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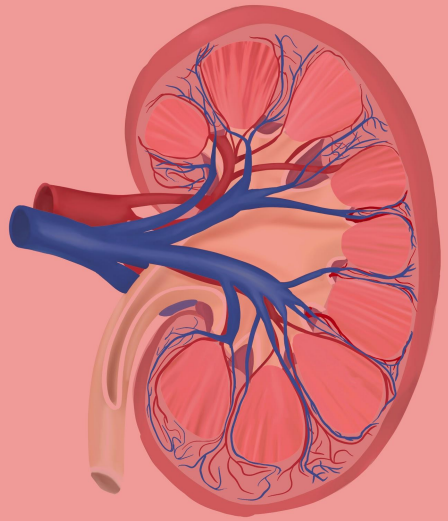
Renal function tests



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Main text

IMPORTANT

Extra Info

Drs Notes

Renal Block - Biochemistry Team

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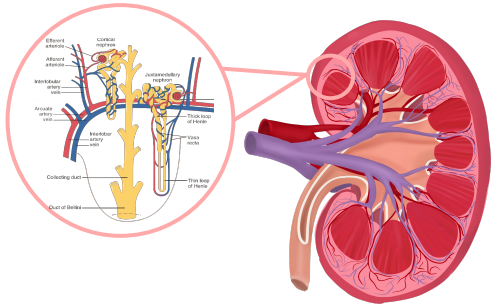
MED439

Objectives:

- Know the physiological functions of the kidney.
- Describe the structure and function of the nephron.
- To have an idea about some examples of renal diseases.
- Identify the biochemical kidney function tests with special emphasis on when to ask for the test, the indications and limitations of each kidney function tests.
- Interpret the kidney function tests properly.

Nephron

- The nephron is the functional unit of the kidney.
- Each kidney contains about 1,000,000 to 1,300,000 nephrons.
- The nephron is composed of **glomerulus** and **renal tubules**.
- The nephron performs its homeostatic function by ultra filtration at glomerulus and secretion and reabsorption at renal tubules.



★ Kidney functions

1 **Regulation of :**
- water and electrolyte balance controlled by aldosterone.
- acid base balance by excreting acids and by regulating the body fluid buffer stores.
- arterial blood pressure controlled by RAAS.

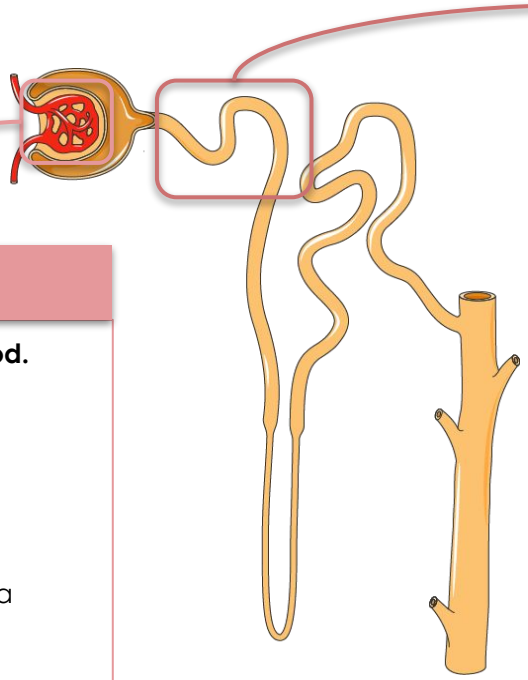
2 **Excretion of :**
- metabolic waste products metabolic wastes will be converted to intoxic (inactive) metabolites in the liver (catabolism reaction), then excreted in the urine by the kidney.
- foreign chemicals.

3 **Hormonal Function :**
- Secretion of erythropoietin which stimulates the production of RBCs by hematopoietic stem cells in the bone marrow.
- activation of vitamin D the kidneys convert vitamin D to its active form which is 1,25-dihydroxyvitamin D_3 (calcitriol) with the help of 1-α-hydroxylase enzyme .
- activation of angiotensinogen by renin a hormone system that regulates blood pressure, fluid and electrolyte balance, as well as systemic vascular resistance.

4 **Metabolic Function :**
- site for gluconeogenesis The kidneys synthesize glucose from amino acids and other non-carbohydrate precursors during prolonged fasting along with the liver, a process referred to as gluconeogenesis.

In male slides only

Each nephron is a complex apparatus comprised of **five basic parts**:



1-Glomerulus

Functions to filter incoming blood.

