

Tubular function

- What is clearance?
 - clearance referred to the theoretical volume of plasma from which a substance is cleared (cleaned) over a period of time and so its unit would be ((mL/min))
- If we assumed that we have a substance (let it be X) that entered the kidney and has been completely cleared into the urine (the concentration of x in the renal vein = zero) then I can claim that 650 ml/min (which is the renal plasma flow) has been cleaned totally from x. So clearance of x in this scenario is equal to renal plasma flow.
- How much is delivered is equal to how much is cleared, in this case. How much is cleared can be calculated by multiplying urine concentration by urine output. How much is delivered is equal to renal plasma flow multiplied by concentration of X in the plasma.
- The condition in which we can use clearance of x as a measure for renal plasma flow is once the substance enters the kidney nothing goes back through the renal vein (the renal vein conc. Of x =zero) which indicate that the substance has been extracted 100%. An example of this substance is PAH (the para-aminohippuric acid, an organic substance not found in humans). If we measure a 24 hour collection, we can calculate the urine flow per minute. And we can figure out the PAH concentration in the urine and we can take a plasma sample to measure plasma PAH concentration. This is called effective renal plasma flow. This means that 90%% of the blood arriving to kidneys reaches the afferent arterioles, while 10% go to the renal capsule and pelvis to supply these structures with oxygen and nutrients.. This means that not all renal blood flow participates in renal function. Although PAH is said to be completely cleared, its concentration in the renal vein is not 0. This is because not all the blood participates in renal functions. A renal vein concentration of 0 is not physiologically achievable.

- A substance can filtered, not reabsorbed, but completely secreted.
- True renal plasma flow is equal to effective renal plasma flow over 0.9.
- To know the renal blood flow, you need to know the hematocrit. It is equal to
 - $$\frac{(\text{Renal Plasma flow})}{(1-HCT)}$$
- Inulin's excretion per minute is equal to inulin provided for excretion per minute. Inulin is provided for excretion by filtration only. So, per minute, we have GFR in addition to inulin's concentration in plasma.
- The renal plasma flow marker is any substance that is completely extracted and secreted and nothing of this substance appears in the renal vein.
- If we increase inulin's concentration in the plasma, and plot it against inulin's clearance, we notice that inulin's excretion increases in a linear curve.
- A freely filtered substance means that we guarantee that 20% of the substance delivered to the kidney is 20%.
- you have to keep in mind that filtration is entirely passive process however secretion is not; it's active process which can mean a variety of things but we care about one criteria which is T max ((saturation)) ; if you deliver small amounts then we are going to secrete the entire amount and whatever plasma entered (650 for example) will be cleaned totally And so clearance = renal plasma flow . but if deliver too much then only 50 % will be secreted and the other 50 % will return back to the circulation through the renal vein and now here you have the clearance of x is less than the renal plasma flow because you are exceeding the T max which you should not .

You should know the T max for any substance that you use and for PAH ;
 T max = 80-90 mg / min

Example 1: if the plasma conc. of PAH = 1 mg/ml and the renal plasma flow = 650 ml/min. How many mg of PAH are being delivered to the kidney in one minute?

Answer: 650 ml will enter the kidney in one min and each ml contains 1 mg of PAH so 650 mg of it will enter the kidney / minute

Now for me to use any substance it should be completely cleared for the plasma once it enter kidney then I should use very small concentrations below the T_{max}

20% of these will be filtered. 80% secreted and 100% will be excreted. Every ml had 1 mg. in a minute we excrete 650 mg/ml urine.

** PAH excretion in the urine /min = PAH urine concentration * urine output

** PAH delivered to kidney /min = Renal plasma flow * PAH plasma concentration

Clearance of PAH = urine / plasma (PAH conc.) * urine output

And due to the fact that the excretion of this substance is complete then the clearance will equal the renal plasma flow. So we can use this substance to measure the renal plasma flow but the resultant number will be equal to 585 and not 650 which we have been talking about since the beginning. and this results from the fact that not all the blood entering the kidneys participate in its function ; about 10 % of blood will go to nourish the renal capsule and other structures . So the clearance of PAH represent only 90 % of the true renal plasma flow which is called effective renal plasma flow which = $585/0.9$ that will approximately equal 650

