MEDICINE
KING SAUD UNIVERSITY

Physiology Team 436

Revised by
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# Renal Clearance

Renal Block

Red: very important.
Green: Doctor’s notes.
Pink: formulas.
Yellow: numbers.
Gray: notes and explanation.

**Physiology Team 436 – Renal Block Lecture 3**



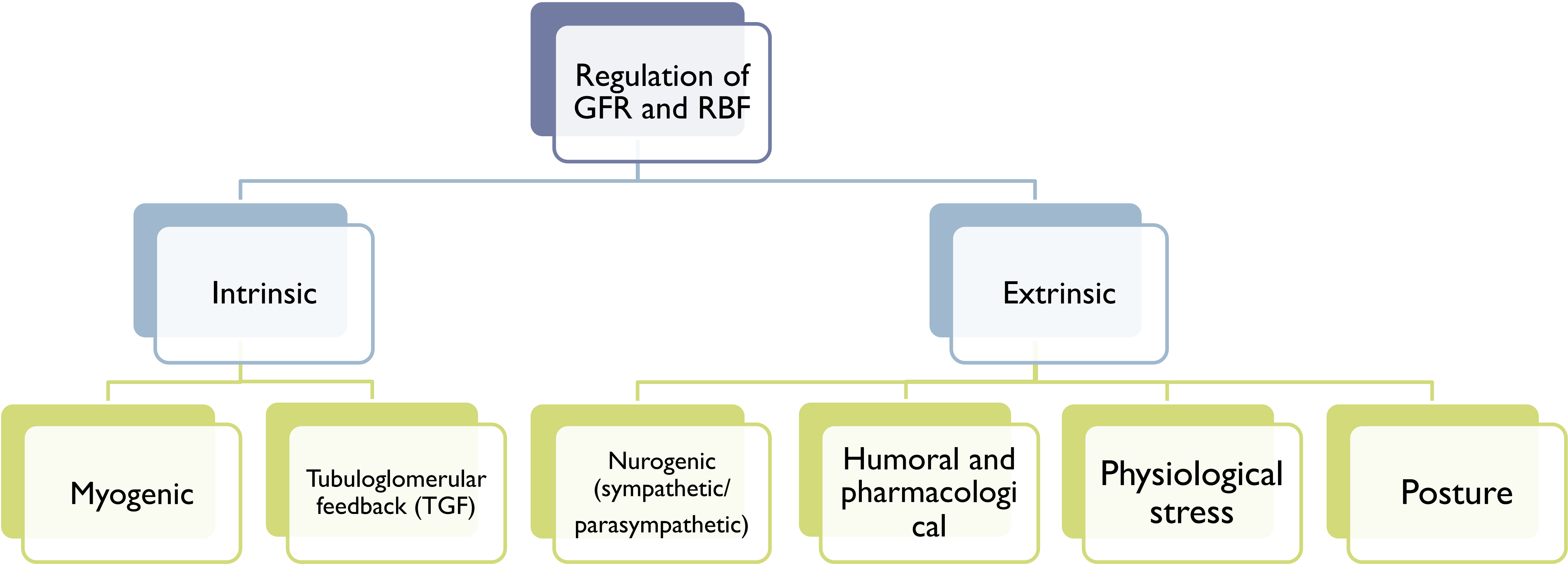
For further understanding please check our “Extra Notes” file which contains extra explanation for reference books.

# Objectives

- Describe the concept of renal plasma clearance.
- Use the formula for measuring renal clearance.
- Use clearance principles for inulin, creatinine etc. for determination of GFR.
- Explain why it is easier for a physician to use creatinine clearance Instead of Inulin for the estimation of GFR.
- Describe glucose and urea clearance.
- Explain why we use of PAH clearance for measuring renal blood flow.

**ONLY IN MALES' SLIDES**

# Regulation of GFR and RBF



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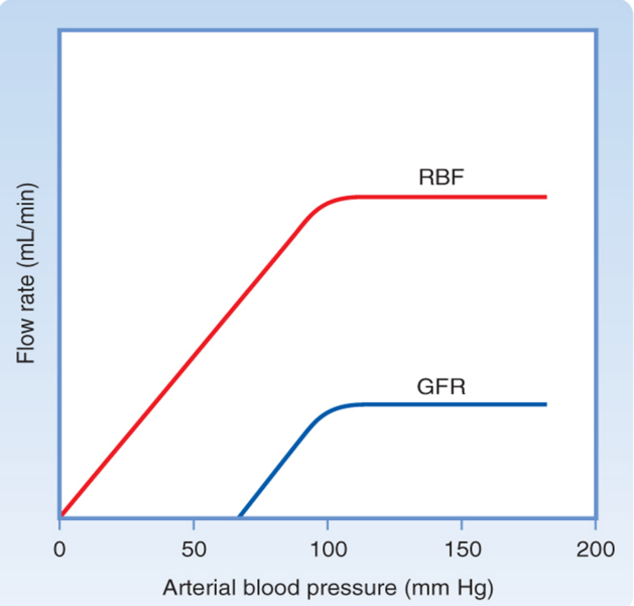
# Intrinsic Regulation of GFR and RBF

## 1) Myogenic mechanism

- normal response of vascular smooth muscle
- that is, increased stretch due to pressure rise depolarises the cells, calcium enters and causes a vasoconstriction
- well developed in the kidney




Koeppen & Stanton: Berne and Levy Physiology, 6th Edition.


Pressure → Stretching → depolarizations → more calcium enters → vasoconstriction

## 2) Tubuloglomerular feedback

- [NaCl] dependent mechanism
- macula densa cells in JGA detect [NaCl] send signals to afferent arteriole
- e.g. ↑ GFR = ↑ [NaCl] filtrate
- sensed by JGA ⇒ arteriole constricts
- (resistance ↑ ⇒ ↓ blood flow)
- mediator can be Adenosine or Renin (mainly, it's Adenosine)

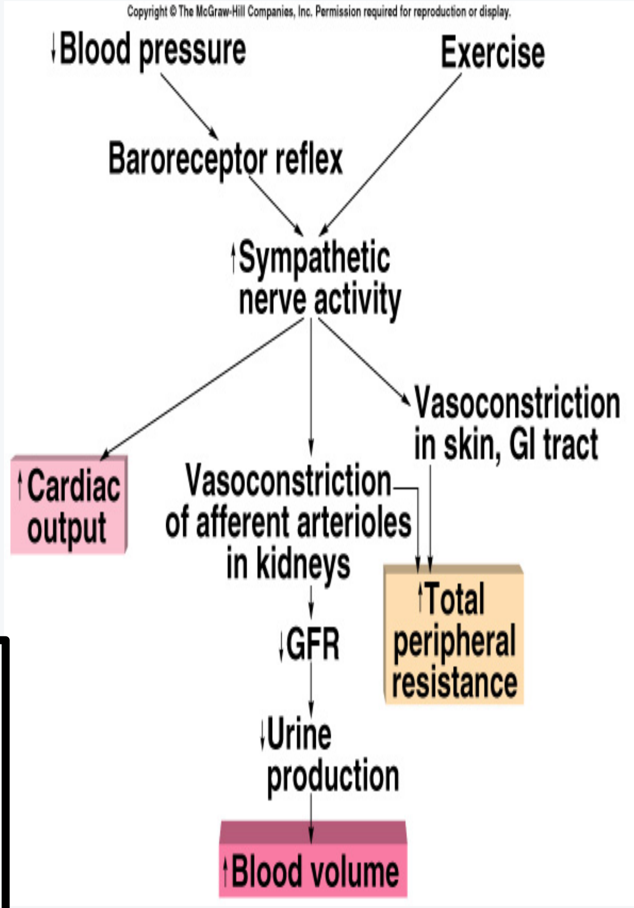
Remember that the Macula Densa is an osmochemo receptor → detect osmolarity of tubular fluids

GFR is high → no time for reabsorption → Nacl is high in tubules → macula densa sends signals to JG → renin release→ vasoconstriction → increased resistance → drop in GFR and RBF

# Extrinsic Regulation of GFR and RBF (Neurogenic factors)

## Sympathetic

- Sympathetic Nerve Fiber: is the major NF to kidney. Stimulation of sympathetic NF causes renal vasoconstriction and results in decrease of RBF and GFR.
- Stimulates vasoconstriction of afferent arterioles. Preserves blood volume to muscles and heart.




