Sheets Physiology

Number	7
Doctor	yanal
Done By	Abdel-muez siyam
Correction	

The ability of the kidney to make concentrated urine:

This feature is very important for our bodies. Following acute renal failure,[which is reversible in 85% of cases except in ICU patients (ICU + Acute renal failure = Higher mortality)], creatinine and urea levels rise, but then go down in the recovery stage (which also includes a satisfactory urine output). Urea and creatinine are not good representatives of the post-injury status of the kidney; so in order to say that the kidney has almost completely returned to normal, it must be able to concentrate urine, meaning that it must be able to make a hyperosmolar medullary interstitium, to which water from the tubular fluid gets attracted under the effect of ADH, eventually producing scant (little) but highly concentrated urine. This ability might take around one year to return to normal after the injury, so this is the last test to be tested.

Note: acute renal injury can result from many causes, including severe bleeding, dehydration, cholera….etc.

If the kidney is successfully able to concentrate urine, we ensure that multiple organs are functioning well, primarily including the kidneys (the ***ascending loop of Henle*** is well capable of establishing the single effect, effectively yielding multiplication of osmolarity in the surrounding interstitium, and ***the collecting duct*** responds to ADH properly, and the blood flow within ***the vasa recta*** is just fine – because too much blood flow washes out all the hyperosmolarity created by the ascending loop of Henle), in addition to the hypothalamus (ADH factory), and the pituitary gland (ADH warehouse).

Note:, The degree of damage of the kidneys is evaluated according to the five criteria or five stages of RIFLE : Risk, injury, failure, end stage failure, loss of kidney function), to determine the renal status. To know the stage, we use several criteria, one of which is the urine output. If the urine output is less than the minimum obligatory urine output, this is called as ***oligurea***.

- For infants, oligurea is characterized by a urine output less than 1 ml/Kg body weight/ hour.
- For children, oligurea is characterized by a urine output less than 0.5 ml/Kg body weight/hour.
- For adults, oligurea is characterized by a urine output less than 0.3 ml/Kg body weight/hour.
    - $\Rightarrow$ **EASIER TO MEMORIZE**: oligurea is when the urine output is less than 300 ml/m^2 body surface area/day.

⇒ It is around 450 – 500 ml/day for adults (BSA around 1.5 m^2).

⇒ If an adult's urine output is less than 100 ml/day, we call it ***anuria*** (as if there is no urine output)

The importance of this ability manifests as the ability to conserve water, and at the same time get rid of all of your body's waste products. If you make diluted urine, you remove all the extra water from your body (in addition to wastes).

Following renal injury, we must test for the kidneys' ability to concentrate urine, in addition to their ability to dilute urine. What we do is that we prevent anything to be given to the patient for 8 hours (this is called NPO [**NOTHING** BY MOUTH], you MUST ensure that the patient didn't drink any water for 8 hours, for example from 12:00 am to 8:00 am), then we give the patient a urine bag and tell him/her to urinate in it. Then we give the patient another bag to urinate again at 8:30 am, then another one at 9:00 am. To say that his kidneys can concentrate urine, at least one of the three bags' urine must have an osmolarity of 1000 mOsm/L (the maximum is 1400, but 1000 is Ok for the test).

Let us assume that you drank one liter of sea water, whose osmolarity is about 2800 mOsm/L. You intuitively think that if you are already dehydrated, you'll get more dehydrated, but why? The answer is simple: those extra 2800 mOsm (since the concentration is 2800 mOsm/L, and you drank 1 L, so the input is 2800 mOsm) will have to get out and be excreted. Your urine's maximal concentration capacity is 1400 mOsm/L, so those 2800 mOsm will actually be flushed out by 2 liters (each liter containing 1400 mOsm, because your kidney cannot concentrate urine above this level, it can't make 1500 or 1600…). Input of 1 liter and output of 2 liters makes you dehydrated.

