UGS

PHYSIOLOGY

☑ Sheet   ○ Slide   ○ Handout

Number	4
Subject	Glucose, Inulin, PAH
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Price:

بسم الله الرحمن الرحيم

- This sheet was written according to the recording of section 1.
- Note: The topic of this lecture is a bit complicated. I tried to make things as clear as possible, just focus while reading.

- **Topics that will be covered during the lecture (guideline when you get lost):**
  1- Composition of plasma and glomerular filtrate at different levels of the nephron.
  2- Filtration, reabsorption and excretion curves of glucose in the body.
  3- Clearance curve of Glucose.
  4- Clearance curves of PAH and Inulin.
  5- Comparison between the clearance curve of inulin and that of glucose and PAH at high concentrations.
  6- Kidney role in maintenance of homeostasis of phosphate, amino acids and water.

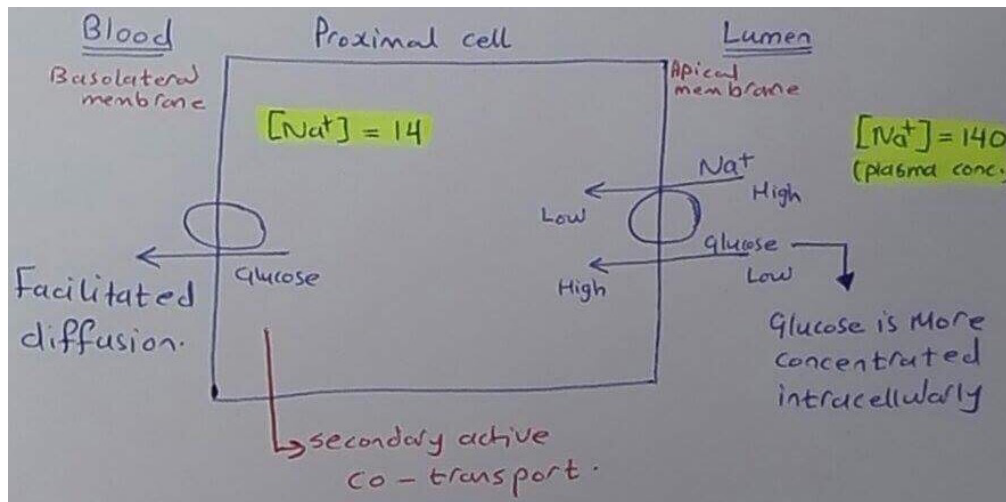
- ❖ **Composition of plasma and glomerular filtrate at different levels of the nephron (Glucose mainly):**
- ➢ A) If you insert a micropipette (2micrometer) within the **Bowman's capsule** and take a sample of the glomerular filtrate then analyze it, you will find that it has the same composition of plasma (without the plasma proteins). This technique is referred to as *Micropuncture technique.*
- ➢ **Accordingly, any molecule that is freely filtered (Molecular weight <70.000 D) is present in the glomerular filtrate with the same concentration as in the plasma:**
  - o **Examples:**
    -Glucose(100mg/dl)
    -Sodium (140meq/dl), <u>Mirror image</u> to the plasma. "meq: milliEquivalent"

- ➢ B) Then, when you insert the micropipette in the late proximal tubules and take a sample of the glomerular filtrate then analyze it, the composition of glomerular filtrate will be different from that of plasma (glucose concentration, for instance)
  - o **Examples:**
    -Glucose is <u>totally</u> reabsorbed in the proximal convoluted tubules. Glucose concentration at the end of proximal tubule will, therefore, be zero. (glucose conc. In the plasma~ 100mg/dl)

- • **Mechanism of glucose reabsorption:**

    -At the apical membrane of proximal cells, Na+ diffuses passively from the luminal tubular fluid towards the proximal cells. Specialized symporter proteins utilize the

potential energy released by downhill movement of Na+ (from 140 in the lumen to 14 inside the proximal cell "check the figure") to drive Uphill movement of Glucose, a process referred to as **secondary active co-transport**.

