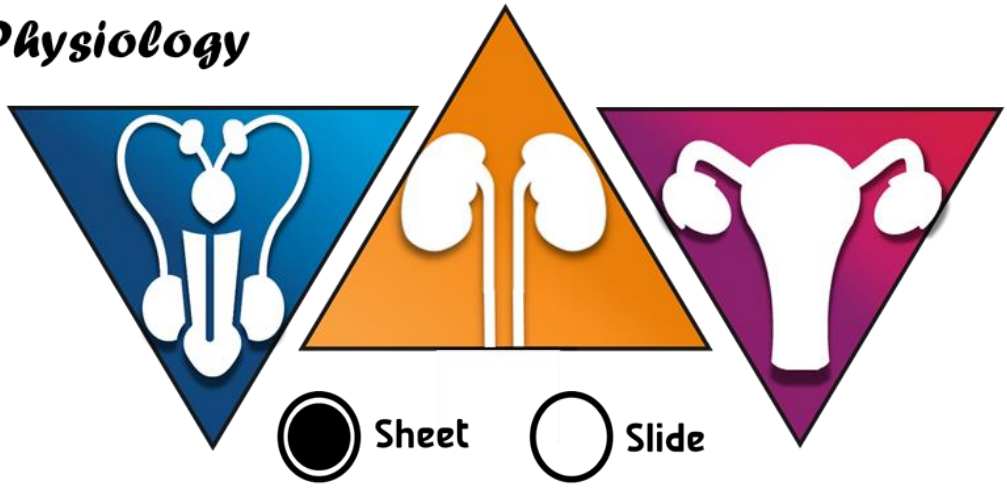
Urogenital system

Physiology



Number: - 3

Done by: - Ahmad Ar'ar

Corrected by: - Mohammad Abid

Doctor: - Yanal

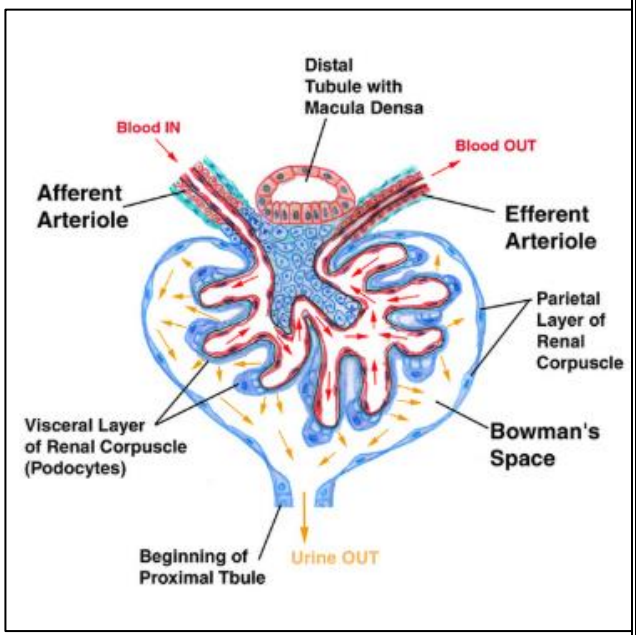
Before you start;

First 3 pages are **extra**, but the boxes in them are **included**, so if you don't want to study these pages, be sure to understand the boxes, which contain important key points. **Last 2 pages** contain Questions which are also **extra**. For those who are watching the video, everything is mentioned but in a slightly different order. Be sure that you understand all the examples, since they are considered an essential part of the lecture as all other parts. Anything extra will be labelled. The doctor said that he consider this lecture extremely important, so give it your attention.

Extra: Summary for the Glomerular Filtration Process

The first step in urine formation is the filtration of large amounts of fluid through the glomerular capillaries into Bowman's capsule—almost 180 liters each day, this process is called Glomerular Filtration. Most of this filtrate is reabsorbed, leaving only about 1 liter of fluid to be excreted each day, although the renal fluid excretion rate may be highly variable depending on fluid intake. The high rate of glomerular filtration depends on a high rate of kidney blood flow, as well as the special properties of the glomerular capillary membranes.

Renal Corpuscle is a term that is used to describe the blood-filtering element of the nephron of the kidney. It has two basic parts; A) Glomerulus, and B) Bowman's capsule. (Figure below)



A) **Glomerulus**: a tuft of fenestrated capillaries composed of **endothelial lining** and **glomerular basement membrane (GBM)**.