So there is no substance that enter the kidney in a conc. of 100% through the renal artery and its conc. in the renal vein will be equal to zero as not all blood entering the kidney will reach the afferent arterioles but it's more like circulating around the kidney (nourishing related structure) and consequently the true renal plasma flow is 10 % more than that of the effective renal plasma flow. However , when we

used the clearance of inulin we said that of inulin conc. 125ml has been filtered /min all of the filtered inulin is going to be excreted not more or less (not more means that unlike the PAH there will be no secretion and not less means that there will be no reabsorption) consequently here the clearance measures the glomerular filtration rate now the question is: if you increase the inulin conc. (for example, you have 1 mg/ml and increase it to 2 or 3 mg/ml) what is the effect on clearance? The relation between the clearance and the conc. will be straight line (remember that clearance is the volume of plasma that is going to be cleaned from x regardless of its' concentration) so the relation will be : the more the concentration in the plasma the same the clearance ((in this case only)) because it is a passive process .on the other hand if it was an active process :

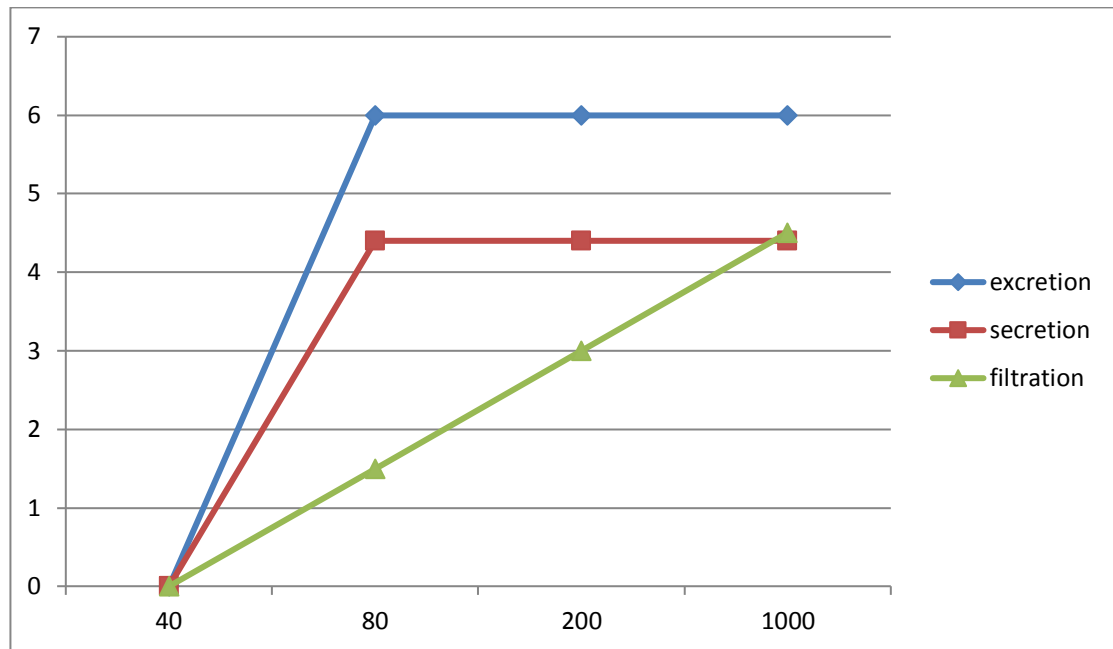
Let's say that 100mg/min of PAH entered the kidney → 20 mg will be filtered and 80 mg secreted → 100 excreted

Or 50mg/min entered the kidney → 10 mg filtered and 40 mg secreted → still in the safe side

Now assuming that 200 mg/min has entered the kidney → 40 mg will be filtered and 80 mg secreted → 80 mg will return back to through the renal vein and so on as the T max is fixed and equal to 80mg/min and so by increasing the conc. you are decreasing the clearance until we reach very high conc. where secretion become negligible and here whatever come into the urine originate from filtered which has not been reabsorbed and so you are cleaning the GFR here so the relation here in PAH differ.