- **Therefore:**

➢ Glucose is reabsorbed **actively** across the apical membrane of proximal cells, after that the glucose will diffuse to the interstitium through facilitated diffusion at the basolateral side.
➢ Active transport is a **carrier-mediated** transport (co-transporter),
➢ An active transport that is carrier mediated always exhibits a **Tmax. (**recall: secretion of PAH)

- **Filtered load of Glucose:**
  Knowing that : [Glucose]= 100mg/dl
  GFR= 125ml/min

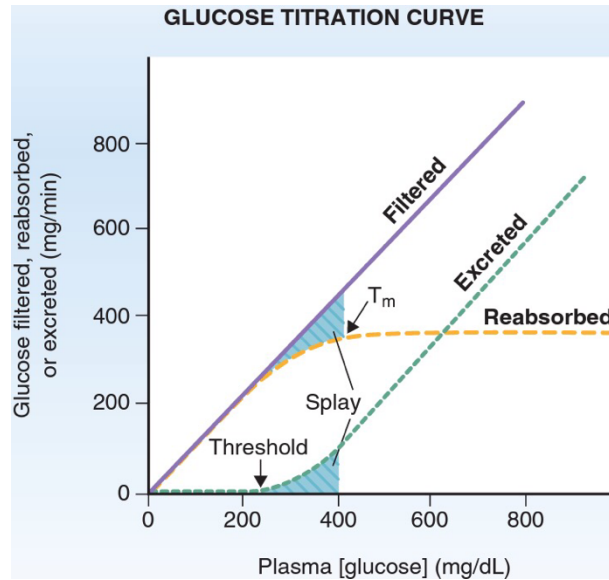 Filtered load = GFR * [Glucose]
  = 125 ml/min*100 mg/dl = 125mg/min (physiological)

  - if [Glucose] = 200mg/dl (not physiological) → Filtered load= 250mg/min

  -THEREFORE, we conclude that the **higher** the **glucose concentration** in the plasma and glomerular filtrate, the **greater** the **filtered load** (How much glucose is being delivered to Bowman's capsule per minute), assuming that GFR is constant.

- **Pay attention:** Glucose is filtered **passively** and reabsorbed **actively.**

❖ Filtration, reabsorption and excretion curves of glucose in the body:

- **Look at the figure blow, and read the following carefully:**

GLUCOSE TITRATION CURVE

✄ **Filtration** of glucose is a **passive process**, filtration curve is, therefore, **linear**, indicating that the **greater** the **plasma [glucose]**, the **greater** the **filtration** (as mentioned earlier)

✄ **Reabsorption** of glucose is an **active process**, reabsorption curve is therefore, linear in the beginning, until reaching the **Tmax**, beyond which any further increase in [glucose] will not increase reabsorption (platue), rather, excretion begins and excretion increases with further increase in [glucose].

✄ Tmax= 320 mg/dl (according to BRS, Tmax= 350mg/dl)
OR Tmax = 375mg/min (assuming that GFR= ml/min)

✄ Therefore, Filtration and reabsorption curves will go linearly side by side until glucose concentration reaches the **Tmax**(320mg/dl), after which the filtration and reabsorption curves split → filtration increases with further increase in glucose concentration, while reabsorption doesn't increase any further and excretion of glucose in the urine begins instead. Before Tmax, excretion is zero (see the curve) as the glucose filtered is totally reabsorbed. After Tmax, the more the glucose filtered, the more it is excreted.

✂ We conclude that as long as [Glucose] in plasma is less than 320 mg/dl, no glucose will appear in urine (no glycosuria).

✂ What we should understand out of this is that it is important to maintain glucose level below the Tmax, otherwise it gets excreted in urine → **glycosuria**.

بس يا ريت الموضوع هيك بهالبساطة والله!