Endothelial Cells have trans-cytoplasmic pores (fenestrations) with a diameter of **50-100 nm**, which is not enough for the filtration of formed elements, only plasma can go through. (These pores form the first barrier for filtration)

GBM has three layers, all of which are highly negatively charged (mainly due to heparin sulphate), so the charge of the molecule will affect its filtration: large molecules with negative charges, which is the case for most of the plasma proteins, will face repulsion that prevents their filtration.

However, ions such as **Cl^-** and **$HCO3^-$** can filter into the Bowman's space although they are negatively charged, because they are too small and not negative enough for repulsion to prevent their filtration. Neutral molecules can pass, but less readily than positive ones with same size.

FACT 1: Negatively Charged Large Molecules Are Filtered Less Easily Than Positively Charged Molecules of Equal Molecular Size. (For any given molecular radius, positively charged molecules are filtered much more readily than are negatively charged molecules.)

B) **Bowman's capsule**: composed of a visceral layer **(Podocytes)** which is continuous with the parietal layer. These continuous layers enclose what is called the Bowman's space. (see the figure above)

Podocytes are epithelial cells surrounding the outer surface of the capillary basement membrane. Between these podocytes, there are spaces through which the plasma is filtered, and these spaces are called **"filtration slits"**, their size is around **25-30 nm**. (Second barrier)

Connecting the podocytes, we have a protein called **Nephrin.** This protein structure, that spans the filtration slits, forms what's called the **slit diaphragm** that allows only structures less **7-9 nm** to filter into the Bowman's space. (Third barrier)

Note: molecules that pass through the first or second barrier, but get stuck by nephrin are phagocytosed by mesangial cells.

We can conclude that only structures with their diameter **less than 7-9 nm can be filtered** (if we are talking about size alone, which is represented by diameter). In terms of molecular weight, we express it as **molecules that are less than 70 kD (approximately)"less than 70000 Daltons (Da)" are the only ones which are filterable.** (Note: the doctor said that the molecular weight of a molecule in Daltons is equal numerically to its molar mass, for example: a mole of glucose weighs 180 grams, and one molecule of glucose equals 180 Da).

Very important : When we say that a substance is **freely filtered** (filterability = 1), we mean that its concentration in the plasma equals its concentration in the filtrate, so it passes through the barriers as if they don't exist, because it's very small. Be careful, 70 kD is the maximum molecular weight for filtration, but we don't mean by that free filtration, however, as the molecular weight approaches 70 kD , filterability decreases rapidly approaching zero (not filterable), and as the molecular weight decreases far less than 70 kD, filterability approaches 1. (Filterability between 0 and 1 reflects partial filtration)

There is no specific molecular weight that below it free filtration occurs, but you can imagine that molecules as far as 5000 Daltons are freely filtered.

FACT 2:

A) **Filterability of Solutes Is Inversely Related to Their Size/Molecular weight.**
B) **Freely filtered substances are those with small molecular weight, and their concentrations in the filtrate equal their plasma concentrations.**
C) **Molecules less than 70 000 Daltons (Da) are filterable, and as we go from 70 000 Da towards zero, filterability increases until it is equal to 1, which means free filtration.**

Note: **CREATININE, Glucose and Urea** all have very low molecular weight (114, 180 and 60 Da respectively), they are all freely filtered. Electrolytes as Na^{+} and Ca^{+2} are also well known to be freely filtered**.**

Note: **Albumin** is the smallest plasma protein, its molecular weight is 69 kD, and its diameter is 6 nm, so according to that it's partially filtered, but what prevents its filtration is the negative charge, so here the charge plays an important role. Other plasma proteins are larger than albumin (filterability = 0), as well as most of them have a big negative charge, so surely they won't filter**.** (Size of albumin causes its filterability to be very low, but it is its negative charge that prevents its filtration)

Note: Be careful, molecules that have low molecular weight, but are bound to proteins will not be filtered.

Glomerular Filtration Rate (GFR): is the amount of plasma that filters per unit time (around 125 ml/min). **GFR is affected by:**

1) **NFP (Net filtration pressure)**
   NFP = GHP – COP – CHP, where GHP is glomerular hydrostatic pressure, COP Is colloid osmotic pressure in glomerular capillaries, and CHP is capsular hydrostatic pressure. (COP in the capsule = zero; proteins don't filter)

GHP: Efferent arteriole has a smaller diameter than the afferent arteriole, and thus it creates some resistance to blood flow, producing the back-up of blood in the glomerulus which is responsible for the high value of GHP.

