GFR

3 main processes involved in urine formation
Glomerular filtration
Tubular reabsorption
Tubular secretion

Glomerular filtration
First step in urine formation.
Ultrafiltrate of plasma .

Filtered fluid is modified in the tubules by reabsorption and secretion of substances.
Urinary excretion =
Filtration – reabsorption + secretion

Definition of GFR
It is the quantity of fluid that is filtered by **all** the nephrons in **both** the kidneys in **unit time**

Normal value
125 ml/mt or **180 L/day** or **7.5 L/hr**
Its magnitude correlates fairly well with surface area, but values in women are 10% lower than those in men even after correction for surface area.

Filtering membrane (explain)
Fenestrated endothelium (70 -90 nm)
The **basement membrane** of glomerular capillary.
The **processes of the podocytes** interdigitate to cover the basement membrane and are separated by apparent gaps called **filtration slits (25 nm).**
All the 3 layers express **negatively charged** proteins retarding the filtration of anionic proteins into Bowman's space.

Factors affecting GFR
GFR = K_f x P_{ef}
K_f: glomerular ultrafiltration coefficient
P_{ef}: net filtration pressure

K_f is the product of **Permeability** of glomerular capillaries & glomerular **surface area** available for filtration

1. Permeability of glomerular capillaries
- Size &
- Charge of the particle

Neutral substances with effective molecular diameters of less than 4 nm are freely filtered, and the filtration of neutral substances with diameters of more than 8 nm approaches zero. Between these values, filtration is <u>inversely proportional</u> to diameter.

Negative charges in filtering membrane **repel** negatively charged substances in blood. This probably explains why albumin, with an effective molecular diameter of approximately 7 nm is not freely filtered.

In a number of glomerular diseases, the negative charges on the filtration barrier are reduced / lost. As a result, the filtration of proteins is increased, and proteins appear in urine **(proteinuria).**

2. Size of capillary bed (surface area)

Contraction of **mesangial cells**→ ↓ the area available for filtration→ Decrease K_f and hence GFR.

Relaxation of mesangial cells facilitates GFR

Contraction of mesangial cells (↓ GFR
Endothelins
Angiotensin II
Norepinephrine
Vasopressin
PAF , PDGF
Tx A_2
PG F_2
LTC_4 & D_4
Histamine

Relaxation
ANP
Dopamine
PG E_2

The **net filtration pressure** represents the sum of the hydrostatic & colloid osmotic forces that either favour or oppose filtration across the glomerular capillaries.

$[(P_{GC} – P_T) – (\pi_{GC} – \pi_T)]$

P_{GC} is the mean hydrostatic pressure in the glomerular capillaries,
P_T the mean hydrostatic pressure in the tubule (Bowman's space),
π_{GC} the oncotic pressure of the plasma in the glomerular capillaries, and
π_T the oncotic pressure of the filtrate in the tubule (Bowman's space).

3.P_{GC}
High (45 mm Hg)
Constant along the capillary
Favours filtration

Systemic arterial pressure
Renal blood flow
Afferent arteriolar resistance
Efferent arteriolar resistance

GFR proportional to BP (outside the autoregulatory range)

Afferent arteriolar resistance

Afferent arteriolar constriction - ↓GFR

" " dilation - ↑ GFR

Efferent arteriolar resistance

Efferent arteriolar constriction - ↑ GFR

" " dilation - ↓ GFR

4.P_T

10mmHg

Opposes filtration

Obstruction of the urinary tract (eg: stones that lodge in the ureter)→ Exert back pressure→ **Increased** P_T→ **Decreases GFR**

5.**Oncotic pressure** in glomerular Capillary

Varies along length of capillary as large volume of fluid is filtered

At afferent end π_{GC} = 20mmHg

At efferent end π_{GC} = 35mmHg

Increased Glomerular Capillary Oncotic pressure opposes filtration (**Decreases** GFR)

- Dehydration→
- Hypoproteinemia →

6. Oncotic pressure in tubules

Under normal conditions, the concentration of protein in the glomerular filtrate is so low that the colloid osmotic pressure of the Bowman's capsule fluid is considered to be **zero**

Net FP = P_{GC} - P_T - $\prod_{GC}$

(mm Hg)

	Afferent end	Efferent end
P_{GC}	45	45
P_T	10	10
π_{GC}	20	35
P_{UF}	15	0

(Guyton

Net FP = 60 - 18 – 32 = 10 mm Hg)