❖ **Theoretically:**
- These theories assume that the affinity of glucose receptors is infinite, thus, when you deliver 320 mg/dl of glucose, 320 glucose-carriers will absorb them totally and no glucose will appear in urine. HOWEVER, the affinity of glucose receptors is NOT infinite (the affinity of the receptor toward the glucose is limited), so this is not the case in reality, and that when you deliver 320 mg/dl of glucose, some glucose molecules are going to escape some receptors and get excreted in urine (glycosuria).

❖ **Practically (what happens in reality):**
- Glucose will appear in urine even at a concentration lower than the Tmax. Why? because there is a deviation of the observed curve from the predicted curve (theoretical curve). Why? Because receptor's affinity is not infinite.

- This deviation of observed curve from the predicted one causes the reabsorption and excretion curves to be rounded in their beginning (see the figure), leaving two spaces (the small black triangles) between reabsorption and excretion curves and the filtration curve, this space is called **splay**.

- **Splay:** is the deviation of observed curve from predicted curve. Or the appearance of glucose in urine before the Tmax .

- according to this:
   ✂ There is a theoretical threshold after which glucose starts to be excreted in urine (Tmax=320mg/dl)
   ✂ And an actual threshold after which glucose starts to appear in urine → 180 mg/dl.
   ✂ **Splay** is the deviation of threshold from the Tmax. (see the figure)
   ✂ Example:

If you deliver 250 mg/dl of glucose, theoretically, it will be reabsorbed totally and nothing is excreted, but **actually**, about 70mg/dl are going to be excreted.

Note: Tmax=375mg/min (assuming GFR=125ml/min)

❖ Clearance curve of glucose:

- We shouldn't view clearance as a new, separate expression. Clearance is actually the other face of excretion, i.e., what is **excreted** in urine per unit time is **freely filtered not reabsorbed** and **cleared from plasma** per unit time (not returned back to the plasma by reabsorption).

✂ **Clearance:** the volume of **plasma** cleared from substance X per unit time. It can also be viewed as the volume of plasma that provides X for excretion, If excretion in urine= zero, then clearance= zero.
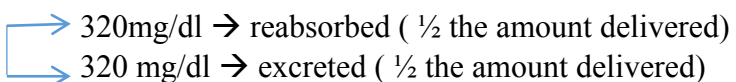
✂ Having said that:
- when [Glucose] <= 180mg/dl → None of glucose will be excreted, and None of plasma will be cleared (what is filtered is totally reabsorbed)

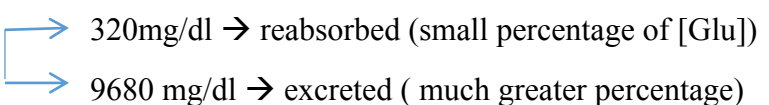-when [Glucose] > 180mg/dl → Some glucose will get excreted in urine, and, therefore, plasma will be cleared of glucose.

- Note: things I'm about to mention follow the theoretical assumptions (Tmax=320mg/dl). Please READ CAREFULLY!

✂ We will go through three – not physiological- examples, in order to understand the clearance curve of Glucose :
➢ Remember: Theoretically, any [Glucose] below the Tmax (320mg/dl) is filtered and fully reabsorbed and none is excreted. Any increment in [Glucose] beyond the 320mg/dl

1) [Glucose] = 640mg/dl ⟶ 320mg/dl → reabsorbed (½ the amount delivered)
⟶ 320 mg/dl → excreted (½ the amount delivered)
- Knowing that GFR=125ml/min, these 125 ml carry the 640mg/dl, thus what carries the 320mg/dl that are excreted is 62.5 ml of the plasma filtered (½ the 125 ml) → Clearance= 62.5 ml/min. (upcoming examples will make things clearer)

2) [Glucose] = 10,000mg/dl ⟶ 320mg/dl → reabsorbed (small percentage of [Glu])
⟶ 9680 mg/dl → excreted (much greater percentage)

