Physiology – Sheet 7

Concentration and Dilution of Urine

The human body uses and loses water every day. In order to regulate its water balance, **water intake must equal water output.** We intake water by drinking variable amounts of water (1600mL), eating food (700mL), and through metabolic reactions (200mL). Water is continuously lost from the body through various routes including the respiratory system (300mL), the GIT (100mL), though the excretion of urine (1500mL), and variable amounts are lost from the skin (600mL). As mentioned previously, water intake must equal water output to ensure water balance so both are equal 2500mL/Day.

The kidneys conserve water by excreting concentrated urine. Scientists were puzzled for years because they did not know how concentrated urine is produced. There is **no** evidence found that indicates water is transported actively, but we know that there is active transport of solutes. The interstitium progressively increases in osmolarity as you go deeper within the medulla, initially being 300 mOsm and increasing to reach 1200-1400 mOsm. Therefore, the only acceptable explanation to how we can produce urine with a concentration of 1200-1400mOsm/L is by removing water uphill.
When there is a water deficit in the body and we need to conserve more water, the kidney forms concentrated urine by continuing to excrete solutes while increasing water reabsorption and so decreasing the volume of water excreted.
Making dilute urine, on the other hand, is a relatively simple process. It occurs when circulating levels of ADH are low. The kidney actively reabsorbs NaCl at the thick ascending limb without water and the tubular fluid becomes dilute (as normal), but at the collecting ducts, the cells will be impermeable to water due to the lack of ADH, thus water cannot move by osmosis and will remain in the filtrate, and we end up with dilute, hypoosmolar urine. The osmolarity could be as low as 50 mOsm/L
The **maximal** urine concentration is 1200-1400 mOsm/L. The **minimal** urine concentration is 50-70 mOsm/L.

- **Obligatory Urine Volume**

The minimal amount of solutes that a completely bedridden human must excrete in a day is about 700 mOsm or 1000 mOsm/Day for an individual that is active. The kidney can concentrate urine up to a maximal volume of 1400 mOsm/L.
The **minimal volume of urine that must be excreted,** or the **obligatory urine volume (MDOVU)**, can be calculated as follows**:**
Example: A normal 70 kg human must excrete 600 mOsm of solutes/day, and if we consider the maximal urine concentrating ability to be 1200 mOsm.L →

600 mOsm/Day ÷ 1200 mOsm/L = 0.5 L/Day

If less than 0.5 L/day were excreted → Oligouria

- **Oliguria:** it is defined as a urine output less than:

< 1 mL/kg/h in infants

< 0.5 ml/kg/h in children

<0.3 ml/kg/h in adults, or less than 300mL/m^2 of body surface area/ day

Oliguria is one of the hallmarks of acute renal failure (ARF) and has been used as a criterion for diagnosing and staging ARF. We have four stages of acute renal failure. We use two tools to classify the severity of ARF:

1) Uric output:
Two types: either normal urine output with a USG of 1.010, or Oliguria which is staged according to whether if it is for 6hrs, 12hrs, or 24 hrs.

2) Creatinine levels in plasma (normal levels range from .7 to 1.3 mg/dL)
- if we have complete renal shut down, the levels go up by about 1 mg/dL
- Urea is ~ 5mMol, and the molecular weight for urea is 60, whereas that of Creatinine is 114 (we use these in converting the conc from mg/dL to mMol)

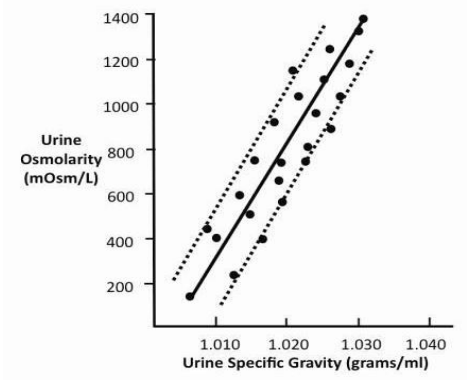
- The lower the uric output and the higher the creatinine levels, the more advanced the ARF. If we think a patient has ARF, we must take a blood sample and a urine sample and conduct tests on them.
- When examining blood samples, we look at the potassium levels, urea levels and sodium levels (sodium levels don't tell us much because of their close relationship with water).
- As for the urine samples, we check the pH (acidosis → affects enzymes), and a high urine specific gravity, we check for the presence of glucose, protein, RBCs and WBCs. If RBCs are found in the urine this is called hematuria. Hematuria can either be **macroscopic** (visible and red in color) or **microscopic** (not visible, need a light microscope to view RBCs).
- **Painless hematuria is malignant unless proven otherwise.** Painless hematuria should not be ignored, and at the very least non invasive procedures should be done, such as performing an ultra sound, to examine the kidneys and bladder. Painful hematuria is not as serious.

