The glomerular filtration rate (GFR):

Objectives:
1. Describe the theories of regulation of Glomerular filtration (GFR).
2. Find the errors in clinical methods of assessment of renal function and measurement of GFR.
3. Simplified the mode of movement of different molecules through the filtration membrane.
4. Describe the mechanisms of glucose reabsorption and define the terms transport maximum and renal plasma threshold.

![Diagram of Regulation of Glomerular Filtration](image-url)
GFR
is the volume of filtrate produced by both kidneys per minute. The GFR averages 115 ml per minute in women and 125 ml per minute in men. This is equivalent to 7.5 L per hour or 180 L per day (about 45 gallons)! Since the total blood volume averages about 5.5 L, this means that the total blood volume is filtered into the urinary tubules every 40 minutes. Most of the filtered water must obviously be returned immediately to the vascular system, or a person would literally urinate to death within minutes.

Regulation of Glomerular Filtration Rate
Vasoconstriction or dilation of afferent arterioles affects the rate of blood flow to the glomerulus, and thus affects the glomerular filtration rate. Changes in the diameter of the afferent arterioles result from both extrinsic regulatory mechanisms (produced by sympathetic nerve innervation), and intrinsic regulatory mechanisms (those within the kidneys, also termed renal autoregulation). These mechanisms are needed to ensure that the GFR will be high enough to allow the kidneys to eliminate wastes and regulate blood pressure, but not so high as to cause excessive water loss.

Sympathetic Nerve Effects
An increase in sympathetic nerve activity, as occurs during the fight-or-flight reaction and exercise, stimulates constriction of afferent arterioles. This helps to preserve blood volume and to divert blood to the muscles and heart. A similar effect occurs during cardiovascular shock, when sympathetic nerve activity stimulates vasoconstriction. The decreased GFR and the resulting decreased rate of urine formation help to compensate for the rapid drop of blood pressure under these circumstances.

Hormonal and Autacoid Control of Renal Circulation:
There are several hormones and autacoids that can influence GFR and renal blood flow. Some of them increase the GFR like Endothelial-derived nitric oxide and Prostaglandins and other decrease the GFR like Endothelin.

Renal Autoregulation
When the direct effect of sympathetic stimulation is experimentally removed, the effect of systemic blood pressure on GFR can be observed. Under these conditions, surprisingly, the GFR remains relatively constant despite changes in mean arterial pressure within a range of 70 to 180 mmHg (normal mean arterial pressure is 100 mmHg). The ability of the kidneys to maintain a relatively constant GFR in the face of fluctuating blood pressures is called renal autoregulation.

Changes in blood supply and the blood pressure (80 to 180) affects the GFR only small degree. The mechanisms are:

1. **Tubuloglomerular Feedback in Autoregulation of GFR**

   Low GFR cause a low flow rate at the juxta-glomerular apparatus (J-G) leading to overabsorption of Na and Cl in the ascending loop, so low ion concentration at J-G cells lead to:
   
   a. Dilation of the afferent arteriole.
   b. Release of rinin from J-G leading to the formation of angiotensin 1 and 2 causing efferent arteriolar constriction.

2. **Myogenic Autoregulation of Renal Blood Flow and GFR**
The ability of individual blood vessels to resist stretching during increased arterial pressure, a phenomenon referred to as the myogenic mechanism. Blood vessels respond to increased wall tension or wall stretch by contraction of the vascular smooth muscle. This helps to prevent excessive increases in renal blood flow and GFR when arterial pressure increases.

3. Other Factors

A high protein intake is known to increase both renal blood flow and GFR 20 to 30 per cent within 1 or 2 hours. The explanation is that the high-protein meal increases the release of amino acids into the blood, which are reabsorbed in the proximal tubule. Because amino acids and sodium are reabsorbed together by the proximal tubules, increased amino acid reabsorption also stimulates sodium reabsorption in the proximal tubules. This decreases sodium delivery to the macula densa, which elicits a tubuloglomerular feedback–mediated decrease in resistance of the afferent arterioles. This raises renal blood flow and GFR. This increased GFR allows sodium excretion to be maintained at a nearly normal level while increasing the excretion of the waste products of protein metabolism, such as urea.

A similar mechanism may also explain the marked increases in renal blood flow and GFR that occur with large increases in blood glucose levels in uncontrolled diabetes mellitus. Because glucose, like some of the amino acids, is also reabsorbed along with sodium in the proximal tubule, increased glucose delivery to the tubules causes them to reabsorb excess sodium along with glucose. This, in turn, decreases delivery of sodium chloride to the macula densa, activating a tubuloglomerular feedback–mediated dilation of the afferent arterioles and subsequent increases in renal blood flow and GFR.

**Inulin**, a polysaccharide which is not produced in the body, is found in the roots of certain plants and must be administered intravenously to a patient to measure GFR. It is freely filtered, no absorption or secretion and not metabolized and non-toxic but its use is for research purposes only. The rate of inulin clearance is equal to the GFR which is about 125ml/min.
Substance is | example | Renal clearance rate
--- | --- | ---
Not filtered | proteins | zero
Filtered not reabsorbed or secreted | inulin | Equal to GFR
Filtered but partially reabsorbed | Urea | Less than GFR
Filtered but completely reabsorbed | Glucose | Zero
Filtered, reabsorbed, and secreted | $K^+$ | Variable

Other substances used to measure GFR but less accurate like plasma creatinine which is mildly secreted along the proximal tubule. Creatinine is a by-product of muscle metabolism and is cleared from the body fluids almost entirely by glomerular filtration. Therefore, the clearance of creatinine can also be used to assess GFR. Because measurement of creatinine clearance does not require intravenous infusion into the patient, this method is much more widely.

**Tubular load:**

Each substance is absorbed according to transport system, so once the transport system reaches a maximum, the substance will appear in urine (not re-absorbed). The renal plasma threshold is the minimum plasma concentration of a substance that results in the excretion of that substance in
the urine. An important example is the urine glucose. In normal people; urine glucose is zero because plasma glucose concentrations normally remain below this threshold value. The renal plasma threshold for glucose is 180 to 200 mg per 100 ml. This means that at plasma glucose above 200mg/min glucose will start to appear in urine (a condition called glycosuria) and this is seen in uncontrolled diabetes mellitus.

Hyperglycemia (increased plasma glucose level) is caused by the inadequate secretion or action of insulin. When this hyperglycemia results in glycosuria, the disease is called diabetes mellitus. A person with uncontrolled diabetes mellitus also excretes a large volume of urine because the excreted glucose carries water with it as a result of the osmotic pressure it generates in the tubules. This condition should not be confused with diabetes insipidus, in which a large volume of dilute urine is excreted as a result of inadequate ADH secretion.

The tubular maximum (Tm) is the maximum capacity of the tubule to excrete a substance. The Tm for glucose is 320 mg/min. this number represents the maximum capacity of the tubules to excrete glucose and any increase of tubular glucose above this number no increase will appear in glucose excretion. This means that if the plasma glucose is 400mg/ml or even higher the renal glucose will stop at 320.