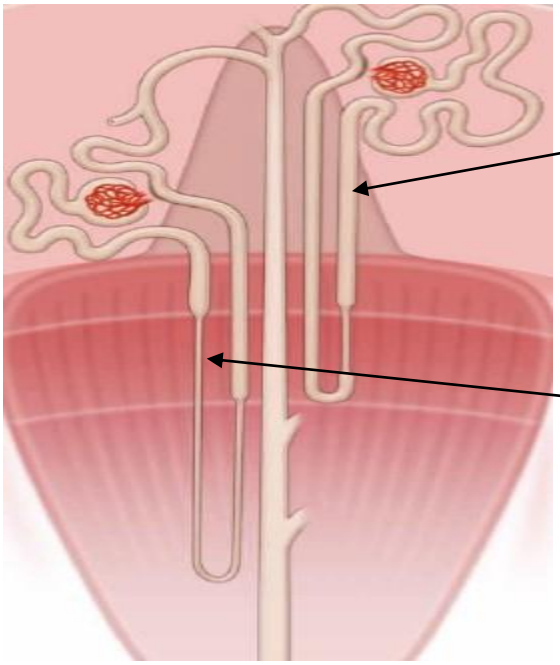
The ability of the kidney to make concentrated urine requires the following:

(1) Juxtamedullary nephrons:

Which are those nephrons whose Bowman's capsule lie near the cortico-medullary junction (inner cortex), and have long loop of Henle.

Species lacking such nephrons cannot make concentrated urine (e.g. fish), which makes sense because water is always available, so why conserve it?!

Desert animals have most of their nephrons as juxtamedullary, so they can concentrate their urine up to 10,000 mOsm/L, thus they don't need to make too much urine (they just make little amount, but highly concentrated).

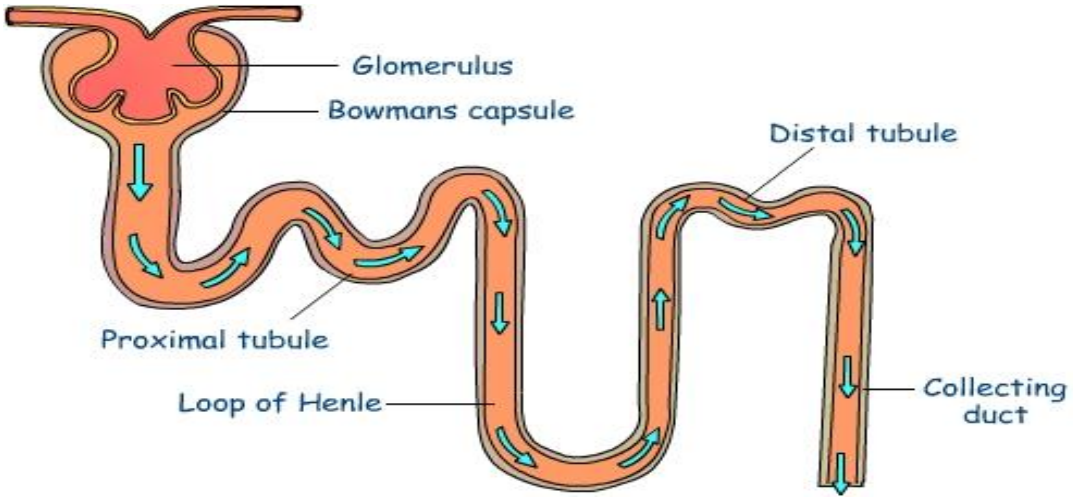


This is a cortical nephron which has a **short** loop of Henle, and such nephrons constitute the vast majority of human nephrons (85%)

This nephron is a juxtamedullary nephron, which has a **long** loop of Henle, spanning the medulla for a longer distance. Such nephrons constitute around 15% of human renal nephrons and are especially important in urine concentration.

Osmolarity of the tubular fluid:

- In Bowman's capsule and the PCT, it is 300 mOsm/L (same as plasma).
- The more we go down (***desending***) the osmolarity increases (400, 500 …1200)
- The more we go up (***asending***) the osmolarity decreases (to reach 100)
- In the collecting duct, depending on the availability of ADH, urine osmolarity might increase or decrease. Thus the osmolarity of urine could be as low as 50 mOsm/L (very diluted), or as high as 1400 mOsm/L (very concentrated).



Note that the tubular fluid descends then ascends, so the currents (flow) are in opposite directions. This is referred to as countercurrent mechanism/theory. The thick ascending limb of Henle contributes to the formation of the hyperosmolar

interstitium, by reabsorbing NaCl and K^+ , so this part of the tubule is called the countercurrent multiplier.