- knowing that GFR is 125mg/dl, about 25ml will carry the 320mg and about 100ml will carry the excreted 9680mg (it is proportional). Note: 10,000 is never physiological and incompatible with life, just for the purpose of illustration.
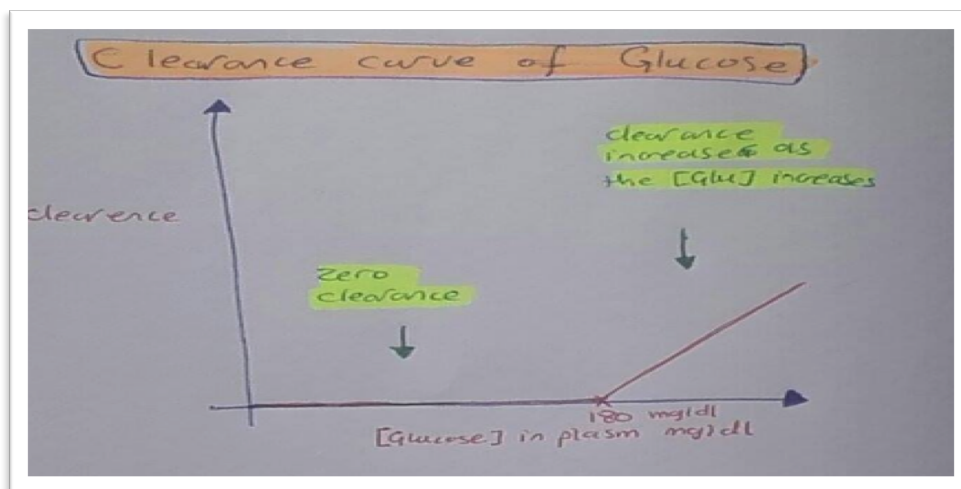
3) [Glucose] = 20,000 mg/dl. ⟶ 320mg/dl → reabsorbed (very small prtion of the 20,000)

⟶ 199680mg/dl → excreted (much greater portion)

- Here, approximately 120 or more of the GFR will carry the [Glucose] execreted.

�֍ Accordingly, what we can notice out of this is that the greater the glucose concentration and the more it goes beyond Tmax, the reabsorption portion becomes small and negligible and the clearance portion becomes greater and greater until it reaches 125ml/min (100% clearance).

✖ Thus, actually, whenever [glucose] is less than 180mg/dl, none of it will get execreted (totally reabsorbed), when it approaches 180mg/dl and beyond, it starts to get excreted in urine, and the more the glucose concentration goes above the theshold the less the proportion reabsorbed and the more the [glucose] gets execreted in urine and cleared from the plasma until the clearance is 100% at very high concentrations.

- Again, these numbers are not physiological and incompatible with life. Normal glucose concentration in the body is 70-110mg/dl, it can go up to 180mg/dl before it gets excreted in urine causing **glycosuria**. *Actually, 180mg/dl is too high as we start diagnosing diabetes at a fasting [glucose]=126mg/dl.*

--------------------------------------figure (A)--

❖ **Clearance curve of inulin:**

- **Note**: please keep in mind that we will go through the inulin clearance in order to make a comparison between inulin clearance with glucose and PAH clearance curves at high concentrations.

⚒ Inulin is an important glomerular marker, that is charactarized by being :
1) freely filtered
2) not reabsorbed
3) not secreted

- In other words, what is delivered of inulin in the plasma and filtered will be completely excreted (100% clearance).

⚒ Thus, the clearance of inulin is independent of the inulin plasma concentration, whether inulin concentratin in the plasma is 1mg/dl (1.25mg/min) or 2mg/dl (2.5mg/min), all these are delivered by the 125ml and they are completely cleared from the plasma, whatever the 125ml carry is going to be excreted and this is what we mean by **clearance**! The whole amount of substance X is excreted in urine.

