PHYSIOLOGY

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Number

7

Subject

Concentration & Dilution of Urine

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Concentration & Dilution of Urine

This sheet was written according to the recording of section 1, this topic is considered one of the most difficult topics in the renal physiology, therefore the order of ideas is kind of different from that in the record and hopefully made easier.

➢ When do we say someone has acute renal injury? There are 5 stages:-

1) **Risk** – We say someone is at risk of developing acute renal injury when his:
   Urine output ($\dot{V}$) = Less than 0.5 mL/kg/hour for 6 hours
   OR when GFR decreases for more than 25%
   OR when creatinine in the plasma (P_{cr}) increases 1.5 folds

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2) **Injury** – We say someone has acute renal injury when his:
   Urine output ($\dot{V}$) = Less than 0.5 mL/kg/hour for 12 hours
   OR when GFR decreases for more than 50%
   OR when creatinine in the plasma (P_{cr}) increases 2 folds

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3) **Failure** – We say someone has acute renal failure when his:
   Urine output ($\dot{V}$) = Less than 0.3 mL/kg/hour for 24 hours
   OR when GFR decreases for more than 75%
   OR when creatinine in the plasma (P_{cr}) increases 4 folds

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4) **Loss** – We say someone has lost his kidney functions when the acute renal injury persisted for more than 4 weeks. (Injury is still reversible until 2 weeks)

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5) **End-stage renal failure** – When the acute injury persists for 3 months and the patient needs dialysis & kidney transplantation.

✵ Clinical Correlate

Whenever you notice someone having persistent bleeding, vomiting or diarrhea, bear in mind that he might have lost too much fluids. In such cases you have to take him to the emergency in order to give him IV fluids (Normal Saline), even before correcting the cause of vomiting/diarrhea. This is done to protect the kidney, because there's a very high chance that he might develop **acute renal injury**.

In the past, they used to call the case "acute renal failure"

Nowadays, clinicians use more the term "acute renal injury" and they both have the same meaning.

❖ **Why do we (humans) have to drink water in order to live?**

- Under normal diet & physical exercise (بالحياة الطبيعية), the body makes 1000 mOsm/day of waste products and it MUST get rid of these 1000 mOsm in urine.
- A bed-ridden person's body makes 700 mOsm/day.
- A healthy kidney can make up to 1400 mOsm/L of concentrated urine. This concentrating ability in human kidneys is limited maximally to 140. (This means that 1 L of urine can carry maximum 1400 mOsm of waste products).

- If a healthy kidney can make concentrated urine of 1400 mOsm/L, how many liters would the body need to carry the 700-1000 mOsm that it has to excrete?
  - ➔ If 1400 mOsm are carried in 1 L, 700 mOsm will be carried in 0.5 L (500 mL)

    So, 0.5 L of urine MUST be excreted daily.

    If the body doesn't get any fluid supply, it won't be able to excrete these 0.5 L, thus, waste products like Na+, K+, creatinine, urea, etc… would just accumulate in the body of yours.

Note: The unit "mOsm (mili-osmole)" stands for number of moles of a certain substance. In this topic, the substance that we are talking about is waste products that are going to be excreted in the urine eventually.
e.g.) 700 mOsm/L, by this we mean 700 mili-osmole of waste products in 1 L of urine.

❖ **Some species in the desert can survive without water, how is this possible?**

➔ This is because kidneys of these species have an enormous concentrating ability that can reach up to 10,000 mOsm/L concentrated urine, so only few mL of urine would be enough to carry all the waste products from the body of that animal;
(the urine would be very concentrated that it'd seem like urinating pure salt).

❖ **What will happen when you drink sea water?**

Sea water is hyperosmolar; e.g. Red Sea: 2400 mOsm/L ||| Dead Sea: 4000 mOsm/L.

Sea water is very concentrated with waste products; i.e. Salt is NaCl; too much Na^+ therefore, drinking if you drink sea water you will need to excrete more urine in order to get rid of these waste products you ingested with sea water.