Glomerular hydrostatic pressure is determined by three variables, each of which is under physiological control: **(1) arterial pressure** (however, it is buffered by auto-regulatory mechanisms that maintain a relatively constant glomerular pressure as blood pressure fluctuates; will be taken in the next lecture), **(2) afferent arteriolar resistance** (constriction of afferent arterioles reduces GFR; the difference between afferent and efferent arterioles' diameter becomes less), and (3) **efferent arteriolar resistance** (moderate levels of constriction increases GFR).

COP: high proteins (ex: multiple myeloma) high COP, low blood proteins → low COP

CHP: for example, if there is a kidney stone blocking the tubules, CHP will increase.

2) **Surface Area of the Glomerulus**
3) **Permeability of the Glomerulus** (related to number of channels/pores per unit area)

Filtration coefficient K_f = surface area * permeability

THUS;

Fact 3:

GFR = NFP * K_f

K_f = Surface area of glomerulus multiplied by its permeability

Note: GFR is directly proportional to NFP, surface area, as well as permeability.

The Beginning of the Lecture

We will start the lecture with a new concept, which is **filtered load.**

Filtered Load is defined as the amount (mg) of substance X that is filtered per unite time (min).

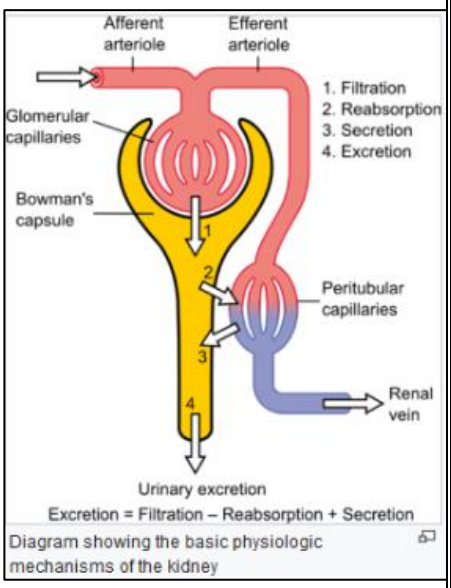


Diagram showing the basic physiologic mechanisms of the kidney

Now, if substance X is <u>freely filtered</u>, then its concentration in the filtrate will be equal to its plasma concentration, thus

Filtered load = how much volume is being filtered multiplied by the plasma concentration of X;

Filtered load = GFR * P_x

Where P_x is the plasma concentration of X.

For example, if the concentration of X was 2 mg/ml, calculate the filtered load. (GFR = 125 ml/min).

Filtered load = 125 ml/min * 2 mg/ml = 250 **mg/min** (notice the unit).

The doctor asked why we use plasma concentration of X instead of using its filtrate concentration. Simply because X is freely filtered and its concentration will be the same in both, and that blood concentration is easily measured. (If the substance was not freely filtered, then its filtrate concentration <u>will be less</u> than its plasma concentration).

Side Topic: what determines if a substance can or can't filter?

It's the <u>SIZE</u> and the <u>CHARGE</u> of the molecule. (Refer to fact 1 and 2 in the boxes in the summary, they are included)

Notes from the doctor:

- A substance with molecular weight of 64.5 kD but negatively charged <u>may</u> not filter, but a substance with mw of 72 kD and positively charged <u>may</u> filter. (we said approximately 70 kD is the maximum MW)

- Layers of **glomerular basement membrane** are all **negatively charged**, and this is the reason that justifies why the charge of molecules affects their filtration.

- In certain diseases, as minimal change nephrotic syndrome, glomerular basement membrane loses its negative charges (**Extra**: pathogenesis is not well understood, but maybe it's the result of altered secretion of lymphokines by T-cells). **Albumin**, which is negatively charged with a molecular weight that is slightly less than 70 kD (= 69 kD), doesn't face anything preventing its filtration, thus the following occurs ; proteinuria → hypoalbuminemia → generalised edema, so it's common to test albumin in urine when there is edema in lower limbs and face.

Now back to substance X;

If this substance, in addition of being **freely filtered**, is **NOT Reabsorbed,** and is **NOT Secreted,** then this substance can be used to measure GFR. **"Glomerular Marker"**

Let's discuss each one of them:

Freely filtered: to make sure that the volume of plasma being filtered takes with it <u>all its content of X</u> (conc in plasma = conc in filtrate).

Not reabsorbed: to make sure that all the substance that is being filtered is being excreted in urine, so we <u>don't underestimate GFR</u>.

Not secreted: to make sure that what's excreted in urine is totally from filtration without secretion, so we <u>don't overestimate GFR</u>.