Factors facilitate filtration :

- high pressure in the glomerular capillaries, which is a result of their position between two arterioles.
- the semipermeable glomerular basement membrane, which has a molecular size cutoff value of approximately 66,000 Da.

The volume of blood filtered per minute is the glomerular filtration rate (GFR), and its determination is essential in evaluating renal function.

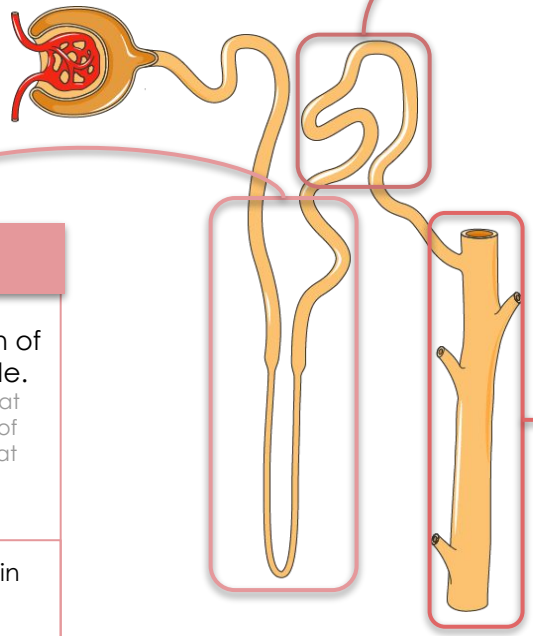
2-Proximal convoluted tubule

Returns the bulk of each valuable substance back to the blood circulation.

- **75%** of the water, sodium, and chloride.
- **100%** of the glucose (up to the renal threshold) the renal threshold of glucose is 180 mg/dl when it exceeds that in the tubule, the extra amount can't be reabsorbed and it will be excreted.
- almost all of the amino acids, vitamins, and proteins.
- varying amounts of urea , uric acid, and ions, such as magnesium , calcium and potassium.
  (With the exception of water and chloride ions "because they reabsorbed passively" , the process is active that is the tubular epithelial cells use energy to bind and transport the substances across the plasma membrane to the blood).
- Secretes products of kidney tubular cell metabolism, such as hydrogen ions, and drugs, such as penicillin.

In male slides only

Each nephron is a complex apparatus comprised of **five basic parts**:



3-Loop of Henle

Facilitates the reabsorption of water, sodium, and chloride.
(it reabsorbs 25% of the solutes that remained after the reabsorption of proximal tubules , don't forget that it's passively reabsorbed).

The osmolality in the medulla in this portion of the nephron increases steadily from the corticomedullary junction inward .

4-Distal convoluted tubule

- The filtrate entering this section of the nephron is close to its final composition (which is urine).
- Effects small adjustments to achieve electrolyte and acid-base homeostasis (under the hormonal control of both antidiuretic hormone "**ADH**" and aldosterone).

The distal convoluted tubule is much **shorter** than the proximal tubule, with two or three coils that connect to a collecting duct.

5-Collecting duct

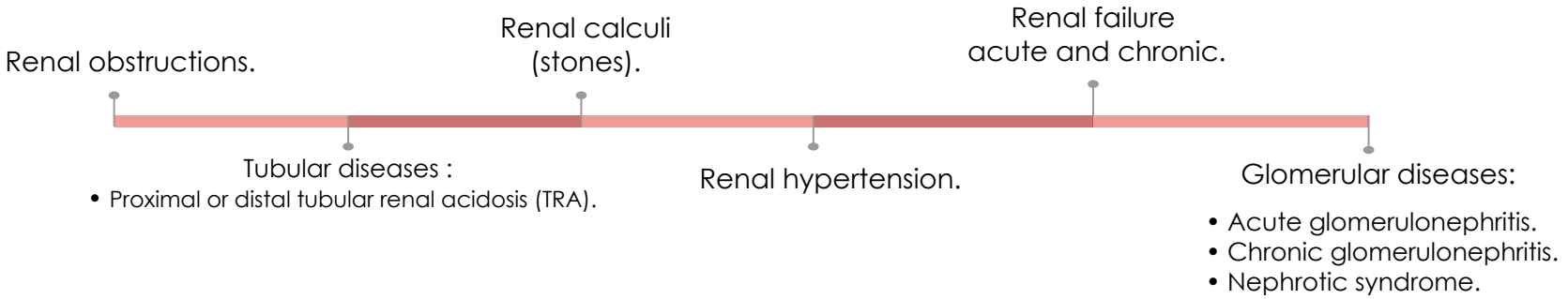
- The collecting ducts are the **final site** for either concentrating or diluting urine.
- The hormones ADH and aldosterone act on this segment of the nephron to control reabsorption of water and sodium.
- Chloride and urea are also reabsorbed here (partially) .
- The collecting ducts in the medulla are **highly permeable** to urea so urea will diffuse down its concentration gradient out of the tubule and into the medulla interstitium, increasing its osmolality.