➔ *e.g.) If you drink 1 L of water from the red sea, you will add 2400 mOsm to the 700-1000 that you have to excrete, therefore you'd have to excrete 3400 mOsm. In this case, you would have to excrete about 2.4 L instead of 0.5 L!*

In other words, drinking sea water will just make you more dehydrated.

- Acute renal injury is not uncommon!
  - 0.1% in the population
  - 3-7% in hospitalized patients
  - 25-30% in ICU patients (many of these have multi-organ failure, including renal failure)

➔ **In an MI patient,** the last function that gets back to normal is EF (ejection fraction), so when EF becomes normal then the MI patient can go home.

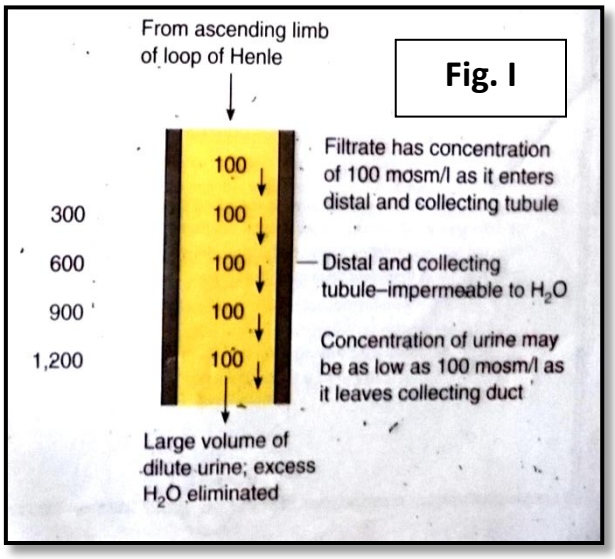
➔ **In an acute renal injury patient,** the last function that gets back to normal in kidneys is the ability to concentrate & dilute solutes in the urine, so when this gets back to normal then you can say that the patient's kidney is back to its full function.

i.e. Plasma concentrations of creatinine and urea would go back to normal during the first week after treating the renal injury, while the ability to concentrate/dilute urine would return after a year! That's the last test to confirm that kidney has full function.

- How is this test done?
  - ☞ Tell the patient NOT to drink water and ask him NOT to urinate for 8 hours
  - ☞ Then ask him for a spot urine sample
  - ☞ Keep taking a urine sample every 30 minutes, for 3 times, up to the 3rd sample you must get concentrated enough urine. (we'll talk about this in detail later in this sheet)

Unfortunately, this test is rarely done in the clinic, eventhough it's very important.

❖ What is the mechanism by which the kidney concentrates urine?



- In the collecting duct, the fluid entering is hypoosmolar (100 mOsm/L)
- If water is not reabsorbed from the collecting duct, the osmolarity will remain 100 but with active reabsorption of NaCl, the concentration will be reduced from 100 to 50 mOsm/L
- If this was the case, then in order to remove the toxic 1000 mOsm, you would have to excrete about 20 L of urine! (Large volume of diluted urine) (Fig. I)

✕ Definitely that's NOT what happens in here. Let's see what actually happens…

In order for the kidney to make concentrated urine, three conditions must be met:

1) Long loop of Henle

Some species in the desert have very long loop of Henle, therefore they have an enormous ability to concentrate urine, whileas Beavers have a short loop of Henle and their ability to concentrate urine is very modest.

2) Hyperosmolar interstitium (1200-1400 mOsm/L) surrounding the collecting ducts

This comes from 2 sources:

I. **<u>700 mOsm/L from the single effect:</u>** The reabsorption of NaCl or Na/K/2Cl without the reabsorption of water.
(Remember NA/K/2Cl cotransporter in ascending limb of Henle's loop).

If you take <u>diuretics</u>, there'll be more Na+ and water excretion, thus the osmolarity of interstitium will be less than 700 (hypoosmolar).