This substance that achieves all these criteria is **Inulin** (glomerular marker), its molecular weight is 5000 Daltons, and it is freely filtered, not reabsorbed, not secreted. According to these characteristics, we can say:

Amount that is filtered per min = Amount that is excreted per min

Filtered Load = the amount that is excreted per min

$$\mathbf{GFR * P_{inu} = U_{inu} * V}$$

Where P_{inu} is the plasma concentration of inulin, U_{inu} is the urine concentration of inulin, and V is the urine flow rate (ml/min).

We conclude that we use **inulin** to **measure GFR**. P_{inu} is obtained by simple blood test, whereas V and U_{inu} are obtained by collecting urine and examining it. Knowing all of these, we calculate GFR;

$$\mathbf{GFR = (U_{inu} / P_{inu}) * V}$$

$$\mathbf{Also, GFR = (U_{inu} / P_{inu}) * V = \underline{Clearance\ of\ inulin}\ ??}$$

In order to understand it, you should know first what clearance is**.**

Clearance

By definition, the renal clearance of a substance is **the volume of plasma that is completely cleared of the substance by the kidneys per unit of time**. Or as the doctor likes to define it, is **the volume of plasma that provides a substance for excretion in the urine per unit time**.
(Everything will be explained just continue reading).

Although there is no single volume of plasma that is completely cleared of a substance, renal clearance provides a useful way of quantifying the excretory function of the kidneys. Let's take two examples, the first one is **PAH** (from the previous lecture), it is freely filtered, not reabsorbed, completely secreted if < Tmax, meaning that all the plasma (650 ml) that enters the renal corpuscle every minute will be completely cleared, resulting in 100% clearance, or clearance that is equal to 650 ml/min (650 ml out of 650 ml is completely cleared every min).

Let's take another example which is **inulin (very important)**. Inulin is not secreted at all, and all inulin in urine comes from filtration (125 ml/min). As it is freely filtered, all inulin molecules in these 125 ml will be filtered into the bowman's space, and as it is not reabsorbed at all, all filtered load will be excreted in urine, meaning that we have <u>completely cleared</u> these 125 ml of plasma, and we <u>have not</u> cleared any additional volume (NO Secretion), **resulting in a Clearance that is equal to 125 ml/min, which is equal to GFR.**

Now we can say:

$$\mathbf{Clearance\ of\ inulin\ (\ C_{inu}\ ) = (\ U_{inu} / P_{inu}\ ) * V = GFR}$$

To be more precise, the general formula for the clearance of any substance is;

$$C_x = (U_x / P_x) * V$$

and **only for inulin**, this formula is equal to **GFR**. (You can look at it as $V * U_x$ which is the amount of substance that is excreted, and divide it by P_x to know how much volume in the blood correspond to this amount)

The doctor said that clearance is a difficult concept to grasp, but here is an extra clarification through which I really like to understand clearance.

Extra: read the text, then have a look at the example, then read the text again and I am sure you will get the idea.

Imagine **clearance** as: the initial volume – the volume that is required to produce the same initial concentration from the substance that is left in the blood and not excreted in urine.

For example, assume that we have a substance Y, its concentration in the plasma is 4 mg/ml , it is freely filtered, not reabsorbed, and 0.6 of what's remaining in the plasma after filtration is secreted (assume it 1260 mg), considering GFR = 125 ml , Renal plasma flow = 650 ml/min, V = 1 ml/min , **calculate the clearance.**

First of all, filtered load per min = GFR * P_Y = 125 * 4 = 500 mg.

The amount of all Y in Renal plasma flow = 4 mg/ ml * 650 = 2600 mg.

What is left in the Renal plasma flow after filtration = 2600 – 500 = 2100 mg.

(extra) What is secreted = 0.6 of what's left = 0.6 * 2100 = 1260 mg **(given)**

What finally remains in the plasma = 2600 – filtered – secreted =

2600 – 500 – 1260 = 840 mg (now we want to know the volume that is required to produce a concentration of 4 mg/ml from the remaining 840 mg of Y)

Concentration = amount / volume, 4 = 840/volume → volume = **210 ml (this means that we still have 210 ml of plasma with the same initial concentration of Y)**

Clearance = 650 ml – 210 ml = <u>440 ml</u> (440 ml of plasma is completely cleared)

Now we want to calculate clearance using the original formula;

U_Y = (500 + 1260)mg / 1 ml = 1760 mg/ml

$C_Y = (U_Y / P_Y) * V = (1760/4) * 1 =$ **440 ml**

The reason for which I solved through the first method is that I found it more beneficial in understanding the concept of clearance, which is the main purpose for the whole example, **it's completely extra**.