Why test the renal functions ?

- Many diseases affect renal function.
- In some, several functions are affected.
- In others, there is selective impairment of glomerular function or one or more of tubular functions.
- Most types of renal diseases cause destruction of complete nephron.

Examples of renal diseases

In male slides only



Measurements of GFR

- The glomerular filtration rate (GFR) provides a useful index of the number of functioning glomeruli.
- It gives an estimation of the degree of renal impairment by disease.
- Accurate measurement of GFR by clearance tests requires determination of the concentration in **plasma** and **urine** of a substance that is:

01

Freely filtered at glomeruli.

02

Neither reabsorbed nor secreted by tubules.**

03

Better if the substance is present endogenously.

04

Its concentration in plasma needs to remains constant throughout the period of urine collection. So the doctor has to tell the patient to avoid anything that can increase the creatinine levels like heavy exercise

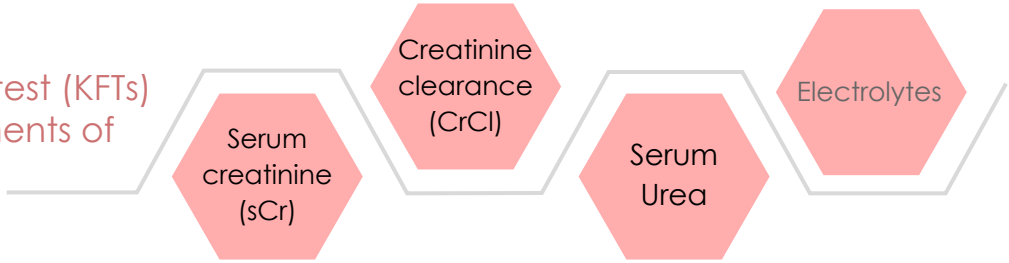
05

Easily measured.

Creatinine meets most of these criteria 4/5

**except No.2 because 10% of creatinine is secreted by the tubules

Routine kidney function test (KFTs) include the measurements of



From the most important to the least respectively
1- serum creatinine.
2- creatinine clearance.
3- serum urea.

★ Both serum Cr and Cr clearance are used as kidney function tests to :

- Confirm the diagnosis of renal disease.
- Follow up the treatment.
  e.g.check for the response of the treatment before and after dialysis
- Give an idea about the severity of the disease.
  (Does it affect Glomerular function or renal functions or both?)

★ Serum Cr is a better KFT than Cr clearance because:

- Serum creatinine is more accurate.
- Serum creatinine level is constant throughout adult life.

Serum creatinine (sCr)

(55-120 µmol/L in adult)

Serum creatinine shows how well the kidneys are working. high levels mean the kidneys are not working as they should. The amount of creatinine in the blood depends partly on the amount of muscle tissue the body have. Men generally have higher creatinine levels than women.

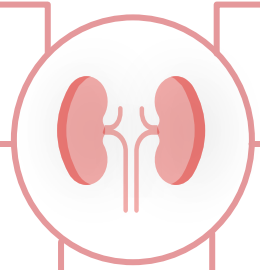
Plasma creatinine remains fairly constant throughout adult life.

Creatinine is the end product of creatine catabolism.

Creatinine is **not reabsorbed** by the renal tubules.

Plasma creatinine is an endogenous substance **not affected by diet**.
e.g. if we eat meat it won't rise the creatinine levels in our plasma, because it will be degraded and may be excreted in the feces. that's why sCr is a good marker because it's ENDOGENOUS

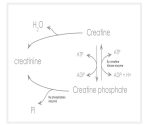
Note that the units and the values are **very important**



Creatinine in the plasma is filtered freely (passive)at the glomerulus and **secreted by renal tubules** (**10 %** of urinary creatinine).
Means the creatinine is freely filtered at the glomerulus but it's secreted by PCT about 10% so if they wanna calculate the GFR to be more accurate they will substrat 10% from it because they don't want the amount that being secreted by the tubules , they want the amount that being filtered at the glomerulus.

