Sheet No.3

Physiology

Genitourinary system

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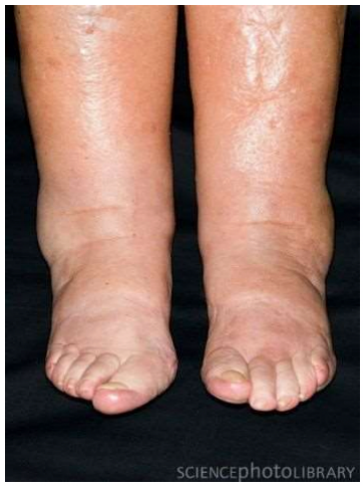
Wish you a happy ride :)

Clinical Applications of Glomerular Filtration Rate

Edema



- Some kidney diseases [Or the likes of HTN and DM] result in damage to the glomerular capillaries, increasing their permeability to large proteins. This leads to an increase in Bowman's capsule colloid pressure, drawing more water from plasma to the capsule and increasing the filtered fluid.
- Also, Proteins are lost in the urine, causing a deficiency in blood colloid pressure, which worsens the situation ➔ decreases blood volume, and increases interstitial fluids, ultimately causing edema.
- It typically occurs in the lower extremities and abdomen.

Regulation of Glomerular Filtration

We will start with the silly "why", why do we need to regulate GFR?

- Maintaining a constant GFR is crucial for homeostasis of body fluids and efficient kidney function.
- High GFR: the kidney is unable to reabsorb necessary substances, leading to loss in urine.
- Low GFR: waste products are not efficiently filtered and remain in the body.

Now that we understand the first silly "Why", new question comes to mind, what are the determinants of GFR? The purpose of doing this is to find physiological regulators of GFR. Not all of them will be.

1. **K_f and Net Filtration Rate**

It isn't the net filtration rate we are interested in but one of its factors. Starling forces? Nope. Then what? You know an increase in GFR leads to an increase in net filtration rate. And thus, there must be a proportion constant to make the equation works. This constant is named **Glomerular capillary filtration coefficient** [Kf]. "$GFR = Net\ filration\ pressure \times K_f$"

- As the name implies, a constant, constituted of factors that can't be changed under physiological conditions. [More specifically can't change significantly not that it can't be changed at all. It's normally not highly variable.]
- The factors are K_f = hydraulic conducitivty x surface area" Here we are talking about the property of kidney's tissue in filtration itself, any change in its structure would directly affect function and changes K_f.

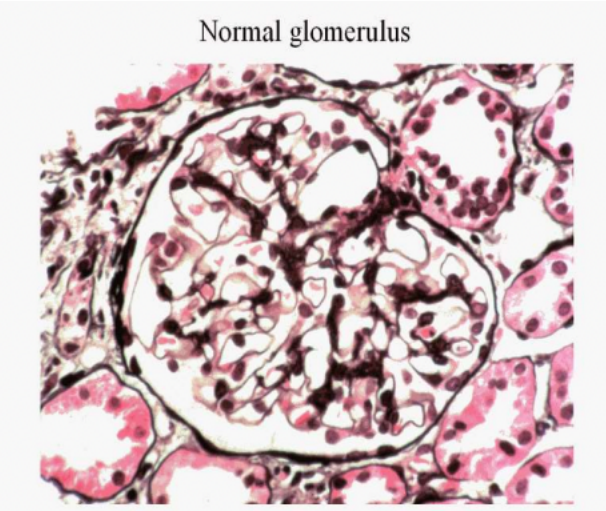
Normal values:

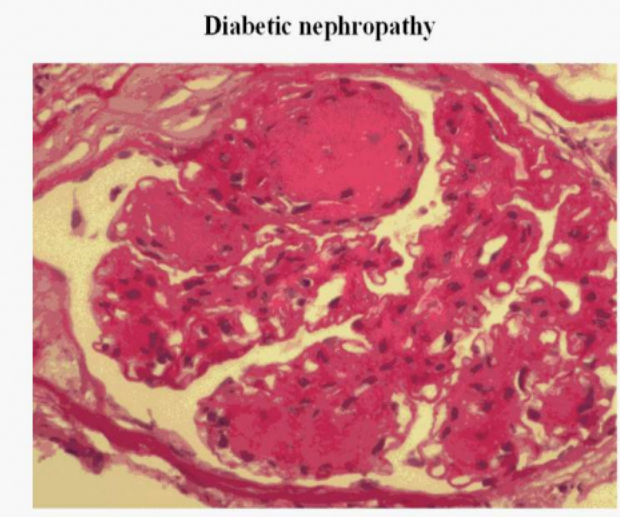
- GFR = 125 ml/min, Net filtration pressure = 10 mmHg, Kf = 12.5 ml/min per mmHg or 4.2 ml/min per mmHg/ 100gm.

- You can expect the normal tissue's filtration coefficient to be significantly smaller as filtration isn't its main function. We found it to be 0.01! A staggering 400x smaller than the kidneys!

