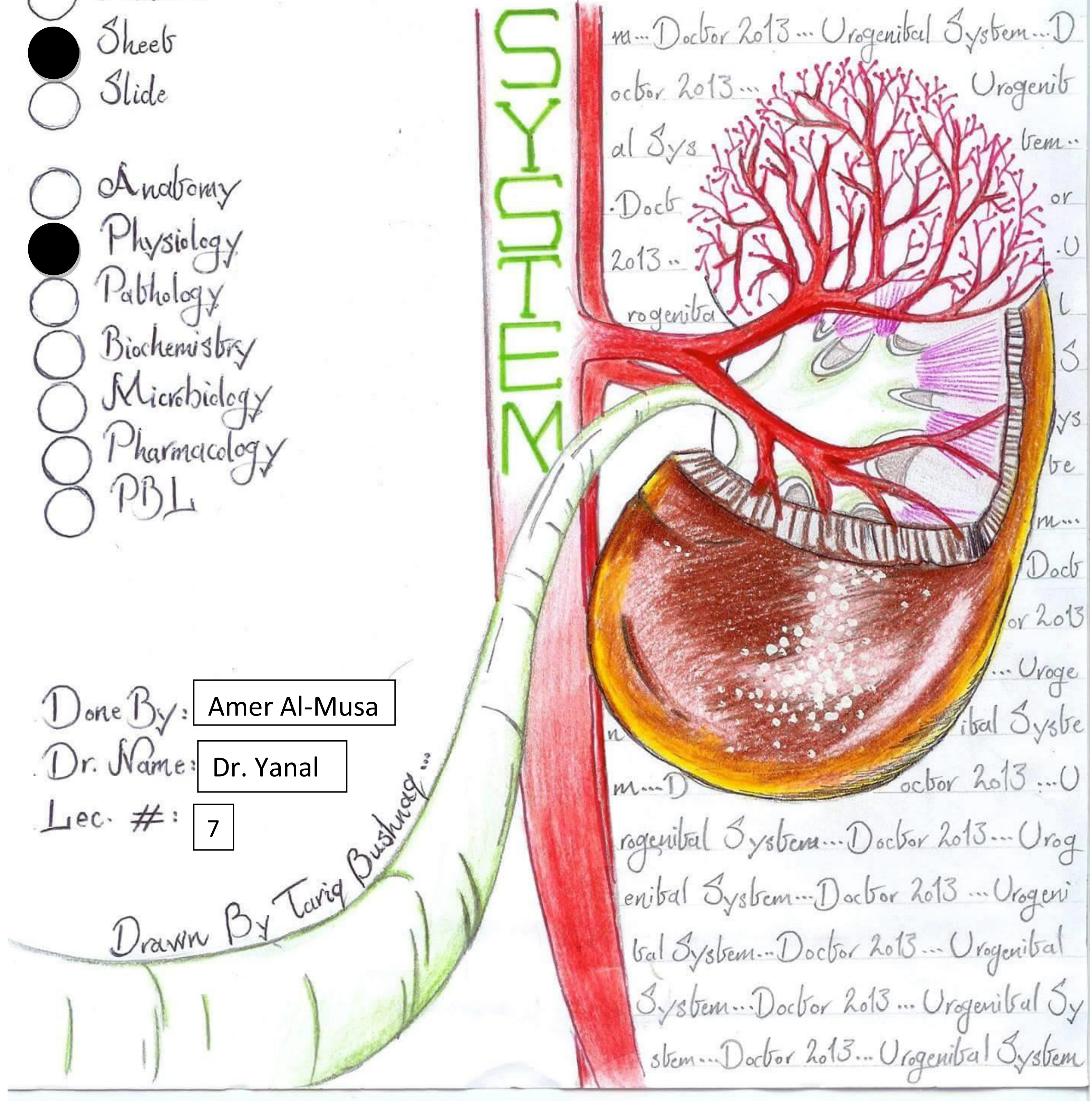
URO-GENITAL SYSTEM



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Lec. #: 7

Dilution and Concentration of Urine

Note: the sequence of this sheet is different than that of the lecture; however the same concepts are explained.

I. Introduction:

Osmolarity is defined as the ***number*** of osmoles (Osm) of solute per liter (L) of solution: 1 mol glucose = 1 Osm; 1 mol albumin = 1 Osm ; 1 molNaCl = 2 Osm (due to dissociation in water).