- Cardiovascular shock:
  - Decreases glomerular capillary hydrostatic pressure.
  - Decreases urine output (UO).

## Parasympathetic

- There are some parasympathetic NF to efferent arterioles, most predominantly to juxtamedullary nephrons and sphincters of vasa recta. Stimulation of parasympathetic NF causes renal vasodilation and results in increase in RBF and GFR.

NF: Nerve Fiber

# Extrinsic Regulation of GFR and RBF Continue

2) Humoral and pharmacological factors:

- Epinephrine, Nor-Epinephrine, Angiotensin II, Prostaglandin (F), and Thromboxane cause renal vasoconstriction and results in decrease in RBF and GFR.
- Acetylcholine, Bradykinin, Prostaglandin (D, E, and I), and bacterial pyogens cause renal vasodilation and results in increase in RBF and GFR.

Very Important: Know that PG F causes vasoconstriction , while PG D/I/E cause vasodilation

3) Physiological Stress:

cold, deep anesthesia, fright, sever exercise, hypoxia and ischemia

stimulate sympathetic NF leading to renal vasoconstriction and decrease in RBF.

4) Posture:

RBF increases in supine than sitting than standing.

Changing the posture from lying to standing leads to a decrease of about 15% in RBF due to the stimulation of sympathetic NF.

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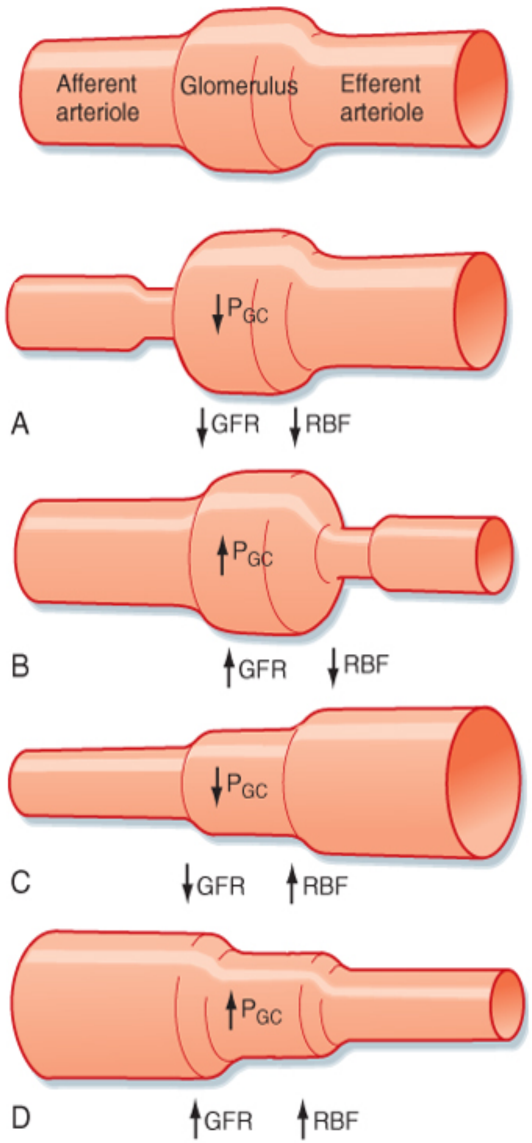





- **Normal**
- **Afferent arteriolar constriction**
- **Efferent arteriolar constriction**
- **Efferent arteriolar dilatation**
- **Afferent arteriolar dilatation**

A) Afferent arteriolar constriction

**Due to:** Renin/Adenosine
**Causes:** Low GFR low RBF low Pgc

B) Efferent arteriolar constriction:

**Due to:** ANG II
**Causes :** Increased GFR and Pgc and Decreased renal blood flow

C) Efferent arteriolar dilation:

**Due to:** parasympathetic activation
**Causes:** Decreased GFR and Pgc and Increased RBF

D) Afferent arteriolar dilation

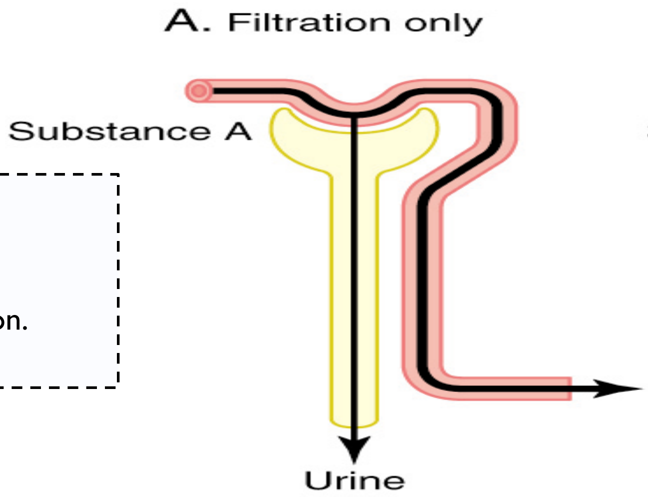
**Due to:** -
**Causes:** increased GFR, RBF and Pgc

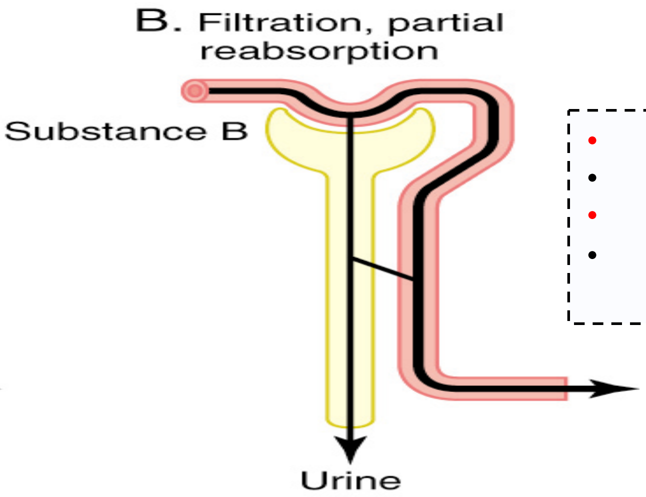
# Concepts Of Clearance

| | |
|---|---|
| **Definition** | **The clearance value of a certain substance :**<br>*[means the volume of plasma which is cleared from this substance in urine each minute].* |
| **Calculation** | **The formula is :** $C = \frac{U \times V}{P}$<br>**C =** Renal clearance (ml/min)<br>**(V) =** Volume of urine (ml /min). *(urine flow rate)*<br>**(U) =** Conc. of the substance in urine (mg/ml).<br>**(P) =** Conc. of the substance in plasma/serum (mg/ml).<br>**U X V =** Excretion rate of substance . |
| **Plasma Clearance Tests** | **The properties of any** exogenous **substance *used in*** plasma *clearance tests* ***are:***<br>1. Stays in the plasma (does not enter the RBC's).<br>2. Does not affect the renal functions.<br>3. Not metabolized by the kidney.<br>4. Easily measured in plasma & urine.<br>5. Non toxic. |
| **Assume** | If the substance is freely filtered at the glomeruli and is not reabsorbed, secreted or metabolized in the nephron *(such as Inulin)*, then:<br>Amount filtered per minute = Amount excreted per minute<br>$[sub]_{plasma} \times GFR = [sub]_{urine} \times$ urine flow rate |