98% of the body creatine is present in the muscles where it functions as store of **high energy** in the form of creatine phosphate or creatine.

About 1-2 % of total muscle creatine or creatine phosphate pool is converted daily to creatinine through the spontaneous, non enzymatic loss of water or phosphate.
recall in MSK block the creatine will be converted to creatinine by losing H_2O and creatine phosphate will be converted to creatinine by removing phosphate group , or as we know the pathway reversible so the creatine phosphate can be converted to creatine and then will be converted to creatinine , this whole path doesn't need enzymes and this makes creatinine in kidney tests highly specific as there are no enzymes that can be detected.



Creatinine clearance (CrCl)

- Clearance is the volume of plasma cleared from the substance excreted in urine per minute.
- Creatinine clearance measures how well creatinine is removed from your blood by your kidneys. The test is on a sample of urine collected over 24 hours.
- ★ It could be calculated from the following equation:

You should know the **limitation** of this equation which is the the volume of urine because maybe there will be some mistakes during collecting the urine.

$$\textbf{Clearance (ml/min)} = \frac{U \times V}{P}$$

- U: Concentration of creatinine in **U**rine µmol/L
- V: **V**olume of urine ml/min. Urine is collected through 24h period then it's mathematically converted to amount(ml) per minute
- P: Concentration of creatinine in the serum (**P**lasma) µmol/L

In **children**
the GFR should be related to **surface area,** when this is done, results are similar to those found in young adults (110 ml/min).
Kidney function is proportional to kidney size, which is proportional to body surface area. In young adults, there's a normal **mean value** of the body surface which is 1.73 m^2, while it is **variable** in children "that's why we should relate the GFR to surface area in children".

in the **adults** between 20-40 year old **adults**.
Their **creatinine clearance** is usually about **110 ml/min .**
it's less in female due to low muscle mass

in **individuals over 8o years** of age and females
Their **creatinine clearance** falls slowly but progressively to about **70 ml/min.**

Serum creatinine (sCr)

Creatinine clearance (CrCl)

Serum Urea

Cockroft-gault formula for estimation of GFR

- As indicated in the previous slide , the creatinine clearance is measured by using a 24-hour urine collection, but this does introduce the potential for errors in terms of completion of the collection.
  The doctor will ask the patient to collect his/her urine during 24 hours and the doctor will calculate it by using the formula in the previous slide but this way is **not accurate** due to some mistakes during collecting the urine ,for instance maybe the patient will put some of the water on the urine sample .
- An alternative and convenient method is to employ various formulae devised to calculate creatinine clearance using parameters such as serum creatinine level, sex, age, and weight of the subject.because measurement of creatinine clearance was not that accurate they tried to use another way which is better than measuring the creatinine clearance but unfortunately this way also has some limitations .

★ **An example is the Cockcroft-Gault Formula:**

Where **K** is a constant that varies with sex:
1.23 for male & 1.04 for females.
The constant **K** is used as females have a relatively lower muscle mass.

$$GFR = \frac{K \times (140 - age) \times \text{Body weight}}{\text{Serum creatinine } (\mu mol/L)}$$

Serum creatinine is inversely proportional to GFR, so high serum creatinine levels mean that the GFR is low.

When we measure it in old machines it will be in **mg/dl** so we have to convert it to **µmol/L**
How to convert it ? By the conversation factor
The conversion factor is (**88.4**)
1 mg/dl = 88.4 µmol/l
e.g : 2 mg/dl x 88.4 µmol/L = 176.8 µmol/L
another e.g : 176.8 µmol/L ÷ 88.4 µmol/L = 2 mg/dl

- The formula above is good because we **excluded urine** and replace it with easier parameters.
- ★ It **should NOT** be used if : (the **limitations** for this formula)

Serum creatinine is changing rapidly . e.g. the muscle mass of bodybuilders are changing

Low muscle mass
e.g : muscle wasting

The diet is unusual
e.g: strict vegetarian.
lack of proteins will decrease the muscle mass.

Obesity.
As we see on the formula the body weight is **directly proportional** to the GFR so if the patient has high body weight the GFR will be high which will be **normal** for him but if the GFR in the normal range for a patient has a high body weight this will indicate that there's a problem in his renal function .

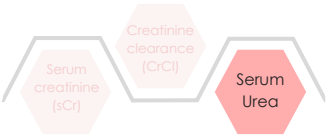
★ Creatinine clearance is only recommended in the following conditions :

Patients with early (minor) renal disease.

