**NNANNA NANCY**

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MBBS

**Assignment Title:** Renal Physiology for MBBS student  
**Course Title:** Renal Physiology Body Fluid and Temperature Regulation  
**Course Code:** PHS 303

1. Discuss the role of kidney in homeostasis.

Kidney plays an important role in glucose homeostasis, both in the post-absorptive and postprandial period. Kidney produces glucose by gluconeogenesis in the renal cortex and uses glucose for covering energy needs of the medulla. Kidney participates also to the reabsorption of filtered glucose in order the terminal urine was devoided of glucose, as long as blood glucose did not exceed 180mg/dL. Reabsorption of glucose is mediated by sodium-glucose cotransporters (SGLT1 et SGLT2) expressed in S1 and S3 segments of proximal tubule. SGLT2 is the main sodium-glucose cotransporter responsible for 90% of glucose reabsorption. In type 2 diabetics, renal gluconeogenesis and glucose utilisation are increased by 30%. Surprisingly, renal glucose reabsorption is increased, participating to worsening of hyperglycemia. This results from the increase in the renal threshhold of glucose reabsorption (220mg/dL) and from an overexpression of SGLT2 in response to hyperglycemia and of cytokine secretion. The administration of SGLT2 inhibitors to type 2 diabetic patients induced a decreased in the renal threshhold of glucose reabsorption (80mg/dL) and strongly reduced kidney glucose reabsorption. The inhibitors of SGLT2 are the only antidiabetic molecules able to correct the excessive renal glucose reabsorption in type 2 diabetics and thus to contribute, by an original mechanism, to the lowering of blood glucose level.

**Glucose** reabsorption. Apart from the important **role** in gluconeogenesis and the **role of renal** cortex in **glucose** uptake, the **kidneys** contribute to **glucose homeostasis** by filtering and reabsorbing **glucose**.

kidneys’ contributions to maintaining glucose homeostasis are significant and include such functions as release of glucose into the circulation via gluconeogenesis, uptake of glucose from the circulation to satisfy their energy needs, and reabsorption of glucose at the level of the proximal tubule. Renal release of glucose into the circulation is the result of glycogenolysis and gluconeogenesis, respectively involving the breaking down and formation of glucose-6-phosphate from precursors (eg, lactate, glycerol, amino acids). With regard to renal reabsorption of glucose, the kidneys normally retrieve as much glucose as possible, rendering the urine virtually glucose free. The glomeruli filter from plasma approximately 180 grams of D-glucose per day, all of which is reabsorbed through glucose transporter proteins that are present in cell membranes within the proximal tubules. If the capacity of these transporters is exceeded, glucose appears in the urine. The process of renal glucose reabsorption is mediated by active (sodium-coupled glucose cotransporters) and passive (glucose transporters) transporters. In hyperglycemia, the kidneys may play an exacerbating role by reabsorbing excess glucose, ultimately contributing to chronic hyperglycemia, which in turn contributes to chronic glycemic burden and the risk of microvascular consequences.

Maintenance of glucose homeostasis involves several complementary physiologic processes, including glucose absorption (in the gastrointestinal tract), glycogenolysis (in the liver), glucose reabsorption (in the kidneys), gluconeogenesis (in the liver and kidneys), and glucose excretion (in the kidneys).

1. Discuss the process of micturition ?

**What is Micturition?**

Micturition is a process where urine is expelled from the body. Animals and humans have a specialized system of organs known as the excretory system to eliminate the waste products from the body. In other words, the process of expelling urine from the body is called micturition. It is brought about by reflex contraction of a special muscle called the detrusor muscle after voluntary relaxation of the sphincter muscle.

The human excretory system consists of a pair of kidneys and ureters, a urinary bladder, and a urethra. The kidneys play a major role in the process of urine formation and its excretion. The urine formed is stored in the urinary bladder.

Micturition is also known as voiding phase of bladder control and lasts for a short time. As the bladder becomes full, the stretch receptors increase their firing rate. This increase the urge to urinate and causes micturition reflex. It sometimes even causes involuntary urination.