Q/ how can the osmolarity of urine be less than 300 mOsm/L (how to dilute urine)?

A: It is possible because NaCl *can be actively reabsorbed* from the collecting duct (unlike water), leaving water behind, which dilutes the urine.

(2) Minimum medullary blood flow

Around 95% of the blood is directed towards the cortex, while only 5% goes to the medulla via vasa recta. If the medullary blood flow increased to 10%, following the use of vasodilators or an increase in the blood pressure for example (both of which push more blood through the vasa recta), the osmolarity of the medullary interstitium will not reach what is expected; because a lot of the NaCl and the urea there will be washed away with blood, so the *maximum* osmolarity urine can have is 900 mOsm/L for example (instead of 1400 mOsm/L). The normal flow is just enough to maintain a hyperosmolar interstitium; this is referred to as the countercurrent exchange. The vasa recta also descend and ascend. When it enters, the osmolarity of its blood is 300 mOsm/L, and the exiting osmolarity is around 320 mOsm/L.

(3) Reabsorption of NaCl from the countercurrent multiplier:

This reabsorption must not be accompanied with water (single effect). Also, this condition implies that the patient is **not on diuretics**, because diuretics inhibit NaCl reabsorption, preventing maximum osmolarity of the medullary interstitium, and subsequently the urine (max may reach 800 mOsm/L).

So in order to concentrate urine, we must ensure no diuretic therapy, no vasodilators, and we **need** ADH (which inserts water channels in the collecting ducts, allowing the passive movement of water from the tubular fluid to the medullary interstitium, increasing the osmolarity of urine to maximally be 1400 mOsm/L).

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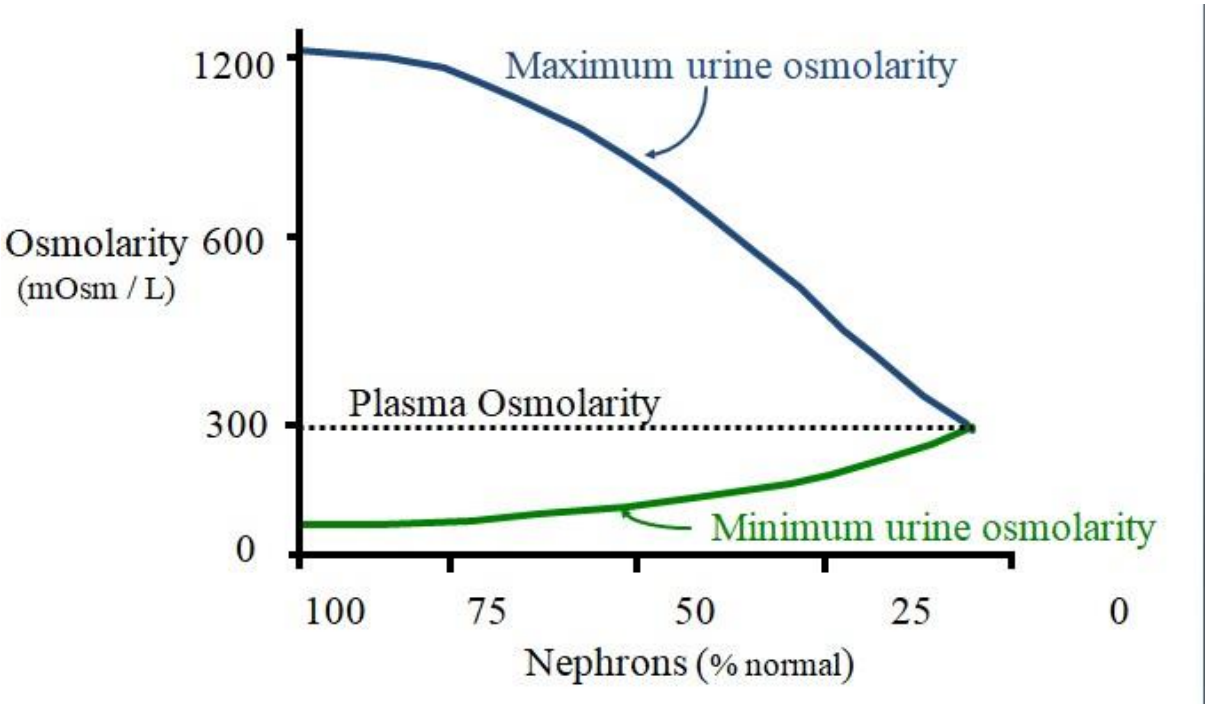
The figure below shows the number of functioning nephrons (from 100% to 0%), relating it to the osmolarity of urine.

