Introduction:

It is of great importance to ask the following question: Why is it important for us to concentrate or dilute urine? An important function of the kidney is to regulate the osmolarity of the plasma. A change of only 1% in the osmolarity of plasma is sufficient to change the concentration of urine produced by the kidneys. This function requires the presence of a healthy kidney and appropriate concentration of ADH in blood.

The average intake of water per day is 2500 ml, and so is the average output. The following table summarizes water intake and output. The number that concerns us most in this lecture is the Urine output of 1500 ml/day.

<table>
<thead>
<tr>
<th>Water Intake (total 2500 ml/day)</th>
<th>Water Output (total 2500 ml/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drinking</td>
<td>1600</td>
</tr>
<tr>
<td>Food</td>
<td>700</td>
</tr>
<tr>
<td>Product of metabolism</td>
<td>200</td>
</tr>
<tr>
<td></td>
<td>Urine</td>
</tr>
<tr>
<td></td>
<td>1500</td>
</tr>
<tr>
<td></td>
<td>Respiration</td>
</tr>
<tr>
<td></td>
<td>300</td>
</tr>
<tr>
<td></td>
<td>Skin</td>
</tr>
<tr>
<td></td>
<td>600</td>
</tr>
<tr>
<td></td>
<td>G.I</td>
</tr>
<tr>
<td></td>
<td>100</td>
</tr>
</tbody>
</table>

Most Cases of Acute Renal Failure are manifested as decreased urine output (oliguria) which is defined as : urine volume < 300 ml/day/m² body surface area. Some references prefer the following table for oliguria:

<table>
<thead>
<tr>
<th>Age group</th>
<th>Urine output to be considered oliguria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants (up to 1 year)</td>
<td>&lt; 1 ml/kg/h</td>
</tr>
<tr>
<td>Children</td>
<td>&lt; 0.5 ml/kg/h</td>
</tr>
<tr>
<td>Adults</td>
<td>&lt;0.3 ml/kg/h (This equals 400 ml/day for adults)</td>
</tr>
</tbody>
</table>

The previous is important to know because for a person with healthy kidneys the “minimum obligatory urine output” is 500 ml/day and values well below that is considered oliguria. The way we derived this number is as follows:

- The body normally produces 700 mOsm/day of waste products that must be excreted.
Concentration & Dilution of Urine

- The maximum concentrating ability of the kidneys is 1400 mOsm/L
- Concentration = # of moles / Volume (L) .... Since the maximum concentration is 1400 ➔ 
  1400 = 700 / Volume (L) ➔ Volume = 0.5 liter

A healthy kidney is able to produce concentrated or diluted urine according to the physiologic or pathologic circumstances of the body. That is, urine is normally hypertonic (650 mOsm/L), however if we deprive a person of water, the kidney can further concentrate this urine to 1400 mOsm/L. Conversely, if a person drinks large amounts of water, the kidney would produce diluted (hypotonic) urine.

This is particularly important in the evaluation of post Acute Renal Failure patients, because the concentrating capacity of the kidney is the last function of the kidney to be restored. So the restoration of this capacity is an indicator of good prognosis.

**Mechanism of Urine Concentration:**

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

1. Hyperosmolar interstitium in the renal medulla surrounding the collecting duct (Also called corticopapillary osmotic gradient).
2. Water permeable collecting duct, which requires the presence of ADH

The main idea is that if the interstitium surrounding area 6 and 7 in the diagram (the collecting duct) is hyperosmolar and the collecting duct is permeable to water, water will move –by osmosis- into the interstitium leaving the tubular fluid concentrated.

This indicates that –theoretically- in order to change the concentration of urine, we can either change the hyperosmotic environment surrounding the collecting duct or change the permeability of the duct to water. In reality the latter mechanism is the primary mechanism used in healthy individuals.

Now let us discuss the previous requirements for concentrating urine:
1. **The production of hyperosmolar interstitium in the renal medulla:**

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 1400 mOsm/L in the inner medulla as illustrated by the asterisk in the figure below. Two mechanisms are responsible for the creation of this osmotic gradient; the countercurrent multiplication and urea recycling.