**Human Urine**

On average, a normal adult excretes 1 to 1.5 L of urine per day. Normal human urine is a light yellow fluid majorly consisting of 95 per cent water and 5 per cent solid wastes. It is slightly acidic with a pH close to 6.

Many endocrinal disorders can be diagnosed through urine analysis. For example, if a patient has diabetes, the presence of glucose and ketone bodies in the urine can help detect the disease. Thus it is a major clinical diagnostic element.

**Micturition Process**

Micturition process consists of two phases:

* Storage phase
* Voiding phase

**Storage Phase**

The urinary bladder is a balloon-shaped, hollow, muscular, organ that acts as the storage organ for urine. The urinary bladder in a healthy urinary system can store up to 16 ounces of urine for 2 to 5 hours easily. The circular sphincter muscles prevent leakage of urine. They close tightly around the opening of the bladder into the tube (urethra) that allows the passage of urine outside the body.

**Voiding Phase**

When the bladder is filled with urine, the nerves in it are triggered, which in turn stimulates the need to urinate. The brain signals urinary bladder to contract. The receptors of the urinary bladder send a signal to the central nervous system , in response to which the nervous system sends a signal that incites the contraction of the urinary bladder.  Through the urinary opening at the urethra, the urine is eliminated, and the process is called micturition. The neural mechanism involved is called the micturition reflex.

**Problems Associated With Micturition**

There are several factors which affect the process of micturition. Some of these can be due to physical trauma or disease; others are psychological in nature.

**Following are a few disorders that affect micturition:**

* Detrusor Instability – This is a condition where the detrusor muscle contracts without any apparent reason. This muscle is responsible for contracting the bladder and help with the micturition process. As a result, detrusor instability results in urinary incontinence.
* Urinary Retention – This condition is characterized by the inability to empty the bladder completely. The onset may be gradual or sudden. The causes can range from a blockage in the urethra, nerve problems and weak bladder muscles.
* Spinal Cord Trauma – Injuries to t;he spinal cord, specifically the tenth thoracic vertebra (T10) can cause the bladder to be overactive or cause urinary incontinence.

**Management of Micturition Disorders**

* The nerve pathway to the urinary tract should be intact.
* The bladder capacity should be normal.
* Normal muscle tone should be observed in the sphincters, detrusors, and pelvic floor muscles.
* There should be no obstruction to the urine flow in any region of the urinary tract.
* The environmental and psychological factors that inhibit micturition should be absent.
* The coordinated activity of sympathetic, parasympathetic, and somatic nerves help in normal micturition.

**Key Points on Micturition**

* Urine is collected in the nephrons and flows into the ureters.
* The smooth muscle contractions of ureters facilitate micturition.
* The urine is stored in a hollow, muscular, elastic organ known as the urinary bladder.
* The urine flows out of the body through the urethra.

1. Discuss the juxtaglomerular apparatus.

**Juxtaglomerular Apparatus**

The juxtaglomerular apparatus is the location of renin-secreting cells and the macula densa and lies at the junction between the loop of Henle and the distal nephron at which the tubule comes in close proximity to the afferent arteriole.

The juxtaglomerular cells (JG cells, or granular cells) are cells in the **kidney** that synthesize, store, and secrete the enzyme renin. They are specialized smooth muscle cells mainly in the walls of the afferent arterioles (and some in the efferent arterioles) that deliver blood to the glomerulus.

The juxtaglomerular apparatus is a specialized structure formed by the distal convoluted tubule and the glomerular afferent arteriole. It is located near the vascular pole of the glomerulus and its main function is to regulate blood pressure and the filtration rate of the glomerulus. The macula densa is a collection of specialized epithelial cells in the distal convoluted tubule that detect sodium concentration of the fluid in the tubule. In response to elevated sodium, the macula densa cells trigger contraction of the afferent arteriole, reducing flow of blood to the glomerulus and the glomerular filtration rate. The juxtaglomerular cells, derived from smooth muscle cells, of the afferent arteriole secrete renin when blood pressure in the arteriole falls. Renin increases blood pressure via the renin-angiotensin-aldosterone system. Lacis cells, also called extraglomerular mesangial cells, are flat and elongated cells located near the macula densa.