# Renal Handling of The Different Substances

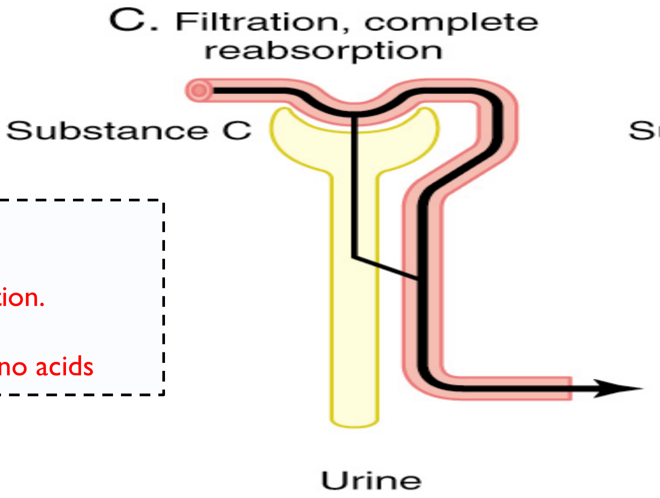
- Filtration only.
- No secretion.
- No reabsorption.
- Complete excretion.
- Ex. : Inulin

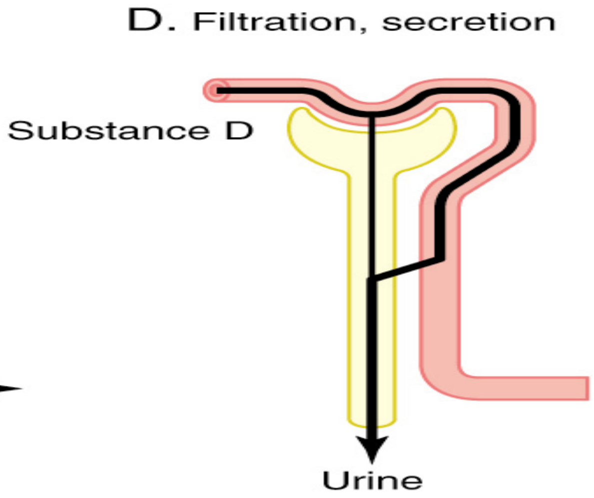



- Filtration.
- No secretion.
- Partial reabsorption.
- Ex. : Urea & Sodium (electrolytes)

- Filtration.
- No secretion.
- Complete reabsorption.
- No excretion.
- Ex. : Glucose & Amino acids




- Filtration.
- Secretion.
- No reabsorption.

Ex. : Creatinine & P.A.H.A



**Every single word in this slide is VERY IMPORTANT !*

*P.A.H.A (Para-Aminohippuric acid)*

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# Concepts of Clearance

**Amount of substance excreted = (filtered – reablsorbed + secreted)** { U x V = GFR x Px ± Tx }

The amount of any substance = conc. X volume

**[ Before starting the lecture, we have to know ] :**

- **What does clearance mean ?**
  كمية الدم التي تم تنظيفها من مادة معينة.

Clearance is for blood not kidney

↑clearance = ↑efficacy of the kidney

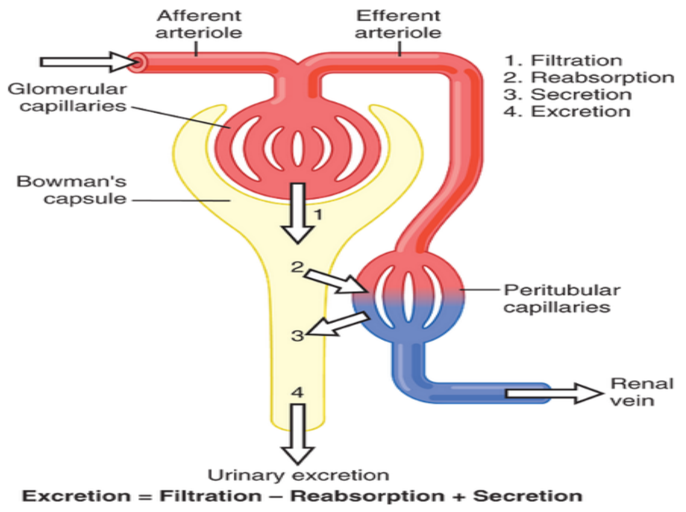
- Increased Filtration = increased Excretion
- Increased Reabsorption = Decreased Excretion
- Increased Secretion = Increased Excretion

- **What does the clearance depend on?**

1) Clearance of a substance depend on excretion. If excretion is high = clearance will be high
   لو ثبتنا ال concentration كل ما صار الاكسكريشن اكثر للمادة وطلع بال urine اكثر زاد ال clearance

2) Conc. of substance in plasma, if its high = clearance will be *less*

3) Clearance of a substance depend on it GFR and tubular activities.



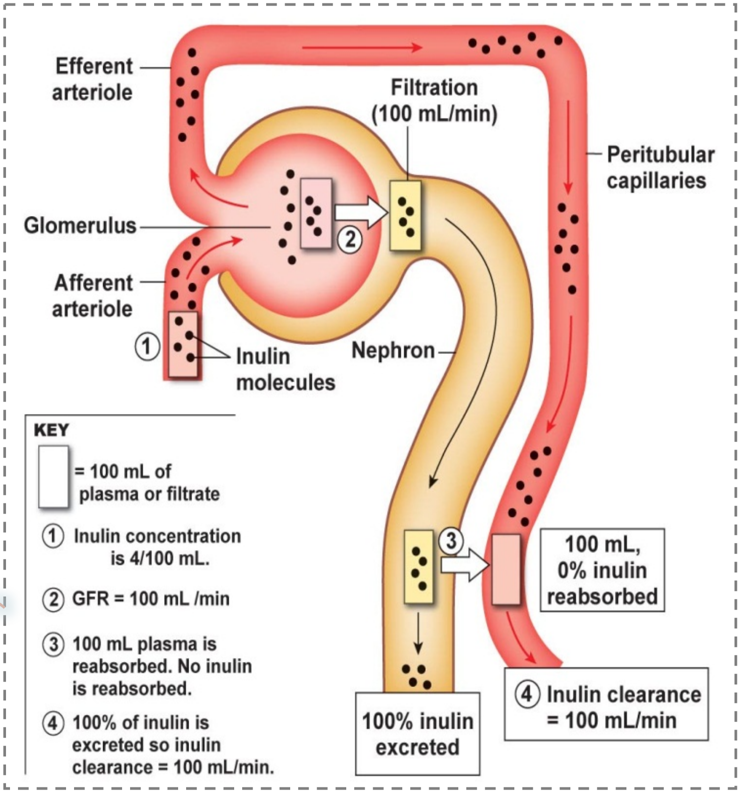

- if Plasma conc. of inulin = 1mg/100ml
- Urinary conc of Inulin = 120 mg /100ml
- Urine flow (UV) = 1 ml /min then, the clearance of inulin will be?
- C = 120 ml/min