An osmolarity of 300 mOsm/L is similar to that of plasma. If urine osmolarity is 300 mOsm/L *regardless* of water status, we call this ***Isosthenuria***. When you give the patient excess water, the normal response is to get diluted urine (below 300) and when you deprive him/her from water, the urine must get concentrated (above 300).



In isosthenuria, urine's osmolarity remains 300 mOsm/L whether drinking or not, meaning that the kidney is **unable** to concentrate or dilute urine, which is usually the outcome of nephron loss due to chronic renal failure.

This case is reached when only 25% of functioning nephrons are present (if the patient is left with less than half kidney).

Patients may have a normal urinary output and still be suffering from renal failure, but how? By *Isosthenuria,* because the patient who excretes 1.5 L/day is actually only excreting 450 mOsm of wastes per day (the urine's osmolarity is ALWAYS 300 mOsm/L, the kidney is failing to concentrate or dilute the urine).

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Measuring the osmolarity of the urine:

I. ***Osmometer***:

A device which depends on the freezing point of the solution. Pure water's freezing point is 0 C^0. If you put 1 osmole of a solute in 1 liter of water, this solution's freezing point becomes -1.86 C^0 (each 1 osmole put depresses the freezing point by 1.86 degrees).

Note that 1 Osmole = 1000 mOsmole

Example: A urine sample is collected and sampled by an osmometer in the lab. Its freezing point was found to be -0.5 degrees. What is the osmotic concentration of this sample?

Answer: Each 1000 mOsmole/L → -1.86 degrees
The total has a freezing point of -0.5 degrees, so the concentration = (1000* (-0.5))/(-1.86) = 270 mOsmole/L.

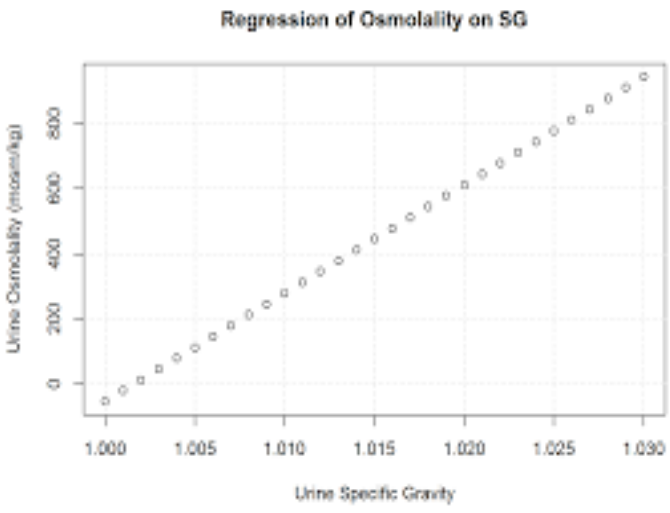
The use of osmometers is actually limited to research purposes, and not suitable for routine clinical utility.

II. Specific gravity:

⇒ Equals Weight of urine/weight of water.

We bring a water container, and gently put some urine on its surface. Lighter urine can't push deep against the water surface and thus do not get immersed by water (it is like having a clear water-urine interface). Heavier –denser- urine samples get slightly immersed (only the bottom part of the urine sample will be pushed against and immersed in water). More heavy samples are more immersed and so on.

Higher osmolarity means more particles, meaning that the urine now weighs more and is denser, so it is expected to be immersed when poured over water (at least partially). What we are concerned with is the number of the specific gravity, because different numbers correlate with different osmolarities. It might be 10, 20,…….40 (too high) [it is actually 1,040 over1000 (not 40 times)].



This curve shows the relationship between specific gravity of urine and its osmolarity. For simplicity, we'll take the last two digits of the specific gravity and multiply them with 40, yielding the osmolarity.