- Note: Urea could be used as a glomerular marker. We excrete 20-60% of the urea filtered, therefore the clearance of urea is ~50% of the GFR. If the urea which is filtered is not reabsorbed or secreted, this means that all filtered load is excreted (all of the 125 mL/min is going to be cleared) and clearance of urea then equals GFR and it can be used as a marker. If 50% of the urea is reabsorbed then 50% is excreted and the clearance is 50% of the 125 mL/min.

- In renal disease the obligatory urine volume (minimal volume of urine that must be excreted) may be increased due to impaired urine concentrating ability

Example:
If the maximum urine osmolarity= 300 mOsm/L and 600 mOsm of solute must be excreted each day to maintain electrolyte balance, what is the obligatory urine volume?

600 mOsm/Day ÷ 300 mOsm/L = 2 L/day



❖ **Urine Specific Gravity**

In order to make sure the kidneys are functioning normally, we must conduct a test to find out the osmolarity of the urine, which is measured by an osmomter. Not all medical centers have osmometers and therefore this test is often replaced by testing for:

The **urine specific gravity (USG). USG= Weight of solutes/ Weight of water.**

It is used to provide an estimate of urine solute concentration. The higher the USG, the more concentrated the urine.

In most cases, USG increases linearly with increasing urine osmolarity. USG is a measure of **weight of solutes** in a given volume so we determine its value by considering both the number and the size of the solute molecules. Osmolarity, however, is only concerned with the number of solute molecules in a given volume regardless of their size, each molecule has the same effect in dragging water.

The relationship between USG and osmolarity is altered when there are significant amounts of large molecules in the urine, such as RBCs, WBCs, proteins, glucose in a patient with diabetes, radio contrast media (used for diagnostic purposes), or some types of antibiotics. If any of these are present, the USG will be too high and this falsely suggests very concentrated urine even though the osmolarity is normal.

- Since USG is weight of urine divided by the weight of water, a value of 1 would mean that urine has the same weight as water and this is very unlikely. In the human body it normally ranges from 1.002 to 1.028 g/mL (above 1.025 → concentrated). It rises by 0.001 for every 35 to 40 mOsm/L increase in urine osmolarity.
- To estimate osmolarity, you take the last two digits of the USG and you multiply by 40, example: 1.003 * 40 = 120 mOsm

- Osmolarity of plasma is 300 mOsm, anything below it is hypo-osmolar and anything above it is hyper-osmolar.

- When the USG is 1.025, the osmolarity is equal to 1000
- We must ask the patient to not drink water for 24 hours, then we take 3 samples of spot urine, one each 30 minutes. If in any of these 3 samples you have a USG of 1.025 then the patient is in good shape.

- If the USG was 1.010 (regardless if patient drank water a few hours ago or didn't), the osmolarity is 400, and it means that the kidney can't concentrate the urine and this is a type of polyuric renal failure (usually renal failure is associated with polyuria)

❖ **Making Concentrated Urine:**

The kidneys conserve water by excreting concentrated urine. In order to form concentrated urine, two conditions must be met:

1- **Hyperosmolar interstitium around the medullary collecting ducts**
2- **ADH to permit water permeability**

In the case that these two conditions are met, the interstitium and the tubular fluid will be at equilibrium, and a concentration of 1400 mOsm/L (maximal urine concentration) can be reached. **Concentration of urine is the last function of the kidney to be retained following acute renal failure**.

- There are certain mechanisms that contribute to having a **<u>hyperosmolar interstitium</u>**:

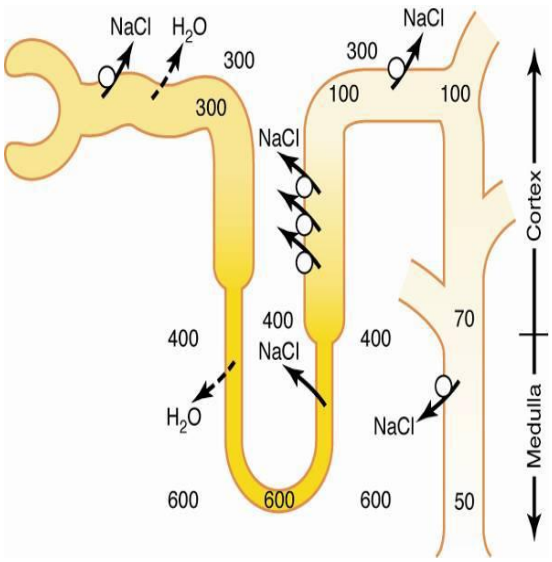
i. The **single effect** describes the fact that the ***thick ascending limb*** of the loop of Henle is not permeable to water, but is permeable to NaCl. This allows NaCl to be actively transported and to accumulate in the interstitium causing it to become hyperosmolar. We multiply the osmolarity of the interstitium due to this and therefore the thick ascending limb of Henle is called the **Counter Current Multiplier**.