1. **Discuss the role of kidney in regulation of blood pressure.**

The **kidneys** play a central **role** in the **regulation of arterial blood pressure**. A large body of experimental and physiological evidence indicates that **renal control** of extracellular volume and **renal** perfusion **pressure** are closely involved in maintaining the **arterial** circulation and **blood pressure**.

**The kidneys and their influence on blood pressure**

The kidneys play a central role in the regulation of arterial blood pressure. A large body of experimental and physiological evidence indicates that renal control of extracellular volume and renal perfusion pressure are closely involved in maintaining the arterial circulation and blood pressure. Renal artery perfusion pressure directly regulates sodium excretion; a process known as pressure natriuresis, and influences the activity of various vasoactive systems such as the renin–angiotensin–aldosterone (RAS) system . Along with vessel morphology, blood viscosity is one of the key factors influencing resistance and hence blood pressure. A key modulator of blood viscosity is the renin-angiotensin system (RAS) or the renin-angiotensin-aldosterone system (RAAS), a hormone system that regulates blood pressure and water balance.

**The blood pressure in the body depends upon:**

• The force by which the heart pumps out blood from the ventricles of the heart - and this is dependent on how much the heart muscle gets stretched by the inflowing blood into the ventricles.

• The degree to which the arteries and arterioles constrict-- increases the resistance to blood flow, thus requiring a higher blood pressure.

• The volume of blood circulating round the body; if the volume is high, the ventricles get more filled, and the heart muscle gets more stretched.

**The kidney influences blood pressure by:**

• Causing the arteries and veins to constrict

• Increasing the circulating blood volume

Specialized cells called macula densa are located in a portion of the distal tubule located near and in the wall of the afferent arteriole. These cells sense the Na in the filtrate, while the arterial cells (juxtaglomerular cells) sense the blood pressure. When the blood pressure drops, the amount of filtered Na also drops. The arterial cells sense the drop in blood pressure, and the decrease in Na concentration is relayed to them by the macula densa cells. The juxtaglomerular cells then release an enzyme called renin.

Renin converts angiotensinogen (a peptide, or amino acid derivative) into angiotensin-1. Angiotensin-1 is thereafter converted to angiotensin-2 by an angiotensin-converting enzyme (ACE), found in the lungs. Angiotensin-2 causes blood vessels to contract -- the increased blood vessel constrictions elevate the blood pressure. When the volume of blood is low, arterial cells in the kidneys secrete renin directly into circulation. Plasma renin then carries out the conversion of angiotensinogen released by the liver to angiotensin-1. Angiotensin-1 is subsequently converted to angiotensin-2 by the enzyme angiotensin converting enzyme found in the lungs. Angiotensin-2m a potent vasoactive peptide causes blood vessels to constrict, resulting in increased blood pressure. Angiotensin-2 also stimulates the secretion of the hormone aldosterone from the adrenal cortex .

Aldosterone causes the tubules of the kidneys to increase the reabsorption of sodium and water into the blood. This increases the volume of fluid in the body, which also increases blood pressure. If the renin-angiotensin-aldosterone system is too active, blood pressure will be too high. Many drugs interrupt different steps in this system to lower blood pressure. These drugs are one of the main ways to control high blood pressure (hypertension), heart failure, kidney failure, and harmful effects of diabetes. It is believed that angiotensin-1 may have some minor activity, but angiotensin-2 is the major bioactive product. Angiotensin-2 has a variety of effects on the body: throughout the body, it is a potent vasoconstrictor of arterioles .

**How the kidneys increase circulating blood volume**

Angiotensin-2 also stimulates the adrenal gland to secrete a hormone called aldosterone. Aldosterone stimulates more Na reabsorption in the distal tubule, and water gets reabsorbed along with the Na. The increased Na and water reabsorption from the distal tubule reduces urine output and increases the circulating blood volume. The increased blood volume helps stretch the heart muscle and causes it to generate more pressure with each beat, thereby increasing the blood pressure. The circulating blood volume is directly proportional to the stretch of the heart muscle.