→ The urine will be more diluted.

In the capillary, flow is very low; 4% of the blood reaches the medulla via vasa recta, this low blood flow maintains hyperosmolarity.

If we give a patient a <u>vasodilator</u>, more than 4% of the blood will reach the medulla via vasa recta → a higher blood flow will wash out any solutes, therefore making the filtrated solution more hypoosmolar.

→ The urine will be more diluted.

II. **<u>500 mOsm/L from urea recycling:</u>**

- Urea is freely filtered from the plasma to nephrons
- Urea "CO(NH2)2" has a molecular weight of 60
- Nitrogen in urea has molecular weight of 14+14= 28 (approximately ½ the molecular weight of urea)
- **"B_{UN}"** is the plasma concentration urea nitrogen.
- 50% of urea is reabsorbed from the proximal tubule

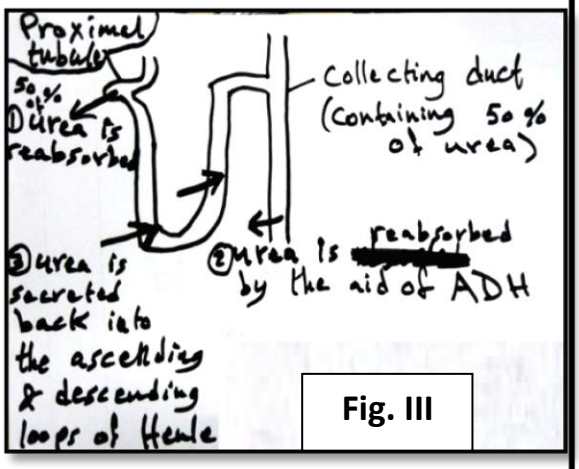
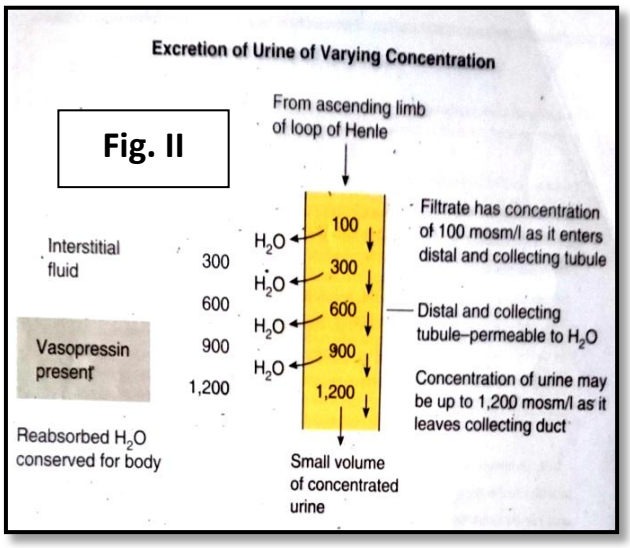


Fig. III

✓ - 50% of urea will reach the collecting ducts;
→ These will be reabsorbed by the aid of **ADH**, when urea reach the interstitium it contributes to its osmolarity by adding 500 mOsm and then gets secreted back into the ascending & descending loops of Henle, adding up 500 mOsm/L of the urine's osmolarity (Fig. III) <u>So 500 from urea cycle + 700 from single effect = 1200</u>

Vegetarian people have a low daily intake of proteins, therefore they don't make that much of urea or other waste products → Less P_{UN} → Less urea filtration → Less osmolar interstitium → More diluted urine.

3) High permeability to water in the collecting ducts



As we said, tubular fluid that reaches the collecting duct has an osmolarity of only 100 mOsm/L. **What actually happens is:**

➔ While the filtrate is passing through the collecting duct, it is passing through a progressively increasing hyperosmotic medium in the collecting tubule (equilibrium horizontally with the osmolarity of the interstitium), until the osmolarity of the tubular fluid equals that of the interstitium (about 1200 – 1400 at the end of the collecting duct). (Fig. II)

This is a result of progressively increasing reabsorption of water from the collecting duct to the interstitium. A condition essential for this to happen is the availability of **ADH**.