Ex) given that the concentration of inulin in the plasma P_{inu} = 2 mg/ml, and that GFR = 125 ml/min, calculate the following:

A) Filtered load:
= GFR * P_{inu} = 125 * 2 = **250 mg/min**

B) Clearance:
Simply, for inulin: clearance = GFR, thus Clearance = **125 ml/min**.

C) Assuming P_{inu} has increased to 4 mg/ml, what happens to:

A) Filtered load:

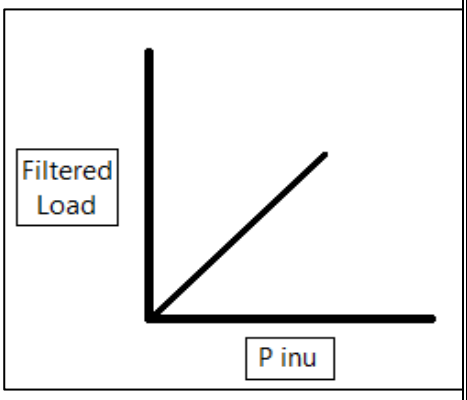
It is increased as will; it will be **500 ml/min.**

B) Clearance:

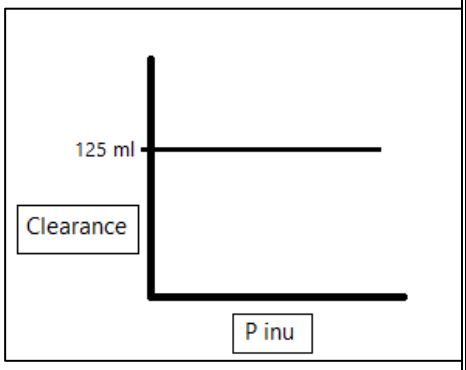
Not affected. For inulin, it is always equal to GFR, so it will be 125 ml/min again.

From the previous example, we should expect the following graphs:

As the concentration of inulin in the plasma increases, the filtered load of inulin will also increase (Filtered load = GFR "which is relatively Constant" * P_{inu} "which is variable", so a change in the concentration will change the filtered load). (Extra: The slope is equal to GFR, assuming it is constant).

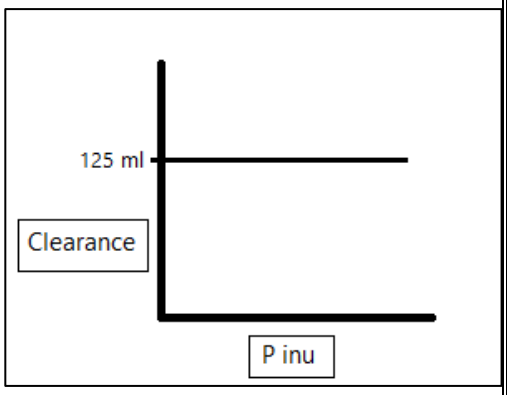


As the concentration of inulin increases, the same volume of plasma will be completely cleared, as it is completely dependent on the volume of plasma that is being filtered, which is always equal to GFR. (125 ml is always being filtered, and it is always the volume that is cleared (no reabsorption, no secretion), so whatever the amount of inulin we have in those 125 ml, all of it will be filtered and excreted, so that these 125 ml of plasma will always be completely cleared)



Continue talking about the relationship between Clearance and P_{inu} :

Note: It is always parallel to the x axis, and the point of intersection with the y axis is always GFR.



Note: If GFR increases, the line shifts upward; likewise, if GFR decreases, the line shifts downward.

Extra: a proof that the Clearance of inulin is constant in a mathematical point of view:

This is because a rise in the plasma concentration produces a corresponding rise in filtered load and thus a corresponding rise in U_{inu} , recalling that: $C_{inu} = (U_{inu} / P_{inu}) * V$, the numerator and denominator of the clearance equation for inulin change in proportion, leaving the quotient (clearance) unchanged.(recall that inulin isn't reabsorbed/secreted)

Also, you should notice that the clearance of inulin is constant and don't decrease at high concentrations as PAH, because it is totally dependent on filtration which is passive (No t-max). Moreover, you should know that at very high concentrations, the clearance of PAH converge to the clearance of inulin, because what is secreted is too small compared to what is filtered to a degree that it becomes negligible, and only what is filtered is being considerable.

A recap from the doctor:

GFR is really important, because it gives you an idea about how many functioning nephrons are there, the less the number of functioning nephrons, the less the GFR, and the higher is the stage of the chronic renal disease (insufficiency).

We measure it through the concept of clearance, and by using inulin, but why inulin specifically?

Freely filtered, not reabsorbed, not secreted.