The actions taken by the kidney to regulate blood pressure are especially important during traumatic injury, when they are necessary to maintain blood pressure and conserve the loss of fluids. The body stores calcium in the bones, but also maintains a constant level of calcium in the blood. If the blood calcium level falls, then the parathyroid glands in the neck release a hormone called parathyroid hormone. Parathyroid hormone increases calcium reabsorption from the distal tubule of the nephron to restore the blood calcium level. Parathyroid hormone aside from stimulating calcium release from bone also causes calcium absorption from the intestine.

Vitamin D is also required by the body to stimulate calcium absorption from the kidney and intestine. Vitamin D is found in milk products. A precursor to vitamin D (cholecalciferol) is made in the skin and processed in the liver. The last phase in the conversion of an inactive form of cholecalciferol into active vitamin D takes place in the proximal tubule of the nephron. Once activated, vitamin D stimulates calcium absorption from the proximal tubule and from the intestine, thereby increasing blood calcium levels.

Kidney stones are abnormalities usually caused by problems in the kidney’s ability to handle calcium. In addition, the kidney’s role in maintaining blood calcium is important in the bone disease osteoporosis that afflicts many elderly people, especially women.

**The kidneys therefore function in the body to:**

• Control the composition of the blood and eliminate wastes by filtration/reabsorption/secretion

• Influence blood pressure by renin secretion

• Help regulate the body’s calcium by vitamin D activation

If for any reason, the kidneys fail to function, then renal dialysis methods (artificial filtration methods) becomes the only alternative to assist the patient to survive by cleansing the blood. This is especially necessary when both kidneys fail.

**Mechanisms of blood pressure control by the kidneys**

1. Intra-renal actions of the renin-angiotensin system in blood pressure control

The renin-angiotensin system (RAS) is a potent modulator of blood pressure, and dysregulation of the RAS results in hypertension. Pharmacological blockade of the RAS with renin inhibitors, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor blockers effectively lowers blood pressure in a substantial proportion of patients with hypertension [10], reflecting the important role for RAS activation as a cause of human hypertension. While in rodents, deletion of RAS genes lowers blood pressure, overexpression causes hypertension [11].

While The distal tubule cells (macula densa) sense the Na in the filtrate, and the arterial cells (juxtaglomerular cells) sense the blood pressure. Studies have shown that chronic infusion of low doses of angiotensin II directly into the kidney caused hypertension with impaired natriuresis due to a shift of the pressure-natriuresis relationship . It is also believed that the existence of local and independent control of RAS activity within the kidney influencing sodium excretion and blood pressure regulation. In this hypothesis, increased circulating levels of angiotensin II are associated with accumulation of angiotensin peptides in the kidney, upregulated expression of angiotensinogen, the primary RAS substrate, in proximal tubule epithelium, and increased excretion of angiotensinogen and angiotensin peptides in urine . In this feed-forward pathway, angiotensin II acting via type 1 angiotensin (AT1) receptors in the kidney induces local activation of the RAS inside the kidney and increases generation of angiotensin II in the lumen of renal tubules, resulting in autocrine and paracrine stimulation of epithelial transporters .

AT1 receptors in the zona glomerulosa of the adrenal gland stimulate aldosterone release, making aldosterone a downstream effector of the RAS. Activation of the mineralocorticoid receptor (MR) in aldosterone-sensitive nephron segments stimulates assembly and translocation of the subunits of the ENaC. Mutations in ENaC subunits that impair its degradation result in enhanced membrane density and open probability of the channels, resulting in Liddle’s syndrome, characterized by severe, early onset hypertension resembling hyper-aldosteronism, but with low levels of aldosterone . Similarly, activating mutations in the gene encoding the MR also cause hypertension that is exacerbated by steroid hormone alterations during pregnancy . These syndromes may highlight the capacity for dysregulation of the MR/ENaC signaling pathway in the kidney to promote hypertension.