# Types of Clearance Tests

| Types of clearance tests | |
| --- | --- |
| Endogenous | Exogenous |
| • Creatinine<br>• Urea<br>• Uric acid | • Inulin<br>• Para amino hippuric acid (PAHA) .<br><br>• Diodrast (di-iodo pyridone acetic acid )<br>**ONLY IN FEMALES' SLIDES** |

- **Inulin :**

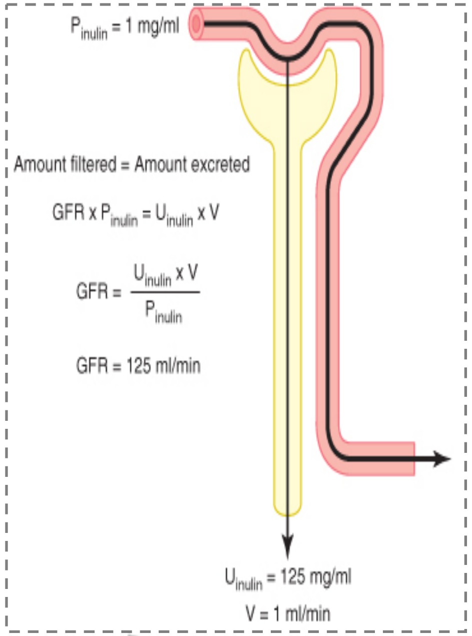
A plant product that is filtered but not reabsorbed or secreted. Used to determine GFR and therefore nephron function.



# Criteria of a Substance Used for GFR Measurement

- Freely filtered
- Not secreted by the tubular cells.
- Not reabsorbed by the tubular cells.
- Should not be toxic
- Should not be metabolized
- Easily measurable.

| Examples of such a substance: | |
|---|---|
| Endogenous | Exogenous |
| Creatinine<br>by-product of skeletal muscle metabolism | Inulin<br>It is a polysaccharide with a molecular weight of about 5200 and it fits all the above requirements. |




example

if Plasma conc. of inulin = 1mg/100ml
Urinary conc. of Inulin = 120 mg /100ml
Urine flow = 1 ml /min

**The clearance of inulin will be?**

**Clearance = GFR** = U x V / PX
= (120 mg/100ml )(1 ml/min ) = 120 ml/min
( 1 mg/100ml )

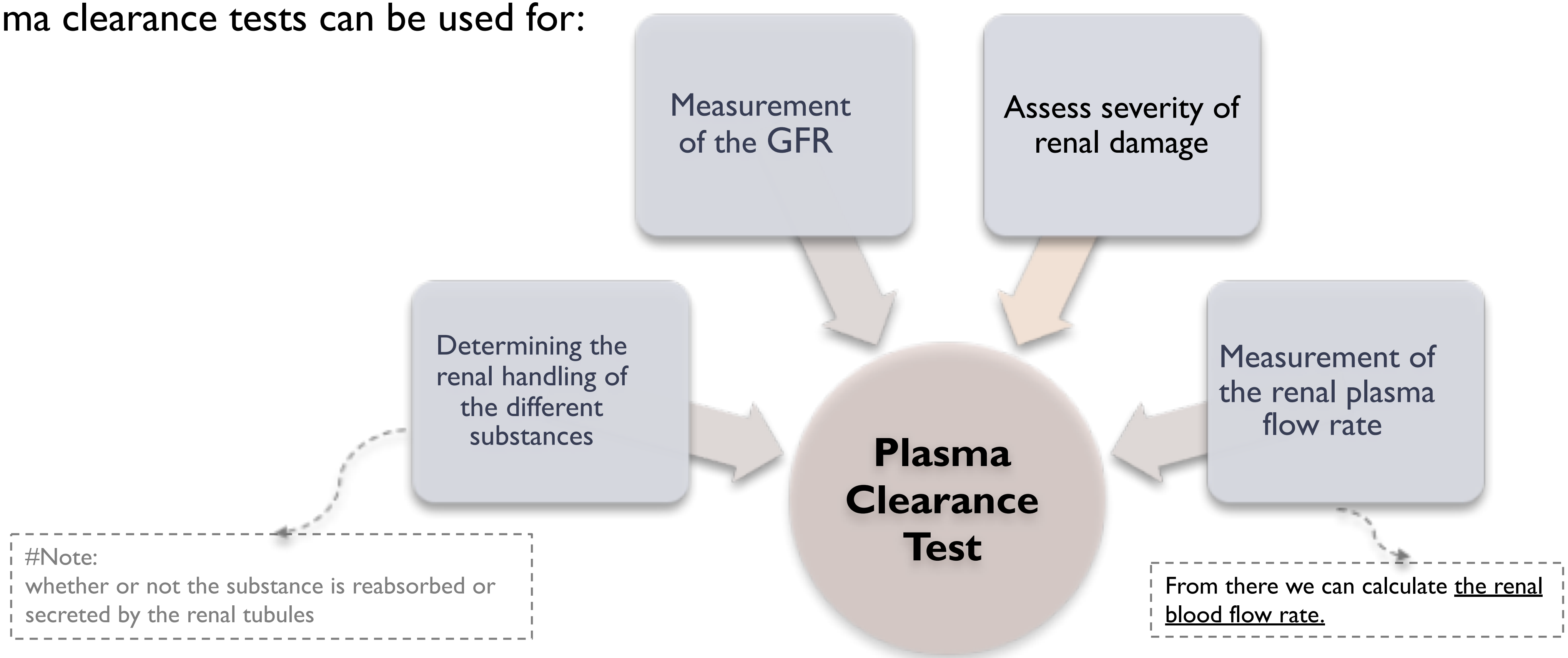
Inulin is better but toxic for human , thus practically we use creatinine



**Video of (Renal Clearance of Inulin) Duration: (2.43)mins**

# Importance of renal clearance

- Plasma clearance tests can be used for:




Clearance values can also be used to determine how the nephron handles a substance filtered into it. In this method the clearance for inulin or creatinine is calculated and then compared with the clearance of the substance being investigated.

# Calculation of tubular reabsorption or secretion from renal clearance

- Clearance measurements are also used to examine renal management of substances absorbed or secreted by the kidney.

| For substances **secreted** by the kidney: |
|---|
| ( $[sub]_{plasma}$ x GFR ) + T = $[sub]_{urine}$ x V (urine flow rate) |
| So, What goes into the nephrons = What leaves the nephrons. |
| Secretion into nephrons is occurring when: C sub. > C inulin |

| For substances **absorbed** by the kidney (Nephrons): |
|---|
| $[sub]_{plasma}$ x GFR = T + ( $[sub]_{urine}$ x V (urine flow rate) |
| So, What goes into the nephrons = What leaves the nephrons. |
| Absorption from nephrons is occurring when: C sub.< C inulin |

| Conclusion | T = ( $[sub]_{plasma}$ x GFR ) - ( $[sub]_{urine}$ x V ) |
|---|---|
| Note | $[sub]_{urine}$ x V = normally zero for glucose & amino acids. |

- Which means: glucose & amino acids will be completely reabsorbed by the renal tubules and there will be no excretion.