ADH

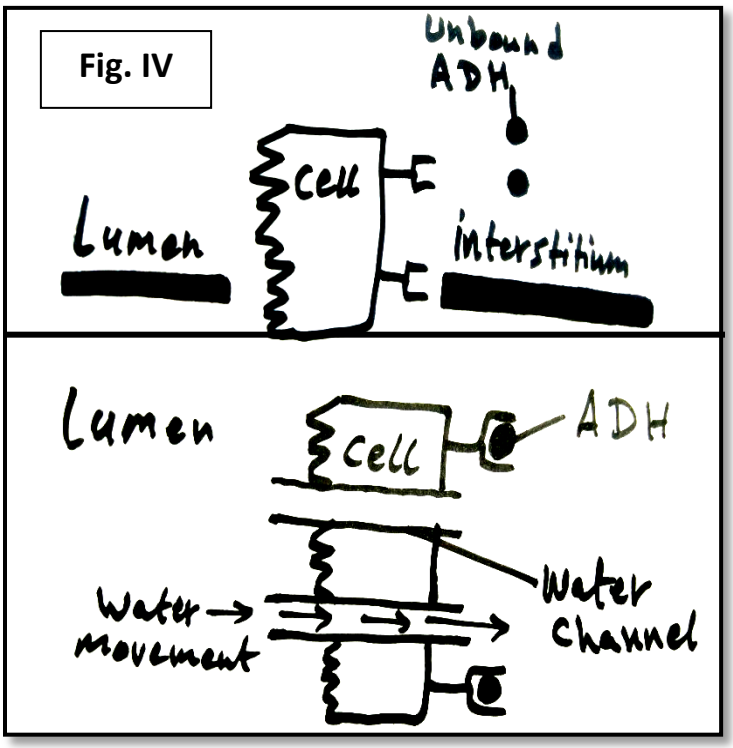
- ADH is a small peptide (9 a.a.) made in the hypothalamus in two different parts:
  - 85% is made in the supraoptic nuclei
  - 15% is made in the paraventricular nuclei
- It is stored in the posterior pituitary
- The hypothalamus has osmoreceptors that are sensitive to 1% increase in osmolarity (~2 mOsm), once this increment of osmolarity takes place, it will secrete ADH.
- The hypothalamus has volume receptors that are sensitive to hypovolemia, therefore any decrement in blood volume by 10%, and it will secrete ADH.
- The hypothalamus has pressure receptors; a considerable drop in blood pressure will result in the secretion of ADH. (Recall from the CVS)

~~ Notice that the most sensitive receptors in the hypothalamus are the osmoreceptors

❖ By what mechanism does ADH favour water reabsorption from the collecting ducts to the interstitium?

- ➢ Its receptors are located on the basolateral surface of cells of the collecting ducts
- ➢ ADH binds to these receptors and form cAMP that act on several protein-forming signalling pathways ending up in forming water channels on luminal surface.
- ➢ The formed water channels will allow the reabsorption of water from the **HYPOosmolar tubular lumen** (100) to the **HYPERosmolar interstitium** (1400) surrounding the nephrons, therefore maintaining an equilibrium between them, both becoming HYPERosmolar (~1400). (Fig. IV)

✹**[Important] Going down the collecting duct, cells have more ADH-receptors** → More water reabsorption → More concentrated urine.



➔ If there is no ADH:-

- **Central diabetes insipidus**: (Corresponds to DM type 1) There's no ADH secretion.
- **Peripheral/Nephrogenic diabetes insipidus**: (Corresponds to DM type 2) There is enough ADH, but the receptors are non-responsive (Kidney pathology)

Note: Glucose & Mannitol will accumulate in the collecting duct, preserving water with them inside the collecting ducts and prevent it from being reabsorbed (This is called **osmodiuresis**).