Diseases that affect Kf and GFR

- **Chronic Hypertension**: [Doctor said] High BP will eventually damage glomeruli ➔ The number of functioning Glomeruli decreases ➔ Decreased surface area ➔ Lowered Kf.
- **Diabetes Mellitus**: [Doctor said] Thickening of basement membrane ➔ Fibrosis, altered extracellular matrix, and eventual lowered Kf.





- **Glomerulonephritis**: Inflammation of glomeruli ➔ damage to endothelial cells and Podocytes ➔ increased permeability and proteinuria ➔ lowered Kf. [These chains are adding not from doctor.]
- **Obesity**: Increased adipose tissue ➔ increased plasma volume and blood pressure ➔ glomerular hyper filtration and hypertrophy ➔ lowered Kf. [These chains are adding not from doctor.]

Then, can K_f be the regulator of GFR?

- While yes, K_f directly affects GFR. Higher Kf ➔ Higher GFR and vice versa. But it can't be used for regulation without causing any pathology.

2. GFR Regulation and Bowman's Capsule Hydrostatic Pressure (P_B)

It normally changes as a function of GFR and not a physiologic regulator, the higher the GFR the higher P_B but not the other way around. If P_B due to whatever cause increases, then it would work in opposition to the hydrostatic pressure in the glomeruli ➔ Decreasing GFR like what will see in cases of pathology.

[Doctor said: The primary function of Bowman's capsule is to serve as a cup for filtration to occur, rather than actively regulating GFR. And P_B is just very small ~10 mmHg for any major regulation to be possible under physiological conditions.]

Disease-related alterations in Bowman's capsule hydrostatic pressure

- Certain conditions, such as stones in the tubule or tubular necrosis, can impair the urinary flow and causes urinary obstruction ➔ Build up in the Bowman's space ➔ Increased hydrostatic pressure opposing filtration.

Despite these disease-related alterations, the body can't intentionally change the hydrostatic pressure in Bowman's capsule to regulate GFR. The tools of a direct regulation are simply not there.

What about oncotic pressure? It must have an effect in a way or another, right?

3. Glomerular Capillary Oncotic Pressure and its Effects on GFR

Factors Influencing Glomerular Capillary Oncotic Pressure (Π_G)

- Arterial Plasma Oncotic Pressure (π_A)
  $\uparrow \pi_A \longrightarrow \uparrow \pi_G$
- Filtration Fraction (FF)
  $\uparrow FF \longrightarrow \uparrow \pi_G$

FF = GFR / Renal plasma flow
= 125 / 650 ~ 0.2 (or 20%)

Filtration Fraction (FF) and Oncotic Pressure Relationship

- Filtration Fraction $= \frac{GFR}{Renal\ Plasma\ FLow}$ from the equation
- When FF increases, oncotic pressure increases due to more fluid being extracted relative to proteins, causing protein accumulation (relative) and increased oncotic pressure.

Can oncotic pressure affect GFR?

- Yes, just walk in the opposite direction, when there is higher oncotic pressure, the net filtration pressure decreases, leading to a decrease in GFR.

Determinants of oncotic pressure in glomeruli

- Plasma proteins: Arterial plasma proteins determine arterial oncotic pressure (high protein levels lead to high oncotic pressure, and vice versa).
- Nutrients or factors affecting protein synthesis can also influence oncotic pressure.

Relationship between Glomerular osmotic pressure/Distance along the capillary/FF

- Here is a **graph** describing the relation of the Glomerular oncotic pressure (Y-Axis) and distance along the glomerular capillary from afferent to efferent (X-Axis)
- Reaching the efferent end an increase in oncotic pressure is observed regardless of any FF value. This is due to fluid extraction, like we said.
- An upward shift (Increase in FF) correlates positively with oncotic pressure and vice versa.

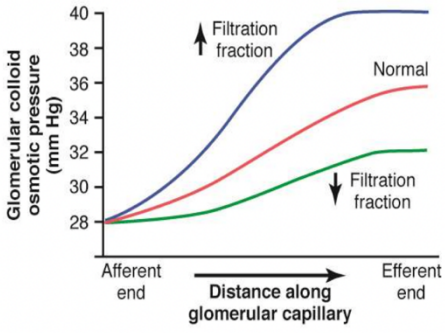
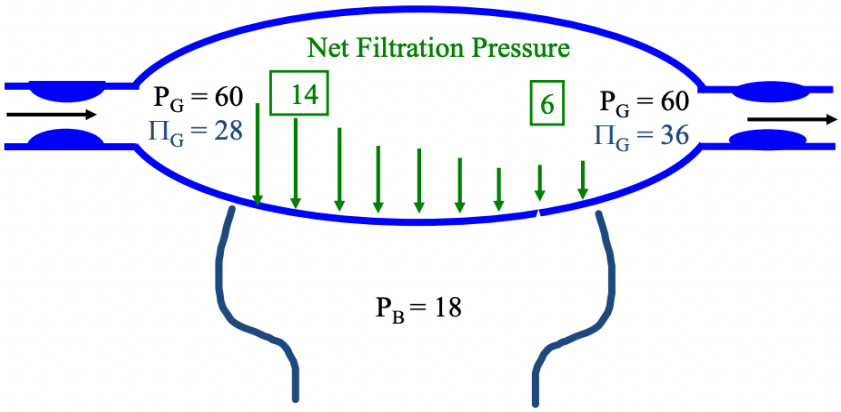


Figure 26-14

The problem still stands, how would we control the oncotic pressure??? We can't just tell the liver to make up different proportions of proteins in different times to magically accommodate for the kidney's needs. It isn't practical nor possible at all.