- T = Amount Transported (amount reabsorbed or secreted)
- C sub. = clearance of substance,
- C inulin = clearance of inulin

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# Calculation of tubular reabsorption or secretion from renal clearance

| Calculation of tubular reabsorption | |
|---|---|
| Substances that are completely reabsorbed from the tubules (amino acids, glucose) | Substances highly reabsorbed (Na+) |
| **clearance = zero** because the urinary secretion is zero. | **clearance < 1%** of the GFR. |

- Reabsorption rate can be calculated= Filtration rate - excretion rate **= (GFR X P*)-(U* X V)**
- * The substance needed to be assessed.

- If excretion rate of a substance is greater than the filtered load, then the rate at which it appears in the urine represents the sum of the rate of glomerular filtration + tubular secretion

- Secretion* = (U* X V) - (GFR X P*).
- * indicate the substance

# Measurement of Renal Blood Flow & Plasma Flow

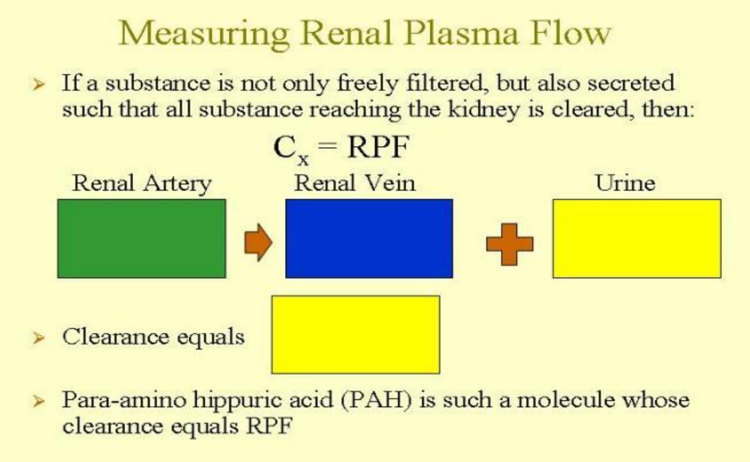
- To measure Renal blood flow:

1. Measure renal plasma flow
2. Calculate actual blood flow from hematocrit

- Substances used for measurement of GFR are not suitable for the measurement of Renal Blood Flow.
- **Because** Inulin clearance only reflects the volume of plasma that is filtered, and not that remains unfiltered and yet passes through the kidney → it is known that only 1/5 of the plasma that enters the kidneys gets filtered, so, we use other substances with special criteria.

- Criteria of substance needed to measure Renal Plasma flow by clearance method : ( Properties )

1. Freely Filtered 2. Rapidly and completely secreted by the RTC
3. Not reabsorbed 4. Non toxic 5. Easily measured .




**Example: Para-amino-hippuric-Acid (PAHA):**

**90%** of plasma flowing through the kidney is completely cleared of PAHA. Even when it goes through peritubular capillaries it get secreted completely



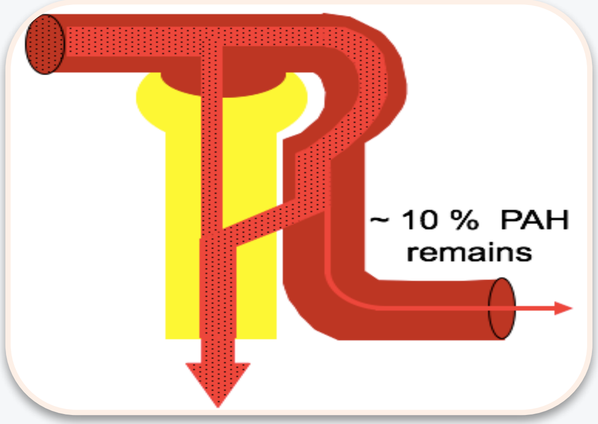
RTC = renal tubular cell

# Para-aminohippuric Acid (PAHA) and its Clearance

- **It is one of the special substances used to measure the RBF (Renal blood flow) .** ( using clearance method )
- **Properties:** When it presents below a certain concentration in the blood; it is completely cleared from the renal plasma by a single circulation through the kidney, due to it being:

1. Freely (easily) filtered
2. Secreted by renal tubules
3. Not reabsorbed after filtration

IMPORTANT




- **Other properties (as mentioned in slide 12):**

Doesn't enter RBC's or other tissue cells - isn't metabolized by tissues -

Not toxic - Not adsorbed to the unfiltrated plasma proteins .

**Effective Renal plasma flow (ERPF) is the clearance of PAHA:**

Amount entering kidney = RPF x PPAHA

Amount entered = Amount excreted

ERPF x PPAHA = UPAHA x V

$$\mathbf{ERPF} = \frac{UPAHA \times V}{PPAHA}$$

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**PAHA Clearance (example):**

- Conc. of PAHA in urine = 25.2 mg/ml
- Conc. of PAHA in arterial blood= 0.05 mg/ml
- Urine flow = 1.1 ml/min

Renal Plasma Flow (CPAH) =
(25.2 x 1.1) / 0.05 = 560 ML/ min

- Hematocrit = 45%

Renal blood flow =
(560 x 100)/(100-45)= 1018 ml/min

# How to Measure Renal Blood Flow PAH Clearance: Example

- If the concentration of PAH in the urine and plasma and the urine flow are as follows:
- Conc. of PAH in urine=25.2 mg/ml
- Urine flow=1.1 ml/min
- Conc of PAH in arterial blood=0.05 mg/ml
- Then CPAH or Renal Plasma Flow=

  (25.2 x 1.1)/0.05 = 560 ML/ min
- Lets say the hematocrit is 45%, then renal blood flow will be:

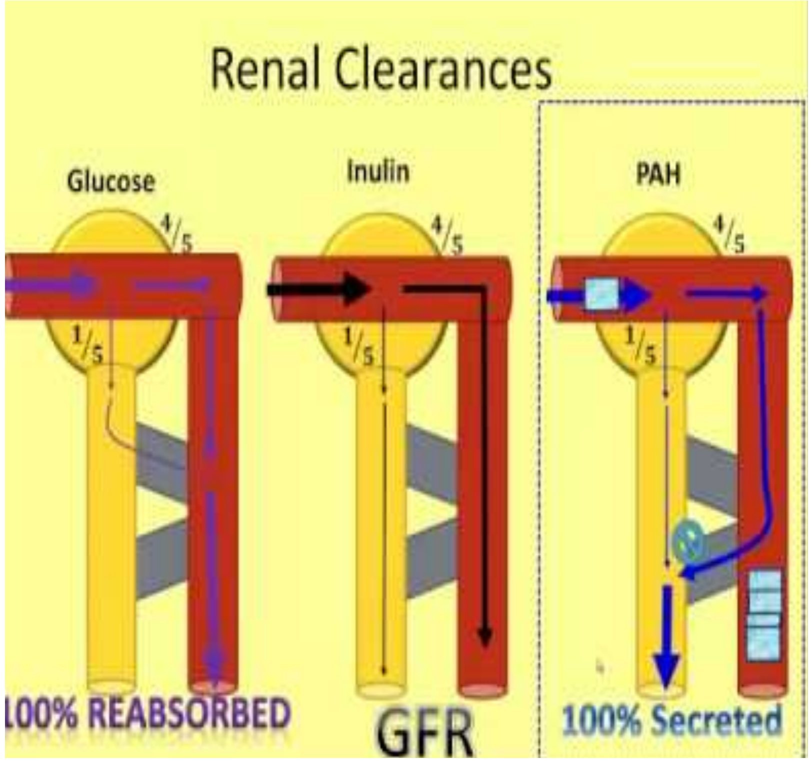
  (560 x 100)/(100-45)= 1018 ml/min

# Renal clearance indications

Renal Clearance gives an indication of the kidneys' function

Clearance can also be used to determine renal handling of a substance

Clearance values can also be used to determine how the nephron handles a substance filtered into it




Which means that inulin is the standard and other substances are compared to it ..