Note: if the substance is secreted, then we can't use GFR in the formula, because it won't be equal to clearance, otherwise you will overestimate GFR. (What's cleared in urine is more than what comes from filtration)

The Problem of Using Inulin: (why we don't use it for daily tests?)

Inulin is an exogenous substance that should be injected, and after being injected, it needs several hours before its concentrations get stabilized, and before that we cannot do our clearance calculations, so it is NOT a practical clinical exam, it is used for medical research purposes.

But, instead of Inulin, what should we use?

We will use an endogenous substance which is Creatinine. Creatinine comes from muscles' phosphocreatine breakdown at a constant rate (very slightly dependent on nutrition).

Extra: Creatine phosphate can be broken down into creatinine, which is then excreted in the urine. A 70-kg man contains around 120g of creatine, with 40% being in the unphosphorylated form and 60% as creatine phosphate. Of that amount, 1–2% is broken down and excreted each day as creatinine.

Creatinine has a molecular weight of 114 Daltons, so it is **freely filtered** (first criterion is achieved). It is **not reabsorbed** (second criterion is also achieved), but it is **slightly secreted (10% is secreted).**

As it is slightly secreted, we know that it can't be used to calculate GFR in the same formula that is used before (it will overestimate GFR, maybe we will get a number like 145 ml instead of 125 ml although GFR is actually 125 ml, 145 ml is the **clearance**). But we said from the first that it is used instead of Inulin, so certainly there is a justification.

When we measure the plasma concentration of Creatinine, we measure that of **Total creatinine**, which includes both, **free creatinine that is filterable (90% of total creatinine)** and **protein bound creatinine which is not filterable (10% of total creatinine)**.

Here is the justification: The 10% of creatinine that is secreted replace the 10% that is not filtered (which we already included it in the plasma concentration P_{cr}), so they cancel each other. The net result is **as if** all the plasma creatinine that we measured is filtered, and that secretion is almost zero, resulting in a condition that is similar to Inulin, which allows us to use **creatinine** as a **glomerular marker**, and justifies why we can put GFR instead of Clearance in the formula of creatinine.

$$C_{cr} = GFR = (U_{cr} / P_{cr}) * V$$

Where C stands for clearance, and cr stands for Creatinine

(You can understand it as the following: U_{cr} is increased by 10% because of secretion, and that P_{cr} which we measure is also 10% more than reality (bound to proteins), resulting in 10% increase in numerator, and 10% increase in denominator, which will finally cancel each other)

Note: creatinine becomes a little bit tricky in end stage renal failure, because GFR is too small here, and thus, the entire number that you measure may be originated from secretion only and not from filtration, you should be cautious.

We all know that P_{cr} is measured easily by simple blood sample, but **how about the measurement of U_{cr} and V ?**

The unit that we were using for V (urine flow) throughout the sheet was ml/min, but how can we measure V in this unit?

What usually happens is that **we ask the patient to collect his/her urine for 24 hours in a urine bag** (for example, starting at 7am with an empty bladder i.e after voiding, until 7 am next day). This 24 hour urine sample helps us in two things:

First of all, we use it to **measure V (urine flow) in ml/min** (dividing it by 24 * 60).

For example, if the 24 hour urine sample volume was 2500 ml, measure V in ml/min.

V = 2500 ml/ day = 2500 ml/ 24 * 60 min = **1.73 ml/min**

Another thing that we can obtain from this 24 hour urine sample is **the concentration of creatinine in urine (U_{cr}).**

Having everything known, **we use the formula to measure GFR in ml/min.**

Extra: why do we use 24 hours, why not less?

To make sure that we get the average concentration of creatinine, as the breakdown of creatine phosphate differs during the day according to many things such as muscle tone and activity. Using 48 hours will be more precise, but it's impractical.

This method of calculating GFR that we were talking about, which is based on both plasma and urine, is called **TRUE GFR, or simply: tGFR.**

The Problem of Using True GFR "tGFR":

Collecting 24 hour urine sample is **inconvenient** and **impractical** for most of the patients, especially elderly (may have dementia for example) and children (there is no guarantee that all urine will be collected in the bag). And from here, the concept of **estimated GFR "eGFR"** has appeared, which **depends only on blood sample (P_{cr}) without urine collection to estimate GFR**. However, this estimation should be close enough to tGFR or otherwise it won't be beneficial.

Before we continue talking about estimated GFR (eGFR), let's take the following example;

Knowing that creatinine is formed in the muscles in a constant and fixed manner, which is around 1.5 to 2 grams daily, and that it is also excreted every day in the same amount (1.5 to 2 g/day), maintaining a constant concentration of creatinine in the blood (because input = output), and considering that the average of creatinine excretion is 1.8 g/day, and that GFR is 125 ml/min, calculate the average plasma concentration of creatinine in mg/dL.