** keep in mind that filtration is a passive process which means that the more the conc. the more the filter load

Example : if we have many known conc of PAH and we wish to draw a curve concerning the filtration and secretion how



**T max for PAH = 80 mg/min

→ the curve of the secretion : where would it be located ? on the left of the filtration curve as secretion will equal 80 % whereas the filtration equal 20 % so most of the urine will come from secretion and so it will be located on the left and once it reach T max it will become constant (as it is illustrated in the curve above)

→ The excretion curve will be on the left of both curves as the excretion is the result of the summation of both curves .

Now the question is : if I want to place the curve of clearance what will be the relation ? the Dr here discussed it in case of inulin taking in consideration that the clearance of inulin is 125 ml/min ? first it will be string and then it goes down in a way that the clearance of PAH converge to the clearance of inulin → equal or a little bit higher as we are at very high plasma conc.

توضيح النقطة السابقة :

Clearance referred to the volume of plasma cleaned .now when you use PAH you have two possibilities : the filtered part with equal 125 ml is going to be cleaned the other one is the secretion : if we have a low conc. we can clean the rest of the plasma entering the kidney (20% from

filtering and 80% secretion) so clearance here = renal plasma flow but if you start to increase the plasma conc. (20 % filtered is already guaranteed) but you can't be sure that the rest of the plasma that will reach the peritubular capillaries will be cleaned so as long as you increase the plasma conc. delivered to the kidney the secretion effect will gradually decrease to the extent that we might reach a level where the filtration = 10000 ml/min whereas the secretion (which is constant) = 80 ml/min which can be ignored when compared to the 10000 ml/min . So what comes in the urine actually come from the filtered not reabsorbed part . (we are cleaning the GFR)

****conclusion :** the more the concentration the less the clearance so it converges to the clearance of inulin

Question : Suppose that we have the proximal tubule and bowman's space entering them plasma with glucose conc. of 100mg/dL. What is the filtered load of glucose ? ((assuming that this is a normal person with $GFR = 125 \text{ ml/min/1.73m}^2$ BSB))

Answer : filtered load (which refer to how many filtered /min) = 125 ml/min . The glucose is reabsorbed from the early proximal tubule through a carrier at the luminal surface (symporters or secondary active transport of glucose along with the movement of sodium down its electrochemical gradient) . "the tubular fluid conc. of glucose in the late proximal tubule = zero"

Due to the fact that it is reabsorbed through a carrier this carrier will show T max (transport maximum or saturation) . The T max for glucose = 375 mg/min (if you wish to change it into /ml you have divide it on 1.25) . this mean that if you deliver 320 mg/dL you guarantee reabsorption of the entire glucose but by increasing the conc. to 520 mg/ml then 200 are going to be excreted (a condition known as glycosuria)

All what is filtered will be reabsorbed. Let us suppose that T_{max} is 320, if you deliver 1000. 320 will be reabsorbed and 680 will be excreted. If you deliver 600, 320 will be reabsorbed and 280 will be excreted. If you

deliver 400, 300 will be reabsorbed and 100 will be excreted. If you deliver 350, 250 will be reabsorbed and 100 will be excreted.

So, here, for the receptor to show you its maximum capacity you need to give a very high amount of glucose (suprasaturated concentration). At normal concentrations, the glucose appears in the urine before it is expected. As long as you increase the filtration, any extra will be excreted. This is the predicted curve.

The threshold for glycosuria is the concentration of glucose in the plasma at which glucose starts appearing in the urine. Threshold is below T-max. This area between T-max and threshold is called splay and it is a phenomenon which explains the appearance of glucose in urine before T-max. In other words, it is the difference between the threshold and T-max.

As long as you have glucose in the urine, this means that glucose plasma concentration is 180 or above. The higher the positive number, the higher the glucose concentration in plasma (+1, +2, +3).

Glucose's molecular weight is 180 gm/mol; it is a small molecule. But it is reabsorbed completely as long as we are below the threshold.

Non-physiological example:

10000 ml.... The 320 is constant, what remains of the 10000 is 9680. These were excreted. This means that almost all glucose filtered is being cleared.

The clearance remains 0, until 180. After that, it converges to inulin's clearance. But we are not to say that glucose's clearance exceeds that of inulin because glucose is not secreted.