Remember that 1 mole of any substance has the same number (Avogadro's number) of particles/molecules regardless of their size. Hence, 1 mole of any substance, regardless of whether it is large, intermediate or small in size, has the same effect in attracting water.

A healthy kidney is capable of producing either concentrated or diluted urine, depending on the body's need to conserve water. In cases of water excess, the produced urine can be as dilute as 30-50mOsm/L (**minimal urine concentration**). In cases of dehydration, the produced urine can be as concentrated as 1200-1400 mOsm/L (**maximal urine concentration**).

Under normal conditions:

- The kidney removes 1000mOsm/day. Considering the average urine output to be 1.5 L/day, and by dividing 1000 over 1.5, we can calculate the average urine osmolarity to be approximately 650 mOsm/L.
- Urine is hyperosmolar (600 -650 mOsm/L): remember that plasma has an osmolarity of 300 mOsm/L. This is used as a reference point, and hence urine with higher osmolarity than plasma is termed hyperosmolar.

II. Acute Renal Failure/Injury:

The most common indicators of ARF are:

1. Elevated plasma urea (normal range 15-40 mg/dL).
2. Elevated plasma creatinine (normal range 0.7-1.3 mg/dL).

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3. Oliguria (decreased urine output): this is defined as urine output<300 mL/day/m^2. Anuria is defined as urine output <100mL/day/m^2. However,in some cases of ARF, where the cause of failure is intrarenal, the volume of produced urine can be normal.

Acute renal failure causes are categorized into:

1. Prerenalcauses: these decrease effective blood flow to the kidney. They include myocardial infarction, bleeding, heart failure and hypotension.
2. Intrarenal causes: these cause damage to the kidney itself. Examples include nephrotoxic drugs likemycin antibiotics and NSAIDs, and nephritis.
3. Postrenal.

Prognosis of ARF:

In cases of reversible ARF that does not progress into chronic renal failure, the last kidney function to be regained during recovery is the ability to concentrate urine. Hence, concentrated urine in a patient recovering from ARF indicates fully regained kidney function. This test can be performed by asking the patient to stop drinking water at midnight and then taking urine samples at 8:00 a.m., 8:30 a.m. and 9:00 a.m. If the osmolarity of any of the samples is >1000 mOsm/L then the patient's kidney has fully regained its function.

III. Measuring Urine Osmolarity

A. Osmometer:

Directly tells us whether urine is hyposmolar, isosmolar, or hyperosmolar. The osmometer depends in its action on the fact that every 1 osmole (1000 mOsm) depresses the freezing point of a liter by-1.86 degrees. So if the freezing point of a solution with unknown osmolarity is -0.93 degrees then the osmolarity of the solution is 0.5 Osm/L (500 mOsm/L). By the same logic, if the freezing point of plasma is -0.5 degrees, then its osmolarity is 285 mOsm/L.The osmometer, however, is not present in all hospitals and laboratories.

B. Specific Gravity Test:

Urine specific gravity (USG) = Weight of urine/ 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.

Since specific gravity depends on weight (unlike osmolarity which only depends on the number of molecules), the relationship between USG and osmolarity is altered when there are significant amounts of large molecules in the urine, such as RBCs, WBCs, proteins, and glucose (in a patient with diabetes). 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(which is practically very unlikely). In the human body it normally ranges from 1.002 to 1.028 g/mL (above 1.025 is concentrated). It rises by 0.001 for every 35 to 40 mOsm/L increase in urine osmolarity.

To estimate osmolarity, we take the last two digits of the USG and multiply by 40. For example: 1.003 * 40 = 120 mOsm. When the USG is 1.025, the osmolarity is equal to 1000.

To perform this test we ask the patient to not drink water for 24 hours, then we take 3 samples of spot urine, one every 30 minutes. If in any of these 3 samples has a USG of 1.025 then the patient is in good shape.

IV. Mechanism of Urine Concentration

The last modification of tubular fluid occurs in the inner medullary collecting ducts. Following that, tubular fluid becomes urine. The collecting duct is the main part of the nephron responsible for determining whether the urine will be concentrated or diluted. Concentrated urine is produced in order to conserve water, while dilute urine is produced in order to get rid of excess water.