In this method the clearance for inulin or creatinine is calculated and then compared with the clearance of the substance being investigated.

# Comparison of clearance of a substance with clearance of inulin

| Comparison of clearance of a substance with clearance of inulin | | |
|---|---|---|
| = inulin clearance | < inulin clearance | > Inulin clearance |
| Only filtered<br>not reabsorbed or secreted | Reabsorbed<br>by nephron tubules | Secreted<br>by nephron tubules |

- Listed below are the approximate clearance rates for some of the substances normally handled by the kidneys:

| Substance | Clearance Rate (ml/min) |
|---|---|
| Glucose | 0 |
| Sodium | 0.9 |
| Chloride | 1.3 |
| Potassium | 12.0 |
| Phosphate | 25.0 |
| Inulin | 125.0 |
| Creatinine | 140.0 |

Remember : Filtered amount + Secreted = Excreted
Filtered amount – Reabsorbed = Excreted

If substance is secreted:
Excreted = Filtered + secreted

If substance is reabsorbed
Excreted = filtered – reabsorbed

# Filtration fraction

- Filtration fraction: is the ratio of GFR to renal plasma flow. "see the equation below"

# Tubular transport maximum (Tmax)

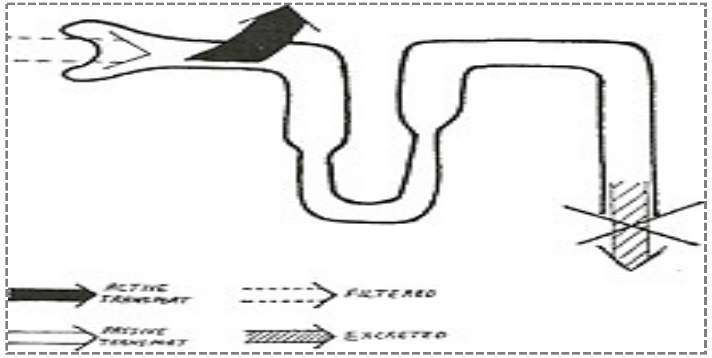
- The Maximum limit/rate at which a solute can be transported across the tubular cells of kidneys is called **tubular transport maximum.**

- **Average Tm for Glucose is 375 mg/min**

Privilege of T-max is given to the important solutes and some organic molecules such as glucose .

# Glucose clearance

- The glucose clearance is zero at plasma glucose values below the threshold and gradually rises as plasma glucose rises.
- We can express the excretion of glucose quantitatively at plasma concentrations beyond the threshold, where the glucose reabsorption rate (Tm) has reached its maximum :

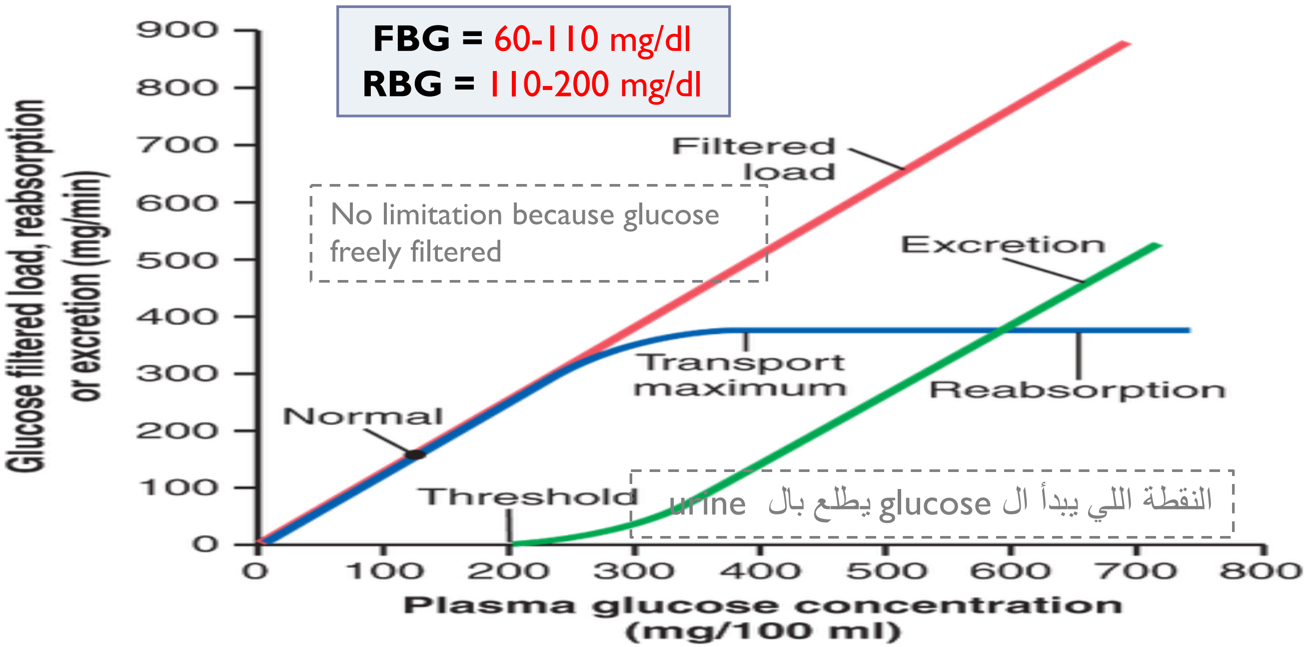


# Renal Threshold

- Is the concentration of a substance dissolved in the blood above which the kidneys begin to remove it into the urine.
- After this level $\Rightarrow$ the filtered load exceeds the absorptive capacity of the tubules.
- Substances of high threshold: glucose, amino acids & vitamins.
- Substances of medium threshold: $K^+$ & urea.
- Substances of low threshold: phosphate & uric acid.
- Substances of no threshold: creatinine, mannitol & inulin.