   - **Corticopapillary gradient**: gradient of osmolarity from cortex: 300 mOsm/L to 1200 mOsm/L deep within the medulla (papilla) and is composed primarily of Urea and NaCl, it is established by urea recycling and countercurrent multiplication. Requires ADH.
   - **Contercurent multiplication**: depends on NaCl reabsorption in the thick ascending limb and countercurrent flow in the descending and ascending limbs of the loop of Henle

ii. Urea Recycling: Urea is reabsorbed from the inner medullary collecting ducts into the medullary interstitial fluid.

iii. Vasa Recta are the capillaries that supply the loop of Henle. Vasa recta equilibrate osmotically with the interstitial fluid of the medulla and serve as countercurrent exchangers. Within the cortex, there is high blood flow and therefore the tubular fluid there has the same omolarity as the interstitium. In the medulla, Na+ that is reabsorbed must not be removed from the area, and so blood flow to the vasa recta must be low (2% of renal blood flow). If we had high blood flow, as in the cases of vasodilation or high blood pressure, the molecules would be "washed out" of the area, preventing hyperosmolarity of interstitium and the maximum concentrating ability of the kidney would be depressed.

As urine enters the proximal tubule, tubular fluid remains isosmotic in the proximal tubule because water and solutes are being reabsorbed in equal proportions so very little change in osmolarity occurs. Here the osmolarity is around 300mOsm/L (It is also 300mOsm/L in the whole cortex). As fluid passes down the descending loop of Henle, water is reabsorbed by osmosis because of the hyperosmolar interstitium (can reach up to 1400 mOsm/L). When the tubular fluid passes through the thick ascending loop it becomes more diluted, because here, sodium, potassium and chloride are reabsorbed and the thick ascending limb of the loop of Henle is impermeable to water so no water reabsorption occurs. Here the osmolarity reaches 100 mOsm/L and so the tubular fluid leaving the distal segment is **hypoosmolar**. For this reason the ascending limb is called the **diluting segment**.



- The other condition needed to form concentrated urine, is the **presence of ADH** to allow water permeability in the collecting ducts.

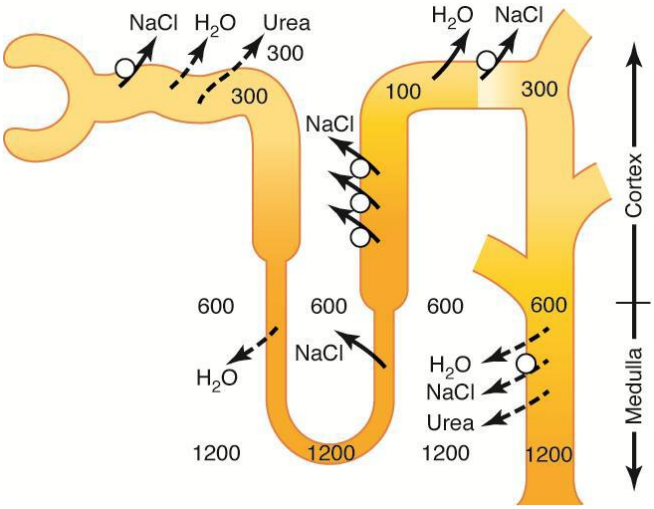
- ADH has two main functions: **1**. Opens water channels **2**. Enhances urea reabsorption (increases urea permeability)

- ADH is a small peptide made up of 9 amino acids. Its synthesis takes place in the magnocellular neurons of the hypothalamus, 85% is made in the supraoptic nuclei and 15% in the paraventricular nuclei. It is stored and released by the posterior pituitary.
- Stimuli for ADH secretion:

1. **Increased osmolarity** (There are osmoreceptors in hypothalamus). An increase of 1% (2-3 mOsm/L) is enough to stimulate ADH secretion.
2. **Decreased blood pressure** (arterial baroreceptor reflex, high-pressure regions such as aortic and carotid sinus, and low-pressure regions such as cardiac atria and cardiopulmonary reflexes). Increased ADH increases water reabsorption, which leads to, increases in blood volume and pressure.
3. **Decreased blood volume.** Not as sensitive as osmolarity. We need a decrease of blood volume by 10% to stimulate ADH release.