⚒ Again, Inulin clearance is independent of plasma concentration. **Thus, how do you expect the inulin clearance curve to look like?** (y axis= clearance, X axis= inulin plasma concentration)

Figure (B)

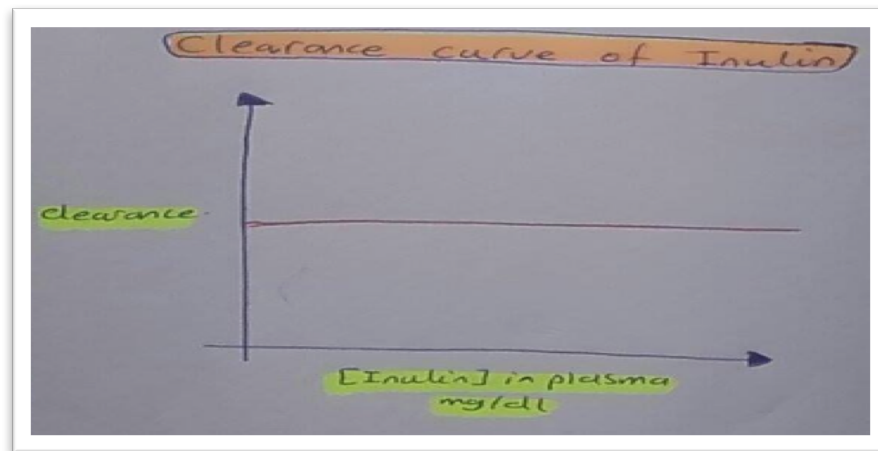
➢ Now, let's go back to figure (A). As you can see, whenever [glucose] = 180mg/dl and above, the clearance of glucose starts and it increases as [Glucose] increases

until it reaches the clearance curve of inulin (100% clearance), when the reabsorption becomes small and negligible.

❖ Clearance curve of PAH:

- Remember, PAH is a renal plasma marker that is charactarized by being:
1) freely filtered
2) not reabsorbed
3) completely secreted

- Thus, PAH in urine comes from two sources :
→ 20% → freely filtered not reabsorbed
→ 80% → secreted

- Secretion is an **active process** (carrier- mediated), thus it exhibits a **Tmax** (remember that inulin is freely filtered and not secreted neither reabsorbed, thus Tmax doesn't concern us)

- knowing Tmax is important because we should not deliver PAH to the peritubular capillaries with a concentration greater than Tmax, otherwise it will get reabsorbed by the renal vein and underestimate the renal plasma flow. (recall: lec1)

- Tmax of PAH= 80mg/dl

- **example**: if you delivered **160mg/dl** of PAH, **80mg/dl** will be excreted and 80mg/dl will be reabsorbed into renal vein, thus what you have cleared is half of the plasma only (not 100%). On the other hand, if [PAH] is 5, 20, 40 …, it will be totally cleared from the plasma. Therefore, for PAH, the more the concentration the less the clearance.

- **Reminder:** don't forget that when we deal with inulin and PAH, we look for 100% plasma clearance (100% excretion in urine); as these two are plasma markers that measure the GFR, whereas when talking about glucose, we want plasma clearance to be 0% , because glycosuria is abnormal (though not always a pathological condition as we will see later).

✂ For PAH, the more you increase the concentration beyond the Tmax, the less the secretion of the substance that will occure. Therefore, at very high concentrations of

PAH, the amount of PAH in urine almost completely comes from PAH that is filtered not reabsorbed and a very small portion comes from secretion, until the PAH excreted in urine only comes from filtration, and approaches the clearance curve of inulin.