Then what's left is

4. **Glomerular hydrostatic pressure (P_G)**



- **Here in this simplified schematic. You notice** an increase of oncotic pressure as the renal blood flow reaches the efferent end but, the glomerular hydrostatic pressure remains **unchanged**. This would lead to a disparity in the Net filtration pressure between the 2 ends. The afferent end would have higher net filtration pressure and the efferent end would have lower net filtration pressure.

But why does the hydrostatic pressure of glomerulus remain unchanged? This has to do with a unique property of the glomerulus.

- Typically, capillaries will have an artery on one side and a vein on the other side. Glomerular capillaries have an afferent arteriole on one side, and an efferent arteriole on the other side. Point is there is 2 arterioles of low compliance on both ends that can maintain constant pressure along the entire capillary. If a vein was on the other hand? It will just expand in response to pressure from the afferent end and the kidney's function would be impaired.
- The significance of this is that these knobs/arterioles can be controlled in on/off manner in which glomerular hydrostatic pressure modulation is achieved ➔ Ultimately, GFR modulation is achieved.

Factors that influence P_G:

- Mean Arterial Pressure
- Afferent arteriolar resistance
- Efferent arteriolar resistance

Adjusting the size of the opening can affect systemic pressure:

- Wider opening results in lower pressure.
- Narrower opening leads to a build-up of pressure.
- This with the bit of "Low complaint arterioles" make the glomerular capillaries like balloons, the more blood infused the higher pressure is achieved, isn't it?

Not quite. There must be a sort of regulation that would happen and I'm not talking about the systemic regulation, no. What I'm saying is there must be an instantaneous process controlling glomerular hydrostatic pressure through modulating GFR & Renal Blood Flow. An "Auto-regulation" of sort.
This is exactly what experiments had demonstrated!

Autoregulation of renal blood flow and GFR but not urine flow

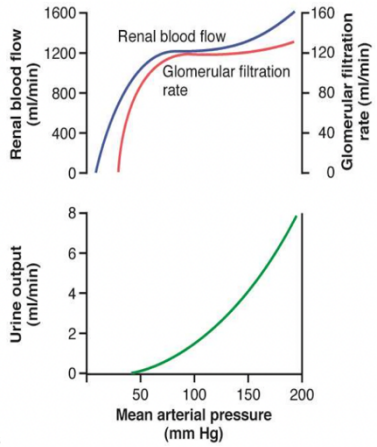
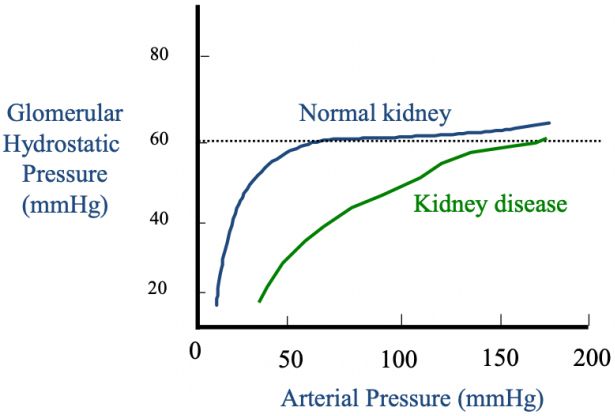


Figure 26-16



- It's found that Glomerular hydrostatic pressure remains constant within a range of 60-150 mmHg of Mean Arterial Pressure (MAP)!
- Also, they demonstrated that Renal blood flow and GFR are subjected to autoregulation. [Stays in plateau]
- While urinary output isn't subjected to autoregulation. Point is ➔ Not all kidney's functions are subjected to autoregulation

[Question the doctor brought up at the end of the lecture]
Q: Wouldn't increasing the GFR ➔ Lowers water and salts concentration ➔ Relieve HTN? Yes!
Except Increasing GFR to eliminate excess fluid during hypertension can have negative consequences:

- Damage to delicate capillary structures.
- Loss of important nutrients.

Instead, the body adjusts reabsorption of water and salt to relieve hypertension. Evidently enough, during hypertension, urinary output increases, leading to diuresis. (Reabsorption mechanisms will be discussed later.)

[You can read this slide on your own. It isn't included in the exam.]

Thank you!

Microalbuminuria

- Definition: urine excretion of > 30 but < 150 mg albumin per day
- Causes: early diabetes, hypertension, glomerular hyperfiltration

Prognostic Value: diabetic patients with microalbuminuria are 10-20 fold more likely to develop persistent proteinuria