- Other conditions may **suppress** secretion of ADH, like alcohol for example leading to too much urine output. (Alcohol is a diuretic).

This figure shows the formation of concentrated urine in the presence of high levels of ADH.



Note that the fluid leaving the loop of Henle is dilute but becomes concentrated as water is reabsorbed from the distal tubules and collecting tubules.

- Increased extracellular osmolarity (NaCl) stimulates ADH release, which increases H_2O reabsorption, and stimulates thirst (intake of water)

If ADH was absent and the osmolarity of the tubular fluid was 30 mOsm/L, you would need to excrete 20 liters of urine a day to remove 600 mOsm from the body. This shows just how important of a role ADH plays in the body. A deficiency in ADH leads to **polyuria** (excessive production of urine) and **polydipsia** (excessive thirst).

- Failure to <u>produce</u> ADH → Central/ Diabetes insipidus

- Failure to <u>respond</u> to ADH → Peripheral/ Nephrogenic diabetes insipidus

❖ Osmolar and Free Water Clearance

Free water clearance (C_{H2O}): Rate of solute-free water excretion.

- Used to estimate the ability to concentrate or dilute urine
- Solute-free water is produced in the diluting segments where NaCl is reabsorbed and free water is left behind in the tubular fluid.
- **Normally is equal to (1 – 2.1) = -1.1 ml/min**
- If the number is positive, then we excrete water more than solute. And if it is negative, we excrete more solutes than water.

- C_{H2O} = V – C osm

C_{H2O}: free water clearance mL/min
V: Urine Flow Rate mL/min
*C osm: Osmolar Clearance (U osm*V)/P osm mL/min*

➔ C_{H2O} = V – (Uosm x V)/ Posm

U osm = urine osmolarity
V = urine flow rate
P = plasma osmolarity

- **Example**: $C_{osm} = \left[\frac{Uosm = 700}{P_{osm} = 300}\right] * V(1ml/\min) = 2.1ml/\min$

- If Uosm < Posm, C_{H2O} = positive value → in the absence of ADH, this solute-free water is excreted and C_{H2O} is positive
- If Uosm > Posm, C_{H2O} = negative value → in the presence of ADH, this solute-free water is not excreted and is reabsorbed by the late distal tubule and collecting ducts and C_{H2O} is negative

- **Example**:

Given the following data, calculate free water clearance
-Urine flow rate = 6.0 ml/min.
-Urine osmolarity = 150 mOsm /L
-Plasma osmolarity = 300 mOsm / L
Is free water clearance in this example positive or negative?

C_{H2O} = V – (Uosm x V)/ Posm
= 6.0 - (150 x 6) 300 = 6.0 - 3.0
= + 3.0 ml / min (positive)

In this case the answer is positive. A **positive** value tells you that the removal of water is greater than the removal of solutes. A **negative** value tells you the removal of solutes is greater than the removal of water.

A quick review on what is needed to concentrate urine:

1. Juxtamedullary nephrons
2. Single effect
3. Urea recycling
4. ADH

❖ The Dr started talking about **Acidosis (lecture 8)**:

- We cannot tolerate large increases or decreases in pH since our enzymes work at an optimal pH and their function could be disrupted.
- H+ concentration in Plasma: 40 nM/L
- Na+ concentration in Plasma: 140 mM/L (3.5 million times greater)
- We can tolerate an increase of H+ up to 160nM/L (4x more) and a decrease to 10nM/L (4x less)
- pH= -log [H+]
- At normal H+ concentration (40 nM/L) → pH = 7.4 (extracellular). The normal range is 7.35-7.45
- Below the normal level → acidosis, Above → Alkalosis
- We can tolerate a greater change in the acidic direction since our body is better designed to handle increased levels in acidity
- Acidosis induces hyperkalemia and increase in <u>free</u> calcium (hypocalcemia)

- Acid Base Balance: controlling H+ concentration in extracellular space
- Each day we produce 300 M of CO2 (huge amount) which is acidic but we don't worry about it since it is a volatile acid
- We worry about the non-volatile acids such as phosphoric and sulfuric acids (fixed acids) → our body produces 80mM of these each day, IF those are distributed along 14 L of ECF → >5mmol/L → the pH would be less than 3 and this is not compatible with life! We must solve this problem by buffering them: by adding 80 mM of bicarbonate. This causes us to lose a lot of bicarbonate → the concentration of bicarbonate is 24mMol/L, and we have 14 L of ECF → (24*14 = 336 mMol) and this is only enough bicarbonate to last for about 5 days. This lost bicarbonate must be replaced by the kidneys.

Done By: Sahar Farhan

Thank you Sally Khateeb and Isam Bseiso for your notes.