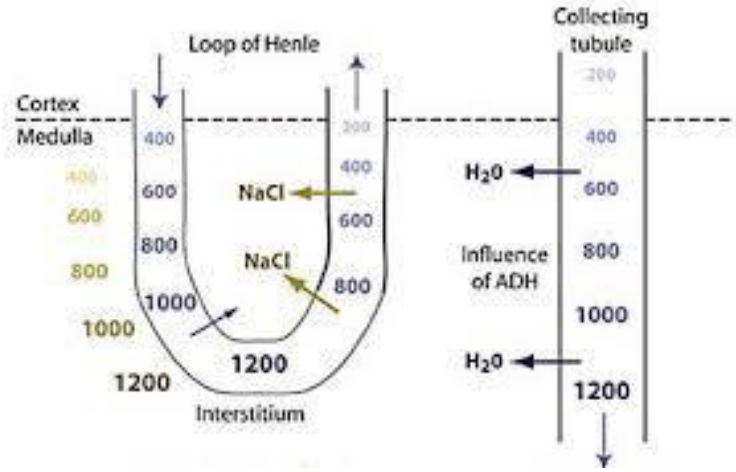
In order for the kidneys (collecting ducts) to be able to concentrate urine, two important factors must be present:

1. Hyperosmolar interstitium in the renal medulla surrounding the collecting duct.

2. Water permeable collecting ducts (i.e water channels must be open so that water can move passively). This requires the presence of ADH.

We will now discuss each of these two factors in details.

1. **The production of hyperosmolar interstitium in the renal medulla:**
   The osmolarity of interstitium everywhere in the body is 300 mOsm/L. However, as we move from the cortex to the papilla in the interstitium of the kidney, there is a progressive increase in osmolarity from 300 mOsm/L in the cortex to around 1200-1400mOsm/L in the inner medulla as illustrated in the figure.**NaCl contributes 700 mOsm/L to the gradient while urea contributes 500 mOsm/L for a total of 1200 mOsm/L.**This osmotic gradient (also called **corticopapillary osmotic gradient**) is extremely difficult to replicate in the lab. Two mechanisms are responsible for the creation of this osmotic gradient; countercurrent multiplication and urea recycling.



A. Countercurrent Multiplication:

This is a function of the thick ascending limb of the loop of Henle (hence this part is called the countercurrent multiplier) whereinNaCl is deposited in the interstetium.This process establishesthe osmotic gradient.
In the thick ascending limb of loop of Henle, NaCl is reabsorbed via the Na+-k+-2Cl-cotransporter. However, **the ascending limb is impermeable to water**, even in the presence of ADH, and so water will not be reabsorbed. This will dilute tubular fluid in the ascending limb and increase the osmolarity of the surrounding medullary interstitium. This function of the thick ascending limb is referred to as the **single effect**.

The single effect followed by the flow of tubular fluid in the descending and ascending limbs leads to an increase, or multiplication of the gradient.

B. Urea Recycling:

This is a function of the inner medullary collecting ducts, wherein urea is deposited in the interstitium. If we track urea from the glomerulus to the end of the collecting duct we notice the following:

1) 50 % of filtered Urea is reabsorbed in the proximal tubules.
2) The thick ascending limb, the distal tubule, and the cortical and outer part of the medullary collecting duct are impermeable to urea; making urea very concentrated at the medullary collecting duct.
3) The inner medullary collecting duct becomes permeable to urea under the effect of ADH, allowing it to move down its concentration gradient from the tubular fluid of the inner medullary to the papillary part of the interstitium, increasing the total osmolarity of the interstitium.
4) Urea is then secreted into the thin descending limb of loop of Henle allowing this cycle to occur over and over.

The role of vasa recta:

The vasa recta are capillaries that follow the same course as the loop of Henle, and they supply the medulla of the kidney. In order to prevent the washout of solutes (urea and NaCl)and loss of the osmotic gradient, the medulla receives very low, sluggish blood supply(only 4% of the total renal blood flow).

In addition, vasa recta participate in **countercurrent exchange** (not to be confused with countercurrent multiplication), a process that helps maintain (and not establish) the osmotic gradient. The mechanism and details of this process were not discussed in the lecture.