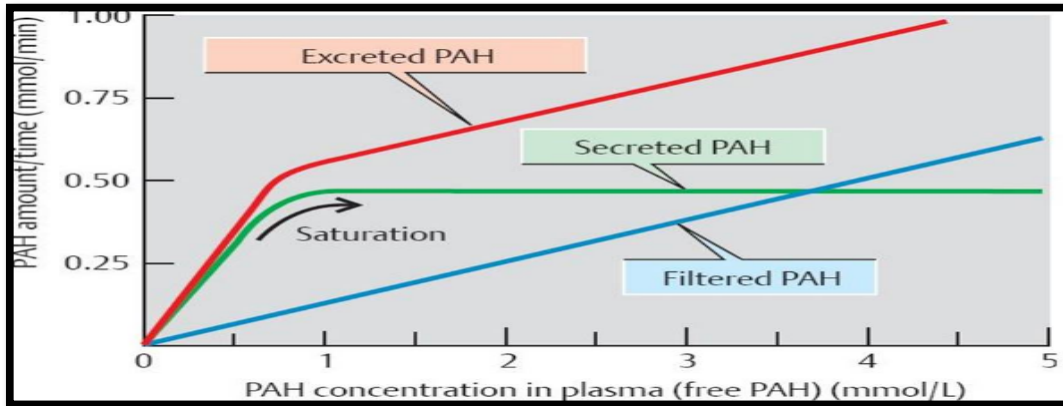**- filtration, secretion and excretion curves of PAH**
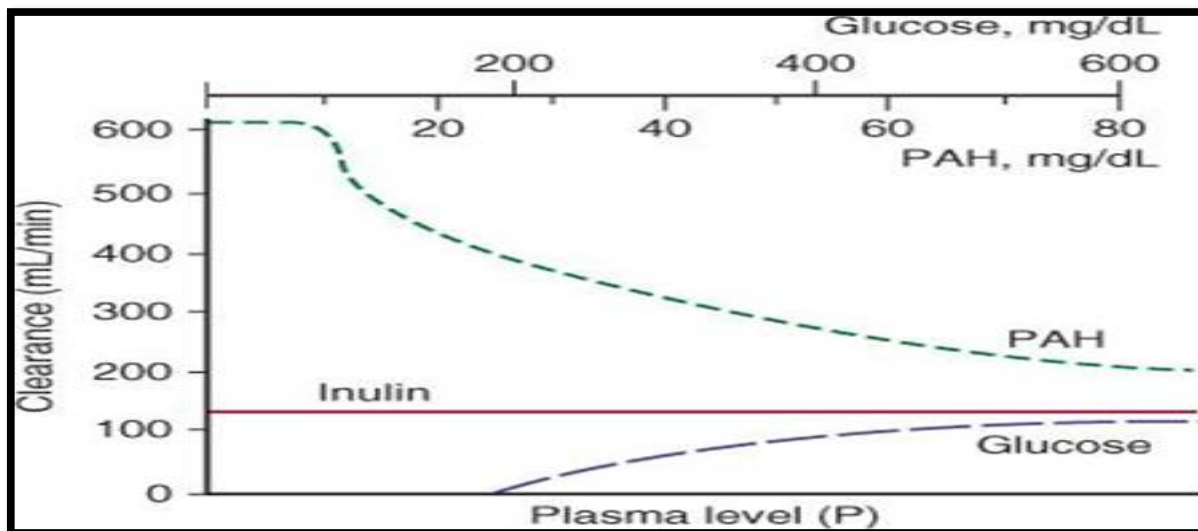

Figure (C)

➢ Notice that at high [PAH], the excretion curve is highly attributable to filtration rather than to secretion.

❖ **Glucose, PAH (high conc.) and inulin clearance curves:**

�֍ Therefore, at high concentrations, both PAH and glucose have clearance that approaches the clearance of inulin.

I wish things are clear now!

❖ Kidney role in glucose homeostasis :

✖ Glucose is reabsorbed with the help of Na+ through two types of transporters :
1) Na+/Glucose luminal transporter 1:
- high affinity
- low capacity
2) Na+/Glucose luminal transporter 2:
- Low affinity
- high capacity

✖ On routine examination, urine samples are tested for proteins, ketone bodies, glucose .. etc. On microscopy, urine samples are tested for the presence for RBCs, WBCs casts .. etc.