Assessment of possible kidney donors.

Detection of renal toxicity of some nephrotoxic drugs.
E.g roaccutane and chemotherapy

Normal adult reference values			Abnormal values
Urinary excretion of creatinine	0.5 - 2.0 g per 24 hours in a normal adult, varying according to muscular weight .		Exceeds 3.5 g per 24 hours .
Serum creatinine	55 – 120 µmol/L ★ **normal** serum creatinine does not necessarily indicate normal renal function as serum creatinine may not be elevated until GFR has fallen by as much as **50% .**		A **raised** serum creatinine is a good indicator of impaired renal function .
Creatinine clearance	**Males**	90 – 140 ml/min	Low creatinine clearance levels mean the patient have chronic kidney disease or serious kidney damage .
	Females	80 – 125 ml/min	



Serum urea
(2.5 - 6.6 mmol/L) in adults

- Serum urea measures the amount of urea in the blood. Urea is a waste product (non-toxic metabolite) made when the protein is broken down in the body so it's affected by diet.

Formation of urea **in the liver**.

Amino acids —Deamination→ Ammonia —Release of→ Urea

More details about urea cycle in GNT block

As a kidney function test, **serum urea is inferior to serum creatinine** because:

- Any condition of increased proteins catabolism (Cushing syndrome, diabetes mellitus, starvation, thyrotoxicosis) increases urea formation.
- High protein diet increases urea formation.
- 50 % or more of urea filtered at the glomerulus is passively reabsorbed by the renal tubules.
- **Dehydration can increase urea .**

Examples of other kidney functions tests (KFTs)

- Cystatin (C)
- Microalbumin
- β_2- Microalbumin (11,800 Da)
- Myoglobin (16,900 Da)

In male slides only
Dr : not important

Dr : **not important** but for you , you have know the types of electrolytes that you can see in the plasma

Normal values of internal chemical environment controlled by the kidneys :	
Sodium	135 to 145 mEq/L
Potassium	3.5 to 5.5 mEq/L
Chlorides	100 to 110 mEq/L
Bicarbonate	24 to 26 mEq/L
Calcium	8.6 to 10 mg/dl
Magnesium	1.6 to 2.4 mg/dl
Phosphorus	3.0 to 5.0 mg/dl
Uric acid	2.5 to 6.0 mg/dl
pH	7.4
Creatinine	0.8 to 1.4 mg/dl
BUN (Blood Urea Nitrogen)	15 to 20 mg/dl

Quiz

Q1: What is the best kidney function test (KFT) to estimate kidney function (KF) ?			
A) serum creatinine	B) urea	C) creatinine clearance	D) inulin
Q2: Which one is a limiting factor of the measurement of creatinine clearance ?			
A) urine volume	B) obesity	C) restrict Salts	D) the exercise
Q3: Which substance is used to diagnose early kidney disease ?			
A) serum creatinine	B) creatinine clearance	C) urea	D) none
Q4: What is the Normal value of serum creatinine ?			
A) 50 µmol/L	B) 55 µmol/L	C) 145 µmol/L	D)153 µmol/L
Q5: What is the site of urea formation ?			
A) stomach	B) kidney	C) liver	D) none
Q6: What is the the substance that remains constant throughout adult life ?			
A) inulin	B) urea	C) creatine	D) creatinine

SAQs :

Q1: what is the criteria of a substance that is used to determine GFR ?

Q2: why the serum urea is inferior to serum creatinine for KFT ?

Q3: what is the limitations of Cockcroft-Gault Formula for Estimation of GFR ?

★ **MCQs Answer key:**

1) A 2) A 3) B 4) B 5) C 6) D

★ **SAQs Answer key:**

1) Freely filtered , not reabsorbed , not secreted , it's plasma concentration remain constant at the duration of urine collection … etc.
2) High protein diet increases urea formation…. check **slide 13**
3) Serum creatinine is changing rapidly,obesity, low muscle mass, unusual diet

Girls team:

- Manal Altwaim
- Duaa Alhumoudi
- Norah Almasaad
- Rania Almutiri
- Alia Zawawi
- Noura Alshathri
- Renad Alhomaidi
- Fatimah Alhelal

Boys team:

- Omar Alsuliman
- Abdullaziz Alomar
- Hamad Almousa
- Abdullah Alanzan
- Abdullah Almazro
- Abdullaziz Alrabiah

You will never have this day again so make it COUNT

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