![Diagram of kidney's osmotic gradient]

I. **The countercurrent multiplication:**

At the end of the proximal tubule the osmolarity of the tubular fluid is still 300 mOsm/L because water and solutes have been reabsorbed proportionally (isosmotically). This is NOT the case in the rest of the nephron; the properties of each of the remaining parts favor the reabsorption of water or solutes preferentially giving rise to changes in osmolarity of the tubular fluid as well as the interstitium. Following are some of these properties and the effects of these properties on the osmolarity of the interstitium and the tubular fluid:
Concentration & Dilution of Urine

a. Cells of the **thick ascending limb** have \([\text{Na}^{+}/\text{K}^{+}/2\text{Cl}^{-}]\) cotransporters on their luminal membrane which move these electrolytes into the cell. They also have a \(\text{Na}^{+}/\text{K}^{+}\) ATPase, \(\text{K}^{+}\) channels, and \(\text{Cl}^{-}\) channels on their basolateral membrane which move these electrolytes from the cell to the interstitium. These cells have tight junctions that are very tight, making them impermeable to water. The end result of the previous properties of these cells is constant reabsorption of \(\text{Na}^{+},\text{K}^{+},\text{Cl}^{-}\) into the interstitium surrounding it without water, making it hyperosmolar, and making the tubular fluid diluted (about 100 mOsm/L at the end of the ascending limb), hence the name “the diluting segment”.

b. Cells of the **descending limb** and **thin ascending limb** of the loop of Henley are only permeable to water – but not to solutes– and given the hyperosmolar environment surrounding it, water will move from the tubular fluid to the interstitium until the osmolarity of the tubular fluid equals that of the interstitium (about 1200 mOsm/L at the deepest part of the loop). This provides a hyperosmolar tubular fluid at the end of the descending limb and hence the name “concentrating segment”. This hyperosmolar fluid facilitates the function of the \([\text{Na}^{+}/\text{K}^{+}/2\text{Cl}^{-}]\) cotransporters present in the thick ascending limb and the process repeats.

II. The role of urea:

The countercurrent multiplication mechanism does NOT account for the entire hyperosmolar gradient. Urea plays an important function accounting for 400-500 mOsm/L of this gradient. If we track urea from the glomerulus to the end of the collecting duct we notice the following:

1. 40-50% of filtered Urea is reabsorbed in the proximal tubules.
2. The thick ascending limb, the distal tubule, and the cortical and part of the medullary collecting duct are impermeable to urea; making urea very concentrated at the medullary collecting duct.
3. The medullary collecting duct is permeable to urea, allowing it to move down its concentration gradient to the inner medullary and papillary part of the interstitium increasing the total osmolarity of the interstitium.
4. Urea is then secreted into the loop of Henley allowing this cycle to occur over and over and preventing the washing out of urea by the vasa recta.

The previous two mechanisms account for the creation of the hyperosmolar gradient in the interstitium. In order to maintain this gradient the blood supply to the renal medulla has special features that prevent the washing out of the solutes in this area. One of these features is that it only represents 4% of the total renal blood flow. The other feature is called the countercurrent exchanger, which was not mentioned 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 only permeable to water in the presence of ADH. ADH has a surface receptor that when stimulated by ADH results in 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
** Nephrogenic Diabetes Insipidus

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.

The mechanism by which the body regulates whether to produce concentrated or diluted urine, is through the osmoreceptors present in the hypothalamus. When these receptors 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 as explained above. Conversely, when the plasma is hyposmolar decreased amount of ADH is produces and secreted to the blood, decreasing the ability of the kidney to reabsorb water and restoring normal osmolarity of the blood.

**Evaluation of urine osmolarity:**

Two methods are used:

1. Osmometer which 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 of water 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). The osmometer, however, is not present in all hospitals and laboratories.
2. Measuring the Specific Gravity of patient’s urine and comparing it to the normal specific gravity of urine (1.015 – 1.024) if we take the last two digits of the specific gravity and multiply them by 40 it gives us an approximate value of osmolarity in mOsm/L.

The problem of using specific gravity is that it depends on the weight of the substances – unlike osmolarity which completely depends on the number of molecules regardless of weight- and therefore Na⁺ for example would exert an effect different from glucose on the specific gravity of urine. So specific gravity can be a good indicator of osmolarity if the urine did not contain substances that are not normally present such as protein, glucose, WBC’s, RBC’s, dyes...

-Painless hematuria is cancer until proven otherwise.

Thank You
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