⇨ In both of these cases, there will be no water reabsorption from the collecting ducts into the interstitium →→ More diluted urine.

❖ Osmolarity (concentration) of urine is measured via the Osmometer;

- ✓ It is used in the test of measuring the urine concentrating ability of the kidney.
- ✓ The osmometer measures the freezing point of urine
- ✓ Water has a freezing point of 0 °Cs

✓ If a solute was added to the water making a solution, freezing point will decrease; every 1 Osm (1000 mOsm/L) of solution will depress the freezing point by 1.86 °C.

e.g.) Normal urine is considered hyperosmolar (hypertonic) (~700-1400 mOsm/L) compared to plasma, thus the freezing point of normal urine is around:

[700 * -1.86 / 1000] to [1400 * -1.86 / 1000] ➔ ~ [-1.302 to -2.604 °C]

➢ The osmometer is not widely used in clinics in many countries; they use something else that is easier than using the osmometer, which is the **specific gravity**.

❖ The specific gravity (SG) = $\frac{Weight\ of\ urine}{Weight\ of\ water}$

- Weight of 1 L of water = 1 kg
- Weight of 1 L or urine has to be more than 1 kg (because urine = water + wastes)
  ➔ *The weight of 1 L of urine can never be 1 kg, or else it'd just be water.*
- The osmolarity is measured by multiplying the last two digits from the SG by 40 **(Osmolarity = SG's last 2 digits * 40)**
- *e.g.) SG = 1.003 → Osmolarity = 03 * 40 = 120 mOsm/L → very diluted*
  *SG = 1.040 → Osmolarity = 40 * 40 = 1600 mOsm/L → very concentrated*

  ⇨ *Notice that how a little difference in the specific gravity can result in a huge difference in concentration!*
- SG is a measure of weight. In order to get accurate results, the urine must be clear of any substances that would increase the weight of the urine apart from the waste products that contribute in the osmolarity of urine.

  Of these substances that urine must be clear of are: WBCs/RBCs (Hematouria), bacteria (Pyuria), contrast media used in IPV (Intravenous Pyelogram), etc…
- If a patient had urine with specific gravity of **25** (last two digits) or more then you say that he is in good shape and the renal injury has been fixed.

➔ So, if the kidney is making concentrated urine what does this indicate?

✓ The hypothalamus & the posterior pituitary are working well, secreting ADH.
✓ The collecting duct is responding well to ADH via receptors.
✓ The interstitium is hyperosmolar (ascending limb of Henle is working well)

❖ Acute renal injury's effect on concentration & dilution of urine:

In acute renal injury, the kidney will lose its ability to concentrate and dilute urine, therefore whatever the patient does/eats/moves/etc… his specific gravity will equal 10.

By SG =10, we mean that the last two digits of SG is 10, so his SG is actually 1.010.

➔ The osmolarity thus will be 10*40 = 400 mOsm/L, and this equals the osmolarity in the plasma, the patient in this case is described to have a condition called **isosthenuria**.

- Acute renal injury is classified into 3 categories according to the cause:-
  - **Prerenal injury**
    - Too much bleeding, vomiting, diarrhea, over-sweating
    - If these persist extensively, the injury can become intrarenal (worse)
    - It has the best prognosis
  - **Intrarenal injury**
    - Acute tubular necrosis
  - **Postrenal injury**
    - Kidney stones (Benign stones are painful ||| Malignant stones are painless)
- Prerenal & intrarenal acute injuries together make up 90% of acute renal injuries (Postrenal makes up 10%).
- When a patient presents with acute renal injury, we can know if the injury is intrarenal or prerenal from the history; If the patient lost a lot of fluids, it's **prerenal** while if the injury was a result of a certain drug, then it's **intrarenal**.

❖ How do we know if the prerenal injury became intrarenal?