Filtered Load = GFR * P_{cr}

1.8 g/day = 125 *60*24 ml/day * **P_{cr}**

1.8 g/day = 180 L/day * **P_{cr}**

P_{cr} = 0.01 g/L = 10 mg/L = **1 mg/ dL**

(Note: you can use the clearance equation, and you can convert units to mg/min from the first, all works)

Now, if GFR decreases to its half, what happens to P_{cr} if your body maintains its daily creatinie excretion (1.8 g/day)?

It will be doubled to 2 mg/dL; by calculations:

Filtered load = GFR * P_{cr}

1.8 g/day = 90 L/day * P_{cr}

P_{cr} = 2 mg/dL

(Filtered load "constant" = GFR * P_{cr}, so if one of them is decreased to 1/2, the other one will increase to *2 in order to maintain a constant amount of creatinine excretion).

A recap from the <u>doctor</u>: because we excrete the same amount of creatinine each day, the only way to compensate the decrease in GFR is to increase the concentration of creatinine in the plasma. **So P_{cr} gives you an idea about GFR**;

$$GFR \propto 1/ P_{cr}$$

GFR is inversely proportional to P_{cr}

Going back to estimated GFR (eGFR):

Estimation of GFR is based on special formulas that biostatisticians and physicians invent in order to calculate GFR without using urine information at all. There are many different formulas that are used, and they all share the usage of P_{cr} for measuring GFR. These formulas are based on studies that biostatisticians do on large samples.

For example, we bring 400 students, we measure their true GFR, and then we measure the average, standard deviation… of their tGFR. After that, we start studying the correlation between their age, height, gender, body weight…. and most importantly P_{cr} and their tGFR. Finally, we try to convert these correlations into a mathematical equation that can predict GFR based on general information, as well as P_{cr} , but without urine information at all.

There are many different formulas, each one uses specific type of information to predict GFR. The doctor said that these formulas are not for memorization, but he explained cockcroft-gault equation fairly well.

Cockcroft-gault equation:

$$eGFR = \frac{(140 - age) * IBW}{72 * P\,inu} \quad (* 0.85 \text{ if Female})$$

IBW: ideal body weight (according to the doctor)

VERY IMPORTANT: This is the only formula that takes body weight into consideration.

140, 72, 0.85 are all constants which are used to complete the equation.

For example, for a given patient, true GFR was 110 ml/min. we tried using the previous equation, we got GFR =105 ml/min (or 115 ml/min as an example), which is close enough to tGFR, so we can use the formula to predict GFR. This is the concept behind Estimating GFR.

When we applied **Cockcroft-gault** equation to patients with diabetic nephropathy, or with glomerulonephritis, eGFR was far away from tGFR. Same thing happened when we applied it to elderly and children. So this equation doesn't work for different kidney diseases, it doesn't work for children. For each case, there is a certain formula that is favored. (There is no formula that works for all cases)

Other formulas:-

MDRD: it is used in the case of chronic kidney diseases (it uses P_{cr}, gender, race and age)

Schwartz: it is used to estimate GFR of children. (It uses P_{cr} and height)

There is a formula that is used in Mayo Clinic.

Note: Cockcroft-gault equation is not representative to all human beings, but it is the **only one that takes body weight into consideration**, and this clarifies the importance of this formula.

But why body weight is important?

Creatinine release depends on **muscle mass**, and this is the reason why body builders may have higher creatinine in their blood although they have totally normal GFR. Let's take the following example: a body builder with P_{cr} =1.6 mg/dL, and a very slim girl with P_{cr} = 1.1 mg/dL. The body builder has totally normal GFR (his body forms creatinine more, and with normal GFR, his P_{cr} will increase, and this increase doesn't reflect any renal impairment or decreased GFR), while the girl may have renal impairment.

This is why body weight and muscle mass are really important in estimating GFR.

We conclude that although Cockcroft-gault formula is not that accurate, but it is the only one that included body weight, which gives it a special advantage.

Note from the doctor: some formulas require P_{cr} in micromoles/Liter, so to convert mg/dL to micromole/L, we multiply by 88.4

A recap from the doctor:

What you should know is the following:-

- Gold standard for kidney function test is to measure true GFR.
- True GFR is not always practical.
- Estimated GFR depends on P_{cr} and many other factors for each formula.
- These formulas don't take body mass into consideration, and this is a big problem (except for Cockcroft-gault formula).
- All formulas share having P_{cr} in the denominator as it is inversely proportional to GFR.

