
Plasma osmolality low →
Na in urine > 20 mmol/l & hypovolemia
  m. Addison, diuretics
  salt losing nephritis
Na in urine < 20 mmol/l & hypovolemia
diarrhoea, vomitus, sweating with
inadequate fluid replacement
Na in urine < 20 mmol/l & oedema
heart failure, cirrhosis, nephrotic sy.
SIADH

DISTURBANCES OF ADH SECRETION AND EFFECTS

Diabetes insipidus, neurogenic (AD)
AVP gene mutation
Acquired forms – damage of hypothalamus
  Complete & partial forms
Diabetes insipidus, renal (X-related & AR)
  Receptor (X) or water channel protein (AR)
  gene mutations
Acquired – kidney diseases
DISTURBANCES OF ADH SECRETION AND EFFECTS

SIADH – inadequate secretion of ADH
- Expansion of ECS
- Hyponatremia, hypoosmolality
- High urine osmolality & high Na in urine
- Increased ANP
- Renal & endocrine functions intact

Hereditary forms and stress ??!!

Disorders of potassium homeostasis
POTASSIUM HOMEOSTASIS

- Serum concentration: 3,8 – 5,5 mmol/l*
- Total amount depends on muscle mass (young > old; man > women)
  37 – 52 mmol/kg body mass
- Intake: 2-6 g/d = 50-150 mmol/d
- Excretion through kidneys 10 – 20 mmol/d (0,4 – 0,8 g/d).
- Inverse association with Na excretion
- GIT excretion is important in kidney failure and in pathological conditions (diarrhoea)

*Depends on method. Preanalytic errors - hemolysis!

FUNCTIONS OF POTASSIUM & INTERPRETATION OF RESULTS

Functions
- intracellular osmotic pressure
- resting & action potential
- enzyme activity, proteosynthesis

Problems:
1. assessment of cell homeostasis from extracellular concentration
2. pH changes: exchange H/K between ECF/ICF
INTERNAL & EXTERNAL BALANCE

**internal – ECF/ICF**
- Acidosis: H⁺ enters the cells, K⁺ out into ECF
- Alkalosis: H⁺ into ECF, K⁺ enters the cells
- K⁺ entry into cells: insulin (together with glucose), aldosterone, adrenaline
- Rapid cellular proliferation (treatment of pernicious anaemia with B₁₂ vitamin)
- Cell necrosis, hemolysis (crush sy, malignancies), K⁺ into ECF

**external – ECF/environment**
- Kidney or GIT retention/losses, parenteral intake
- Dietary deficiency/excess as an additional factor

HYPOKALAEMIA - CAUSES

**Disorders of external balance**
- GIT – diarrhoea, vomitus, tumors of colon, rectum, pancreas
- Kidneys - diuretics, polyuric stage of renal failure, hereditary tubulopathies,
- Primary & secondary hyperaldosteronism, abuse of liquorice, Cushing, ectopic ACTH production

**Disorders of internal balance**
- Treatment of diabetic hyperglycaemia with insulin (K⁺ entry into cells together with glucose)
- Alkalosis
- Rapid cellular proliferation
- Familiar hypokalaemic periodic paralysis (hereditary)
HYPOKALAEMIA - SYMPTOMS

- hypokalaemia < 4.0 mmol/l
- significant < 3.5 mmol/l
- dangerous < 3.0 mmol/l

- Membrane hyperpolarisation
  ✓ Weakness, constipation, ileus, hypotonia
  ✓ Depression, confusion
  ✓ Arrhythmia, potentiation of digitalis toxicity
  ✓ ADH resistance, polyuria, polydipsia
  ✓ ECG flat/inversed T, prolonged PR, ST depression, prominent U

HYPERKALAEMIA - CAUSES

Disorders of external balance
- Decreased excretion. Under GFR 15 ml/min always.
  Anuria: K increase 1 mmol/l daily
  In mild impairment of kidney function only when other factors are present
- Increased intake (infusions, NaCl substitution) only in the case of impaired kidney function
- m. Addison, adrenogenital sy., inhibitors of angiotensin converting enzyme

Disorders of internal balance
- Acidosis
- Cell necrosis - rhabdomyolysis, burns, cytostatic treatment of malignancies
- Digitalis overdosage
- Hyperkalaemic periodic paralysis (hereditary)
- Malignant hypertermia (hereditary)
HYPERKALAEMIA - SYMPTOMS

- hyperkalaemia < 5.5 mmol/l
- significant < 6.5 mmol/l
- dangerous < 7.5 mmol/l

- Low resting potential, short cardiac action potential, increased speed of repolarization
- Can kill without warning
- Ventricular fibrillation and cardiac arrest may be the first signs! (if you do not check K & ECG)
- ECG: abnormal/absent P; broad QRS, peaked T, ST depression

Normokalemia
- Normal PR interval
- Normal P wave
- Normal QRS
- Rounded, normal-size T wave
- U wave shallow if present

Hypokalemia
- Slightly prolonged PR interval
- Slightly peaked P wave
- ST depression
- Shallow U wave
- Prominent T wave

Hyperkalemia
- Decreased R wave amplitude
- Wide, flat P wave
- Prolonged PR interval
- Widened QRS
- Tall, peaked T wave
- Depressed ST segment
Disorders of calcium homeostasis

**CALCIUM**

- Total body 1200 g 30 mol
- ECF 0,9 g 22,5 mmol
- Plasma 0,36 g 9,0 mmol
- Bone / ECF exchange 500 mmol/d
- Daily losses 25 mmol/d (1g)
  - urine 6 mmol (240 GF – 234 reabsorbtion)
  - faeces 19 mmol (+25 food, 12 in, + 6 secr.)
  - skin 0,3 mmol