# Glucose reabsorption

ليش ال threshold عند 200 مو 300 ؟
لأن مو كل النفرونس لها نفس ال efficacy
بعضهم اقل من 300 فتختلف قدرتهم على
نقل الجلوكوز .
و أفضل وأعلى نفرون يكون الماكسيمم 375




**Transport max :** 375 mg/min

**Renal Threshold :** 200mg/dl

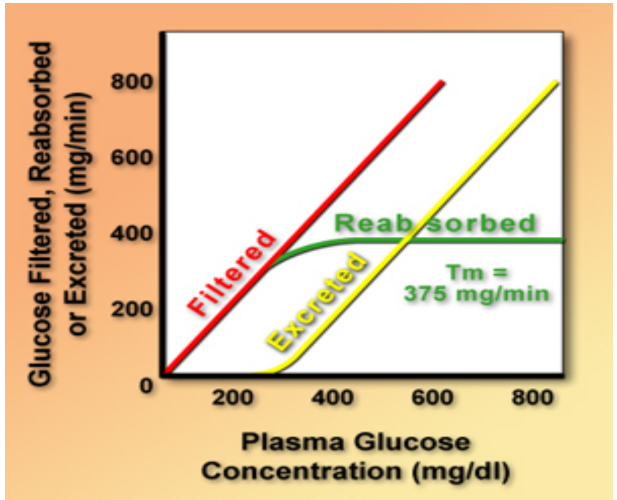
- However, when the plasma concentration of glucose rises above about 200 mg/100 ml, increasing the filtered load to about 250 mg/min, a small amount of glucose begins to appear in the urine. This point is termed the threshold for glucose. Note that this appearance of glucose in the urine .
- (at the threshold) occurs before the transport maximum is reached. One reason for the difference between threshold and transport maximum is that not all nephrons have the same transport maximum for glucose, and some of the nephrons excrete glucose before others have reached their transport maximum. The overall transport maximum for the kidneys, which is normally about 375 mg/min, is reached when all nephrons have reached their maximal capacity to reabsorb glucose .



FBG : Fasting Blood Glucose / RBG : Random Blood Glucose

# Tubular transport maximum for glucose

| Filtered load | GFR x $[P]_{glucose}$<br>↑ plasma [glucose]= ↑ Filtration |
|---|---|
| plasma [glucose] < 200 mg/dl | • Filtered load of glucose is <u>completely reabsorbed.</u><br>• clearance = zero |
| plasma [glucose] > 200 mg/dl | •Filtered load is not completely reabsorbed.<br>• " Threshold" or plasma [glucose] at which glucose is first excreted in urine |
| plasma [glucose] > 300 mg/dl | •Filtered load is not completely reabsorbed.<br>• Na+ - glucose (SGLT) cotransporters are <u>completely saturated.</u><br>• Maximal glucose reabsorption (Tm) |




- Mechanism

Urea Clearance Test (Just read it)

**Evacuates (empty) the patient's bladder.** → **Drinks a glass of water.** → **After 1 hr:** ***Take blood & urine samples*** **and drinks another glass of water.** → **After 2 hrs: Take another** ***urine*** **sample.** → **Calculate the urine vol. /min.**

| If it is above 2 ml /min<br>we get the maximal urea clearance (MC) .<br>MC = 75 ml /min. (normally) . | If it is below 2 ml /min<br>we get the standard urea clearance (SC) .<br>SC = 54 ml /min. (normally) . |
|---|---|

# Tubular Transport Maximum

- **Definition:**

  It is the maximal amount of a substance (in mg) which can be transported (reabsorbed or secreted) by tubular cells/min.

- **Notice:**

Appearance of glucose in urine before the transport maximum is reached is termed "Splay" and results from:

- Nephron variability: "in glomerular size & tubular length".
- Variability in the number of glucose carriers & the transport rate of the carriers.

> Splay is between threshold (180 mg/dL) and Tmax (300 mg/dL)
> Splay differs from one person to another, it depends on:
> 1- nephron ( glomerular size and tubules length)
> 2- glucose carriers ( number and rate of transport)

IMPORTANT NOTES

Renal threshold of glucose = 180 mg/dL,
Tmax= 375 mg/min
(notice how Tmax is a rate while threshold isn't)

- When glucose is less than 180, all glucose is reabsorbed.
- When glucose levels are elevated more than 180 it starts to be excreted in urine; however, reabsorption is still activated ( meaning not all the excess amount is excreted )
- untill it reaches 300 mg/dl where reabsorption stops and everything above 300 mg/dl is excreted.

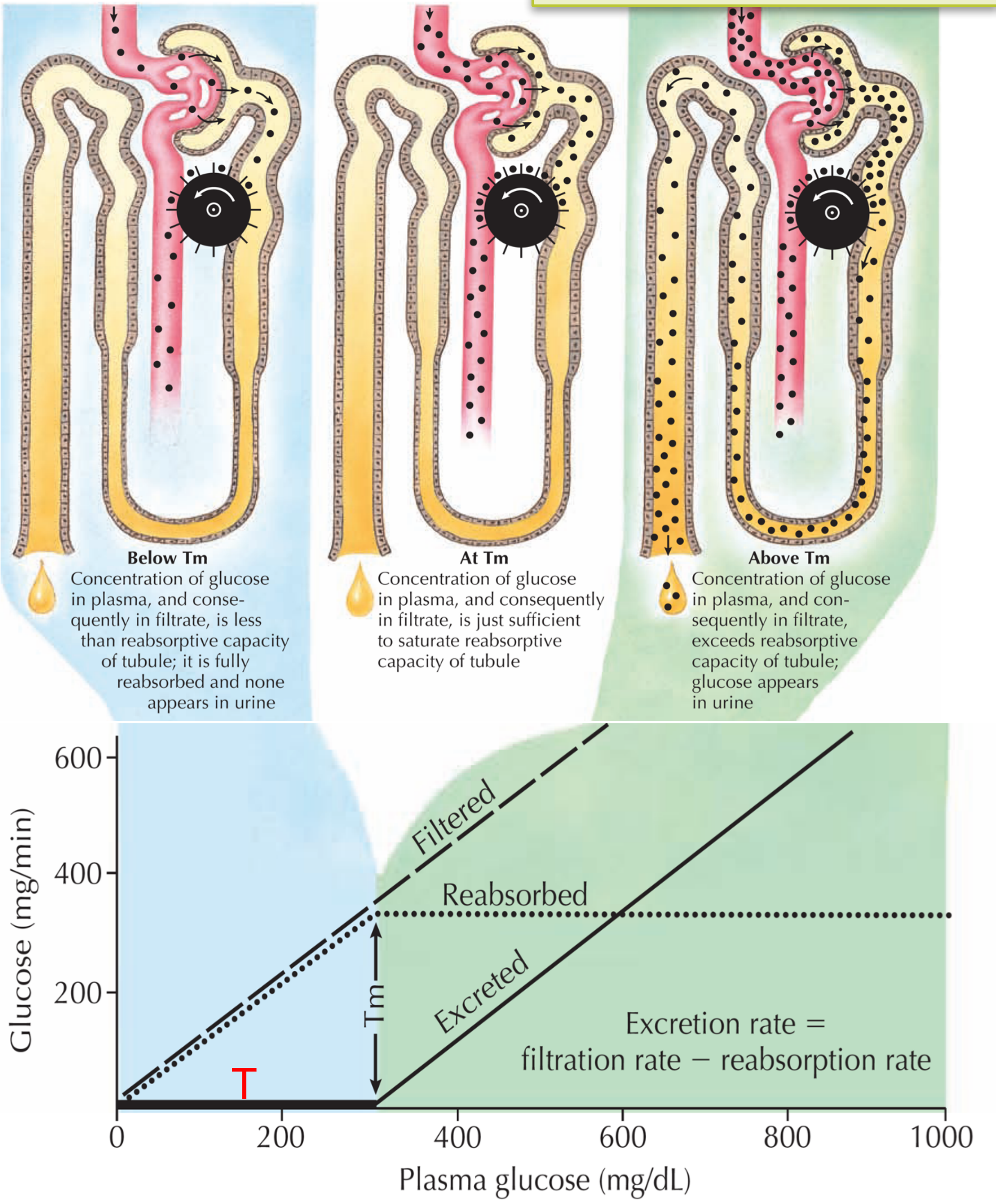
(Glucose concentration of 300 mg/dl equals Tmax 375 mg/min when GFR= 125 ml/min)
300 x 1.25 = 375 mg/min
Will be explained in the next slides

# Tubular Transport Maximum

- Many substances are reabsorbed by carrier mediated transport systems e.g. glucose, amino acids, organic acids, sulphate and phosphate ions.
- Carriers have a maximum transport capacity (**$T_m$**) which is due to **saturation** of the carriers. If $T_m$ is exceeded, then the excess substrate enters the urine.
- Glucose is **freely filtered**, so whatever its [plasma] that will be filtered.
- For amino acids, $T_m$ also very high → no urinary excretion occurs.