For example: If the specific gravity equals 1,025 → the osmolarity = 1000 mOsmole/L

SG = 1,030 → the osmolarity = 1200 mOsmole/L (can write mOsM, cuz mole/L=M)
SG = 1,035 → the osmolarity = 1400 mOsM.

*Note: Osmolarity is due to osmotically active particles in the solution, like small ions. Now there's a point where you should pay attention: if the urine contains other components, like RBCs, WBCs, proteins, casts, or contrast dyes…… such components are not osmotically active (they are not part of the osmolar concentration and do not withdraw water towards them), but they will make the urine heavier/denser, so this sample of urine will have a high specific gravity (and apparent high osmolarity, which is not true).

⇒ If you use specific gravity, urine should not contain osmotically inactive particles, to prevent over-estimation of the osmotic concentration.

⇒ If you get the lab results, you take the last 2 digits and multiply with 40. Imagine a patient who has 1,010 specific gravity whether he drank a lot of water or didn't drink at all → this patient suffers from Isosthenuria.

⇒ If you want to see whether the patient's kidneys can concentrate urine or not, you give him 3 containers as mentioned previously. Now, if any of those three gave a result of 1,025 → kidneys can successfully concentrate urine, because urine osmolarity can reach 1000 (25 x 40).

⇒ Since SG can test the kidneys' ability to concentrate urine, it indicates a healthy hypothalamus, pituitary, ascending Henle loop, and collecting duct

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Assume that a patient has no ADH, what will happen?
No ADH→ no reabsorption of water from collecting duct, so tubular fluid (and subsequently urine) is diluted, let's say around 50 mOsm/L. Now, how many liters of urine will this patient excrete?
We know that a normal individual needs to excrete 1000 mOsmole/day. If the urine's osmolarity is 50 mOsmole/L, then he/she needs to excrete 20 litres of urine per day to get rid of all the 1000. So patients with ADH deficiency will remain in the bathroom urinating, and to prevent dehydration they'll also drink a lot.

No ADH (centrally) or its receptor in the kidney or reduced responsiveness of the receptor (nephrogenic) → polyuria and polydipsia → mistaken for Diabetes Mellitus, so called ***Diabetes insipidus***.

Diagnosis is by symptoms and blood samples (to see blood sugar→ normal)
Note: such patients always prefer cold water –good note by the attending doctor
Treat by ADH preparations.

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Acid – Base balance role of the kidneys:

This balance implies keeping the hydrogen ion concentration in the extracellular space (interstitium) within a limited range.

Q/ Which is more in the plasma: Na^+ or H^+ ?

A/ Absolutely Na^+, because the osmolarity of the plasma equals 300 mOsmol/L. The plasma contains an equal amount of cations and anions, so the 300 are distributed as 150 cations, and 150 anions. Na^+ concentration alone is 140 mmol/L (mEq/L), and all the other cations like K^+, Ca^{+2}, Mg^{+2}, and H^+ share the last 10.
If you remember, Na^+ alone was enough to determine the osmolarity of the plasma (which equals $[Na^+] * 2.1$), and if Na was the only cation in the plasma, we would multiply with 2 instead of 2.1 (as if we're saying that the plasma contains Na^+ and an equal amount of anions (X2), and all the other cations are occupied by the 0.1 in 2.1).

Na^+ concentration is 3.5 million times more than H^+ concentration

$[Na^+] = 140$ mmol/L $= 140 \times 10^{-3} = 1.4 \times 10^{-1}$.
$[H^+] = 40$ nmol/L $= 40 \times 10^{-9} = 4 \times 10^{-8}$.

Remember that $[K^+] = 4$ mmol/L, and that if it doubled → cardiac arrest
and if it reached 1 → paralysis of muscles.

What about H^+? Normally it's around 40nmol/L. Our bodies can accommodate an increase in H^+ up to 160 nmol/L (4 times), or a drop to reach 10 nmol/L (one fourth). Above 160 or below 10 → not compatible with life.