*Small changes in fluxes can have profound effect of plasma Ca*
FUNCTIONS OF CALCIUM

- Structural
- Neuromuscular

- Bone, teeth
- Control of excitability;
  Neurotransmitter release
  Muscle contraction
- Coagulation
- Messenger

PLASMA CALCIUM

TOTAL
2.25 – 2.60 mmol/l

diffusible 54 %
protein-bound 46 %

free - ionized 47 % 7% complexed

CLINICAL CHEMISTRY: TOTAL OR IONIZED?
CALCIUM REGULATING HORMONES

- Parathormon
- Calcitriol
- Calcitonin

FUNCTIONS OF PARATHORMON

**BONE**
- Release of calcium $\uparrow [Ca^{2+}]$
- Osteoclastic resorption

**KIDNEY**
- Calcium reabsorption $\uparrow [Ca^{2+}]$
- 2nd hydroxylation of vit.D $\uparrow$ Ca, P absorption
- Phosphaturia $\downarrow [PO_4]$  
- Decrease of HCO$_3^-$ reabsorption $\downarrow$ pH
HYPOCALCAEMIA - CAUSES

- Hypoparathyroidism
  - Congenital (with Di George sy.)
  - Acquired – autoimmune, surgery, hemochromatosis, tumors
- Pseudohypoparathyroidism
  - 2 hereditary disorders of PTH signaling pathway (cAMP dependent)
- Magnesium deficiency (pseudo ?)
- Deficiency of vitamin D (!)
- Disorders of vitamin D metabolism – end stage renal disease
- Acute pancreatitis, transfusions with citrate, neonatal

HYPOCALCAEMIA - SYMPTOMS

- Stupor, numbness, paraesthesia
- Muscle cramps and spasms „tetany“
- Laryngeal stridor
- Convulsions
- Chvostek+ Trousseau+, long QT on ECG
  - Cataract in chronic hypocalcaemia
  - Rickets (rachitis) in vitamin D deficiency
HYPERCALCAEMIA - CAUSES

- **COMMON (90% of all)**
  - Primary hyperparathyroidism
  - Malignancies – bone metastasis (?), PTHrP and other humoral factors
- **LESS COMMON**
  - Thyreotoxicosis, sarcoidosis
- **UNCOMMON**
  - Lithium treatment, tbc, immobilisation, adrenal failure, renal failure, hereditary
- **BUT ALSO HYPERPARATHYROIDISM WITHOUT HYPERCALCAEMIA**
  - Compensatory in vitamin D deficiency, renal disease

HYPERCALCAEMIA - SYMPTOMS

- Weakness, tiredness, weight loss
- Impaired concentration, drowsiness (coma)
- Anorexia, nausea, vomiting, constipation
- Polyuria, dehydration
- Renal calculi, nephrocalcinosis
- short QT, arrhythmias
Hyper- and hypocalcemia in oral cavity

- Hypercalcemia
  - Jaw bone demineralization
  - Loss of lamina dura
  - Osteitis fibrosa cystica – increased osteoclastic resorption, hemorrhage and cysts formation

- Hypocalcemia
  - Hypoplasia and discoloration of teeth
  - Possible teteany cramps

Disorders of magnesium and phosphates homeostasis
MAGNESIUM

- 60% in bones, higher in ICF than in ECF
- Only 0.3% in blood, 30% protein bound
- Serum 0.7 – 1.0 mmol/l
- Regulator is not known! *adrenal medulla, insulin, parathormone* ???
- Regulated resorbtion from GIT ?
- 8 mmol/d is enough? Is deficiency common?
- Excretion through urine and stool

MAGNESIUM

- Neuromuscular excitability (inhibition – mediated through decreased secretion of acetylcholine?)
- Bone structure
- Enzyme activity, energy production, transport mechanisms, ribosomes
- Regulation of haemocoagulation and membrane function
- Cardioprotective antiischemic, antihypoxic effects
- Sedative effect on NS
- Antihypertensive
- Antithrombotic
MAGNESIUM

- Deficiency associated with soil and plant deficit -> grass tetany of cattle
- Some drugs and stress can increase excretion
- Unhealthy diet (alcohol)
- High doses of calcium (!)

CONSEQUENCES
- Spasmophilia is more often a consequence of Mg deficiency as of Ca
- Tiredness, irritability, tremor
- Dysmenorea, preeklampsia
- arrhythmias

PHOSPHATE

- 85 % in bones
- in ICF and in ECF
- In plasma – phospholipids, phosphate esters and ionized phosphate
- Regulation – PTH, vit. D and calcitonin (together but opposite with calcium)
Hypophosphatemia

- Causes
  - Intestinal malabsorption
    - Vit. D deficiency
    - Use of Mg- and Al-containing acids that bind phosphates
    - Alcohol abuse
    - Malabsorption abuse
  - Increased renal secretion
    - Hyperparathyroidism
- Signs and symptoms
  - Only in higher deficit
  - Disturbed energy metabolism – nerves and muscles dysfunction
  - Erythrocyte, leukocyte and platelets dysfunction
  - ↑ risk of infection
  - Hemorrhage

Hyperphosphatemia

- Causes
  - Destruction of cells – tumors or anticancer therapy
  - Long term using of phosphate-containing drugs (laxatives)
  - Hypoparathyroidism
- Signs and symptoms
  - Symptoms of hypocalcemia – tetany
  - Calcification of tissues