Once $T_m$ is reached for all nephrons, further ↑ in tubular load are not reabsorbed, but are then excreted.

Threshold (T) is the plasma conc. at which tubular load just exceeds $T_m$ for reabsorption, where below threshold all solute molecules are reabsorbed, and above threshold, some solutes are not



# Tubular Transport Maximum

- In man for plasma glucose up to 180 mg/dl, all will be **reabsorbed**. Beyond this level of plasma [glucose], it appears in the urine = Renal plasma threshold for glucose.
- Kidney does NOT regulate [glucose], (insulin and glucagon). Normal [glucose] of 90 mg/dl, so $T_m$ is set way above any possible level of (non-diabetic) [glucose] at 380 mg/min. Thus, ensure that all this valuable nutrient is normally reabsorbed. The appearance of glucose in the urine of diabetic patients = glycosuria, is due to failure of insulin, NOT, the kidney.

Tubules are lined by cells.
Those cells have 2 walls:
1- Luminal membrane: which is the wall facing the lumen (no carriers)
2- Basolateral membrane: wall facing away from lumen ( carries are in basolateral membrane )
--
For a substance to move from lumen to blood it has to cross luminal membrane and basolateral membrane

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# Test yourself IMPORTANT

- There are two possible ways to be asked:

A) The glucose plasma level is in the splay ( between renal threshold= 180 mg/ml and Tmax=375 mg/min

Steps:
Subtract plasma glucose level from renal threshold

Question: If plasma [glucose] = 275 mg/dl and renal threshold=180mg/dl. How many mg/dl wil be exreted?
275-180= 95 mg/dl excreted

B) The glucose plasma level is above Tmax=375mg/min

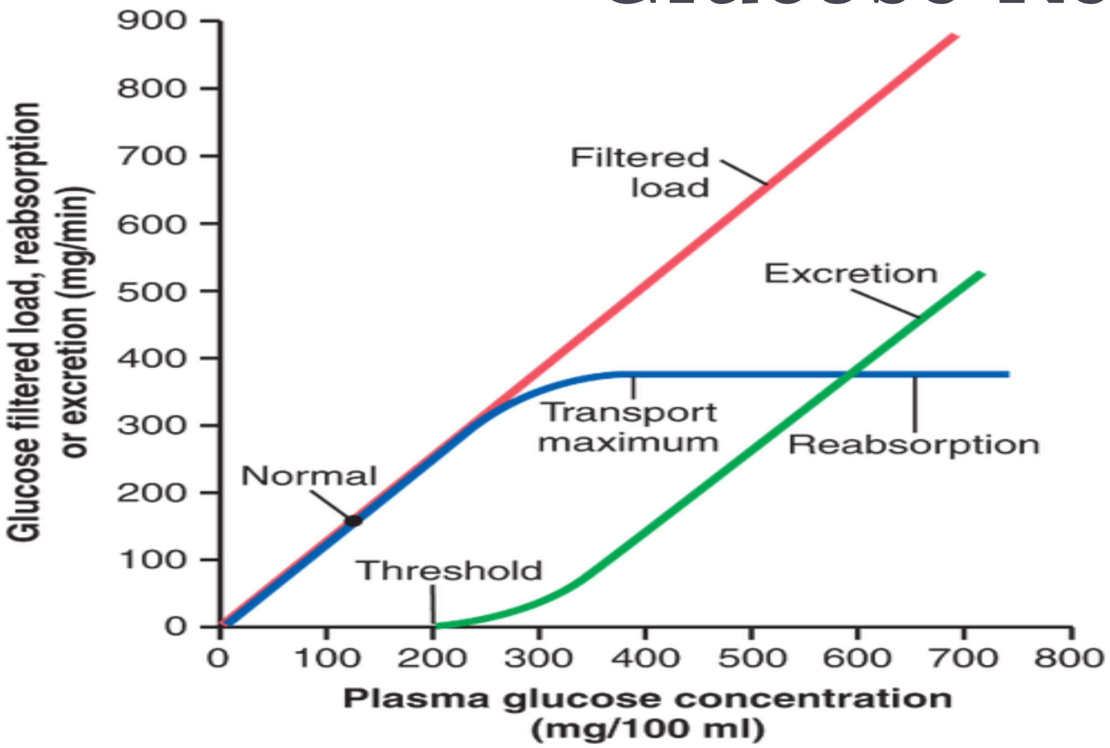
Steps:
1) Calculate filtrated plasma glucose level by multiplying glucose plasma level with GFR/100
2) Subtract filtrated plasma glucose level from Tmax

Question: If Tmax = 375 mg/min and glucose level is 500, how much glucose is excreted if:
A: GFR = 125 ml/min
B: GFR = 90 ml/min

VERY IMPORTANT !!!!

| | |
|---|---|
| A) Filtrated plasma glucose level:<br>500 mg/dl x 1.25 ml/min = 625 mg/min<br>Excreted= 625 – 375 = 250 mg/min | B) Filtrated plasma glucose level:<br>500 mg/dl x 0.9 ml/min = 450 mg/min<br>Excreted= 450 – 375 = 75 mg/min |

# Glucose Reabsorption




This diagram has 3 important curves:
Red line: Filtration ( all glucose is filtered)
Blue line: reabsorption ( up to Tmax )
Green line: excretion ( above Tmax is excreted )

Threshold 180 mg/dl
No excretion before threshold only filtration and reabsorption

Transport Max: 375 mg/min
Renal Threshold: 200 mg/dl
FBG = 60-100 mg/dl
RBG + 110-200 mg/dl

Tubular reabsorption is highly selective. Some substances, such as glucose and amino acids, are almost completely reabsorbed from the tubules, so the urinary excretion rate is essentially zero. Many of the ions in the plasma, such as sodium, chloride, and bicarbonate, are also highly reabsorbed, but their rates of reabsorption and urinary excretion are variable, depending on the needs of the body. Waste products, such as urea and creatinine, conversely, are poorly reabsorbed from the tubules and excreted in relatively large amounts.

Relations among the filtered load of glucose, the rate of glucose reabsorption by the renal tubules, and the rate of glucose excretion in the urine. The transport maximum is the maximum rate at which glucose can be reabsorbed from the tubules. The threshold for glucose refers to the filtered load of glucose at which glucose first begins to be excreted in the urine.

# Thank you!

اعمل لترسم بسمة، اعمل لتمسح دمعة، اعمل و أنت تعلم أن الله لا يضيع أجر من أحسن عملا.

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Link to Editing File

**Special thanks to Team435!**


References:
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- 435 Team.
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- Linda (5th Edition).