Regulation of GFR

Autoregulation

- Myogenic theory
- Tubuloglomerular feedback

Neural

– Sympathetic stimulation

Hormonal

VC – Endothelin, NE , Ang II

VD - ANP , PG , NO , BK

Measurement of GFR

Inulin clearance

Endogenous creatinine clearance

Clearance

Volume of plasma that is completely cleared off a substance in unit time

$$\text{Clearance} = \frac{U\,V}{P}$$

Criteria of substance used to measure GFR

<u>Freely filtered</u>

<u>Not reabsorbed neither secreted</u>

Non-toxic

Not metabolized in the body

Not stored in kidneys

Easy to measure in plasma & urine

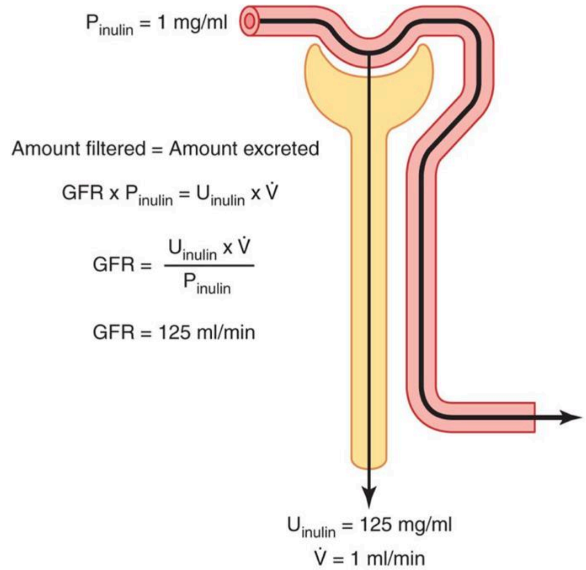
Shouldn’t alter GFR

Inulin clearance

iv loading dose of inulin

followed by a sustaining infusion.

After equilibration with body fluids, urine & plasma samples are obtained and the clearance calculated:



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$$C_{IN} = \frac{UV}{P} = \frac{35 \times 0.9}{0.25} = 126 \text{ ml/mt}$$

Clearance of creatinine (C_{Cr}) can also be used to determine the GFR. The values agree quite well with the GFR values measured with inulin because, although the value for $U_{Cr}V$ is high as a result of tubular secretion, the value for P_{Cr} is also high as a result of nonspecific chromogens, and the errors thus tend to cancel.

Advantages & disadvantages

Creatinine is an endogenous product, so need not be administered

Endogenous creatinine clearance is easy to measure and is a worthwhile index of renal function, but cannot rely on this method when precise measurement of GFR is needed .

Filtration fraction

The fraction of renal plasma flow that is filtered

$$= \frac{GFR}{RPF} = 0.16 - 0.2$$

RENAL CLEARANCE

Definition

Volume of plasma that is completely cleared off a substance in unit time

The equation UV/P can be used to measure clearance of any substance that is present in plasma and excreted by kidneys.

Significance

Renal clearance provides a useful way of quantifying the excretory function of the kidneys.

A comparison of clearance of a substance (**C_x**) with clearance of inulin (**C_{in}**) provides information about the renal mechanisms used to remove the substance from plasma

If $C_x = {}_{in}$ (or $C_x/C_{in} = 1$)

Freely filtered

Neither reabsorbed

Nor secreted

If $C_x < C_{in}$ ($C_x/C_{in} < 1$)

Freely filtered

Partially reabsorbed

Zero clearance

Completely reabsorbed

eg : Glucose

If $C_x > C_{in}$ ($C_x/C_{in} > 1$)

Filtered

Secreted

Not reabsorbed

eg : Creatinine, PAH

Applications

As a measure of GFR

- Inulin clearance
- Endogenous creatinine clearance

As a measure of RPF & RBF

- PAH clearance

As a measure of excretion of waste prod

- Urea clearance

As a measure of osmotic & free water clearance

Urea clearance

Measures the rate of excretion of waste products

Standard urea clearance

(when urine flow < 2ml / mt)

= **54 ml/mt**

Maximal urea clearance

(when urine flow >2ml/mt)

= **75 ml/mt**

Urea clearance below 50 % normal indicates renal damage

Clearance of osmoles

C_{osm} is the amount of water necessary to excrete the osmotic load in a urine that is isotonic with plasma.

Free water clearance

In order to quantitate the gain or loss of water by excretion of a concentrated or dilute urine, the "free water clearance" (C_{H2O}) is sometimes calculated.

This is the difference between the urine volume and the clearance of osmoles (C_{osm}):

where V is the urine flow ra JBte and U_{osm} and P_{osm} the urine and plasma osmolality, respectively

$\mathbf{C_{H2O} = V – C_{osm}}$

With iso-osmotic urine, $C_{H2O} = 0$

With hypotonic urine, C_{H2O} is positive

With hypertonic urine, C_{H2O} is negative