2. **Water permeability of the collecting duct and the role of ADH:**

Tubular fluid that reaches the collecting duct has an osmolarity of less than 100 mOsm/L. While passing through the collecting duct, it is passing through a progressively increasing hyperosmotic medium, which favors the movement of water from the collecting duct to the interstitium until the osmolarity of the tubular fluid equals that of the interstitium (about 1200 – 1400 at the end of the collecting duct). However, the collecting duct is permeable to water only in the presence of ADH.

ADH is synthesized in the hypothalamus (85% by supraoptic nuclei and 15% by paraventricular nuclei) and then stored in the nerve endings of these nuclei in the posterior pituitary, where it is released based on need.

There are 3 stimuli for the release of ADH:

a. Osmoreceptors in the hypothalamus: this is the main mechanism. An increase of 1% in the osmolarity of plasma is enough to stimulate more ADH release.
b. Volume receptors: a 10% decrease in ECF will lead to more ADH release.
c. Pressure receptors: decreased blood pressure leads to ADH release. This mechanism is most evident in cases of bleeding and blood loss.

When osmoreceptors detect an increase in plasma osmolarity, they stimulate the release of ADH from the posterior pituitary, increasing the ability of the kidney to reabsorb water. Conversely, when the plasma is hyposmolar decreased amount of ADH is produced and secreted to the blood, decreasing the ability of the kidney to reabsorb water and restoring normal osmolarity of the blood.

Mechanism of action: ADH binds to its surface receptors(V2) on the basolateral side of inner medullary collecting duct principal cells.A second messenger system is activated that leads to the insertion of water channels (Aquaporin type 2) on the luminal surface of the cells of the collecting duct.

This means that even in the presence of a hyperosmolar interstitium, if ADH is not present* - or the receptors do not respond to ADH**- water will NOT be reabsorbed from the collecting duct and urine will be diluted.

* Central Diabetes Insipidus.
** Peripheral/Nephrogenic Diabetes Insipidus.

Factors than can depress the maximum concentrating ability of the kidney:

- **Low protein diet**: urea is a product of protein metabolism. Hence, vegetarians with low protein intake will produce very little urea. Accordingly, the osmolarity of the interstitium will drop.
- **Increased BP and increased renal blood flow (e.g. due to administration of vasodilators):** Medullary blood flow in the vasa recta will increase, leading to washout of solutes and loss of hyperosmolarity of the interstitium.
- **Diuretics:** they decrease NaCl re-absorption. Therefore, hyperosmolarity of interstitium will be lost. Patients on diuretics lack the abilityto produce urine as concentrated as that of healthy individuals.

Remember that maximal urine concentration can only be as high as the concentration of solutes in the medullary interstitium. For example, if the osmolarity of the interstitium drops to 800mOsm/L, the maximal urine concentration will be 800mOsm/L. In some desert species, the osmolarity of interstitium and concentration of urine can reach 10000 mOsm/L.

V. Extra Notes

- Normal saline (0.9% NaCl in water), which is isotonic, has a concentration of 9gm/L. The molecular weight of sodium chloride is approximately 58.5 grams per mole, so 58.5 grams of sodium chloride equals 1 mole. Since NaCl dissociates into two ions – sodium and chloride – 1 molar NaCl is 2 osmolar. The osmolarity of normal saline can be calculated to be approximately 285 mOsm/L.
- Another isotonic solution is 50gm/L glucose(dextrose). Glucose has a molecular weight of 180. Again, this 5% glucose solution has an osmolarityof 285 mOsm/L.

- Drinking salty sea water:

Dead Sea water has a concentration of 150 gm/L, while that of the red sea has a concentration of 25gm/L. If we assume (and this is not an accurate number) that the osmolarity of this water is 2800mOsm/L, then if you drink 1L of it, you will need to add 1 liter of water (from the interstitium, intracellular compartment etc..) to it before it can be passed as urine, because the maximal urinary concentration that the kidney can produce is 1400mOsm/L. Therefore, if you were dehydrated before drinking this sea water, you will end up being even more dehydrated afterwards.

- Sources of osmolarity of urine:

Solute	**Amount**
Na+	150 mOsm
K+	100 mOsm
Cl-	150 mOsm
Urea	400 mOsm
Acid	80 mOsm
Other	120 mOsm
Total	**1000 mOsm**

However, the contribution of each solute can differ depending on dietary intake.

Thank you.

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