Aldosterone, in addition to stimulation of sodium reabsorption, promotes secretion of potassium into urine. Shibata et al have shown in their studies that regulated phosphorylation of the MR modulates aldosterone responses in the kidney. They showed that phosphorylation of S843 on the MR prevents ligand binding. This form of the MR is present only in intercalated cells of the collecting duct of the kidney where its phosphorylation is differentially regulated by volume depletion and hyperkalemia. For example, in volume depletion, the MR in intercalated cells is dephosphorylated, resulting in potentiation of chloride and sodium reabsorption, allowing a distinct response to volume depletion . Although the MR is classically activated by aldosterone, recent studies suggest that the small GTPase Rac1 may promote hypertension through an MR-dependent pathway, even in the setting of suppressed aldosterone levels.

Hypertensive kidney injury and the progression of chronic kidney disease

The kidney remains a major site for hypertensive target organ damage which is second only to diabetic nephropathy as a primary cause for end-stage renal disease (ESRD). Moreover, the presence of chronic kidney disease (CKD), including that caused by hypertension, has been shown to be a strong independent risk factor for adverse cardiovascular outcomes. Nevertheless, major aspects of clinical hypertensive renal disease remain poorly understood such as the marked differences in individual susceptibility to hypertensive renal damage and the apparent variable reno-protective effectiveness of antihypertensive classes .

Studies have revealed that time-varying SBP was associated with incident CKD, with a steady increase in risk of incident CKD above an SBP of 120 mmHg. Time-weighted SBP was associated with a more rapid decline of kidney function. Diabetes was the strongest predictor of incident CKD, and more rapid decline of kidney function and worse glycemic control were associated with greater risk, thereby supporting the role of BP and other traditional risk factors like diabetes in the initiation and progression of kidney function decline in hypertensive patients with normal kidney function at baseline .

Sodium handling by the kidney is a major determinant of the level of intra- and extra- renal blood pressure, and its under complex physiological control by hormones, inflammatory mediators, and the sympathetic nervous system. It is self-evident that a basic mechanism of efficacy for diuretics and dietary sodium restriction in hypertension is to favorably influence sodium balance and homeostasis. Other antihypertensive agents such as RAS inhibitors, vasodilators, and β-blockers work through a similar mechanism by facilitating pressure-natriuresis. Recent studies have also suggested that WNK signaling pathways, soluble inflammatory mediators, and pathways regulating extra-renal sodium disposition might also be useful targets for enhancing elimination of sodium and reducing blood pressure in hypertension.

The renin-angiotensin system (RAS) is a powerful modulator of blood pressure, and dysregulation of the RAS causes hypertension. Pharmacological blockade of the RAS with renin inhibitors, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor blockers effectively lowers blood pressure in a substantial proportion of patients with hypertension [10], reflecting the important role for RAS activation as a cause of human hypertension. Similarly, in rodent models, deletion of RAS genes lowers blood pressure whereas overexpression causes hypertension .

5) Discuss the role of kidney in calcium homeostasis ?

The **kidney** is critcally important in **calcium homeostasis**. Under normal blood **calcium** concentrations, almost all of the **calcium** that enters glomerular filtrate is reabsorbed from the tubular system back into blood, which preserves blood **calcium** levels.

The maintenance of calcium homeostasis is very important because calcium is the main component of bony skeleton and serves as the intracellular and extracellular messenger in numerous essential cellular events such as neuronal network, immune response, muscle contraction, and hormone secretion. Total body calcium in the adult human is about 1-2 kg and 99% of total calcium exists in bone. Even though only less than 1% of body calcium is in the extracellular space, maintaining the extracellular calcium concentration within a narrow range (8.5-10.5 mg/dL) is very important for calcium homeostasis. Approximately 40% of plasma calcium is protein-bound and 10% of calcium is in a complex with anions like phosphate, citrate, and sulfate etc. Only half of plasma calcium is in its free form (ionized form, iCa2+) and physiologically important. The ionized calcium is tightly regulated by hormones like parathyroid hormone (PTH), 1,25-dihydroxyvitamin D3 (1,25(OH)2D3), calcitonin, and calcium itself. The kidney, intestine, and bone are the main target organs of these regulators, and the kidney plays a key role in the fine regulation of calcium excretion.

Parathryroid hormones forms 1,25-dihydroxycholecalciferol ( activated form of vitamin D) from 25-hydroxycalciferol ( prehormone or proactive form of vitamin D) in the kidney. Vitamin D in turn aids in absorption of calcium from the intestine.