- In prerenal injury, the GFR (filtration) is less than normal but reabsorption is still intact and is still not affected: Urea will be filtered less than normal (more urea will stay in plasma) & The reabsorption of urea is still normal, therefore the concentration of urea in the plasma will become highly elevated → **Urea/Creatinine ratio will become 100** (instead of the normal 40).

  (Remember: Creatinine does not get reabsorbed)

  * Also **Na+ in the urine is low** because there is still reabsorption, so the excretion fraction of sodium is < 1%

- In intrarenal injury, both GFR and reabsorption (tubules) are affected: Here, both plasma urea & creatinine will elevate, but creatinine will increase more → **Urea/Creatinine ratio will become less than 40.**

  * Also **Na+ in the urine is more** because reabsorption is more impaired, and the excretion fraction of sodium is > 2-3%

✓ *As we said earlier, whenever you observe someone with persistent fluid loss, even if his blood pressure is normal, without any hesitation take him to the emergency in order to give him an IV line for few hours (~6 hours) in order to compensate the fluids he lost and to prevent the prerenal injury from becoming intrarenal injury (Acute tubular necrosis).*

This example has the same idea of "**Conn's Syndrome**" that was already covered in the last lecture: Hyperaldosteronism → ↑Plasma Na+ & water → Hypervolemia → Hypertension. If treatment of this disease by surgical removal of tumour was delayed to more than 2-3 months, the hypertension will become permanent.
(The secondary hypertension becomes primary)

❖ When do we say a patient has **oliguria**? (Decrease in urine output)

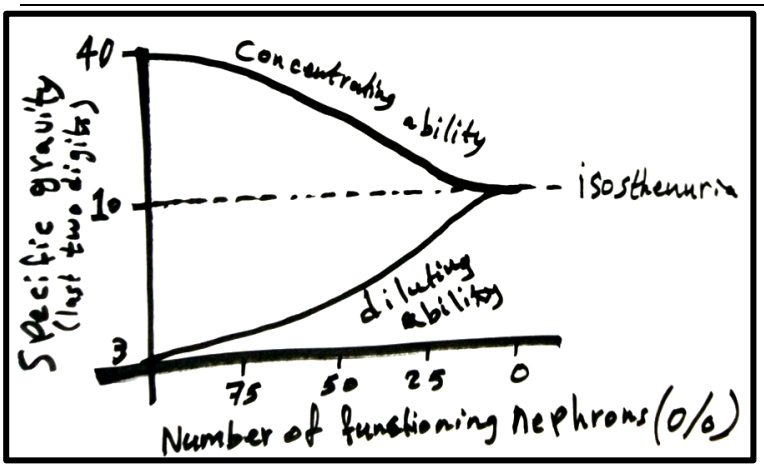
We would not wait a whole day in order to check how much urine output the patient excretes, so we enter a Foley catheter every hour and check out how much he excretes.

- Many numbers indicate if the patient has oligouria, but **DO NOT MEMORIZE ANY**:

➔ Oliguria in adults, when the daily urine output is less than 0.5 L/day = (20 mL/hour)
In children, it's less than 0.5 mL/kg/hour. In infants, it's less than 0.1 mL/kg/hour.

- The only equation by which you can find out if a patient has oliguria and you have to **MEMORIZE** it: ➔ Less than 300 mL/Day/m^2 *BSA ||| (BSA = Body Surface Area)

  e.g.) A man with BSA = 1.5 ➔ 300 * 1.5 = 450 ➔ Minimum urine output should be 450 mL/day or otherwise he is said to have oliguria.



❋ Although most acute renal injury patients have oligouria, some might have polyuria! So even if a patient has a very high urine output do NOT rule out renal injury and check the SG, if it's 10 then he definitely has acute renal injury.

By looking at the following figure, you can notice that:-

1) By losing 25% of the kidney function (when the curve on the x-axis is on 75), the kidney can still concentrate & dilute urine effectively.

2) When the kidney function is fully lost, the specific gravity will be 10 (isosthenuria).

Good Luck <3 **Hala Madrid** <3