Extra Note: low levels of creatinine in blood are not common, and also aren't a cause of medical concern. They may be seen with conditions that result in decreased muscle mass.

Answer to a student's question: In chronic kidney diseases, GFR is decreased, but creatinine filterability is not, and thus we use creatinine to measure GFR. For example, suppose that normal GFR =125 ml/min, and that GFR in a certain chronic kidney condition = 50 ml/min. What happened is that the volume being filtered (functioning nephrons) has decreased too much, although all creatinine molecules in those 50 ml will be completely filtered, so creatinine filterability is not affected. (However, in nephrotic syndromes, **proteins**' filterability is affected, so differentiate between proteins and creatinine, as well as between different stages of chronic renal failure and nephrotic syndromes).

Selected Questions from Guyton and BRS (Extra)

1. Which of the following would cause the greatest decrease in GFR in a person with otherwise normal kidneys?
   A) Decrease in renal arterial pressure from 100 to 80 mmHg in a normal kidney
   B) 50% increase in glomerular capillary filtration coefficient
   C) 50% increase in proximal tubular sodium reabsorption
   D) 50% decrease in afferent arteriolar resistance
   E) 50% decrease in efferent arteriolar resistance
   F) 5 mmHg decrease in Bowman's capsule pressure

2. Given the following measurements, calculate the filtration fraction; Glomerular hydrostatic pressure = 70 mmHg, Bowman's hydrostatic pressure = 20 mmHg, Colloid oncotic pressure in the glomerular capillaries = 35 mmHg, filtration coefficient (Kf) = 10 ml/min/mmHg, Renal plasma flow = 428 ml/min
   A) 0.16 B) 0.20 C) 0.25 D) 0.30 E) 0.35 F) 0.40

3. The maximum clearance rate possible for a substance that is totally cleared from the plasma is equal to which of the following?
   A) GFR
   B) Filtered load of that substance
   C) Urinary excretion rate of that substance
   D) Renal plasma flow
   E) Filtration fraction

4. The GFR of a 26-year-old man with glomerulonephritis decreases by 50% and remains at that level. For which substance would you expect to find the greatest increase in plasma concentration?
   A) Creatinine
   B) K^+
   C) Glucose
   D) Na^+
   E) Phosphate
   F) H^+

5. Which substance is filtered most readily by the glomerular capillaries?
   A) Albumin in plasma
   B) Neutral dextran with a molecular weight of 25,000
   C) Polycationic dextran with a molecular weight of 25,000
   D) Polyanionic dextran with a molecular weight of 25,000
   E) Red blood cells

6. A selective decrease in efferent arteriolar resistance would _____ glomerular hydrostatic pressure, _____ GFR, and _____ renal blood flow.
   A) Increase, increase, increase
   B) Increase, decrease, Increase
   C) Increase, decrease, decrease
   D) Decrease, increase, decrease
   E) Decrease, decrease, increase
   F) Decrease, increase, increase

7. If the renal clearance of substance X is 300 ml/min and the glomerular filtration rate is 100 ml/min, it is most likely that substance X is
   A) Filtered freely but not secreted or reabsorbed
   B) Bound to plasma proteins
   C) Secreted
   D) Reabsorbed
   E) Bound to tubular proteins
   F) Clearance of a substance cannot be greater than the GFR

8. If the GFR suddenly decreases from 150 ml/min to 75 ml/min and tubular fluid reabsorption simultaneously decreases from 149 ml/min to 75 ml/min, which change will occur (assuming that the changes in GFR and tubular fluid reabsorption are maintained)?
   A) Urine flow rate will decrease to 0
   B) Urine flow rate will decrease by 50%
   C) Urine flow rate will not change
   D) Urine flow rate will increase by 50%

9. The following information was obtained in a 20-year-old college student who was participating in a research study in the Clinical Research Unit:
   Plasma: conc inulin = 1 mg/ml, conc X = 2 mg/ml
   Urine: conc inulin = 150 mg/ml, conc X = 100 mg/mL; Urine flow rate = 1 mL/min,
   Assuming that X is freely filtered, which of the following statements is most correct?
   (A) There is net secretion of X
   (B) There is net reabsorption of X
   (C) There is both reabsorption and secretion of X
   (d) The clearance of X could be used to measure the glomerular filtration rate (GFR)
   (E) The clearance of X is greater than the clearance of inulin

Answers respectively: 1-E / 2-E / 3-D / 4-A / 5-C / 6-E / 7-C / 8-A / 9-B

THE END