Please note that although 10 is one fourth of the normal 40, and 160 is four times the normal 40, the range is not equal (as absolute number). So we can tolerate an increase in H^+ of 120 nmol/L (from 40 to 160), but we can only tolerate a drop of 30 nmol/L (40 to 10). This means that our bodies are better equipped to deal with acids than bases. We can deal with more acids but we can't deal with less acids.

$[H^+] = 40$ nmol/L $= 4 \times 10^{-8}$
$\log [H^+] = \log (4 \times 10^{-8}) = \log 4 + \log 10^{-8} = 0.6 + (-8)$
$\log [H^+] = -7.4$ → $- \log [H^+] = 7.4$

P = -log → pH = 7.4

So 10^{-7} contains 10 times more H^+ than 10^{-8}, but pH of 10^{-7} is 7, while the pH of 10^{-8} equals 8. **So the less the pH the more the hydrogen ion concentration.**

The normal range of plasma pH is 7.35 to 7.45
If pH reaches 8 ($[H^+]$ = 10 nmol/L) or drops to 6.8 ($[H^+]$ = 160 nmol/L) → NOT COMPATIBLE WITH LIFE.

H^+ affects every enzyme in the body because every enzyme has its optimal pH. Regarding CNS enzymes, they are suppressed by too much H^+ (low pH), causing coma and death. Take it another way: less H+ → excitation of them → excitation of the neurons and convulsions, and respiratory muscle tetanisation causes death. Generally, every protein is affected by the pH, including enzymes, hormones, and hormone receptors, so we cannot tolerate wide H+ fluctuations.

*Acid: Hydrogen donor; any chemical compound liberating H+ in the solution.
Base: : Hydrogenacceptor; any chemical compound receiving H+ in the solution.

*Acids:
(1)Strong acids:
$HCl \rightarrow H^+ + Cl^-$ ……..complete dissociation (1 mole → 1 mole + 1 mole)
(2)Weak acids:
$H_2CO_3 \longleftrightarrow H^+ + HCO_3^-$ …….incomplete dissociation (not all the 1 mole dissociates, some carbonic acid remain as is,so 1 mole acid does not give 1 mole H^+)

*The same concept applies to bases (Strong vs. weak)

Acid dissociation constant and Henderson-Hasselbalch equation

$$CO_2 + H_2O \xrightarrow{CA} H_2CO_3 \longrightarrow H^+ + HCO_3^-$$

pH = 6.1 + log (HCO_3^-/ CO_2) …….The important thing is that log (base/acid)
So if you know the arterial concentrations of HCO_3^- and CO_2, we can predict the arterial pH.

The equation for another pair: pH = 6.8 + log ($HPO4^{-2}/H_2PO_4^-$)

The equation for another pair: pH = 8.3 + log (NH_3/NH_4^+)

All those three represent buffer systems, and if you know the concentration of each respective base and acid, you can know the pH (isohydric principle).

Our bodies produce 2 kinds of acids:

1- CO_2 (majority): which gets converted to H+ as previously stated.
   Our bodies produce 300 L of CO2/day, corresponding to 10 M of H+.
   We don't really care about this because this is removed through the lungs, so CO2 is a **volatile acid**.

2- **Non-volatile (fixed) acids**: many and include lactic acid, phosphoric acid, sulphuric acid, acetoacetic acid, alpha ketogluteric acid….etc.
   Our body produces around 1mM/Kg/day. These are the dangerous acids that I have to deal with because I can't just exhale them. If someone weighs 80 kgs, then he makes about 80mM/day, which if distributed on his extracellular 14 litres, would result in a [H+] of 80/14 = 5 mM (approximately). This level's pH (2.3) is fatal if not dealt with.

If you happen to have 80 mM of bicarbonate (HCO3-), your problem is solved, because the 80mM of H+ will combine with the bicarbonate, producing CO2, which is exhaled by the lung. This shows that bicarbonate is a precious substance. The problem here is that I'm still losing, because by the end of the day I would have lost 80mM of precious bicarbonate, but how much bicarbonate do we have to begin with?
We have 14 L of extracellular fluid, each containing 24 mM of HCO3-, so we have around 336 mM of bicarbonate (total), which according to our calculations, is only enough to protect us for a few days, but what are we going to do after that? What our bodies actually do is that they *generate* the bicarbonate, and the organ responsible for this process is none other than the ***kidney***.

THE END