✖ What if you find glucose in urine? What is your next step?
- the next step is to test the blood glucose level:
If high → diabetogenic glycosuria
If normal → Nephrogenic glycosuria

✖ In nephrogenic glycosuria, the origin of glycosuria is the kidney, due to low number of receptors. It is a benign condition (IF isolated, with no accompanying loss of proteins or blood …etc.), you can just don't mention it to the patient, and the patient doesn't need follow up.

✖ **Now, is there a role for the kidney in maintaining homeostasis of glucose (maintaining glucose levels within normal range)?**

- Normal range of glucose level in blood is 70-110mg/dl. It should not go any higher or lower than these two limits. Kidney does not support this to happen ! ☹

- Kidney has set the alarm at 180 mg/dl (threshold), any conc. Of glucose below this l80mg/dl will be totally reabsorbed and kidney **DOES NOT** feel responsible to bring it back to its normal level, i.e., if [Glu] is 60mg/dl, it will be reabsorbed totally without being brought up to 70mg/dl. Similarly, if [Glu] is 150mg/dl, it will be reabsorbed totally will not be brought down to 110mg/dl.

- You might have asked yourself, why is that?

Actually, this occurs because the threshold and Tmax for glucose are far from its physiological level in the blood. Suppose that threshold for glucose is 120mg/dl → then we should claim that the kidney plays a role in glucose homeostasis, but this is not the case. As long as physiological levels of glucose are far from its threshold, the kidney doesn't play a role in its homeostasis (doesn't increase or decrease its concentration to physiological levels)

- This is a problem! as if glucose level is 180mg/dl, for example, kidney will reabsorb it totally to the blood, this is dangerous, because we diagnose diabetes mellitus at a fasting glucose level of ~ 126mg/dl. Thus, 180mg/dl is really too much!

- This leads us to the fact that we should control our food intake, so that glucose level in the plasma remains within physiological levels.

Role of the kidney in phosphate and amino acid homeostasis:

✂ Does the kidney play a role in homeostasis of phosphate (PO4-)? Yes!

✂ [PO4-] in plasma is 1mM/L.
  - filtered load = GFR * CONC.
          = 125 ml/min * 1mM/L
          =0.125 mM/min is being filtered per minute.

✂ Tmax for phosphate is 1.25mg/dl. Thus, if you deliver 2 mg/dl of phosphate, 1.25mg/dl will be reabsorbed totally and the rest will be **excreted.** Therefore, you can see that the kidney plays a role in phosphate homeostasis, and any extra phosphate you ingest will be excreted.

✂ The reason behind this is that the Tmax for phosphate is close to its physiological levels in the blood (unlike glucose).

�֎ Does the kidney participate in homeostasis of **amino acids** ? Yes!

→ Amino acids are of three natures: - acidic   - basic   - neutral

→ amino acid receptors are also of three natures: - Acidic receptors   - basic receptors - neutral receptors

→ In addition to these, there are receptors that are specific to certain amino acids, such as cysteine receptor, any defect in this receptor will lead to cysteineuria (appearance of cysteine in urine) which is the nucleus for stone formation.

→ Amino acids have a total molecular weight of 110, which means they are freely filtered in bowman's capsule. **Can we tolerate amino acid loss in urine (amino aciduria) ? definitely NOT!** Therefore, the kidney reabsorbs amino acids totally in the proximal convoluted tubules with the help of Na+.

- **Note**: notice the importance of Na+ in amino acid and glucose reabsorption.

❖ Water reabsorption

✖ 125ml enter the bowman's capsule per minute, and only 1ml exits per minute.

✖ Reabsorption fraction = 124/125 = 99.5% , excretion = 0.5%

✖ Segmental absorption :
- proximal convoluted tubules → 65% (two thirds)
- descending loop of henle → 15%
- ascending loop of henle → 0%
- distal convoluted tubule → 10%
- collecting ducts →~ 9%

If you're into medicine to be ordinary, it's not worth it, you have to do it properly. Pain is temporary, glory is forever.

THE END